POTASSIUM IONTOPHORESIS AS AN EXPERIMENTAL PAIN STIMULUS: ITS PSYCHOPHYSICAL CHARACTERISTICS AND ITS UTILITY FOR INVESTIGATING THE SPINAL MODULATION OF PAIN

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ABSTRACT

The present study investigated the psychophysical characteristics of potassium iontophoresis and its suitability as an experimental pain stimulus. Experiment One investigated the optimal duration of the pain stimulus for reliable reporting across repeated trials, and whether the relationship between stimulus and subject response was linear, logarithmic or a power function. Experiment Two determined the optimal inter-stimulus interval (ISI) for reliable pain reporting and evaluated stimulus history effects, both in terms of session effects and the effects of immediately preceding stimuli. Experiment Three compared potassium iontophoresis with a sodium iontophoresis control.

Linear functions described the stimulus-pain relationship best. No significant differences in the goodness-of-fit coefficients of determination, correlations, or coefficients of variation, were found for the stimulus durations of 1, 2 and 4 seconds. Significant stimulus history effects were found across a session, with adaptation and enhancement of responding for low and moderate intensity stimuli respectively. The effects of the immediately preceding stimuli were suppression or enhancement of pain response depending on the ISI, the preceding stimulus intensity and the present stimulus intensity. Potassium iontophoresis was a significantly more effective pain stimulus than sodium iontophoresis.

It was concluded that potassium iontophoresis is a convenient and reliable experimental pain stimulus. It can be presented rapidly and repeatedly with minimal loss in consistency of subject pain report. Potassium iontophoresis provides a technique for investigating the neural modulation of pain in the relative absence of inflammation processes and tissue damage.

The properties of potassium iontophoresis determined in Experiments One, Two and Three indicated that it could be an ideal nociceptive stimulus for a quantitative analysis of some of the spinal modulation mechanisms predicted by the gate control theory of pain. Clinical and experimental support for the gate control theory of pain was overviewed.

According to the gate control theory of pain a peripheral stimulus that activated both small and large-diameter afferent fibres would be perceived as painful, though there would be some reduction in the intensity of the pain due to the inhibitory action of the large fibre activity.

The present study investigated a prediction of gate control theory that there would be a transient increase in pain above that of the background level - a pulse of pain - as the pain stimulus was being ramped off due to the large fibre activity at the spinal level falling away more quickly due to the different peripheral conduction velocities of large and small fibres. A further prediction was that the more distant the peripheral stimulus was from the spine the greater the pain pulse would be for any given ramp-off rate. Supraspinal pain modulatory mechanisms were overviewed but excluded as possibly obscuring the predicted pain pulse generated through the ramping off of the peripheral nociceptive stimulus.

Fourteen subjects had the experimental pain stimulus of iontophoretically applied potassium ions (K^+) applied to an upper and a lower site on the dominant arm. Each stimulus trial consisted of four seconds of constant pain followed by the stimulus being ramped off. In a threshold detection task a double random staircase method was used to adjust the ramp-off rate. Subjects were asked to indicate if they could detect a brief pulse of additional pain during this ramp-off phase. Subjects were clearly able to detect a pulse of pain at both sites. The average rate of stimulus ramp-off in order to detect a pain pulse was statistically greater for the upper-arm site (14.3 μg K^+/s), than for the lower-arm site (9.4 μg K^+/s). The average ramp-off time required to generate a detectable pain pulse was 192 ms and 261 ms for the upper and lower arm sites respectively.

These results were consistent with the predictions of gate control theory and our ramp-off model. Alternative explanations for the results, including intrinsic differences in nociceptive responding for different dermatomes and anode break excitation, were considered.

It was concluded that the detection of a pain pulse during the ramping off of a peripheral pain stimulus potentially provides a quantitative measure of the spinal modulation of pain as described by the gate control theory of pain. However, further studies would be required to confirm the causal mechanisms that generate the observed pulse of pain.

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CHAPTER 1

INTRODUCTION

1.0 INTRODUCTION

Pain is one of our most pervasive and complex health care problems. It has been estimated that one third of the American population have persistent or recurrent pain problems (Meinhart & McCaffery, 1983). Indeed, it is the most common of medical symptoms (Schoenmacker & Willemsted, 1979), and the single most frequent complaint that patients report to physicians (Harcus, Smith, & Whittle, 1977).

In addition to the personal suffering involved with pain there is also the financial cost to society (Steig, Williams, Timmermans-Williams, Tafuro, & Gallagher, 1986). Surveys have revealed that pain directly accounts for over 700 million lost working days annually in America, at a cost of 60 billion dollars, or 10% of the national budget (Meinhart & McCaffery, 1983). It has been estimated that up to 30% of the population suffer from chronic pain and up to 20% of the population from acute pain, at a cost, to American society alone, of nearly 80 billion dollars annually (Bonica, 1990). Statistics reveal a similar general picture for New Zealand. For instance, nearly three million analgesic prescriptions are made out annually (Hyslop, Dowland, & Hicking, 1983).

Clearly any advances in our understanding and control of pain would be of major benefit, both in terms of alleviating human suffering and in reducing the financial costs to society. Unfortunately, despite extensive investigation, pain remains a complex and not fully understood phenomenon.

Pain has been defined by the Subcommittee on Taxonomy of the International Association for the Study of Pain as "an unpleasant sensory and emotional *experience* associated with actual or potential tissue damage, or described in terms of such damage" (Merskey, 1986, p. 215). Pain is a personal, private experience, but this does not necessarily mean that it cannot be investigated scientifically. Indeed, many not directly observable (latent) variables, such as intelligence or creativity, are studied in psychology. Through the use of ostensive definitions and psychometric and psychophysical methodology it is possible to characterise the pain experience in scientifically meaningful terms.

While there exist many conceptual and methodological problems in pain research, and many aspects of pain remain unsolved, research efforts have made significant progress in our understanding of pain. For instance, over the last two decades there has been substantial advancement in our understanding of the endogenous pain control systems (for review see e.g., Besson & Chaouch, 1987).

1.1 THE ROLE OF EXPERIMENTAL PAIN STIMULI IN PAIN RESEARCH

In studying the psychology of pain there are two major research approaches; experimental and clinical. The experimental approach typically studies pain under controlled laboratory conditions, using an applied and measurable pain stimulus. In contrast, the clinical approach observes people who are suffering from 'real' pathological pain and, typically, under far less controlled conditions. An advantage of the experimental approach then is that there is better control of extraneous variables, and therefore an increased likelihood of establishing causal mechanisms and relationships.

Some of the specific goals of experimentally-induced pain research include; the assessment of analgesic activity, analysis of the mechanisms of pain and analgesia, analysis of the mechanisms of pain report, and the assessment of clinical pain perception (Gracely, 1984).

A critical assumption underlying the experimental investigation of pain is that it has ecological validity. That is, that experimental pain-research findings are generalisable to clinical pain (Over, 1980). However, many pain investigators have contested the validity of experimental pain (Beecher, 1957a; Chapman et al., 1985; Harris & Tolman, 1983; Zwetnow, 1979a).

Cited differences between experimental and clinical pain often include that the experimental pain is of short duration, known by the subject to be nondamaging (an essential ethical requirement), generally predictable, and normally under some control of the subject such as being able to be terminated if desired (Beecher, 1957a; Bromm, 1984). In contrast, clinical pain is typically of long duration, unpredictable, often more severe, less subject to control, and more anxiety provoking (Elton, Stanley, & Burrows, 1983). In particular the reactive, emotional and motivational aspects of experimental pain differ from clinical pain (Beecher, 1957b; Elton et al., 1983; Bromm, 1984).

For these reasons many clinicians are sceptical about the clinical applicability of experimental findings, conceding that while experimental pain research may be good psychophysics, the experimental pain stimuli used are not good analogues of 'real' pain. Though, as Keele and Armstrong (1964) have noted, the differences between experimental and clinical pain have been over-emphasised to the extent that the similarities between the two can easily be overlooked. Ultimately, the issue of whether or not experimental pain is an adequate analogue of clinical pain is an empirical question, and one that is context bound.

It is clear that many advances in our understanding of pain has been made through experimental pain research. The increased knowledge of neural mechanisms subserving pain from both animal and human experimental studies is one example of this (for review see Besson & Chaouch, 1987).

In summary, while care must be exercised in extrapolating from any experimental study, the evidence clearly demonstrates that the results of experimental pain research have provided

much valuable information. Indeed, as Zwetnow (1979b) has observed, pain research is unusual in that it is ".. very seldom in medicine that strictly experimental research may lead so quickly to practical clinical application" (p. 209).

1.2 REQUIREMENTS FOR EXPERIMENTAL PAIN STIMULI

A number of researchers (e.g., Elton et al., 1983; Gracely, 1989; Handwerker & Kobal, 1993; Lahoda, Stacher, & Bauer, 1977; Murrin & Rosen, 1962; Tursky, 1974; Wolff, 1977, 1984; Zwetnow, 1979a) have described the requirements for an ideal experimental pain stimulus for use with humans.

The major requirements for an experimental pain stimulus are:

a) Clearly detectable as a pain sensation

b) Reliably quantifiable from threshold to tolerance levels

c) Demonstrable construct validity with respect to clinical pain

d) Not produce any tissue damage

e) Able to be presented repeatedly and rapidly with minimal carry-over effects

f) Easy to use and safe

a) Clearly detectable as a pain sensation

While this requirement might appear self-evident it is a difficult criterion to meet. It entails that the stimulus should be as pure a sensation of pain as possible and uncontaminated by other types of sensation. For example, a hot object is capable of producing three sensations; pain, heat and pressure. In a threshold detection study, for instance, reliable discrimination between these three sensations may be difficult.

In addition the experimental stimulus should produce as little 'prepain' as possible (Bromm, 1984; Chapman et al., 1985). That is, at levels of stimulation below pain threshold, there should be as little nonpainful sensation as possible. Examples of pre-pain include the tingling

sensation produced by electric current before the onset of pain, the sense of warmth and heat before the sensation of thermal pain, and pressure sensations before the onset of mechanical pressure pain.

b) Quantifiable from threshold to tolerance levels

The experimental pain stimulus should be definable in precise and easily understood physical terms (Zwetnow, 1979a). Ideally the pain stimulus should be able to range continuously from pain threshold to pain tolerance levels in a consistent and regular manner (Lahoda et al., 1977). By obtaining suprathreshold responses over a range of stimulus magnitudes lawful relationships between the stimulus and the experienced pain can be measured.

c) Demonstrable construct validity with respect to clinical pain

Support for construct validity can be obtained by demonstrating a consistent relationship between the characteristics of the experimental pain and the known characteristics of clinical pain. For example, determining that the experimental pain responds similarly to analgesics known to be effective with clinical pain is one method of validation of an experimental pain stimulus (Hilgard, 1978; Sternbach, Murphy, Timmermans, Greenhoot, & Akeson, 1974).

Validity as an experimental pain sensation includes that it be consistent with known physiological processes involved in clinical pain perception. For instance, the experimental pain stimulus should produce a pattern of A-delta or C-fibre nociceptor activation similar to that found in clinical pain (D. D. Price, 1988; Willis, 1985).

d) Not produce any tissue damage

In contrast to the earlier claims of Hardy, Wolff and Goodell (1967, p. 53) that the "adequate stimulus" for pain sensation is the damaging of tissue an important criterion for any experimental pain stimulus is, in fact, that it produces no obvious tissue damage. This goal is consistent with observations that tissue damage is not a necessary requirement of clinical pain.

Indeed, to define pain in terms of tissue damage is considered to be totally inadequate (Wolff, 1977).

e) Able to be presented repeatedly and rapidly with minimal carry-over effects

The ability to present the pain stimulus repeatedly, and over a short period of time, is important, both in terms of convenience and the statistical power gained from repeated trials. The ability to rapidly repeat trials becomes particularly critical in signal detection studies (e.g., (Clark & Goodman, 1974; Lloyd & Appel, 1976; Malow, Grimm, & Olsen, 1980; Yang, Richlin, Brand, Wagner, & Clark, 1985), evoked potential studies (e.g., Chapman, Chen, Colpitts, & Martin, 1981), or when tracking the time course of pain where large numbers of trials are an essential requirement for an adequate analysis.

f) Easy to use and safe

Finally, the pain stimulation technique should be easy to implement over repeated trials. It should not interfere with the mobility and general comfort of subjects, so that they can attend to the required psychophysical tasks with minimal distraction. Naturally, in addition to a lack of tissue damage from the pain stimulus, the stimulus apparatus should present no potential danger or harm to the subject.

1.3 REVIEW OF COMMONLY USED EXPERIMENTAL PAIN STIMULI

A number of different experimental pain stimuli are used in experimental pain research. Each technique has its own strengths and weaknesses with regards the requirements of an ideal pain stimulus. The experimental pain stimuli most often used are:

a) Thermal stimulation

b) Cold pressor stimulation

c) Mechanical pressure stimulation

d) Ischemic stimulation

e) Electrical stimulation

f) Chemical stimulation

1.3.1 a) Thermal stimulation

Thermal pain stimuli include both conduction heat from a thermode (Anton et al., 1985), or radiant heat from an infrared lamp or CO_2 laser (Hardy, Wolf, & Goodell, 1940; Hardy et al., 1967; Bromm, Jahnke, & Treede, 1984). Stimulus application may be either variable-intensity/fixed-time, or variable-time/fixed-intensity.

Problems associated with both conduction and radiant heat include the possibility of damage to the skin. This limits the possible number of stimulus applications to a given site, and largely restricts the technique to determining threshold and lower suprathreshold levels (Hardy et al., 1967). For example, burn injury has been found at 50 °C, while tolerance limits are frequently only reached at 60 °C (Benjamin & Helvey, 1963). Thermodes, and even fast rising temperature radiant devices, are likely to activate mechanoreceptors as well as nociceptors (Handwerker & Kobal, 1993).

Lahoda et al., (1977) have reported a lack of consistent proportional relationship between the intensity of the radiant heat stimulus and the actual amount of heat build-up in the irradiated skin. This appears to be largely due to variations in blood flow, and in obtaining uniform heat absorption on the skin surface (Geldard, 1972). Thermal receptors, apart from thermal nociceptors, may be activated, leading to pre-pain stimulation. And substantial carry-over effects have been found with repeated trials (Hardy et al., 1967).

1.3.2 b) Cold pressor stimulation

The cold pressor method of pain induction typically involves first placing the subject's hand into warm water for a short period of time, and then into cold water. The cold water temperatures have ranged from 0 to 10 °C, though most often well-circulated ice-water at 0 °C is used. Both threshold and tolerance measures are obtainable from this procedure (Benjamin, 1959; Garcia de Jalon, Harrison, Johnson, Kozma, & Schnelle, 1985). While generally considered to be one of the most valid procedures in terms of the qualitative nature of the pain

produced a major disadvantage with the technique is that only a limited number of trials can be given (Wolff, 1977). A long interstimulus interval (ISI), of up to 30 minutes, is typically required for a subject's hand to return to a homeostatic equilibrium before the next trial. Clearly this is an unacceptable delay for studies where a large number of trials are required.

In addition, the measure is dependent on blood flow rates, blood pressure and vasomotor activity (Geldard, 1972; Lahoda et al., 1977). For instance, the numbing of a subject's hand can seriously confound tolerance trials. With prolonged cooling it is possible for the initial painful vasoconstriction to be followed by vasodilation in which the pain levels-off or even reduces in some subjects, thus adding to the unreliability of the stimulus (Kreh, Anton, Gilly, & Handwerker, 1984).

1.3.3 c) Mechanical pressure stimulation

Mechanical methods of pain induction involve the application of pressure against some part of the body; for example, shin-bone, or interdigital webs of the hand (Forster, Anton, Reeh, Weber, & Handwerker, 1988). One form of mechanical stimulation is the use of ultrasound (Gavrilov, Gersuni, Ilyinski, Tsirulnikov, & Shchekanov, 1977). Mechanical stimuli have been commonly used for clinical pain testing due to the relative ease of application.

Problems that have been found with this technique include a lack of consistent proportional relationship between applied pressure and reported pain, possible damage to the skin (e.g., bruising), and the confound of pressure sensation (Fiorgione & Barber, 1971). The stimulation of low-threshold mechanoreceptors is made more problematic as the mechanoreceptors adapt faster during prolonged application of the mechanical stimuli, resulting in a constantly changing ratio of nociceptive and pressure sensation (Adriaensen, Gybels, Handwerker, & Van Hees, 1984). A survey by Wolff (1977) found mechanical pressure to be the most unreliable of all the experimental pain induction methods.

1.3.4 d) Ischemic stimulation

Ischemic pain induction is based on the draining of venous blood from the arm by restricting blood flow with a tourniquet (Smith & Beecher, 1968). The pain of ischemia is linked to the release of algesic biochemicals from exercising muscle under conditions of low blood flow (Sicuteri, Franchi, & Michelacci, 1974).

Two main procedures are the maximal effort and the sub-maximal effort procedures (Beecher, 1966; Rupp, Badian, Farber, Malerczyk, & Sittig, 1984; Sternbach, Deems, Timmermans, & Huey, 1977). With the maximal effort procedure the subject's arm is made ischemic by applying a tourniquet, followed by a hand contraction exercise until no further contractions are possible. Pain rapidly builds to tolerance level over a 3 to 4 minute period.

With the submaximal effort procedure blood is first drained from a subject's arm using the pressure of an elastic bandage, a tourniquet is then applied above the elbow and the elastic bandage removed. A set number of hand contraction exercises are then completed, after which the subject waits for the pain to slowly mount. Pain tolerance level is typically reached in 20 to 30 minutes. It has been claimed that the longer period of pain for the submaximal effort procedure more closely approximates clinical pain (Beecher, 1966). With both procedures threshold and tolerance measures are obtainable.

While generally it is agreed that the pain produced by ischemia does closely approximate many types of clinical pain a major disadvantage is the length of time required to complete a single trial, frequently longer than 30 minutes (Beecher, 1966). As with cold pressor stimulation this severely limits the number of trials that can be given.

It has also been reported that the tourniquet may produce more pain than the ischemia (Wolff, 1977), and that the pain is partly a function of muscular development and motivational factors that influence exercise performance required to produce the ischemia (Benjamin, & Helvey, 1963).

1.3.5 e) Electrical stimulation

Electrical stimulation has been a popular and widely used form of noxious stimulation (e.g., Cross, Tursky, & Lodge, 1975; Rollman & Harris, 1987; Tursky, 1974). A major advantage is the ability to accurately deliver a prescribed current duration and intensity. However, electrical stimulation does have a number of methodological problems. Most studies use alternating current (AC), but there is little consensus over which frequency or waveform is optimal (e.g., K.P. Price & Tursky, 1975; Tursky & O'Connel, 1972). Pulse frequency and rate of current rise is known to influence the painfulness of the stimulus (Notterman, 1966). With each researcher using their own preferred parameters it can be difficult to compare studies.

There has also been confusion over what parameter should be used to measure the intensity of electric shock; voltage, amperage, or wattage (power) (Cross et al., 1975; Hill, Flanary, Kornetsky, & Wikler, 1952). This problem is increased by the fact that all three measures are partly a function of impedance - with impedance itself being a function of three constantly changing factors within the human body; resistance, capacitance and inductance (Tursky, 1974). Such considerations can also have major effects on the psychophysics of pain measurement. For instance, Hill et al. (1952) have suggested that wattage correlates best with subject report for electrical pain. A psychophysical implication of this is that, as wattage is proportional to the square of the amperage [power (watts) = I^2*R: I = amperage, R = resistance] then, if wattage is taken as the unit of stimulus measurement, the resultant power exponents will be half those of the power exponents based on amperage or voltage units.

Electrical stimulation also has low ecological validity in that while most people find electric shock aversive the sensation bears little qualitative relationship with clinical pain. The fact that electrical stimulation excites all nerve fibres, not just those associated with nociception, has lead Geldard (1972) to refer to it as the "great nonadequate stimulus" (p. 324). At the higher pain levels the pain sensation is also accompanied by the extraneous sensation of muscle contraction.

1.3.6 f) Chemical stimulation

Chemical methods involve direct chemical stimulation of nociceptive nerve endings at various tissue depths. For instance, cutaneous surface application to a blister base cutaneous (e.g. Bleehen & Keele, 1977), intracutaneous injection (e.g., hypertonic saline or isotonic potassium chloride injection: e.g., Armstrong, Dry, & Keele, 1951; Armstrong, Dry, Keele, & Markham, 1953; Wolff, 1977), or close arterial injection (e.g., Mense & Schmidt, 1974). These methods often provide good analogues of clinical pain, both in terms of the perception of the nature of the pain and possibly of the underlying physiological processes normally involved. The algesic chemicals applied are often those that are naturally released following normal tissue trauma; for example, bradykinin, acetylcholine and histamine.

However, major problems associated with chemical methods include the tissue damage that occurs at the site of stimulation, and the inability to precisely quantify the stimulus, with the onset and time course of the nociceptive stimulation being hard to standardise (Geldard, 1972; Gracely, 1989; Wolff, 1977). The long refractory period before a second stimulation is possible also limits the number of trials that are possible in a session (Wolff, 1977; Zwetnow, 1979a). The often extensive inflammatory reactions produced by many nociceptive chemicals can also complicate the interpretation of nociceptor excitation.

Having reviewed some of the problems associated with the commonly used experimental pain stimuli it is clear that none meet all the requirements of an ideal pain stimulus. Of course the limitations associated with an experimental pain stimuli depends upon the context of the study. Certainly a great deal of important research has been conducted with the above reviewed experimental pain stimuli. Nevertheless, the development and characterization of additional experimental pain stimuli should be a priority within the field of experimental pain research.

One form of chemical stimulation that holds some promise in overcoming many of the difficulties associated with the more commonly used experimental pain stimuli is the iontophoretic application of potassium ions (K^+) to the skin (Benjamin & Helvey, 1963).

CHAPTER 2

DEPENDENT MEASURES

2.0 DEPENDENT VARIABLE MEASURES OF PAIN

In order to accurately determine the characteristics of potassium iontophoresis as an experimental pain stimulus a reliable and valid measure of pain stimulation must be employed. Pain is a complex subjective experience that can be difficult to accurately and reliably quantify. Nevertheless, a wide range of methodologies have been developed to measure the experience of pain in humans. The criteria for an ideal pain-measurement include: being relatively free of subject-response bias, sensitive to pain changes, easy to use, reliable, able to assess the multiple dimensions of pain, and valid for both experimental and clinical pain (Gracely & Dubner, 1981; Price, 1988).

In the present study Visual Analogue Scales (VAS) were used for all pain measurements in Experiments One, Two and Three. Other pain measures which have been used successfully in pain research studies, but which were not used in the present study for various methodological reasons included;

a) Physiological measures

b) Behavioural measures

c) Signal detection theory measures

d) Pain tolerance measures

2.0.1 a) Physiological measures

Physiological measures of pain include heart rate, galvanic skin response (GSR), respiratory response, and a variety of neurological measures, including electromyographic recordings (EMG), microelectroneurographic recording of single fibres, electroencephalographic

recordings (EEG), and brain evoked potentials (BEPs) (Fernandes De Lima et al., 1982; for reviews see Chen, 1993a, 1993b; Handwerker & Kobal, 1993). Biochemical assays (e.g., cortisol levels) have also been used in an attempt to track pain states. More recently, non-invasive brain scans such as regional cerebral blood flow (rCBF), magnetic resonance imaging (MRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT) have been increasingly used to study pain responding (Chen, Dworkin, Haug, Gehrig, 1989; Chen, 1993a, 1993b).

However, in addition to the complexity of the apparatus required - especially for some of the brain scan measures such as PET and SPECT - there are a number of considerations and problems associated with most of the physiological measures. First, recordings such as EEG, EMG and BEPs may be contaminated by recording artifacts. Second, many of the measures are non-quantitative in nature. For instance, EEG recordings often rely on visual inspection. Accordingly standardized protocols and statistical rules need to be developed to analyse such data.

A major limitation of physiological measures is that the complex nature of pain perception has yet to be satisfactorily reduced to a single physiological measure. That is, physiological measures lack both specificity and reliability, and all physiological measures are known to be susceptible to bias (Chapman et al., 1985; Chen, 1993a, 1993b; Murrin & Rosen, 1962). While physiological measures such as BEP have been found to correlate with subjective pain report (e.g., Fernandes De Lima et al, 1982), and are sensitive to the effects of analgesic drugs and their antagonists (e.g., Chen & Chapman, 1980), still no *dependable* relationship has been found between the psychological variable of pain and a physiological measure.

D.D. Price (1988) has made the interesting point that a physiological measure cannot override a genuine subjective pain report. In determining the pain a person is perceiving we still must ultimately use subjective data (i.e., some measure of the subjective experience of pain - such as verbal report) to validate any physiological objective measure.

2.0.2 b) Behavioural measures

Behavioural measures that have been used to measure pain perception include muscle twitch, facial expression, moaning, bracing, rubbing, impaired mobility and medication use (Fordyce, 1976; Linton, Melin, & Götestam, 1985). While such measures have an intrinsic behavioural objectivity, and are often behaviours of direct clinical relevance, they are influenced by a wide range of factors, and have often been found to be unreliable measures of nociception or pain (Fordyce, 1988; Huskisson, 1974; Keefe & Dunsmore, 1992a, 1992b). Finally the assessment of pain behaviour is more relevant for clinical pain, rather than experimentally induced pain, as the short duration and often low intensity of experimental pain is unlikely to result in overt responses that can be easily observed or quantified.

2.0.3 c) Signal detection theory measures

Signal detection theory (SDT) proponents have claimed that the SDT model provides a way of separating individual sensitivity to pain from willingness to report pain; a separation of the sensory and cognitive-motivational components of the pain experience.

Unfortunately there are serious problems with the interpretation of the SDT model when applied to pain perception. One of the most important of these is that decreases in sensory discriminability (d') cannot be taken as an unambiguous measure of reduced perceived painfulness or analgesia (Gracely, 1979; Rollman, 1977), as some SDT proponents have suggested. Indeed, an increase in painfulness can decrease pain discriminability (Jones, Planas, & Anuza, 1982). In more general terms, the SDT measures are not direct or unbiased, and they are not immune to demand characteristics (Grossberg & Grant, 1978). SDT Sensory discriminability measures reflect level of attention, motivation to perform and fatigue state, as well as the ability to detect differences in stimulus intensities (Grossberg & Grant, 1978). Methodological differences in conducting and analysing SDT studies are known to influence the experimental results (Rollman, 1977).

2.0.4 d) Pain tolerance measures

Pain tolerance is the maximum level noxious stimulation that a person is prepared to withstand. It is believed to approximate acute clinical pain better than threshold stimulation as it involves arousal and anxiety. The cold pressor test is commonly used for tolerance trials.

However, with tolerance measures only a limited number of trials are possible without the risk of inter-trial carry-over effects, and even tissue trauma. And tolerance measures are influenced by motivational and cognitive factors such as perceived social desirability of being able withstand the pain, the test instructions provided and the social context of the testing situation (Blitz & Dinnerstein, 1968; Chapman et al., 1985; Gelfand, 1964; Murrin & Rosen, 1962; Wolff, 1977). There is the additional limitation that only a single measurement is obtained, and this does not provide information about the relationship between the applied stimulus and pain responding over a range of suprathreshold values.

In summary, the above pain measures have limitations in terms of either cost, convenience, reliability or validity. Consequently the visual analogue scale (VAS) was selected as the pain measure for Experiments One, Two and Three.

2.1 VISUAL ANALOGUE SCALE (VAS)

The VAS was selected as it is easy to construct and to administer, and it has high face validity (Deschamps, Band, & Coldman, 1988; D.D. Price, Harkins, & Baker, 1987). It has consistently been shown to be reliable and precise for both the sensory and affective dimensions of pain (Huskisson, 1974; Jensen, Karoly, & Braver, 1986; Ohnhaus & Adler, 1975). It is also easily understood by subjects and is quick to administer, making it suitable for repeated testing (McCormack, Horne, & Sheather, 1988).

An advantage of this magnitude estimation procedure is that, in contrast to threshold or tolerance measures, it provides stimulus-response information to suprathreshold stimuli over a range of stimulus levels which are ecologically valid with respect to most clinical pain.

The scale has good subject generality, providing satisfactory assessment of pain for both children and adults (McGrath, 1987). It has been found to be equally satisfactory for both experimental and clinical pain (D.D. Price, et al. 1987; D.D. Price, McGrath, Rafii, & Buckingham, 1983). It has good concurrent validity, correlating highly with other accepted measures of pain (Woodforde & Merskey, 1972). Reports of difficulties in using the VAS tend to be associated with factors such as the loss of ability to think abstractly, mental disorganization and the elderly (Kremer, Atkinson, & Ignelzi, 1981; Scott & Huskisson, 1976).

While there is some debate over the measurement scale that is appropriate for VAS scores the present study has treated the VAS as being an interval scale. There is considerable support in the literature for this position (e.g., D.D. Price et al., 1987; Ohnhaus & Adler, 1975). It has even been claimed that VAS scores produce a ratio scale measure of pain (D.D. Price et al., 1983). More general arguments for treating VAS scores as interval data include that the underlying assumptions apply to many other accepted forms of psychological measurement, and, secondly, that the empirical results of studies employing VAS as an interval scale have been replicable and congruent with theoretical expectations (McCormack et al., 1988).

While verbal rating scales have been shown to be reliable, valid and objective (Gracely & Dubner, 1987; Gracely, McGrath, & Dubner, 1978a, 1978b), by restricting responses to a limited number of verbal descriptor categories they may lack the potential precision and sensitivity of the VAS (Ohnaus & Adler, 1975; Marchand, Charest, Chenard, Lavignolle, & Laurencelle, 1993).

In the present study, for all experiments, the single dimension of perceived sensory intensity was measured. A horizontal scale without intermediate divisions was used as this has been found to be the most reliable of VAS formats (Jensen et al., 1986). The use of numbers or labels at intermediate points has been found to lead to bias through score clustering (Scott & Huskisson, 1976).

It is well established that pain is a multidimensional phenomenon that cannot be completely explained by any single unidimensional measure (Chapman et al., 1985; Clark, Carrol, Yang, & Janal, 1986; D.D. Price, Barrell, & Gracely, 1980; D.D. Price et al., 1987). This has been reflected in the development of such multidimensional pain measures as the McGill Pain Questionnaire (MPQ) (Melzack, 1975a). Melzack and Torgerson (1971) have categorised pain in terms of a sensory dimension that measures the sensory location and intensity, an affective dimension that measures the emotional response to the pain, and an evaluative dimension that measures the total reaction to the pain experience. Tursky, Jamner, and Friedman (1982) developed a Pain Perception Profile (PPP) that measured pain in terms of quantitative sensory intensity, qualitative sensation and the reaction to the pain experience.

The two more commonly measured dimensions are sensory intensity and the affect dimension of unpleasantness. Both clinical studies (D.D. Price, Harkins, Rafii, & Price, 1986) and experimental studies (Duncan, Bushnell, & Lavigne, 1989; Gracely & Dubner, 1987; Gracely et al., 1978a; Gracely, Dubner, & McGrath, 1979; D.D. Price et al., 1987) have shown that people can respond differentially on these two dimensions. For instance, the emotional dimension has been found to be more influenced by the psychological context in which the pain occurs (D.D. Price et al., 1987).

However, the present study has confined measurement solely to the sensory dimension. It must be acknowledged that such a unidimensional measure of pain is a simplification of a complex perception. Nevertheless, the sensory intensity dimension does, in itself, provide important and useful information regarding pain processing. Of the various pain dimensions

pain intensity is "probably the most salient" and the most common clinically assessed pain dimension (Jensen & McFarland, 1993, p. 195).

In addition, previous studies have found that the sensory and effective dimensions often track each other in many situations: that is, the two dimensions are often highly correlated (D.D. Price et al., 1987). In a previous study using potassium iontophoresis (Humphries & Johnson, 1990) subjects were instructed to rate both the sensory intensity and the unpleasantness dimensions of pain according to the instructions of D.D. Price et al. (1983). Averaged over the six subjects a high correlation of 0.93 was found between the ratings on the sensory intensity and unpleasantness scales. Though this inability to differentiate sensory and affective pain dimensions may be an artifact of the VAS, which may be less sensitive at distinguishing between the two pain dimensions compared to verbal descriptor scales (Duncan et al., 1989; Gracely et al., 1978b).

There is the potential confound that if subjects are instructed to scale the dimensions separately they tend to scale only the sensory intensity (Chapman et al., 1985). Some of the subjects in the study by Humphries and Johnson (1990) reported that differentiating the two dimensions was confusing - and that this was especially so where there was a high correlation between ratings on the two scales. Therefore, it would seem that in the absence of an expectation for an experimental manipulation to differentially impact on the sensory and affective dimensions of pain, the use of the two scales together may only provide redundant information. In addition, the added task complexity of scaling two dimensions may even lead to less reliable and valid responding on both scales. The pain stimulus manipulations used in the present study were comparable to those used by Humphries and Johnson, consequently only the sensory-intensity scale was employed in all experiments. There is some evidence that subjects can more reliably rate sensory intensity than affective scales such as unpleasantness. For instance, Gracely and Dubner (1987) found within-subject correlations of 0.96 for sensory intensity and 0.89 for unpleasantness. Finally, the validity of sensory and affective scales can be questioned to some extent in that responses on the two scales may tell us as much about how people use words to

describe pain as much as capturing the multidimensionality of pain with an associated underlying neurophysiology (Hall, 1981).

2.2 PAIN THRESHOLD MEASURES

In Experiments Four and Five pain threshold was determined using the double random staircase method of Cornsweet (1962). Pain threshold is that point, on a continuum of increasing stimulus intensity, that separates nonpainful experience from painful experience.

There are a number of problems associated with threshold measures of pain. First, similar to tolerance measures, pain threshold measures are susceptible to a variety of psychological variables such as subject expectancy, the instructional set given to subjects and demand characteristics - though these effects are generally not as pronounced with pain threshold measures compared to pain tolerance measures (Blitz & Dinnerstein, 1968; Melzack, 1985).

Second, pain threshold detection may also be confounded with the detection of non-noxious prepain sensations (e.g., Mumford & Bowsher, 1976; Yarnitsky & Ochoa, 1990). With potassium iontophoresis a subject must decide when the initial pricking sensation detected at low stimulus intensities should be rated as "painful".

Nevertheless, threshold measures are capable of providing reliable and valid data provided well controlled experimental methodology is employed (e.g., Hardy et al., 1967; Harris & Tolman, 1983). In the present study the above problems associated with pain threshold detection are minimized as the subjects provide their own internal standard for establishing the pain threshold point. That is, changes in stimulus magnitude, rather than absolute stimulus magnitude, are used to detect *changes* in threshold detection. In Experiment Four threshold detection differences are determined at different arm sites in the same subject. In Experiment Five threshold detection differences are determined for different anode electrolytes in the same subject. Therefore, in both Experiments Four and Five, instructional set, the demands of

social desirability and other potentially confounding variables are held constant by the within-subject design.

In Experiments Four and Five the double random staircase method (Cornsweet, 1962; Gracely, 1988; Gracely, Lota, Walter, & Dubner, 1988) was used to adjust the rate of nociceptive stimulus ramp-off in order to determine the threshold of detection of a generated pain pulse. With the single staircase adaptive procedure the stimulus value presented on one trial is dependent on the subject's response to the previous trial. If the subject detects a stimulus then the stimulus level is stepped-down for the next trail, if the subject does not detect the stimulus then the stimulus level is stepped-up. This adaptive tracking procedure eventually results in the subject's responses oscillating around the threshold value that is to be determined.

A number of parameters determine the efficiency of this procedure (Cornsweet 1962; Hannay, 1986). These parameters are 1) The starting stimuli levels. These should be reasonably close to the threshold levels so that trials are not wasted in the initial approach to the threshold. 2) The initial step sizes from one stimulus level to the next. 3) The criteria for making a change to the level of the stimulus. 4) The criteria for making a change to the direction of the stimulus changes. 5) The criteria for determining the amount of change in the stimulus level. Too large a step size will tend to overshoot the threshold and give a relatively insensitive measure. Too small a step size is inefficient in that an unnecessarily large number of trials are required to approach the threshold. Maximum efficiency and precision is obtained when, once the threshold is approached, the step size is the size of the just noticeable difference (JND) for that stimulus. 6) The criteria for ending the series. A sufficient number of trials is required in order to obtain a 'plateau' threshold oscillation without running unnecessary trials that add no useful information. A common procedure is to terminate the trials after a predetermined number of response reversals. 7) The method used to calculate the actual threshold values.

The major advantage of the random staircase procedure is that, provided the above parameters are suitably selected, it is economical and efficient. That is, in contrast to some other

psychophysical methods - for example, the method of constant stimuli - most of the stimuli presented are close to the threshold, and so provide useful information. However, a disadvantage of the single random staircase method is that, to some extent, the subject becomes aware of the procedure, and the order in which the stimuli are presented. This can lead to manipulation of the threshold by the subject; for instance, by response anticipation or response preseveration .

The double random staircase can control for response interdependences that lead to subject bias. With this procedure two staircases are run concurrently. The staircase selected for determining the stimulus level on any given trial is randomly selected from the two concurrent staircases in operation. The consequence is that if the subject predetermines their response in any way, or uses an irrelevant or random strategy, then responses will tend to be inconsistent with the presented stimulus. The overall result under such conditions will be that the staircases will drift apart in a random walk. If the two staircases converge and overlap then the subject must be attending and responding to the stimulus presented in each trial. The double random staircase is therefore not only efficient but also relatively free from subject bias. For analysis the results of the two staircases may be considered as replications, or they be combined to give a single threshold value.

CHAPTER 3

POTASSIUM IONTOPHORESIS

3.0 POTASSIUM IONS AS A PAIN STIMULUS

Extracellular K^+ can have a depolarizing effect on nerve cell membrane potentials, increasing the probability of an action potential being generated (Barker & Levitan, 1974; Conway, 1957). Over a wide concentration range Hodgkin and Horowicz (1959) had reported a linear relationship for membrane depolarization as a function of the log of extracellular K^+ concentration (see Figure 1).

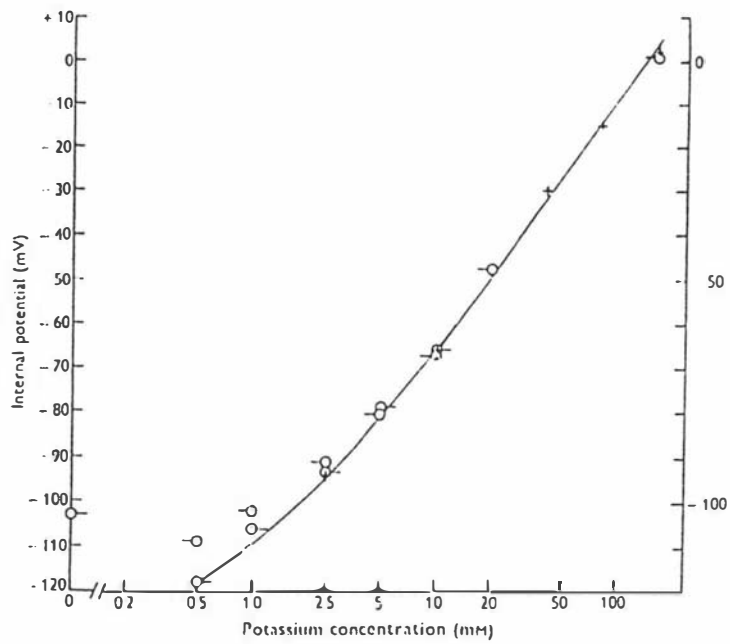


Figure 1. Depolarization of muscle fibre cell membrane potential as a function of the log of extracellular K^+ concentration. Crosses are membrane potentials after an equilibration period of 10-60 minutes; circles are membrane potentials 20 to 60 seconds after a sudden change in K^+ concentration (-o after a sudden increase in K^+, o- after a sudden decrease in K^+). Graph adapted from Hodgkin and Horowicz (1959, p. 135).

The depolarization effect of extracellular K^+ can directly result in nociceptor afferent discharge, or, the nociceptors can become sensitized toward other stimuli that might otherwise have failed to induce neural activity (Uchida & Murao, 1974; Zimmermann, 1984).

