Mycobacterial toxin induces analgesia in buruli ulcer by targeting the angiotensin pathways

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Résumé en anglais	*Mycobacterium ulcerans*, the etiological agent of Buruli ulcer, causes extensive skin lesions, which despite their severity are not accompanied by pain. It was previously thought that this remarkable analgesia is ensured by direct nerve cell destruction. We demonstrate here that M. ulcerans-induced hypoesthesia is instead achieved through a specific neurological pathway triggered by the secreted mycobacterial polyketide mycolactone. We decipher this pathway at the molecular level, showing that mycolactone elicits signaling through type 2 angiotensin II receptors (AT2Rs), leading to potassium-dependent hyperpolarization of neurons. We further validate the physiological relevance of this mechanism with in vivo studies of pain sensitivity in mice infected with M. ulcerans, following the disruption of the identified pathway. Our findings shed new light on molecular mechanisms evolved by natural systems for the induction of very effective analgesia, opening up the prospect of new families of analgesics derived from such systems.

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