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NEUROSCIENCE

Bacteria get on your nerves

During infection, the inflammatory immune response can cause pain by activating nociceptor neurons. A bacterial pathogen also seems to stimulate pain directly, modulating the immune response in its favour.

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In his first-century-BC treatise *De Medicina*, Aulus Cornelius Celsus described the four cardinal signs of acute inflammation: *rubor* (redness), *tumor* (swelling), *calor* (warmth) and *dolor* (pain). In the context of innate immunity, inflammation reflects local vasodilation and the influx of leukocyte cells to injured or infected tissue locations, amid a flurry of lipids, enzymes, and cytokine and chemokine molecules. However, the fascinating work of Chiu *et al.*[1], published on *Nature*'s website today, shows that acute pain accompanying infections with the bacterium *Staphylococcus aureus* is primarily caused by the direct activation of peripheral sensory neurons (nociceptors) by bacterial components and toxins, rather than by host-derived inflammatory mediators. Disconcertingly, this may be to the pathogen's gain; in response to bacterial stimulation, the nociceptor terminals could release certain neurotransmitter molecules that impair the proper recruitment and activation of innate immune cells.

Consequences of local inflammation are continual pain and hyperalgesia — an exaggerated pain response to low-intensity stimuli[2]. Mechanistically, such enhanced responsiveness is triggered by molecules that are released into the local milieu of injured or infected tissue; these molecules are recognized by specific receptors on the peripheral terminals of afferent neurons, which reach out to every millimetre of the body's exterior and interior. The activation of these receptors induces a concentration-dependent depolarization of the terminals, triggering kinase enzymes that phosphorylate various terminal receptors and channels to produce continuing afferent activity and enhanced response to subsequent stimuli[3].

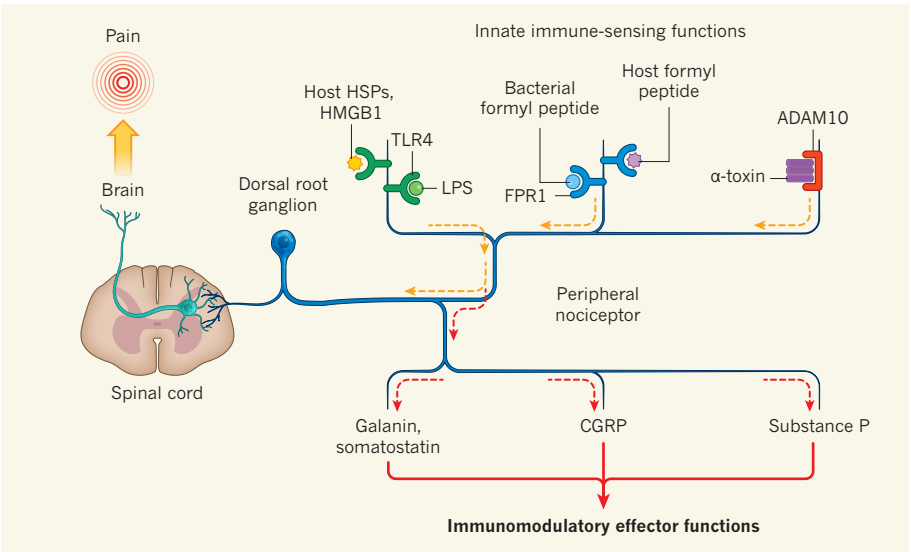

Figure 1 | Immune-related functions of peripheral nociceptors. Terminal fibres of peripheral afferent nociceptors express receptors that allow direct activation of these neurons by host-derived formyl peptides and possibly HSPs and HMGB1 released from injured tissues and by bacterial products (lipopolysaccharide (LPS) is detected by TLR4; formyl peptides are detected by FPR1; and staphylococcal α-toxin is detected by ADAM10). Chiu and colleagues' data suggest[1] that in addition to transducing a pain signal to the central nervous system through the dorsal root ganglion (yellow arrows), this stimulation elicits antidromic action potentials (red arrows) that evoke the release of bioactive peptides such as substance P, CGRP, galanin and somatostatin from the peripheral terminal. This antidromic signalling can thus modulate the local inflammatory response.

