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Pain

Role of spinal cyclooxygenase-2 and prostaglandin E2 in fentanyl-induced hyperalgesia in rats

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Abstract

Background: Accumulated evidence suggests that spinal cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) may be implicated in the development of opioid-induced hyperalgesia.
Methods: Rats received subcutaneous fentanyl injections at different doses (20–80 μg kg^{-1}), four separate times at 15-min intervals. Some rats only received fentanyl (60 μg kg^{-1} × 4 doses) with or without surgical incision. Fentanyl-induced hyperalgesia was evaluated via a tail-pressure or paw-withdrawal test. The concentrations of spinal COX-2, EP-1 receptor (EP-1R) mRNA, and PGE2 were measured. The effects of the COX-2 inhibitor, parecoxib (intraperitoneal 10 mg kg^{-1}), or the EP-1R antagonist, SC51089 (intraperitoneal 100 μg kg^{-1}), on hyperalgesia and spinal PGE2 were examined.
Results: Acute repeated injections of fentanyl dose-dependently induced mechanical hyperalgesia, which reached a peak at the 1st day and persisted for 1–4 days postinjection. This hyperalgesia could be partly or totally prevented by the pretreatment of either parecoxib or SC51089. Consistently, the levels of spinal COX-2 mRNA and PGE2 were also dose-dependently increased, reaching a peak at the first day and persisting for 2 days postinjection. Pretreatment with parecoxib could block the increase in spinal PGE2 and had no effects on spinal COX-2 and EP-1R mRNA. Fentanyl injection enhanced incision-induced mechanical and thermal hyperalgesia.
Conclusions: Acute repeated fentanyl administration dose-dependently produced mechanical hyperalgesia and augmented surgery induced postoperative hyperalgesia. This behavioural change was paralleled with an increase in spinal COX-2 mRNA and PGE2 after fentanyl administration. Inhibition of COX-2 or blockade of EP-1R can partly or totally prevent hyperalgesia.

Keywords: cyclooxygenase-2; fentanyl; opioid-induced hyperalgesia; prostaglandin E2; surgery

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Editor's key points

- Repeated opioid administration can induce hyperalgesia and can result in chronic postsurgical pain.
- The roles of cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) and its receptor, EP-1R, in the development of acute fentanyl-induced hyperalgesia was investigated in a rat model.
- Repeated fentanyl administration dose-dependently causes mechanical hyperalgesia and worsens surgery-induced postoperative hyperalgesia.
- Hyperalgesia was accompanied by increases in spinal COX-2 and PGE2 and was prevented by inhibitors of COX-2 or blockade of EP-1R.
- COX-2 and PGE2 seem to be involved in fentanyl-induced hyperalgesia and possibly chronic postsurgical pain.

Opioid-induced hyperalgesia (OIH) is defined as the paradoxical effect that opioids decrease pain thresholds and increase atypical pain unrelated to the original, preexisting pain.[1] OIH often occurs upon repeated injections with opioid drugs such as morphine, remifentanil, or fentanyl in animal models.[2–5] Recently, in some clinical settings acute exposure to opioids, such as perioperative remifentanil or fentanyl, was implicated in induction of hyperalgesia and partly contributed to chronic postsurgical pain, a significant problem with a high incidence (10–50%).[6–8] Recent evidence indicated that perioperative OIH was mainly associated with the use of high doses of remifentanil.[5,9] Remifentanil is a short-acting opioid and is widely used intraoperatively. However, the role of long-acting opioids such as fentanyl and sufentanil in perioperative OIH, is unclear, although a few studies suggest that fentanyl, especially at high doses, induced hyperalgesia and increased postoperative pain in animal models and human trials.[3,9,10]

