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Research Paper

The importance of brain PGE_2 inhibition versus paw PGE_2 inhibition as a mechanism for the separation of analgesic and antipyretic effects of lornoxicam in rats with paw inflammation

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Abstract

Objectives Lornoxicam is a non-selective cyclooxygenase inhibitor that exhibits strong analgesic and anti-inflammatory effects but a weak antipyretic effect in rat models. Our aim was to investigate the mechanism of separation of potencies or analgesic and antipyretic effecls of lornoxicam in relatioin to its effect on prostaglandin E_2 (PGE_2) production in the inflammatory paw and the brain.

Methods A model of acute or chronic paw inflammation was induced by Freund's complete adjuvant injection into the rat paw. Lornoxicam (0.01–1 mg/kg), celecoxib (0.3–30 mg/kg) or loxoprofen (0.3–30 mg/kg) was administered orally to the rats and the analgesic and antipyretic effects were compared. The paw hyperalgesia was assessed using the Randall–Selitto test or the flexion test. Dorsal subcutaneous body temperature was measured as indicator of pyresis. After the measurement of activities, the rats were sacrificed and the PGE_2 content in the paw exudate, cerebrospinal fluid or brain hypothalamus was measured by enzme-immunoassay.

Key findings In a chronic model of arthritis, lornoxicam, celecoxib and loxoprofen reduced hyperalgesia with an effective dose that provides 50% inhibition (ED50) of 0.083, 3.9 and 4.3 mg/kg respectively, whereas the effective dose of these drugs in pyresis was 0.58, 0.31 and 0.71 mg/kg respectively. These drugs significantly reduced the PGE_2 level in paw exudate and the cerebrospinal fluid. In acute oedematous rats, lornoxicam 0.16 mg/kg, celecoxib 4 mg/kg and loxoprofen 2.4 mg/kg significantly reduced hyperalgesia to a similar extent. On the other hand, lornnoxicam did not affect the elevated body temperature, whereas celecoxib and loxoprofen siginificantly reduced the pyrexia to almost the normal level. These drugs significantly reduced the PGE_2 level in inflamed paw exudate lo almost the normal level. On the other hand, lornoxicam did not change PGE_2 level in the brain hypothalamus, whereas celecoxib and loxoprofen strongly decreased it.

Conclusions Lornoxicam exhibits strong analgesic but weak antipyretic effects in rats with paw inflammation. Such a separation of effects is related to its efficacy in the reduction of PGE_2 levels in the paw and brain hypothalamus.

Keywords analgesic activity; antipyretic activity; lornoxicam; PGE_2; rat paw oedema

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Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed and are first choice drugs for the treatment of pain and inflammation arising from chronic and acute inflammatory diseases. The main mechanism of NSAID action involves the inhibition of cyclooxygenase (COX) and thus of prostaglandin production. It is well known that COX exists as two isoforms, COX-1 and COX-2; these isoforms catalyse the same reaction but differ in terms of the regulation of their expressions.[1–3] COX-1 is constitutively expressed

in almost every cell type and induces prostaglandins mainly for use in housekeeping functions. COX-2, meanwhile, is readily induced by pro-inflammatory cytokines and mitogens and accounts for the majority of prostaglandin production during inflammation. The expression of COX-2 varies both in quality and quantity depending on the tissue and the course of the inflammatory response. The therapeutic actions of NSAIDs, such as their anti-inflammatory, analgesic and antipyretic effects, can be mainly explained by the inhibition of COX-2. A large number of NSAIDs are commercially available and traditional NSAIDs, such as aspirin, ibuprofen, diclofenac and indometacin, inhibit both COX-1 and COX-2, while several COX-2 selective inhibitors, such as celecoxib and rofecoxib, exhibit a preference toward COX-2.[4–6] The pharmacological profiles of these NSAIDs may be different depending on many factors, such as the degrees of potency and selectivity for COX-1 and COX-2, the distribution in target tissues and cells and the different characteristics of existence of the two COX isoforms in each disease.

