Postsynaptic spinal mu opioid receptor-expressing neurons are required for morphine antihyperalgesia

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ABSTRACTS FOR POSTER PRESENTATIONS

A. Molecular and Cellular Biology

A01 - Immune Mediators

(600/Paper 312) Systemic morphine administration reduces local cytokine expression after incision
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The enhanced production of cytokines is a hallmark of acute inflammation including inflammation occurring in the setting of surgical incision. Recent studies demonstrate that several cytokines participate in the enhancement of nociception which occurs after incision. Since opioids like morphine interact with neutrophils, macrophages and other immunocytes, it is possible that morphine exerts some of its antinociceptive action by altering the vigor of the local inflammatory response. In these studies we used a murine hind paw incisional model to study the role of morphine in modulating incisional inflammation. We measured the effects of pre-incisional morphine administration on nociceptive thresholds and cytokine production in incised skin. We also followed neutrophil infiltration in these wounds. In other experiments mice were treated with daily morphine injections for 4 days followed by hind paw incision and cytokine analysis in order to study the effects of chronic morphine administration. As expected, the incised mouse hind paws displayed profound alldynia within 30 minutes of incision and this effect was stable for 24 hours. Morphine dose-dependently reduced these incision-stimulated cytokine levels as well. Separate analyses measuring myeloperoxidase (MPO) and using immunohistochemistry demonstrated that morphine strongly and dose-dependently reduced the infiltration of neutrophils into the peri-incisional tissue. Chronic morphine pretreatment caused mechanical allodynia, but had no overall effect on incision-stimulated skin cytokine levels. The administration of morphine prior to incision reduces the expression of multiple locally produced cytokines possibly by reducing acute phase neutrophil infiltration. Chronic morphine treatment sensitizes skin, but does not have major effects on incision-stimulated cytokine production. These findings have implications surrounding pain management, risk of infection and wound healing.

A02 - Mechanisms of Opioid Action

(603/Paper 312) Postsynaptic spinal mu opioid receptor-expressing neurons are required for morphine anti-hyperalgesia
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Lumbar intrathecal (i.t.) injection of Dermorphin-saporin (500 ng) in rats has been shown to selectively destroy spinal cord dorsal horn neurons expressing the mu-opioid receptor (MOR) with resulting attenuation of antinociceptive effects of systemic and i.t. morphine to low intensity (44 C) but not high (52 C) heat and increased responding in the formalin test. The current study examined the effects of i.t. Derm-sap on morphine antinociception during capsaicin-induced thermal hyperalgesia and in the formalin test. Effects of Derm-sap on primary afferent thermal nociceptors were assessed in baseline hotplate and tail flick testing and after systemic loperamide, a peripherally restricted mu opioid antagonist. Sixteen male rats and twenty female rats received a single lumbar intrathecal injection of 10 ul of PBS or Derm-sap (500 ng). Sensitivity to mu opioids was evaluated on the 44 C hotplate test under baseline conditions in the female rats and three hours after topical plantar capsaicin cream (0.94%) in the male rats. Effects of morphine (10 mg/kg, s.c.) on formalin behavior (25 ul of 5%) was evaluated in female rats for 90 min after plantar formalin injection. Immunohistochemical staining for GIRK2, a postsynaptic potassium channel essential for morphine analgesia, was evaluated in lumbar dorsal horns of PBS and Derm-sap rats. Derm-sap produced: 1) no change in baseline tail flick responses; 2) reduced antinociceptive effects of systemic morphine in the 44 C hotplate test after plantar capsaicin; 3) reduced antinociceptive effects of systemic morphine, but not loperamide, in the 44 C hotplate test; 4) reduced antinociceptive effects of morphine in the formalin test and 4) decreased GIRK2 staining in the dorsal horn. These observations demonstrate an important role for dorsal horn MOR-expressing neurons in analgesic and anti-hyperalgesic actions of morphine.