Continuous morphine infusion induces allodynia through *Delta-2* opioid receptors in the spinal cord

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Morphine with its potent analgesic property has been widely used for the treatment of various kinds of acute pain and for long-term treatment of severe chronic pain. However, the chronic use of morphine is complicated by unwanted side-effect, including a paradoxical increase in pain sensitivity (i.e. hyperalgesia and allodynia). Indeed, continuous morphine infusion by osmotic pump caused allodynia in mice. The morphine-induced allodynia was inhibited by an antisera against dynorphin. However, the selective *k*-opioid receptor antagonist, nor-BNI did not prevent the morphine-induced allodynia. Dynorphin is rapidly degrated by a dynorphin-converting enzyme (cystein protease), to leucine-enkephalin (Leu-ENK). The morphine-induced allodynia was inhibited by an antisera against Leu-ENK. We also showed that the morphine co-administrated with Leu-ENK-converting enzyme inhibitors, phosphoramidon and bestatin produced much stronger behavioral responses than morphine alone. Furthermore, the morphine-induced allodynia was inhibited by intrathecal injection of the non-selective delta-opioid receptor antagonist, naltrindole or selective delta-2 opioid receptor antagonist, naltriben, while the selective delta-*1* opioid receptor antagonist, BNTX had no effect. Taken together, these results suggest that continuous morphine infusion-induced allodynia may be triggered through the delta-2 opioid receptors activated by Leu-ENK which is formed from dynorphin in the spinal cord.