COX-2 is constitutively expressed in the central nervous system (CNS) and is highly induced in the CNS during inflammatory conditions.[7] It is well documented that peripheral inflammation involves an increase in COX-2-mediated prostaglandin synthesis in the CNS, including the spinal cord, elevating the prostaglandin E_2 (PGE_2) levels in the cerebrospinal fluid (CSF), which contributes to peripheral pain responses (hyperalgesia and allodynia). Intrathecal or systemic administration of selective COX-2 inhibitors reduced the central PGE_2 levels and hyperalgesia.[8–12] Fever is also triggered by an elevation of PGE_2 in the brain, which is brought about after infection in response to pyrogenic cytokines, such as interleukin (IL)-1, IL-6, tumour necrosis factor-α and interferons, which are produced by activated cells in the periphery.[13–15] Yamagata *et al.*[16] demonstrated in rats that brain endothelial cells play a critical role in PGE_2 production during fever by expressing COX-2 and microsomal-type PGE synthase. The systemic administration of selective COX-2 inhibitors, such as NS-398, nimesulide and celecoxib, significantly suppressed the febrile response and PGE_2 synthesis in the brain.[16–18] As COX-1 and COX-2 are expressed centrally and peripherally, NSAIDs are likely to exhibit their analgesic and antipyretic effects by inhibiting both central and peripheral prostaglandin production; however, the role of central production of prostaglandins and the relationship between them in pain and pyresis have not been well understood.

Lornoxicam is an oxicam-type NSAID that is mainly used in Japan and Europe; it inhibits both COX-1 and COX-2 similarly and is one of the strongest analgesic agents to have been tested amongst commercially available NSAIDs. We previously reported that the antipyretic effect of lornoxicam was about 22 times less (ED50 (dose producing 50% of maximum effect) = 6.2 mg/kg) in yeast-induced febrile rats than its analgesic effect (ED50 = 0.28 mg/kg) in rat yeast-induced paw hyperalgesia,[19] although comparable NSAIDs, including diclofenac,[19] aspirin,[20] celecoxib[21] and loxoprofen,[22] showed an equipotent or stronger antipyretic effect in animal models. In this paper, we compared the anti-inflammatory, analgesic and antipyretic effects of lornoxicam with those of other commercially available NSAIDs (celecoxib, a selective COX-2 inhibitor, and loxoprofen, a non-selective inhibitor) in a rat model of adjuvant-induced inflammation, and examined the relationship between these effects and prostaglandin inhibition in the paw and the brain hypothalamus.

Materials and Methods

Drugs and reagents

Lornoxicam (Lorcam; Taisho Pharmaceutical, Tokyo, Japan), celecoxib (Celecox; Astellas Pharmaceutical, Tokyo, Japan) and loxoprofen (Loxonin; Daiichi-Sankyo, Tokyo, Japan) were purchased as commercially available drugs. *Mycobacterium tuberculosis* H37 RA (DIFCO Laboratories, MI, USA), liquid paraffin (Wako, Tokyo, Japan), carboxymethyl cellulose sodium salt (CMC; ICN Biomedicals, Aurora, OH, USA) and PGE_2 enzyme-immunoassay (EIA) kit (Cayman Chemical, Ann Arbor, USA) were obtained from the indicated sources.

Animals

Eight-week-old male Lewis rats and six-week old male wistar rats (Charles River Japan, Kanagawa, Japan) were housed under conditions of controlled temperature (23 ± 3°C), humidity (50 ± 20%) and lighting (lights on, 0700–1900 h), and were used after at least five days of acclimation. All the animal experiments reported here were reviewed and approved by the Taisho Pharmaceutical Animal Care Committee and conformed to the Japanese Experimental Animal Research Association Standards defined in the Guidelines for Animal Experiments (1987).

Evaluation of paw swelling, paw hyperalgesia and pyretic response in arthritic rats

Arthritis was induced in Lewis rats by the injection of Freund's complete adjuvant (FCA; 0.8 mg of *Mycobacterium tuberculosis* in 0.1 ml of liquid paraffin) into the left hind footpad (day 0). Sixteen days after the injection of the FCA, the contralateral right footpad volume was measured using a plethysmometer (Neuroscience, Tokyo, Japan). The pain threshold was determined as the number of squeaking vocalizations induced by five consecutive gentle flexions of the ankle joint of the contralateral right paw. Body temperature was determined using an electronic laboratory animal monitoring system (BioMedic Data Systems, NJ, USA). Briefly, microchip battery-free transponders (14 mm × 2.2 mm, 120 mg) were implanted subcutaneously in the dorsal thoracic area using a needle two days before the measurement. The body temperature was then read using a DAS-504 Pocket Scanner. Lornoxicam (0.01–1 mg/kg), celecoxib (0.3–30 mg/kg) and loxoprofen (0.3–30 mg/kg) were suspended in a 0.5% CMC aqueous solution and were gavaged orally from day 16 to day 19 once a day for four consecutive days. The pharmacological indices were assessed on day 16 and

day 20 at indicated times. Rats that were not injected with FCA were used as normal controls.