Potassium ions are the most common intracellular cation, ranging in concentration from 100 to 150 mmoles per litre. Given that an extracellular K^+ concentration of 20-30 mmoles is sufficient to produce pain, then the release of intracellular K^+ is certainly a possible pain producing mechanism (Smith, 1962, cited in Keele, 1970).

Numerous clinical studies have indeed noted this pain producing action when intracellular K^+ is released from cells into the extracellular space. Examples of this include; pain from tissue rupture during traumatic injury (Benjamin, 1959; Benjamin, & Helvey, 1963), by red blood cell haemolysis during a cardiac infarction (Keele, 1975; Uchida & Murao, 1974), and from muscle tissue under conditions of muscular activity and anoxia (Monnier, 1975; Uchida & Murao, 1974). Under certain conditions there may even be primary afferent depolarization (PAD), where axons are directly depolarized by potassium released by the normal neuronal activity of adjacent nerve fibres (Somjen, 1979).

In an experimental context, the application of potassium chloride solutions to blister bases (Armstrong et al., 1953; Keele & Armstrong, 1964; Ong, Singer, & Wallace, 1980), or the injection of potassium chloride solutions (Iggo, 1974), have produced pain reports. The pain associated with K^+ has been found to be perceptually similar to that produced by acetylcholine, capsaicin, and bradykinin (Ong et al., 1980). Subjective qualitative pain reports have ranged from a stinging sensation progressing through to an intense deep burning, as a function of increasing amounts of applied K^+.

It has been determined that locally applied K^+ can activate C polymodal nociceptors (Bessou & Perl, 1969; Kumazawa & Perl, 1977), as well as A-delta fibres (Kumazawa & Mizumura, 1977; Uchida & Murao, 1974). It appears that K^+ is able to exert this effect on both the axon

and the endings of these pain afferents (Ong et al., 1980). Owing to their lack of myelin sheath and small diameter the C-fibres have been found to be particularly sensitive to the chemical influences of K^+ in the immediate extracellular environment (Guilbaud, 1988; Monnier, 1975). Mense and Schmidt (1974) found that the thin afferents of muscle fibre nociceptors were also preferentially activated by K^+.

All the above experimental and clinical based studies demonstrate the potential pain-producing action of K^+, and which indicate that K^+ may serve a useful role as an an experimental pain stimulus.

3.1 POTASSIUM IONTOPHORESIS AS AN EXPERIMENTAL PAIN STIMULUS

A seldom-used experimental pain stimulus is the iontophoretic application of K^+ to the skin (Benjamin & Helvey, 1963). Iontophoresis (ion transfer) is the migration of ions under the influence of an applied electric potential (Tyle & Kari, 1988). This effect provides a noninvasive means of introducing ionic substances into the body that would not normally pass through the epidermal barrier. Positive ions can be introduced from the positive electrode (anode) and negative ions from the negative electrode (cathode).

As shown in Figure 2, the facilitated transfer of ions across the normally impermeable strateum corneum occurs primarily at the various skin pores; mainly the sebaceous ducts, the hair follicles and the sweat ducts. Ions are transported mostly to the dermal layers of the stratum papillare and stratum basale, with minor transport to the subcutaneous deeper layers, and the underlying vascular tissue. (Glass, Stephen & Jacobson, 1980; Keele & Armstrong, 1964; Magerl & Handwerker, 1988)

This iontophoretic process has been found to be nondamaging to the epidermal layer provided that excessive current densities are not applied (Siddiqui, Roberts, & Pollack, 1985). Indeed iontophoresis has been used clinically to administer a wide range of pharmaceuticals (Tyle & Kari, 1988).

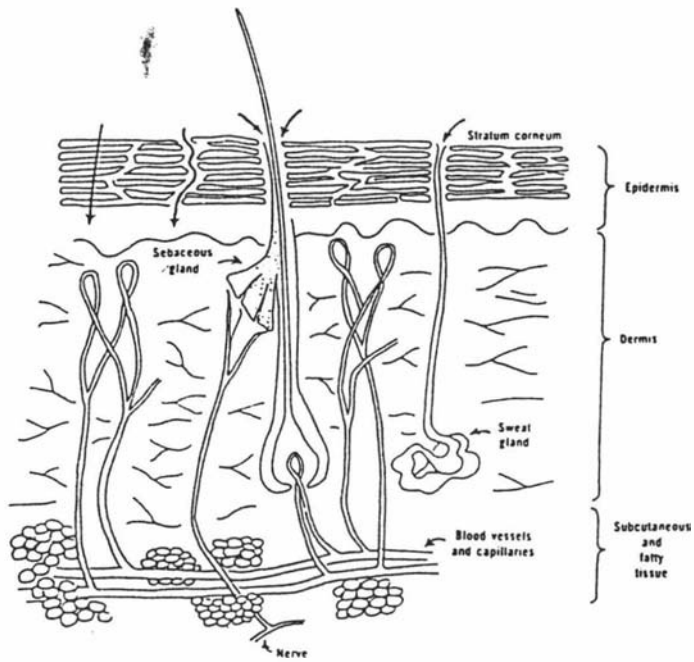


Figure 2. Cross-section of human epidermis showing the iontophoretic transport of ions across the epidermal barrier. The sites of epidermal penetration are A) diffusion through channels between cells, B) through sebaceous ducts and C) through sweat ducts. Adapted from Martin, Swarbrick, and Cammarata, 1983, p. 428.

The iontophoretic delivery of ions requires a DC electric current. By making the body part of a DC circuit the potassium ions at the anode, are able to migrate through the epidermal barrier. The preferential response of nociceptors to the iontophoretic introduction of K^+ may be a function of their superficial location (for instance, the nociceptive 'free' nerve endings found in

the stratum basale), compared to the more deeply situated receptors, such as the pressure receptors (Benjamin & Helvey, 1963).

3.2 PRIOR RESEARCH WITH POTASSIUM IONTOPHORESIS

Studies that have used potassium iontophoresis to induce pain (Benjamin, & Helvey, 1963; Coyne & Peck, 1980; Ong et al., 1980; Voudouris, 1981; Voudouris, Peck, & Coleman, 1985, 1989) provide some support that potassium iontophoresis may possess many of the characteristics required in an ideal pain stimulus. Unfortunately the research focus of most of these studies was not directly aimed at determining the psychophysical characteristics of potassium iontophoresis as a pain stimulus.

Two studies determined the reliability of potassium iontophoresis as a pain stimulus. An unpublished pilot study by Voudouris (1981, cited by Voudouris et al., 1985) claimed that potassium iontophoresis produced no session effects over a three day period, and that the relationship between the stimulus intensity and the subject pain report was linear in nature.

Benjamin and Helvey (1963) tested the reliability of potassium iontophoresis in terms of intrasubject and intersubject variability. By determining tolerance levels for five subjects on 10 different occasions over 13 days the results indicated that while the between-subject variability was large the within-subject variability was comparatively small. Benjamin and Helvey concluded that ".. differences of pain endurance can be measured and expressed in a quantitative way with this test" (p. 568).

While the Benjamin and Helvey (1963) study provides some support for the suitability of potassium as a quantitative pain stimulus a number of issues need to be clarified. First, it is more appropriate to determine the amount of potassium delivered in terms of amperage, rather than voltage. For any given applied voltage the amperage passing through the body (the amount of potassium entering the body) will be a function of skin resistance (based on Ohm's

Law: amperage = voltage / resistance). Given that there are large individual differences in skin resistance (Tursky, 1974) the use of voltage as an independent variable measure of delivered potassium is not satisfactory. All recent studies of potassium iontophoresis use amperage as the direct measure of potassium delivery.

Second, an alternative means of determining the reliability of the pain stimuli would have been desirable, apart from comparing within-subject variability with between-subject variability. Benjamin and Helvey took the *relatively* low levels of within-subject variability to indicate consistency in subject responding across sessions. However, the comparison reflects the large between-subject variability - the differences in pain perception and report known to exist between individuals (see Tursky & O'Connell, 1972) - as much as any lack of variability within the individual.

Third, it would be useful to obtain a description of the characteristics of the potassium iontophoretic stimulus over a range of pain levels, rather than obtaining a single tolerance measure.

In summary, relatively few studies have employed potassium iontophoresis as an experimental pain stimulus, and only a small subset of those studies have attempted to characterise the properties of the stimulus. Given the potential usefulness of the potassium iontophoresis as a pain stimulus further research is warranted to determine its psychophysical characteristics and its potential as an experimental pain stimulus.

CHAPTER 4

OVERVIEW OF THE INVESTIGATION OF POTASSIUM IONTOPHORESIS

4.0 GENERAL AIMS OF THE INVESTIGATION OF POTASSIUM IONTOPHORESIS

The general aims of the present study were to investigate the pain-inducing characteristics of iontophoretically applied K^+. Given the relative lack of prior psychophysical research with potassium iontophoresis it was necessary to first determine the psychophysical parameters associated with this pain stimulus. This follows the approach of Hardy et al. (1967) with thermal stimuli, and Tursky (1974) with electric shock, of developing a systematic program to identify and define all the factors that are relevant to a pain stimulus. The stimulus was evaluated in terms of the properties required of an ideal experimental pain stimulus.

As a result of Experiments One, Two and Three it was determined that potassium iontophoresis was uniquely suitable for an investigation of the spinal modulation of nociceptive peripheral input. The stimulus was used to investigate the gate control theory of pain by ramping off a previously constant peripheral nociceptive stimulus down to no stimulation, while monitoring perceived pain levels induced by the change in stimulus intensity.

4.1 OVERVIEW OF THE EXPERIMENTAL STUDIES

Experiment One[1]

The purpose of Experiment One was to determine the psychophysical function that best described the relationship between the iontophoretic pain stimulus and subject pain reports, as well as the optimal duration of the pain stimulus for reliable pain reporting. In addition, the effects of stimulus duration on the perceived intensity of the induced pain were investigated.

Experiment Two[1]

The purpose of Experiment Two was to determine the optimal inter-stimulus-interval (ISI) for reliable pain reporting. Stimulus history effects were investigated, in terms of both changes in subject responding across a session, and the influence of the immediately preceding stimulus on subject responding to the present stimulus.

Experiment Three[1]

The purpose of Experiment Three was to determine the extent to which the perceived pain was the specific result of the iontophoretically applied K^+. This was accomplished by comparison of the nociceptive effects of K^+ with the effects of a sodium ion (Na^+) control condition.

Experiment Four

The ability of potassium iontophoresis to stimulate both large and small diameter peripheral nerve fibres was used to investigate the underlying mechanism of the gate control theory of pain. The difference in conduction velocities of the large and small diameter peripheral afferents was utilised to produced differential levels of activity in the large and small diameter fibres at the spinal level during the ramping off of a potassium iontophoretic stimulus. A prediction of the gate control theory of pain was that while the applied nociceptive stimulus was being ramped off the perceived magnitude of pain would, in fact, briefly increase producing a pulse of pain.

Experiment Five

Part of Experiment Four was replicated with a sodium control condition to establish that the perceived increase in pain that occured during the ramping off of the potassium iontophoretic stimulus was a function of the applied K^+, and not simply the result of the electrical stimulation.

Footnote 1: Published as "Iontophoretically applied potassium ions as an experimental pain stimulus for investigating pain mechanisms" (Humphries, Long, & Johnson, 1994). (See Appendix A)

CHAPTER 5
GENERAL METHOD

5.0 GENERAL METHOD FOR EXPERIMENTS ONE, TWO AND THREE

The following general method section presents the apparatus and procedural descriptions that were common to Experiments One, Two and Three. Details specific and unique to each experiment are presented in the relevant individual sections for those experiments.

5.1 SUBJECTS

A separate group of six volunteer undergraduate and graduate students, with ages ranging from 20 to 38 years, was used in each experiment. Prior to participation all subjects completed a consent form that outlined the general nature of the experiment (e.g., see Appendix B). Subjects also completed a health check-list to determine if any contraindicating medical conditions were present (e.g., see Appendix C). Subjects were advised at the beginning of every session that they were free to terminate participation at any stage of the study. No subjects that completed a familiarisation session withdrew from any of the experiments.

5.2 APPARATUS

The iontophoretic pain generator consisted of a computer controlled[2] constant current power source designed to deliver a selected amount of current ranging from 0 to 25 mA. Intensity levels could be selected in 0.1 mA steps. The amount of K^+ delivered was directly proportional to the applied current. In accordance with Faraday's law one mA-s of current delivered 0.405 µg of K^+ - (Brady & Humiston, 1980).

Footnote 2: All computer software for the running of all experiments was written by the author in Turbo Pascal 6. Timing was by an 'Optimer' subroutine which, within the compiled Pascal program, was accurate to 4 ms.

The electrodes that were attached to the subject's arm were similar to those described by Benjamin and Helvey (1963) and Voudouris et al. (1985). The anode consisted of a silver plate suspended in a plastic bowl with no base. This bowl was placed against the volar surface of the subject's arm (see Figure 3).

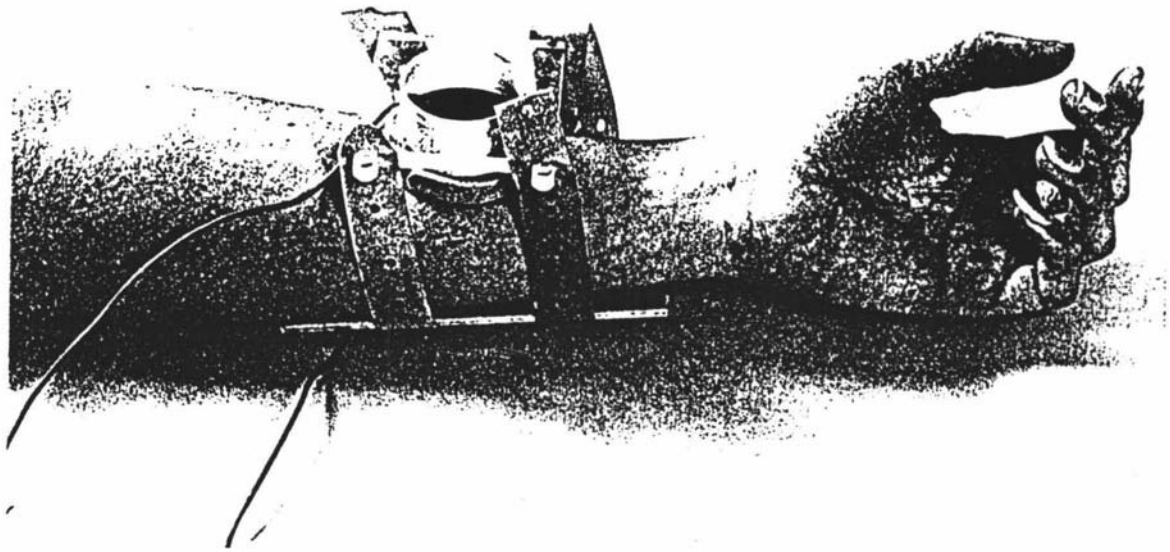


Figure 3. The placement of the anode bowl containing the potassium chloride gel on the volar surface of the subject's arm, with the opposing cathode silver plate on the dorsal surface of the arm.

The subject's skin acted as the base for the bowl. This arrangement allowed a potassium chloride gel [3% (w/v) potassium chloride; 1.0% (w/v) biological grade agar] in the bowl to be in direct contact with the subject's skin. The contact surface area of the gel was 12.5 cm^2. The use of the potassium chloride solution in gel form prevented the solution leaking from the electrode bowl, permitting the anode to be attached to the subject's arm without the need for excessive pressure to seal the base of the anodal bowl against the skin of the subject .

The cathode consisted of a silver plate (4 cm by 13 cm) covered with several layers of saline-saturated medical gauze [4% (w/v) sodium chloride] placed against the dorsal surface of the subject's arm. The medical gauze prevented direct skin contact with the cathodal silver plate, thereby avoiding any possibility of electrical skin burns.

Pain induced by DC current is normally more pronounced under the cathode as the greater neural depolarization is produced at this site (BeMent & Ranck, 1969; Berger, Gravenstein, Edwin, & Munson, 1982; Ranck 1981). Cathodal threshold currents have been found to be one half to three quarters the anodal values (Kenshalo, 1968). However, the large area of the cathode in the present study decreases the cathodal current density, thereby reducing the possibility of inducing pain through the direct effects of the cathodal current. Thus the cathode functions as the inactive, or indifferent, electrode. Thus, while standard DC electric shock stimulation produces pain predominantly at the cathode, potassium iontophoresis produces pain predominantly at the site where the K^+ is transported through the epidermis; that is, at the anode.

5.2.1 VAS measure

In all three experiments pain reports were recorded using a 15 cm VAS presented in the centre of a VGA monochrome computer screen. For all experiments the sensory scale anchors were "no pain sensation at all" and "very strong sensation of pain" (Figure 4).

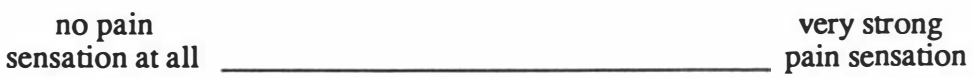


Figure 4. Visual analogue scale (VAS) - sensory intensity scale. Not reproduced to scale. The length of line presented on the computer screen was 15 cm.

The anchor descriptions were selected on the basis that they would most likely allow most of the VAS to be used (Scott & Huskisson, 1976; Sriwatanaku et al., 1983). A cursor mark on the VAS could be moved through a three-key control panel (Figure 5). The 'left' and 'right' cursor position keys that would slide the cursor in 1 mm steps in the appropriate direction, as long as the key was held down. The selection key allowed the final cursor position to be saved onto the computer. The cursor position was recorded as the distance in millimetres from the left anchor point.

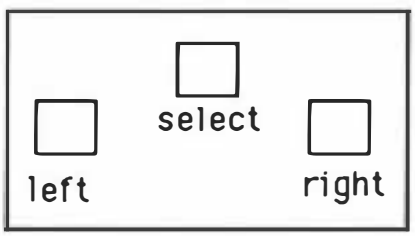


Figure 5. Three-key control panel for moving the cursor on the computer VDU presented VAS. Not reproduced to scale.

5.3 PROCEDURE

A standard protocol was adhered to on all sessions. As pain responding has been shown to vary as a function of the time of day the subjects were tested at the same time each day in order to avoid any possible diurnal confounds, which have been indicated by some studies (e.g., Procacci & Maresca, 1984). Prior to applying the electrodes the palmar and volar surfaces of the subject's arm were prepared by light scrubbing with warm soapy water followed by an acetone / 90% alcohol solution (1:10 v/v). This procedure lowered and stabilized the resistance of the skin so that the required amperages could be obtained from the constant current generator without excessively high or variable voltages that could confound the response to the potassium-stimulus (Champion & Hodge, 1983; Hill et al., 1952; Tursky & Watson, 1964)

Subjects were seated at a table in a small quiet room with the electrodes attached to the dominant arm. As small laterallity effects have been found for pain responding (Wolff, & Jarvik, 1964) for all experimental sessions the same arm was used on each subject to avoid possible confounds. It has been reported that the dominant arm, though slightly less sensitive than the non-dominant arm, may produce somewhat more reliable data (Wolff, 1977). The dominant arm rested on the table throughout the experiment. A cutoff switch was positioned by the free arm of the subject with which they could terminate any of the stimulus administrations immediately. The cutoff switch was not used during any of the experiments.

A familiarisation session the day before the first experimental session was provided in order to give the subjects an opportunity to learn the nature of the tasks and to become familiar with using the VAS. In addition, the familiarisation session helps to reduce and stabilize possible high levels of anxiety associated with an unknown pain stimulus, as anxiety may intensify the pain experience (Arntz, Dreessen, & De Jong, 1994; Cornwall & Donderi, 1988; Jospe, 1978; Sternbach, 1968)

Subjects were asked to rate on the VAS the intensity of the pain stimulus. Subjects were informed that the stimuli intensities would randomly vary, that it would not be possible to predict any pattern, and that they should rate each stimulus independently of the others (see Appendix D)

Subject responses during the familiarisation session were used to determine the range of stimulus levels the subjects would be exposed to over the experimental sessions. Stimulus ranges were individually selected for each subject so that most of the scale on the VAS would be used, though avoiding the extremes of the scale to minimize anchor effects (Hilgard et al., 1974). Stimulus intensities ranged from 0.12 to 10.0 μg of K^+ delivered per second (0.3 to 25 mA of applied DC current).

Immediately prior to each experimental session subjects were administered the range of stimuli which would be delivered during the experiment. Along with the preparatory cleaning of the subject's arm this helped to lower and stabilize electrode resistance (Tursky, 1974). It also served to refamiliarise the subjects with the experimental stimuli and the response procedures. Skin resistance was measured prior to the start of the main session with a Data Precision 936 Multimeter set to the 20 KΩ DC range. For most subjects resistance was 5 kΩ or less prior to the start of each session. High resistances would result in higher voltages being generated by the constant current source that, in turn, could lead to spuriously high pain perceptions. At the start of all sessions subjects were reminded of the details of the experimental task.

During the familiarisation phase there would occasionally be a localised breakdown of tissue resistance (Kenshalo, 1968) which would be felt as a concentration of pain in small areas under the cathode silver plate. As this pain could confound the pain reports from the anodal K^+ subjects that reported it were run on another day.

All pain stimuli were preceded by a warning beep on the computer one second prior to the start of the pain stimulus. The warning signal was to ensure that the subjects would be attending to the stimulus when it was delivered. Signalled or predictable pain stimuli may be perceived as somewhat less painful (Jones & Furedy, 1989; D.D. Price et al., 1980; Staub, Tursky, & Schwartz, 1971), though this effect would be constant across all experimental conditions. For Experiment One the duration of the stimuli varied from 1 to 4 seconds. For Experiments Two and Three the duration of the stimulus was set at one second. For all stimulus intensities the current was ramped up and ramped down over a 500 ms period.

Subjects responded, by moving a cursor on the computer presented VAS, to indicate the intensity of perceived pain immediately after the end of the stimulus presentation. The cursor could be slid back and forth on the VAS until the subject was satisfied with their selection. The subject would then push the selection key so that their decision would be recorded by

computer. There was no time limit imposed on making a response beyond that a response had to be made before the next trial started.

At the beginning and end of all sessions throughout the study the site of electrode placement was checked for possible skin reactions. At the completion of each experiment subjects were debriefed as to the purpose of the study, and any questions about the experiment were explained.

In Experiments One and Two, only four stimulus intensities were used for each subject, and these were presented in a random order. Teghtsoonian and Teghtsoonian (1983) have cautioned that successive judgments of the same stimulus may not be independent because of familiarisation with, and memorization of, the stimulus set. Consequently, the steps between stimuli of adjacent intensity were kept small enough to reduce the categorisation of stimuli and responses on the basis of remembered responses. That is, there was always some response overlap between adjacent intensity stimuli. The same sequence of trials was used in all experimental sessions, and the second half of a session repeated the sequence of trials in the first half.

5.3.1 Experimental design

All experiments were within-subjects repeated measures designs. This design was selected as, in contrast to between-subjects designs, it permitted the measurement of change occurring within individuals. This is particularly appropriate for pain studies where there are typically large individual differences on pain response measures, and consequently group results may not always accurately portray the actual processes occurring within individual subjects. The large individual differences found in pain studies also increases within-group variance so that often inconveniently large group sizes are required with between-subject designs if there is to be sufficient power to detect the effects of experimental manipulations.

5.4 STATISTICAL ANALYSIS

All data were analysed using the SPSS.PC+ V4.0.1 statistical package (Norusis, 1988). The within-subjects design data were analysed with a repeated measures analysis of variance using the SPSS.PC MANOVA commands. For maximum statistical power the univariate (mixed model) tests of significance were used whenever the test assumptions were met. With the small sample sizes Mauchly's test of sphericity and Box's M test of homogeneity provided a relatively conservative test for the use of the univariate tests. If the univariate test assumptions could not be met then multivariate analyses were performed. For multivariate analyses the Pillais multivariate criteria was used.

For data with skewed distributions medians were used as the measure of central tendency, rather than arithmetic means. No data were transformed prior to analysis.

CHAPTER 6

STIMULUS DURATION

6.0 INTRODUCTION: THE EFFECTS OF STIMULUS DURATION ON SUBJECT RESPONDING

In order to avoid excessive pain for subjects, and to minimize possible carry-over effects, a short duration pain stimulus is desirable. However, there is also the possibility that short duration stimuli do not give subjects sufficient time to make a reliable judgment. In an earlier study (Humphries & Johnson, 1990) some subjects reported that if the one-second stimulus duration delivered had been longer they might have been able to judge the pain sensation more consistently. However, a study by K.P. Price and Tursky (1975) found that for electric shock the correlation between pain reports for stimulations of 1 and 2.5 seconds was 0.98. This was taken to indicate that the subjects could judge the short duration stimuli as consistently as the longer duration stimuli.

Psychophysical pain studies most frequently report power functions to describe the relationship between pain stimulus levels and subject report (e.g., Babkoff, 1978; Cross, et al., 1975; Rollman & Harris, 1987). Indeed, the power exponent is seen to be a measure of sensory transduction (Stevens, 1957) for which there may be a "correct exponent value" (Cross et al., 1975, p. 9).

However, the apparent appropriateness of the power function may simply reflect the ability of such functions to fit nearly any monotonically increasing trend (Jones, 1980; Poulton, 1968). If goodness of fit is the criterion for implying that a function reflects some underlying psychophysical relationship then the onus is to demonstrate that no alternative functions with the same number of constants can provide a similar goodness of fit (McCallum & Goldberg, 1975; Poulton, 1968). Voudouris et al. (1985) reported a linear relationship for iontophoretic

pain. However, the extent to which the relationship could have been described by a logarithmic or power function was not provided.

An objective of Experiment One was to determine the stimulus duration that provided the most consistent subject responding over repeated trials for pain induced by potassium iontophoresis. Linear, logarithmic and power functions were calculated as linear functions(McCallum & Goldberg, 1975; Stam, Petrusic, & Spanos, 1981), logarithmic functions (McCallum & Goldberg, 1975) and power functions (Cross et al., 1975; Rollman & Harris, 1987; Tursky et al., 1982) have all been reported for pain perception (Kenshalo, Anton, & Dubner, 1989). While power functions have been most frequently reported for the perception of experimentally induced pain, Voudouris et al. (1985) had specifically reported a linear function for potassium iontophoresis, and the results of membrane depolarisation studies with extracellular K^+ indicate a possible logarithmic relationship (at least at the level of initial nociceptive neural transduction). Hence, it is desirable to investigate all three functions as each function is a potential candidate for most accurately describing the nociceptive action of iontophoretically applied K^+.

6.1 METHOD

Subjects

The general details are provided in Chapter 5.1. Six volunteer students, with ages ranging from 21 to 32 years, completed a consent form (Appendix B) and a health check-list (Appendix C) prior to participation in the experiment.

Apparatus

The general details are provided in Chapter 5.2. A single set of electrodes were positioned on the subject's arm as shown in Figure 3.

Procedure

In each of three daily sessions subjects were exposed to three blocks of 20 random intensity stimuli. For each subject only four intensity levels were used. Because of individual variation in pain responsivity the stimulus intensity levels were not the same for all subjects. That is, individual differences were explicitly acknowledged, with the stimulus range adjusted for each subject so that a roughly constant proportion of the VAS was covered for each subject. Stimulus intensities, over all subjects, ranged from 1.64 to 9.02 $\mu gK^+/s$ (4 to 22 mA). Within each block all stimuli were of either 1, 2, or 4 seconds duration. The blocks were presented in counterbalanced order across daily sessions for the group of subjects. Relatively long ISIs of 40 seconds, and four minute rest periods between trial blocks, were to minimise any potential carry-over effects between trials. This was intended to maximise the consistency of subject responding to each of the four intensity levels administered to each subject.

At the end of the final session all subjects were given a questionnaire to complete in order to ascertain their qualitative perception of the pain stimulus, the treatment integrity of the experiment and the subject's perception of the experiment in general (Appendix D).

6.2 RESULTS AND DISCUSSION

On the basis of the questionnaire responses it was determined that subjects were unable to detect the stimulus categories, and that they perceived no pattern to the random stimulus presentations. Despite being asked to rate each stimulus on its own, three of the subjects reported that as a strategy for deciding the level of pain they compared to the previous trial. All subjects rated the stimulus as being realistically painful. The lower intensities were often rated as producing a "pricking" or "stinging" sensation, while the higher intensities were more often associated with a "burning" sensation, often deep and widespread. These qualitative pain reports are consistent with those obtained in previous studies (Humphries & Johnson, 1990; Voudouris et al., 1985, 1989; Ong et al., 1980). For most subjects the pain reports to the

higher level stimuli were somewhat lower than during the familiarisation session when the stimulus levels were set for each subject.

Linear, logarithmic and power functions were calculated by averaging subject results over all sessions and all stimulus durations. Semi-log and double-log coordinates were used to determine the linearity of the logarithmic and power functions respectively. The coefficient of determination (r^2) was used as a measure of goodness of fit for all three functions.

There have been criticisms of the correlation coefficient based statistics being used as a measure of goodness of fit, as correlations tend to be high for any monotonically related data (Birnbaum, 1973, 1974; Coleman, Graf, & Alf, 1981; Parker, Casey, Ziriax, & Silberberg, 1988). This reduces the sensitivity of the measure for discriminating between the goodness of fit for different functions, especially if different studies are being compared where methodological differences may also be influencing the obtained correlations. Nevertheless, correlation coefficients are commonly used as a measure of goodness of fit (e.g., Rollman & Harris, 1987). In the present study the *relative* fit of competing functions are compared using data from the same experimental design. Thus the coefficients of determination provide a valid comparison within the context of the parameters associated with the current experimental design.

Table 1 shows the goodness of fit for the linear, logarithmic and power functions, with the exponent for the power function. Individual, as well as group results, are reported, as group data are often not representative of individual behaviour (McCallum & Goldberg, 1975; Algom, Raphaeli, & Cohen-Raz, 1986). This is especially true in psychophysical pain research, where large individual differences are often found (e.g., Cross et al., 1975; Rollman & Harris, 1987; Tursky & O'Connell, 1972)

Rather than treat individual differences solely as unexplained error, and pool the data to average that error away, the present study, in addition to examining group data, also examined the data

of individual subjects. For instance, if the power function (or any other function) is to be a general principle that describes pain perception at the psychological level then it should be consistently present in individual subjects.

Table 1. Coefficients of determination (r^2) for linear, logarithmic and power functions for the relationship between iontophoretic potassium stimulus and pain report on the pain-intensity VAS. Experiment One.

	Function			
Subject	**Linear**	**Logarithmic**	**Power**	**(Exponent)**
1	0.74	0.74	0.61	(2.98)
2	0.90	0.90	0.71	(3.26)
3	0.88	0.85	0.85	(3.46)
4	0.85	0.83	0.83	(2.76)
5	0.77	0.79	0.72	(4.69)
6	0.92	0.81	0.90	(2.67)
Average	0.84	0.82	0.77	(3.30)

Overall, the linear function provided the best description of the stimulus-response relationship, with the difference between the linear and power function approaching significance with a .05 alpha level criterion, t (5) = 2.54, $p < .06$. (These same trends were found in Experiments Two and Three, where there were significant differences between the linear and power function correlations). Though there can be large individual differences with pain perception the individual results were generally consistent with the group data.

On the basis of the coefficients of determination in Table 1, all three functions tested could be considered to provide an adequate description of the stimulus-response relationship. This

illustrates the danger of presenting a single function in support of a particular perceptual model (Anderson, 1970; Jones, 1980). The relationship between pain stimuli and pain reports would be expected to be monotonic, and this monotonicity alone is enough to produce high goodness-of-fit correlation values (Parker et al., 1988). At the very least, then, it is necessary to demonstrate that a particular function provides a better description of the data than alternative functions.

The limited stimulus and response range used in the present study restricts the ability to differentiate the goodness of fit of alternative functions (Teghtsoonian & Teghtsoonian, 1986). Nevertheless, responses for most subjects covered most of the VAS with an average response range of 122 mm on the 150 mm VAS, with a mean response, averaged over all subjects, of 56 mm and a standard deviation of 37 mm. Thus, even with this relatively large range in reported pain - a range with clinical validity, as most people suffering from pain predominantly experience pain in this region - all three functions were capable of providing a good description of the stimulus-pain relationship.

It is possible that the more frequently reported power function for pain perception (e.g., Rollman & Harris, 1987; Stevens, Carton, & Shickman, 1958) could have provided the more accurate description of the stimulus-pain relationship if a more extreme stimulus range had been used. In addition, the subjects in the present experiments were not verbally prompted in any way to make ratio judgements on the VAS, so the methodology did not encourage the resultant subject data to fit a power function (Laming, 1989; Poulton, 1979, 1984). The use of a VAS, where subjects are free to choose their own units, also tends to result in subjects scaling their sensation magnitudes on absolute rather than ratio scales leading to power functions (Zwislocki & Goodman, 1980).

The exponent values for the power functions ranged from 2.67 to 4.69, with a mean of 3.30 (Table 1). This is consistent with the variability found in previous studies using electrocutaneous stimulation. Individual exponents in those studies have ranged from 1.65 to

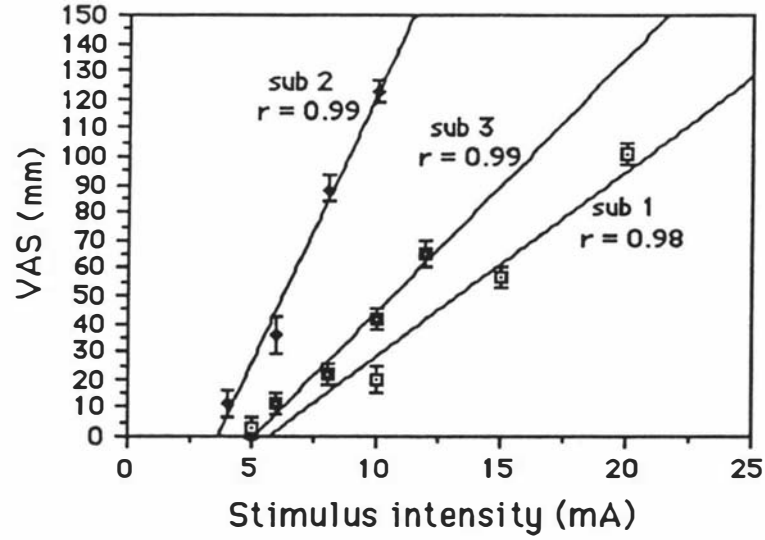
4.08 for a group of thirty subjects (Cross et al., 1975), from 0.5 to 3.1 for a group of 6 subjects (Tashiro & Higashiyama, 1981), and from 0.29 to 9.93 for a group of 40 subjects (Rollman & Harris, 1987).

Electrocutaneous stimulation power exponents, based on group data, have ranged from a low of 0.7 after correction for threshold (Beck & Rosner, 1968) through to a high of 4.5 (Stevens, 1965). Though the majority of pain studies normally report values below 3.0 (e.g., Algom et al., 1986; Jones & Gwynn, 1984). The higher exponents have been associated with stimuli near the detection threshold, and with relatively narrow stimulus ranges that are not greater than the detection threshold by more than a factor of two or three (Cross et al., 1975; Poulton, 1968, 1975; Teghtsoonian, 1973).

Our relatively high mean value of 3.30 may be a characteristic of potassium iontophoretic stimulation, or it may be partly attributable to the small range of stimulus intensities used. In addition, the present study did not use a threshold correction factor for the power function. Threshold correction factors, which describe the stimulus in terms of intensity above threshold level, can lower the exponent value (Beck & Rosner, 1968; Rollman, 1974), especially if the pain threshold is used, as opposed to the sensation threshold. Ekman, Frankenhaeuser, Levander, and Mellis (1964, 1966) obtained a small reduction in power exponent from 1.81 to 1.54 using a sensation threshold correction. Correcting for pain threshold Bromm and Treede (1980) reduced their power exponent value for electric shock from 1.44 to 1.0. Rollman (1974) obtained an even greater reduction in power exponent when using a pain threshold correction, though they concluded that the uncorrected power law provided the better description of the subjective effects of the stimulus.

Nevertheless, our results do support the description by Voudouris et al. (1985) that the relationship between potassium iontophoretic stimulation and pain report is linear. Figure 6 shows the linear regression line of best fit for all six subjects in Experiment One.

A



B

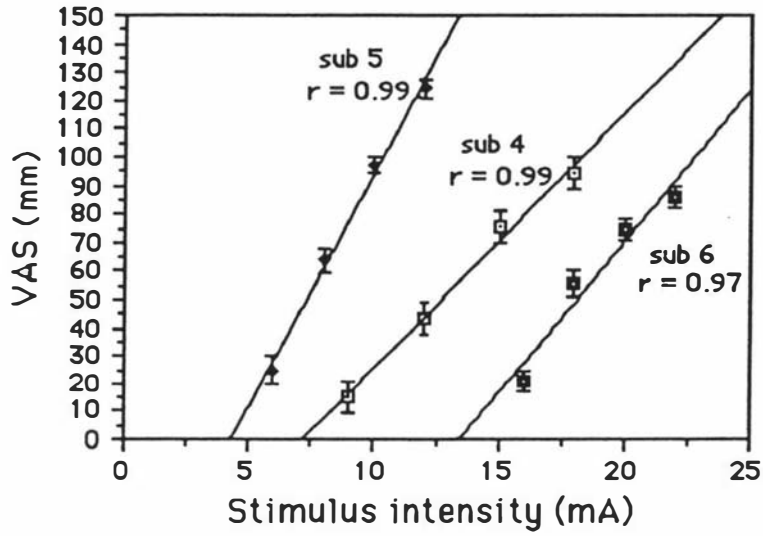


Figure 6. VAS pain responses as a function of stimulus intensity. Each data point is the arithmetic mean of 15 responses. For all subjects the linear regression equation is an accurate representation of the stimulus-response relationship, with correlations ranging from 0.97 to 0.99. The error bars are the standard error of the mean. The figure is divided into Parts A and B for clarity of presentation. Experiment One.

In terms of the regression equation parameters there is a great deal of individual variability, consistent with previous pain studies (e.g., Rollman & Harris, 1987). For instance, at 10 mA

(4.1 μgK+/s) subject 2 reports 122 mm on the VAS, whereas at the higher stimulus level of 16 mA (6.6 μgK+/s) subject 6 rates this only at 20 mm. The widely varying regression slopes for individual subjects is consistent with the finding of markedly different dynamic ranges (the ratio of the strongest to the weakest stimulus that can be reported) found in other studies (e.g., Rollman & Harris, 1987).

For all subjects the linear regression function is an accurate description of the stimulus-response relationship. The correlations in Figure 6 are based on the mean responses for each of the four stimulus levels each subject received. Mean responses were used rather than a median measure as only an overall slight positive skew of 0.25 was found for the distribution of responding for each subject on each of the four stimulus levels. The overall skewness was obtained by taking the average amount of skew across subjects and stimulus levels The obtained level of skew was not significantly different from zero, t (23) = 1.07, $p > .05$.

Because the linear function provided the best fit (see Table 1), the linear function correlations were used as a measure of subject reliability in responding across the stimulus durations of 1, 2 and 4 seconds. Averaging the results for all subjects over each session, the linear correlations were not statistically different ($p > .05$), and were consistently high for all stimulus durations (r = 0.91, 0.92 and 0.91 for the 1-, 2- and 4-second stimulus durations, respectively).

However, these correlations provide a measure of fit to the regression line, not the individual stimulus levels, even with high correlations in the 0.90s. In order to overcome this limitation, coefficients of variation (CV) were calculated to provide a direct measure of response variability for each stimulus intensity. Initially all responses were converted to a ratio score by dividing response by stimulus so that the standardized subject data could be combined. The ratio score permits comparison or pooling of subject responses though each subject may have had different absolute levels of the applied stimulus due to individual differences in pain responding (Hilgard et al., 1974). A CV was then calculated for each subject for each stimulus

level for each session. An overall CV for each condition was calculated by averaging all subject CVs.

