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Research Report

Opioid-induced latent sensitization in a model of non-inflammatory viscerosomatic hypersensitivity

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ARTICLE INFO

Article history:
Accepted 11 August 2010
Available online 19 August 2010

Keywords:
IBS
Opioid-induced latent sensitization

ABSTRACT

Exposure to opioids can induce a state of "latent sensitization" characterized by long-lasting enhanced responses to subsequent cutaneous injury. Here, we explored the possibility that prior treatment with morphine could induce a state of latent sensitization to visceral pain conditions. Following butyrate enemas to induce non-inflammatory visceral pain, acute morphine administration produced dose-related inhibition of referred viscerosomatic hypersensitivity. Treatment with morphine for a period of six days resulted in a persistent hyperalgesia that resolved many days after termination of drug administration. In morphine pre-exposed rats, butyrate-induced referred hypersensitivity was enhanced and extended in duration. No differences were observed in the morphine dose–response curve in suppression of acute nociception (i.e., the hot-plate assay) when morphine pre-exposed rats were compared to naïve rats indicating that opioid antinociceptive tolerance was not present. However, the morphine dose–response curve to suppress evoked viscerosomatic hypersensitivity was displaced to the right by approximately 4-fold in morphine pre-exposed rats. Induction of viscerosomatic hypersensitivity resulted in an increased labeling of CGRP-, but not substance P-positive cells in the lumbar dorsal root ganglia; increased labeling was not affected by prior exposure to morphine. The data indicate that a period of morphine exposure can induce a state of "latent sensitization" to subsequent visceral pain characterized by extended duration of hypersensitivity. This condition likely reflects enhanced visceral "pain" intensity as a consequence of persistent pronociceptive adaptive changes.

1. Introduction

Opioids are the most potent analgesics currently available, and are widely used to treat severe acute pain, cancer pain and have emerging use in the treatment of chronic non-malignant pain. Opioid use is sometimes associated with analgesic tolerance that can occur within days and requires increased dosing to maintain desired analgesic effects (Dogrul et al., 2003; Hanks et al., 2001; Rivat et al., 2002; Sim et al., 2007). There is a growing awareness that

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Abbreviations: CGRP, Calcitonin gene-related peptide; DRG, Dorsal root ganglion; IBS, Irritable bowel syndrome; MPE, Maximum possible effect; RVM, Rostral ventromedial medulla

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doi:10.1016/j.brainres.2010.08.032

exposure to opioids can cause the development of opioid-induced hyperalgesia in preclinical models and possibly in humans (Angst and Clark, 2006; Koppert et al., 2003). For example, clinical studies with volunteers undergoing surgery revealed that pre-operative opioid administration can result in increased post-operative pain and an increased need for analgesics (Hood et al., 2003). Clinical studies revealed that former opioid addicts on methadone maintenance therapy exhibited decreased pain tolerance in a cold-pressor test (Compton et al., 2001). Opioid-induced hyperalgesia has been demonstrated in numerous animal studies (Celerier et al., 2000; Laulin et al., 1998, 1999; Ossipov et al., 2004; Vanderah et al., 2001). Animals that received subcutaneous or intrathecal infusions of morphine developed behavioral signs of thermal hyperalgesia and tactile allodynia while the opioid was still being administered (Gardell et al., 2002; Vanderah et al., 2001). Likewise, individuals undergoing methadone maintenance therapy demonstrated hyperalgesia and cold allodynia while still taking methadone (Athanasos et al., 2006; Doverty et al., 2001).