Tissue preparation, measurement of PGE_2 content in cerebrospinal fluid and paw exudate in arthritic rats

On day 20 after the FCA injection, the rats were deeply anaesthetized with sodium pentobarbital, the CSF was obtained and the animals were sacrificed. The exudate of the right hind paw was collected according to the method of Noguchi *et al.*[23] Briefly, the right hind paw was injected with 0.1 ml of 10 μM indometacin to prevent the further production of eicosanoids and the paw was lacerated with a scalpel, suspended over the bottom of a polypropylene centrifuge tube with an Eppendorf pipette tip, and centrifuged (2000*g*, 15 min, 4°C) to obtain the inflammatory exudate. The CSF and the inflammatory exudate were then centrifuged again (700*g*, 1 min, 4°C) and the supernatants were stored at −80°C until PGE_2 measurement. The PGE_2 content was determined using a PGE_2 EIA kit.

Comparison of paw hyperalgesia and pyretic reaction in rats with acute hind paw inflammation

FCA-induced acute oedema was induced by injecting 0.1 ml of 1% FCA into the left hind paws of Wistar rats. The next day, the effect of the drugs on paw hyperalgesia and pyretic reaction was evaluated. The pain threshold was measured using the Randall–Selitto test with an analgometer (Muromachi Kikai, Tokyo, Japan) and the body temperature was measured as described above. Lornoxicam (0.16 mg/kg), celecoxib (4 mg/kg), loxoprofen (2.4 mg/kg) or vehicle (0.5% CMC in water) was orally administered 2 h before the pharmacological evaluation.

Comparison of PGE_2 content in paw exudate and hypothalamus in rats with acute hind paw inflammation

Just after the pharmacological evaluation, the rats were sacrificed and the inflamed paw and the brain hypothalamus tissue were taken for the PGE_2 measurement. Rat paw exudate was collected using the method described above. The hypothalamus tissue was minced and homogenized in ice-cold phosphate-buffered saline containing 10 μM of indometacin with a Polytron tissue homogenizer for 30 s on ice. Four millilitres of acetone was then added to the sample, and the precipitate was removed by centrifugation at 2000*g* for 10 min at 4°C. The supernatant was carefully poured into a test tube and evaporated to dryness under a stream of nitrogen and re-suspended in EIA buffer. The amount of PGE_2 was measured using a PGE_2 EIA kit.

Data analysis

The results were expressed as the mean ± SEM. The percentage compared with the control was calculated using the difference between the drug-treated group and the vehicle control. Differences between the normal and vehicle control group were analysed using an *F*-test, followed by Student's *t*-test or a Welch *t*-test. Differences between the vehicle control and the drug treatment group were tested using a Bartlett test, followed by a multiple comparison test using the Dunnett test or Welch *t*-test with Bonferroni correction. $P < 0.05$ was considered statistically significant. Dose–response curves for the percentage of the vehicle control were fitted with a four-parameter logistic function using a nonlinear least-squares regression method. ED50 was derived by interpolation from the fitted four-parameter equation.

Results

Effect of lornoxicam, celecoxib and loxoprofen on paw swelling and hyperalgesia after repeated doses in arthritic rats

Marked swelling and hyperalgesia were observed in the contralateral paw of FCA-treated rats on day 16 after injection. When the drugs were administered therapeutically for four days (days 16–19), lornoxicam, celecoxib and loxoprofen significantly reduced paw swelling in a dose-dependent manner, with ED50 values of 0.12, 10.0 and 4.8 mg/kg, respectively (Figure 1a, Table 1). Lornoxicam, celecoxib and loxoprofen also reversed the hyperalgesia in a dose-dependent manner, with ED50 values of 0.17, 4.1 and 11.5 mg/kg, respectively (Table 1).