The CV is known to be inversely proportional to stimulus intensity (Gescheider, 1988). This inverse relationship was found in Experiment One, with the coefficient of variation decreasing from 78% for the lowest stimulus intensity to 13% for the highest stimulus intensity; a significant decrease, $F(3,15) = 22.17$, $p < .01$. The change in CV as a function of stimulus intensity had a significant linear trend, $t = 5.38$, $p < .01$. While the CV changed significantly as a function of stimulus intensity the duration of the stimulus had no significant effect. The CVs for the 1-, 2- and 4-second stimulus durations were 30.9, 26.7 and 33.3% respectively. There was no significant interaction between stimulus intensity and stimulus duration. On the basis of the linear correlation coefficients and the CVs it would appear that increasing stimulus duration from 1 through to 4 seconds produces no systematic increase in consistency of subject responding to repeated trials of the pain stimuli.

Cross et al. (1975) reported that an increase in stimulus intensity was required for the one-second duration stimuli compared to the 2.5-second duration stimuli for detection of pain threshold and pain tolerance. The increase in stimulus intensity being 29.0% for threshold detection and 14.8% for pain tolerance. In the present study ratio scores were calculated to determine if an increase in stimulus duration increased the perceived stimulus intensity. Ratio scores were calculated by dividing the subject response by the stimulus intensity.

Table 2 shows the mean ratio scores and mean VAS responses for Experiment One as a function of stimulus duration. The range of the means, for each stimulus duration condition, is also given. This is the range from the mean response to the lowest intensity stimulus to the mean response for the highest intensity stimulus. This provides a measure of the impact of stimulus duration on the effective range of responding.

Table 2. Mean ratio scores, mean VAS responses and Range of VAS means as a function of stimulus duration. Experiment One.

Stimulus Duration (s)	Mean Ratio Score	Mean VAS Response(mm)	Range of the Means (mm)
1	4.56	51	78
2	4.75	55	88
4	5.32	61	85

There was a trend for perceived intensity of the pain stimulus to increase with an increase in stimulus duration. For the VAS responses this was an overall increase of 10 mm or 19.6%. This increase is consistent with the results of Cross et al. (1975), however, in the present study, none of these trends, either for the main effects of duration, $F(2,4) = 1.27$, $p > .05$, or for a stimulus-intensity vs duration interaction, $F(6,30) = 1.55$, $p > .05$, were significant. Given the consistent increase in mean ratio score and VAS responding across the stimulus durations obtained in the present study, and the consistency of these results with Cross et al. (1975), the lack of significance here is possibly due to the low subject numbers.

On the basis of the linear correlation coefficients and the CVs it would appear that increasing stimulus duration from 1 through to 4 seconds produces no systematic increase in consistency of subject responding to repeated trials of the pain stimuli. The relatively consistent range of the means across the different stimulus durations (Table 2) argues against potentially higher correlations being found for longer duration stimuli simply as a function of increased stimulus and response ranges.

Therefore, despite the self reports by earlier subjects that a longer duration stimulus may assist in producing more consistent pain reports, there is no evidence that increasing stimulus duration improves the reliability of subject reports over repeated trials. This is consistent with

the results obtained by K.P. Price and Tursky (1975) who found a constant high reliability in responding despite manipulations of stimulus duration from 1 to 2.5 seconds.

One can only speculate as to why the subjective impression reported by subjects that longer stimulus durations would allow greater response consistency was not supported by the present study. One possible explanation is that longer duration stimuli can be more reliably reported, but only if presented as isolated trials. With repeated trials the extra report-reliability may be countered by larger carry-over effects associated with longer duration stimuli that add 'unexplained' variance to responding to the current stimulus. Consistent with this hypothesis the largest CV in the present study was for the 4-second duration stimuli, though the difference in CVs was not significant.

Given the desirability of short duration stimuli (i.e., one second), and the fact that there is no advantage in longer duration stimuli in terms of a demonstrable increase in reliability in subject responding, one-second duration stimuli were used in Experiments Two and Three.

Experiment One used a constant ISI of 40 seconds in order to reduce possible carry-over effects across trials. The objective of Experiment Two was to vary the ISI in order to measure the effects of different ISIs on the reliability of subject responding and to investigate stimulus history effects in terms of both changes in subject responding across a session, and the influence of the immediately preceding stimulus on subject responding to the present stimulus.

CHAPTER 7

INTERSTIMULUS INTERVAL

7.0 INTRODUCTION: THE EFFECTS OF INTERSTIMULUS INTERVAL ON SUBJECT RESPONDING TO POTASSIUM IONTOPHORESIS

The ability to present the pain stimulus repeatedly, and over a short period of time is important, both in terms of convenience and the statistical power gained from repeated trials. For example, the ability to rapidly repeat trials becomes particularly critical in signal detection studies, where large numbers of trials are an essential requirement for an adequate analysis (e.g., Clark & Goodman, 1974; Lloyd & Appel, 1976), or where time is critical, such as monitoring the on-going effects of an analgesic. While it is desirable that ISIs should be as short as possible the confounding influence of carry-over effects, which may increase with shorter ISIs, also needs to be considered.

Pain responsivity is influenced by stimulus history in a complex manner that involves both peripheral and central processes (D.D. Price & McHaffie, 1988; Wall, 1988). Depending on the type of stimulus, stimulus intensity, stimulus duration, rate of stimulus delivery, and the site of stimulation, the result of repetitive nociceptive stimulation can be either an increased sensitivity to nociceptive stimuli - hyperalgesia (e.g., Hardy et al., 1967; LaMotte, Thalhammer, Torebjörk, & Robinson, 1982; LaMotte, Thalhammer, & Robinson, 1983) or a reduced sensitivity to nociceptive stimuli - hypoalgesia (e.g., LaMotte & Campbell, 1978; D.D. Price, Hu, Dubner, & Gracely, 1977; Torebjörk, LaMotte & Robinson, 1984).

Most experimental studies investigating the neural mechanisms of hyper and hypoalgesia have used thermal stimuli. Studies employing relatively intense noxious thermal stimuli that lead to some degree of tissue damage have tended to report hyperalgesia (e.g., Hardy et al., 1950). For instance, Meyer & Campbell (1981) found that damaging burns at 53°C for 30 seconds

produced sensitization in monkey A-delta mechanical receptors and hyperalgesia in humans. Though this was accompanied by a reduction in monkey C polymodal nociceptive afferent activity.

With less intense nociceptive stimuli hyperalgesia is often associated with C polymodal nociceptive activity. For example, after a relatively mild injury of a thermal stimulation of 50°C for 100 seconds sensitization of monkey C polymodal nociceptive afferents correlated cross-species with human hyperalgesia (LaMotte et al., 1982, LaMotte et al., 1983). Heat stimulation just a few degrees above threshold produced sensitization of monkey C polymodal nociceptors (Beital & Dubner, 1976a). At higher stimulus levels of 55°C the C polymodal receptors were inactivated. Torebjörk et al. (1984) found that human hyperalgesia correlated cross-species with monkey C mechanothermal nociceptor sensitization following a conditioning stimulus of 50°C thermode heat with a duration of 100 seconds, which was described as mild heat injury. In summary, thermal pain reports are both A-delta and C polymodal mediated. Thermal hyperalgesia appears to be associated with enhanced C-fibre nociceptor activity with mild injury, and enhanced A-delta activity with more severe injury (Price, 1988).

Pain adaptation often occurs with lower intensity nociceptive stimuli. Lahoda et al. (1977) found habituation to repeated electric shock stimulus trials, with higher pain thresholds and tolerances during the second block of an experimental session. LaMotte and Campbell (1978), using 3-second CO2 laser thermal stimulation with average ISIs of 25 seconds, also found pain adaptation in humans. Most of this adaptation occured within the first few trials, and it correlated cross-species with a reduction in monkey C-fibre afferent activity. Primate studies have found that adaptation can also occur in myelinated A-delta mechanothermal nociceptors with repeated thermal and mechanical stimulation (e.g., Georgopoulos, 1976; Perl, 1968).

With 3-second ISI heat pulses D.D. Price et al. (1977) found that perceived intensity of first pain progressively reduced. At the same time, however, the perceived intensity of second pain

increased. The reduction in first pain intensity correlated cross-species with a reduction in monkey A-delta heat nociceptive afferent activity, while the increase in second pain correlated with an increase in spinothalamic tract neuron activity (D.D. Price, Hayes, Ruda, & Dubner, 1978). At longer ISIs than 3 seconds (from 4 to 80 seconds) the central summation of second pain was not found.

Using electric shock as the pain stimulus Higashiyama and Tashiro (1987, 1989) not only observed a session effect for change in perceived pain, they also reported a stimulus intensity interaction. For low intensity pain stimuli the subject magnitude estimates remained constant, independent of session block. For below pain threshold stimuli which produced tactile sensations the subject magnitude estimates decreased across the session.

In addition to the effects that can occur across a session prior studies have also shown that neural activity and pain reports may be influenced by the intensity of the immediately preceding stimulus and the rate of stimulus presentation. LaMotte and Campbell (1978) reported that, for thermal stimuli, faster rates of stimulus presentation (ISI 25 s) resulted in lower pain ratings than lower rates of presentation (ISI 225 s). In addition, pain ratings were of greater magnitude when the preceding stimulus was of low intensity compared to when it was of higher intensity. Other studies have found similar inverse relationships between perceived intensity of thermal pain sensation and the rate of presentation and intensity of the preceding stimulus (e.g., Beital & Dubner, 1976b; Campbell & Meyer, 1983; Chudler, Anton, Dubner, & Kenshalo, 1990). In all these studies human pain reports correlated cross-species with monkey C polymodal nociceptor activity

Experiment Two investigated both enduring session effects and the effects of immediately preceding pain stimuli on pain perception as a function of ISI. For the session effect, on the basis of prior research, albeit using a different experimental pain stimuli, it was predicted that some adaptation to the nociceptive stimulus might occur (hypoalgesia) with repeated trials across a session. As potassium iontophoresis produces little tissue damage (see Chapter 9.1)

and the stimulus intensities in Experiment Two were of low-to-moderate intensity, hypoalgesia would be consistent with the studies of Lahoda et al. (1977) and LaMotte & Campbell (1978), who also used relatively non-damaging nociceptive stimuli.

However, hyperalgesia due to C-fibre nociceptor sensitization, has also been reported for relatively low intensity nociceptive stimulation. Given that potassium iontophoresis preferentially stimulates unmyelinated C-fibres, and that the prior studies using thermal stimulation may have stimulated relatively more A-delta heat nociceptors that sensitize to higher intensity stimuli, then C-fibre sensitization, with a resultant hyperalgesia, may occur with potassium iontophoresis.

For the effects of the immediately preceding stimulus it was predicted that there would be an inverse relationship between magnitude of pain sensation and the rate of stimulus presentation. That is, lower rates of stimulus presentation would produce higher levels of pain sensation. In addition, there would be an inverse relationship between magnitude of pain sensation and intensity of the preceding stimulus. That is, there would be higher pain ratings when the preceding stimulus was of low intensity compared to when it was of higher intensity.

7.1 METHOD

Subjects

The general details are provided in Chapter 5.1. A separate group of 6 volunteer students not used in Experiment One, with ages ranging from 20 to 36 years, completed a consent form and a health check-list prior to participation in the experiment.

Apparatus

The general details are provided in Chapter 5.2. A single set of electrodes were positioned on the subject's arm as shown in Figure 3.

Procedure

In each of three daily sessions six subjects were exposed to 60 one-second duration stimuli. As in Experiment One for each subject only four stimulus intensity levels were used. Stimulus intensities ranged from 2.87 to 6.56 μgK+/s (7-16 mA) for five of the subjects, and 6.56 to 9.02 μgK+/s (16-22 mA) for subject six. Within a daily session all ISIs were either 10, 20, or 40 seconds. The order of the ISI sessions was counterbalanced across the subject group, with each subject receiving each of the ISI sessions once.

7.2 RESULTS AND DISCUSSION

All subjects reported that they were unable to detect any stimulus categories, and that they could perceive no pattern to the stimulus presentations. Coefficients of determination for the linear, logarithmic and power functions for individuals were consistent with the overall group results (Table 3).

Table 3. Coefficient of determination (r^2) for linear, logarithmic and power functions for the relationship between iontophoretic potassium stimulus and pain report on the pain-intensity VAS. Experiment Two.

	Function			
Subject	**Linear**	**Logarithmic**	**Power**	**(Exponent)**
1	0.90	0.90	0.85	(2.46)
2	0.85	0.85	0.72	(2.68)
3	0.86	0.83	0.77	(3.07)
4	0.92	0.90	0.85	(2.20)
5	0.77	0.76	0.71	(2.27)
6	0.74	0.71	0.77	(5.71)
Average	0.84	0.83	0.79	(3.06)

The linear function provided a significantly better description of the stimulus-response relationship than the power function, t (5) = 2.72, $p < .05$. The power function exponent was again somewhat higher than that reported in most other studies. These results replicate, with six previously untested subjects, the findings of Experiment One.

Linear function goodness of fit correlations were determined across the three treatment conditions, as in Experiment One. For the ISIs of 10, 20 and 40 seconds the respective correlations were 0.92, 0.92 and 0.93. These correlations were not significantly different ($p > .05$). The CVs were 35.8, 30.9 and 31.1% for the 10-, 20-, and 40-second ISIs respectively, there was no consistent trend, and they were not significantly different , F (2,4) = 1, $p > .05$.

In order to investigate pain response changes over a session all responses were converted to ratio scores by dividing response by stimulus level. Sessions were dichotomized into first-half and second-half session blocks, each block consisting of 30 trials. The applied pain stimuli were dichotomized as being of either low or moderate intensity. The low intensity stimulus consisting of the two lower stimulus levels, and the moderate intensity stimulus consisting of the two higher stimulus levels that were presented to each subject. The stimulus levels were dichotomized in order to increase the sample size of the group means. The ratio scores and VAS scores obtained are presented in Table 4.

Table 4. Ratio scores and VAS scores (in brackets) as a function of ISI, session block and stimulus level. Experiment Two.

	ISI (s)					
	10		20		40	
	Session Block					
Stimulus Level	1st half	2nd half	1st half	2nd half	1st half	2nd half
Low	3.4 (32)	3.5 (32)	4.0 (36)	3.9 (35)	3.7 (34)	2.9 (27)
Moderate	7.0 (104)	7.4 (110)	6.8 (100)	6.8 (101)	6.7 (100)	7.0 (104)

A three-way (2*2*3) repeated measures analysis of variance determined the effects of stimulus level, session block and ISI. The only significant main effect was for stimulus level, in which the moderate intensity stimuli had a higher response ratio (7.0) than the low intensity stimuli (3.6), $\underline{F}(1,5) = 94.37$, $\underline{p} < .01$, but this was not of direct interest. The lack of a main effect for ISI contrasts with the results of prior studies: for example, LaMotte and Campbell (1978) and Chudler et al. (1990) - although they had used different, and greater, ISI ranges; 25 to 225 seconds and 30 to 180 seconds respectively. However, our failure to find a significant effect may be due to the lack of experimental power with only six subjects. For our experimental results the drop in ratio score for the low intensity stimulus condition occurred almost entirely under the 40-second ISI condition. While this may simply be a chance effect these potential interactions need to be investigated further with larger subject numbers. Our sample results were not consistent with the inverse relationship found in prior studies; where greater magnitude pain reports were associated with lower stimulus presentation rates.

There was a significant interaction between session block and stimulus level, $\underline{F}\ (1,5) = 8.92$, $\underline{p} < .05$. In terms of the ratio scores, for the low intensity stimuli there was an 8.2% decrease in responding to the pain stimulus from the first-half to the second-half session block (ratio scores dropped from 3.7 to 3.4), while for the moderate intensity stimuli there was a 3.2% increase (ratio scores increased from 6.8 to 7.1). While significant, these changes were small in terms of changes in VAS responding: there was a decrease from an average of 34 to 31mm for the low intensity stimuli, and an increase from 101 to 105 mm for the moderate intensity stimuli.

These results are similar to the findings of Higashiyama and Tashiro (1987, 1989) in that differential session effects have been found for different stimulus intensities. However, their studies found a decrease in magnitude estimates across sessions for low intensity (prepain) stimuli while magnitude estimates remained constant for higher intensity (painful) stimuli - their higher intensity stimuli being 2.8 to 3.8 times the pain threshold current. In contrast, in the present study, all stimuli were perceived as painful - that is, all stimulus intensity levels were rated higher than zero on the VAS scale. Our results show that it is possible to adapt to a low

level of a pain stimulus while, at the same time, showing an enhanced response to a higher level of the same pain stimulus.

In addition to changes in responding that occurred over a session the effects of immediately preceding stimuli on responding were also investigated. Ratio scores were used to evaluate the influence of the immediately preceding stimulus on responding to the present stimulus. Immediately preceding stimuli and present stimuli were both dichotomized as being of either low or moderate pain intensity. The ratio scores and VAS scores obtained are presented in Table 5.

Table 5. Ratio scores and VAS scores (in brackets) as a function of the present and immediately preceding stimulus pain levels. Experiment Two.

	ISI (s)					
	10		20		40	
	Preceding Stimulus Level					
Stimulus Level	Low	Moderate	Low	Moderate	Low	Moderate
Low	2.6 (22)	4.0 (39)	3.6 (29)	4.2 (39)	2.9 (25)	3.5 (34)
Moderate	7.2 (108)	7.2 (108)	7.0 (104)	6.5 (97)	7.1 (106)	6.5 (97)

A three-way (2*2*3) repeated measures analysis of variance of the ratio scores determined the effects of preceding-stimulus intensity, present-stimulus intensity and ISI on responding. There were significant interactions between the preceding and present stimuli, F (1,5) = 29.11, $p < .01$, and between the ISI and preceding stimuli, F (2,10) = 7.55, $p < .01$. For low-intensity nociceptive stimuli: there was a significantly higher pain response to a low intensity stimulus when it was preceded by a moderate intensity stimulus compared to when it was preceded by a low intensity stimulus. This effect was significant for all ISIs [ISI 10 seconds, t (5) = 3.62, $p < .05$; ISI 20 seconds, t (5) = 3.30, $p < .05$; ISI 40 seconds, t (5) = 3.13, $p <$

.05], and the magnitude of the difference was greatest for the 10-second interval. Figure 7 shows the change in ratio scores. This result was in contrast to the inverse relationship reported in prior studies.

Responses to moderate intensity stimuli changed significantly only for the 40-second ISI, t (5) = 3.40, $p < .05$; with a lower pain response following a moderate intensity stimulus compared to following a low intensity stimulus. This result was consistent with the previously reported inverse relationship where "The higher the value of the preceding stimulus, the less the magnitude of the response.." (LaMotte & Campbell, 1978, p.522).

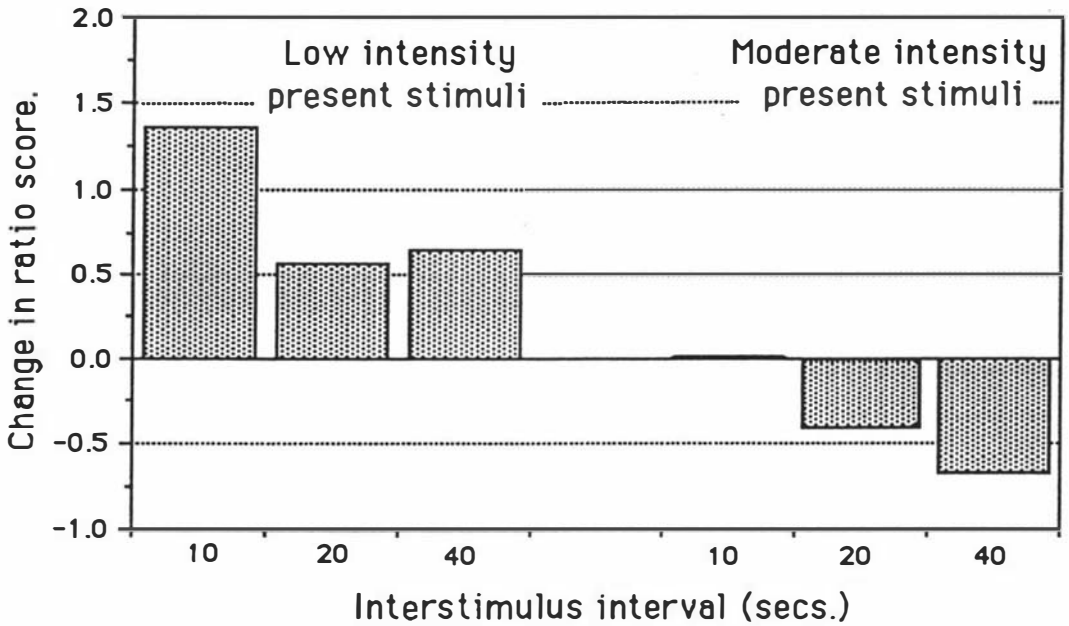


Figure 7. The change in ratio scores as a function of ISI, intensity level of the present stimulus, and intensity level of the immediately preceding stimulus in Experiment Two. Change in ratio score = ratio scores of (present stimuli preceded by moderate intensity stimuli) - (present stimuli preceded by low intensity stimuli). Positive scores indicate that responding to the present stimulus is higher if the previous stimulus was of a moderate rather than low intensity.

The effect of immediately preceding stimuli can account for a large proportion of the variance in subject responding. For example, with an ISI of 10 seconds for low intensity stimuli preceded by low intensity stimuli the standard deviation of the ratio scores was 1.58, while the systematic change in ratio score due to the change in intensity of the preceding stimulus from the low to moderate condition was 1.35 (Figure 7).

The relatively large change in ratio score for low intensity present-stimuli with a 10-second ISI (Figure 7) is consistent with our largest CV of 35.8% for this ISI. In designing a study a balance needs to be made between short ISIs allowing greater trial numbers and the possibility of increased 'unexplained' response variability due to carry-over effects at these shorter time intervals. Consideration also needs to be given to response changes across a session (Table 4). On the basis of our results one possible strategy with potassium iontophoresis would be to use low ISIs (10 to 20 seconds) with only stimuli in the moderate intensity range, thus avoiding the relatively larger carry-over effects and session effects found for low intensity stimuli. Of course other factors need to be considered in addition to these psychophysical requirements of minimizing unexplained variability in subject responding. Nevertheless, such a strategy could be particularly advantageous when attempting to track changes in pain, as in following the time course of an analgesic, where a large number of unbiased responses are required repeatedly within short 'time windows'.

The pooling of K^+ at the site of neural excitation from the preceding stimulus does not explain the observed carry-over effects for two reasons. First, when the pain stimulus is ramped off, the pain perception dies away immediately regardless of stimulus intensity. This indicates that the small amount of potassium applied (typically 3 μg per trial) is cleared rapidly from the site of neural activation. Given this apparent rapid clearance it is unlikely that residual amounts of potassium 10, 20 or 40 seconds later could have much influence.

Second, a pooling of potassium would be expected to increase pain reports for moderate intensity stimuli preceded by moderate intensity stimuli, compared to when preceded by low

intensity stimuli. In fact, there is no significant difference at the 10- and 20-second intervals, and at the 40-second interval there is even a significant decrease in responding. The lack of increase in pain reports for the moderate intensity stimuli could not be attributed to a ceiling effect as most of the VAS ratings for these stimuli were some distance from the upper scale anchor.

The changes induced by the preceding stimuli were able to be detected with ISIs as short as 10 seconds. This indicates that the onset and offset of the influence of the preceding stimuli were relatively rapid. These 'micro changes' need to be distinguished from the longer lasting session effects. For instance, the reported time course for most hyperalgesic and hypoalgesic states is normally in the order of minutes and even hours (Hardy et al., 1950; LaMotte, Shain, Simone, & Tsai, 1991). An area of investigation would be to determine whether the changes detected in the present study represent relatively transient nociceptive neural changes of sensitization and adaptation occurring at the peripheral level, or whether they are more central in nature.

Alternative explanations, independent of pain processing mechanisms, also need to be considered for these effects. There are a number of general response biases that could have influenced responding on the magnitude estimation task. For instance, despite the subjects being instructed to rate each stimulus independently of the others this will not eliminate sequential effects (Ward, 1987) in which the stimuli and responses to prior trials can influence responding to the present stimulus presentation (Staddon, King, & Lockhead, 1980; Ward, 1979).

Previous pain research indicates that these sequential effects can be complex. For example, time-order errors (TOEs) in pain perception are a function of both stimulus duration and ISI. Geertsma (1958) reported a positive TOE for 2.5-second ISIs with electric shock pain, where there was a tendency to rate the first of a pair of identical pain stimuli as the more painful of the two. In the same study a negative TOE was found for 14.5-second ISIs. This result was

consistent with other studies employing different stimuli where, normally, positive TOEs occur at short ISIs and increasingly negative TOEs with longer ISIs (Jamieson & Petrusic, 1975). Jones et al. (1982), also using electric shock and with an ISI of 250 ms, found a positive TOE for pre-pain stimuli, no TOE for faintly painful stimuli, and a negative TOE for moderately painful stimuli.

In the present study the direction of the changes for the low intensity stimuli (Figure 7) are consistent with a centering bias, with responses biased in the direction of the immediately preceding stimulus (Cross, 1973). That is, a tendency to give a higher rating to the present stimulus when the preceding stimulus was of greater magnitude. However, the moderate intensity stimuli results are not consistent with such an interpretation. In addition, the relatively large effects obtained in the present experiment, up to 50% changes in the ratio score for the 10-second low-intensity stimuli, make it unlikely that these changes could be explained purely in terms of some general response bias. For instance, Geertsma's (1958) study reported only a 1%-3% change in reported pain due to TOEs. The threshold nature of the changes in perceived pain due to TOEs was indicated in the study of Stevens (1957) who reported that the 'error' introduced by time order effects is small, often being less than the JND.

Experiments One and Two have described many of the important nociceptive characteristics associated with potassium iontophoresis. However, it is important to determine how much of the pain produced by potassium iontophoresis is directly attributable to the potassium ions as direct current electrical stimulation itself can be a pain stimulus. Consequently, Experiment Three compares the effects of iontophoretically applied K^+ with a Na^+ control in order to clarify the specific nociceptive properties of K^+.

CHAPTER 8

SODIUM CONTROL

8.0 INTRODUCTION: POTASSIUM IONTOPHORESIS COMPARED WITH A SODIUM CONTROL

A large number of studies have used electrical stimulation, including direct current stimulation, as an experimental pain stimulus (e.g., Cross et al., 1975; Rollman, & Harris, 1987; Vierck, Cooper, Franzén, Ritz, & Greenspan, 1983). With potassium iontophoresis direct current is used to deliver the K^+ through the epidermal barrier. This raises the possibility that at least some of the pain produced by potassium iontophoresis is the result of the electric current itself independent of the nociceptive action of K^+.

Vierck et al.(1983) have reported that for experienced subjects the pain detection threshold for direct current averages 12 mA, at a current density of 0.6 mA/mm^2. The current densities used in all experiments in the present study were always less than the reported pain threshold value reported by Vierck et al. (1983), with our highest current density stimulus value being 0.018 mA/mm^2 (at 22 mA).

However, it is difficult to compare studies that use different electrodes as electrode configuration is an important factor in determining pain intensity (Tursky, 1974). In addition, the total applied current in the present study was sometimes greater than that reported by Vierk et al. (1983) for pain threshold. It is possible, therefore, that the pain produced by potassium iontophoresis could, particularly at higher stimulus intensities, be a combination of K^+ and direct current stimulation of the pain nerve fibres.

To determine the extent to which the pain produced by potassium iontophoresis is a direct result of the applied K^+ a Na^+ control was run in Experiment Three. The sodium ion was

selected as the control electrolyte as most pain studies using electrical stimulation do not use dry electrodes in order to prevent skin irritation and burning, and saline (sodium chloride based) solutions or gels are most commonly used as the conducting electrolyte.

In addition, in Experiment Three the psychophysical functions that were investigated in Experiments One and Two were determined with 9 additional subjects, and with the stimuli presented at random intensities over a nominated range, rather than constrained to four prescribed intensity levels.

8.1 METHOD

Subjects

The general details are provided in Chapter 5.1. A separate group of 9 previously untested volunteer students not used in Experiments One or Two, with ages ranging from 20 to 36 years, completed a consent form and a health check-list prior to participation in the experiment.

Apparatus

The only change from the general apparatus described in Chapter 5.2 was that the 3% (w/v) potassium chloride anode gel was replaced with a 3% (w/v) sodium chloride anode gel for the sodium condition. A single set of electrodes were positioned on the subject's arm as in Experiment One, and as shown in Figure 3.

Procedure

In each of two daily sessions subjects were exposed to 60 one-second duration stimuli, with an ISI of 15 seconds. Because of individual variation in pain responsivity the range of stimulus intensity levels was not the same for all subjects. Stimulus intensities ranged from 7 to 22 mA (2.87- 9.02 $\mu gK^+/s$). In the first session the stimuli were presented at random intensities over a nominated range, but were always in whole mA units. Not constraining the stimuli to four preselected intensity levels as in the first experiment allows a more accurate determination of the psychophysical function that best describes the stimulus-response relationship. The second

the psychophysical function that best describes the stimulus-response relationship. The second session repeated the trial sequence of the first session. The order of presentation of the K^+ or Na^+ ions was counterbalanced across the two daily sessions.

8.2 RESULTS AND DISCUSSION

Coefficients of determination for the linear, logarithmic and power functions (Table 6) were consistent with the results in Experiments One and Two. For the K^+ condition the linear function provided a significantly better description of the stimulus-response relationship than the power function, $t(8) = 3.02$, $p < .05$.

Table 6. Coefficients of determination (r^2) for linear, logarithmic and power functions for the relationship between iontophoretic potassium stimulus and pain report on the pain-intensity VAS for both the potassium and sodium groups. Experiment Three.

	Function					
	Linear		Logarithmic		Power (exponent)	
Subject	Na^+	K^+	Na^+	K^+	Na^+	K^+
1	0.85	0.96	0.83	0.96	0.84 (3.52)	0.94 (2.28)
2	0.83	0.89	0.76	0.87	0.86 (3.33)	0.87 (3.15)
3	0.89	0.92	0.84	0.93	0.88 (2.99)	0.88 (1.32)
4	0.79	0.89	0.74	0.87	0.82 (2.47)	0.85 (1.43)
5	0.95	0.92	0.94	0.94	0.93 (3.35)	0.80 (2.72)
6	0.86	0.88	0.83	0.89	0.90 (2.98)	0.84 (2.03)
7	0.91	0.89	0.91	0.87	0.84 (3.33)	0.87 (2.63)
8	0.86	0.85	0.80	0.79	0.79 (2.09)	0.72 (1.91)
9	0.81	0.84	0.77	0.87	0.80 (3.15)	0.83 (1.60)
average	0.86	0.89	0.82	0.89	0.85 (3.02)	0.84 (2.12)

The overall potassium power exponent was significantly smaller than the sodium exponent (Table 6), t (8) = 5.06, $p < .01$. While, in terms of delivered current and sequence of trials for each subject, the pain stimuli were identical for both the sodium and potassium iontophoresis conditions there was a significantly greater average range of responding for the potassium condition (123 mm) compared to the sodium condition (94 mm), t (8) = 2.90, $p < .05$. This indicates that the *effective* stimulus range was greater in the potassium condition, due to the ability of potassium to generate higher pain levels. The overall lower potassium power exponent obtained in our study is consistent with intramodal range effects, in which larger stimulus ranges tend to produce smaller power exponents (Poulton 1968; Teghtsoonian, 1973). Though the intramodal range effect is much smaller than that found for cross-modality comparisons (Teghtsoonian, 1973). However, if a range effect was producing the exponent difference then we would expect a significant negative correlation between the percentage change in response range (as an indicator of change in effective stimulus range) and percentage change in power exponent. For our nine subjects there was no significant relationship (r = -0.14, $p > .05$). Clearly, differential nociceptive effects of the sodium and potassium ions overrides any intramodal range effect which may also be influencing the power exponents.

In summary, in addition to electrode configuration and size (Higashiyama & Tashiro, 1990; Tursky, 1974), the nature of the electrolyte that carries the applied current across the dermal barrier can influence the psychophysical parameters that describe the stimulus-response relationship. Thus it would be difficult to compare studies using different conducting pastes, formulated with different active electrolytes, even if those studies have used the same electrical parameters and electrode configurations. This emphasises the fact that the carrier of electric current in physiological tissue is not electrons but ions, and that the particular ions involved in the charge flow will determine the effects that the applied current will have on neural tissue - including any nociceptive transduction.

Figure 8 shows the linear regression lines for each subject for the sodium and potassium conditions.

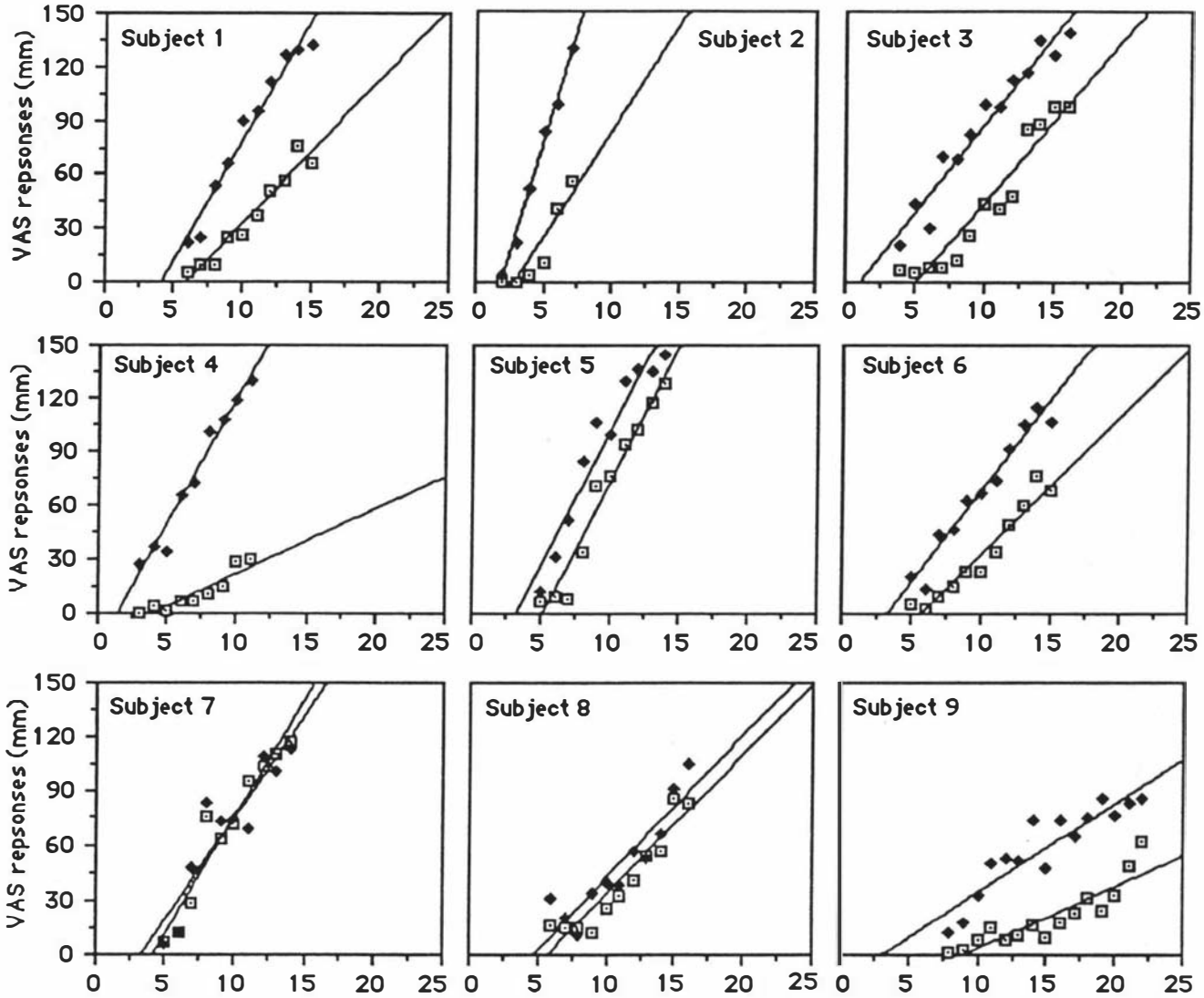


Figure 8. The linear regression lines for each subject for sodium and potassium iontophoresis in Experiment Three. The data points are the arithmetic means for responses at each stimulus level. The squares represent the sodium iontophoresis, the closed triangles the potassium iontophoresis. Experiment Three.

Consistent witrh the results in Experiment One (see Figure 6) there were large individual differences in dynamic range, both for the K+ and Na+ stimuli. Averaged over all subjects, the obtained regression line slope was greater for the K^+ condition (12.4) than for the Na^+

condition (8.6). However, this difference was not quite significant with a .05 alpha level criterion, t (8) = 2.21, $p < .06$.

For all subjects except for Subject 7 the potassium iontophoresis produced higher levels of pain at all stimulus intensities. For the lowest, median and highest stimuli levels for each subject there were significant higher levels of pain response to the potassium stimulus compared to the sodium stimulus (see Table 7). This result is consistent with the possibly lower dynamic range found for K^+, as suggested by the difference in the regression line slopes for K^+ and Na^+.

Table 7. Average VAS pain response for both sodium and potassium iontophoresis. Experiment Three.

Stimulus Level	Na^+ VAS(mm)	K^+ VAS(mm)	Significance of Difference
Lowest	5	17	t (8) = 4.39*
Median	32	74	t (8) = 5.78*
Highest	78	120	t (8) = 3.84*

* $p < .01$

There is a large amount of individual variability in how much potassium iontophoresis increases the painfulness of a given applied current relative to that produced by sodium iontophoresis. For most subjects, however, the increase was substantial. In addition, subjects were more likely to spontaneously report the potassium stimulus as producing a burning effect.

CHAPTER 9

GENERAL DISCUSION: EXPERIMENTS ONE, TWO AND THREE

9.0 GENERAL DISCUSSION OF EXPERIMENTS ONE, TWO AND THREE

The general objectives of Experiments One, Two and Three were to investigate the pain-inducing characteristics of iontophoretically applied K^+. This involved evaluating the stimulus in terms of the properties required of an ideal experimental pain stimulus, and determining the psychophysical parameters associated with the pain stimulus.

9.1 POTASSIUM IONTOPHORESIS, AND THE REQUIREMENTS FOR AN EXPERIMENTAL PAIN STIMULUS

The results of Experiments One, Two and Three confirm that potassium iontophoresis does possess many of the characteristics required of an experimental pain stimulus. These requirements can be assessed using the criteria provided in Chapter 1.2; that is, that an ideal experimental pain stimulus be a) clearly detectable as a pain sensation, b) reliably quantifiable from threshold to tolerance levels, c) have demonstrable construct validity with respect to clinical pain, d) not produce any tissue damage, e) be able to be presented repeatedly and rapidly with minimal carry-over effects, and f) be easy to use and safe.

a) Clearly detectable as a pain sensation

By structured interviews, at the conclusion of Experiment One, a qualitative description of the pain stimulus was obtained. The stimulus was rated genuinely painful by all subjects. At low stimulus intensities it was typically described as a pricking-stinging sensation, at higher intensities it was reported as a deep, widespread, burning sensation. Many subjects commented on the "non-electrical" nature of the stimulus in that it did not produce an expected electric shock sensation. These reports were consistent with structured interview reports

obtained in an earlier study with six other subjects (Humphries & Johnson, 1990), and with the reports of other studies (Benjamin & Helvey, 1963; Ong et al., 1980; Voudouris et al., 1985).

Occasionally pain was detected at the cathode site. This most often took the form of pain felt at small isolated areas under the cathode. This indicated a localised breakdown of resistance at those points, with an attendant high current density leading to cathodal neural depolarization. As the cathodal pain might confound the pain produced by the potassium iontophoresis subjects that reported this pain were run on later sessions. Attention to cleaning the skin, in order to uniformly lower skin resistance, seemed to be the best protection against cathodal pain developing.

The sodium control used in Experiment Three demonstrated that the perceived pain was substantially the result of the specific pain-producing action of the potassium ion. This is consistent with previous studies that have demonstrated the nociceptive action of K^+. However, there were large unexplained individual differences in the increase in perceived pain as a result of the potassium administration, relative to the sodium control. The extent that this indicates systematic differences in reaction to the potassium administration, or is partly a methodological artifact arising from testing subjects across days, is uncertain.

b) Quantifiable from threshold to tolerance levels

The stimulus was easy to quantify as the relationship between potassium infusion and applied direct current makes it possible to precisely determine and deliver selected quantities of K^+. Unlike electrical stimulation techniques that use an AC power source the DC source with potassium iontophoresis does not introduce problems with impedance. As the pain stimulus is the delivered K^+ neither are there problems determining whether the independent variable measure should be amperage, voltage, or power. With potassium iontophoresis the stimulus is directly quantified in terms of rate of delivery of K^+, and this is directly proportional to applied current.

