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Preemptive analgesia by zaltoprofen that inhibits bradykinin action and cyclooxygenase in a post-operative pain model

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Abstract

The post-operative pain state results from a barrage of primary afferent inputs exposed to products of tissue damage such as bradykinin and prostaglandins and the central sensitization by the continuing inputs. This provides the rationale for preemptive analgesia, whereby the blockade of primary afferent inputs prior to injury may result in a reduction of post-operative pain. 2-(10,11-Dihydro-10-oxo-dibenzo[*b,f*]thiepin-2-yl) propionic acid (zaltoprofen) is a unique compound that inhibits cyclooxygenase (COX) and exhibits anti-bradykinin activity. The present study evaluated the preemptive analgesic effect of zaltoprofen in a post-operative pain model produced by plantar incision. When orally, but no intrathecally, administered 30 min prior to incision, zaltoprofen significantly increased the withdrawal threshold 2 h and 1–3 days after incision at 10 mg/kg. While the bradykinin B_1 antagonist des-Arg^{10}-HOE-140, the selective COX-1 inhibitor SC-560, and the selective COX-2 inhibitor celecoxib did not affect post-operative pain, the B_2 antagonist HOE-140 dose-dependently relieved the post-operative pain at 2–200 μg/kg with a time course similar to that of zaltoprofen. The B_2 receptor mRNA was expressed in the hindpaw and the expression did not change before and 24 h after surgery. These results suggest that zaltoprofen produces the preemptive analgesic effect peripherally by blocking the B_2 pathway.
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1. Introduction

Tissue damage caused by inflammation, trauma or ischemia releases a number of chemical mediators that can originate locally or from cells that infiltrate the site of inflammation. Bradykinin is an endogenous peptide formed in plasma and peripheral tissues and once formed, it exerts the actions by the activation of two distinct bradykinin receptors, B_1 and B_2 (for reviews, see Marceau et al., 1998; Calixto et al., 2000; Couture et al., 2001). It has been well established that B_2 receptors are constitutively present throughout the peripheral and central nervous systems and that they are responsible for carrying out most of the physiological responses attributed to kinins. On the other hand, B_1 receptors are rarely present in normal tissues, but they can be up-regulated under pathological conditions including tissue trauma or injury or following treatment with certain agents such as endotoxins, complete Freund's adjuvant, or cytokines. Prostaglandins (PGs) are lipid mediators produced from arachidonic acid by the constitutive cyclooxygenase (COX)-1 or by COX-2, which is induced by inflammatory and mitogenic stimuli at the site of injury and in the spinal cord (Narumiya et al., 1999; Ito et al., 2001). PGs also elicit diverse inflammatory responses through respective membrane receptors. Both bradykinin and PGs are among the most potent autacoids involved in vascular, inflammatory and pain processes (Calixto et al., 2000; Couture et al., 2001; Ito et al., 2001). A mixture of these products of tissue damage known as inflammatory 'soup' sensitizes peripheral nociceptors by initiating a cascade of events that change ionic

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conductances of the nociceptor peripheral terminal (Julius and Basbaum, 2001). Peripheral sensitization results in a reduction in the threshold of nociceptive afferent terminals at the site of injury, followed by central sensitization caused by an increased excitability of spinal neurons. This phenomenon may contribute the severity of post-operative pain, one of common causes of tissue injury in humans. The preemptive analgesia is based on the assumption that the administration of an analgesic drug before surgical operation, whose effect continues into post-operative period, can reduce both the incisional and inflammatory pain and in this way can reduce peripheral and central sensitization.