Effect of lornoxicam, celecoxib and loxoprofen on hyperalgesia and pyresis after single doses in arthritic rats

On day 16, 3 h after a single oral drug administration, lornoxicam, celecoxib and loxoprofen reversed the hyperalgesia in dose-dependent manner with ED50 values of 0.083, 3.9 and 4.3 mg/kg, respectively (Figure 1b, Table 1). The analgesic potency of lornoxicam was about 47- and 52-fold more potent than celecoxib and loxoprofen, respectively. The vehicle-treated rats also showed a significantly higher body temperature of 37.3 ± 0.08°C ($n = 24$) compared with the normal control rats (36.6 ± 0.06°C, $n = 24$). Unlike in analgesia, lornoxicam, celecoxib and loxoprofen significantly decreased body temperature with similar efficacies (Figure 1c). The effective dose at which the body temperature was decreased by 1°C was 0.58 mg/kg for lornoxicam, 0.31 mg/kg for celecoxib and 0.71 mg/kg for loxoprofen (Table 1).

Effect of lornoxicam, celecoxib and loxoprofen on the PGE_2 content in paw exudate and CSF in arthritic rats

The PGE_2 content in the CSF and the contralateral paw exudate significantly increased in the vehicle control group on day 20 after FCA injection. The administration of lornoxicam, celecoxib or loxoprofen significantly decreased the PGE_2 content in CSF in a dose-dependent manner, with ED50 values of 0.018, 0.73 and 2.4 mg/kg, respectively (Figure 2a, Table 1). In addition, these drugs strongly decreased the PGE_2 content of inflammatory paw exudates, with ED50 values of 0.32 mg/kg for loxoprofen, though lornoxicam and celecoxib yielded inhibitory rates of over 50% at the lowest dose in each experiment (Figure 2b, Table 1). The inhibitory rate was 85.6% for lornoxicam (0.1 mg/kg). 74.7% for celecoxib (3 mg/kg) and 78.8% for loxoprofen

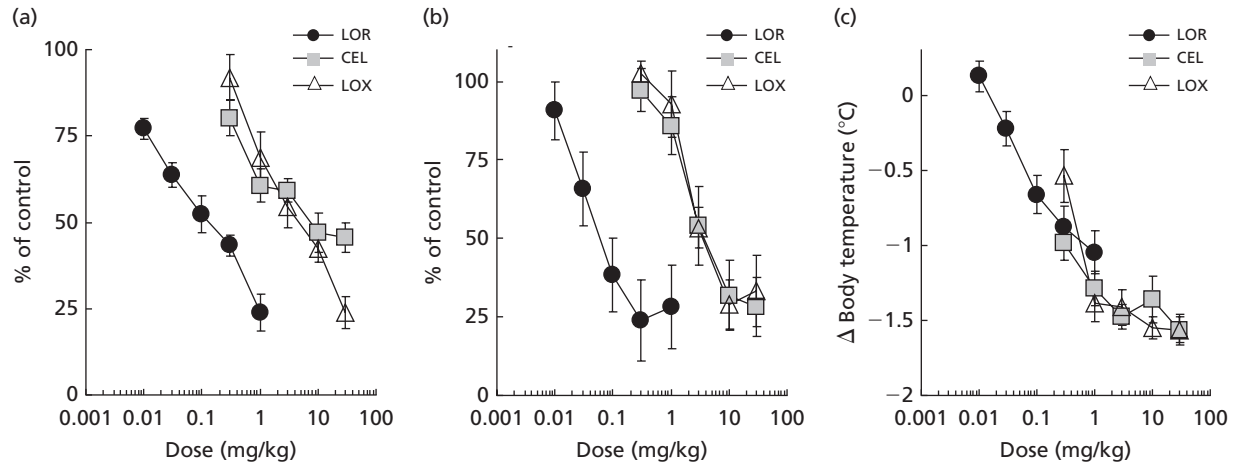

Figure 1 Effect of lornoxicam, celecoxib and loxoprofen on paw swelling (a), paw hyperalgesia (b) and pyresis (c) in FCA-induced arthritic rats. Rats received an intraplantar injection of *M. tuberculosis* (0.8%, 0.1 ml/paw) to induce arthritis (day 0). The drugs were administered by gavage once a day for four consecutive days (day 16–19). On day 16, joint flexion-induced pain and body temperature were measured 3 h after the first drug dosage. On day 20, the contralateral paw volume was measured. The percentage compared with the control was calculated using the difference between the drug-treated group and the vehicle control. Data are expressed as the mean ± SEM, $n = 8$.

(3 mg/kg). These NSAIDs decreased the PGE_2 levels more potently in the paw exudate than in CSF.