The psychophysical functions obtained in Experiments One, Two and Three indicate that it is possible to deliver specified levels of suprathreshold stimuli over a relatively wide range of reported pain. Other experimental studies, using our computer controlled iontophoretic apparatus, have run threshold and repeated tolerance trials (Breakwell, 1992; Douglas, 1994).

c) Demonstrable construct validity with respect to clinical pain

The qualitative descriptions of the nature of the stimulus indicates that the pain was perceived to be genuinely painful. The non-electrical nature of the stimulus means that it is perceptually a more valid sensation than that normally produced by direct electrical stimulation.

The large between-subject variability compared to within-subject variability conforms to the pattern generally found for individual differences in reporting pain (Beecher, 1957a; Cross et al., 1975; Rollman & Harris, 1987; Tursky & O'Connell, 1972).

Additional studies using potassium iontophoresis to study the effects of distraction on pain reporting (Breakwell, 1992; Douglas, 1994) were consistent with the known effects of distraction on clinical pain (Levine, Gordon, Smith, & Fields, 1982; Turk, Meichenbaum, & Genest, 1983), and other experimental pain stimuli (McCaul & Malott, 1984; for a meta analysis see Fernandez & Turk, 1989)

d) Not produce any tissue damage

Even with higher stimulus intensity levels and repeated trials there was no apparent tissue damage. A mild erythemia of the skin, accompanied by allodynia (a tenderness to light stroking), that disappeared within minutes was the most noticeable reaction that occurred, and then only in some subjects. The erythemia sometimes took the form of isolated patches approximately 2-3 mm diameter, both inside and outside of the anode site. The occurrence of a response away from the electrode site suggested that the inflammation was neurally modulated, rather than a direct inflammation reaction to the applied potassium ions. A similar reddening of the skin around the cathode also occurred in some subjects.

Potassium iontophoresis provides an opportunity to investigate the neural modulation of pain in the relative absence of inflammation processes and tissue damage, even with high stimulus intensities. In contrast, at high stimulus intensities with repeated stimulation, many experimental pain stimuli (for instance, thermal or mechanical) can produce substantial tissue trauma, with the attendant direct release of pain producing chemicals such as histamine, serotonin, various kinins and prostaglandins (Hurley, 1984). While these inflammation responses may confer some clinical validity for these stimuli (Dubner, 1991) being part of natural pain producing mechanisms (e.g. with acute inflammation attending thermal stimuli: LaMotte et al., 1983; Torebjörk et al., 1984) the ability to study reactions to painful stimulation relatively isolated from these tissue trauma processes could provide a useful analytical tool.

e) Able to be presented repeatedly and rapidly with minimal carry-over effects

The combined results of Experiments One and Two indicate that short duration iontophoretic stimuli of one second can be applied rapidly with no substantial loss in subject response consistency over repeated trials, both in terms of immediate trial-to-trial effects and session effects. This was found to be particularly so for moderate intensity pain stimuli. Clearly these are desirable characteristics for an experimental pain stimulus. In particular, an important requirement of any experimental pain stimulus is that it produces reliable pain reports in subjects: that is, that subjects can report varying stimulus intensities accurately and consistently over a large number of trials and sessions.

Experiment Two demonstrated that even with ISIs as short as 10 seconds there is no significant change in reliability in responding as measured by the correlations of the linear functions, or by changes in responding across a session. This contrasts with the frequently high levels of carry-over effects associated with some other experimental pain stimuli; such as cold pressor, ischemic, mechanical and thermal.

f) Easy to use and safe

Overall the findings are consistent with the report of Siddiqui et al. (1985) that iontophoresis is ".. a simple, safe and well documented method of introducing ions or polar substances into the skin.. " (p. 732). The potassium ion itself would not be expected to produce any general adverse systemic effects as the total amount delivered over a session would rarely exceed four mg. This can be compared to the normal daily dietary intake of between 2,800 mg and 3,900 mg of potassium (Gilman, Goodman, & Gilmar, 1980). The amperage required to drive the K^+ across the dermal barrier is much less than that required to produce tissue damage due to heating effects or the direct effects of the electric current (Karlsmark, et al., 1986; Kenshalo, 1968).

The electrical safety of the apparatus is ensured as the isolated power supply is limited to a maximum of 40 volts, and the placing of the electrodes across only one arm of the subject avoids any possibility of the current passing through the heart area.

The gel solution in the anode bowl allows some movement of the subject's arm so that the electrode connections produce as little discomfort as possible. This is particularly important in pain studies where pain responding can be influenced by distraction (Hodes, Howland, Lightfoot, & Cleeland, 1990; Miron, Duncan, & Bushnell, 1989).

The computer controlled presentation of stimuli and automatic recording of subject responses permits convenient recording of subject responding, even over long sessions.

9.2 THE PSYCHOPHYSICS OF POTASSIUM IONTOPHORESIS

The results of Experiments One, Two and Three indicate that a two-constant linear function provided the best description of the relationship between applied stimulus and pain report over a range that is most often encountered with clinical pain. It is also possible that a three-constant power function (i.e., a power function with a threshold correction: e.g., Higashiyama & Tashiro, 1987) would provide an even better fit. However, such an improved fit may not

reflect an actual underlying power psychophysical function; it may simply be the result of a three-constant function's ability to better fit monotonically increasing data.

McCallum and Goldberg (1975) have argued that criteria aside from goodness of fit should be used in deciding whether a linear function should be discarded for more complex functions. In pain perception neural processing should supply the most appropriate criterion. Unfortunately pain perception is the result of complex neural processing at both the peripheral and central level. It is unlikely that our knowledge of such processes will let us a priori decide which function should best be applied to psychological pain reports for some time.

Furthermore, if the functions reflect context effects that are intrinsic to the measurement process (Algom & Marks, 1990; Anderson, 1975; Foley, Cross & O'Reilly, 1990; Gescheider & Hughson, 1991), in addition to the nociceptive processing, interpretation of the functions are made even more difficult. As Poulton (1967, 1968) has noted with regards to range effects, the exponent may be a procedural artifact that is a function of the experimental conditions as much as the neural processes that underlie pain perception. Finally, there is no reason to expect the evolutionary forces that have shaped pain perception to have constrained the underlying physiological processes to fit any simple psychophysical law.

In summary, given the wide range in individual variation, and the fact that the exponent value can be changed by a number of stimulus, context and cognitive factors, any search for *the* true pain exponent (e.g., Cross et al., 1975; Tursky, 1974) would appear to be misplaced.

In all three experiments there was a relatively large variation in response consistency, as measured by the function correlation coefficients. For example, the linear function correlation coefficients ranged from 0.79 to 0.96. This indicates that it would be advantageous to screen subjects according to their psychophysical ability to reliably rate the pain stimulus. For Experiments Four and Five subjects with a linear function correlation coefficient of less than

.85 were to be excluded from the studies. (In fact, no subjects were excluded on the basis of this relatively modest criterion).

The finding of pain adaptation for low intensity pain stimuli and enhanced pain responding for moderate intensity pain stimuli across a session (Experiment Two) may be a result of the differences in responding between A-delta and C-fibre afferents. C-fibre activity has been associated with burning pain, while A-delta activity has been associated with pricking pain (Torebjörk & Hallin, 1973, 1976; Torebjörk & Ochoa, 1980; Willis, 1985). D.D. Price (1972) and D.D. Price et al. (1977) concluded, on the basis of myelinated A-fibre and unmyelinated C-fibre afferent conduction velocities, that A-delta activity mediated first pain, whereas second pain was C-fibre mediated. First pain nociceptor adaptation and second pain central summation has been reported for repeated thermal stimulation (D.D. Price et al., 1978; D.D. Price et al., 1977).

In the present study, the subject's reports of a pricking pain at low stimulus intensities and burning sensations at higher stimulus levels is consistent with a 'low-intensity stimulus' A-delta suppression and a 'higher-intensity stimulus' C-fibre induced summation. However, the time course for adaptation and summation reported by D.D. Price et al. (1978) and D.D. Price et al. (1977) was for four consecutive heat pulses, at which point the changes appeared to have plateaued. In the present study subjects were given a number of stimulus trials prior to the main session in order to familiarize the subject with the experimental task and stabilize skin resistance, and then the session effects were observed over extended trials. Thus the long-term session changes observed in our study do not match the time course of the changes found by the studies of Price et al.

Nevertheless, other studies have reported similar long-term session changes as found in our study. When stimulus intensity was randomized and the thermal stimuli were applied to the same site with an ISI of 28 seconds pain suppression was observed across 63 session trials; although most suppression occurred during the first 18 trials, and the adaptation was associated

with C-fibre activity (LaMotte & Campbell, 1978). Lahoda et al. (1977) have reported habituation across a session for electric shock that produced a "pricking pain sensation" (p. 52). Thus their obtained pain habituation is consistent with an A-delta adaptation.

In summary, it is difficult to compare the results of studies using thermal and mechanical nociceptive stimuli with potassium iontophoresis as different stimuli have different neural stimulus properties (Torebjörk, 1974). For example, Price et al. (1978) found that the responses of monkey A-delta nociceptors decreased with repeated thermal stimuli but not electric shock. Speculatively, the differential change in pain response to low and higher intensity nociceptive stimuli may be, respectively, A-fibre and C-fibre mediated. In addition, the pain report changes may be directly due to changes in peripheral nociceptor sensitivity. Though, given the time course of the changes that occur across a session following a pre-session 'warm-up', the changes in nociceptive processing may well be the result of slow central changes.

As with the Higashiyama and Tashiro studies (1987, 1989) our results support the possibility of separate neural adaptation mechanisms for different intensities of a peripheral stimulus. Although they explained their results in terms of the differential adaptation rates between A-alpha fibres mediating touch, and A-delta and C-fibres mediating pain.

The results for the ISI * Preceding-Stimulus interaction (Experiment Two) were consistent with the inverse relationship found in prior studies (higher pain ratings when the preceding stimulus was of low intensity compared to when it was of higher intensity), but only for the moderate-intensity present-stimuli. For the low-intensity present-stimuli a positive relationship was found. It is possible that our low intensity stimuli were generally less nociceptive than the range of stimuli used in prior studies. For example, LaMotte and Campbell (1978) used 3-second duration thermal stimuli in the range 40 to 50°C; Chudler et al. (1990) used 2-second duration thermal stimuli in the range 45 to 49°C.

The results of Experiment Two highlight that both ISI and stimulus intensity are important factors when investigating stimulus history effects. This applies both to overall session effects and the changes produced by immediately preceding stimuli. Most previous studies have not attempted to measure the interaction between pain stimulus intensity and ISI. Though the effect on wide dynamic range and nociceptive specific neurons in the dorsal horn is known to be influenced by the interaction between ISI and intensity of the preceding stimulus (Hoffman Dubner, Hayes, & Medlin, 1981). The results of the present study show that a detailed understanding of pain processing can only be developed by taking such interactions into account. For example, whether there was suppression or enhancement of pain response was dependent on the ISI, the preceding stimulus intensity and the present stimulus intensity.

Further studies need to clarify the extent to which the short-term effects of prior stimuli are due to general sequential dependency and other response bias factors, or are intrinsic to the neural modulation of pain. The magnitude of the carry-over effects observed suggests that nociceptive processing is the main factor.

9.3 THE USE OF POTASSIUM IONTOPHORESIS TO INVESTIGATE PAIN MECHANISMS

The results of Experiments One, Two and Three indicate that potassium iontophoresis provides a convenient experimental pain stimulus that can deliver precisely quantified magnitude of nociceptive stimulation. The nociceptive stimulation can also be rapidly changed in intensity. In addition prior research has found that the increased levels of extracellular K^+ produced by potassium iontophoresis has a general depolarization effect on neural tissue. These characteristics combine to make potassium iontophoresis uniquely suitable for an investigation of the spinal modulation of nociceptive peripheral input.

Experiment Four uses potassium iontophoresis to investigate the gate control theory of pain (Melzack & Wall, 1965). Gate control theory has been one of the most influential theories of pain, providing an heuristically useful model of nociceptive spinal modulation (Liebeskind &

Paul, 1977; D.D. Price, 1988). Research guided by the gate control theory has lead both to a better understanding of pain processing, and better ways of controlling pain.

CHAPTER 10

OVERVIEW OF THE GATE CONTROL THEORY OF PAIN

10.0 OVERVIEW OF THE GATE CONTROL THEORY OF PAIN

The major proposal of the gate control theory of pain is that the flow of nociceptive nerve impulses from the peripheral nerve system to the central nervous system are modulated in the dorsal horns of the spinal column (for reviews see Besson & Chaouch, 1987; Fields & Basbaum, 1978; Willis & Coggeshall, 1978). This neural mechanism is considered to act as a pain gate in which nociceptive transmission may be facilitated or inhibited at the spinal level.

According to the original gate control proposal the first central transmission (T) cells in the substantia gelatinosa (SG) of the spinal dorsal horns were part of a set of fibres that made up the spinothalamic 'pain' pathway. If the T cells were sufficiently activated then pain might be experienced. That is, if the ascending output from the T cells exceeded a critical level then the Action System would be activated - a system of neural processes that involve spinal and a wide range of supraspinal centres, and that underlie and determine how we experience and react to nociceptive stimulation.

The activity of the T cells was dependent, at least partly, on the relative activity of the large-diameter low-threshold mechanoreceptive (A-beta) primary afferents and small-diameter (A-delta and C) primary afferent nerve fibres. The large-diameter and small-diameter afferent fibres project not only to the T cells, but also to interneurons which exert an inhibitory effect on the terminals of both the large and small afferent fibres where they synapse with the T cells (Figure 9). The large-diameter primary afferents were held to exert a presynaptic inhibition of the release of transmitter from the primary nociceptive afferents. Inhibition was enhanced by large fibre activity, and reduced by small fibre activity (Melzack & Wall, 1965, 1988).

In summary, the extent to which we perceived pain depended, at least in part, on the ratio of the large and small-diameter peripheral fibre activity. Small-diameter activity, associated with nociception, would tend to increase T cell activity (open the pain gate). Large-diameter activity, associated with non-noxious mechanical sensation, would tend to reduce T cell activity (close the pain gate). Thus, the transmission of peripheral nociceptive inputs could be modulated by non-nociceptive peripheral inputs. One proposed example of such pain modulation is the rubbing of a painful irritation. The rubbing preferentially activates large-diameter fibres which tend to decrease T cell transmission, thereby lowering the level of pain (Melzack & Wall, 1965).

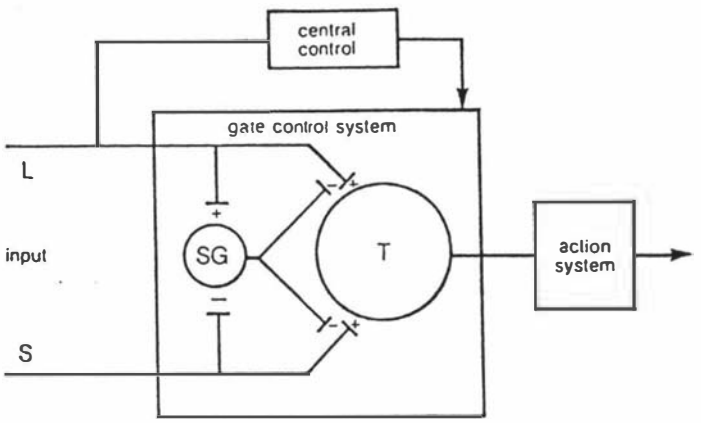


Figure 9. Schematic diagram of the gate control theory of pain mechanisms, as proposed by Melzack and Wall (1965). SG = substantia gelatinosa, T = transmission cell, L = large-diameter fast afferents, S = small-diameter slow afferents. - = inhibitory + = facilitatory. Adapted from Melzack and Wall (1965, p. 971).

Melzack and Wall (1988) also hypothesized that there were descending central controls, which could modulate nociceptive transmission at the spinal level. That is, central processes could also open and close the spinal pain gate. In summary, the transmission of peripheral

nociceptive messages was believed to be under both a peripheral segmental control and a central supraspinal control. Thus their model formally included both central and psychological factors as an integral part of pain processing.

Subsequent studies have found neurophysiological evidence in support of gate control theory. The substantia gelatinosa (SG) of the spinal cord dorsal horn has been found to have a role in the modulation of nociceptive transmission from the periphery to the central nervous system (Cervero & Iggo, 1980; Fitzgerald, 1981; Steedman, Molony, & Iggo, 1985). For instance, Calvillo, Madrid and Rudomin (1982) found that C-fibre input is presynaptically depolarized by low threshold afferent fibre activity, consistent with the proposal of presynaptic inhibition by Melzack and Wall (1965). Pohl et al. (1992) considered the segmental decrease in calcitonin gene related protein-like material (CGRP-LM), as a result of low intensity cutaneous electrical stimulation that activated A-beta afferents, to be consistent with the gate control theory proposition that impulses in large-diameter primary afferents presynaptically inhibit the release of neurotransmitters from small-diameter fibres. C-fibre inputs have been found to be inhibited in the spinal cord dorsal horn by A-fibre inputs which activate an inhibitory enkephalinergic interneuron (Duggan, Hall, & Headley, 1976; Jessel & Iversen, 1977; Ruda, 1982).

While Melzack and Wall (1965) originally proposed a presynaptic inhibitory mechanism (though not discounting the possibility of post-synaptic influences) subsequent studies have found both pre-synaptic inhibition (Calvillo, 1978; Fitzgerald & Woolf, 1981; Hentall & Fields, 1979; for review see Willis & Coggeshall, 1978) and post-synaptic inhibition (Hongo, Jankowska, & Lundberg, 1968) of dorsal horn neurons produced by electrical stimulation of peripheral afferents (for review see Besson & Chaouch, 1987).

Indeed the neuroanatomy and neurophysiology of spinal nociceptive modulation is clearly more complicated than that depicted in Melzack and Wall's original model. For example, convergent neurons (wide dynamic range neurons - WDR) that are often associated with the T cells of gate control theory have been found to be subject not only to large-diameter primary afferent

segmental inhibition, as proposed by the gate theory, but also to small-diameter afferent mediated segmental inhibition (Gregor & Zimmermann, 1972; Handwerker, Iggo, & Zimmermann 1975; Hillman & Wall, 1969). Recent schematic diagrams depicting the morphological-functional relationships of the dorsal horns (e.g., Coderre, Katz, Vaccarino, & Melzack, 1993; Fields, Heinricher, & Mason, 1991) serve to emphasise the simplification embodied in Melzack and Wall's original gate control theory.

Nevertheless, while there is criticism of gate control theory (Liebeskind & Paul, 1977; Nathan, 1976; Wagman & Price, 1969; Weisenberg, 1977; Willis & Coggeshall, 1978) the segmental spinal inhibition of nociceptive peripheral afferents by large-diameter non-nociceptive afferents has been extensively studied, and repeatedly confirmed (Mendell, 1966; D.D. Price & Wagman, 1970; Salter & Henry, 1987; Wall, 1978). Spinal nociceptive inhibition has been produced both by electrical stimulation (Dickenson, Hellon, & Woolf, 1981; Handwerker et al., 1975) and mechanical stimulation of peripheral afferents (Young & Nord, 1975).

So while the underlying physiology and anatomy of the gate control theory remains to be fully determined a principle tenet of the theory, that nociceptive peripheral input can be modulated at the spinal level by non-nociceptive peripheral inputs, is experimentally well established. Indeed the theory has been said to be "an excellent first approximation of the neural interactions underlying the transmission of nociceptive information" (D.D. Price, 1988, p.221).

10.1 CLINICAL SUPPORT FOR GATE CONTROL THEORY

There is considerable clinical support for the spinal modulation of nociceptive transmission, as proposed by gate control theory. For instance, a prediction of gate theory is that any disease process that preferentially attacked large-diameter low-threshold afferent fibres would lead to an increase in nociceptive spinal transmission due to the release from inhibition at the spinal

level. The loss of A-alpha and A-beta afferents in diabetes has been suggested as a factor in diabetic pain (Melzack & Wall, 1965).

Transcutaneous Electrical Nerve Stimulation (TENS), dorsal column stimulation and peripheral vibratory stimulation all provide additional support for a gate control mechanism of pain modulation. Indeed, gate control theory lead directly to the introduction of both TENS and dorsal column stimulation for the alleviation of pain (Wall & Sweet, 1967).

10.2 TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS)

The cited rationale for TENS is that the applied peripheral electrical stimulation preferentially activates large-diameter cutaneous afferents leading to the spinal inhibition of nociceptive transmission (Basbaum & Fields, 1984; Besson & Chaouch, 1987; Mannheimer & Lampe, 1984; Melzack & Wall, 1965; Meyerson, 1983; Monk, 1993). Though the gate control explanation does not exclude central effects (Pomeranz & Chiu, 1976), autonomic effects (Abram, Asiddao, & Reynolds, 1980; Thomas, Anton, Kenshalo, Williams, & Dubner, 1993), or possible psychological mechanisms (Fields, 1987).

TENS has been widely used (e.g., Guieu, Tardy-Gervet, Blin, & Pouget, 1990; Hansson & Ekblom, 1983; Long, 1976) and has been successful in the clinical treatment of low back pain (Cheng & Pomeranz, 1987; Lampe & Dunne, 1987; Marchand, Charest, Chenard, Lavignolle, & Laurencelle, 1993), arthritic pain (Mannheimer & Carlson, 1979), and myofacial pain (Cheng & Pomeranz, 1987; Francini, Maresca, & Zoppi, 1981). It is also effective in reducing experimental pain (Andersson & Holmgren, 1976) and has anti-nociceptive effects in animals (Jorum & Shyu, 1988).

While pain relief is dependent on a wide range of factors that includes the type of stimulation used, the personality characteristics of the patient, the skill of the practitioner and the type of pain experienced (Parry, 1980) TENS can be an effective clinical intervention (Long &

Hagfors, 1975; Woolf, 1989). The initial success rate for chronic pain patients, as measured by a substantial decrease in perceived pain, is typically over 50% of patients in the short-term, although this does normally drop to 20-30% in the long-term - after about a year of treatment (Bates & Nathan, 1980; Long, 1976).

It is difficult to run truly adequate double-blind controls with an intervention such as TENS, and many TENS studies have been poorly controlled. Nevertheless, many well controlled studies have demonstrated a reduction of both pain threshold and suprathreshold pain levels with TENS (e.g., Bushnell, Marchand, Tremblay, & Duncan, 1990; Marchand et al., 1993).

TENS has been categorized as being either high-frequency low-intensity, or low-frequency high-intensity. It is believed that these two different forms of TENS reduce perceived pain by different mechanisms. Low-frequency (< 10 Hz) high-intensity TENS (generally as high a pain level as the patient is prepared to reasonably tolerate), is believed to produce pain relief through counter-irritation with the release of endogenous opioids (Eriksson, Sjölund, & Nielzen, 1979; Woolf, Mitchelll, & Barrett, 1980). Low-frequency high-intensity TENS is sometimes referred to as acupuncture-like TENS (AL-TENS), as the release of endogenous opioids, and reversal of pain relief induced by it with the opioid antagonist naloxone, is similar to that found with acupuncture and electroacupuncture (Sjölund & Eriksson, 1979a, 1979b; Mayer, Price, & Raffi, 1977).

Low-frequency high-intensity TENS may be a form of DNIC (diffuse noxious inhibitory control) analgesia (Bing, Villanaueva, & Le Bars, 1990; Bushnell et al., 1990), and it may also be related to stress analgesia (Duranti, Pantaleo, & Bellini, 1988). DNIC involves the reduction of pain through the inhibition of wide-dynamic-range cells to local nociceptive inputs due to the effects of a distant (intersegmental) peripheral *nociceptive* conditioning stimulus (Le Bars, Dickenson, & Besson, 1979a, 1979b; Talbot, Duncan, & Bushnell, 1989; for reviews see Le Bars, Dickenson, Besson, & Villanueva, 1986; Le Bars & Villanueva, 1988; Roby-Brami, Bussel, Willer, & Le Bars, 1987). All noxious stimuli (e.g., mechanical, electrical

thermal) are effective, with the resultant hypoalgesia being proportional to the magnitude of the conditioning stimulus (Le Bars, Chitour, & Clot, 1981). DNIC has been shown to reduce both first and second pain (D.D. Price & McHaffie, 1988). The hypoalgesia occurs during and for several minutes after the conditioning stimulus (Le Bars & Villanueva, 1988; Willer, De Broucker, & Le Bars, 1989). The effects of peripheral noxious counter-irritation mediated by a supraspinal descending mechanism have been experimentally verified in humans (Talbot, Duncan, Bushnell, & Boyer, 1987; Talbot et al., 1989; Willer, Roby, & Le Bars, 1984).

It is important to distinguish DNIC from a reduction in pain through a spinal-level gating action. With DNIC the site of peripheral conditioning stimulation can be distant from the site of the pain indicating a non-segmental action (Bing et al., 1990). DNIC is believed to be triggered by A-delta activation and it is completely blocked by naloxone in humans (Bing et al., 1990). The DNIC inhibitions can be explained, at least in part, by depression in the transmission of nociceptive signals at the spinal level, but require a complex loop ascending from and descending to the spinal cord that involves the brain stem and spinoreticular tracts (Willer et al., 1989). The importance of the supraspinal component is indicated by the finding that the DNIC cannot be demonstrated in spinalized animals.

It is believed that low-frequency high-intensity TENS is a supraspinal mechanism (Andersson 1979; Meyerson, 1983) that is dependent on peripheral A-delta nociceptor stimulation (Johnson, Hajela, Ashton, & Thompson, 1991; Shin, Kim, & Chung, 1986), rather than a segmental inhibition of the transmission of nociceptive messages by large-diameter peripheral non-nociceptive myelinated afferents (Handwerker et al., 1975). However, greater effects have been found for ipsilateral conditioning stimuli in comparison with contralateral (Duranti et al., 1988). This suggests a possible segmental action, consequently a spinal-level gate effect cannot be totally excluded as a partial explanation for its effectiveness.

The typical time course for low-frequency high-intensity TENS is a delayed onset which is then followed by a long-lasting reduction in pain (Eriksson et al., 1979; Hansson & Ekblom,

1983; Melzack, 1975b). For instance, twenty to thirty minutes of conditioning stimuli were required to obtain maximal depression of nociceptive flexion reflex (Chung, Fang, Cargill, & Willis, 1983) and depression of spinothalamic tract (STT) cell activity (Chung, Fang, Hori, Lee, & Willis, 1984). Return to baseline threshold values took 60 to 90 minutes following the application of a conditioning peripheral stimulus (Duranti et al, 1988), and clinical pain relief has been reported to last for hours (Nathan & Wall, 1974)

However, TENS is also known to be effective when applied at high-frequencies and *low intensities* that are below the pain threshold (Andersson, 1979). In a clinical setting high-frequency low-intensity TENS is usually applied to produce a strong, but comfortable, paresthesia within the site of pain (Johnson et al., 1991). High-frequency low-intensity TENS has been found to be clinically more effective for treating chronic pain than low-frequency high intensity TENS (Nelson & Currier, 1991).

For high-frequency low-intensity TENS the most effective pain reduction has been obtained at 20-80 Hz (Johnson, Ashton, Bousfield, & Thompson, 1989; Sjölund, 1985). A number of studies have found the optimal frequency to be between 40 to 100 Hz (Johnson et al., 1989; Johnson, Hajela, et al., 1991). For instance, pulse frequencies between 20 and 80 Hz were found to be the most effective for reducing cold-induced pain in humans (Johnson et al., 1989). Clinical surveys have shown that patients have a preference for these frequencies and 40 to 100 Hz is commonly used in the clinical treatment of acute and chronic pain (Mannheimer & Carlsson, 1979). The stimulation of peripheral nerves at 80 Hz has also produced the most suppression of C-fibre evoked reflex in rats (Sjölund, 1979).

The frequencies and intensities associated with high-frequency low-intensity TENS preferentially activates low-threshold A-beta primary afferent fibres (Johnson, Ashton, & Thompson, 1991b), and this is consistent with gate control theory that activation of those peripheral afferents will inhibit the transmission of nociceptive information in the dorsal horn. The pain relief it provides is localized to the stimulated segment and is not naloxone reversible

(Colquhoun, 1993; Freeman, Campbell, & Long, 1983; Hansson, Ekblom, Thomsson & Fjellner, 1986; Pertovaara & Kemppainen, 1981). The time course of high-frequency low-intensity TENS, a rapid increase in pain threshold that does not greatly outlast the applied stimulus (Johnson, Ashton, & Thompson, 1991a), is also consistent with a segmental gate action .

Gate control theory has been proposed as the main neuronal basis for high-frequency low-intensity TENS (Besson & Chaouch, 1987; Fitzgerald, 1982; Mannheimer & Carlsson, 1979; Melzack & Wall, 1965; Wall, 1978; Wall & Sweet, 1967). With experimentally induced noxious-pinch pain high-frequency low-intensity TENS was observed to reduce cat dorsal horn cell activity more effectively than low-frequency high-intensity stimulation (Garrison & Foremen, 1994). Garrison and Foreman proposed that high-frequency low-intensity stimulation more effectively activated large-diameter myelinated neurons, and that the observed reduction in dorsal horn activity was consistent with the predictions of the gate control theory of pain.

10.3 DORSAL COLUMN STIMULATION

Direct stimulation of the dorsal column is another effective technique for the control of chronic pain (Nashold & Friedman, 1972; Nielson, Adams, & Hosobuchi, 1975; Sweet & Wepsic, 1974), the underlying mechanism of which is also believed to be a spinal-level gate action (Foreman, Beal, Applebaum, Coulter, Willis, 1976; Handwerker et al., 1975; Lindblom, Taper, & Wiesenfeld, 1977). The dorsal column has many A-beta afferents but few A-delta afferents (Shealey, Mortimer, & Hagfors, 1970). Therefore, according to gate control theory, dorsal horn stimulation should maximise pain relief without itself causing pain. Activation of the fibres in the dorsal columns produces the same dorsal horn inhibition as is produced by peripheral stimulation (Hillman & Wall, 1969).

Analogous with the segmental inhibition in the spinal dorsal horns trigeminal nociceptive neurons have been found to be segmentally inhibited by local afferent influences from A-beta A-alpha orofacial fibres (Dickenson et al., 1981; Hu & Sessle, 1979; Young, 1978). As with the spinal gating mechanism the balance of large-diameter and small-diameter afferents determines the transmission of nociceptive inputs.

10.4 PERIPHERAL VIBRATORY STIMULATION

The reduction of the painful itch by scratching or rubbing, and the reduction of causalgia pain by bathing, could both be explained as the result of preferential activation of large-diameter afferents (Melzack & Wall, 1965). Indeed, since the formulation of gate control theory there has been a systematic search for methods to clinically treat both acute and chronic pain based on activation of peripheral afferent fibres by conditioning stimuli (Besson & Chaouch, 1987; Bushnell et al., 1990; Lundeberg, 1983).

The excitation of C polymodal nociceptors by mechanical stimulation does not produce the same level of reported pain as a similar level of peripheral activity induced by a heat stimulus Beitel & Dubner, 1976b; Van Hees & Gybels, 1981). The possible explanation for this differential effect is that the mechanical stimulus also activates A-beta afferents which results in a spinal inhibitory effect on nociceptive transmission through a spinal gating action.

Vibratory peripheral stimulation has been observed to reduce experimentally induced pain (Ekblom & Hansson, 1982; Lundeberg, Abrahamsson, Bondesson, & Haker, 1988; Melzack & Schecter, 1965; Wall & Cronly-Dillon, 1960), acute clinical pain (Hanson & Ekblom, 1984; Lundeberg, Nordemar, & Ottoson, 1984), and chronic clinical pain (Guieu et al., 1990; Lundeberg, 1984a, 1984b). Thus the pain reducing ability of vibratory stimulation is well established, though the exact mechanism of long-term alleviation of both acute and chronic pain still remains to be clarified (Abram Reynolds, & Cusick, 1981; Meyerson, 1983).

Vibratory stimulation is also known to be effective in animals (Handwerker et al., 1975; Salter & Henry, 1987, 1989, 1990; Wagman & Price, 1969). Both TENS and vibration induced inhibition of nociceptive transmission at the spinal level is resistant to naloxone (Freeman et al., 1983; Hansson et al., 1986; Lundeberg, 1983; Sjölund & Eriksson, 1979a, 1979b). This suggests that they may share a common neural mechanism.

The most common frequencies used for the reduction of pain with vibratory stimuli are from 50 to 150 Hz (Duranti et al, 1988). For instance, Guieu, Tardy-Gervet, & Giraud (1992) found that 100 Hz was more effective than 2Hz for relief from painful itch. Ekblom and Hansson (1982) obtained the most effective pain relief - a greater than 50% pain reduction - with vibration frequencies of 100 to 200 Hz for light pressure and 50 to 100 Hz for moderate pressure.

The higher frequency mechanical vibration has relatively short induction times with an increase in pain threshold being obtained in most studies within 10 minutes (Ekblom & Hansson, 1982) and often less than 5 minutes (Guieu et al, 1992; Lundeberg, 1983). The pain relief continues through the stimulation period, and then slowly subsides following the termination of the stimulus (Ekblom & Hansson, 1982). While only a brief post stimulation pain relieving effect is often reported, pain relief can be prolonged after stimulus termination. Lundeberg (1983) has reported up to 12 hours pain relief in many patients.

The most likely explanation for the pain reducing effects of peripheral vibration (especially from 50 to 150 Hz) is reported to be the activation of large-diameter myelinated afferents (Duranti et al., 1988; Ekblom & Hansson, 1982; Guieu et al., 1992; Melzack & Schecter, 1965) which results in a pain-inhibitory segmental gate control mechanism (Lundeberg, 1983; Ottoson, Ekblom, & Hansson, 1981; Pantaleo, Duranti, & Bellini, 1986; Pertovaara, 1979)

The transmission of mechanical peripheral vibration is by rapidly conducting, non-nociceptive, primary afferent neurons (Hunt, 1961; Hunt & McIntyre, 1960). Superficial and deep

cutaneous mechanoreceptors are known to be sensitive to vibration (Ferrington, Nail, & Rowe, 1977; Valbo & Hagbarth, 1968), as are the pacinian corpuscles (Homma, Kanda, & Watanabe, 1971; Johansson, Landstrom, & Landstrom, 1982), and the primary endings of the muscle spindle (Hason & Houk, 1975). The afferents of all these receptors are large-diameter myelinated nerve fibres. Finally, nociceptive neurons in the spinal dorsal horn are known to be preferentially depressed by peripheral vibration (Salter & Henry, 1987).

That the effects of vibration are not naloxone reversible (Guieu et al., 1992; Hansson et al., 1986; Lundeberg, 1985; Salter & Henry, 1987) and are restricted to the body segment stimulated (Lundeberg, 1983) is also consistent with a spinal level gate action. The possibility that vibration simply gives rise to a fatigue or conduction failure in the peripheral nociceptive fibres (Ertekin, Citakoglu, & Ertekin, 1980; Ignelzi & Nyquist, 1976; Wall & Gutnick, 1974) has been rejected (Janko & Trontelj, 1980). However, as with TENS, autonomic effects may also play a role (Lundeberg, 1983).

In summary, a large amount of clinical and experimental evidence, using a variety of non-noxious conditioning stimuli, has established that nociceptive peripheral input can be modulated by non-nociceptive peripheral inputs as proposed by the gate control theory of pain.

10.5 THE TIME COURSE FOR SPINAL PAIN MODULATION MECHANISMS

Melzack and Wall (1965) proposed that there would be both spatial and temporal summation at the T cells. For instance, a definite time period would be required for integrating the peripheral input. Small, fast, variations in peripheral input from large-diameter afferent fibres might be ineffective in modulating noxious peripheral stimuli. Nevertheless the known time course of spinal neural mechanisms suggests that relatively rapid changes in large-diameter peripheral input may be able to modulate the transmission of noxious stimuli. Wall (1988) has described the time course of gate control action due to peripheral inputs at the first synapse to be in the

order of milliseconds to seconds, as opposed to slower mechanisms, such as descending controls, that act over minutes or hours.

Experimental studies, using spinalized or decerebrate animals, investigating the inhibition of transmission of nociceptive stimulation at the spinal level by activity in large-diameter peripheral afferents indicate that the modulation effects are indeed rapid. For instance, Salter and Henry (1986, 1987) have reported the depression of wide dynamic range (WDR) neurons 15 to 50 ms after start of innocuous cutaneous vibration. After the end of the vibration there was a return to baseline levels in the WDR neurons within 500 ms. Dickenson et al. (1981) found that the inhibitory segmental effects of A-alpha and A-beta stimulation on the trigeminal input in the rat did not outlast the conditioning stimulation, even when it was applied for 2 to 5 minutes.

Woolf and Wall (1982) investigated A-afferent mediated inhibition of A-fibre and C-fibre activity in WDR convergent neurons in the SG units of the dorsal horn and found inhibition occurring within 20 to 70 ms of the start of the conditioning stimuli. The inhibition duration lasted only from 30 to 100 ms following the termination of the conditioning stimuli. A-beta inhibition of C-fibres has been found to last for 75 ms (Mendell, 1966) and 200 to 300 ms (Fitzgerald, 1982) following the conditioning stimuli. With dorsal column stimulation, Foreman et al. (1976) obtained maximum depression of high threshold STT cells at 5 to 10 ms, with a duration of about 150 ms. Clearly, the spinal modulation of nociceptive neural activity can have a rapid time course - at least in the absence of descending controls (Lindblom et al., 1977).

The rapid modulatory changes detected at the spinal level, in response to large-diameter afferent inputs, suggest that such changes may be measurable in terms of perceived pain. That is, it may be possible to measure changes in perceived pain to a nociceptive peripheral stimulus as a function of relatively rapid changes in large-diameter peripheral input.

However, the observed rapid modulation of nociceptive transmission at the spinal level is clearly at odds with the clinical and experimental findings for the action of high-frequency low-intensity TENS, peripheral mechanical vibration, and dorsal column stimulation, all of which have a somewhat delayed onset of maximal effectiveness, and prolonged effects beyond the termination of the conditioning stimulus (Lindblom et al., 1977). In clinical studies pain can be relieved for several hours following the termination of the conditioning stimulation (Mayer & Liebeskind, 1974). This contrasts with the known neurophysiological action of nociceptive spinal cord modulatory mechanisms that begin in milliseconds and terminate within seconds of peripheral stimulus offset.

In summary, for all of the procedures that induce pain relief through the stimulation of peripheral afferents, in addition to the purely spinal level gating action, some form of supraspinal control must also be involved in order to account for delayed onset and prolonged pain inhibition in response to the peripheral conditioning stimuli. Consequently the influences of supraspinal controls must be considered when investigating spinal gating mechanisms.

CHAPTER 11

SUPRASPINAL INFLUENCES ON PAIN PROCESSING

11.0 SUPRASPINAL INFLUENCES ON SPINAL NOCICEPTIVE PROCESSING

Higher centres of the CNS can modulate nociceptive sensory function at the spinal level. Accordingly, in order to understand the process of spinal gating account must be taken of supraspinal influences (for reviews see Basbaum & Fields, 1978; Besson & Chaouch, 1987; Dubner & Bennett, 1983; Willis, 1988; Willis & Coggeshall, 1978; Yaksh, 1986). These supraspinal influences may account for the delayed onset and prolonged pain inhibition in response to peripheral conditioning stimuli. The supraspinal effects may be either descending or ascending in nature, or both.

11.1 DESCENDING SUPRASPINAL INFLUENCES

The time course of peripheral conditioning stimuli producing pain inhibition is consistent with the time course observed for some supraspinal descending controls. For example, from behavioural observations, the duration of the inhibition following activation of the descending nucleous raphe magnus (NRM) system was approximately 45 minutes, with a latency of onset of 15 minutes (Murphy & Behbehani, 1993).

