

# ***L Plantarum* Synbiotic Formula**

## **References**

It takes nerve to dampen inflammation. Christine N Metz and Kevin J Tracey. Vol. 6, No. 8 August 2005 Nature Immunology.

Stimulation of the vagus nerve via the  $\alpha 7$  nicotinic acetylcholine receptor can dampen macrophage function. This anti-inflammatory pathway seems to signal through the Jak2-STAT3 pathway.

Stimulation of the vagus nerve attenuates macrophage activation by activating the Jak2-STAT3 signaling pathway. Wouter J de Jonge, Esmerij P van der Zanden et al. Vol. 6 No. 8. August 2005 Nature Immunology.

Acetylcholine released by efferent vagus nerves inhibits macrophage activation. Here we show that the anti-inflammatory action of nicotinic receptor activation in peritoneal macrophages was associated with activation of the transcription factor STAT3. STAT3 was phosphorylated by the tyrosine kinase Jak2 that was recruited to the  $\alpha 7$  subunit of the nicotinic acetylcholine receptor. The anti-inflammatory effect of nicotine required the ability of phosphorylated STAT3 to bind and transactivate its DNA inflammation and postoperative ileus by activating STAT3 in intestinal macrophages. We conclude that the vagal anti-inflammatory pathway acts by  $\alpha 7$  subunit-mediated Jak2-STAT3 activation.

A nervous connection. Claude Libert. Nature, Vol. 421, 23 January 2003.

The molecular details of a connection between the nervous system and the inflammatory response to disease have been uncovered. This suggests new avenues of research into controlling excessive inflammation. The inflammatory response to microorganisms, and way of controlling it. Many bacteria contain lipopolysaccharide in their cell walls, which stimulates macrophages. These immune cells then make and release various cytokine (alarm) molecules, including tumour-necrosis factor (TNF) and interleukin-1. But too much TNF in the blood can be harmful, leading to excessive inflammation and septic shock. Several drugs inhibit steps in TNF synthesis. In addition, Tracey and colleagues (Tracey, K.J. et al. Science 234, 470-474 1986) have found that when the vagus nerve detects interleukin-1, it releases

acetylcholine, which binds to the  $\alpha 7$  receptor on macrophages and inhibits cytokine production. This suggests possible new ways of controlling inflammation through electrically stimulating the vagus nerve, by acupuncture or with the use of nicotine which mimics acetylcholine. (see Figure )

Nicotinic acetylcholine receptor  $\alpha 7$  subunit is an essential regulator of inflammation.

Hong Wang, Man Yu, Mahendar Ochani, Carol Ann Amelia, Mahira Tanovic et al.  
Nature, vol. 421, 23 January 2003.

Excessive inflammation and tumour-necrosis factor (TNF) synthesis cause morbidity and mortality in diverse human diseases including endotoxaemia, sepsis, rheumatoid arthritis and inflammatory bowel disease. Highly conserved, endogenous mechanisms normally regulate the magnitude of innate immune responses and prevent excessive inflammation. The nervous system through the vagus nerve, can inhibit significantly and rapidly the release of macrophage TNF, and attenuate systemic inflammatory responses. Thus there is significant potential for developing cholinergic agonists that target  $\alpha 7$  subunits on peripheral immune cells for use as anti-inflammatory cytokines. Vagus nerve stimulators can enhance the anti-inflammatory activity of the cholinergic anti-inflammatory pathway in animals; furthermore, vagus nerve stimulators have already been used safely in humans with seizure disorders. As TNF is already a clinically validated drug target for rheumatoid arthritis and Crohn's disease, it is now reasonable to consider the therapeutic potential for targeting the nicotinic acetylcholine receptor  $\alpha 7$  subunit to inhibit TNF, either by direct pharmacological approaches, or through increasing activity in the vagus nerve.

Activation of human CD4 cells with CD3 and CD46 induces a T-regulatory cell 1 phenotype. Claudia Kemper, Andrew C. Chan, Jonathan M. Green et al. Nature, Vol. 421, 23 January 2003.

The immune system must distinguish not only between self and non-self, but also between innocuous and pathological foreign antigens to prevent unnecessary or self-destructive immune responses. Unresponsiveness to harmless antigens is established through central and peripheral processes. Whereas clonal deletion and anergy are mechanisms of peripheral tolerance, active suppression by T-regulatory 1 (tr1) cells has emerged as an essential factor in the control of anuttractive cells.

The Cholinergic Anti-Inflammatory Pathway Regulates the Host Response during Septic Peritonitis. David Westerloo, Llona Giebelen, Sandrine Florquin, Joost Daalhuise et al. *The Journal of Infectious Disease* 2005;191:2138-48. The nervous system, through the vagus nerve, can down-regulate inflammation in vivo by decreasing the release of tumor necrosis factor- $\alpha$  by endotoxin-stimulated macrophages. This anti-inflammatory effect is mediated by an interaction between acetylcholine, the principal neurotransmitter of the vagus nerve, and cholinergic nicotinic acetylcholine receptors on macrophages.

The vagal nerve as a link between the nervous and immune system in the instance of polymicrobial sepsis. Wolfram Kessler, Tobias Traeger, Alexandr Westerholt et al. *Langenbecks Arch Surg*, DOI 10/1007/s00423-006-0031-y. Best of Forum Papers presented at the Annual Meeting of the German Society of Surgery, 2-5 May 2006, Berlin, Germany.

The role of the vagal nerve in the autonomic nervous system is widely well known. Recently, an additional function was revealed serving as a connector between the nervous and immune system. This connection is called the cholinergic inflammatory pathway. Through stimulation of the acetylcholine receptors located upon the macrophages, the unspecific immune system can be directly influenced. Method: The vagal nerve was completely transected directly posterior to its passage through the diaphragm. The effect of complete vagotomy was analyzed using a murine model of polymicrobial peritonitis. Survival and clinical course of vagotomized or sham-operated mice were analyzed. After surgery, vagotomy led to a significantly increased mortality (64.7%) in comparison to sham-vagotomized animals (34%). Vagotomized animals reveal elevated serum cytokine levels (TNF, IF- $\gamma$ , IL-10 and MCP-1) The vagal nerve is therefore an important modulator of the immune system.

The Vagus Nerve: A tonic Inhibitory Influence Associated With Inflammatory Bowel Disease in a Murine Model. Jean Eric Ghia, Patricia Blennerhassett et al *Gastroenterology* 2006;131:1122-1130.

Background and Aims: The recently proposed Inflammatory Reflex describes an interaction between the vagus nerve and peripheral macrophages, resulting in attenuation of pro-inflammatory cytokine release in response to systemic exposure to bacterial endotoxin. Conclusion: The vagus nerve plays a counter-inflammatory

role in acute colitis via a macrophage-dependent mechanism involving hexamethonium-sensitive nicotinic receptors. The identification of a counter-inflammatory neural pathway would open new therapeutic avenues for treating acute exacerbations of inflammatory bowel disease.

Cholinergic regulation of epithelial ion transport in the mammalian intestine.

CL Hirota and DM McKay. *British Journal of Pharmacology* 2006 149, 463-479. Acetylcholine is critical in controlling epithelial ion transport and hence water movements for gut hydration. The epithelial lining of the intestine separates two biological compartments: the gut lumen from the interstitium. Under normal circumstances, the polarized epithelial cells impede the movement of luminal material into the body and regulate the passage of a variety of substances-nutrients, electrolytes and water- from lumen to body and vice versa. The ability to secrete and absorb electrolytes and fluids is critical to maintain proper hydration of the organism. The cholinergic system is a principal player in enteric homeostasis,

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