Comparison of the effect of lornoxicam, celecoxib and loxoprofen on hyperalgesia and pyresis in acute oedematous rats

Twenty-four hours after the intraplantar injection of 1% FCA, marked hyperalgesia was observed in the inflamed hind paw in response to mechanical compression (a decrease in the pain threshold by 63.9 mmHg, compared with the threshold in normal rats). At the same time, the dorsal subdermal temperature of the rats significantly increased by 2.38 ± 0.19°C compared with the normal control group. Lornoxicam (0.16 mg/kg), celecoxib (4 mg/kg) or loxoprofen (2.4 mg/kg) was administered 2 h before the assay and all the drugs significantly reversed the hyperalgesia (by 72.0%, 70.1% and 51.9%, respectively) (Figure 3a). On the other hand, the administration of lornoxicam did not have any effect on FCA-induced pyrexia, although celecoxib or loxoprofen markedly reversed body temperature by 90.5% and 84.7%, respectively (Figure 3b).

Comparison of the effect of lornoxicam, celecoxib and loxoprofen on PGE_2 content in the hind paw exudate and the brain in acute oedematous rats

The PGE_2 content in FCA-injected paw exudate (5.26 ± 0.69 ng/paw) and the hypothalamus area of the brain (9.24 ± 0.96 ng/g) were significantly higher than those in normal rat paw (0.66 ± 0.15 ng/paw) or normal rat hypothalamus (0.83 ± 0.08 ng/g), respectively. Lornoxicam, celecoxib or loxoprofen significantly inhibited the PGE_2 content in inflamed paw exudates, with inhibition rates of 80.8%, 74.0% and 103.3%, respectively (Figure 4a). On the other hand, lornoxicam did not decrease the brain PGE_2 level at all, whereas celecoxib and loxoprofen inhibited PGE_2 formation in the brain by 92.3% and 105.1%, respectively (Figure 4b).

Discussion

In this study, we confirmed that the equivalent to a clinical dose of lornoxicam exhibited a strong analgesic effect but a significantly weak antipyretic effect in FCA-induced paw

Table 1 Summary of in-vivo efficacy studies for lornoxicam, celecoxib and loxoprofen in FCA-induced arthritic rats

	ED50 (95% confidence limits) (mg/kg)		
	Lornoxicam	Celecoxib	Loxoprofen
Paw swelling (day 20)[a]	0.12 (0.084–0.18)	10.0 (5.3–27.6)	4.8 (3.2–7.6)
Hyperalgesia (day 20)[a]	0.17 (0.062–0.60)	4.1 (2.2–7.9)	11.5 (8.8–15.0)
Hyperalgesia (day 16, 3 h)[a]	0.083 (0.031–0.22)	3.9 (2.1–7.4)	4.3 (2.6–7.2)
Pyresis (day 16, 3 h)[b]	0.58 (0.36–1.3)	0.31 (0.078–0.71)	0.71 (0.25–1.3)
PGE_2 in CSF (day 20)	0.018 (0.011–0.027)	0.73 (0.57–0.92)	2.4 (1.4–4.1)
PGE_2 in paw exudate (day 20)[a]	<0.01	<0.3	0.32 (0.029–0.69)

[a]Paw swelling, hyperalgesia and PGE_2 in paw exudate were assessed in the contralateral paw. [b]Effective dose at which the body temperature was decreased by 1°C.

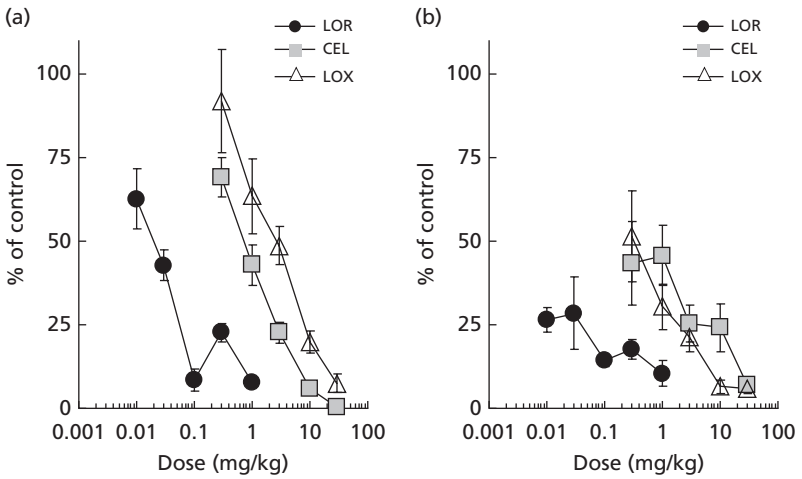

Figure 2 Effect of lornoxicam, celecoxib and loxoprofen on PGE_2 content in CSF (a) and paw exudate (b) in FCA-induced arthritic rats. On day 20, after measurement of behavioral responses, rats were sacrificed and the CSF andthe contralateral hind paw were removed. PGE_2 was extracted by the method described in Materials and Methods. The PGE_2 content was measured using EIA. The percentage compared with the control was calculated using the difference between the drug-treated group and the vehicle control. Data are expressed as the mean ± SEM, $n = 8$.

