

ENDOTOXIN --- GRAM-NEGATIVE BACTERIA

In our discussions of IMMUNO-SYNBIOTIC (probiotics + prebiotics) we repeatedly refer to endotoxin, also called lipopolysaccharide (LPS). Endotoxin is only one of many, many toxic substances produced by the gram-negative and gram-positive bacteria that dominate a rotten microbiota. (Other toxins include phenol, cresol, guanidine, D-lactate, indican, tricarballylate, hippurate, D-arabinatol, benzoate, p-hydroxybenzoate, phenylacetate, p-hydroxyphenylacetate, propionate, dihydroxyphenylpropionate.)

But LPS from gram negatives provoke the most pernicious immune reactions. Gram-negative bacilli are ultra nasty. Gram-negative sepsis can quickly become life-threatening because of its ability to cause a crash in blood pressure and to affect many organs, but especially the kidneys.

The reason gram-negatives are so lethal is because of a structural molecule in their cell walls --- endotoxin. This endotoxin, the source of life-threatening crises from gram-negative sepsis, is the very same endotoxin absorbed chronically in small quantities even from a normal gut microbiota, and in quantities sufficient to contribute to chronic disease from an abnormal gut microbiota. The dozens of strains of E. coli typically occurring in human microbiota are the major gram-negative producers of endotoxin.

Endotoxin is a lipopolysaccharide molecule (LPS) hanging from the bacterial cell wall. This LPS molecule carries a significant negative charge under physiological conditions (thus the name gram-negative). Endotoxin is released from gram-negatives as they die, but even when alive, they secrete it as a kind of deadly machine gun that perturbs countless body functions. When endotoxin binds to the immune system's Toll-like receptors, a sequential cascade of inflammation is triggered. Complicating matters is that the endotoxin is not only in the blood in gram-negative sepsis, but also in tissues and in the interstitium. --- Again --- even in the absence of a severe crisis with gram-negative sepsis, LPS produced by rotten gut microbiota can cause an unimaginable diversity of symptoms associated with Immuno-Neuro-Endocrine stress.

Malo, et al. Thyroid Hormone Positively Regulates the Enterocyte Differentiation Marker Intestinal Alkaline Phosphatase Gene. Mole Endocrinol, 2004. ----- Thyroid hormone (T3) is a critical regulator of intestinal epithelial development and homeostasis. One critical function of T3 in the intestines is the production of alkaline phosphatase. Intestinal alkaline phosphatase is a major defense against gram-negative bacteria and the endotoxin they produce.

[Note: Even though there may or may not be a direct connection between intestinal alkaline phosphatase and systemic alkaline phosphatase (primarily found in liver, kidney, and bone, but really in all cells), it is interesting to note that low serum alkaline phosphatase is one confirming indicator of low thyroid function.]

Ross, et al. Intestinal Alkaline Phosphatase is a Gut Mucosal Defense Factor. Proc Natl Acad Sci, 2008. ----- Under conditions of starvation and many chronic diseases, the gut barrier becomes impaired. Intestinal alkaline phosphatase deficiency has been identified as a major contributor to the intestinal mucosal impairment. Intestinal alkaline phosphatase has the ability to detoxify LPS and prevent bacterial invasion across the gut mucosal barrier. Intestinal alkaline phosphatase detoxifies LPS by removing the two phosphate groups found in the carbohydrates of the LPS molecule. Thus, intestinal alkaline phosphatase (with production dependent on T3 activity) functions as an adaptive mechanism to help manage potentially toxic effects of gram-negative bacteria normally found in the small intestine.

Yu. Effect of endotoxin on hormonal responses to thyrotropin and thyrotropin-releasing hormone in dogs. Am J Vet Res, 1998. Dogs were given TSH or TRH on two occasions. 24 hours before the second challenge with TSH or TRH, dogs were given 5 mcg of endotoxin/kg of body weight. Treatment with endotoxin was associated with reduced baseline concentration of T3 and increased baseline concentration of rT3 and FT4. Endotoxin resulted in reduced peak serum concentrations of TT4 after TSH and TRH. However, peak serum concentration of FT4 after TSH and TRH were not affected by endotoxin. It was concluded that endotoxin affects several aspects of thyroid gland function, including T4-binding, deiodinase activity, and the thyroid response to TSH and TRH.

SUMMARY of T3 - LPS RELATIONSHIP: We have a positive feedback loop (vicious cycle) --- with Low T3 Syndrome inhibiting the defense against the production of endotoxin by E. coli (and other gram-negative bacteria) --- and --- the resulting increased endotoxin further decreasing T3 --- which results in more endotoxin --- which ...

Neutrophils, macrophages, and dendritic cells release a lipase enzyme to inactivate LPS once it has been absorbed through the gut wall. The lipase inactivates LPS throughout the blood stream and in all other tissues. Subsequently, however, when the LPS binds to complexes in monocytes, dendritic cells, macrophages, and B cells, it promotes the secretion of many pro-inflammatory cytokines, along with nitric oxide and various

prostaglandins. LPS also initiates damage by reactive oxygen species as well as the release of a pyrogen

Some forms of LPS are thought to cause autoimmune-based responses, such as flare-ups of multiple sclerosis. Some have also been implicated in Guillain-Barre syndrome.

Many studies show that increased endotoxin load (resulting from increased population of LPS-producing bacteria in the gut) is associated with certain types of obesity. In studies on laboratory mice, injections of endotoxin from E. coli will produce obesity and insulin resistance, while other studies show a contributing role of LPS from other bacteria contributing to obesity and insulin resistance in humans. The endotoxin interferes with the gut-adipose axis via various inflammatory mediators, thus causing the obesity and insulin resistance.