

Differential effects of OP-1206 α -CD and loxoprofen Na in inflammatory and neuropathic pain models in the rat

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OP-1206 α -CD is an orally active prostaglandin E1 (PGE1) analogue. The present experiments were designed to compare anti-inflammatory and anti-hyperalgesic effects of orally administered OP-1206 α -CD with a non-steroidal anti-inflammatory drug (NSAID), loxoprofen Na, in the rat. In addition, the effect of OP-1206 α -CD on loxoprofen Na-induced gastrointestinal ulceration was investigated. Oral administration of loxoprofen Na (1-10 mg/kg) elicited anti-inflammatory and antinociceptive effects on carrageenin-induced edema and yeast-induced mechano-hypersensitivity, respectively. In contrast, oral administration of OP-1206 α -CD (150 μ g/kg) *per se* did not show any therapeutic effect in the models used. Treatment with OP-1206 α -CD did not affect the effects produced by loxoprofen Na. However, OP-1206 α -CD (150 μ g/kg) administered serially six times over a period of 4 days reduced thermal hyperalgesia resulting from a chronic sciatic nerve constriction injury (CCI) model, whereas loxoprofen Na (3 and 10 mg/kg) had no significant beneficial effect. Gastrointestinal ulceration was induced by orally administered loxoprofen Na (30 and 100 mg/kg), but not by OP-1206 α -CD (150 μ g/kg). Treatment with OP-1206 α -CD (150 μ g/kg) attenuated the ulcerogenic effect of loxoprofen Na (30 mg/kg). These results suggest that OP-1206 α -CD exhibits beneficial effects on neuropathic pain resulting from partial nerve ischemia, but not on inflammation-induced or acute inflammatory pain.

Key words: neuropathic pain, inflammatory pain, thermal hyperalgesia, mechano-hypersensitivity, OP-1206 α -CD.

Introduction

Injury to peripheral nerves frequently leads to in-

tractable neuropathic pain states, which are clinically expressed as allodynia and/or hyperalgesia (KINGERY, 1997; WOOLF & MANNION, 1999).

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Similarly, using 4 partial sciatic nerve chronic constriction injury (CCI) model in the rat (BENNETT & XIE, 1988), a comparable development of thermal but also tactile allodynia has been described (ATTAL et al., 1990; BENNETT & OCHOA, 1991; PRICE et al., 1991; SELTZER et al., 1991; MAO et al., 1992a, b, c; NUYTEN et al., 1992; PALECEK et al., 1992; SOTGIU et al., 1992, 1993). Although the mechanism underlying the development of neuropathic pain after partial nerve injury is unclear, it has been postulated that nerve ischemia resulting from CCI may play an important role (MYERS et al., 1991, 1993). In accord with this hypothesis it has been demonstrated that systemic treatment with OP-1206 α -CD, an orally active PGE1 analogue (17S-20-dimethyl-trans-delta 2-PGE1 alpha-cyclodextrin clathrate), is effective in improving local nerve blood flow and attenuates thermal hyperalgesia induced by CCI of the sciatic nerve in rats (YAMAMOTO et al., 1995). In addition, more recent data show that a direct intra-aortic infusion of PGE1 is effective in improving local spinal cord blood flow (FUKUMOTO et al., 2003) and inhibits microglial lipopolysaccharide-induced TNF- α release (CHUAI et al., 2002). TNF- α has been demonstrated to play a key role in the development of pain behavior after chronic peripheral nerve injury (SCHAFERS et al., 2004).

Loxoprofen Na, a non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic effects in rats, is widely prescribed for the treatment of many pathological conditions, including rheumatoid arthritis, osteoarthritis, gouty arthritis, the joint and muscle discomfort associated with systemic lupus erythematosus and other musculoskeletal disorders (MISAKA et al., 1981; FUTAKI et al., 1993). Although it has been shown that intrathecal administration of ketorolac, an NSAID, alleviates thermal hyperalgesia and cold allodynia in the sciatic nerve CCI rat (PARRIS et al., 1996), the effects of orally administered NSAIDs against these symptoms in this model have not been systematically documented.

