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Delayed postoperative latent pain sensitization revealed by the systemic administration of opioid antagonists in mice

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ABSTRACT

The long-lasting post-surgical changes in nociceptive thresholds in mice, indicative of latent pain sensitization, were studied. The contribution of kappa opioid and N-methyl-D-aspartate (NMDA) receptors was assessed by the administration of nor-binaltorphimine or MK-801; dynorphin levels in the spinal cord were also determined. Animals underwent a plantar incision and/or a subcutaneous infusion of remifentanil (80 μg/kg), and mechanical thresholds (von Frey) were evaluated at different times. On day 21, after complete recovery of mechanical thresholds and healing of the wound, one of the following drugs was administered subcutaneously: (−)-naloxone (1 mg/kg), (+)-naloxone (1 mg/kg), naloxone-methiodide (3 mg/kg), or nor-binaltorphimine (5 mg/kg). Another group received subcutaneous MK-801 (0.15 mg/kg) before nor-binaltorphimine administration. Dynorphin on day 21 was determined in the spinal cord by immunoassay. In mice receiving remifentanil during surgery, the administration of (−)-naloxone or nor-binaltorphimine induced significant hyperalgesia even 5 months after manipulation. Nociceptive thresholds remained unaltered after (+)-naloxone or naloxone-methiodide. On day 21 after manipulation, the administration of MK-801 prevented nor-binaltorphimine-induced hyperalgesia. No changes in dynorphin levels were observed before or after opioid antagonist administration. In conclusion, surgery produced latent pain sensitization evidenced by opioid antagonist-precipitated hyperalgesia. The effect was stereospecific, centrally originated, and mediated by kappa opioid receptors. The blockade of nor-binaltorphimine-induced hyperalgesia by MK-801, suggests that NMDA receptors are also involved. Our results show for the first time that surgery induces latent, long-lasting changes in the processing of nociceptive information that can be induced by non-nociceptive stimuli such as the administration of opioid antagonists.

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1. Introduction

In a mouse model of post-surgical pain we have previously shown that the intraoperative administration of remifentanil enhances and extends postoperative pain sensitization (Cabañero et al., 2009a,b; Campillo et al., 2010; Célérier et al., 2006). It has also been reported that animals previously injured or exposed to opioids develop long-lasting pain vulnerability shown by increased susceptibility to develop hyperalgesia in response to new stimuli or opioid administration (Cabañero et al., 2009a; Rivat et al., 2002, 2007). This phenomenon is known as *latent pain sensitization* (Rivat et al., 2007) and may reflect the transition from acute to chronic pain.

In animals exposed to pain or opioids, latent pain sensitization can be evidenced by the naloxone test (Célérier et al., 2001; Kim et al., 1990; Laulin et al., 2002; Li et al., 2001; Richebe et al., 2005), in which the abrupt blockage of the opioid receptors precipitates hyperalgesia. This response has been tentatively explained by an increase in endogenous opioid peptides and/or increased signaling activity at the opioid receptors (Célérier et al., 2001). However, the specific type of endogenous opioids and/or the opioid receptors implicated remain unclear.

In addition, *N*-methyl-D-aspartate (NMDA) antagonists prevent naloxone-precipitated hyperalgesia in rats previously exposed to opioids (Laulin et al., 2002; Richebe et al., 2005). Although the NMDA receptor system seems to have an important role in latent pain sensitization, the series of events leading to its activation after exposure to opioids is unknown. It has been proposed that exposure to opioids up-regulates spinal dynorphin, that in turn would induce the release of excitatory transmitters from primary afferents (Gardell et al., 2002a,b; Vanderah et al., 2001). Dynorphin is an endogenous opioid with antinociceptive (binding to kappa opioid receptors), and pronociceptive effects, possibly acting on NMDA and/or bradykinin

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receptors (Lai et al., 2006; Tan-No et al., 2002). Thus, dynorphin could play a role maintaining a balance between opioid-dependent antinociception and the pronociceptive systems. In a mouse model of post-incisional pain, we reported that the intraoperative administration of remifentanil increases spinal dynorphin levels between days 2 and 10 after surgery (Campillo et al., 2010). The increased dynorphin may disrupt the initial equilibrium between the two pain modulating systems, inducing postoperative hyperalgesia lasting up to 10–14 days. The recovery of nociceptive thresholds could be related to the return of dynorphin levels to basal values, and/or to a new high-regulating equilibrium reached between the two pain modulating systems (Célérier et al., 2001).

In the present study, we used a mouse model of post-incisional pain that closely mimics the surgical procedure in humans and explored whether latent pain sensitization may occur after a surgical injury (incision) and/or remifentanil administration; we also investigated the role of the dynorphin/kappa opioid receptor system and NMDA receptors in this phenomenon. Our results could contribute to a better understanding of the underlying mechanisms involved in persistent pain after surgery in humans.

2. Material and methods

2.1. Animals

Swiss CD1 male mice weighing 25–30 g obtained from Charles-River (CRIFFA, France) were used in all experiments. Animals were housed four per cage and maintained in a room under a 12 h light/dark cycle (lights on at 8 AM), at controlled temperature (21 ± 1 °C) and relative humidity (55 ± 10%). Food and water were available *ad libitum* except during behavioral evaluation. All procedures and animal handling met the guidelines of the European Communities directive 86/609/EEC regulating animal research. The protocol was approved by the institutional review board of our institution (CEEA-PRBB, Barcelona, Spain).

