A Bacterial Toxin with Analgesic Properties: Hyperpolarization of DRG Neurons by Mycolactone

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Résumé en anglais	Mycolactone, a polyketide molecule produced by , is the etiological agent of Buruli ulcer. This lipid toxin is endowed with pleiotropic effects, presents cytotoxic effects at high doses, and notably plays a pivotal role in host response upon colonization by the bacillus. Most remarkably, mycolactone displays intriguing analgesic capabilities: the toxin suppresses or alleviates the pain of the skin lesions it inflicts. We demonstrated that the analgesic capability of mycolactone was not attributable to nerve damage, but instead resulted from the triggering of a cellular pathway targeting AT_2 receptors (angiotensin II type 2 receptors; AT_2R), and leading to potassium-dependent hyperpolarization. This demonstration paves the way to new nature-inspired analgesic protocols. In this direction, we assess here the hyperpolarizing properties of mycolactone on nociceptive neurons. We developed a dedicated medium-throughput assay based on membrane potential changes, and visualized by confocal microscopy of bis-oxonol-loaded Dorsal Root Ganglion (DRG) neurons. We demonstrate that mycolactone at non-cytotoxic doses triggers the hyperpolarization of DRG neurons through AT_2R, with this action being not affected by known ligands of AT_2R. This result points towards novel AT_2R-dependent signaling pathways in DRG neurons underlying the analgesic effect of mycolactone, with the perspective for the development of new types of nature-inspired analgesics.

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Liens
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