More recent findings suggest that previous exposure to opioids for some period of time results in a long-lasting increase in the response to a subsequent injury (e.g., a surgical procedure) or to normally non-noxious or noxious stimuli applied to cutaneous tissues (i.e., hyperalgesia). This phenomenon persists long after cessation of the period of opioid administration, and has been termed "latent pain sensitization" (Celerier et al., 2001). The main features of opioid-induced latent sensitization are (1) increased intensity and extended duration of pain and (2) reduced responsiveness to the analgesic effects of pain management drugs. Patients that have had previous exposure to opioids can exhibit an increased duration and intensity of pain in multiple conditions, such as migraine headache (Jakubowski i et al., 2005), sphincter of Oddi dysfunction (Freeman et al., 2007), post-operative pain (Rapp et al., 1995; Sim et al., 2007) or during childbirth (Meyer et al., 2007) when compared to opiate naive patients. Prior exposure of rats to morphine infusion resulted in pain hypersensitivity in a model of surgical incision, even though baseline sensory thresholds had returned to normal values (Rivat et al., 2009). Although the mechanism underlying this phenomenon remains unclear, it has been proposed that opioids can elicit neuroplastic adaptations following some period of exposure (Gardell et al., 2002, 2003; Okada-Ogawa et al., 2009) These neuroplastic changes persist even after behavioral signs of enhanced abnormal pain have resolved, and might underlie heightened nociception in response to an additional insult (Laboureyras et al., 2009; Ossipov et al., 2003, 2004; Simonnet, 2009).

Based on these observations, we have determined whether the "latent sensitization" could also be demonstrated in other pain states with potential clinical relevance. We have used an established animal model thought to be representative of irritable bowel syndrome (IBS), where colonic hypersensitivity is brought about by intracolonic injections of sodium butyrate (Bourdu et al., 2005).This treatment induces robust visceral and referred cutaneous hypersensitivity within 3 days post treatment without inflammation-induced mucosal damage in the colon.

2. Results

2.1. *Morphine reverses non-inflammatory referred visceral hypersensitivity*

Intracolonic administration of butyrate produced viscerosomatic hypersensitivity, as indicated by a significant ($p<0.05$) reduction in mean withdrawal threshold to 0.3±0.05 g from a pre-treatment baseline value of 6 g when von Frey filaments were applied to the back of the rats, corresponding to lumbar dermatomes. Morphine produced dose-dependent reversal of viscerosomatic hypersensitivity, indicated by an A_{50} (95% C.L.) of 7.7 mg/kg (1.5–38.2 mg/kg) (Fig. 1).

2.2. *Rats previously exposed to morphine do not show antinociceptive tolerance 14 days after pump removal*

The rats implanted with morphine pumps displayed morphine-induced antinociception 6 h after pump implantation, as indicated by a significant ($p<0.05$) increase in hot-plate latency to 16.3±0.8 s from a baseline mean of 11.2±0.6 s (Fig. 2A). On day 6 after pump implantation, morphine-induced hyperalgesia was indicated by a significant ($p<0.05$) reduction in hot-plate latency to 8.2±0.4 s (Fig. 2A), and resolution of hyperalgesia was indicated by a normalized hot-plate latency of 12.0±0.9 s on day 20 (Fig. 2A). Saline-infused rats did not show significant changes in hot-plate latency over this time period (Fig. 2A). At day 20 (14 days after removal of the pumps), dose–response curves for morphine in the hot-plate test were generated with saline-treated and morphine-treated groups. Morphine produced equivalent antinociceptive effects in both groups (Fig. 2B.). The A_{50} (95% C.L.) for the saline-infused group, 3.4 mg/kg (0.4–8.3 mg/kg), was not significantly ($p>0.05$) different from that for the morphine-infused group, which was 3.6 mg/kg (0.6–4.8 mg/kg). These data indicate that the antinociceptive tolerance to morphine has resolved by 2 weeks after termination of the previous morphine exposure.

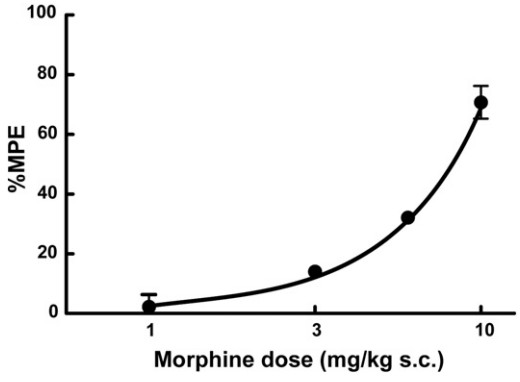

Fig. 1 – Morphine produces dose-dependent anti-allodynia in an animal model of experimental IBS. Rats received morphine (1, 3, 6, and 10 mg/kg, s.c.) after receiving intracolonic butyrate solution. Withdrawal thresholds to von Frey filaments were determined 30 min after morphine administration. (n=6 per group).