The brain influences immune function through a powerful neural reflex that suppresses the release of a key pro-inflammatory cytokine, tumor necrosis factor α (TNFα), after immune challenge. The efferent motor pathway of this reflex is in the splanchnic nerves, not the vagi. This reflex regulates inflammation but does not suppress fever.

With the present “discovery article” we would like to introduce to the readers of Temperature our recent study that focused on a neural reflex that controls inflammation.1

The idea of a neural reflex that controls the degree of inflammation induced by an immune challenge has been around since the beginning of the last decade when the group of researchers led by Kevin Tracey in New York introduced the concept of the inflammatory reflex.2

The authors discovered that electrically stimulating the vagus nerve during endotoxemia resulted in a profound inhibition of plasma tumor necrosis factor α (TNFα) levels.2 Since then a detailed description, based on a series of brilliant and original studies (for a comprehensive review, see ref. 3), of the efferent motor pathway of this reflex, termed the cholinergic anti-inflammatory pathway, has been completed and generally accepted by the majority of the international scientific community. The pathway proposed is complex: (1) the vagus nerves, activated by an immune insult, drive the splenic sympathetic nerves to release noradrenaline in the spleen; (2) this noradrenaline then activates a population of T lymphocytes that release acetylcholine (ACh); (3) ACh binds to nicotinic ACh receptors containing the α7 subunit present on macrophages to inhibit the release of TNFα.

The lack of a clear enhancement of the inflammatory response to endotoxin after vagotomy, together with the absence of any direct neural link between the vagus and splenic post-ganglionic sympathetic nerves, confirmed previous findings.6 While the higher levels of TNFα in splanchnectomized rats might have been expected to exacerbate fever, they evidently made no measurable difference within the time course of our experiment.

These results demonstrate the existence of a neural reflex that exerts a significant influence on inflammation, and thereby, immune function. Activity in the greater splanchnic nerves regulates the levels of a key pro-inflammatory cytokine, TNFα, which is a necessary and sufficient mediator of inflammation. Inflammation, in turn, is the gateway to innate and adaptive immunity. Our results also reinforce the concept that fever and the inflammatory reflex are two distinct physiological responses, mediated by distinct sympathetic pathways, triggered by the same immune challenge (Fig. 1). On one side, activation...
of the sympathetic drives to brown adipose tissue, cutaneous vasoconstriction and the heart produce the classic febrile response.\textsuperscript{7} On the other, it activates the efferent motor pathway of the inflammatory reflex, via the greater splanchnic sympathetic nerves to the spleen and probably other abdominal visceral organs. The afferent arm of the inflammatory reflex, though not investigated in this study, is likely to be humoral, similar to that established for fever.\textsuperscript{7}

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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Figure 1. Immune challenges such as i.v. LPS are sensed peripherally but are relayed to the central nervous system (CNS) mainly by humoral signals. In response to immune challenge, the brain activates two distinct sets of sympathetic pathways: the efferent motor pathway of the inflammatory reflex and the sympathetic outputs that cause tachycardia and fever. The efferent motor pathway of the inflammatory reflex traverses the greater splanchnic sympathetic nerves, which in turn drive the post-ganglionic sympathetic nerves to the spleen, liver, gastro-intestinal (GI) tract and adrenal glands. The final effect of this reflex is to inhibit TNFα production. Fever is caused by activation of sympathetic pathways to brown adipose tissue (BAT), cutaneous blood vessels (CBV) and the heart, raising body temperature and heart rate.
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