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BACTERIAL TOXINS

A 'pain-relieving' toxin

> the analgesic effect of the *M. ulcerans* toxin is mediated by AT2R signalling

Mycobacterium ulcerans is the causative agent of Buruli ulcer, which is an infectious skin disease characterized by ulcerative lesions that are painless in the early stages. It has been proposed that the absence of pain in the lesions is due to the destruction of nerves by the *M. ulcerans* toxin mycolactone. However, Marion, Song, Christophe *et al.* now report that mycolactone does not cause nerve damage in infected mice but that it instead interferes with the host angiotensin pathway, resulting in decreased pain sensation (known as hypoesthesia).

The authors showed that mice that were infected with *M. ulcerans* had decreased sensitivity to nociceptive pain compared with control mice and that this effect was not associated with nerve damage in inoculated footpads. Furthermore, injection of synthetic or purified mycolactone induced a loss of pain sensation in the absence of nerve damage; this, together with the finding that the hypoesthesia was reversible, shows that the analgesic effect is not due to nerve degeneration.

The authors went on to examine whether neural pathways are affected by the mycobacterial toxin. They found that mycolactone treatment decreased the membrane potential in mouse primary neurons and that hyperpolarization was mediated by the K^+ channel TRAAK. Using a large-scale siRNA screen and *in vitro* binding assays, the authors identified the host membrane protein angiotensin II type 2 receptor (AT2R; which had previously been implicated in pain sensitivity) as the target receptor for *M. ulcerans* mycolactone. In agreement with this, inhibition of AT2R decreased mycolactone-induced hyperpolarization in mouse neuronal cells.

So, how does mycolactone-mediated AT2R activation modulate the K^+ channel? The authors showed that binding of mycolactone to AT2R triggers an intracellular signalling cascade that involves the induction of phospholipase A2 and the release of arachidonic acid. The prostaglandin synthase COX1 metabolizes arachidonic acid into prostaglandin, which stimulates the TRAAK channel and thus K^+ release.

Finally, the authors sought to determine the physiological relevance of this signalling pathway *in vivo*, and they found that *At2r*-knockout mice that were injected with mycolactone were more sensitive to pain than wild-type mice. In addition, treatment of *M. ulcerans*-infected mice with AT2R or prostaglandin synthesis inhibitors increased pain sensitivity in the treated mice compared with control littermates, which led the authors to conclude that the analgesic effect of the *M. ulcerans* toxin is mediated by AT2R signalling.

This study uncovers a novel pathogenic mechanism of *M. ulcerans* that leads to decreased sensation of pain from the inflicted lesions.

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ORIGINAL RESEARCH PAPER Marion, E., Song, O.-R., Christophe, T. *et al.* Mycobacterial toxin induces analgesia in Buruli ulcer by targeting the angiotensin pathways. *Cell* http://dx.doi.org/10.1016/j.cell.2014.04.040 (2014)