The present study was designed to compare anti-inflammatory and anti-hyperalgesic effects of orally administered OP-1206 α -CD, loxoprofen Na and their combination on the pain behavioral indices using a CCI model and/or carrageenin-induced knee joint inflammation model and yeast-induced mechano-hypersensitivity in rats. Moreover, effects of OP-1206 α -CD on loxoprofen Na-induced gastrointestinal ulceration were investigated.

Material and methods

Animals

Male Sprague-Dawley rats (Charles River Japan, Yokohama, Japan) aged 4, 5 and 7 weeks were maintained on an alternating 12-hr light-dark cycle (light: 08:00–20:00 hr) with controlled temperature ($24\pm 2^\circ\text{C}$) and relative humidity ($55\pm 15\%$) for at least 1 week before the experiment. The animals were given standard laboratory chow and tap water *ad libitum*, and experimental procedures were performed during the daytime. Animal housing and care and the present protocols complied with the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985) were approved by the ethical standard stipulated by the Animal Experimental Committee of Ono Pharmaceutical Co., Ltd.

Carrageenin-induced paw edema

The carrageenin-induced paw edema model (WINTER et al., 1962) with slight modification was used. Drugs were administered orally just before carrageenin injection in 5-week-old male Sprague-Dawley rats. Hind paw edema was induced in rats by intradermal injection of 0.1 mL of 1% lambda-carrageenin in saline in the plantar surface of the right hind paw. Paw volume was measured before and at hourly intervals for 5 hr after carrageenin injection. A single investigator, who was blinded to the drug treatment, performed the measurement of paw volume.

Yeast-induced mechano-hypersensitivity

The method of RANDALL & SELITTO (1957) was used with slight modification. Drugs were administered orally to 4-week-old male Sprague-Dawley rats just before 0.1 mL injection of 10% brewer's yeast in the plantar surface of the right hind paw to induce edema. The pain threshold to pressure on the inflamed paw was measured before and at hourly intervals for 5 hr after yeast injection. A single investigator, who was blinded to the drug treatment, performed the measurement of pain threshold.

Thermal hyperalgesia in rat CCI model

Surgical procedure

The right sciatic nerve of 7-week-old male Sprague-Dawley rats was tied loosely according to the method of BENNETT & XIE (1988) with slight modification under sodium pentobarbital (40 mg/kg, i.p.; supplemented as and when necessary) anesthesia. Briefly, the right sciatic nerve was surgically exposed and tied loosely with two 4-0 chromic sutures using a square knot (MYERS et al., 1993). As a sham-operated control, the left sciatic nerve was mobilized without tying. Bilateral incisions were closed with 4-0 silk sutures, and the rats were allowed to recover in their normal environment.

Measurement of thermal hyperalgesia

Paw-withdrawal latency was measured with a previously described device (HARGREAVES et al., 1988). Briefly, rats were put in a clear plexiglas box placed on an elevated glass plate and allowed 5–10 min to habituate. A radiant heat source (PLANTAR TEST 7371, UGO BASIL, Italy) was positioned under one of the hind paws and the time required indicating withdrawal of the stimulated paw was measured. The time between withdrawal and replacement of the paw on the floor (withdrawal duration) was also measured. Both hind paws were tested in a semi-random sequence.

The maximum thermal hyperalgesia was observed on day 7 after nerve ligation and lasted for 4 weeks (BENNETT & XIE, 1988). In the present study, drugs were administered orally from day 7 after nerve ligation to estimate the effects of drugs on thermal hyperalgesia induced by sciatic nerve CCI. To evaluate the effects of drugs, paw withdrawal latencies of the right and left hind paws were measured alternately 4 hr after the sixth drug administration on day 10 after nerve ligation (YAMAMOTO et al., 1995).