Supraspinal descending control processes (Besson, Guilbaud, & Le Bars, 1975; Dickenson, Oliveras, & Besson, 1979; Hall, 1979) can produce inhibition of spinal cord nociceptive neurons (Basbaum & Fields, 1984; Carstens, Klumpp & Zimmermann, 1980; Oliveras Besson, Guilbaud, & Liebeskind, 1974). Electrical stimulation of the medulla (Fields, Basbaum, Clanton, & Anderson, 1977) midbrain (Gray & Dostrovsky, 1983; Yezierski, 1990) thalamus (Gerhart, Yezierski, Fang, & Willis, 1983) and cortex (Yezierski, Gerhart,

Schrock, & Willis, 1983) have all been shown to be able to produce dorsal horn nociceptive inhibition. These inhibitory mechanisms can involve depression of both A-delta and C-fibre activity (Rivot, Chaouch, & Besson, 1980).

Electrical stimulation studies have shown the NRM and the periaqueductal gray (PAG), the two most widely studied brain sites, to have an important role in an endogenous descending nociceptive control system on the dorsal horn neurons (Dawson, Dickenson, Hellon, & Woolf, 1981; Fields et al., 1977; Giesler, Gerhart, Yezierski, Wilcox, & Willis, 1981; Murphy & Behbehani, 1993).

PAG stimulation can inhibit both wide-dynamic range and nociceptive specific neurons in the spinal dorsal horns (Basbaum & Fields, 1978; Mayer & Price, 1976; Sessle, Hu, Dubner, & Lucier, 1981). It has been concluded that opiate analgesia and electrical stimulation analgesia activate common pathways as the systemic administration of naloxone, a specific opiate antagonist, can block the effects of both (Basbaum & Fields, 1978; Mayer & Price, 1976).

Supraspinal electrical and chemical stimulation that activates descending controls is clinically effective at reducing pain and can produce antinociception in both humans and animals (Gybels 1979; Hosubuchi, Adams, & Linchitz, 1977; Mazars, Merienne, & Cioloca, 1976, 1979; Richardson & Akil, 1977). This spinal modulation of pain stimuli via descending controls is believed to underlie at least some of the effects of hypnosis, placebos, attention, stress, and analgesics such as morphine (e.g., Amit & Galina, 1986; Fernandez & Turk, 1989; Finer, 1974; Willer, Bergeret, & Gaudy, 1985).

The brain stimulation studies indicate the existence of an endogenous analgesic system. But the exact circumstances that activate descending controls under normal conditions remains to be fully determined. Electrical stimulation of the brain is an unnatural stimulus, and it is still unclear how natural supraspinal inputs influence the descending control mechanism (Yezierski, 1990). Little is known about the comparative effects of NRM and segmental inhibition of

neurones in the dorsal horn (Dickenson et al., 1981). A number of investigators have suggested that somatosensory stimuli might activate an endogenous analgesia system, though their studies were carried out in decerebrate animals (Fields & Basbaum, 1978).

Studies have shown that a strong behavioural analgesia can be induced by noxious stimuli in which ascending nociceptive messages activate cells in the PAG or nucleus raphe magnus, resulting in the activation of the descending analgesic system (Basbaum & Fields, 1978, 1984). The supraspinal sites involved in descending control do receive large-diameter somatosensory inputs (Murphy & Behbehani, 1993; Roberts, Eaton, & Salt, 1992). For instance, stimulation of the ventrobasal thalamus, (which includes the ventroposterior lateral (VPL) and ventroposterior medial (VPM) nuclei, which, in turn, are effective in activating descending controls) activates, at least in part, the same primary somatosensory pathways that are activated by high frequency conventional TENS and dorsal column stimulation (Bushnell et al., 1990).

Non-noxious somesthetic inputs originating in low threshold specific peripheral receptors are carried by fast A-fibres to the nucleus ventro-postero lateralis (VPL) (Benabid, Henriksen, McGinty, & Bloom, 1983) and LRN (Murphy & Behbehani, 1993). Indeed, the rationale for stimulating the somatosensory thalamus (the more lateral ventrobasal areas) was derived from dorsal column stimulation, which in turn, was prompted by gate control theory. Thus, in summary, it is clearly possible that large-diameter peripheral inputs could have a role in the supraspinal descending control of pain.

11.2 ASCENDING SUPRASPINAL INFLUENCES

An ascending system of anti-nociception has also been studied (Condes-Lara & Omana Zapata, 1988; Nashold & Friedman, 1972; Qiao & Dafny, 1988) in which ascending large-diameter peripheral inputs may directly modulate nociceptive perception at the supraspinal levels, with a mechanism similar to the spinal gate control (Benabid et al., 1983). For example, Roberts et

al. (1992) propose that the pain of deafferentation injuries are the result of a large-diameter small-diameter fibre imbalance at the thalamic level, in addition to the gating action in the spinal dorsal horns. That is, large-diameter fibre input to the thalamus can modulate nociceptive input at that level (Kakigi & Shibasaki, 1992). This ascending control may well involve even higher cortical functions, as indicated by cortical evoked potential (EP) studies (e.g., Follett & Gebhart, 1992), though these cortical EPs have not been directly linked to nociceptive mechanisms. Stimulation of the VPL, used to mimic an increase in non-noxious thalamic afferent input, has been shown to inhibit neuronal activity, indicating a supraspinal nociceptive inhibitory mechanism (Benabid et al., 1983)

11.3 SUPRASPINAL CONTROLS AND GATE CONTROL THEORY

The supraspinal control mechanisms are speculative in terms of their ability to override the rapid large-diameter afferent modulation of nociceptive transmission at the spinal level. No studies have shown that such a rapid-acting supraspinal control exists. Though, of course, the slower acting controls demonstrated by TENS, DNIC, vibratory stimuli and dorsal column stimulation are well established. Whatever supraspinal control mechanisms are operating to modulate the perception of nociceptive peripheral inputs, rapid short-term changes in nociceptive transmission, produced by changes in large-diameter primary afferent activity at the spinal level, may still produce concomitant changes in perceived pain.

It is reasonable, therefore, to investigate the possibility that modulatory changes in nociceptive transmission at the spinal level, due to relatively rapid changes in large-diameter afferent input, is measurable in terms of changes in perceived pain levels. An assumption with such an investigation is that no supraspinal mechanism will rapidly override or 'shut down' the large-diameter afferent modulation of nociceptive transmission at the spinal level where the time course of such spinal changes is in the order of a few hundred milliseconds.

Indeed, descending controls may be inherently inefficient at totally overriding the relatively rapid fluctuations in nociceptive transmission occurring at the spinal level due to the time delay associated with descending transmission time. The descending transmission time would introduce a latency of effect that, even with fast conducting, myelinated, descending fibres would be in the order of 15 to 20 ms (e.g., Rivot et al., 1980). That is, such a control mechanism would permit a 'time window' that would allow some nociceptive transmission through to supraspinal levels, allowing perception of the change in nociceptive transmission.

CHAPTER 12

INVESTIGATION OF GATE CONTROL THEORY USING POTASSIUM IONTOPHORESIS

12.0 INVESTIGATION OF GATE CONTROL THEORY BY RAMPING OFF A POTASSIUM IONTOPHORETIC PAIN STIMULUS

The rapid modulatory changes to nociceptive transmission, resulting from the balance between large-diameter and small-diameter primary afferents at the spinal level, might be expected to be superimposed on top of any longer-lasting peripheral or CNS changes induced by a peripheral nociceptive stimulation. That is, the rapid-acting spinal modulatory changes due to the changes in relative activity of the large and small-diameter peripheral inputs - as proposed by the gate control theory of pain - may be measurable in terms of levels of perceived pain.

The ability to measure such changes would permit a quantitative investigation of one of the main tenets of gate control theory; that nociceptive transmission is a function of the balance between large-diameter non-nociceptive peripheral inputs and small-diameter nociceptive peripheral inputs. Indeed one of criticisms of gate control theory is that "the tenets of the theory are not so much incorrect as they are currently too general", and that there is a "lack of quantitative specifications concerning the proposed interactions" (D.D. Price, 1988, p.221).

Experiment Four attempts to quantitatively assess pain perception as a function of the relative activity of large and small afferent fibres. The different conduction velocities of large-diameter non-nociceptive fibres and small-diameter nociceptive fibres can be utilized to produce differential levels of activity in the two types of afferent fibre at the spinal level.

The thinly myelinated A-delta afferents have conduction velocities in humans of between 5 and 28 m/s (Adriaensen, Gybels, Handwerker, & Van Hees, 1983). For example, using

microneurographic techniques, mean A-delta conduction velocities in humans have been reported at 19.2 (SD = ± 7.2) (Adriaensen et al.). This is consistent with other human studies (Van Hees, 1976), and with animal studies that have typically found conduction velocities from 2 to 30 m/s for the A-delta group (e.g., Brown & Iggo, 1967; Perl, 1968).

Human C-fibres mainly have conduction velocities of between 0.5 and 2 m/s (Torebjörk 1974; Torebjörk & Hallin, 1974, 1976; Van Hees & Gybels 1972, 1981). Any velocity less than 2.5 m/s is considered to belong to the mammalian unmyelinated C-fibre group (Douglas & Ritchie, 1962; Gasser, 1950); or below 1.3 m/s according to Bessou and Perl (1969).

The myelinated A-beta afferents have neural conduction velocities predominantly around 50 m/s (Treede, Jahnke, & Bromm, 1984). Fields (1990) has reported the conduction velocities of A-beta fibres to be 33 to 75 m/s - with C polymodal afferents being 0.5 to 2 m/s, and A-delta afferents being 5 to 30 m/s. For the purposes of calculation in the present study typical average neural conduction velocities are taken to be 1 m/s for C-fibres, 15 m/s for A-delta fibres and 50 m/s for A-beta fibres.

A constant peripheral stimulus that activated both large-diameter and small-diameter peripheral afferent fibres would be perceived as painful, but, according to the gate control theory, there would be some reduction in the intensity of the pain due to the inhibitory action of the large fibre activity at the spinal level.

If the peripheral stimulus was then removed, that is, ramped off over a period of a few hundred milliseconds, then the large-diameter afferent (A-beta) activity at the spinal level would rapidly cease due to the relatively rapid transmission of neural impulses along those fast conducting fibres. However, activity in the small-diameter afferents (A-delta and especially C-fibres) at the spinal level would remain temporarily at the original levels due to their relatively slow neural conductance. Consequently, for a brief period of time, while the absolute level of nociceptive neural input at the spinal level would remain unchanged, the inhibitory action of the

large-diameter fast-conducting afferents would be absent. Gate control theory predicts that as the pain stimulus was being removed there would be a brief increase in nociceptive transmission at the spinal level. This effect would be consistent with the known rapid action of spinal nociceptive modulation. The increase in spinal nociceptive transmission may then be perceived as a transient increase in pain above that of the background level - that is, a pulse of pain would be detected. This pulse of pain would be followed by a decrease in pain, finally dropping away to no pain, as the nociceptive peripheral input eventually also dropped to zero at the spinal level.

Potassium iontophoresis was selected as the experimental pain stimulus as the results of our first three experiments indicated that it possessed a number of characteristics that made it a suitable pain stimulus for investigating the neural modulation of pain as proposed by gate control theory. First, the intensity of the potassium iontophoretic stimulus can be rapidly changed. Second, potassium iontophoresis produces stimulation of both large-diameter and small-diameter afferent fibres. Extracellular K^+ can depolarize A-beta, A-delta and C-fibres. This makes it possible to study the interaction between these different afferent fibres at the spinal level. In addition, there is relatively little session carry-over effects, making it suitable for the repeated administrations needed to detect the pain pulse. Finally, potassium iontophoresis produces relatively little inflammation, so the effects of peripheral neural stimulation can be investigated in the relative absence of these reactions. This probably contributes to the fact that, even after repeated trials of long duration, the stimuli can be ramped off quickly with no apparent after effects, such as lingering residual pain.

The effects of ramping off the potassium stimulus in terms of effective stimulation at the spinal level can be depicted in graphical form. Figure 10a shows the rate of applied K^+ 'seen' at the spinal level for large-diameter, fast, A-beta afferents and the smaller-diameter, slower, A-delta and C-fibre afferents, for a peripheral stimulation site on the subject's arm 60 cm from the spine. The ramp off of the applied stimulus starts at the 100 ms, and is ramped down to zero at a constant rate over 300 ms. Based on the nominated typical average conduction velocities of

50 m/s for A-beta fibres, 15 m/s for A-delta fibres and 1 m/s for C-fibres, the applied K^+ seen at the spinal level would start to fall at 112 ms in the A-beta fibres, at 140 ms in the A-delta fibres and not until 700 ms in the C-fibres. The applied K^+ seen at the spinal level would drop to zero by 412 ms, 440 ms and 1000 ms for the A-beta, A-delta and C-fibres, respectively.

During the time period from 112 ms to 700 ms the C-fibre activity at the spinal level would remain unchanged, while the fall-off in A-beta activity would, in accordance with gate control theory, allow increased nociceptive transmission at the spinal level. This increase in nociceptive spinal transmission should be associated with a concomitant pulse of pain, if it is not overridden by ascending or descending controls.

A further prediction of gate control theory would be that the greater the distance the peripheral stimulus was from the spine the greater the pulse of pain would be, because the temporal separation between a neural signal carried by the large-diameter fast-conducting afferents and the slower small-diameter afferents would increase with increased distance travelled. Figure 10b shows the rate of applied K^+ seen at the spinal level for large-diameter, fast, A-beta afferents and the smaller-diameter, slower, A-delta and C-fibre afferents, for a peripheral stimulation site on the subject's arm only 30 cm from the spine. The ramp off of the applied stimulus starts at the 100 ms, and is ramped down to zero at a constant rate over 300 ms, the same rate as for the applied stimulus site 60 cm from the spine.

In this case the applied K^+ seen at the spinal level would start to fall in half the time as for the 60 cm condition. That is, at 106 ms in the A-beta fibres, at 120 ms in the A-delta fibres and 400 ms in the C-fibres. The applied K^+ seen at the spinal level would drop to zero by 406 ms, 420 ms and 500 ms for the A-beta, A-delta and C-fibres, respectively. The differential levels of K^+ between the A-beta fibres and the C-fibres seen at the spinal level is much less in the 30 cm condition (Figure 10b) than the 60 cm condition (Figure 10a). Accordingly the increase in nociceptive spinal transmission, and concomitant transient pulse of pain, should be much less

in the 30 cm condition, compared to the 60 cm condition, for the same peripheral noxious stimulus being ramped off.

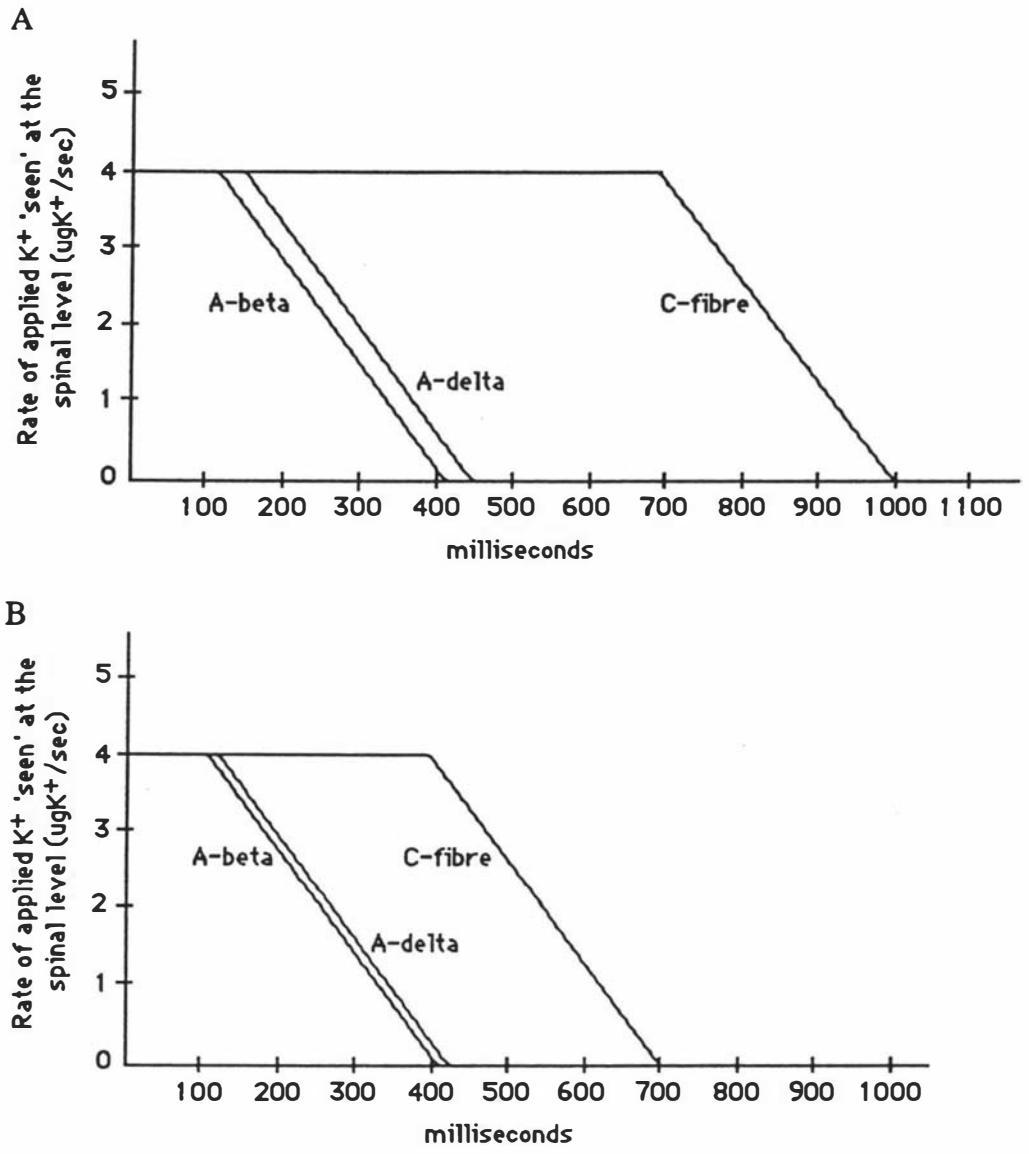


Figure 10. The rate of applied K^+ 'seen' at the spinal level for large-diameter, fast, A-beta afferents and the smaller-diameter, slower, A-delta and C-fibre afferents. For a peripheral stimulation site on the subject's arm 60 cm from the spine (A) and 30 cm from the spine (B). The K^+ stimulus is ramped to zero over 300 ms in both A and B. In the 60 cm condition there is greater differential for K^+ seen at the spinal level for the C-fibres compared to the A-beta fibres, and this differential extends over a longer period of time.

If increased nociceptive transmission is a function of an imbalance of C-fibre activity over A-beta activity then the model predicts that steeper ramp off rates may be required at stimulation sites closer to the spine in order to produce a pulse of pain. For instance, if the ramp off time of the applied K^+ stimulus at the 30 cm site is decreased from 300 ms (Figure 10b) to 100 ms (Figure 11) then the K^+ differential seen at the spinal level for the C-fibres compared to the A-beta fibres will substantially increase during the ramp-off phase. When the ramp-off time is shortened to 100 ms then for nearly 300 ms the K^+ seen at the spinal level for C-fibres remains unchanged while the K^+ seen at the spinal level for the A-beta fibres is at zero (Figure 11). This difference in the K^+ seen at the spinal level for the A-beta and C-fibres persists for over 250 ms. This contrasts with the condition where the ramp-off time is 300 ms (Figure 10b), in which this total contrast between the K^+ seen at the spinal level for the A-beta and C-fibres never develops.

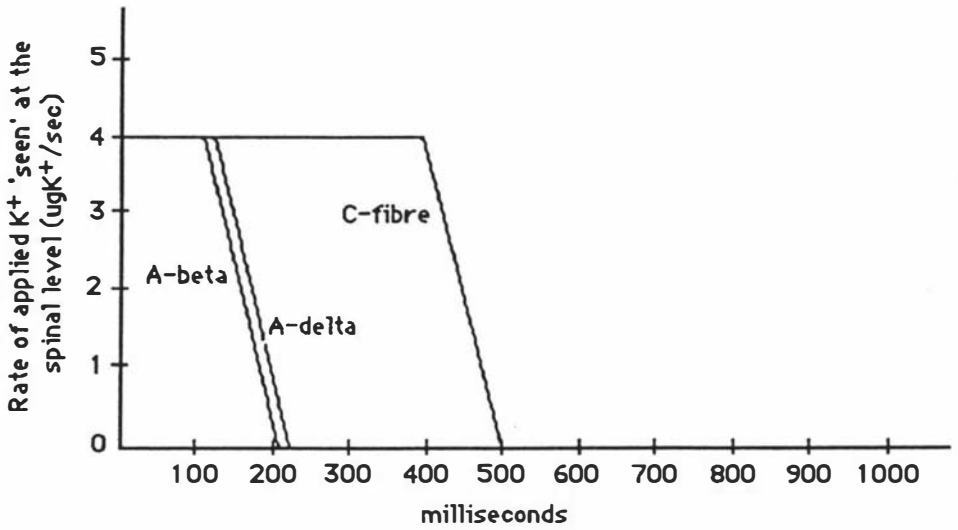


Figure 11. The rate of applied K^+ 'seen' at the spinal level for large-diameter, fast, A-beta afferents and the smaller-diameter, slower, A-delta and C-fibre afferents, for a peripheral stimulation site 30 cm from the spine. The K^+ stimulus is ramped to zero over 100 ms. The K^+ differential seen at the spinal level for the C-fibres compared to the A-beta fibres substantially increases during the ramp-off phase when the ramp-off time is reduced from 300 ms (Figure 10b) to 100 ms.

The subject's reaction times in responding to the perceived pain pulse could also be used as a measure of the nociceptive processes involved. That is, the difference in reaction times for the upper and lower arm sites could be used to determine the mode of peripheral transmission of the nociceptive information. The difference in reaction time between the two sites would be a function of the distance between the two arm stimulation sites and the velocity of peripheral neural conductance. Specifically, the reaction time difference could be calculated by dividing the distance between the two arm sites by the neural velocity. Based on an average distance between the two arm sites of 30 cm, and conduction velocities of 50 m/s for A-beta fibres, 15 m/s for A-delta fibres and 1 m/s for C-fibres then if the nociceptive message were carried by C-fibres the reaction time difference would be approximately 300 ms. If the nociceptive message were carried by A-delta fibres then the reaction time difference would be approximately 20 ms. If, however, the nociceptive message from the spine was due to a fall off in A-beta activity at the spinal level relative to A-delta and C-fibre input then the difference in reaction time would be only 6 ms. That is, if the ramp-off model prediction based on gate control theory is correct then the peripheral transmission time for the activation of the pain pulse would be faster than the fastest nociceptive signals carried by the A-delta afferents.

12.1 MATHEMATICAL SIMULATION MODEL OF RAMPING OFF A POTASSIUM IONTOPHORETIC PAIN STIMULUS

The activity of the dorsal horn T cells in response to large and small-diameter afferent inputs has been mathematically modelled (Britton & Skevington, 1989). Their simulation model considers the activity of a single T cell stimulated by one A-delta or C-fibre, one A-beta nerve fibre, and one inhibitory and one excitatory SG cell. This simplified model is believed to adequately describe the basic T cell processes (M.A.J. Chaplain, personal communication, September, 29, 1994).

On the basis of the ramp-off model of Humphries, Johnson and Long (1993) Britton, Skevington and Chaplain (1995) mathematically modelled T cell activity during the ramp-off phase of potassium iontophoresis pain stimulus, as proposed for Experiment Four. Their results for simulated T cell output in response to the ramping off of the pain stimulus, are in good agreement with the prediction that a pulse of pain should be generated (see Figure 12). As the simulation model shows, activity in the simulated T cell is observed to transiently increase before decreasing during the ramping-off phase of the peripheral pain stimulus. If this increase in T cell activity exceeded a critical level then an increase in pain should be perceptible.

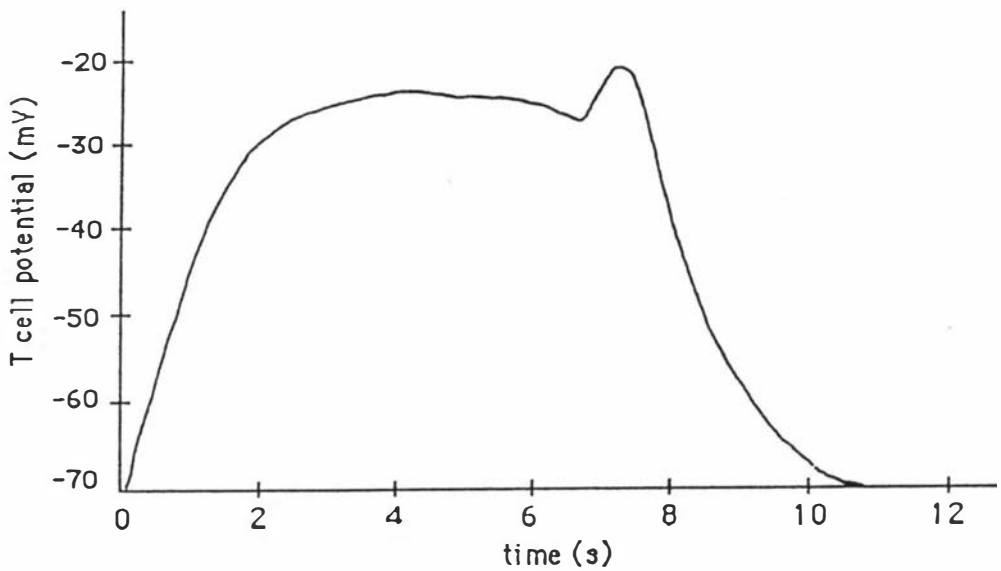


Figure 12. Mathematically modelled T cell activity in response to the simulated ramping off of a peripheral potassium iontophoretic pain stimulus. Adapted from M.A.J. Chaplain, personal communication, September, 29, 1994).

12.2 ASSUMPTIONS UNDERLYING THE RAMPING OFF OF POTASSIUM IONTOPHORETIC STIMULI

In order for the predictions of the ramping-off model to be valid a number of assumptions are made concerning the ramping off of the potassium iontophoretic pain stimulus.

First, it is assumed that the neural activity of the primary afferents tracks reasonably well the rate at which the K^+ stimulus is being applied. That is, that the levels of K^+ seen at the spinal level, as depicted in Figures 10 and 11 are, in fact, reasonable approximations of the neural activity in the respective afferent fibres. Experiments One, Two and Three have shown that, for the levels of applied K^+ used in the present experiment, there is a good linear relationship between the applied stimulus levels of K^+ and the resultant perceived pain. In addition, following removal of the applied stimulus, there is a rapid return to baseline levels of no perceived pain, even for pain tolerance trials (Douglas, 1994). This indicates that, even with relatively high extracellular levels of K^+, following removal of the stimulus there is a rapid clearance of the K^+. Given the powerful effects extracellular K^+ has on neural functioning it is not surprising that the body has efficient clearing mechanisms of extracellular K^+ around nerve cells, both by diffusion and also by active transport involving the sodium-potassium pump (Somjen, 1979).

In addition, it is not necessary that the relationship between the rate of applied stimulus and the resultant neural activity be a strictly linear one. Indeed, any monotonic stimulus-activity relationship, for both the large-diameter and small-diameter afferents, would be sufficient to produce the effects predicted by the ramp-off model.

Second, it is not necessary that the neural activity of the different diameter afferent fibres is the same before the ramping-off phase. The relative activity of each fibre type during the constant stimulus phase would not be critical, and the predictions of the model would be met provided that the A-beta and C-fibre afferents were both stimulated at least to a moderate degree. A-beta,

A-delta and C-fibres are all known to be activated by increases in extracellular K^+ (Guilbaud, 1988; Monnier, 1975; Uchida, & Murao, 1974).

Third, the rapid fall-off in A-delta activity, leading to lower nociceptive transmission associated with these fibres, might cancel the effects of increased nociceptive transmission during the ramp-off phase, when it is predicted that there is decreased A-beta inhibition of the C-fibres. The nociceptive stimulus should therefore preferentially stimulate C-fibres so that the pain experienced is predominantly C-fibre based. Iontophoretically applied K^+ would seem to be ideally suited to this requirement as unmyelinated C-fibres are especially sensitive to chemical stimulation, including K^+ depolarization (Guilbaud, 1988; Monnier, 1975), and this preferential C-fibre activation is consistent with the frequent report of burning pain with K^+ iontophoresis (Humphries et al., 1994; Ong et al., 1980; Voudouris et al., 1985). Cutaneous C-fibres nociceptors are also known to occur in greater density than cutaneous A-delta nociceptors and unmyelinated fibres outnumber myelinated fibres approximately 4 to 1 (Burgess & Perl, 1973; Iggo, 1974) which may add to preferential nociceptive transmission by C-fibres with the cutaneous stimulation of K^+ iontophoresis.

Finally, the time course of peripheral afferent activity at the spinal level, as depicted in Figures 10 and 11, is based on our nominated average neural conductance velocities for each class of fibre. Naturally each nerve fibre class has a range of conduction velocities, and to some extent these velocities can overlap (Fitzgerald & Lynn, 1977; Georgopoulos, 1976). Nevertheless, in order to estimate the *overall* effect of the relative velocities it is appropriate to use an average velocity, and specifically the arithmetic mean for data with a relatively normal distribution.

Similarly, there will be some temporal dispersion (Mendell, 1966) of the primary afferent input at the spinal level for each afferent class because of the range of velocities within each class. This is especially so for the slower conducting C-fibres from a stimulation site some distance from the spine. However, this does not negate the predictions of the ramp-off model as indicated by the first-order approximation provided in Figures 10 and 11. Indeed temporal

dispersion will be greatest for the slower conducting C-fibres where the slower transmission velocities for that class (< 1 m/s) will delay even further any change in neural activity seen at the spinal level as a result of any peripheral changes in neural stimulation. This would have the effect of increasing the production of a pain pulse predicted by the ramp-off model.

12.2.1 ASSUMPTIONS INVOLVING SUSTAINED NOCICEPTIVE NEURAL PROCESSES

Other changes in nociceptive neural processing also have to be considered before accepting the predictions of the ramp-off model. Peripheral nociceptive stimulation is capable of inducing a number of peripheral and CNS changes, which in turn influence subsequent nociceptive processing. That is, the perception of pain is not a simple moment to moment analysis but involves a dynamic process that integrates information over time.

Repeated stimulation of cutaneous nociceptors can lead to sensitization of those receptors (Bessou & Perl, 1969; Campbell & Meyer, 1983; Croze, Duclaux, & Kenshalo, 1976: Koltzenburg, Kress, & Reeh, 1992; Kumazawa & Perl, 1977; Lamotte et al., 1983: Meyer & Campbell, 1981). Significant after-discharge has been observed in C-fibre nociceptors, where neural activity can continue after the cessation of the applied stimulus for seconds to many minutes (Beital & Dubner, 1976a; Iggo, 1960; Torebjörk & Hallin, 1974).

In addition to the sensitization and after-discharge in peripheral receptors, nociceptive stimuli are capable of inducing a number of other relatively sustained changes in the CNS (LaMotte, Lundeberg, & Torebjörk, 1992; Thalhammer & LaMotte, 1982; Woolf, 1983). Perl, Kumazawa, Lynn, and Kenins (1976) and Kenshalo, Leonard, Chung, and Willis (1979a, 1979b) were the first to show that noxious peripheral stimuli can change the sensitivity of dorsal horn neurons to further noxious stimuli. For example, there is a sensitization of nociceptive spinal cord dorsal horn neurons following stimulation of C-fibres (Chung, Kenshalo, Jr., Gerhart, & Willis, 1979) with repeated thermal heating (Kenshalo et al, 1979a; D.D. Price et al., 1978), or with the application of chemicals (Dougherty & Willis, 1992). A

more substantial contributor to after sensations than peripheral nociceptor after-discharge may be nociceptive nonspecific neuron (WDR neuron) activation by C-fibres. This can produce a central long-lasting neural after-discharge (Mendell, 1966; D.D. Price et al., 1978; Zimmermann, 1979).

A "wind-up" (Mendell, 1966, p. 319) in which the responses of nociceptive nonspecific neurons increases with repeated stimulation of C-fibres has been observed (Davies & Lodge, 1987; Gerber & Randic, 1989; Thompson & Woolf, 1991; Villanueva, Bing, Bouhassira, & Le Bars, 1989; Wagman & Price, 1969; Wall & Woolf, 1984), and this is consistent with the increase in pain sensation with repetitive stimulation (Collins, Nulsen, & Randt, 1960). The effect is believed to be due to a slow temporal summation in WDR neurons that can occur with stimulus repetition rates greater than 3 Hz (Handwerker et al, 1975; D.D. Price, 1972; D.D. Price et al., 1977; D.D. Price et al., 1978).

Finally, there can be an expansion of receptive fields of dorsal horns (McMahon & Wall, 1984; Woolf & King, 1990) following repeated mechanical (Cervero, Handwerker, & Laird, 1988), chemical and electrical nerve stimulation (Cook, Woolf, Wall, & McMahon, 1987).

None of these effects that occur slowly over an extended period of time would negate the predictions of the ramp-off model; that short-term changes in large and small-diameter peripheral input can modulate nociceptive transmission. It would be assumed that the rapid-acting ramp-off effects would be superimposed on top of any sustained changes in nociceptive processing that might also be present.

As wind-up is associated with relatively short ISIs of less than three seconds it would not be expected to occur in Experiment Four where the ISI is longer. Indeed, any after-discharge or wind-up associated with C-fibre activity would only serve to increase the differential between A-beta and C-fibre activity during the ramp-off phase of the peripheral stimulus, thereby

potentially increasing the intensity of the predicted impulse of pain following the decrease in A-beta input.

In Experiment Three, with moderate intensity stimuli of a level similar to that used in Experiment Four, a session effect indicating some relatively long-term changes on nociceptive processing was found. However, there was only a 3.2% increase in responding to the iontophoretic stimulus across a session, a statistically significant though relatively small change in responding.

CHAPTER 13

EXPERIMENT FOUR
INVESTIGATION OF THE GATE CONTROL THEORY OF PAIN

13.0 INTRODUCTION: INVESTIGATION OF THE GATE CONTROL THEORY OF PAIN

The objective of Experiment Four was to establish a constant peripheral pain stimulus using iontophoretic administration of potassium and then ramp that stimulus off to see if a pain pulse could be produced during the ramp-off phase. In accordance with the gate control theory of pain it was predicted that a peripheral stimulus site closer to the spine would require a greater ramp-off rate in order to produce a detectable pain pulse. In addition, if the pain pulse was a result of the drop off in A-beta activity at the spinal level then the difference in reaction time for two stimulation sites that are at a different distance from the spine should be dependent on the neural conduction velocity of the fast-conducting non-nociceptive A-beta afferents.

13.1 METHOD

Subjects

The subjects were 14 volunteer students, with ages ranging from 20 to 30 years. Prior to participation all subjects completed a consent form that outlined the general nature of the experiment. Subjects also completed a health check-list to determine if any contra-indicating medical conditions were present. Subjects were paid $15 per session and were free to terminate participation at any stage of the study.

Apparatus

The computer-controlled constant-current iontophoretic pain generator and the electrodes that were attached to the subject's arm were those described for the first three experiments. However, two sets of electrodes were used in the present experiment.

Procedure

A standard protocol was adhered to for all sessions. Subjects were seated at a table with a dual set of stimulus electrodes attached to the dominant arm. The lower potassium anode provided a pain stimulus to the volar surface of the arm approximately eight centimetres from the wrist. The upper potassium anode was placed on the subject's bicep. For each anode a cathode was placed on the opposing surface of the arm. The electrode set-up on the lower arm site was the same used in the first three experiments. The subject's arm rested on a cushioned support throughout the experiment. A cut-off switch was positioned by the subject's nondominant hand, with which they could terminate any of the stimulus administrations immediately. The cut-off switch was not used during the experiment.

The stimulus trials in a session alternated between the upper and lower anode sites with an inter-stimulus interval (ISI) of 10 seconds for each stimulus presentation. That is, each stimulus site had an ISI of 20 seconds. A trial consisted of a warning beep on the computer followed by a one-second ramp up to a preselected pain intensity level that was maintained for four seconds. The preselected stimulus levels were adjusted for each subject prior to the main session so that the perceived pain levels for the upper and lower stimulus sites were the same, and were reported by the subject to be mildly to moderately painful. The pain was most often reported as a combination of a pricking-stinging sensation with some burning.

Subjects were told that at the end of the 4-second period of constant pain the pain would be either ramped off smoothly or that there would be a brief pulse of additional pain stimuli before ramping off. In fact, only the rate at which the stimulus was ramped off was varied. No pulse of additional pain stimulus was given on any trial. The subjects were asked to indicate if any

pain pulse was detected by immediately removing their nondominant hand from a microswitch positioned on the table in front of them. The threshold-detection reaction times were from the onset of the stimulus ramp-off until the microswitch was released. Timing was accurate to within 4 ms, and all reaction times were automatically recorded by computer.

For both the upper and lower stimulus sites the double random staircase method was used to adjust the rate of stimulus ramp-off to determine the threshold of detection of the pain pulse. For each subject the initial ramp-off rate was selected so that over a session there would be some convergence of the 'upper rate' and 'lower rate' staircases at each arm site if a pain pulse were detected. Typically the 'faster' ramp was set at 200 ms and the 'slower' ramp at 500 ms. The initial ramp-off rates were determined for each subject on the basis of their performance during a familiarisation session.

The changes in the rate of ramp-off were under computer control, with the rate-of-change step being doubled if there was not a reversal of subject response within three successive trials. If there was a reversal in responding after only one trial then the rate-of-change step was halved. At each arm-site the initial step was set at 100 ms for the staircase with the faster ramp time and 200 ms for the staircase with the slower ramp time. The minimum rate-of-change step possible was 10 ms, the maximum 300 ms. Rate of ramp-off limits were set at a minimum of 80 ms and a maximum of 2000 ms. These limits were not reached during the experiment. On each trial at the given arm-site one of the two concurrent staircases were selected at random. The session ended when 30 trials had been completed on all four staircases. The nominal limit of 30 trials per staircase (60 trials per arm site) was set in order to minimize the possibility of pain stimulus carry-over effects influencing subject responding. The 30-trail limit allowed sufficient response reversals to obtain stable threshold measures.

Prior to the collection of data in the main session practice trials were provided in order to refamiliarise the subjects with the task and to lower and stabilize electrode resistance. For most subjects resistance was 5 kΩ or less prior to the start of data recording.

At the end of the experiment all subjects were debriefed as to the purpose of the experiment, and the need for the deception of having them believe that they were being given pain pulses was explained.

13.2 RESULTS AND DISCUSSION: TIME OF RAMP OFF OF NOCICEPTIVE STIMULUS

One subject failed to obtain convergence on the staircase procedure. As this indicates that the subject was using an irrelevant decision making strategy (Cornsweet, 1962), this subject was dropped from any further analysis.

The remaining subjects ($\underline{N}$ = 13) were all able to clearly detect a pain increase during the ramp-off phase - provided the ramp-off rate was sufficiently fast. This pulse of pain is consistent with the neural modulation processes that are postulated to occur at the spinal level according to gate control theory (Melzack & Wall, 1965; Wall, 1988). That is, the transient pulse of pain is consistent with a segmental spinal interaction between nociceptive and non-nociceptive inputs resulting in a decreased inhibition of nociceptive transmission as A-beta activity decreased at the spinal level while C-fibre input transiently remained unchanged. This postulated effect would be superimposed on whatever other peripheral, spinal and supraspinal changes in nociceptive sensitivity may also be occurring over longer periods of time.

For each subject the double random staircases converged rapidly and gave highly consistent data by the last four subject response reversals on each random staircase. Figures 13 and 14 illustrate the difference in detectability of the pain pulse at the upper and lower stimulus sites obtained by the double random staircase method. Rate of ramp-off of K^+ delivery is plotted against the 30 trials used for each staircase. Figure 13 shows the individual results of two subjects. Figure 14 shows the group average for all 13 subjects.

