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Viewpoint

The inflammatory reflex: the current model should be revised

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In this issue of *Experimental Physiology*, Bratton *et al.* (2012) report negative results. The authors have failed to find a synaptic connection from vagal preganglionic neurons to splenic sympathetic postganglionic neurons in the rat. Furthermore, the authors have shown that vagal efferent neurons do not drive the ongoing activity of splenic neurons. Although negative results are a common subject of jokes among scientists, they can be significant. Identification of the limitations of a current model (and this is what good negative results often do) is as necessary for improving our understanding as proposing a new model (which is often based on positive results). Bratton *et al.* (2012) tested the current model of the neuroanatomical substrate of the inflammatory reflex and, more specifically, the efferent arm of the reflex. What is the inflammatory reflex?

In the past, the terms neurogenic inflammation, reflex inflammation and, occasionally, inflammatory reflex were used to refer to axon reflexes and some multineuronal spinal reflexes that mediate local inflammatory reactions. These reflexes have been implicated in inflammatory vasodilatation and in the production of multiple ingredients of what is commonly known as the inflammatory soup. A new meaning of the term inflammatory reflex has emerged during the last decade (Tracey, 2002; Rosas-Ballina & Tracey, 2009). Although it is still a work in progress, the principal feature of the new meaning is that it refers to systemic inflammation. In systemic inflammation, the inflammatory soup (vaguely similar to what is found at local inflammation sites) is cooked in the spleen, liver and perhaps other organs for remote consumption; it circulates throughout the body and exerts profound systemic effects, both adaptive (combating an infection) and detrimental (causing multiple organ dysfunction and failure). According to the new thinking, systemic levels of inflammatory mediators in systemic inflammation are controlled by the nervous system, and this control is realized via the inflammatory reflex. In contrast to reflexes in local inflammation, the arc of the proposed reflex is more complex; it involves neurons located in the brain and possibly travels through several brain structures. This reflex is thought to constitute the basis for homeostatic regulation of inflammation, similar to the regulation of heart rate or body temperature (Tracey, 2002; Rosas-Ballina & Tracey, 2009). The proposed regulation is thought to involve integration of inflammatory signals in the brain and co-ordination of effector responses. However, several elements of this innovative model may require further experimental testing and perhaps conceptual modifications.

The afferent arm of what later became known as the inflammatory reflex attracted attention first. In the late 1980s and early 1990s, several groups proposed that peripheral-to-brain signalling by nerves is important for triggering various components of the systemic inflammatory response (for review, see Romanovsky *et al.* 2005). The component with which I am most familiar is fever. Two procedures were used to block the transduction of peripheral pyrogenic signals by nerves: surgical vagotomy and capsaicin-induced inactivation (desensitization) of abdominal sensory nerves expressing the transient receptor potential vanilloid-1 (TRPV1) channel. Either procedure attenuated the febrile response to bacterial lipopolysaccharide, thus seeming to demonstrate the importance of signals conveyed to the brain by nerves. However, the majority of early studies ignored the fact that surgical vagotomy caused severe complications, including thermogenic deficiency. In later studies, when caution was exercised to prevent these complications, most – if not all – effects of vagotomy on fever disappeared. Several of these later studies were especially convincing, because they were conducted by the same authors who reported an attenuation of fever by vagotomy in their earlier papers. As for desensitization by capsaicin, studies from my laboratory have shown that it blocks the first phase of lipopolysaccharide-induced fever via a non-neural, non-TRPV1-mediated mechanism (Romanovsky *et al.* 2005). Hence, even though there is still some evidence (not reviewed here) suggesting that the immune system may send signals to the brain via nerves, it is hard to find experimental support for the proposition that signals conveyed by nerves are crucial (or even important) for driving effector responses, at least in the case of fever. Is a reflex an adequate model for afferent signals reaching the brain by non-neural (humoral) routes?

The efferent arm of the inflammatory reflex is a newer construction. To explain the exaggeration of hypothermia and other symptoms of lipopolysaccharide-induced shock by vagotomy, Borovikova *et al.* (2000) proposed that efferent vagal activity, via a nicotinic receptor-mediated mechanism, inhibited the production of some components of the inflammatory soup, such as tumour necrosis factor-α. This cholinergic anti-inflammatory pathway became the efferent arm of the inflammatory reflex. Initially, effector processes controlled by this pathway were thought to be localized in the liver. Subsequently, the focus shifted to the spleen; activation of splenic sympathetic nerves and the resultant suppression of the cytokine response in the spleen were shown to play dominant roles (Nance & Sanders, 2007; Rosas-Ballina & Tracey, 2009). To explain how the vagal anti-inflammatory pathway activates sympathetic suppression of splenic cytokine production, a synaptic connection has been proposed between vagal preganglionic neurons and sympathetic postganglionic neurons that innervate the spleen (Rosas-Ballina & Tracey, 2009).

By using neuroanatomical and electrophysiological approaches, Bratton *et al.* (2012) attempted to identify the proposed vago-splenic synapses. The anatomical approach encompassed injecting an anterograde tracer into the dorsal motor nucleus of the vagus and a retrograde tracer into the spleen and then searching for synaptic connections between anterogradely and retrogradely labelled

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neurons in sympathetic ganglia innervating the spleen. No connections were found. The electrophysiological approach included searching for effects of vagal efferent stimulation on the activity of splenic-projecting neurons in the suprarenal ganglion. No effects were recorded. The lack of anatomical or physiological support for synapses of preganglionic vagal neurons on postganglionic sympathetic neurons suggests that the current model of the efferent arm of the inflammatory reflex should be revised.

Other features of the proposed control of systemic inflammation may also require rethinking. It has been suggested that the brain gathers information about immune signals, integrates it, and uses the integrated signal to drive co-ordinated effector responses (Tracey, 2002; Rosas-Ballina & Tracey, 2009). This line of thinking derives from the times when biological regulation was erroneously thought to mimic engineering control. It is now becoming accepted that the complexity of neural regulation generally does not grow out of intrinsically complex rules governing a unified control system. For example, the thermoregulation system can be better modelled as a federation of relatively independent thermoeffector loops driven by various local temperatures rather than as a centralized control system computing some mean body temperature as a basis for driving effector responses (Romanovsky, 2007; McAllen *et al.* 2010).

The control of inflammation via the inflammatory reflex is a highly important and innovative model. Over the coming decades, many of the currently proposed features of this model will probably be tested in direct experiments. We may see some examples of what Thomas Huxley called the great tragedy of science, i.e. the slaying of a beautiful hypothesis by an ugly fact. But whether future tests produce negative results, such as those of Bratton *et al.* (2012), or positive ones, they will improve our understanding of the neural regulation of immune functions.

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