2-(10,11-Dihydro-10-oxo-dibenzo[*b*,*f*]thiepin-2-yl)propionic acid (zaltoprofen) (Kameyama et al., 1987) is a non-steroidal anti-inflammatory drug (NSAID), which prevents the development of inflammation by blocking the synthesis of PGs. When orally administered, zaltoprofen was shown to possess a strong analgesic activity against inflammatory pain, but not thermal pain, in rats. Interestingly, zaltoprofen showed a strong inhibitory effect on bradykinin-induced pain at 5–20 mg/kg. Among conventional NSAIDs, indomethacin was less potent than zaltoprofen and diclofenac and ibuprofen did not affect the bradykinin-induced pain at 200 mg/kg. This unique property of zaltoprofen prompted us to examine whether it was effective in preemptive analgesia. A rat model of post-operative pain involving a brief surgical incision at the plantar hindpaw has been developed in rats (Brennan et al., 1996). This model is distinguished by persistent, quantifiable, mechanical hyperalgesia lasting several days, the time course of which has similarities to patient's pain after surgery. In the present study, we demonstrated that zaltoprofen was effective in preemptive analgesia through the B_2 pathway.

2. Materials and methods

2.1. Drugs

Zaltoprofen and its sodium salt were supplied by Nippon Chemipher (Tokyo, Japan) and celecoxib and 5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-trifluoromethyl pyrazole (SC-560) were kindly donated from Pfizer Inc. (New London, CT). The B_2 antagonist icatibant (HOE-140) and the B_1 antagonist des-Arg^{10}-HOE-140 were purchased from Sigma–Aldrich (St. Louis, MO). All other chemicals were of reagent grade.

2.2. Animals

Five-week-old ddY male mice (Shizuoka Laboratory Center, Hamamatsu, Japan) weighing 22 ± 2 g were used in this study. The animals were housed in a group before surgery and individually after operation in a 12-h light–darkness cycle, a constant temperature of 22 ± 2 °C, and 60 ± 10% humidity. They were allowed free access to food and water over the experimental period. Each animal was used for one experiment and killed at the end of the experiment. All animal experiments were conformed to the regulations of the Animal Care Committee of Osaka Medical College and conducted in accordance with the guidelines of the ethics committee of the International Association for the Study of Pain (Zimmermann, 1983).

2.3. Surgical procedure

The post-operative pain model was prepared in mice with skin, fascia, and muscle incision under surgically clean conditions essentially according to the procedure described by Brennan et al. (1996). Briefly, after anesthetized with an intraperitoneal administration of pentobarbital (60 mg/kg), a 5-mm longitudinal incision was made with a number 11 blade, through skin and fascia of the plantar aspect of the foot. The plantaris muscle was elevated and incised longitudinally. After gentle pressure for hemostasis, the skin was apposed with two sutures of 6-0 nylon thread. After surgery, the incision was checked daily and animals with any sign of wound infection were excluded from the study.

2.4. Drug administration

Zaltoprofen, SC-560 and celecoxib were suspended in 0.5% solution of carboxymethyl cellulose (CMC) and administered orally in a volume of 0.5 ml. HOE-140 and des-Arg^{10}-HOE-140 were dissolved in saline and administered subcutaneously. For intrathecal administration, sodium salt of zaltoprofen was dissolved in saline (5 μl) and injected slowly into the subarachnoid space of mice. All drugs were prepared on the day of experiments and administered 30 min before or 5 min after operation.

2.5. Assessment of mechanical hyperalgesia

For behavioral assessment of mechanical hyperalgesia, mice were placed individually on an elevated metal grid covered with a clear plastic cage. Withdrawal responses to punctuate mechanical stimulation were determined using calibrated von Frey filaments. The filaments were applied to the paw at an increasing force until the mouse withdrew its hind limb. The site of stimulation was in the plantar aspect of the foot adjacent to the wound. The withdrawal thresholds were measured before and then up to day 5 after surgery following drug or vehicle administration.

2.6. Reverse transcription-polymerase chain reaction (RT-PCR) analysis

Male ddY mice were decapitated before and 24 h after surgery. Immediately after decapitation, hindpaws and lumbar spinal cords were carefully dissected and subjected to the isolation of total RNA and high-stringency step-down RT-PCR as described previously (Doi et al., 2002). The RT-

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