To analyze the magnitude of thermal hyperalgesia, the difference score was calculated by subtracting the paw withdrawal latency of the sham-operated side (left paw) from that of the ligated side (right paw). A negative score thus indicates a lower threshold on the ligated side, or hyperalgesia. A single investigator, who was blinded to the drug treatment, performed the measurement of the paw withdrawal latency.

Drug treatment

Drugs were administered six times orally: after measurement of paw withdrawal latency on day 7; twice at >6 hr intervals on days 8 and 9; and at least 4 hr before measurement of paw withdrawal latency on day 10 post-ligation of the sciatic nerve.

Gastrointestinal ulceration

Male Sprague-Dawley rats (7-week-old) were fasted for 16 hr prior to drug exposure. Twenty-four hr after oral administration of drugs, the rats were sacrificed and the small intestines were isolated and placed in 80% ethanol. The ulcerogenicity of each rat was scored according to the following signs: 0: no lesion; 1: obscure lesions; 2: <5 clear lesions; 3: >5 clear lesions; 4: bore and/or adhesion (OCHI et al., 1999).

Drugs

OP-1206 α -CD (17S-20-dimethyl-trans- δ 2-PGE1 alpha-cyclodextrin clathrate), synthesized in our laboratories and containing 3.13% of its active principle (OP-1206), was used throughout the experiments. Dosages of OP-1206 α -CD were expressed in terms of OP-1206. Loxoprofen Na was obtained from Shin Poong Pharmaceutical Co., Ltd. (Seoul, Korea). Methylcellulose (MC) was obtained from Sigma (St. Louis, MO, USA). OP-1206 α -CD and the vehicle, α -CD, were dissolved in distilled water. Loxoprofen Na was suspended in 0.5% MC solution.

Statistical analysis

The results were expressed as the mean \pm S.E.M., and statistical significance of differences was analyzed using Student's t-test and Dunnett's multiple comparison test between the control and each drug-treated group. The combined effects of OP-1206 α -CD and loxoprofen Na were analyzed by the two-way analysis of variance. Differences with a p-value of <0.05 were considered statistically significant.

Results

Effects of OP-1206 α -CD and loxoprofen Na on carrageenin-induced paw edema in rats

In control animals receiving 0.5% MC with α -CD, the volume of the paw injected with carrageenin increased by approximately 80% for 2–4 hr after injection. Loxoprofen Na (1–10 mg/kg) dose-dependently inhibited carrageenin-induced paw edema for 5 hr after injection when compared with the control group (Fig. 1). In addition, oral administration of loxoprofen Na (1–10 mg/kg) with OP-1206 α -CD (150 μ g/kg) elicited an anti-inflammatory effect in the rat paw edema model, whereas treatment with OP-1206 α -CD (150 μ g/kg) did not affect paw edema (Fig. 2). The combined effect of OP-1206 α -CD with loxoprofen Na (10 mg/kg) on rat paw edema was not significant ($F = 0.876$, $P = 0.458$).

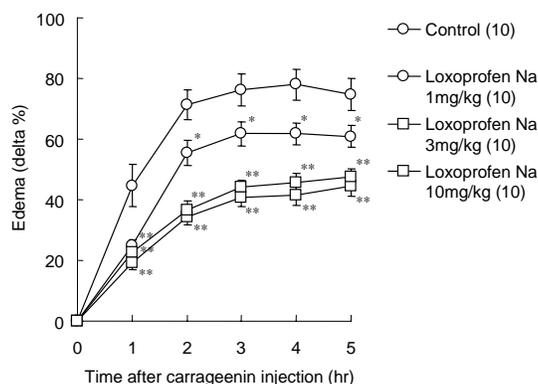


Fig. 1. Effects of loxoprofen Na on carrageenin-induced paw edema in rats. Values represent the mean \pm S.E.M. Significant differences where $p < 0.05$ (*) and $p < 0.01$ (**) compared with the control (Methyl Cellulose + α -CD) at the respective time-intervals were verified statistically with the Dunnett's multiple comparison test.