The results in Figures 13 and 14 are consistent with the predictions of gate control theory; that the production of a pain pulse is a function of distance of the stimulus from the spine. That is,

that a peripheral nociceptive stimulus site closer to the spine would require a greater ramp-off rate in order to produce a detectable pain pulse.

To further analyse the staircase data the last four response reversals on each staircase were used. For the double random staircase method used this gave eight data points for each electrode site for each subject. All following data analysis for Experiment Four is based on this data.

It was first determined how consistent subject responding was on the two staircases of each double random staircase by comparing the average ramp-off times of each staircase. This comparison provides a quantitative measure of subject response consistency at each arm site, and whether a sufficient number of trials were run in order to allow the staircases to converge sufficiently. Averaged across all subjects, the difference between the mean value of the two staircases of each double staircase was 22.6 ms. Viewing the two staircases in a double staircase as a replication of the same condition (Cornsweet, 1965) this small difference indicates that sufficient trials were run in order to obtain a consistent measure.

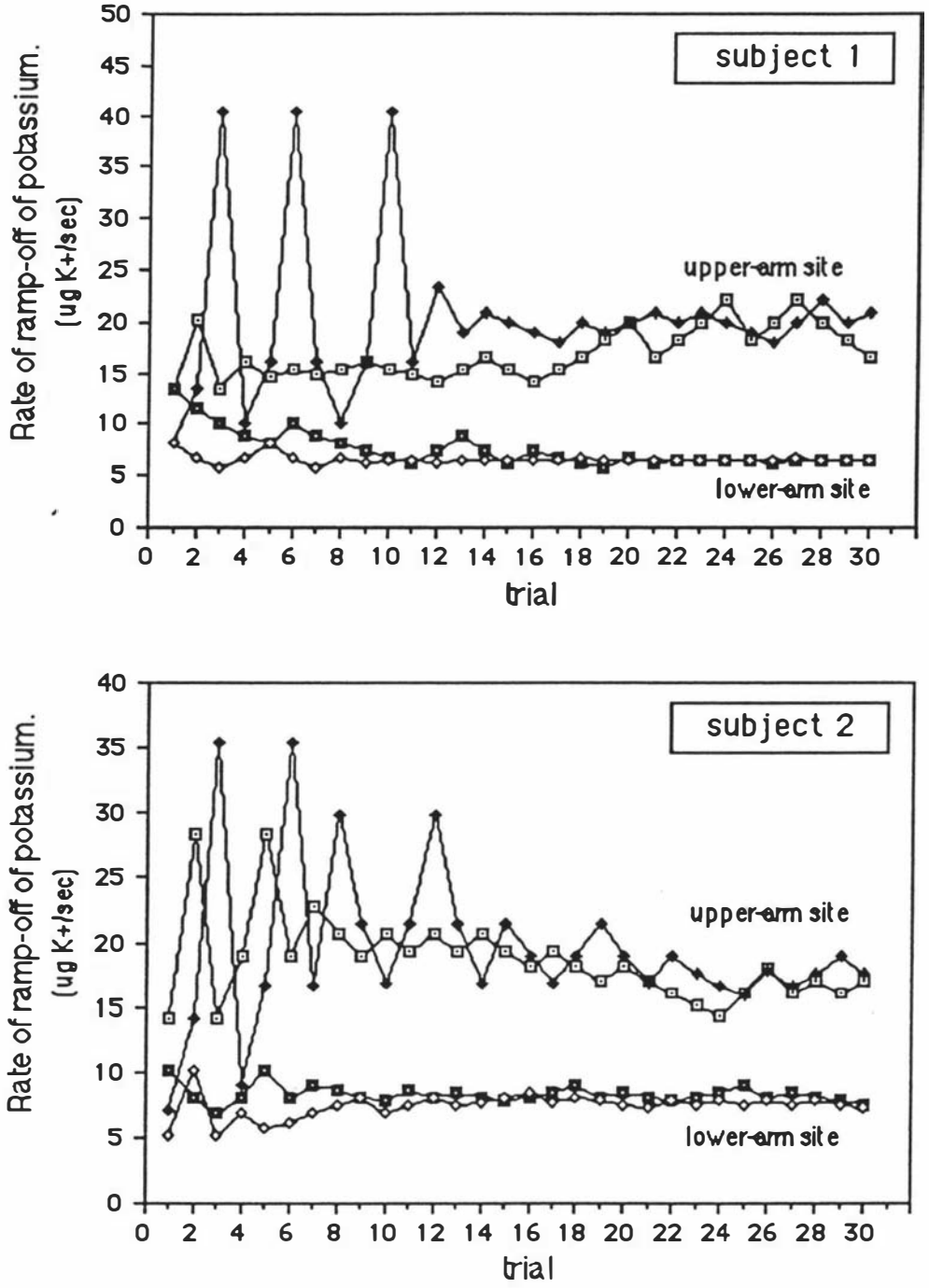


Figure 13. Threshold detection of the pain pulse during the ramping off of the iontophoretic potassium peripheral pain stimulus. The double random staircase method was used at both the upper and lower arm sites. The rate of ramp-off of the applied K^+ is plotted against the 30 trials for each staircase. The individual results are for Subject One and Subject Two.

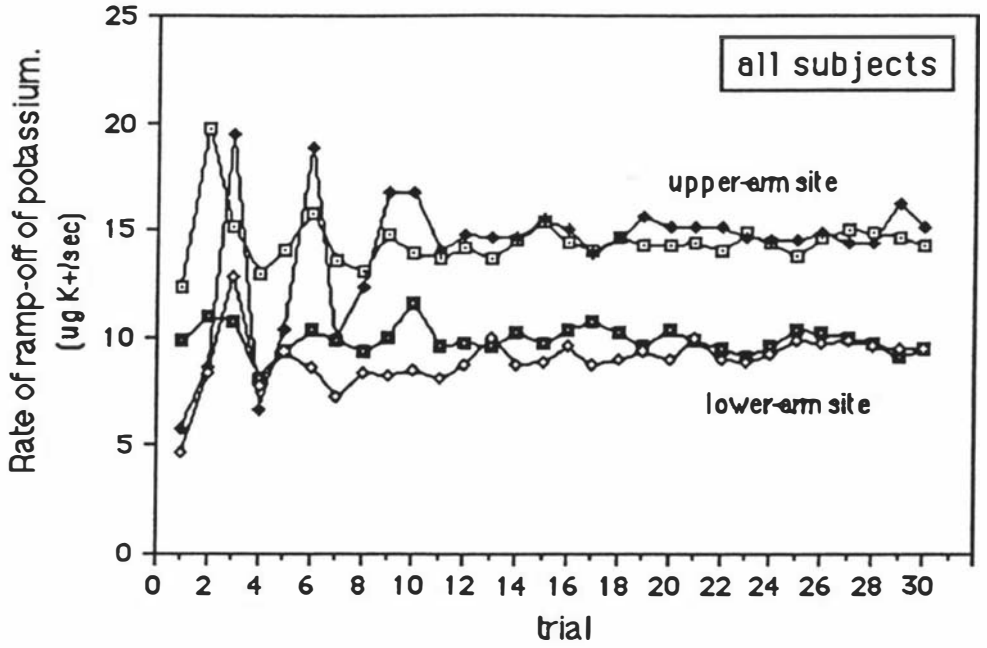


Figure 14. Threshold detection of the pain pulse during the ramping off of the iontophoretic potassium peripheral pain stimulus. The double random staircase method was used at both the upper and lower arm sites. The rate of ramp-off of the applied potassium is plotted against the 30 trials for each staircase. Each data point is the mean value of all subjects (N= 13).

As Figures 13 and 14 show the potassium iontophoretic nociceptive stimulus was able to provide stable subject responding over repeated trials with no drift once the threshold values had been located by the double random staircase method.

The ramp-off time difference, between the reversal point where subjects could not detect a pain pulse and the reversal point where a pain pulse could be detected, averaged over all the individual staircases, was 37.7 ms. That is, averaged over all subjects, this change in ramp-off time was sufficient to differentiate the presence or absence of a perceived pain pulse. This small change in ramp time required to locate the pain pulse establishes that the double random staircase method was able to give an accurate measure of pain-pulse threshold. The small

change in ramp time also eliminates the possibility that subjects could have used length of ramp-off time as a response cue. In addition, by self-report at the end of the experiment all subjects reported that they were indeed attending to the pain pulse as the cue to base their reactions on.

The mean rate of stimulus ramp-off in order to detect a pain pulse was significantly greater for the upper-arm site [14.3 $\mu gK^+/s$, (35.3 mA/s)] than for the lower-arm site [9.4 $\mu gK^+/s$, (23.2 mA/s)], t (12) = 3.75, $p < .01$] (see Table 8).

Table 8. Applied stimulus level and the ramp-off rate for the upper and lower arm sites to produce threshold detection of a pain pulse. Experiment Four.

subject	upper stimulus level $\mu gK^+/s$	lower stimulus level $\mu gK^+/s$	upper ramp rate $\mu gK^+/s$	lower ramp rate $\mu gK^+/s$
1	4.1	4.1	18.8	6.5
2	2.8	2.0	17.3	7.9
3	2.4	1.2	15.3	13.4
4	2.0	1.2	10.8	10.6
5	2.0	2.0	14.5	8.4
6	1.6	1.2	7.0	4.8
7	2.4	2.4	10.0	5.4
8	2.8	1.6	23.2	13.2
9	2.4	2.0	9.2	5.1
10	3.2	2.0	18.0	19.1
11	2.4	1.6	11.9	8.9
12	2.8	3.2	21.8	9.8
13	2.0	2.0	8.2	9.2
average	2.6	2.1	14.3	9.4

A 52% greater rate of ramp-off of delivered potassium had to be employed at the upper-arm site, relative to the lower-arm site, in order to produce a perceptible pain pulse. The difference in ramp-off rate corresponded to an average ramp-off time of 192 and 261 ms for the upper and lower arm sites, respectively.

Averaged over all subjects, the upper-arm site required significantly higher stimulus intensities than the lower-arm site, t (12) = 3.25, $p < .01$, in order to establish similar constant perceived pain levels before the ramping off of the stimulus; with 2.6 $\mu gK^+/s$ (6.3 mA/s) to the upper arm and 2.1 $\mu gK^+/s$ (5.1 mA/s) to the lower arm. The different overall level of initial stimulation at the two arm sites was a possible confound that may have produced the different ramp-off rates required to produce a pain pulse at the different arm sites.

However, for five subjects (subjects 1, 5, 7, 12 & 13), the same intensity stimuli were delivered to both sites, or the greater intensity stimulus was delivered to the lower site. For these five subjects the average rate of stimulus ramp-off in order to detect a pain pulse remained significantly greater for the upper-arm site [14.7 $\mu gK^+/s$ (36.2 mA/s)], than for the lower-arm site [7.9 $\mu gK^+/s$ (19.4 mA/s)], t (4) = 2.73, $p < .05$.

For the remaining 8 subjects, who had a greater initial stimulus level at the upper-arm site, their average rate of stimulus ramp-off in order to detect a pain pulse was also significantly greater for the upper-arm site [14.1 $\mu gK^+/s$ (34.8 mA/s)], than for the lower-arm site [10.4 $\mu gK^+/s$ (25.6 mA/s)], t (7) = 2.61, $p < .05$. That is, for both sub-groups of subjects, a significantly greater rate of ramp-off of delivered potassium was required at the upper-arm site in order to produce a perceptible pain pulse. Therefore the different levels of initial stimulation at the two arm sites does not provide an explanation for the different ramp-off rates required to produce the perceived pain pulse.

In addition, the higher stimulus levels at the upper site would have exposed subjects to a longer ramp-off time for any given rate of ramp-off. This might be expected to give subjects a better

opportunity to detect a pain pulse at the upper site, in direct contrast to the prediction of gate control theory; that the pain pulse should be more detectable at the lower arm site.

13.3 RESULTS AND DISCUSSION: REACTION TIMES TO THE NOCICEPTIVE STIMULUS

The subject's reaction times in responding to the perceived pain pulse were used to determine the mode of peripheral transmission; the reaction times being a function of the velocity of peripheral neural conductance.

The subject reaction times were based on reactions to the pain pulse over the trials covering the last 4 response reversals on the double random staircases. Reaction time distributions for all subjects had a small but consistent positive skew. Averaged over all subjects, the mean skew was 0.64, with a standard deviation of 0.06. Because the reaction time distributions were positively skewed medians were used as the measure of central tendency for all subject reaction times.

Table 9 shows the median reaction times for all subjects for the lower and upper arm sites. Averaged over all subjects, the reaction time for the upper-arm site was 550 ms and 610 ms for the lower-arm site. That is, reaction times were 60 ms faster than the lower arm site.

The average distance from the lower-arm site to the spine was 63.4 cm (SD = 4.4). For the upper-arm site the average distance was 33.6 cm (SD = 1.6). The average difference in distance between the two arm sites was 29.8 cm. On the basis of the difference in reaction times for the two arm sites and the difference in distance between the two sites it is possible to estimate the peripheral neural conduction velocity that initiated the subjects responding to the pain pulse with the formula:

$$\text{peripheral neural velocity} = \frac{\text{distance between the two arm sites}}{\text{difference in reaction time for the two arm sites}}$$

A number of factors need to be considered in this calculation. Central processing time is generally measured to be between 130 and 190 ms for nociceptive input (Campbell & LaMotte, 1983; Carmon, Dotan, & Sarne, 1978; Carmon, Mor, & Goldberg, 1976; D.D. Price et al., 1977). The peripheral efferent conduction time in order to initiate a motor response can be estimated to be in the order of 20 ms - based on an efferent conduction velocity of 50 m/s over a distance of approximately one metre (Yarnitsky & Ochoa, 1990). As the difference in reaction times between the two arm sites is found by subtracting the reaction time for one arm site from the reaction time for the other site, and as central processing time and efferent conduction time are both assumed to be the same for the two arm sites in the present study, then both central processing time and efferent conduction time cancel out and are removed from the calculation of peripheral conduction velocity.

The direct depolarizing action of K^+ is likely to by-pass the nociceptor utilization time (Campbell & LaMotte, 1983) associated with natural noxious stimuli. In any case, receptor utilization time is also assumed to be similar at both arm stimulation sites, and, as with central processing time and efferent conduction time, is removed from the calculation when determining the difference between reaction times at both sites.

For each subject the neural conduction velocity was calculated by dividing the difference in distance between the two arm sites for that subject by the difference in reaction time between the two sites for that subject. The resultant neural conduction velocity, averaged over all subjects, was 5.1 m/s (see Table 9). This afferent conduction velocity is considered to be the lower limit for A-delta peripheral afferents (Adriaensen et al., 1983; Van Hees, 1976).

However, the overall difference between the reaction times for the lower and upper arm sites was not statistically significant, t (12) = 1.38, $p > .05$. Therefore, the obtained reaction time difference can not be confidently ascribed to the difference in arm distance from the stimulation sites to the spine. Indeed, for five of the subjects reaction times were faster for the lower arm site. Clearly then, other factors were influencing subject reaction times apart from the 'arm

distance' variable. Nevertheless, the obtained reaction times can be used to exclude the possibility that the peripheral afferent signal was due to C-fibre activity, where reaction time latencies are typically in the order of one second (e.g., Bromm, 1984; Campbell & LaMotte, 1983). However, the obtained reaction times do not clarify whether they are the result of an A-delta mediated 'first pain' response (Campbell & LaMotte, 1983; D.D. Price et al., 1977) or are due to an A-beta spinal modulation effect as proposed by our ramp-off model and consistent with the predictions of gate control theory.

Table 9 Median reaction times to the perceived pain pulse Experiment Four.

subject	lower arm-site reaction time (ms)	upper arm-site reaction time (ms)	difference (ms)
1	957	458	499
2	459	546	-87
3	662	630	32
4	416	474	-58
5	591	571	20
6	665	662	3
7	829	652	177
8	518	493	25
9	474	479	-5
10	445	475	-30
11	668	585	83
12	636	451	185
13	608	672	-64
average	610	550	60

One possible confound was that for some subjects different stimulus intensity levels in terms of applied K^+ were used at each arm site. However, even for those subjects that had the same levels of applied K^+ at each arm site there was no clear pattern with the reaction times, with one of those subjects (#13) still having a faster reaction time at the lower arm site.

Variability in response times is typically high for near-threshold stimuli (Babkoff, Bergman, & Brandeis, 1974). In addition, the random double staircase method introduces fluctuations around the threshold value for the pain-pulse nociceptive stimulus. Given the large changes in response time as a function of nociceptive stimulus intensity, especially near threshold (Campbell & LaMotte, 1983; Hull, 1949; Sticht & Foulke, 1966a, 1966b), this could introduce further response-time variability. Indeed, there was a relatively large amount of response-time variability in the present experiment, with a mean reaction time of 573 ms and an average standard deviation, across subjects and arm-sites, of 132 ms.

The limited number of trials employed to determine reaction time in the present experiment, combined with the relatively large unsystematic reaction time variance, could make any measure of central tendency, including the median measure used, unreliable. These effects could have contributed to the statistically nonsignificant result obtained for the difference between the reaction times for the lower and upper arm sites.

Other mechanisms, apart from a decrease in A-beta activity at the spinal level, could possibly account for a perceived pain pulse during the ramp-off phase. When a steady current applied to a nerve is suddenly withdrawn an action potential can be generated in the nerve. This anode break excitation (Douglas & Ritchie, 1962; Mendell & Wall, 1964, 1965; Van Den Honert & Mortimer, 1981) can be avoided by ramping the electrical stimulus off over a period of time, rather than creating a sudden break.

Studies that have investigated anodal block using similar applied currents levels as the present study, albeit with direct nerve stimulation and much shorter constant current times in the order of milliseconds, have avoided anode break excitation by using decay constants of from 1 to 30 ms (Accornero, Bini, Lenzi, & Manfredi, 1976; Burke & Ginsborg, 1956; Van Den Honert & Mortimer, 1981). In the context of the present study this is equivalent, in terms of overall rate of ramp-off, to stimulus ramp-off times of approximately 3 to 60 ms. In the present study a median ramp-off time of 261 ms at the lower-arm site was still able to produce a perceptible

pain pulse. This suggests that the pain pulse was not a result of anode break excitation. However, while the ramp-off time was longer in the present study than in most studies that have reported anodal break excitation effects the present experiment was based on threshold detection, which would be maximally sensitive to detecting the effect.

An additional basis for an anodal block effect may exist in the present study. While the potassium ions lead to depolarization of the nerve fibres any possible accompanying anodal hyperpolarizing action of the potassium anode may have tended to counter that effect (Ranck, 1980, 1981). This anode block preferentially blocks the larger diameter myelinated A-fibres before the thinner unmyelinated C-fibres (Mendell & Wall, 1964). The blocking effect at the anode might partially account for the change in pain reports from a pricking sensation at low current settings, when all fibres are conducting, through to a burning sensation at higher current levels, when many of the A-fibres are blocked and nociceptive peripheral transmission is preferentially mediated by the C-fibres.

With the removal of the applied electrical stimulus the anodal blocking action would disappear, possibly leading to a spontaneous excitation upon the stimulus removal. In addition, the accumulated potassium could take a brief time to diffuse away so that it could now exert its full depolarizing effects in the absence of the anodal block. These neural mechanisms might account for any pulse of pain felt during the stimulus ramp-off period. However, anodal block effects, or other peripheral stimulus mechanisms such as anode break excitation, do not account for why a stimulus site closer to the spine would require a much greater ramp-off rate in order to produce a detectable pain pulse. Most importantly, it can not be discounted that the perceived pain pulses may have been a function of all three effects; anode break excitation, anodal hyperpolarization (with or without the additive effects of K^+ accumulation), and the imbalance of peripheral afferent input as predicted by gate control theory.

In order to help establish that the pain pulse was a function of the applied extracellular K^+, and not just the result of withdrawing the applied electrical current, Experiment Five was run with a Na^+ control to compare the effects of Na^+ with the known nociceptive effects of K^+.

CHAPTER 14

EXPERIMENT FIVE: INVESTIGATION OF GATE CONTROL THEORY WITH A SODIUM CONTROL

14.0 INTRODUCTION: INVESTIGATION OF GATE CONTROL THEORY WITH A SODIUM CONTROL

Experiment Five compared the pain generated by the ramping off of the K^+ stimulus with the ramping off of a Na^+ stimulus in order to determine if the generated pain pulse was a direct function of the nociceptive action of K^+. As in Experiment Three, the sodium ion was selected for the control condition as sodium chloride based saline solutions or gels are the most commonly used electrolytes in studies that employ electrical shock as the nociceptive stimulus. Given that extracellular Na^+ does not have the depolarizing capacity of extracellular K^+ the Na^+ condition can be equated with the effects attributable to that of an applied electric current. It was predicted that if the pain pulse was a function of the specific depolarizing action of K^+ then, at any given stimulus site, faster ramp-off times would be required with the Na^+ condition to produce a pain pulse. In the Na+ condition it was predicted that a pain pulse would eventually result at faster ramp-off rates from anode break excitation.

14.1 METHOD

Subjects

The subjects were eight volunteer students who had not participated in the earlier experiments, with ages ranging from 20 to 32 years. Prior to participation all subjects completed a consent form that outlined the general nature of the experiment. Subjects also completed a health check-list to determine if any contraindicating medical conditions were present. Subjects were paid $15 per session and were free to terminate participation at any stage of the study.

Apparatus

The only change from the apparatus described in the general section was that the 3% w/v potassium chloride anode gel was replaced with a 3% w/v sodium chloride anode gel for the Na^+ condition.

Procedure

A standard protocol was adhered to for all sessions. Subjects were seated at a table with a single set of stimulus electrodes attached to the dominant arm approximately eight centimetres from the wrist. This was the same stimulation site used in Experiments One, Two and Three, and the lower stimulation site used in Experiment Four. The subject's arm rested on a cushioned support throughout the experiment. A cut-off switch was positioned by the subject's non-dominant hand, with which they could terminate any of the stimulus administrations immediately. The cut-off switch was not used during the experiment.

The stimulus trials in a session had an ISI of 20 seconds. A trial consisted of a warning beep on the computer followed by a one-second ramp up to a preselected pain intensity level that was maintained for four seconds. The preselected stimulus levels were adjusted for each subject during a familiarisation session so that the pain level for the K^+ condition were reported by the subjects to be mildly to moderately painful. The pain was most often reported as a combination of a pricking-stinging sensation with some burning. For each subject the same stimulus intensity level, in terms of applied current, was used for the Na^+ condition as was used for the K^+ condition. The familiarisation session also gave the subjects an opportunity to learn the nature of the task, and to reduce possible high levels of anxiety associated with an unknown pain stimulus.

As in Experiment Four the subjects were told that at the end of the 4-second period of constant pain the pain would be either ramped off smoothly or that there would be a brief pulse of additional pain stimuli before the ramp-off phase. In fact, only the rate at which the stimulus was ramped off was varied; no pulse of additional pain stimulus was given on any trial. The

subjects were asked to indicate if any pain pulse was detected by immediately removing their nondominant hand from a microswitch positioned on the table in front of them. And, as in Experiment Four, the threshold detection reaction times were from the onset of the stimulus ramp-off until the microswitch was released, the timing was accurate to within 4 ms, all reaction times were automatically recorded by computer, and the double random staircase method was used to adjust the rate of stimulus ramp-off to determine the threshold of detection of the pain pulse.

The parameters for setting up and controlling the double random staircase were the same as in Experiment Four. For each subject the initial ramp-off rate was selected so that over a session there would be some convergence of the 'upper rate' and 'lower rate' staircases at each arm site if a pain pulse were detected. On each trial one of the two concurrent staircases was selected at random. The session ended when 30 trials had been completed on both staircases. The nominal limit of 30 trials per staircase (60 trials total at the arm site) was set in order to minimize the possibility of pain stimulus carry-over effects influencing subject responding. The 30-trail limit per staircase allowed sufficient response reversals to obtain stable threshold measures.

Prior to the collection of data in the main session some practice trials were provided in order to refamiliarise the subjects with the task and to lower and stabilize electrode resistance. For most subjects resistance was 5 kΩ or less prior to the start of data recording.

There were two main daily sessions, with subjects receiving either the K^+ *or* the Na+ condition on any given day. The K^+ and Na^+ conditions were presented in counterbalanced order across the eight subjects.

14.2 RESULTS AND DISCUSSION

The prediction that a faster ramp-off time would be required with the Na^+ condition compared to the K^+ condition to produce a perceptible pain pulse was supported. As Table 10 shows, with the exception of one subject, a faster ramp-off rate was required to produce the pain pulse. For many subjects the increase in ramp rate required in the Na^+ condition was substantial.

Table 10. Ramp rate required to produce a perceptible pain pulse for K^+ and Na^+ stimulation. Experiment Five.

Subject	K^+ (μg/s)	Na^+ (μg/s)
1	6.5	13.5
2	13.4	11.0
3	7.6	21.4
4	3.5	19.0
5	7.0	9.4
6	10.1	39.1
7	7.7	12.9
8	4.0	6.1
average	7.5	16.5

The rate of stimulus ramp-off required to produce a pain pulse was significantly less when using K^+ as the electrolyte (7.5 μg K^+/s), than when using Na^+ (16.5 μg Na^+/s), t (7) = 2.55, $p < .05$. This is an overall 54% decrease in the rate of stimulus ramp-off when using K^+ as the nociceptive stimulus.

This result confirms that it is the direct nociceptive action of K^+ that is responsible for the pain pulse reported by most subjects during the ramping off of the iontophoretically applied K^+ stimulus. Potassium ions are known to have a general depolarizing and hence activating effect

on all peripheral afferent fibres. Consequently the finding that it is indeed the K^+ that is responsible for the pain perceived during the ramp off of the K^+ nociceptive stimulus is consistent with the ramp-off model and the prediction of gate control theory that the relative changes in afferent activity could lead to a pain pulse during the ramping off of an applied peripheral nociceptive stimulus.

Nevertheless, other interpretations need to be considered. It is possible that the iontophoretically delivered extracellular K^+ simply depolarizes the nociceptive afferents and makes them more susceptible to other nociceptive mechanisms - such as anode break excitation. Hence the pain pulse felt during relatively slow ramp-off rates, when anode break excitation would not normally be expected, may be anode break excitation occurring in K^+ sensitized nociceptors

For one subject the ramp-off rate required to produce a pain pulse was actually less in the Na+ condition. This may be a confound introduced by testing the K^+ and Na^+ conditions across days, or it may reflect a genuine individual difference. For instance, in Experiment Three, with a constant nociceptive stimulation, not all subjects found K^+ to be significantly more pain inducing than Na^+.

CHAPTER 15

GENERAL DISCUSION: EXPERIMENTS FOUR & FIVE

15.0 GENERAL DISCUSSION OF EXPERIMENT FOUR AND FIVE

The pulse of pain generated at both arm sites was consistent with the predictions of the gate control theory of pain. That a greater ramp rate was required at the arm site closer to the spine was also consistent with gate control theory. However, the results for peripheral neural conduction velocity that generated the pain-pulse reactions were inconclusive. Due to the large individual variation in reaction times for both arm sites a statistically significant difference in reaction time was not found. The fact that reaction times were faster at the lower-arm site for some subjects shows that other factors in addition to peripheral neural conduction time were influencing reaction times at the two sites. In order to reduce reaction time variability associated with a threshold detection task it may be preferable to study reaction times to suprathreshold pulses by ramping the pain stimulus off at ramp rates above that required for threshold detection.

Significantly greater rates of K^+ delivery were required at the upper arm site compared to the lower arm-site in response to a constant rate of delivery of K^+ during the four second period of constant pain. This shows that there were nociceptive processing differences between the two sites. Thus the obtained differences in ramp-off rates required to generate a pain pulse at the two arm sites may not have been due to a gate control mechanism, but simply an intrinsic difference in response to a nociceptive stimulus for the two different dermatome sites. Regional differences in nociceptor distribution and pain responding to nociceptive stimuli are well known (e.g., LaMotte et al., 1983).

In summary, the results of the present study were generally consistent with the predictions of gate control theory, and no data directly contradicted the predictions. However, further studies are required to confirm the causal mechanisms that generated the observed pain pulse.

15.1 CONCLUSIONS AND IMPLICATIONS FOR FUTURE RESEARCH

Further experiments are required to determine whether the pain pulse is generated by a reduction in A-beta activity, or an increase in A-delta activity during the stimulus ramp-off phase. An additional experiment, using electrodes located on the subjects legs, could be used in an attempt to replicate the arm-site findings of Experiment Four. If the same pattern of responding were obtained with the leg sites - with a greater ramp rate required at the less distal leg site to generate a pain pulse - then this would provide further support for the gate control theory predictions. At the same time it would reduce the possibility that the greater ramp rate required at the less distal site is merely intrinsic to the particular dermatomes tested.

An additional advantage of using leg sites is that a greater separation could be achieved between the upper and lower sites making it easier to differentiate the peripheral conduction times for the two sites, and consequently improving the estimation of the peripheral neural conduction velocities. Finally the greater leg distance would more easily permit the testing of multiple sites at varying distances from the spine. If a consistent relationship between ease of generating a pain pulse and distance to spine could be established then this would constitute more substantial support for the gate control theory predictions and our ramp-off model.

Microneurographic studies have measured activity in human cutaneous nociceptors (Valbo & Hagbarth, 1968; Adriaensen et al., 1983). Ideally microneurographic experiments are required to confirm that the pattern of neural stimulation obtained is that which is assumed by the ramp-off model. That is, that during the constant stimulus phase potassium iontophoresis does indeed activate both A-beta and C-fibre receptors, and that there is a relatively rapid fall-off in activity in both types of receptor during the nociceptive stimulus ramp-off phase. In particular microneurographic studies would be able to discount the possibility that the pain

pulses are the result of local action potential generating mechanisms such as anode break excitation producing increased activity in A-delta nociceptors during the stimulus ramp-off phase. Though it can be difficult to microneurographically record A-delta activity (Torebjörk, 1994). In addition, it is possible that a combination of mechanisms are operating, such as anode break excitation, anodal hyperpolarization and peripheral afferent imbalance. Consequently, measures of neural activity may not easily determine if the ramp-off model is a contributory factor in the generation of the pain pulse.

In addition to Experiments One Two and Three, Experiments Four and Five further show that potassium iontophoresis can be a useful investigative tool for studying pain mechanisms. The ramping off of the potassium iontophoretic peripheral pain stimulus may provide a quantitative methodology for investigating the spinal modulation of nociceptive information as proposed by the gate control theory of pain. Providing a quantitative measure of spinal pain modulation would answer one of the criticisms of D.D. Price (1988) about the lack of quantitative specifications associated with the gate control theory of pain.

The technique of ramping off a peripheral nociceptive stimulus may be useful for investigating many processes associated with the spinal modulation of pain. For instance, future studies could investigate the extent to which pain pulses can be generated while there are descending controls closing the gate. With factors believed to modulate nociceptive transmission at the spinal level through descending controls, such as some analgesics (e.g., Duggan et al., 1976; Le Bars & Besson, 1981) it might be predicted that it would be be more difficult to open the pain gate in the presence of such inhibitory descending influences and produce the pain pulse through the ramping off a peripheral pain stimulus. That is, the descending controls would be contributing to, and overriding to some extent, the inhibitory influences of A-beta afferent activity. Consequently, under such conditions, the removal of A-beta activity might be not be expected to increase to such an extent as normal the nociceptive transmission from the first synapses of the dorsal horn. Thus, while speculative, it may be possible that the pain pulse

generated through the ramping off of a peripheral nociceptive stimulus may provide a quantitative measure of the extent of descending spinal inhibitory mechanisms.

In general, the investigation of pain processing during the application of a pain stimulus varying in intensity would seem to have the potential to provide much additional information regarding pain processing mechanisms. Most studies typically measure subject responses to constant pain stimuli, albeit often delivered in relatively short duration pulses. Few studies have investigated responding to continuously varying nociceptive stimulation. Potassium iontophoresis would appear to possess suitable characteristics for the continual application of a nociceptive stimulus that could be continuously and accurately varied in intensity as required. Given the clinical relevance and problems associated with fluctuating pain a methodology that allows us to study how *changing* nociceptive stimuli are processed should provide many useful insights into the neural mechanisms that determine how we perceive pain.

REFERENCES

Abram, S.E., Asiddao, C.B., & Reynolds, A.C. (1980). Increased skin temperature during TENS. *Anesthesia and Analgesia, 59*, 22-25.

Abram, S.E., Reynolds, A.C., & Cusick, J.F. (1981). Failure of naloxone to reverse analgesia from transcutaneous electrical stimulation in patients with chronic pain. *Anesthesia and Analgesia, 60*, 81-84.

Accornero, N., Bini, G., Lenzi, G.L., & Manfredi, M. (1977). Selective activation of peripheral nerve fibre groups of different diameter by triangular shaped stimulus pulses, *Journal of Physiology, 273*, 539-560.

Adriaensen, H., Gybels, J., Handwerker, H.O., & Van Hees, J. (1983). Response properties of thin myelinated (A-delta) fibres in human skin nerves. *Journal of Neurophysiology, 49*, 111-122.

Adriaensen, H., Gybels, J., Handwerker, H.O., & Van Hees, J. (1984). Nociceptor discharges and sensations due to prolonged noxious mechanical stimulation - a paradox. *Human Neurobiology, 3*, 53-58.

Algom, D., & Marks, L.E. (1990). Range and regression, loudness scales, and loudness processing: Toward a context-bound psychophysics. *Journal of Experimental Psychology: Human Perception and Performance, 16*, 706-727.

Algom, D., Raphaeli, N., & Cohen-Raz, L. (1986). Integration of noxious stimulation across separate somatosensory communication systems: A functional theory of pain. *Journal of Experimental Psychology: Human Perception and Performance, 12*, 92-102.

Amit, Z., & Galina, Z.H. (1986). Stress-induced analgesia: Adaptive pain suppression, *Physiological Reviews, 66*, 1091-1120.

Anderson, N.H. (1970). Functional measurement and psychophysical judgment. *Psychological Review, 77*, 153-170.

Anderson, N.H. (1975). On the role of context effects in psychophysical judgment. *Psychological Review, 82*, 462-482.

Andersson, S.A. (1979). Pain control by sensory stimulation. In: J.J. Bonica, J.C. Liebeskind & D. Albe-fessard (Vol. Eds.), *Advances in Pain Research and Therapy: Vol 3,* (pp. 569-585). NY: Raven Press

Andersson, S.A., & Holmgren, E. (1976). Pain threshold effects of peripheral conditioning stimuli. In: J.J. Bonica and D.G. Albe-fessard (Eds.), *Advances in Pain Research and Therapy, Vol 1*, (pp. 761-768). NY: Raven Press.

Anton, F., Handwerker, H.O., Kreh, A., Reeh, P.W., Walter, E., & Weber, E. (1985). Influence of acetylsalicylic acid and salicylic plasma levels on psychophysical measures of long-standing natural pain stimuli. In H.L. Fields (Ed.), *Advances in Pain Research.* (pp. 781-789). NY: Raven Press.

Armstrong, D., Dry, R.M.L., & Keele, C.A. (1951). Method for studying chemical excitants of cutaneous pain in man. *Journal of Physiology, 115*, 59-61.

Armstrong, D., Dry, R.M.L., Keele, C.A., & Markham, J.W. (1953). Observations on chemical excitants of cutaneous pain in man. *Journal of Physiology*, 120, 326-351.

Arntz, A., Dreessen, L., & De Jong, P. (1994). The influence of anxiety on pain: Attentional and attributional mediators. *Pain, 56*, 307-314.

Babkoff, H. (1978). Electrocutaneous psychophysical input-output functions and temporal integration. *Perception & Psychophysics, 23*, 251-257.

Babkoff, H., Bergman, Y., & Brandeis, R. (1974). Response probability and response latency to threshold electrocutaneous stimuli. *Perception & Psychophysics, 15*, 417-424.

Barker, J.L., & Levitan, H. (1974). Studies on mechanisms underlying non-narcotic analgesia. In J. Bonica. (Ed.), *Advances in Neurology: Vol 4. International Symposium in Pain* (pp. 503-511). NY: Raven Press.

Basbaum, A.I., & Fields, H.L (1978). Endogenous pain control systems: Review and hypothesis. *Annals of Neurology, 4*, 451-462.

Basbaum, A.I., & Fields, H.L (1984). Endogenous pain control systems: Brainstem spinal pathways and endorphin circuitry. *Annual Review of Neuroscience, 7*, 309-338.

Bates, J.V.A., & Nathan, P.W. (1980). Transcutaneous electrical nerve stimulation for chronic pain. *Anaesthesia, 35*, 817-822.

Beck, C., & Rosner, B.S. (1968). Magnitude scales and somatic evoked potentials to percutaneous electrical stimulation. *Psychophysiology & Behaviour, 3*, 949-983.

Beecher, H.K. (1957a). Limiting factors in experimental pain. *Journal of Chronic Disease, 4*, 11-21.

Beecher, H.K. (1957b). The measurement of pain. Prototype for the quantitative study of subjective responses. *Pharmacological Review, 9*, 59-209.

Beecher, H.K. (1966). Pain: One mystery solved. *Science, 151*, 840-841.

Beitel, R.E., & Dubner, R. (1976a). Response of unmyelinated (c) polymodal nociceptors to thermal stimuli applied to monkey's face. *Journal of Neurophysiology, 39*, 1160-1175.

Beitel, R.E., & Dubner, R. (1976b). Fatigue and adaptation in unmyelinated (C) polymodal nociceptors to mechanical and thermal stimuli applied to the monkey's face. *Brain Research, 112*, 402-406.

BeMent, S.L., & Ranck, J.B. Jr. (1969). A quantitative study of electrical stimulation of central myelinated fibres. *Experimental Neurology, 24*, 147-170.

Benabid, A.L., Henriksen, S.J., McGinty, J.F., & Bloom, F.E. (1983). Thalamic nucleus ventro-postero-lateralis inhibits nucleus parafascicularis response to noxious stimuli through a non-opioid pathway. *Brain Research, 280*, 217-231.

Benjamin, F.B. (1959). Release of intracellular potassium as the physiological stimulus for pain. *Journal of Applied Physiology, 14*, 643-646.

Benjamin, F.B., & Helvey, W.M. (1963). Iontophoresis of potassium for experimental determination of pain endurance in man. *Proceedings of the Society for Experimental Biology and Medicine, 113*, 566-568.

Berger, J.J., Gravenstein, J.S., Edwin, M.D., & Munson, M.D. (1982). Electrode polarity and peripheral nerve stimulation. *Anesthesiology, 56*, 402.

Besson, J.M., & Chaouch, A. (1987). Peripheral and spinal mechanisms of nociception. *Physiological Reviews, 67*, 67-186.

Besson, J.M., Guilbaud, G., & Le Bars, D. (1975). Descending inhibitory influences exerted by the brain stem upon the activities of dorsal horn lamina V cells induced by intra-arterial injection of bradykinin into the limbs. *Journal of Neurophysiology, 248*, 725-739.

Bessou, P., & Perl, E.R. (1969). Responses of cutaneous sensory units with non-myelinated fibres to noxious stimuli. *Journal of Neurophysiology, 32*, 1025-1043.

Bing, Z., Villanaueva, L., & Le Bars, D. (1990). Acupuncture and diffuse noxious inhibitory controls: naloxone-reversible depression of activities of trigeminal convergent neurons. *Neuroscience, 37*, 809-818.

Birnbaum, M.H. (1973). The devil rides again: Correlation as an index of fit. *Psychological Bulletin, 79*, 239-242.

Birnbaum, M.H. (1974). Reply to the devil's advocates: Don't confound model testing and measurement. *Psychological Bulletin, 81*, 854-859.

Bleehen, T., & Keele, C.A. (1977). Observations on the alogenic actions of adenosine compounds on the human blister base preparation. *Pain, 3*, 367-377.

Blitz, B., & Dinnerstein, A.J. (1968). Effects of different types of instructions on pain parameters. *Journal of Abnormal Psychology, 73*, 276-280.

Bonica, J.J. (1990). General considerations of chronic pain. In J.J. Bonica (Ed.). *The management of pain* (pp. 180-183). Philadelphia: Lea & Febiger.

Brady, J.E., & Humiston, G.E. (1980). *General chemistry* (2nd ed.). NY: Wiley and Sons.

Breakwell, G. (1992). *The effects of three different types of distraction on pain induced by the iontophoretic administration of potassium ions.* Unpublished master's thesis, Massey University, Palmerston North, New Zealand.

