Kappa opioids inhibit the GABA/glycine terminals of rostral ventromedial medulla projections in the superficial dorsal horn of the spinal cord

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December 3, 2021

Abstract

Background and Purpose: Descending projections from neurons in the rostral ventromedial medulla (RVM) make synapses within the superficial dorsal horn of the spinal cord that are involved in acute nociception and the development of chronic pain and itch. In addition, this projection plays an important role in mediating the analgesic effects of opioids. However, our knowledge about the spinal synaptic targets of RVM projections and their modulation by opioids is unknown. Experimental Approach: We used ex vivo optogenetic stimulation of RVM descending fibres and whole-cell patch-clamp recordings from superficial dorsal horn (SDH) neurons to identify the target neurons and to investigate their descending synaptic inputs. Key Results: We demonstrate that SDH neurons are targeted by descending GABA/glycine inhibitory inputs from the RVM, although glycinergic inputs predominate. These SDH neurons had diverse morphological and electrical properties. This inhibitory synapse was presynaptically suppressed by the kappa opioid receptor agonist U69593. By contrast, the mu-opioid receptor agonist DAMGO inhibited only a subset of RVM-SDH synapses, acting both pre- and postsynaptically, while the delta-opioid receptor agonist deltorphin II had little effect. Conclusion and Implications: Developing reliable and effective alternatives to opioid analgesics requires a detailed, mechanistic understanding of how opioids interact with nociceptive circuits. This study selectively and systematically characterises the synaptic connections between RVM projection neurons and their SDH targets to advance our knowledge of how this descending projection is organised and modulated. In addition, it improves our understanding of how opioids alter spinal pathways involved in the sensations of pain and itch.

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