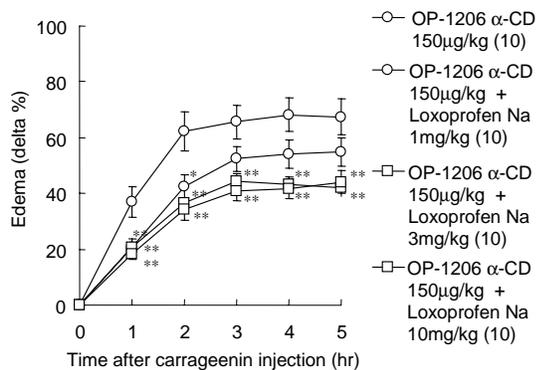


Fig. 2. Effects of OP-1206 α -CD *per se* or combined with loxoprofen Na on carrageenin-induced paw edema in rats. Values represent the mean \pm S.E.M. Significant differences where $p < 0.05$ (*) and $p < 0.01$ (**) from OP-1206 α -CD at the respective time-intervals were verified statistically with the Dunnett's multiple comparison test.

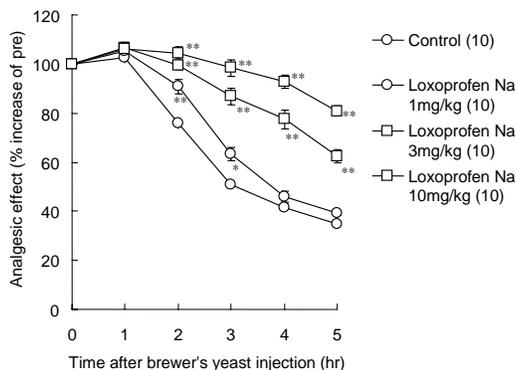


Fig. 3. Effects of loxoprofen Na on yeast-induced mechano-hypersensitivity in rats. Values represent the mean \pm S.E.M. Significant differences where $p < 0.05$ (*) and $p < 0.01$ (**) from control (Methyl Cellulose + α -CD) at the respective time-intervals were verified statistically with the Dunnett's multiple comparison test.

Effects of OP-1206 α -CD and loxoprofen Na on yeast-induced mechano-hypersensitivity in rats

Loxoprofen Na (1–10 mg/kg) showed a dose-dependent anti-hyperalgesic effect against yeast-induced paw mechano-hypersensitivity in rats for 2–5 hr after injection compared with control animals receiving 0.5% MC with α -CD (Fig. 3). Although loxoprofen Na (1–10 mg/kg) with OP-1206 α -CD (150 μ g/kg) elicited an antinociceptive effect, the latter did not show any effect against the inflamed paw with the same dosage (Fig. 4). The combined effect of OP-1206 α -CD with loxoprofen Na (10 mg/kg) on yeast-induced paw hyperalgesia was not significant even when the AUC was assessed ($F = 0.317$, $P = 0.813$).

Effects of OP-1206 α -CD and loxoprofen Na on thermal hyperalgesia in the rat CCI model

On day 7 after sciatic nerve CCI, there was no difference in the pre-drug right/left paw withdrawal latencies and difference score level of each group (Tab. 1). Four hours after administration (day 10 after sciatic nerve CCI), paw withdrawal latencies of the uninjured paws did not show any difference between any two groups. Administration of loxoprofen Na (3 and 10 mg/kg) had no effect on the paw withdrawal latency of the injured paw or difference score level compared with control animals receiving 0.5% MC with α -CD. However, administration of OP-1206 α -CD (150 μ g/kg) significantly suppressed paw withdrawal latencies of the injured paws and difference score level. Moreover, combined treatment of OP-1206 α -CD (150

