PKC-dependent activation of mitogen-activated protein kinase in the development of hyperalgesia by ultra-low doses of morphine

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A growing body of evidence suggests that administration of opioids leads not only to analgesia, but may also lead to a paradoxical sensitization to acute pain. It has been shown that systemic administration of doses of morphine one thousand lower than the analgesic ones induced a hyperalgesic response (Mahani, 2008; Lee et al., 2011). However, the mechanism underlying the opioid-induced hyperalgesia has not yet been clarified. We have previously demonstrated that systemic administration of an ultra-low dose of morphine (1 μg/kg) induced a thermal hypernociception (hot plate test) through the selective activation of the μ opioid receptor (MOR) and the hyperphosphorylation of Protein Kinase C (PKC) appears to be the key intracellular element following the MOR activation (Galeotti et al. 2006). Here we chose to investigate the spinal and supraspinal intracellular signal transduction cascades modulated by PKC that might be involved in the development of the morphine-induced hyperalgesia. In particular, we focused our attention on the members of mitogen-activated protein kinases (MAPKs), ERK, JNK, p38. Following injection of morphine (1μg/kg), the phosphorylation of ERK, p38 and JNK within spinal cord was enhanced through a PKC-dependent mechanism since pretreatment with the PKC blocker calphostin C prevented the increased phosphorylation of these proteins. The effect of an ultra-low dose of morphine on the MAPKs phosphorylation was investigated also in supraspinal areas, such as periaqueductal grey (PAG), thalamus and frontal cortex. Even if the PKC phosphorylation was increased in all areas, these studies showed a supraspinal regionally selective PKC-dependent phosphorylation of MAPKs. In the PAG we detected a selective hyperphorylation of ERK1, in the thalamus the MAPKs were not modulated, in the cortex only JNK and ERK were hyperphosphorylated. Conversely to the spinal cord, no supraspinal modification of p38 phosphorylation was detected suggesting p38MAPK activation as a selective spinal mechanismin the development of hyperalgesia by ultra-low doses of morphine. Here, we also investigated the levels of transcription factors modulated by PKC and MAPKs, such as p-c-jun and p-CREB. Only a spinal increased expression and activation of these transcription factors was detected indicating a prominent role of MAPK-mediated spinal processes. I.c.v. administration of selective p38, ERK, and JNK inhibitors prevented the thermal hypernociception induced by morphine showing the involvement of all MAPK members to the production of thermal pain hypersensitivity. These results indicate the important role of the PKC-MAPK signaling pathway in the induction of hyperalgesia by ultra-low doses of morphine. Thus, blocking this pathway might reduce the morphine paradoxical effect improving the opioid efficacy in the clinical management of pain.

Lee et al., (2011) Pain Physician 14:145-161.
Mahani (2008) J Neurosci Res 86:471–479.
Galeotti et al. (2006) Pain. 123, 294–305.