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# CENTRAL ANALGESIC EFFECTS OF THE NON-STEROIDAL ANTI- INFLAMMATORY DRUGS

A thesis presented in partial fulfilment of the  
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## ABSTRACT

In addition to their well-known peripheral analgesic effects, non-steroidal anti-inflammatory drugs also exert antinociceptive actions at the central level. However, it is not clear if these central effects are spinally or supraspinally mediated nor whether cyclooxygenase inhibition or the interaction of these drugs with neurones in a different way is responsible for these central analgesic actions. This project investigated the possible central analgesic mechanisms of action of these drugs. It involved the use of *in vitro* neonatal rat hemisectioned spinal cord preparations and sheep implanted with indwelling cervical intrathecal catheters.

The dorsal root of the neonatal rat hemisectioned spinal cord preparations was electrically stimulated in such a way to evoke excitatory postsynaptic potentials in the ipsilateral ventral root. All records from this *in vivo* technique were identified as artefacts and no further experiments were carried out.

Conscious, unrestrained, non-lame sheep chronically implanted with indwelling cervical intrathecal catheters were submitted to mechanical noxious stimulation of the left radius. They received cumulative intrathecal doses of ketoprofen, phenylbutazone, salicylic acid and tolfenamic acid as well as repetitive intrathecal administration of normal saline without significantly affecting mechanical thresholds. The same drugs and normal saline were also given intravenously and only ketoprofen and tolfenamic acid significantly raised the nociceptive thresholds.

The involvement of spinal opioidergic and  $\alpha_2$ -adrenergic mechanisms in the hypoalgesia induced by the intravenous administration of ketoprofen in sheep was investigated. The prior intrathecal administration of naloxone and atipamezole at a dose that had no effect on nociceptive thresholds and reversed the analgesia mediated by intravenous fentanyl and xylazine, respectively, almost completely reversed the antinociceptive effects mediated by intravenous ketoprofen.

These studies confirm that non-steroidal anti-inflammatory drugs can produce hypoalgesia even when inflammation is absent and, although they did not have a direct effect on the spinal cord, their analgesic action appeared to be spinally mediated by opioidergic and adrenergic descending inhibitory systems.

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## ABBREVIATIONS

|                                  |   |
|----------------------------------|---|
| [Ca <sup>2+</sup> ] <sub>i</sub> | Intracellular calcium concentration.                                  |
| 5-HT                             | Serotonin.  |
| AA                               | Arachidonic acid.   |
| ACh                              | Acetylcholine.  |
| ACSF                             | Artificial cerebral spinal fluid.                                     |
| AMPA                             | α-amino-3-hydroxy-5-methyl-4-isoxalone propionic acid.                |
| ANOVA                            | Analysis of variance.   |
| AUC                              | Area under the curve.   |
| AUC30                            | Area under the threshold change vs. time curve values for 30 minutes. |
| AUC60                            | Area under the threshold change vs. time curve values for 60 minutes. |
| BDNF                             | Brain-derived neurotrophic factor.                                    |
| C5                               | Cervical vertebra 5.  |
| CaM                              | Calcium-calmodulin complex.   |
| CaMKII                           | Calcium/calmodulin-dependent protein kinase II.                       |
| cAMP                             | 3',5'-cyclic guanosine monophosphate.                                 |
| CDI                              | Calcium-dependent inactivation.                                       |
| cGMP                             | 3',5'-cyclic guanosine monophosphate.                                 |
| CGRP                             | Calcitonin gene-related peptide.                                      |
| CNS                              | Central nervous system.   |
| COX                              | Cyclooxygenases.  |
| COX-1-li                         | COX-1-like immunoreactivity.  |
| COX-2-li                         | COX-2-like immunoreactivity.  |
| cPGI <sub>2</sub>                | Carbaprostacyclin.  |
| CSF                              | Cerebral spinal fluid.  |
| DHN                              | Dorsal horn neurones.   |
| DLF                              | Dorsolateral funiculus.   |
| DP                               | Prostaglandin D receptor.   |
| DRCAP                            | Dorsal root compound action potential.                                |
| DRG                              | Dorsal root ganglion.   |

|                       |   |
|-----------------------|---|
| DR-VRP                | Dorsal root-ventral root potential.                 |
| e.p.s.p.              | Excitatory postsynaptic potential.                  |
| EEA                   | Excitatory amino acid.                              |
| eNOS                  | Endothelial nitric oxide synthase.                  |
| EOX                   | Epoxygenases.                                       |
| EP                    | Prostaglandin E <sub>2</sub> receptor.              |
| GABA                  | $\gamma$ -Aminobutyric acid.                        |
| HETE                  | Hydroxyeicosatetraenoic acids.                      |
| i.c.v.                | Intracerebroventricular, intracerebroventricularly. |
| i.p.                  | Intraperitoneal, intraperitoneally.                 |
| i.t.                  | Intrathecal, intrathecally.                         |
| i.v.                  | Intravenous, intravenously.                         |
| IL-1 $\beta$          | Interleukin-1 $\beta$ .                             |
| iNOS                  | Inducible nitric oxide synthase.                    |
| Ins(1,4,5) <i>P</i> 3 | Inositol-(1,4,5) triphosphate.                      |
| LOX                   | Lipoxygenases.                                      |
| L-PGDS                | Lipocalin-type prostaglandin D synthase.            |
| LPS                   | Lipopolysaccharide.                                 |
| LTs                   | Leukotrienes.                                       |
| mGluRs                | Metabotropic glutamate receptors.                   |
| MSR                   | Monosynaptic compound action potential.             |
| N                     | Newtons.  |
| NF $\kappa$ B         | Nuclear factor $\kappa$ B.                          |
| NMDA                  | <i>N</i> -methyl-D-aspartate.                       |
| nNOS                  | Neuronal nitric oxide synthase.                     |
| NO                    | Nitric oxide.                                       |
| NOS                   | Nitric oxide synthase.                              |
| NRM                   | Nucleus raphe magnus.                               |
| NSAIDs                | Non-steroidal anti-inflammatory drugs.              |
| p.o.                  | <i>Per os</i> , oral administration.                |
| PAG                   | Periaqueductal grey.                                |
| PGs                   | Prostaglandins.                                     |
| PKA                   | Protein kinase A.                                   |
| PKC                   | Protein kinase C.                                   |

|                  |                                    |
|------------------|------------------------------------|
| PLA <sub>2</sub> | Phospholipase A <sub>2</sub> .     |
| PLC              | Phospholipase C.                   |
| PMNLs            | Polymorphonuclear leukocytes.      |
| PTK              | Protein tyrosine kinase.           |
| RVM              | Rostral ventromedial medulla.      |
| SP               | Substance P.                       |
| TNF- $\alpha$    | Tumour necrosis factor- $\alpha$ . |
| trkA             | Tyrosine kinase A.                 |
| trkB             | Tyrosine kinase B                  |
| Tx               | Thromboxane.                       |





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