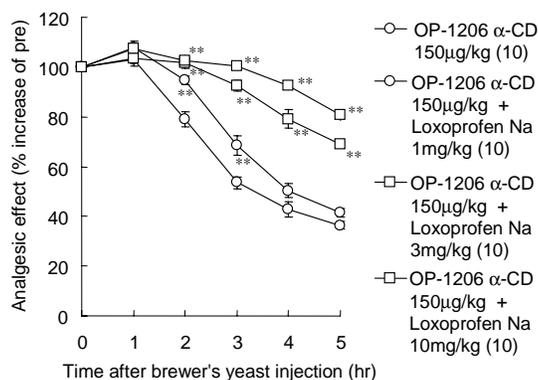


Fig. 4. Effects of OP-1206 α -CD *per se* or combined with loxoprofen Na on yeast-induced mechano-hypersensitivity in rats. Values represent the mean \pm S.E.M. Significant differences where $p < 0.05$ (*) and $p < 0.01$ (**) from OP-1206 α -CD at the respective time-intervals were verified statistically with the Dunnett's multiple comparison test.

μ g/kg) with loxoprofen Na (3 and 10 mg/kg) prolonged paw withdrawal latencies of the injured paws and difference score level. The combined effect of OP-1206 α -CD with loxoprofen Na on thermal hyperalgesia was not significant ($F = 0.703$, $P = 0.500$).

Effect of OP-1206 α -CD on loxoprofen Na-induced gastrointestinal ulceration in rats

Single oral administration of loxoprofen Na (30–

Table 1. Effect of OP-1206 α -CD and loxoprofen Na on thermal hyperalgesia in rat sciatic nerve chronic constriction injury model.

Drug	n	Predrug			Postdrug		
		R PWL (s)	L PWL (s)	DS (s)	R PWL (s)	L PWL (s)	DS (s)
Control	10	8.67±0.81	12.45±0.81	-3.78±0.17	9.73±0.51	13.55±0.40	-3.82±0.20
Loxoprofen-Na 3 mg/kg	10	7.58±0.24	11.38±0.34	-3.80±0.17	9.92±0.44	13.34±0.52	-3.42±0.31
Loxoprofen-Na 10 mg/kg	10	8.96±0.63	12.74±0.61	-3.78±0.13	8.94±0.55	12.32±0.50	-3.38±0.17
OP-1206 α -CD 150 μ g/kg	10	8.95±0.62	12.76±0.60	-3.81±0.18	11.61±0.51	13.76±0.50	-2.15±0.25 *
OP-1206 α -CD 150 μ g/kg + Loxoprofen Na 3 mg/kg	10	9.05±0.49	12.85±0.50	-3.80±0.19	12.16±0.46	13.79±0.51	-1.63±0.19 *
OP-1206 α -CD 150 μ g/kg + Loxoprofen Na 10 mg/kg	10	7.87±0.53	11.67±0.67	-3.80±0.25	10.99±0.67	13.11±0.72	-2.12±0.22 *

Drugs were administered six times orally and at least 4 h before measurement of paw withdrawal threshold. R PWL: Right Paw Withdrawal Latency, L PWL: Left Paw Withdrawal Latency, DS: Difference Score Significantly different from control, * $P < 0.001$. $n = 10$. Values are means \pm S.E.M.

Table 2. Effect of OP-1206 α -CD and loxoprofen Na-induced gastrointestinal ulceration in rats.

Drug	n	Ulcer index (score)
Control	10	0.0 \pm 0.0
Loxoprofen-Na 10 mg/kg	10	0.9 \pm 0.4
Loxoprofen-Na 30 mg/kg	10	2.4 \pm 0.3 **
Loxoprofen-Na 100 mg/kg	10	3.2 \pm 0.1 **
OP-1206 α -CD 150 μ g/kg	10	0.0 \pm 0.0
OP-1206 α -CD 150 μ g/kg + Loxoprofen Na 10 mg/kg	10	0.2 \pm 0.1
OP-1206 α -CD 150 μ g/kg + Loxoprofen Na 30 mg/kg	10	1.1 \pm 0.4
OP-1206 α -CD 150 μ g/kg + Loxoprofen Na 100 mg/kg	10	2.8 \pm 0.1 ##

Drugs were administered orally 24 h before the rats were euthanized. Visible gastric lesions were scored (score scales: no lesions = 0, obscure lesions = 1, less than 5 clear lesions = 2, more than 5 clear lesions = 3, bore and/or adhesion = 4). Significantly different from control, ** $P < 0.01$, and from OP-1206 α -CD, ## $P < 0.01$. $n = 10$. Values are means \pm S.E.M.