Preclinical studies suggest that neuroinflammation, especially in the spinal cord, as indicated by the upregulation of proinflammatory factors such as prostaglandin E2 (PGE2)[11–13] and cyclooxygenase-2 (COX-2),[14,15] contributes to the development of OIH. However, current data cannot explain the relationship between acute OIH and changes in proinflammatory factors such as COX-2 and PGE2 in the spinal cord. COX-2, one of two COX isoforms, is particularly relevant for inflammation-induced PGE2 formation. PGE2 is a key mediator of exaggerated pain sensation in acute and chronic pain conditions through the activation of four PGE2 receptor subtypes (EP1–4).[16] Notably, the EP1 receptor (EP-1R) played a key role in facilitating the generation of nociception induced by injury and inflammation and contributing predominantly to PGE2-associated hyperalgesia.[16–18] The aim of this study was to determine the role of the spinal COX-2/PGE2/EP-1R pathway in the acute fentanyl-induced hyperalgesia in rats.

Methods

Animals

The experimental protocol was approved by Institutional Laboratory Animal Care and Use Committee of Sun Yat-sen University and experiments are reported in accordance with relevant aspects of the ARRIVE guidelines. Adult male Sprague–Dawley rats (Sun Yat-Sen University LAC, Guangzhou, China), weighing 200–250 g at the start of the experiments, were used. The rats were housed under conditions of controlled temperature (20–24°C) and humidity (40–70%) and were habituated to the environment for at least 3 days before the experiments. Two or three rats were kept in each cage, under a 12 h light and dark cycle, with free access to food and water. Drug administration and behaviour tests were performed during the daytime.

Behaviour tests

Mechanical nociceptive thresholds of the tail were assessed by the tail-pressure test with the use of a ZH-YLS-3E Analgesy Meter (Zhenghua, Anhui, China) as described previously.[19,20] Briefly, the distal part of the tail was supported by a plinth while pressure, linearly increasing at a rate of 10 g s^{-1}, was applied with a cone-shaped pusher. The proximal 2 cm of the tail was marked, and with each successive trial on the same day, a new pressure point was positioned 0.25 cm proximal to the site of the previous pressure point. The end-point was defined as the first motor response of struggling against the pressure. The baseline mechanical nociceptive threshold was between 300 and 320 g. A cut-off point, in the absence of response, was set at 600 g, to avoid tissue damage. Before the experiment, rats received a 3-day training session.

The thermal nociceptive test was carried out as described previously.[21] A plantar test apparatus (IITC, Chicago, IL, USA) was used to evaluate thermal nociception. Briefly, the rat was placed in a plexiglass box on a glass plate. A beam of light passed through the glass to the middle plantar aspect of the hind paw near the toes ipsilateral to the surgical site. The intensity of the beam was set at 30 W and the diameter was 5 mm. The paw withdrawal latency was recorded as the length of time between the onset of the light beam and paw withdrawal. The 20-s cut-off time was used to avoid tissue damage.

Surgery

Rats were anaesthetized with 1.5–2% isoflurane (Jiupai Company, Hebei, China) delivered via a nose cone.[22] Adequate anaesthesia was ascertained by the lack of pedal withdrawal response to a nociceptive stimulus. After the plantar aspect of the left hind paw was sterilized with a 10% povidone–iodine solution, a 1-cm longitudinal incision was made through the skin, fascia, and muscle. The incision started 0.5 cm from the proximal edge of heel and extended to the toes, as described previously.[23] A 4-0 silk was used to suture the skin. All incisions were made after the second injection of fentanyl or normal saline. The rats in the sham surgery groups received anaesthesia but without surgical incision.

Drugs

Fentanyl citrate (Humanwell, Yichang, China) was dissolved in normal saline for subcutaneous (s.c.) administration at the volume of 0.1 ml 100 g^{-1} body weight. According to the previous studies,[3] fentanyl at doses of 20, 40, 60, or 80 μg kg^{-1} was given repeatedly four times. Parecoxib Sodium (Pfizer, Dalian, China) and SC 51089 (EP-1R antagonist; Pfizer, New York, NY, USA) were dissolved in normal saline for intraperitoneal administration at the volume of 0.1 ml 100 g^{-1} body weight at the doses of 10 mg kg^{-1} and 100 μg kg^{-1}, respectively.