Role of dopamine D_4 receptor in the development of morphine-induced analgesic tolerance

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Morphine is one of the most effective analgesic used in the clinical management of pain. However, long-term use of morphine can cause many side effects including respiratory depression, constipation, analgesic tolerance, hyperalgesia and addiction. The mechanisms underlying morphine tolerance are complex and nowadays it is not yet completely understood. As a primary mediator of morphine analgesia, the mu opioid receptor (MOR) contributes to morphine tolerance through downregulating the expression of MOR and its uncoupling from G-proteins in the dorsal horn of the spinal cord. It has been reported that the colocalization of the dopamine D_4 receptor with MOR in the dorsal striatum counteracts the addictive effects induced by morphine through a putative D_4R-MOR heteroreceptor that modulates dopamine signaling from nigral dopamine nerve cells. As D_4R is also expressed in both the dorsal root ganglia (DRG) and dorsal horn neurons, we hypothesize that D_4R could interfere the development of morphine-induced tolerance to its analgesic effects at dorsal horn level.

Using a chronic treatment paradigm of morphine with the D_4R agonist PD168,077, we have first investigated the nociceptive response to noxious thermal stimulation (tail flick), mechanical stimulation (von Frey) and to persistent noxious chemical stimulation (formalin). Furthermore, using immunohistochemical techniques, we have studied primary afferent fibers (peptidergic and non-peptidergic C fibers), spinal interneurons and NK1 spinal projection neurons, and the balance between glutamate and GABA in the dorsal horn.

Results from the evaluation of analgesic activity showed that D_4R activation prevents the development of morphine-induced analgesic tolerance. In addition, D_4R preserves the appropriate balance between glutamate and GABA for a proper analgesic effect by modulating the spinal circuit. The present results give support for the existence of antagonistic functional D_4R-MOR receptor-receptor interaction in the dorsal horn that could help to the development of a new pharmacology strategy in the treatment of pain.

Funding: CTS161 (Junta de Andalucía)