100 mg/kg) resulted in mucosal ulceration in the small intestine. This effect was dose-dependent with the maximum effect elicited after treatment with 100 mg/kg (Tab. 2). Oral administration of OP-1206 α -CD at 150 μ g/kg did not induce any mucosal lesions. Co-administration of OP-1206 α -CD (150 μ g/kg) and loxoprofen Na (10–100 mg/kg) did not potentiate loxoprofen-induced mucosal lesions but rather the ulcerogenic effect of loxoprofen Na (30 mg/kg) was attenuated. On the whole, the combined effect of OP-1206 α -CD with loxoprofen Na on gastrointestinal ulceration was not significant ($F = 2.51$, $P = 0.065$).

Discussion

There is no substantial evidence to suggest that prostaglandins played a role in neuropathic and/or inflammatory pain states in a study. In the present

study, the anti-inflammatory and analgesic effects of orally administered OP-1206 α -CD (a PGE1 analogue; PG-prostaglandin) or loxoprofen Na (an NSAID) *per se* or in combination on carrageenin-induced paw edema, yeast-induced mechano-hypersensitivity and sciatic nerve CCI-induced thermal hyperalgesia in rats were studied. In addition, the effects of OP-1206 α -CD on loxoprofen Na-induced gastrointestinal ulceration were investigated.

Loxoprofen Na is extensively prescribed for treatment of musculoskeletal disorders (MISAKA et al., 1981; FUTAKI et al., 1993; KAWAI et al., 1998). NSAIDs attenuate production of proinflammatory prostaglandins by inhibiting cyclooxygenase (COX) or PGG/H synthase (FLOWER et al., 1972). However, the general side-effects of NSAIDs, such as gastrointestinal ulcer induction and renal failure, are also considered to be the

result of COX inhibition (CRYER & FELDMAN, 1992; RAINSFOLD, 1999). In the present study, loxoprofen Na showed anti-inflammatory effects in rat carrageenin-induced edema and anti-hyperalgesic effects in the brewer's yeast-induced mechano-hypersensitivity model in rats, results that are consistent with previous findings (MISAKA et al., 1981; FUTAKI et al., 1993). However, orally administered loxoprofen Na did not attenuate thermal hyperalgesia in the rat sciatic nerve CCI model. Cumulative data suggest that NSAIDs may exert their analgesic effect in the central nervous system. For example, spinal administration of NSAIDs elicits antinociception in the rat formalin test (MALMBERG & YAKSH, 1993), and suppresses thermal hyperalgesia induced by spinally injected N-methyl-D-aspartate and substance P (YAKSH & MALMBERG, 1993). Although it may be argued that the use of acute nociception models associated with inflammation could hinder interpretation of the central activities of NSAIDs, the doses employed in those studies were so low as to negate any peripheral activity. Although spinal administration of ketorolac, an NSAID, attenuates thermal hyperalgesia and cold allodynia in the rat sciatic nerve CCI model of neuropathic pain (PARRIS et al., 1996), intravenous injection of ketorolac does not attenuate tactile allodynia in the rat neuropathic pain model (LASHBROOK et al., 1999). In fact, it has been reported that ibuprofen, an NSAID, cannot improve post-herpetic neuralgia clinically (MAX et al., 1988).