inflammatory rats. No other commercially available NSAIDs have shown such a separation of these effects. As described below, the analgesic and antipyretic effects of these NSAIDs are related to their efficacy in reducing PGE_2 in the rat paw and brain hypothalamus.

We compared the analgesic and antipyretic effects of lornoxicam, celecoxib and loxoprofen in an established arthritic model induced by FCA, which is commonly used for evaluating the potency of NSAIDs.[24,25] We confirmed that intraplantar injection of FCA induced acute and then chronic paw inflammation and that the rats exhibited mechanical hyperalgesia and pyrexia. This meant that we could assess the pharmacological effects in the same rats. Lornoxicam, celecoxib and loxoprofen are used clinically for the treatment of pain in rheumatoid arthritis at doses of 4 mg three times daily (about 0.24 mg/kg per day), 100 mg twice daily (about 4 mg/kg per day) and 60 mg three times daily (about 3.6 mg/kg per day), respectively. Otherwise, lornoxicam and loxoprofen are used in the treatment of acute pain at doses of 8 mg (about 0.16 mg/kg) and 60–120 mg (about 1.2–2.4 mg/kg), respectively. The ED50 values for anti-inflammatory and analgesic effects in the arthritic model (Table 1) agreed well with the clinical dosages. The ratios of ED50 value (day 16) between antipyrexia and analgesia of

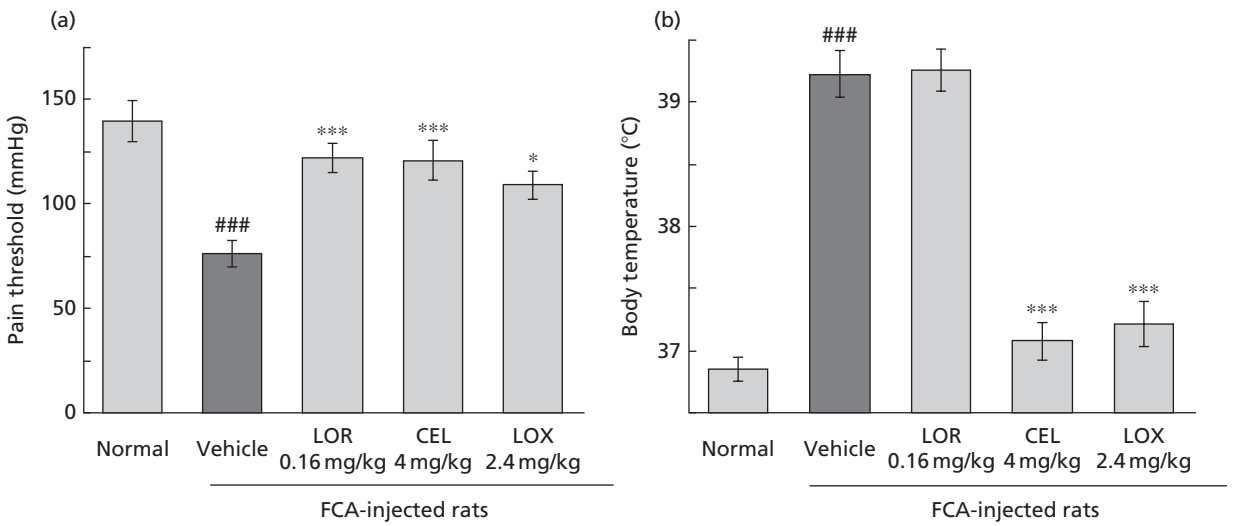

Figure 3 Effect of lornoxicam, celecoxib and loxoprofen on paw hyperalgesia (a) and pyrexia (b) in FCA-induced acute oedematous rats. Rats received an intraplantar injection of *M. tuberculosis* (1%, 0.1 ml/paw) to induce paw inflammation. The next day, each drug was administered orally and 2 h later, the body temperature and the pain threshold of the inflamed paw in response to mechanical compression were measured. LOR, lornoxicam; CEL, celecoxib; LOX, loxoprofen. Data are expressed as the mean ± SEM, $n = 8$. $^{*}P < 0.05$; $^{***}P < 0.001$ vs vehicle control (Dunnett test); $^{\#\#\#}P < 0.001$ vs normal control (Student's *t*-test).