The concept that infectious microbes can directly activate pain receptors, rather than acting through an immune-cell intermediary, has emerged in recent years (Fig. 1). Supporting data include the discoveries that lipopolysaccharide (LPS) molecules of the outer membrane of Gram-negative bacteria can stimulate production of the vasodilator CGRP from dorsal root ganglion (DRG) neurons[4] and that the LPS co-receptors TLR4 and CD14, which are normally found on immune cells, are also expressed on trigeminal nociceptive neurons[5]. Moreover, exposure of the mouse urinary tract to live pathogenic *Escherichia coli* bacteria or purified LPS triggered pain by a mechanism that depended on TLR4 but not on the inflammatory response of the immune system's neutrophils or mast cells[6]. Furthermore, LPS binding to TLR4 and its co-receptors on DRG neurons prompted the release of nociceptin, an opioid-related peptide that is upregulated during peripheral inflammation and is associated with hyperalgesia[7].

Chiu and colleagues' results are surprising because they reveal that the activation of pain receptors by *S. aureus* involves neither TLR2, the key immune-system pattern-recognition receptor (PRR) for cell-wall components of Gram-positive bacteria, nor MyD88, a universal adaptor protein that is involved in transducing TLR signals. Instead, they detected two alternative receptor-mediated activation pathways in mouse nociceptors. These neurons expressed FPR1, a G-protein-coupled PRR that responds to formyl peptides on the *S. aureus* cell wall. Moreover, they express ADAM10, a cell-surface metalloprotease enzyme that binds to and facilitates the activity of the pore-forming staphylococcal α-toxin, thereby leading to rapid calcium fluxes within the nociceptors (Fig. 1). These pathways produced changes in pain-perception threshold that were proportional to the bacterial load but, strikingly, the changes were independent of the magnitude of the inflammatory responses.

At first glance, the expression of PRRs for microbial components on nociceptors could imply an evolutionary benefit for the host in return for experiencing acute pain due to infection. A classic study[8] noted that the stimulation of DRG neurons by signals originating from peripheral nociceptors triggers vasodilation. Moreover, antidromic (opposite direction) activities in the small peripheral nociceptor can promote the release of vasodilators at its peripheral terminal. Subsequent work[9,10] emphasized a key role of CGRP and the neurotransmitter substance P in initiating

neuron-mediated inflammation, a collection of processes that aid pathogen clearance by the immune system.

Unexpectedly, however, Chiu *et al.* found that genetic ablation of all nociceptors in mice was associated with greater lymph-node swelling — a sign of immune activation — in response to *S. aureus* infection. The authors' further analysis revealed that CGRP and other nociceptive afferent-derived peptides (galanin and somatostatin) have previously unknown anti-inflammatory properties that limit the release of cytokines by macrophages, a key immune cell type.

Perhaps these results reflect yet another capacity of *S. aureus* to manipulate and thwart the innate immune-response pathways that are normally effective against 'lesser' pathogens; the large number of virulence factors that this bacterium releases subvert the normal function of phagocytes and the complement system of innate immunity[11,12]. Or one could propose an alternative role for nociceptor expression of TLR4 and FPR1, because these receptors respond to damage-associated molecular patterns such as HMGB1, HSPs or mitochondrial formyl peptides released from host cells after injury[13] (Fig. 1). In this sense, bacteria-induced pain could be an epiphenomenon in a broader selective advantage provided by pain-induced behavioural responses that limit traumatic tissue damage.

The current paper adds to the emerging view of the extensive and complex interaction between the peripheral nervous system and the innate immune system. Sensory afferent nociceptor neurons express receptors that detect bacteria and their toxins, leading to downstream signal transduction and the local release of vasoactive and immunomodulatory peptides; all of this is concurrent with the propagation of action potentials by the axonal processes of these cells and the subjective experience of pain.

There is evidence that this interplay is not limited to the body's peripheral nociceptors but extends to other sensory receptor systems. For instance, T2R38, the receptor for bitter taste, was recently found to detect molecules secreted by the bacterium *Pseudomonas aeruginosa*, stimulating effective clearance of this pathogen[14]. Could other sensory systems (visual, auditory and olfactory) receive direct molecular input from pathogens or the commensal microbiota? Better understanding of these processes could provide innovative targets and approaches to improve treatment outcome in infection-associated disorders. ■

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