Britton, N.F., Skevington, S.M. (1989). A mathematical model of the gate control theory of pain. *Journal of Theoretical Biology, 137*, 91-105.

Britton, N.F., Skevington, S.M., & Chaplain, M.A.J. (1995). *Mathematical modelling of acute pain.* Manuscript submitted for publication.

Bromm, B. (1984). The measurement of pain in man. In: B. Bromm (Ed.), *Pain measurement in man: Neurophysiological correlates of pain* (pp. 3-13). NY: Elsevier

Bromm, B., Jahnke, M.T., & Treede, R.D. (1984). Responses of human cutaneous afferents to CO_2 laser stimuli causing pain. *Experimental Brain Research, 55*, 158-166.

Bromm, B., & Treede, R.D. (1980). Withdrawal reflex, skin resistance reaction and pain rating due to electrical stimulation in men. *Pain, 9*, 339-354.

Brown, A.G. & Iggo, A.A. (1967). A quantitative study of cutaneous receptors and afferent fibres in the cat and the rabbit. *Journal of Physiology, 193*, 707-733.

Burgess, P.R., & Perl, E.R. (1973). Cutaneous mechanoreceptors and nociceptors. In A. Iggo (Ed.). *Handbook of sensory physiology, Vol 2, Somatosensory system* (pp. 29-78). Heidelberg: Springer.

Burke, W., & Ginsborg, B.L. (1956) The electrical properties of the slow muscle fibre membrane. *Journal of Physiology, 132*, 586-598.

Bushnell, M.C., Marchand, S., Tremblay, N., & Duncan, G. (1990). Electrical stimulation of peripheral and central pathways for the relief of musculoskeletal pain. *Canadian Journal of Physiology and Pharmacology, 69*, 697-703.

Calvillo, O. (1978). Primary afferent depolarization of C fibres in the spinal cord of cat. *Canadian Journal of Physiology and Pharmacology, 56*, 154-157.

Calvillo, O., Madrid, J., & Rudomin, P. (1982). Presynaptic depolarization of unmyelinated primary afferent fibres in the spinal cord of the cat. *Neuroscience, 7*, 1389-1400.

Campbell, J.N., & LaMotte, R.H. (1983). Latency to detection of first pain. *Brain Research, 266*, 203-208.

Campbell, J.N., & Meyer, R.A. (1983). Sensitization of unmyelinated nociceptive afferents in monkey varies with skin type. *Journal of Neurophysiology, 49*, 98-110.

Carmon, A. Dotan, Y., & Sarne, Y.(1978). Correlation of subjective pain experience with cerebral evoked responses to noxious thermal stimulations. *Experimental Brain Research, 33*, 445-453.

Carmon, A., Mor, J., & Goldberg, J. (1976). Evoked cerebral responses to noxious thermal stimulation in humans. *Experimental Brain Research, 25*, 103-107.

Carstens, E., Klumpp, D., & Zimmermann, M. (1980). Differential inhibitory effects of medial and lateralmidbrain stimulation on spinal neuronal discharges to noxious skin heating in the cat. *Journal of Neurophysiology, 43*, 332-342.

Cervero, F., & Iggo, A. (1980). The substantia gelatinosa of the spinal cord. *Journal of Neurology, 103*, 717-772.

Cervero, F., Handwerker, H.O., & Laird, J.M.A. (1988). Prolonged noxious stimulation of the rat's tail: Responses and encoding properties of dorsal horn neurons. *Journal of Physiology, 404*, 419-436.

Champion, R.A., & Hodge, R. (1983). The application of the preparatory-response hypothesis to changes in base skin resistance. *Psychophysiology, 20*, 59-62.

Chapman, C.R., Casey, K.L., Dubner, R., Foley, K.M., Gracely, R.H., & Reading, A.E. (1985). Pain measurement: An overview. *Pain, 22*, 1-31.

Chapman, C.R, Chen, A.C.N., Colpitts, Y.M., & Martin, R.W. (1981). Sensory decision theory describes evoked potentials in pain discrimination. Psychophysiology, 18, 114-120.

Chen, A.C.N. (1993a). Human brain measures of clinical pain: A review I. Topographic mappings. *Pain, 54*, 115-132.

Chen, A.C.N. (1993b). Human brain measures of clinical pain: A review II. Tomographic imagings. *Pain, 54*, 133-44.

Chen, A.C.N., & Chapman, C.R. (1980). Aspirin analgesia evaluated by event-related evoked potentials in man: possible central action in brain. *Experimental Brain Research, 39*, 359-364.

Chen, A.C.N., Dworkin, S.F., Haug, J., & Gehrig, J. (1989). Topographic brain measures of human pain and pain responsivity. *Pain , 37*, 129-141.

Cheng, R.S.S., & Pomeranz, B. (1987). Electrotherapy of chronic musculoskeletal pain: Comparison of electroacupuncture and acupuncture-like transcutaneous electrical nerve stimulation. *Clinical Journal of Pain, 2*, 143-149.

Chudler, E.H., Anton, F., Dubner, R., & Kenshalo, D.R. (1990). Responses of nociceptive SI neurons in monkeys and pain sensation in humans elicited by noxious thermal stimulation: Effect of interstimulus interval. *Journal of Neurophysiology, 63*, 559-569.

Chung, C.M., Fang, Z.R., Cargill, C.L., & Willis, W.D. (1983). Prolonged, naloxone-reversible inhibition of the flexion reflex in cat. *Pain, 15*, 35-53.

Chung, C.M., Fang, Z.R., Hori, Y., Lee, K.H., & Willis, W.D. (1984). Prolonged inhibition of primate spinothalamic tract cells by peripheral nerve stimulation. *Pain, 19*, 259-275.

Chung, J.M., Kenshalo, D.R., Jr., Gerhart, K.D., & Willis, W.D. (1979) Excitation of primate spinothalamic neurons by cutaneous C-fibre volleys. *Journal of Neurophysiology, 42*, 1354-1369.

Clark, W.C., Carrol, J.D., Yang, J.C., & Janal, M.N. (1986). Multidimensional scaling reveals two dimensions of thermal pain. *Journal of Experimental Psychology, 12*, 103-107.

Clark, W.C., & Goodman, J.S. (1974). Effects of suggestion on d' and Cx for pain detection and pain tolerance. *Journal of Abnormal Psychology, 83*, 364-372.

Coderre, T.J. Katz, J., Vaccarino, A., & Melzack, R. (1993). Contribution of central neuroplasticity to pathological pain: Review of clinical and experimental evidence. *Pain, 52*, 259-285.

Coleman, B.J., Graf, R.G., & Alf, E.F. (1981). Assessing power function relationships in magnitude estimation. *Perception & Psychophysics, 29*, 178-180.

Collins, W.F. Nulsen, F.E., & Randt, C.T. (1960). Relation of peripheral nerve fibre size and sensation in man. *Archives of Neurology and Psychiatry, 3*, 381-385.

Colquhoun, D. M. (1993). Electrical neurostimulation for angina pectoris. *The Medical Journal of Australia, 158*, 440-442.

Condes-Lara, M., & Omana Zapata, I. (1988). Suppression of noxious thermal evoked responses in thalamic central lateral nucleus by cortical spreading depression. *Pain*, 32, 199-204.

Conway, E.J. (1957). Nature and significance of concentration relations of potassium and sodium ions in skeletal muscle. *Physiological Review, 37*, 84-132.

Cook, A.J., Woolf, C.J., Wall, P.D., & McMahon, S.B. (1987). Dynamic receptive field plasticity in rat spinal dorsal horn following primary afferent input. *Nature, 325*, 151-153.

Cornsweet, T.N. (1962). The staircase-method in psychophysics. *American Journal of Psychology, 75*, 485-491.

Cornwall, A., & Donderi, D.C. (1988). The effect of experimentally induced anxiety on the experience of pressure pain. *Pain, 35*, 105-113.

Coyne, T.M., & Peck, C. (1980). Pain and depression as a function of effectiveness of perceived control. In Peck, C., & Wallace, M. (Eds.). *Problems in pain* (pp. 121-127). Sydney: Pergammon Press.

Cross, D.V. (1973). Sequential dependencies and regression in psychophysical judgments. *Perception & Psychophysics, 14*, 547-552.

Cross, D.V., Tursky, B., & Lodge, M. (1975). The role of regression and range effects in the determination of the power function for electric shock. *Perception & Psychophysics, 18*, 9-14.

Croze, S., Duclaux, R., & Kenshalo, D.R. (1976). The thermal sensitivity of the polymodal nociceptors in the monkey. *Journal of Physiology, 263*, 539-562.

Davies, S.N., & Lodge, D. (1987). Evidence for the involvement of N-methyl aspartate receptors in 'wind-up' of class 2 neurones in the dorsal horn of the rat. *Brain Research, 424*, 402-406.

Dawson, N.J., Dickenson, A.H., Hellon, R.F., & Woolf, C.J. (1981). Inhibitory controls on thermal neurones in the spinal trigeminal nucleus of cats and rats. *Brain Research, 209*, 440-445.

Deschamps, M., Band, P.R., & Coldman, A.J. (1988). Assessment of adult cancer pain: Shortcomings of current methods. *Pain, 32*, 133-139.

Dickenson, A.H., Hellon, R.F., & Woolf, C.J. (1981). Tooth pulp input to the spinal trigeminal nucleus: A comparison of inhibitions following segmental and raphe nucleus stimulation. *Brain Research, 214*, 73-87.

Dickenson, A.H., Oliveras, J.L., & Besson, J.M. (1979). Role of the NRM in opiate analgesia as studied by microinjection technique in the rat. *Brain Research, 170*, 95-111.

Dougherty, P.M., & Willis, W.D. (1992). Enhanced responses of spinothalamic tract neurons to excitatory amino acids accompanying capsaicin-induced sensitization in the monkey. *Journal of Neuroscience, 12*, 883-894.

Douglas, W. (1994). *Does distraction affect various parameters of pain differently?* Unpublished master's thesis, Massey University, Palmerston North, New Zealand.

Douglas W.W., & Ritchie, J.M. (1962). Mammalian nonmyelinated nerve fibres. *Physiological Reviews, 42*, 297-334.

Dubner, R. (1991). Neuronal plasticity and pain following peripheral tissue inflammation or nerve injury. In: M.R. Bond, J.E. Charlton and C.J. Woolf (Eds.), *Proceedings of the VIth World Congress on Pain, Vol 4, Pain Research and Clinical Management*, (pp. 263-276). NY: Elsevier.

Dubner, R., & Bennett, G.J. (1983). Spinal and trigeminal mechanisms of nociception. *Annual Review of Neuroscience, 6*, 381-418.

Duggan, A.W., Hall, J.G., & Headley, P.M. (1976). Morphine enkephalin and the substantia gelatinosa. *Nature, 264*, 456-458.

Duncan, G.H., Bushnell, M.C., & Lavigne, G.J. (1989). Comparison of verbal and visual analogue scales for measuring the intensity and unpleasantness of experimental pain. *Pain, 7*, 295-303.

Duranti, R., Pantaleo, T., & Bellini, F. (1988). Increase in muscular pain threshold following low frequency-high intensity peripheral conditioning stimulation in humans. *Brain Research, 452*, 66-72.

Ekblom, A., & Hansson, P. (1982). Effects of conditioning vibratory stimulation on pain threshold of the human tooth. *Acta Physiologica Scandinavica, 114*, 601-604.

Ekman, G., Frankenhaeuser, M., Levander, S., & Mellis, I. (1964). Scales of unpleasantness of electrical stimulation. *Scandinavian Journal of Psychology, 5*, 257-261.

Ekman, G., Frankenhaeuser, M., Levander, S., & Mellis, I. (1966). The influence of intensity and duration of electrical stimulation on subjective variables. *Scandinavian Journal of Psychology, 7*, 58-64.

Elton, D., Stanley, G., & Burrows, G. (1983). *Psychological control of pain.* NY: Grune & Stratton.

Eriksson, M.B.E., Sjölund, B.H., & Nielzen, S. (1979). Long term results of peripheral conditioning stimulation as an analgesic measure in chronic pain. *Pain, 6*, 335-347.

Ertekin, N., Citakoglu, K., & Ertekin, C. (1980). Effects of continuous vibration on sural nerve action potentials. *Applied Neurophysiology, 43*, 305-312.

Fernandez, E., & Turk, D.C. (1989). The utility of cognitive coping strategies for altering pain perception: A meta-analysis. *Pain, 38*,123-135.

Fernandes De Lima, V., Chatrian, G.E., Lettich, E., Canfield, R., Miller, R.C., & Soso, M. (1982). Electrical stimulation of tooth pulp in humans. I. Relationships among physical stimulus intensities, psychological magnitude estimates and cerebral evoked potentials. *Pain, 14*, 207-232.

Ferrington, D.G., Nail, B.S., & Rowe, M. (1977). Human tactile detection threshold: Modification by inputs from specific tactile receptor classes. *Journal of Physiology, 272*, 415-433.

Fields, H.L. (1990). In: H.L Fields (Ed.), *Pain syndromes in neurology*, (pp. 2). London: Butterworths.

Fields, H.L. (1987). *Pain.* NY: McGraw-Hill.

Fields, H.L., & Basbaum, A.I. (1978). Brainstem control of spinal pain-transmission neurons. *Annual Review of Physiology, 40*, 217-248.

Fields, H.L., Basbaum, A.I., Clanton, C.H., & Anderson, S.D. (1977). Nucleus raphe magnus inhibition of spinal cord dorsal horn neurons. *Brain Research, 126*, 441-453.

Fields, H.L., Heinricher, M.M., & Mason, P. (1991). Neurotransmitters in nociceptive modulatory circuits. *Annual Review of Neuroscience, 14*, 219-245.

Finer, B. (1974). Clinical use of hypnosis in pain management. In J. Bonica. (Ed.) *Advances in Neurology: Vol 4. International Symposium in Pain* (pp. 573-579). NY: Raven Press.

Fiorgione, A.G., & Barber, T.X. (1971). A strain gauge pain stimulator. *Psychophysiology, 8*, 102-106.

Fitzgerald, M. (1981). A study of the cutaneous afferent input to the substantia gelatinosa. *Neuroscience, 6*, 2229-2237.

Fitzgerald, M. (1982). The contralateral input to the dorsal horn of the spinal cord in the decerebrate spinal rat. *Brain Research, 236*, 275-287.

Fitzgerald, M., & Lynn, B. (1977). The sensitization of high threshold mechanoreceptors with myelinated axons by repeated heating. *Journal of Physiology, 265*, 549-563.

Fitzgerald, M., & Woolf, C.J. (1981). Effects of cutaneous nerve and intraspinal conditioning on C fibre afferent terminal excitability in decerebrate spinal rats. *Journal of Physiology, 318*, 25-39.

Foley, H.J., Cross, D.V., & O'Reilly, J.A. (1990). Pervasiveness and magnitude of context effects: Evidence for the relativity of absolute magnitude estimation. *Perception & Psychophysics, 48*, 551-558.

Follett, K.A., & Gebhart, G.F. (1990). Modulation of cortical evoked potentials by stimulation of raphe magnus in rats. *Journal of Neurophysiology, 67*, 820-828.

Fordyce, W.E. (1976). *Behavioural methods in chronic pain and illness.* St Louis: Mosby.

Fordyce, W.E. (1988). Pain and suffering. *American Psychologist, 43*, 276-283.

Foreman, R.D., Beall, J.E., Applebaum, A.E. Coulter, J.D., & Willis, W.D. (1976). Effects of dorsal column stimulation on primate spinothalamic tract neurons. *Journal of Neurophysiology, 39*, 534-546.

Forster, C., Anton, F., Reeh, P.W., Weber, E., & Handwerker, H.O. (1988). Measurement of the analgesic effects of aspirin with a new experimental algesimetric procedure. *Pain, 32*, 215-222.

Francini, F. Maresca, M. Procacci, P., & Zoppi, M. (1981). The effects of non-painful transcutaneous electrical nerve stimulation on cutaneous pain threshold and muscular reflexes in normal men and in subjects with chronic pain. *Pain, 11*, 49-63.

Freeman, T.B., Campbell, J.N., & Long, D.M. (1983). Naloxone does not affect pain relief induced by electrical stimulation in man. *Pain, 17*, 189-195.

Garcia de Jalon, P.D., Harrison, F.J., Johnson, K.I., Kozma, C., & Schnelle, K. (1985). Modified cold stimulation technique for the evaluation of analgesic activity in human volunteers. *Pain, 22*, 183-189.

Garrison, D.W. & Foreman, R.D. (1994). Decreased activity of spontaneously and noxiously evoked dorsal horn cells during transcutaneous electrical nerve stimulation (TENS). *Pain, 58*, 309-315.

Gasser, H.S. (1950). Unmedullated fibres originating in the dorsal root ganglia. *Journal of General Physiology, 33*, 651-690.

Gavrilov, L.R., Gersuni, G.V., Ilyinski, O.B., Tsirulnikov, E., & Shchekanov, E.E. (1977). A study of reception with the use of focused ultrasound. I. Effects on the skin and deep receptor structures in man. *Brain Research, 135*, 265-277.

Geertsma, R.H. (1958). Time-order errors in comparative judgments of hurtfulness. *Journal of Experimental Psychology, 55*, 284-288.

Geldard, F.A. (1972). *The human senses* (2nd ed.). NY: Wiley & Sons.

Gelfand, S. (1964). The relationship of experimental pain tolerance to pain threshold. *Canadian Journal of Psychology, 18*, 36-42.

Georgopoulos, A.P. (1976). Functional properties of primary afferent units probably related to pain mechanisms in primate glabrous skin. *Journal of Neurophysiology, 39*, 71-83.

Gerber, G., & Randic, M. (1989). Participation of excitatory amino acid receptors in the slow excitatory synaptic transmission in the rat spinal cord in vitro. *Neuroscience Letters, 106*, 220-228.

Gerhart, K.D., Yezierski, R.P., Fang, Z.R., & Willis, W.D. (1983). Inhibition of primate spinothalamic tract neurons by stimulation in ventral posterior lateral (VPLc) thalamic nucleus: Possible mechanisms. *Journal of Neurophysiology, 49*, 406-423.

Gescheider, G.A. (1988). Psychophysical scaling. *Annual Review of Psychology, 39*, 169-200.

Gescheider, G.A., & Hughson, B.A. (1991). Stimulus context and absolute magnitude estimation: A study of individual differences. *Perception & Psychophysics, 50*, 45-57.

Giesler, G.J., Jr., Gerhart, K.D., Yezierski, R.P., Wilcox, T.K., & Willis, P.D. (1981). Postsynaptic inhibition of primate spinothalamic neurones by stimulation in the nucleus raphe magnus. *Brain Research, 204*, 184-188.

Gilman, A.G., Goodman, L.S., & Gilmar, A. (1980) *The pharmacological basis of therapeutics* (6th ed.). NY: MacMillan.

Glass, J.M., Stephen, R.L., & Jacobson, S.C. (1980). The quantity and distribution of radiolabelled dexamethasone delivered to tissue by iontophoresis. *International Journal of Dermatology, 19*, 519-525.

Gracely, R.H. (1979). Psychophysical assessment of human pain. In: J.J. Bonica, J.C. Liebeskind and D. Albe-fessard (Eds.), *Advances in Pain Research and Therapy, Vol 3*, (pp. 805-824). NY: Raven Press.

Gracely, R.H. (1984). Subjective quantification of pain perception. In: B. Bromm (Ed.), *Pain measurement in man: Neurophysiological correlates of pain* (pp. 371-387). NY: Elsevier

Gracely, R.H. (1988). Multiple-random staircase assessment of thermal pain sensation. In R. Dubner, G.F. Gebhart, & M.R. Bond (Eds.). *Proceedings of the Vth World Congress on Pain*, (pp. 391-394). Amsterdam: Elsevier.

Gracely, R.H. (1989). Methods of testing pain mechanisms in normal man. In P.D. Wall and R. Melzack (Eds.). *Textbook of pain.* (pp. 257-268). NY: Churchill Livingston.

Gracely R.H. & Dubner, R. (1981). Pain assessment in humans - a reply to Hall. *Pain, 11*, 109-120.

Gracely, R.H., & Dubner, R. (1987). Reliability and validity of verbal descriptor scales of painfulness. *Pain, 29*, 175-185.

Gracely, R.H., Dubner, R. & McGrath, P. (1979). Narcotic analgesia: Fentanyl reduces the intensity but not the unpleasantness of painful tooth pulp sensations. Science, 203, 1261-1263.

Gracely, R.H., Lota, L., Walter, D.J., & Dubner, R. (1988). A multiple random staircase method of psychophysical pain assessment. *Pain, 32*, 55-63.

Gracely, R.H., McGrath, P, & Dubner, R. (1978a). Ratio scales of sensory and affective verbal pain descriptors. *Pain, 5*, 5-18.

Gracely, R.H., McGrath, P., & Dubner, R. (1978b). Validity and sensitivity of ratio scales of sensory and affective verbal pain descriptors: Manipulation of affect by Diazepam. *Pain, 5*, 19-29.

Gray, B.G., & Dostrovski, J.O. (1983). Descending inhibitory influences from periaqueductal gray, nucleus raphe magnus, and adjacent reticular formation. I. effects on lumber spinal cord nociceptive and nonnociceptive neurons. *Journal of Neurophysiology, 49*, 932-947.

Gregor, M., & Zimmermann, M. (1972). Characteristics of spinal neurones responding to cutaneous myelinated and unmyelinated fibres. *Journal of Physiology, 221*, 555-576.

Grossberg, J.M., & Grant, B.F. (1978). Clinical Psychophysics: Applications of ratio scaling and signal detection methods to research on pain, fear, drugs, and medical decision making. *Psychological Bulletin, 85*, 1154-1176.

Guieu, R, Tardy-Gervet, M.F., Blin, O., & Pouget, J. (1990). Pain relief achieved by transcutaneous electrical nerve stimulation and/or vibratory stimulation in a case of painful legs and moving toes. *Pain, 42*, 43-48.

Guieu, R, Tardy-Gervet, M.F., & Giraud, P. (1992). Met -enkephalin and beta-endorphin are not involved in the analgesic action of transcutaneous vibratory stimulation. *Pain, 48*, 83-88.

Guilbaud, G. (1988). Peripheral and central electrophysiological mechanisms of joint and muscle pain. In: R. Dubner, G.F. Gebhart, and M.R. Bond (Eds.), *Proceedings of the Vth World Congress on Pain*, (pp. 201-215). Amsterdam: Elsevier.

Gybels, J.M. (1979) Electrical stimulation of the central gray for pain relief in humans: A critical review. In: J.J. Bonica, J.C. Liebeskind and D. Albe-fessard (Eds.), *Advances in Pain Research and Therapy, Vol 3*, (pp. 499-509). NY: Raven Press.

Hall, J.G. (1979). Supraspinal inhibition of spinal neurons responding to nociceptive stimulation. *Neuroscience Letters, 14*, 165-169.

Hall, W. (1981). On "ratio scales of sensory and affective verbal pain descriptors". *Pain, 11*, 101-7.

Handwerker, H.O., Iggo, A., & Zimmermann, M. (1975). Segmental and supraspinal actions on dorsal horn neurons responding to noxious and non-noxious skin stimuli. *Pain, 1*, 147-165.

Handwerker, H.O., & Kobal, G. (1993). Psychophysiology of experimentally induced pain. *Physiological Reviews, 73*, 639-671.

Hannay, H.J. (1986). *Experimental Techniques in Human Neuropsychology*. NY: Oxford Press.

Hansson, P., & Ekblom, A. (1983). Transcutaneous electrical nerve stimulation (TENS) as compared to placebo (TENS) for the relief of acute oro-facial pain. *Pain, 15*, 157-165.

Hansson, P., & Ekblom, A. (1984). Afferent stimulation induced pain relief in acute orofacial pain and its failure to induce sufficient pain reduction in dental and oral surgery. *Pain, 20*, 273-278.

Hansson, P., Ekblom, A., Thomsson, M., & Fjellner, B. (1986). Influence of naloxone on relief of acute orofacial pain by transcutaneous electrical nerve stimulation (TENS) or vibration. *Pain, 1*, 323-329.

Harcus, A.W., Smith, R.B., & Whittle, B.A. (Eds.). (1977). *Pain -New perspectives in measurement and management*. London: Churchill Livingston.

Hardy, J.D., Wolff, H.G., & Goodell, H. (1940). Studies on pain. A new method for measuring pain threshold: Observations on spatial summation of pain. *Journal of Clinical Investigation, 19*, 649-657.

Hardy, J.D., Wolff, H.G., & Goodell, H. (1967). *Pain sensations and reactions*. NY: Hafner.

Hardy, J.D., Wolff, H.G., & Goodell, H. (1950). Experimental evidence on the nature of cutaneous hyperalgesia. *Journal of Clinical Investigation, 29*, 115-140.

Harris, G., & Tolman, G.B. (1983). The validity of experimental pain measures. *Pain, 17*, 369-376.

Hason, Z., & Houk, J.C. (1975). Analysis of response properties of deefferented mammalian spindle receptors based on frequency response. *Journal of Neurophysiology, 38*, 663-672.

Hentall, I.D., & Fields, H.L. (1979). Segmental and descending influence on intraspinal thresholds of single C-fibres. *Journal of Neurophysiology, 42*, 1527-1537.

Higashiyama, A., & Tashiro, T. (1987). Magnitude estimates for electric shock. *Japanese Psychological Research, 29*, 81-88.

Higashiyama, A., & Tashiro, T. (1989). Magnitude estimates for electrical pulses: Evidence for two neural mechanisms. *Perception & Psychophysics, 45*, 537-549.

Higashiyama, A., & Tashiro, T. (1990). Electrocutaneous spatial integration at threshold: The effects of electrode size. *Perception & Psychophysics, 48*, 389-397.

Hilgard, E.R. (1978). Pain perception in man. In R. Leibowitz & Hans-Lukas Teuber (Eds.). *Perception* (pp. 849-875). NY: Springer-Verlag.

Hilgard, E.R, Ruch, J.C., Lange, A.F., Lenox, J.R., Morgan, A.H., & Sachs, L.B. (1974). The psychophysics of cold pressor pain and its modification through hypnotic suggestion. *American Journal of Psychology, 87*, 17-31.

Hill, H.E., Flanary, H.G., Kornetsky, C.H., & Wikler, A. (1952). Relationship of electrically induced pain to the amperage and the wattage of shock stimuli. *Journal of Clinical Investigation, 31*, 261-266.

Hillman, P., & Wall, P.D. (1969). Inhibitory and excitatory factors influencing the receptive fields of lamina 5 spinal cord cells. *Experimental Brain Research, 9*, 284-306.

Hodes, R.L., Howland, E.W., Lightfoot, N., & Cleeland, C.S. (1990). The effects of distraction on responses to cold pressor pain. *Pain, 412*, 109-114.

Hodgkin, A.L., & Horowicz, P. (1959). The influence of potassium and chloride ions on the membrane potential of single muscle fibres. *Journal of Physiology, 148*, 127-160.

Hoffman, D.S., Dubner, R., Hayes, R.L., & Medlin, T.P. (1981). Neuronal activity in the medullary dorsal horn of awake monkeys trained in a thermal discrimination task. I Responses to innocuous and noxious thermal stimuli. *Journal of Neurophysiology, 46*, 409-427.

Homma, S., Kanda, K., & Watanabe, S. (1971). Tonic vibration reflex in human and monkey subjects. *Japanese Journal of Physiology, 21*, 419-430.

Hongo, T., Jankowska, E., & Lundberg, A. (1968). Post-synaptic excitation and inhibition from primary afferents in neurons of the spinocervical tract. *Journal of Physiology, 199*, 569-592.

Hosobuchi, Y., Adams, J.E., & Rutkin, B. 1973). Chronic thalamic stimulation for the control of facial anaesthesia dolorosa. *Archives of Neurology, 29*, 158-161.

Hu, J.W., & Sessle, B.J. (1979). Trigeminal nociceptive and non-nociceptive neurons: Brain stem intranuclear projections and modulation by orofacial, periaqueductal gray and nucleus raphe magnus stimuli. *Brain Research, 170*, 547-552.

Hull, C.L. (1949). Stimulus intensity dynamism (V) and stimulus generalization. *Psychological Review, 36*, 67-26.

Humphries, S., & Johnson, M.H. (1990, April). *The reliability and validity of iontophoretically applied potassium ions as an experimental pain stimulus.* Paper presented at the Vth World Congress on Pain, Adelaide.

Humphries, S.A., Johnson, M.H., & Long, N.R. (1993, August). *An investigation of the gate control theory of pain by ramping-off the experimental pain stimulus of potassium iontophoresis.* Abstract No. 468. Poster session presented at the VIIth World Congress on Pain, France.

Humphries, S.A., Long, N.R , & Johnson, M.H. (1994). Iontophoretically Applied Potassium Ions as an Experimental Pain Stimulus for Investigating Pain Mechanisms. *Perception & Psychophysics, 56*, 637-648.

Hunt, C.C. (1961). On the nature of vibration receptors in the hind limb of the cat. *Journal of Physiology, 155*, 175-186.

Hunt, C.C., & McIntyre, A.K. (1960). An analysis of fibre diameter and receptor characteristics of myelinated cutaneous afferent fibres in cat. *Journal of Physiology, 153*, 99-112.

Hurley, J.V. (1984). Inflammation. In J.R. Anderson (Ed.), *Muir's textbook of pathology* (12th ed.) (pp. 4.1-4.38). London: Edward Arnold.

Huskisson, E.C. (1974). Measurement of pain. *Lancet, 9*, 1127-1131.

Hyslop, J., Dowland, J., & Hicking, J. (1983). *Health facts New Zealand.* Wellington: Department of Health.

Iggo, A. (1960). Cutaneous mechanoreceptors with afferent C fibres. *Journal of Physiology, 152*, 337-353.

Iggo, A. (1974). Cutaneous receptors. In J. Hubbard (Ed.). *The peripheral nervous system* (pp. 347-404). NY: Plenum Press.

Ignelzi, R.J., & Nyquist, J.K. (1976). Direct effect of electrical stimulation on peripheral nerve evoked activity: Implications in pain relief. *Journal of Neurosurgery, 45*, 159-165.

Jamieson, D.G., & Petrusic, W.M. (1975). Pairing effects and time-order errors in duration stimuli. *Perception & Psychophysics, 18*, 107-113.

Janko, M., & Trontelj, J.V. (1980). Transcutaneous electrical nerve stimulation: A microneurographic and perceptual study. *Pain, 9*, 219-230.

Jensen, M.P., Karoly, P., & Braver, S. (1986). The measurement of clinical pain intensity: A comparison of six methods. *Pain, 27*, 117-126.

Jensen, M.P. & McFarland, C.A. (1993). Increasing the reliability and validity of pain intensity measurement in chronic pain patients. *Pain, 55*, 195-203.

Jessel, T.M., & Iversen, L.L (1977). Opiate analgesics inhibit substance P release from rat trigeminal nucleus. *Nature, 268*, 549-551.

Johansson, R.S., Landstrom, U., & Landstrom, R. (1982). Responses of mechanoreceptive afferent units in the glabrous skin of the human hand to sinusoidal skin displacements. *Brain Research, 244*, 17-25.

Johnson, M.I., Ashton, C.H., Bousfield, D.R., & Thompson, J.W. (1989). Analgesic effects of different frequencies of transcutaneous electrical nerve stimulation on cold-induced pain in normal subjects. *Pain, 39*, 231-236.

Johnson, M.I., Ashton, C.H., & Thompson, J.W. (1991a). An in depth study on the use of transcutaneous electrical nerve stimulation (TENS) by chronic pain patients: Implications for clinical use of TENS. *Pain, 44*, 221-229.

Johnson, M.I., Ashton, C.H., & Thompson, J.W. (1991b). The consistency of pulse frequencies and pulse patterns of transcutaneous nerve stimulation (TENS) used by chronic pain patients. *Pain, 44*, 231-234.

Johnson, M.I., Hajela, V.K., Ashton, C.H., & Thompson, J.W. (1991). The effects of auricular transcutaneous electrical nerve stimulation (TENS) on experimental pain threshold and autonomic function in healthy subjects. *Pain, 46*, 337-342.

Jones, K.E., & Furedy, J.J. (1989). Effects of signalling parameters on human electroshock perception: Informational control versus stimulus error. *Australian Journal of Psychology, 41*, 79-87.

Jones, B. (1980). Algebraic models for integration of painful and nonpainful electric shocks. *Perception & Psychophysics, 28*, 572-576.

Jones, B., & Gwynn, M. (1984). Functional measurement scales of painful electric shocks. *Perception & Psychophysics, 35*, 193-200.

Jones, B., Planas, M., & Anuza, T. (1982). Painfulness decreases the discriminability of electric shock. *Perception & Psychophysics, 32*, 187-191.

Jorum, E., & Shyu, B.C. (1988). Analgesia by low frequency nerve stimulation mediated by low-threshold afferents in rats. *Pain, 32*, 357-365.

Jospe, M. (1978). *The placebo effect in healing*. Massachusetts: Lexington.

Kakigi, R., & Shibasaki, H. (1992). Mechanisms of pain relief by vibration and movement. Journal of Neurology, Neurosurgery, and Psychiatry, 55, 282-286.

Karlsmark, T., Thomsen, H.K., Danielsen,L., Aulund, O., Nielsen, O., & Nielsen, K.G. (1986) Immediate dermal changes in pig skin after exposure to moderate amounts of heat and electrical energy. *The Journal of Investigative Dermatology, 87*, 528-532.

Keefe, F.J., & Dunsmore, J. (1992a). Pain behaviour: Concepts and controversies. *American pain Society Journal, 1*, 92-100.

Keefe, F.J., & Dunsmore, J. (1992b). The multifaceted nature of pain behaviour. *American pain Society Journal, 1*, 112-114.

Keele C.A. (1970). Chemical causes of pain and itch. *Annual Review of Medicine, 21*, 67-74.

Keele, K.D. (1975). A physician looks at pain. In M. Weisenberg (Ed.). *Pain: Clinical and experimental perspectives* (pp. 45-52). Saint Louis: C.V. Mosby Company.

Keele, C.A., & Armstrong, D. (1964). *Substances producing pain and itch.* London: E. Arnold.

Kenshalo, D.R. (1968). *The Skin Senses.* Springfield: Charles C Thomas.

Kenshalo, D.R., Jr., Anton, F., & Dubner, R. (1989). The detection and perceived intensity of noxious thermal stimuli. *Journal of Neurophysiology, 62*, 429-436.

Kenshalo, D.R., Leonard, R.B., Chung, J.M., & Willis, W.D. (1979a). Facilitation of the responses of primate spinothalamic cells to cold and mechanical stimuli by noxious heating of the skin. *Pain, 12*, 141-152.

Kenshalo, D.R., Leonard, R.B., Chung, J.M., & Willis, W.D. (1979b). Responses of primate spinothalamic neurons to graded and to repeated noxious heat stimuli. *Journal of Neurophysiology, 42*, 1370-1389.

Koltzenburg, M., Kress, M., & Reeh, P.W. (1992). The nociceptor sensitization by bradykinin does not depend on sympathetic neurons. *Neuroscience, 46*, 465-473.

Kreh, A., Anton, F., Gilly, H., & Handwerker, H.O. (1984). Vascular reactions correlated with pain due to cold. *Experimental Neurology, 85*, 533-546.

Kremer, E., Atkinson, J.H., & Ignelzi, R.J. (1981). Measurement of pain: Patient preference does not confound pain measurement. *Pain, 10*, 241-248.

Kumazawa, T., & Mizumura, K. (1977). Thin-fibre receptors responding to mechanical, chemical, and thermal stimulation in the skeletal muscle of the dog. *Journal of Physiology, 273*, 179-194.

Kumazawa, T., & Perl, E.R. (1977). Primate cutaneous sensory units with unmyelinated (C) afferent fibres. *Journal of Neurophysiology, 40*, 1325-1338.

Lahoda, R., Stacher, G., & Bauer, P. (1977). Experimentally induced pain: Measurement of pain threshold and pain tolerance using a new apparatus for electrical stimulation of the skin. *International Journal of Clinical Pharmacology, 15*, 51-56.

Laming, D. (1989). Experimental evidence for Fechner's and Steven's laws. *Behavioural & Brain Sciences, 12*, 277-278.

LaMotte, R.H., & Campbell, J.N. (1978). Comparison of responses of warm and nociceptive C-fibre afferents in monkey with human judgments of thermal pain. *Journal of Neurophysiology, 41*, 509-528.

LaMotte, R.H., Lundberg, L.E.R., & Torebjörk, H.E. (1992). Pain, hyperalgesia and activity in nociceptive C units in humans after intradermal injection of capsaicin. *Journal of Physiology, 448*, 749-764.

LaMotte, R.H., Shain, C.N., Simone, D.A., & Tsai, E-Fun P. (1991). Neurogenic hyperalgesia: Psychophysical studies of underlying mechanisms. *Journal of Neurophysiology*, *66*, 190-211.

LaMotte, R.H., Thalhammer, J.G., & Robinson, C.J. (1983). Peripheral neural correlates of magnitude of cutaneous pain and hyperalgesia: A comparison of neural events in monkey with sensory judgments in human. *Journal of Neurophysiology*, *50*, 1-26.

LaMotte, R.H., Thalhammer, J.G., Torebjörk, H.E., & Robinson, C.J. (1982). Peripheral neural mechanisms of cutaneous hyperalgesia following mild injury by heat. *Journal of Neuroscience*, *2*, 765-781.

Lampe, J., & Dunne, B. (1987). Symmetrical biphasic TENS waveform for the treatment of back pain. *Clinical Journal of Pain*, *3*, 145-151.

Le Bars, D., & Besson, J.M. (1981). The spinal site of action of morphine in pain relief: from basic research to clinical applications. *Trends of Pharmacological Science*, *2*, 323-325.

Le Bars, D., Chitour, D., & Clot, A.M. (1981). The encoding of thermal stimuli by Diffuse Noxious Inhibitory Controls (DNIC). Brain Research, 230, 394-399.

Le Bars, D., Dickenson, A.H., & Besson, J.M. (1979a). Diffuse noxious inhibitory controls (DNIC) I. Effects on dorsal horn convergent neurones in the rat. *Pain*, *6*, 283-304.

Le Bars, D., Dickenson, A.H., & Besson, J.M. (1979b). Diffuse noxious inhibitory supraspinal involvement and theoretical implication. *Pain*, *6*, 305-327.

Le Bars, D., Dickenson, A.H., Besson, J.M., & Villanueva, L. (1986). Aspects of sensory processing through convergent neurons. In: T.L. Yaksh (Ed.), *Spinal Afferent Processing* (pp. 467-504). NY: Plenum Press.

Le Bars, D., & Villanueva, L. (1988). Electrophysiological evidence for the activation of descending inhibitory controls by nociceptive afferent pathways. In: H.L. Fields and J.M. Besson (Eds.), *Progress in Brain Research, Vol 77*, (pp. 275-299). Amsterdam: Elsevier.

Levine, J.D., Gordon, N.C., Smith, R. and Fields, H.L. (1982). Post-operative pain: Effect of extent of injury and attention. *Brain Research*, *234*, 500-504.

Liebeskind, J.C., & Paul, L.A.(1977). Psychological and physiological mechanisms of pain. *Annual Review of Psychology*, *28*, 41-60.

Lindblom, U., Tapper, D.N., & Wiesenfeld, Z. (1977). The effect of dorsal column stimulation on the nociceptive response of dorsal horn cells and its relevance for pain suppression. *Pain, 4*, 133-144.

Linton, S.J., Melin, L., & Götestam, K.G. (1985). *Behavioural analysis of chronic pain and its management.* In M. Hersen, A. Bellack, & H. Eisler (Eds.). Progress in Behaviour Modification, 18. NY: Academic Press.

Lloyd, M.A., & Appel, J.B. (1976). Signal detection theory and the psychophysics of pain: An introduction and review. *Psychosomatic Medicine, 38*, 79-94.

Long, D.M. (1976). Cutaneous afferent stimulation for the relief of pain. *Progress in Neurology & Surgery, 7*, 35-51.

Long, D.M., & Hagfors, N. (1975). Electrical stimulation in the nervous system: The current status of electrical stimulation of the nervous system for the relief of pain. *Pain, 1*, 109-123.

