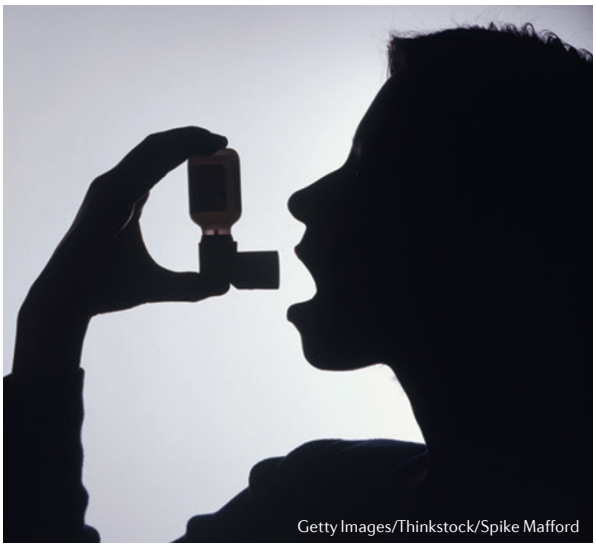
INFLAMMATORY DISEASES

# Adding insult to allergy

> silencing of nociceptors reduced immune cell counts, attenuated bronchial hyper-sensitivity and normalized voluntary wheel-running behaviour

The lungs are innervated by sensory neurons that respond to noxious stimuli to induce protective airway reflexes, for example, coughing. Lung nociceptors are also thought to contribute to inflammatory lung disease, but the mechanisms involved are not clear. Talbot *et al.* now identify mediators of neuroimmune crosstalk in the lungs and demonstrate that silencing lung nociceptors attenuates inflammation in a model of asthma.

The authors used a mouse model of allergic asthma, in which ovalbumin (OVA) sensitization is carried out over several days followed by airway OVA challenge to induce lung inflammation and airway hypersensitivity. Following OVA challenge, the numbers of $CD45^+$ immune cells in the lungs and bronchial hypersensitivity were lower in transgenic mice lacking nociceptors than in controls. Conversely, in wild-type mice, administration of capsaicin, a TRPV1 agonist that activates nociceptors, exacerbated immune cell responses following OVA challenge.



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QX-314 is a membrane-impermeable $Na^+$ channel blocker that does not silence neurons when applied alone, but when co-administrated with a TRPV1 agonist, the charged QX-314 molecule can enter through the open TRPV1 channel pore and silence neurons. The authors demonstrated that, in OVA-challenged mice, QX-314 alone was effective in silencing nociceptors and reducing neuropeptide release, which may be due to activation of TRPV1 by the release of endogenous inflammatory mediators. Interestingly, QX-314-mediated silencing of nociceptors reduced immune cell counts, attenuated bronchial hypersensitivity and normalized voluntary wheel-running behaviour in OVA-challenged mice.

Next, the authors investigated candidate molecules that could be involved in signalling between lung nociceptors and immune cells. The cytokine interleukin-5 (IL-5) has a well-established role in modulating the immune cell response in asthma, and OVA-challenged mice treated with QX-314 had decreased expression of IL-5 in the lungs. Furthermore, *in vitro* patch clamp recording and $Ca^{2+}$ responses of nociceptors exposed to IL-5 indicated direct activation by this cytokine.

The resident lung immune cells type 2 innate lymphoid cells (ILC2s) are known to express receptors for neuropeptides, including vasoactive intestinal peptide (VIP), which is expressed at high levels in lung nociceptors. The authors investigated the role of VIP in OVA challenge-induced inflammation. They found that nociceptors from naive mice released VIP when stimulated with capsaicin *in vitro*, and VIP levels in the lungs were increased in OVA-challenged mice. Blocking the type 2 VIP receptor in mice during OVA challenge decreased overall immune cell counts in the lungs, and decreased activation of ILC2s specifically. This suggests that VIP mediates nociceptor-driven inflammation in the lungs.

Together, these findings suggest that nociceptors are activated during lung inflammation, and nociceptors further exacerbate inflammation by release of a pro-inflamamtory neuropeptide. Thus, silencing overactive nociceptors may be a promising strategy to attenuate lung inflammation in allergic asthma.

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