Previous studies show that OP-1206 α -CD, a PGE1 analogue, has a potent vasodilating and anti-platelet action and that this effect is longer lasting and more potent than PGE1 (FERREIRA & VANE, 1967; TSUBOI et al., 1980a, b; FUJITANI et al., 1986). It has also been reported that OP-1206 α -CD, at a comparable dose as used in the present study, attenuates thermal hyperalgesia after sciatic nerve constriction injury in rats (YAMAMOTO et al., 1995). In the present study, using 6 repetitive administrations of 150 μ g/kg, a comparable suppression of thermal hyperalgesia was observed. In a more recent study, we have reported that OP-1206 α -CD at a dose of 150 μ g/kg improves local spinal cord blood flow after induction of spinal canal stenosis in rat, and that this effect is associated with a significant improvement in walking dysfunction otherwise seen in control, vehicle-treated animals (NAKAI et al., 2002). As nerve constriction injury reduces nerve blood flow by 58%, ischemia could be an important early component of the pain mechanism. In addition, it has been postulated that nerve ischemia sufficient to

initiate development of behavioral hyperesthesia in the ipsilateral limb could produce wallerian degeneration (MYERS et al., 1993). Previous studies have demonstrated that treatment with OP-1206 α -CD at 100 and 300 μ g/kg improves thermal hyperalgesia and increases sciatic nerve blood flow in the rat CCI model (SAWARAGI et al., 1996). It has also been shown that a comparable treatment regimen is effective in inhibiting the prolongation of electromyogenic discharges evoked by thermal stimulus in the rat CCI model (FUJITANI, 1996).

Taken together, these data jointly suggest that the treatment effect observed in the present study is likely related to an increased local nerve blood flow at the site of nerve ligation. In contrast to a potent therapeutic effect of OP-1206 α -CD in chronic nerve constriction model, no significant therapeutical effect after an identical treatment protocol on the inflammation-induced nociceptive behavior was detected. In addition, no additive therapeutic effect of OP-1206 α -CD if combined with loxoprofen Na treatment was seen. There was no augmentation of inflammatory pain by exogenous PGE1, and NSAIDs did not exhibit any effect on neuropathic pain although endogenous PGEs were suppressed. Therefore, it may be suggested that the increase of nerve blood flow may be caused by vasodilatation and is different from the inflammation-facilitating action of PGEs. In addition, it may be suggested that PGEs blocked by NSAIDs and PGE1 showing anti-inflammatory properties have different actions.

The major side-effects of NSAIDs include gastrointestinal ulceration and bleeding, hepatorenal dysfunction and organ failure besides skin reactions (RAINSFORD, 1999). Thus, we investigated the effects of OP-1206 α -CD on loxoprofen Na-induced gastrointestinal ulceration. In this study, gastrointestinal ulceration was induced by orally administered loxoprofen Na, but not OP-1206 α -CD. It is well known that PGs can protect against ulceration caused by aspirin, indomethacin, bile, ethanol, thermal insult and NaOH through probable cytoprotective effects on the mucosal barrier (GOODMAN & GILMAN, 1985). In addition, misoprostol, a PGE1 analogue, has been used to treat NSAID-associated gastrointestinal ulcers; it is intended to replenish mucosal-protective PGs depleted by NSAID inhibition of COX-1 (RASKIN, 1999). Therefore, together with these findings, our present study suggests that OP-1206 α -CD does not accelerate loxoprofen Na-induced gastrointestinal ulceration but rather elicits the beneficial effect of suppressing the development of ulcer formation.

Conclusion

The data from the present study demonstrate that treatment with OP-1206 α -CD has a significant therapeutic effect on neuropathic pain behavior after chronic nerve constrictive injury and that this effect is likely mediated by increased local blood flow at the site of nerve ligation. An identical treatment regimen is not effective in modulating inflammation-mediated pain behavior. In contrast to loxoprofen Na, treatment with OP-1206 α -CD did not trigger gastric ulceration and in contrary elicited a suppressive effect on gastrointestinal ulcer formation resulting from NSAIDs treatment.

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