NEUROIMMUNOLOGY

Pain — blame it on the bug, eh?

Although it is not completely understood, the pain that is associated with acute bacterial infections is thought to be secondary to activation of the immune system. Clifford Woolf and colleagues now show that bacteria directly activate pain responses by triggering nociceptor neurons. Furthermore, activation of these sensory neurons by bacteria leads to the release of neuropeptides that can suppress immune responses to the infection.

The authors aimed to investigate the mechanisms by which *Staphylococcus aureus* (which is a common cause of wound infections) induces pain. Pain thresholds were assessed by infecting mice with *S. aureus* and then measuring their sensitivity to mechanical, heat- or cold-associated stress. Mice showed signs of hyperalgesia within 1 hour of *S. aureus* infection, with the pain response peaking 6 hours after infection and beginning to decrease after 24 hours. Surprisingly, the kinetics of the pain response did not correlate with the kinetics of tissue swelling or with the kinetics of immune cell recruitment. By contrast, bacterial loads in the tissue closely correlated with pain hypersensitivity, which suggests that bacteria may directly

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interact with sensory neurons. In keeping with this idea, pain perception during *S. aureus* infection was not decreased in mice deficient for Toll-like receptor signalling components, or in mice lacking neutrophils, monocytes or lymphocytes. Indeed, antibody-mediated depletion of neutrophils or monocytes led to higher bacterial loads and to increased pain hypersensitivity.

To test whether bacteria directly induce pain, the authors applied heat-killed bacteria to dorsal root ganglia (DRG) sensory neurons. Various strains of heat-killed bacteria, including *S. aureus*, induced robust calcium fluxes in DRG neurons. Additional experiments suggested that bacterial *N*-formylated peptides trigger mechanical (but not heat) hyperalgesia by activating nociceptors. Furthermore, they showed that α -haemolysin, which is a pore-forming toxin produced by *S. aureus*, binds to and activates a subset of nociceptor neurons and directly induces mechanical, heat and cold hypersensitivity.

The authors proceeded to examine how the activation of nociceptors by bacteria can modulate immune responses. Conditional ablation of nociceptors abolished pain responses

during *S. aureus* infection and this was associated with increased local inflammation, despite there being similar bacterial tissue loads in nociceptor-deficient and control mice. Microarray analyses showed that receptors for the neuropeptides calcitonin gene-related peptide (CGRP), galanin and somatostatin are highly expressed by neutrophils, monocytes and macrophages. Furthermore, the treatment of macrophages with these neuropeptides suppressed their production of tumour necrosis factor in response to *S. aureus*. Finally, the exposure of DRG neurons to supernatant from *S. aureus* cultures or to α -haemolysin promoted the release of CGRP in a dose-dependent manner.

This study shows that bacterial products can directly activate nociceptors to induce pain and the release of immunosuppressive neuropeptides. The authors suggest that pathogenic bacterial strains have evolved to trigger nociceptors in order to suppress the host immune system and increase their own spread in infected tissues.

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ORIGINAL RESEARCH PAPER Chiu, I. M. et al. Bacteria activate sensory neurons that modulate pain and inflammation. *Nature* <http://dx.doi.org/10.1038/nature12479> (2013)