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*G. Boeckstaens*

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Excessive activation of the immune system is prevented by anti-inflammatory mediators such as corticosteroids and anti-inflammatory cytokines. Recently, it became clear that the brain not only senses peripheral inflammation through vagal afferent nerve fibers, but also provides an integrated response dampening the immune system through vagal efferents. This so-called anti-inflammatory pathway has been introduced as a third system by which the immune system is modulated. In sepsis, the anti-inflammatory effect is mediated by modulation of splenic macrophages, whereas in the gut, vagal nerve fibers synapse with enteric cholinergic neurons interacting with resident intestinal macrophages. In this chapter, the preclinical data underscoring the importance of this pathway are summarized, and its clinical significance is reviewed. Finally, the current data supporting its relevance to human disease and its therapeutic potential will be discussed. Insight in the mechanisms underlying these crucial properties will lead to better understanding of immune-mediated diseases and ultimately to improved anti-inflammatory therapies.

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