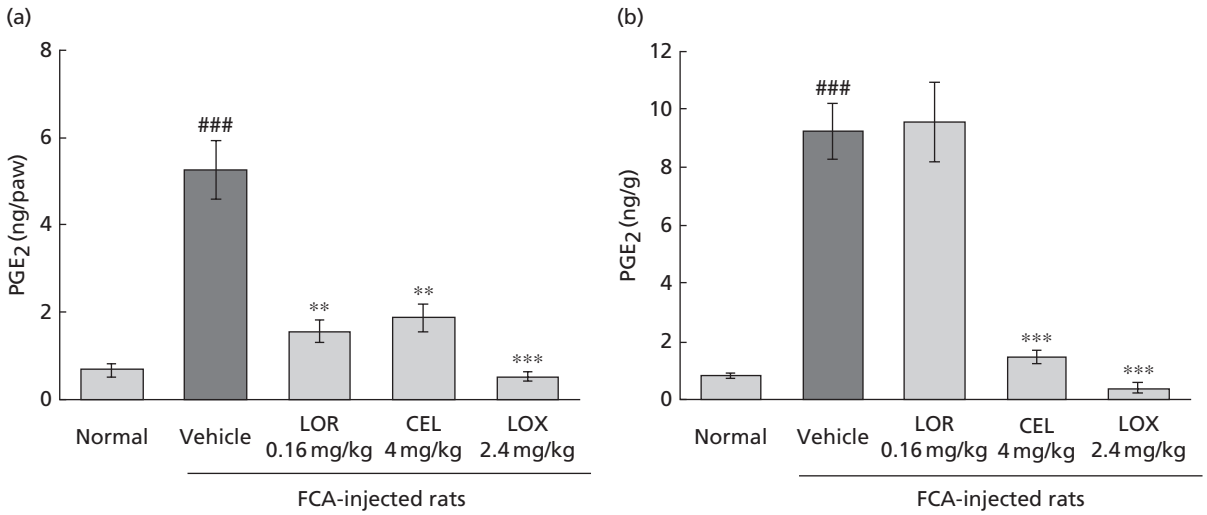

Figure 4 Effect of lornoxicam, celecoxib and loxoprofen on PGE_2 content in inflamed paw exudate (a) and hypothalamus (b) in FCA-induced acute oedematous rats. Rats received an intraplanter injection of *M. tuberculosis* (1%, 0.1 ml/paw) to induce paw inflammation. The next day, each drug was administered orally and 2 h later, the PGE_2 content in the inflamed paw exudate and the hypothalamus tissue in the brain was measured using EIA. LOR, lornoxicam; CEL, celecoxib; LOX, loxoprofen. Data are expressed as the mean ± SEM, $n = 8$. $^{**}P < 0.01$; $^{***}P < 0.001$ vs vehicle control (Welch *t*-test with Bonferroni correction); $^{###}P < 0.001$ vs normal control (Welch *t*-test).

lornoxicam, celecoxib and loxoprofen were 0.14, 12.6 and 6.1, respectively. Thus, in humans, lornoxicam could possibly show a weak antipyretic effect at a dose where the pain response is significantly attenuated.

