Pharmacological activation of dopamine D4 receptor prevents morphine-induced tolerance at the rat dorsal horn level

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Morphine is one of the most effective drugs used for pain management. However, prolonged exposition to morphine produces a wide variety of side effects such as tolerance to analgesia, hyperalgesia and addiction. Downregulation of the mu opioid receptor (MOR) and its uncoupling to G-proteins in the dorsal horn are likely to contribute to the development of morphine tolerance. Previous studies demonstrated that dopamine D4 receptor (D4R) activation prevents morphine addiction by modulating dopamine signaling from nigral dopamine cells. This effect seems to be the result of an antagonistic receptor-receptor interaction involving a D4R-MOR heteroreceptor which could exist in the dorsal striatum. As D4R is expressed in dorsal horn neurons, we hypothesize that D4R could interfere in the development of morphine-induced tolerance to its analgesic effects. Here, using a chronic paradigm of combined treatment of morphine with the D4R agonist PD168.077, we investigated the nociceptive response to three noxious stimuli: thermal (tail-flick test), mechanical (von Frey test) and chemical (formalin test). Moreover, using immunohistochemistry, western blot and qRT-PCR, we have evaluated alterations in the primary circuitry of pain and the balance between glutamate and GABA within dorsal horn. Results from the evaluation of analgesic activity of chronic combined treatment of morphine with PD168,077 showed that D4R prevents the development of morphine-induced analgesic tolerance. The present results give support for the existence of antagonistic functional D4R-MOR receptor-receptor interaction in the dorsal horn that could help to the development of a new pharmacology strategy in the treatment of pain.

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