Testing the relationship between gut permeability, elevation of systemic lipopolysaccharides and chronic disease

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Abstract

The aim of my thesis was to test whether an increase in the permeability of the gut is accompanied by an increase in the level of systemic lipopolysaccharides (LPS), also referred to as endotoxin. These two parameters were firstly concurrently determined in healthy women after the treatment with a single dose of aspirin which is thought to temporarily increase the paracellular permeability of the intestine. Gut permeability and the levels of systemic LPS in healthy women were then compared with those in women with Crohn’s disease (CD) as the latter are thought to have chronically elevated paracellular permeability of the gut. Both groups also ingested a high fat drink which is reported to results in the elevation of systemic LPS. In addition, faecal calprotectin, a biomarker of ongoing inflammation in the gut, and LPS-binding protein (LBP), a proposed indirect biomarker for the exposure to LPS in the systemic circulation, were determined both in healthy women and in those with CD.

Data indicated that both temporary and chronic increase in the paracellular permeability of the small intestine can be reliably determined by the 3-h excretion of lactulose. Further the combination of levels of faecal calprotectin and 3-h excretion of lactulose and mannitol is the most sensitive tool to distinguish between healthy subjects and those with CD. Hence, it is evident that the combination of those three parameters can be used to assess gut health. In contrast, the current available methods for the direct assessment of the systemic level of LPS/endotoxin i.e. the Limulus Amebocyte Lysate (LAL) assay for the quantification of endotoxin or ELISAs for the quantification of LPS, are not reliable as the former is interfered by constituents of serum and the latter failed to detect LPS from sources other than those provided from the manufacturer of the kit. Hence, studies suggesting that the consumption of high fat meals lead to elevations of systemic endotoxin and those suggesting that levels of
systemic endotoxin is associated with the onset of metabolic syndrome are questionable. It is therefore advisable to repeat those studies when accurate methods for the quantification of LPS/endotoxin in the systemic circulation are available.
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List of Abbreviations

AOAH  Acyloxyacyl hydrolase
CD    Crohn's disease
CD14  Cluster of differentiation 14
CRP   C-reactive protein
DA    Dispersing Agent
DCs   Dendritic cells
ELISA Enzyme-linked immunosorbent assay
GALT  Gut-associated lymphoid tissue
HDL   High-density lipoprotein
HF    High fat
IAP   Intestinal alkaline phosphatase
IBD   Inflammatory bowel disease
Ig A  Immunoglobulin A
IL-1β Interleukin-1β
INFβ  Interferon β
IRAK1 Interleukin-1 receptor-associated kinase 1
IRF3  Interferon regulatory factor 3
KO    Knock out
LAL   Limulus Amebocyte Lysate
LBP   Lipopolysaccharide-binding protein
LDL   Low density protein
LMR   Lactulose - Mannitol - Ratio
LPS   Lipopolysaccharide
LRW   LAL reagent water
LTA   Lipoteichoic acid
MALP-2 Macrophage-activating lipoprotein 2
MAPK  Mitogen-activated protein kinase
MD-2  Myeloid differentiation factor 2
MyD88 Myeloid differentiation factor 88
NF-kB Nuclear factor kB
OD    Optical density
O-PS  O-polysaccharide
OS    Oligosaccharide
PPC   Positive Product Control
PPs   Payer's patches
SHIP  SH-2 containing inositol phosphatase
TG    Triglyceride