Prostanoid synthesis, especially that of PGE_2, is essential for inducing inflammation, hyperalgesia and pyrexia. Peripheral inflammation increases prostaglandin levels at the site of inflammation, which contributes directly to the inflammation and pain. In addition, peripheral inflammation also increases the central prostanoid level. To elucidate the mechanism of separation of the effects of lornoxicam, we compared its effects on PGE_2 production in rat paw exudates and in the brain hypothalamus in the same rat. Peripheral administration of lipopolysaccharide (LPS) or yeast evokes acute fever and is often used as a febrile model. However, the pain response can not be evaluated in these models. So, we first examined whether several inflammatory stimuli could induce the pain and febrile responses following unilateral hind paw injection. Only FCA (1%), and not LPS (2%), yeast (20%) or carrageenan (1%), induced significant and persistent pain and febrile responses simultaneously (data not shown). A significant increase in body temperature and mechanical hyperalgesia was evoked 24 h after the injection of FCA. These behavioural responses were associated with a substantial increase in PGE_2 levels in both the hypothalamus and the inflamed paw exudate. Oral administration of a dose of lornoxicam (0.16 mg/kg) equivalent to that used clinically strongly inhibited the hyperalgesia and PGE_2 production in the paw, but exhibited no effect on the body temperature or PGE_2 production in the hypothalamus. Samad *et al.*[11] showed a widespread induction of COX-2 expression in spinal cord neurons and in other regions of the CNS, including the hypothalamus, after unilateral hindpaw injection of FCA and mechanical hyperalgesia. We showed that celecoxib, a selective COX-2 inhibitor, significantly inhibited PGE_2 production in both the paw and the hypothalamus of rats. Moreover, it has been reported that nimesulide and other selective COX-2 inhibitors significantly suppressed the febrile response and increased PGE_2 production in the brain.[17,18] These findings indicate that the increase in PGE_2 production in the brain is mediated by inducible COX-2, which plays a critical role in the febrile response.

It remains to be elucidated why lornoxicam shows such a separation effect, though lornoxicam strongly inhibits COX-2 activity *in vitro* and *in vivo*.[19,26] We have preliminary data that lornoxicam (1–10 mg/kg) reduced the hypothalamus PGE_2 level in a dose-dependent manner in yeast-induced febrile rats (data not shown). The potency of its PGE_2 reduction is consistent with the potency of its antipyretic effect (ED50 = 6.2 mg/kg) previously described. So we speculate that lornoxicam, as well as other NSAIDs, could inhibit COX activity in the brain. The weak inhibitory effect of lornoxicam in the brain might be, in part, explained by a lower distribution to the brain than to other organs. Indeed, brain penetration, as determined from brain and plasma concentrations 1 h after the oral administration, was 0.01 for lornoxicam,[27] which was lower than that of 1.7 for celecoxib[18] and 0.04 for loxoprofen. Lornoxicam distributes at a lower concentration in the brain, compared with other NSAIDs. Interestingly, lornoxicam strongly decreased the PGE_2 level in CSF in the established arthritic rats. According to the ED50 values, the inhibitory potency of lornoxicam in CSF PGE_2 is about 41 and 133 times those of celecoxib and loxoprofen, respectively. The inhibitory ratio was associated with the analgesic effect, not the antipyretic effect. After systemic administration of NSAIDs, drugs have to penetrate the blood–CSF barrier or the blood–brain barrier to distribute to the CNS, and the extent of permeability of each drug would vary at many levels in

each area of the CNS. The concentration of lornoxicam in the CSF or spinal cord might be higher than that in the brain parenchyma. The spinal cord is one of the sites where COX-1 and COX-2 are expressed and NSAIDs act to produce hyperalgesia.[28] On the other hand, it has been reported that brain endothelial cells are the site of PGE_2 production, and play a central role in inducing fever.[16] Our data agree with these findings that PGE_2 production in the brain is associated with fever rather than peripheral hyperalgesia, and that production in the CSF, and maybe spinal cord, likely contributes to the establishment and maintenance of peripheral hyperalgesia.

NSAIDs are indicated for the treatment of pain in postoperative, post-traumatic and immunocompromised patients, who are likely candidates for infection. As fever is recognized as a common sign of various diseases, including infection, excessive and long-term treatment with NSAIDs would be a risk for masking infection. In addition, some reports indicate the potential of antipyretics to cause a worsening of prognosis when injected into the preoptic-anterior hypothalamus in infected rabbits.[29,30] Thus, an NSAID with a strong analgesic and anti-inflammatory effect and a weaker antipyretic effect would be a useful alternative in the clinical treatment of pain. We do not have data on whether or not lornoxicam would exhibit a weaker antipyretic effect in humans, because lornoxicam does not have an indication in febrile diseases. No NSAIDs have been confirmed to have such a separation of effect in human studies. It would be valuable, and a future issue, to clarify the significant characteristics of lornoxicam in humans.

Conclusions

In conclusion, lornoxicam, a non-selective NSAID, exhibited a strong analgesic effect but a weak antipyretic effect in rat paw inflammation. The separation of the analgesic and antipyretic effect is related to its efficacy in the reduction of PGE_2 levels in the paw and brain hypothalamus.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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