Lundeberg, T.C.M. (1983). Vibratory stimulation for the alleviation of chronic pain. *Acta Physiologica Scandinavica, Supplement 523*, 1-51.

Lundeberg, T. (1984a). Long-term results of vibratory stimulation as a pain relieving measure for chronic pain. *Pain, 20*, 13-23.

Lundeberg, T. (1984b). The pain suppressive effect of vibratory stimulation and transcutaneous electrical nerve stimulation (TENS) as compared to aspirin. *Brain Research, 294*, 201-209.

Lundeberg, T. (1985). Naloxone does not reverse the pain-reducing effect of vibratory stimulation. *Acta Anaesthesiologica Scandinavica, 29*, 212-216.

Lundeberg, T., Abrahamsson, P., Bondesson, L., & Haker, E. (1988). Effect of vibratory stimulation on experimental and clinical pain. *Scandinavian Journal of Rehabilitation Medicine, 20*, 149-159.

Lundeberg, T., Nordemar, R., & Ottoson, D. (1984). Pain alleviation by vibratory stimulation. *Pain, 20*, 25-44.

Magerl, W., & Handwerker, H.O. (1988). A reliable model of experimental itching by iontophoresis of histamine. In R. Dubner, G.F. Gebhart, & M.R. Bond (Eds.). *Proceedings of the Vth World Congress on Pain.* (pp. 536-540). NY: Elsevier.

Malow, R.M., Grimm, L., & Olsen, R.E. (1980). Differences in pain perception between myofacial pain dysfunction patients and normal subjects: A signal detection analysis. *Journal of Psychosomatic Medicine, 24*, 303-309.

Mannheimer, C., & Carlsson, C. (1979). The analgesic effect of transcutaneous electrical nerve stimulation (TENS) in patients with rheumatoid arthritis. A comparative study of different pulse patterns. *Pain, 6*, 329-334.

Mannheimer, J.S., & Lampe, G.N. (1984). *Clinical transcutaneous electrical nerve stimulation.* Philadelphia: F.A.Davis.

Marchand, S., Charest, J., Chenard, J-R., Lavignolle, B., & Laurencelle, L. (1993). Is TENS purely a placebo effect? A controlled study on chronic low back pain. *Pain, 54*, 99-106.

Martin, A., Swarbrick, J., & Cammarata, A (1983). *Physical Pharmacy*. Philadelphia: Lea & Febiger.

Mayer, D.J., & Liebeskind, J.C. (1974). Pain reduction by focal electrical stimulation of the brain: An anatomical and behavioural analysis. *Brain Research, 68*, 73-93.

Mayer, D.J., & Price, D.D. (1976). Central nervous system mechanisms of analgesia. *Pain, 2*, 379-404.

Mayer, D.J., & Price, D.D., & Raffi, A. (1977). Antagonism of acupuncture analgesia in man by the narcotic antagonist naloxone. *Brain Research, 121*, 368-372.

Mazars, G.J. Merienne, L., & Cioloca, C. (1976). Contribution of thalamic stimulation to the physiopathology of pain. In: J.J. Bonica and D. Albe-Fessard (Eds.), *Advances in Pain Research and Therapy, Vol 1*, (pp. 483-485). NY: Raven Press.

Mazars, G.J. Merienne, L , & Cioloca, C. (1979). Comparative study of electrical stimulation of posterior thalamic nuclei, periaqueductal gray and other midline mesencephalic structures in man. In: J.J. Bonica, J.C. Liebeskind, and D. Albe-Fessard (Eds.), *Advances in Pain Research and Therapy, Vol 3*, (pp. 541-546). NY: Raven Press.

McCormack, H.M., Horne, D., & Sheather, S. (1988). Clinical applications of visual analogue scales: A critical review. *Psychological Medicine, 18*, 1007-1019.

McCallum, P., & Goldberg, H. (1975). Magnitude scales for electrocutaneous stimulation. *Perception & Psychophysics, 17*, 75-78.

McCaul, K.D. & Malott, J.M. (1984). Distraction and coping with pain. *Psychological Bulletin, 95*, 516-533.

McGrath, P.A. (1987). An assessment of children's pain: A review of behavioural, physiological and direct scaling techniques. *Pain, 31*, 147-176.

McMahon, S.B., & Wall, P.D. (1984). Receptive fields of rat lamina 1 projection cells move to incorporate a nearby region of injury. *Pain, 19*, 235-247.

Meinhart, N.T., & McCaffery, M. (1983). *Pain: A nursing approach to assessment and analysis.* Connecticut: Appleton-Century-Crofts.

Melzack, R. (1975a). The McGill pain questionnaire: Major properties and scoring methods. *Pain, 1*, 277-299.

Melzack, R. (1975b). Prolonged relief of pain by brief, intense transcutaneous somatic stimulation. *Pain, 1*, 357-373.

Melzack, R. (1985). Concepts of pain measurement. In R. Melzack (Ed.). *Pain measurement and assessment*, (pp. 1-6). NY: Raven.

Melzack, R., & Schecter, B. (1965). Itch and vibration. *Science, 147*, 1047-1048.

Melzack, R., & Torgerson, W.S. (1971). On the language of pain. *Anesthesiology, 34*, 50-59.

Melzack, R., & Wall, P.D.(1965). Pain mechanisms: A new theory. *Science, 150*, 971- 979.

Melzack, R., & Wall, P.D. (1988). *The Challenge of pain* (2nd ed.). London; Penguin Books

Mendell, L.M. (1966). Physiological properties of the unmyelinated fiber projection to the spinal cord. *Experimental Neurology, 16*, 316-332.

Mendell, L.M., & Wall, P.D.(1964). Presynaptic hyperpolarization: A role for fine afferent fibres. *Journal of. Physiology, 172*, 274-294.

Mendell, L.M., & Wall, P.D.(1965). Responses of single dorsal cord cells to peripheral cutaneous unmyelinated fibres. *Nature*, *206*, 97-99.

Mense, S., & Schmidt, R.F. (1974). Activation of group IV afferent units from muscle by algesic agents. *Brain Research*, *72*, 305-310.

Mersky, H. (1986). Classification of chronic pain. *Pain*, *3 (Supplement)*, 215-217.

Meyer, R.A., & Campbell, J.N. (1981). Myelinated nociceptor afferents account for the hyperalgesia that follows a burn to the hand. *Science*, *213*, 1527-1529.

Meyerson, B.A. (1983). Electrostimulation procedures: Effects, presumed rationale, and possible mechanisms. In: J.J. Bonica, U. Lindblom and A. Iggo (Eds.), *Advances in Pain Research and Therapy, Vol 5*, (pp. 495-534). NY: Raven Press.

Miron, D., Duncan, G.H., & Bushnell, M.C. (1989). Effects of attention on the intensity and unpleasantness of thermal pain. *Pain*, *39*, 345-352.

Monk, B.E. (1993). Transcutaneous electronic nerve stimulation in the treatment of generalized pruritus. *Clinical and Experimental Dermatology*, *18*, 67-68

Monnier, M. (1975). *Functions of the nervous system, Vol 3, Sensory functions and perception*. NY: Elsevier.

Mumford, J.M. & Bowsher, D. (1976). pain and protopathic sensibility. A review with particular reference to the teeth. *Pain*, *2*, 223-243.

Murphy, A.Z., & Behbehani, M.M. (1993). Role of norepinephrine in the interaction between the lateral reticular nucleus and the nucleus raphe magnus: An electrophysiological and behavioural study. *Pain*, *55*, 183-193.

Murrin, K.R., & Rosen, M. (1962). Measurement of pain. In C.A. Keele (Ed.). *Assessment of pain in man and animals* (pp. 17-38). Edinburgh: Livingston.

Nashold, B.S., & Friedman, H. (1972). Dorsal column stimulation for control of pain. Preliminary report on 30 patients. *Journal of Neurosurgery*, *36*, 590-597.

Nathan, P.W.(1976). The gate control theory of pain: A critical review, *Brain*, *99*, 123-158.

Nathan, P.W., & Wall, P.D. (1974). Treatment of post herpetic neuralgia by prolonged electrical stimulation. *British Medical Journal*, *3*, 645-647.

Nelson, R.M. & Currier, D.P. (1991). *Clinical Electrotherapy* (2nd. ed.). NY: Appleton & Lange.

Nielson, K.D. Adams, J.E., & Hosobuchi, Y. (1975). Phantom limb pain. Treatment with dorsal column stimulation. *Journal of Neurosurgery, 42*, 301-307.

Norusis, M.J. (1988). *SPSS/PC+ Advanced Statistics Guide* (2nd ed.). Chicago: SPSS Inc.

Notterman, S.L.H. (1966). Measurement of the pain threshold determined by electrical stimulation and its clinical application: Part 1. Method and factors possibly influencing the pain threshold. *Neurology, 16*, 1071-1086.

Ohnhaus, E.E., & Adler, R. (1975). Methodological problems in the measurement of pain: A comparison between the verbal rating scale and the visual analogue scale. *Pain, 1*, 379-84.

Oliveras, J.L., Besson, J.M. Guilbaud, G., & Liebeskind, J.C. (1974). Behavioural and electrophysiological evidence of pain inhibition from midbrain stimulation in the cat. *Experimental Brain Research, 20*, 32-44.

Ong, B., Singer, G., & Wallace, M. (1980). Pain sensations produced by alogens in humans. In Peck, C., & Wallace, M. (Eds.). *Problems in pain* (pp. 101-110). Sydney: Pergammon Press.

Ottoson, D., Ekblom, A., & Hansson, P. (1981). Vibratory stimulation for the relief of pain of dental origin. *Pain, 10*, 37-45.

Over, R. (1980). Clinical and experimental pain. In Peck, C., & Wallace, M. (Eds.). *Problems in pain* (pp. 94-98). Sydney: Pergammon Press.

Pantaleo,T., Duranti, R., & Bellini, F. (1986). Effects of vibratory stimulation on muscular pain threshold and blink response in human subjects. *Pain, 24*, 239-250.

Parker, S., Casey, J., Ziriax, J.M., & Silberberg, A. (1988). Random monotone data fit simple algebraic models: Correlation is not confirmation. *Psychological Bulletin, 104*, 417-423.

Parry, W.C.B. (1980). Pain in avulsion lesions of the brachial plexus. *Pain, 9*, 41-53.

Perl, E.R. (1968). Myelinated afferent fibres innervating the primate skin and their response to noxious stimuli. *Journal of Physiology, 197*, 593-615.

Perl, E.R., Kumazawa, T., Lynn, B., & Kenins, P. (1076). Sensitization of high-threshold receptors with unmyelinated (C) afferent fibers. *Progress in Brain Research, 43*, 263-276.

Pertovaara, A. (1979). Modification of human pain threshold by specific tactile receptors. *Acta Physiologica Scandinavica, 107*, 339-341.

Pertovaara, A., & Kemppainen, P. (1981). The influence of naloxone on dental pain threshold elevation produced by peripheral conditioning stimulation at high frequency. *Brain Research, 215*, 426-429.

Pohl, M., Collin, E., Bourgoin, S., Clot, A.M., Hamon, M., Cesselin, F., & Le Bars, D. (1992). In vivo release of calcitonin gene-related peptide-like material from the cervicotrigeminal area in the rat. Effects of electrical and noxious stimulations of the muzzle. *Neuroscience, 50*, 697-706.

Pomeranz, B., & Chiu, D. (1976). Naloxone blockade of acupuncture analgesia: Endorphin implicated. *Life Science, 19*, 1757-1762.

Poulton, E.C. (1967). Population norms of top sensory magnitudes and S.S. Steven's exponents. *Perception & Psychophysics, 2*, 312-316.

Poulton, E.C. (1968). The new psychophysics: Six models for magnitude estimation. *Psychological Bulletin, 69*, 1-19.

Poulton, E.C. (1975). Range effects in experiments on people. *American Journal of Psychology, 88*, 3-32.

Poulton, E.C. (1979). Models for biases in judging sensory magnitude. *Psychological Bulletin, 86*, 777-803.

Poulton, E.C. (1984). A linear relation between loudness and decibels. *Perception & Psychophysics, 36*, 338-342.

Price, D.D. (1972). Characteristics of second pain and flexion reflexes indicative of prolonged central summation. *Experimental Neurology, 37*, 371-387.

Price, D.D. (1988). *Psychological and neural mechanisms of pain.* NY: Raven Press.

Price, D.D., Barrell, J.J., & Gracely, R.H. (1980). A psychophysical analysis of experiential factors that selectively influence the affective dimension of pain. *Pain, 8*, 137-139.

Price, D.D., Harkins, S.W., & Baker, C. (1987). Sensory-affective relationships among different types of clinical and experimental pain. *Pain, 28*, 297-307.

Price, D.D., Harkins, S.W., Raffi, A., & Price, C. (1986). A simultaneous comparison of fentanyl's analgesic effects on experimental and clinical pain. *Pain, 24*, 197-203.

Price, D.D., Hayes, R.L., Ruda, M., & Dubner, R. (1978). Spatial and temporal transformations of input to spinothalamic tract neurons and their relation to somatic sensations. *Journal of Neurophysiology, 41*, 933-946.

Price, D.D, Hu, J.W., Dubner, R., & Gracely, R.H. (1977). Peripheral suppression of first pain central summation of second pain evoked by noxious heat pulses. *Pain, 3*, 57-68.

Price, D.D., McGrath, P.A., Raffi, A., & Buckingham, B. (1983). The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain, 17*, 45-56.

Price, D.D., & McHaffie, J.G. (1988). Effects of heterotopic conditioning stimuli on first and second pain in a psychophysical evaluation in humans. *Pain, 34*, 245-252.

Price, D.D., & Wagman, I.H. (1970). Physiological roles of A and C fibre inputs to the spinal dorsal horn of Macaca mulatta. *Experimental Neurology, 29*, 383-399.

Price, K.P., & Tursky, B. (1975). The effect of varying stimulus parameters on judgments of nociceptive electrical stimulation. *Psychophysiology, 12*, 663-666.

Procacci, P., & Maresca, M. (1984). General considerations in pain measurement in man. In: B. Bromm (Ed.), *Pain measurement in man: Neurophysiological correlates of pain* (pp. 431-434). NY: Elsevier

Qiao, T., & Dafny, N. (1988). Dorsal raphe stimulation modulates nociceptive responses in thalamic parafascicular neurons via an ascending pathway: further studies on ascending pain modulation pathways. *Pain, 34*, 65-74.

Ranck, J.B. Jr. (1980). Electrical stimulation of neural tissue. In R.F. Rusher (Ed.). *Methods in medical research, Vol 11*, (pp. 262-269). Chicago: Year Book Publishers.

Ranck, J.B. Jr. (1981). Extracellular stimulation. In M.M. Patterson & R.P. Kesner (Eds.). *Electrical stimulation research techniques* (pp. 1-36). NY: Academic press.

Richardson, D.E., & Akil, H. (1977). Pain reduction by electrical brain stimulation in man. Part 1. Acute administration in periaqueductal and periventricular sites. *Journal of Neurosurgery, 47*, 178-183.

Rivot, J.P. Chaouch, A., & Besson, J.M. (1979). The influence of naloxone on the C fibre response of dorsal horn neurones and their inhibitory control by raphe magnus stimulation. *Brain Research, 176*, 355-364.

Rivot, J.P. Chaouch, A., & Besson, J.M. (1980). Nucleus raphe magnus modulation of responses of rat dorsal horn neurons to unmyelinated fibre inputs: Partial involvement of serotonergic pathways. *Journal of Neurophysiology, 44*, 1039-1057.

Roberts, W.A., Eaton, S.A., & Salt, T.E. (1992). Widely distributed GABA-mediated afferent inhibition processes within the ventrobasal thalamus of rat and their possible relevance to pathological pain states and somatotropic plasticity. *Experimental Brain Research, 89*, 363-372.

Roby-Brami, A., Bussel, B., Willer, J.C., & Le Bars, D. (1987). An electrophysiological investigation into the pain-relieving effects of heterotropic nociceptive stimuli. *Brain, 110*, 1497-1508.

Rollman, G.B. (1974). Electrocutaneous stimulation. In F. A. Geldard (Ed.). *Cutaneous communication systems and devices* (pp. 38-51). Austin, TX: Psychonomic Society.

Rollman, G.B. (1977). Signal detection theory measurement of pain: A review and critique. *Pain, 3*, 187-211.

Rollman, G.B., & Harris, G. (1987). The detectability, discriminability, and perceived magnitude of painful electric shock. *Perception & Psychophysics, 42*, 257-268.

Ruda, M.A. (1982). Opiates and pain pathways: demonstration of enkephalin synapses on dorsal horn projection neurons. *Science, 215*, 1523-1524.

Rupp, W., Badian, M., Farber, G., Malerczyk, V., & Sittig, W. (1984). Analgesic effects of acetylsalicylic acid, HP 494, and placebo on standardized ischemic pain in healthy volunteers. In: B. Bromm (Ed.), *Pain measurement in man: Neurophysiological correlates of pain* (pp. 483-489). NY: Elsevier

Salter, M.W., & Henry, J.L. (1986). Differential effects of peripheral vibration on nociceptive versus non-nociceptive neurones in the lumbar dorsal horn of the cat. Neuroscience Abstracts, 12, 736.

Salter, M.W., & Henry, J.L. (1987). Evidence that adenosine mediates the depression of spinal dorsal horn neurons induced by peripheral vibration in the cat. *Neuroscience, 22,* 631-650.

Salter, M.W., & Henry, J.L. (1989). Physiological characteristics of response of wide dynamic range spinal neurones to cutaneously applied vibration in the cat. *Brain Research, 507,* 69-84.

Salter, M.W., & Henry, J.L. (1990). Differential responses of nociceptive vs non-nociceptive spinal dorsal horn neurones to cutaneously applied vibration in the cat. *Pain, 40,* 311-322.

Schoenmacker, J.N., & Willemsted, C. (1979). Psychological evaluation of pain relief. In J. Beks (Ed.). *The management of pain* (pp. 374-390). Oxford: Exerpta Medica.

Scott, J, & Huskisson, E.C. (1976). Graphic representation of pain. *Pain, 2,* 175-184.

Sessle, B.J. Hu, J.W., Dubner, R., & Lucier, G.E. (1981). Functional properties of neurons in cat trigeminal subnucleus caudalis (medullary dorsal horn). II. Modulation of responses to noxious and nonnoxious stimuli by periaqueductal gray, nucleus raphe magnus, cerebral cortex, and afferent influences, and effect of naloxone. *Journal of Neurophysiology, 45,* 193-207.

Shealey, C.N., Mortimer, J.T., & Hagfors, N.R. (1970). Dorsal column electroanalgesia. *Journal of Neurosurgery, 32,* 560-564.

Shin, H.K., Kim, J , & Chung, J.M. (1986). Inhibition and excitation of the nociceptive flexion reflex by conditioning stimulation of a peripheral nerve in the cat. *Experimental Neurology, 92,* 335-348.

Sicuteri, F., Franchi, G., & Michelacci, S. (1974). Biochemical mechanisms of ischemic pain. In J. Bonica. (Ed.) *Advances in Neurology: Vol 4. International Symposium in Pain* (pp. 39-44). NY: Raven Press.

Siddiqui, O., Roberts, M., & Pollack, A.E. (1985). The effect of iontophoresis and vehicle pH on the in-vitro permeation of lignocaine through human striatum corneum. *Journal of Pharmaceutical Pharmacology, 37*, 732-735.

Sjölund, B.H. (1979). Peripheral nerve stimulation suppression of C-fibre evoked flexion reflex in rats. Part 1. Parameters for continuous stimulation. *Journal of Neurosurgery, 63*, 612-616.

Sjölund, B.H. (1985). Peripheral nerve stimulation suppression of C-fibre-evoked flexion reflex in rats. *Journal of Neurosurgery, 63*, 612-616.

Sjölund, B.H., & Eriksson, M.B.E. (1979a). Naloxone-reversible depression of C-fibre evoked flexion reflex in low spinal cats after conditioning electrical stimulation of primary afferents. *Neuroscience. Letters, Supplement 3*, S264.

Sjölund, B.H., & Eriksson, M.B.E. (1979b). The influence of naloxone on analgesia produced by peripheral conditioning stimulation. *Brain Research, 173*, 295-301.

Smith, G.M., & Beecher, H.K. (1968). Experimental production of pain in man: Sensitivity of a new method to 600 mg. of aspirin. *Clinical Pharmacology and Therapeutics, 10*, 213-216.

Somjen, G.G. (1979). Extracellular potassium in the mammalian central nervous system. *Annual Review of Physiology, 41*, 159-177.

Sriwatanaku, K., Kelvie, W., Lasagna, L., Caliman, J., Weis, O., & Mehta, G. (1983). Studies with different types of visual analogue scales for measurement of pain. *Clinical & Pharmacological Therapeutics, 34*, 235-239.

Staddon, J.E.R., King, M., & Lockhead, G.R. (1980). On sequential effects in absolute judgment experiments. *Journal of Experimental Psychology: Human Perception and Performance, 6*, 290-301..

Stam, H.J., Petrusic, W.M., & Spanos, N.P. (1981). Magnitude scales for cold pressor pain. *Perception & Psychophysics, 29*, 612-617.

Staub, E., Tursky, B., & Schwartz, G.E. (1971). Self-control and predictability: Their effects on reactions to aversive stimuli. *Journal of Personality and Social Psychology, 18*, 157-162.

Steedman, W.M., Molony, V , & Iggo, A. (1985). Nociceptive neurons in the superficial dorsal horn of the cat lumber spinal cord and their primary afferent inputs. *Experimental. Brain Research, 58*, 171-182.

Steig, R.L., Williams, R.C., Timmermans-Williams, G., Tafuro, F., & Gallagher, L.A. (1986). Cost benefits of interdisciplinary chronic pain treatment. *Clinical Journal of Pain, 1*, 189-193.

Sternbach, R.A. (1968). *Pain: A psychophysiological analysis*, NY: Academic Press.

Sternbach, R.A., Deems, L.M., Timmermans, G., & Huey, L.Y. (1977). On the sensitivity of the tourniquet pain test. *Pain, 3*, 105-110.

Sternbach, R.A., Murphy, R.W., Timmermans, G., Greenhoot, J.H., & Akeson, W.H. (1974). Measuring the severity of clinical pain. In J. Bonica. (Ed.) *Advances in Neurology: Vol 4. International Symposium in Pain* (pp. 281-288). NY: Raven Press.

Stevens, S.S. (1957). On the psychophysical law. *Psychological Review, 64*, 153-181.

Stevens, S.S. (1965). Matching functions between loudness and ten other continua. *Perception & Psychophysics, 1*, 5-8.

Stevens, S.S., Carton, A.S., & Shickman, G.M. (1958). A scale of apparent intensity of electric shock. *Journal of Experimental Psychology, 56*, 328-334.

Sticht, T.G., & Foulke, E. (1966a). Reaction time to electrocutaneous onset and offset stimulation. *Psychonomic Science, 4*, 213-214.

Sticht, T.G., & Foulke, E. (1966b). Reaction time to the onset and offset of electrocutaneous stimulation as a function of rise and decay time. *Perception & Psychophysics, 1*, 361-365.

Sweet, W.H., & Wepsic, J.G. (1974). Stimulation of the posterior columns of the spinal cord for pain control: Indications, technique and results. *Clinical Neurosurgery, 21*, 278-310.

Talbot, J.D., Duncan, G.H., & Bushnell, M.C. (1989). Effects of diffuse noxious inhibitory controls (DNICs) on the sensory-discriminative dimension of pain. *Pain, 36*, 231-238.

Talbot, J.D., Duncan, G.H., Bushnell, M.C., & Boyer, M. (1987). Diffuse noxious inhibitory controls (DNICs): Psychophysical evidence in man for intersegmental suppression of noxious heat perception by cold pressor pain. *Pain, 30*, 221-232.

Tashiro, T., & Higashiyama, A. (1981). The perceptual properties of electrocutaneous stimulation: Sensory quality, subjective intensity, and intensity-duration relation. *Perception & Psychophysics, 30*, 579-586.

Teghtsoonian, R. (1973). Range effects in psychophysical scaling and a revision of Stevens' law. *American Journal of Psychology, 86*, 3-27.

Teghtsoonian, M., & Teghtsoonian, R. (1983). Consistency of individual exponents in cross-modal matching. *Perception & Psychophysics, 33*, 203-214.

Teghtsoonian, R., & Teghtsoonian, M. (1986). Scaling loudness over short ranges: A reply to Poulton. *Perception & Psychophysics, 39*, 73-75.

Thalhammer, J.G., & LaMotte, R.H. (1982). Spatial properties of nociceptor sensitization following heat injury of the skin. *Brain Research, 231*, 257-265.

Thomas, D.A., Anton, F., Kenshalo, D.R., Williams, G.M. Jr., Dubner, R. (1993). Noradrenergic and opioid systems interact to alter the detection of noxious thermal stimuli and facial scratching in monkeys. *Pain, 55*, 63-70.

Thompson, S.W.N., & Woolf, C.J. (1991). Primary afferent-evoked prolonged potentials in the spinal cord and their central summation: Role of NMDA receptor. In: M.R. Bond, J.E. Charlton and C.J. Woolf (Eds.), *Proceedings of the VIth World Congress on Pain, Vol 4, Pain Research and Clinical Management*, (pp. 291-297). NY: Elsevier.

Torebjörk, H.E. (1974). Afferent C units responding to mechanical, thermal and chemical stimuli in human non-glabrous skin. *Acta Physiologica Scandinavica, 92*, 374-390.

Torebjörk, H.E. (1994). Nociceptor dynamics in humans. In G.F. Gebhart, D.L. Hammond, & T.S. Jensen(Ed.s). *Proceedings of the 7th World Congress on pain, Vol 2, Progress in pain research and management.* Seattle: IASP Press.

Torebjörk, H.E., & Hallin, R.G. (1973). Perceptual changes accompanying controlled preferential blocking of A and C fibre responses in intact human skin nerves. *Experimental Brain Research, 16*, 321-332.

Torebjörk, H.E., & Hallin, R.G. (1974). Identification of afferent C units in intact human skin nerves. *Brain Research, 67*, 387-403.

Torebjörk, H.E., & Hallin, R.G. (1976). Skin receptors supplied by unmyelinated (C) fibres in man. In: Y. Zotterman (ed.), *Sensory function of the skin in primates*, (pp. 475-487). Oxford: Pergamon

Torebjörk, H.E., LaMotte, R.H., & Robinson, C.J. (1984). Peripheral neural correlates of magnitude of cutaneous pain and hyperalgesia: Simultaneous recordings in humans of sensory judgments of pain and evoked responses in nociceptors with C-fibres. *Journal of Neurophysiology, 51*, 325-339.

Torebjörk, H.E., & Ochoa, J.L. (1980). Specific sensations evoked by activity in single identified sensory units in man. *Acta Physiologica Scandinavica, 110*, 445-447.

Treede, R-D, Jahnke, M.T., & Bromm, B. (1984). Functional properties of CO_2 Laser activated nociceptive fibres in an intact human skin nerve. In: B. Bromm (Ed.), *Pain measurement in man: Neurophysiological correlates of pain* (pp. 65-78). NY: Elsevier

Turk, D.C., Meichenbaum, D. & Genest, M. (1983). *Pain and behavioural medicine: A cognitive behavioural perspective.* NY: Academic Press.

Tursky, B. (1974). Physical, physiological, and psychosocial factors that effect pain reaction to shock. *Psychophysiology, 11*, 95-112.

Tursky, B., Jamner, L.D., & Friedman, R. (1982). The pain perception profile: A psychophysical approach to the assessment of pain report. *Behaviour Therapy, 13*, 376-394.

Tursky, B., & O'Connell, D. (1972). Reliability and interjudgment predictability of subjective judgments of electrocutaneous stimulation. *Psychophysiology, 9*, 290-295.

Tursky, B., & Watson, P.D. (1964). Controlled physical and subjective intensities in electric shock. *Psychophysiology, 1*, 151-162.

Tyle, P., & Kari, B. (1988). Iontophoretic devices. In P. Tyle (Ed.). *Drug delivery devices: Fundamentals and* applications (pp.421-454). NY: Dekker.

Uchida, Y., & Murao, S. (1974). Potassium-induced excitation of afferent cardiac sympathetic nerve fibres. *American Journal of Physiology, 226*, 603-607.

Valbo, A.B., Hagbarth, K.E. (1968). Activity from skin mechanoreceptors recorded percutaneously in awake human subjects. *Experimental Neurology, 21*, 270-289.

Van Den Honert, C., & Mortimer, J.T. (1981). A technique for collision block of peripheral nerve: Single stimulus analysis. *IEEE Transactions of the Biomedicine and Engineering, 28*, 373-378.

Van Hees, J. (1976). C fibre input during painful and non-painful skin stimulation with radiant heat. In: J.J. Bonica and D. Albe-Fessard (Eds.), *Advances in Pain Research and Therapy, Vol 1,* (pp. 35-40). NY: Raven Press.

Van Hees, J., & Gybels, J.M. (1972). Pain related to single afferent C fibres from human skin. *Brain Research, 48*, 397-400.

Van Hees, J., & Gybels, J.M. (1981). C-nociceptor activity in human nerve during painful and non painful skin stimulation. *Journal of Neurology Neurosurgery and Psychiatry, 44*, 600-607.

Vierck, C.J., Cooper, B.Y., Franzén, O., Ritz, L.A., & Greenspan, J.D. (1983). Behavioural analysis of CNS pathways and transmitter systems involved in conduction and inhibition of pain sensations and reactions in primates. In: J.M. Sprague and A.N. Epstein (Eds.), *Progress in Psychobiological and Physiological Psychology, Vol. 10.* (pp. 113-165). NY: Academic Press.

Villanueva, L., Bing, Z., Bouhassira, D., & Le Bars, D. (1989). Encoding of electrical, thermal, and mechanical noxious stimuli by subnucleous reticularis dorsalis neurons in the rat medulla. *Journal of Neurophysiology, 61*, 391-402.

Voudouris, N.J. (1981). *The conditionability of positive and negative placebo effects in experimental pain.* Unpublished honour's thesis, La Trobe University, Victoria, Australia.

Voudouris, N.J., Peck, C., & Coleman, G. (1985). Conditioned placebo responses. *Journal of Personality & Social Psychology, 48*, 47-53.

Voudouris, N.J., Peck, C., & Coleman, G. (1989). Conditioned response models of placebo phenomena: Further support. *Pain, 38*, 109-116.

Wagman, I.H., & Price, D.D. (1969). Responses of dorsal horn cells of M. mulatta to cutaneous and sural nerve A and C fibre stimuli. *Journal of Neurophysiology, 32*, 803-817.

Wall, P.D. (1978). The gate control theory of pain mechanism. A re-examination and re-statement. *Brain, 101*, 1-18.

Wall, P.D. (1988). Stability and instability of central pain mechanisms. In: R. Dubner, G.F. Gebhart, and M.R. Bond (Eds.), *Proceedings of the Vth World Congress on Pain, Vol 3, Pain Research and Clinical Management* (pp. 13-24). NY: Elsevier..

Wall, P.D., & Cronly-Dillon, J.R. (1960). Pain, itch, and vibration. *Archives of Neurology, 2*, 365-375.

Wall, P.D., & Gutnick, M. (1974). Ongoing activity in peripheral nerves. *Experimental Neurology, 43*, 580-593.

Wall, P.D., & Sweet, W.H. (1967). Temporary abolition of pain in man. *Science, 155*, 108-109.

Wall, P.D., & Woolf, C.J. (1984). Muscle but not cutaneous C-afferent input produces prolonged increases in the excitability of the flexion reflex in the rat. *Journal of Physiology, 356*, 443-458.

Ward, L.M. (1979). Stimulus information and sequential dependencies in magnitude estimation and cross-modality matching. *Journal of Experimental Psychology: Human Perception and Performance, 5*, 444-459.

Ward, L.M. (1987). Repeated magnitude estimations with a variable standard: Sequential effects and other properties. *Perception & Psychophysics, 13*, 193-200.

Weisenberg, M. (1977). Pain and pain control. *Psychological Bulletin, 84*, 1088-1044.

Willer, J.C., Bergeret, S., & Gaudy, J-H.(1985). Epidural morphine strongly depresses nociceptive flexion reflexes in patients with postoperative pain. *Anesthesiology, 63*, 675-680.

Willer, J.C., De Broucker, T., & Le Bars, D. (1989). Encoding of nociceptive thermal stimuli by diffuse noxious inhibitory controls in humans. *Journal of Neurophysiology, 62*, 1028-1038.

Willer, J.C., Roby, A., & Le Bars, D. (1984). Psychophysical and electrophysical approaches to the pain-relieving effects of heterotopic nociceptive stimuli. *Brain, 107*, 1095-1112.

Willis, W.D. (1985). *The pain system.* NY: Karger.

Willis, W.D. (1988). Anatomy and physiology of descending control of nociceptive responses of dorsal horn neurons: Comprehensive review. *Progress in Brain Research, 77*, 1-29.

Willis, W.D., & Coggeshall, R.E. (1978). Sensory mechanisms of the spinal cord. NY ; Plenum Press.

Wolff, B.B. (1977). The role of laboratory pain induction methods in the systematic study of human pain. *Acupuncture and Electrotherapeutic Research International Journal, 2*, 271-305.

Wolff, B.B. (1984). Methods of testing pain mechanisms in normal man. In P.D. Wall and R. Melzack (Eds.). *Textbook of pain.* (pp. 186-194). NY: Churchill Livingston.

Wolff, B.B., & Jarvik, M.E. (1964) "Relationship between superficial and deep somatic thresholds of pain with a note on handedness". *American Journal of Psychology, 77*, 580-599.

Woodforde, J.M. & Merskey, H. (1972). Some relationships between subjective measures of pain. *Journal of Psychosomatic Research, 16*, 173-178.

Woolf, C.J. (1983). Evidence for a central component of post-injury pain hypersensitivity. *Nature, 306*, 686-688.

Woolf, C.J. (1989). Segmental afferent fibre-induced analgesia: Transcutaneous electrical nerve stimulation (TENS) and vibration. In: R. Melzack and P.D. Wall (Eds.), *Textbook of Pain,* (pp. 884-896). Edinburgh : Churchill Livingstock.

Woolf, C.J., & King, A.E. (1990). Dynamic alterations in the cutaneous mechanoreceptive fields of dorsal horn neurons in the rat spinal cord. *Journal of Neuroscience, 10*, 2717-2726.

Woolf, C.J., Mitchell, D., & Barrett, G.D. (1980). Antinociceptive effect of peripheral segmental electrical stimulation in the rat. *Pain, 8*, 237-252.

Woolf, C.J., & Wall, P.D. (1982). Chronic peripheral nerve section diminishes the primary afferent A-fibre mediated inhibition of rat dorsal horn neurones. *Brain Research, 242*, 77-85.

Yaksh, T.L. (1986). *Spinal Afferent Processing.* NY: Plenum.

Yang, J.C., Richlin, D., Brand, L., Wagner, J., & Clark, W.C. (1985). Thermal sensory decision theory indices and pain threshold in chronic pain patients and healthy volunteers. *Psychosomatic Medicine*, *47*, 461-468.

Yarnitsky, D., & Ochoa, J.L. (1990). Studies of heat pain sensation in man: perception thresholds, rate of stimulus rise and reaction time. Pain, 40, 85-91.

Yezierski, R.P. (1990). Effects of midbrain and medullary stimulation on spinomesencephalic tract cells in the cat. *Journal of Neurophysiology*, *63*, 240-255.

Yezierski, R.P., Gerhart, R.D., Schrock, B.J., & Willis, W.D. (1983). A further examination of the effects of cortical stimulation on primate spinothalamic tract cells. *Journal of Neurophysiology*, *49*, 424-441.

Young, R.F. (1978). Experimental modulation of medullary dental pulp units by mechanical stimulation of orofacial fields. *Experimental Neurology*, *49*, 813-821.

Young, R.F., & Nord, S.G. (1975). Experimental modulation of medullary dental pulp units by mechanical stimulation of orofacial fields. *Experimental Neurology*, *49*, 813-821.

Zimmermann, M. (1979). Peripheral and central nervous mechanisms of nociception, pain and pain therapy: Facts and hypothesis. In: J.J. Bonica, J.C. Liebeskind and D. Albe-fessard (Eds.), *Advances in Pain Research and Therapy*, *Vol 3*, (pp.3-32). NY: Raven Press.

Zimmermann, M. (1984). Neurobiological concepts of pain, its assessment and therapy. In: B. Bromm (Ed.), *Pain measurement in man: Neurophysiological correlates of pain* (pp. 15-35). NY: Elsevier

Zwetnow, N.N. (1979a). Is pain measurable? In J. Beks (Ed.). *The management of pain* (pp. 212-229). Oxford: Exerpta Medica.

Zwetnow, N.N. (1979b). The significance of experimental work in pain research. In J. W. Beks (Ed.). *The management of pain* (pp. 196-211). NY: Elsevier.

Zwislocki, J.J., & Goodman, D.A. (1980). Absolute scaling of sensory magnitudes: A validation. *Perception & Psychophysics*, *28*, 28-38.

APPENDIX A

PUBLICATION OF EXPERIMNTS ONE, TWO AND THREE IN THE JOURNAL 'PERCEPTION & PSYCHOPHYSICS'

APPENDIX B

SUBJECT CONSENT FORM USED IN EXPERIMENT ONE

CONSENT FORM FOR EXPERIMENTAL SUBJECTS

IONTOPHORETIC PAIN STIMULUS EXPERIMENT

I am requesting the help of students to assist by volunteering as subjects for an experiment.

The purpose of the experiment is to investigate the reliability and validity of a pain stimulus. The stimulus holds some promise in being able to be delivered in controlled and accurate amounts. This would be of benefit in pain research studies.

In the experiment in which you are being asked to participate you would be required to attend four sessions.

Session 1: One hour. Familiarisation with the response form and exposure to all levels of the pain stimuli to be used in the experiment.

Sessions 2, 3, 4: 1 1/2 hours each. Exposure to 60 trials of the pain stimuli at varying intensities and stimulus durations (from 1 to 4 seconds).

The nature of the pain stimulus is the application of potassium ions to the skin (the forearm) using an electric current. The electric current itself is not sufficient to produce any shock. This type of pain stimulus does not produce any permanent tissue damage.

Once all the data is collected, and before analysis, all names will be removed and the data identified by code numbers only, ensuring your complete anonymity.

At the end of the study there will be a debriefing and an opportunity for you to ask any questions you may have. For those interested a copy of the written report will be supplied.

If you are prepared to participate in this study please sign below. I remind you that the purpose of this consent form is to give you some idea of what the experiment requires of you. It is *not* a contract that in any way obliges you to complete the experiment. At any stage of the study you are free to terminate your participation.

Steven Humphries.

I volunteer to act as a subject in the experiment outlined above.

Subject name: .....

Signature: ..... Date: .....

APPENDIX C

SUBJECT MEDICAL CHECKLIST USED IN EXPERIMENT ONE

SUBJECT MEDICAL CHECK-LIST

IONTOPHORETIC PAIN STIMULUS EXPERIMENT

Subject name .....

Please answer the following questions by circling the appropriate response.

1) Are you in good health? yes / no

2) Do you have any known heart condition? yes / no

3) Have you ever had any form of epilepsy? yes / no

4) Are you currently using medication of any type? yes / no

5) Are you pregnant? yes / no

6) In the past 6 months have you suffered from any painful injury or condition that has lasted more than a week? yes / no

7) Have you ever had an injury or any medical condition that you think may affect your ability to sense pain? yes / no

If you have any doubts about your health you should not participate in this study.

Signature: ..... Date: .....

APPENDIX D

QUESTIONNAIRE USED IN EXPERIMENT ONE

POTASSIUM IONTOPHORESIS PAIN EXPERIMENT QUESTIONNAIRE

Subject name .....

1) Would you describe the pain stimulus used as being realistically painful?

2) Can you describe the nature of the pain stimulus?

3) Did you use any particular strategy for deciding the level of the pain stimuli?

4) Did you detect any sequence in which the pain stimuli were presented?

5) Do you have any comments regarding the ethics of the experiment?

6) What did you believe the purpose of the experiment was?

7) General comments about any aspect of the experiment: