

## **Low-dose morphine induces hyperalgesia through activation of G alphas, protein kinase C, and L-type Ca<sup>2+</sup> channels in rats.**

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Opioids can induce analgesia and also hyperalgesia in humans and in animals. It has been shown that systemic administration of morphine induced a hyperalgesic response at an extremely low dose. However, the exact mechanism(s) underlying opioid-induced hyperalgesia has not yet been clarified. Here, we have investigated cellular events involved in low-dose morphine hyperalgesia in male Wistar rats. The data showed that morphine (0.01 microg i.t.) could elicit hyperalgesia as assessed by the tail-flick test. G(alphas) mRNA and protein levels increased significantly following exposure to the hyperalgesic dose of morphine. Furthermore, morphine at an analgesic dose (20 microg i.t.) significantly decreased cAMP levels in the dorsal half of the lumbar spinal cord, whereas the tissue cAMP levels were not affected by morphine treatment at a hyperalgesic dose. Intrathecal administration of nifedipine, an L-type calcium channel blocker, antagonized the hyperalgesia induced by the low-dose of morphine. Furthermore, pretreatment with the selective protein kinase C (PKC) inhibitor chelerytrine resulted in prevention of the morphine-induced hyperalgesia. KT 5720, a specific inhibitor of protein kinase A (PKA), did not show any effect on low-dose morphine-induced hyperalgesia. These results indicate a role for G(alphas), the PLC-PKC pathway, and L-type calcium channels in intrathecal morphine-induced hyperalgesia in rats. Activation of ordinary G(alphas) signaling through cAMP levels did not appear to play a major role in the induction of hyperalgesia by low-dose of morphine. (c) 2007 Wiley-Liss, Inc.

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