2.2. Surgery

We used the incisional postoperative pain model adapted from rats (Brennan et al., 1996) and validated in mice in our laboratory (Cabañero et al., 2009a,b; Campillo et al., 2010; Célérier et al., 2006). Animals were anesthetized with sevoflurane delivered for 30 min via a nose mask (induction, 3.5% v/v; surgery, 3.0% v/v) in a sterile operating room. A 0.7 cm longitudinal incision was made with a number 20 blade through the skin and fascia of the plantar surface of the right hind paw, starting 0.3 cm from the proximal edge of the heel extending toward the toes. The underlying plantaris muscle was exposed and incised longitudinally, keeping the muscle origin and insertion intact. After homeostasis with slight pressure, the skin was closed with two 6–0 silk sutures and the wound covered with povidone-iodine antiseptic ointment. After surgery, the animals were allowed to recover under a heat source in cages with sterile bedding.

2.3. Drugs

Sevoflurane (Sevorane®; Abbot Laboratories S.A., Madrid, Spain), remifentanil (Ultiva®, GlaxoSmithKline, Madrid, Spain), and (−)-naloxone hydrochloride (Naloxona KERN PHARMA®, Kern Pharma, Barcelona, Spain) were supplied by the Department of Anesthesiology of the Hospital del Mar (Barcelona, Spain). (+)-Naloxone hydrochloride was obtained from the National Institute on Drug Abuse (Bethesda, MD, USA). Nor-binaltorphimine dihydrocloride (nor-BNI), naloxone-methiodide and dizocilpine hydrogen maleate (MK-801) were purchased from Sigma (St. Louis, MO, USA).

Drug doses were selected on the basis of previous studies (Cabañero et al., 2009a; Campillo et al., 2010): remifentanil (80 μg/kg), was infused subcutaneously (s.c.) over a period of 30 min (rate 0.8 ml/h) using a pump (KD Scientific Inc., Holliston, MA). (−)-Naloxone (1 mg/kg, a non receptor-specific dose) (Célérier et al., 1999, 2000, 2001; Richebe et al., 2005), (+)-naloxone hydrochloride (1 mg/kg) (at the same doses of the active isomer), and naloxone methiodide (3 mg/kg) (at a ratio 3:1) were used with reference to (−)-naloxone, as previously used in our laboratory (Pol et al., 1995). In vivo doses of Nor-BNI (5 mg/kg) (Endoh et al., 1992), and MK-801 (0.15 mg/kg) (Bilsky et al., 1996; Célérier et al., 1999, 2001) were selected according to previous reports, and administrated as a s.c. injection of 250 μl.

All drugs were dissolved in saline (NaCl 0.9%), and were injected at the same dose and route to sham-treated animals that served as control.

2.4. Behavioral testing

Hyperalgesia to punctate mechanical stimulus (referred as mechanical hyperalgesia throughout the text) served as a measure of nociception. Before the experiments, animals were habituated to the equipment (without nociceptive stimulation) for 2–3 days. All behavioral experiments were performed between 9:00 AM and 4:00 PM.

Mechanical hyperalgesia was measured by the hind paw withdraw response to von Frey filament stimulation. Animals were placed in methacrylate cylinders (30 cm high, 9 cm diameter; acquired from Servei Estació, Barcelona, Spain) with a wire grid bottom through which the von Frey filaments were applied (bending force range from 0.008 to 2 g; North Coast Medical, Inc., San Jose, CA). Animals were allowed to habituate for 2 h before testing, to achieve immobility. The filament force was increased or decreased according to the response. The upper limit value (2 g) was assigned when there was no response, and the threshold of response was calculated using the up–down method (Chaplan et al., 1994). Paw shaking or licking were considered nociceptive-like responses. Both hind paws were alternately tested.

2.5. Dynorphin immunoassay

In the control group, we used the lumbar spinal cord (from L4–L6) of 2 animals per sample. In the experimental group remifentanil + incision (Section 2.6), we used the ipsilateral and contralateral spinal cord from the same spinal section (L4–L6) of 4 animals per sample.

After sacrifice, the spinal cord was removed and frozen in liquid nitrogen. To perform the assay, tissue samples were placed in 1 N acetic acid, disrupted with a homogenizer (Ultra-Turf, T8; Ika Werke, Staufen, Germany), and incubated for 30 min at 95 °C. After centrifugation at 12,000 rpm for 20 min (4 °C) the supernatant was lyophilized and stored at −80 °C. Protein concentrations were determined using the bichinchoninic acid method (BCA™ Protein Assay Kit, Thermo Scientific, Rockford, IL, USA) with bovine serum albumin as standard. Immunoassay was performed with a commercial enzyme immunoassay kit using a specific antibody for dynorphin A (1–17) (Peninsula Laboratories, Belmont, CA). Each experiment was repeated at least four times. Standard curves were constructed and the dynorphin content determined with the Prism program (GraphPad, San Diego, CA).

2.6. Experiments performed

2.6.1. Behavioral studies

Mechanical thresholds were evaluated using von Frey filaments. Special care was taken to reduce interindividual variability and to use the smallest number of animals per group. After the habituation period, the average of the measures of two to three consecutive days was obtained and the baseline response calculated. Experiments were performed in mice receiving one of the following treatments:

- Sevoflurane + s.c. saline, a treatment that does not alter nociceptive thresholds (Célérier et al., 2006) (the group will be referred as control or sham-treated group).

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