Allodynia and Hyperalgesia in Adjuvant-Induced Arthritic Rats: Time Course of Progression and Efficacy of Analgesics

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ABSTRACT

The complete Freund’s adjuvant (CFA)-induced arthritic rat model has extensively served as a laboratory model in the study of arthritic pain. However, the time courses of allosthrinia and hyperalgesia and the efficacies of different analgesics have not fully been analyzed in this model. Mechanical allodynia, thermal and joint hyperalgesia, and other disease development parameters (body weight, mobility, paw volume, and joint stiffness) were measured on postinoculation days (PIDs) 0 to 28 in rats. Acute analgesic efficacies of drugs were evaluated on PID 9 when degrees of allodynia, hyperalgesia, and joint stiffness in the ipsilateral paw reached almost the maximum, although those in the contralateral paw changed only slightly. In the ipsilateral paw, thermal hyperalgesia reached the maximum on PID 1, whereas mechanical allodynia and joint hyperalgesia progressively developed during the first 7 or 8 days, being tuned in to arthritis development. In the contralateral paw, thermal hyperalgesia never occurred, whereas mechanical allodynia and joint hyperalgesia developed after PID 11. Morphine and tramadol had full efficacies for all the pain parameters tested at sedation-inducing doses. Indomethacin and diclofenac significantly but partially improved thermal and joint hyperalgesia. Amitriptyline significantly reduced thermal and joint hyperalgesia only at sedation-inducing dose. Acetaminophen, carbamazepine, and gabapentin had, at the most, very small efficacies. In conclusion, the present study provided integrated information about the time course of pain and other disease development parameters in the CFA-induced arthritic rats, and clarified acute efficacies of different categories of analgesics for the allodynia and hyperalgesia.

The complete Freund's adjuvant (CFA)-induced arthritic rat model has extensively served as a laboratory model in the study of arthritic pain. Mechanical allodynia, thermal hyperalgesia and pain on joint movement (joint hyperalgesia), which are prominent features in arthritic pain, have proved to be present in it (Tatsuo et al., 1994; Jasmin et al., 1998; Bertorelli et al., 1999). The time courses of their progression after the CFA inoculation, however, have not been fully analyzed. The first aim in the present study, therefore, was to provide integrated information about the time courses of pain (mechanical allodynia, thermal hyperalgesia, and joint hyperalgesia) and other disease development parameters after the CFA inoculation into the single hind paw in rats. Surprisingly, there are no studies that have fully evaluated the analgesic efficacies of different categories of analgesics on mechanical allodynia, thermal hyperalgesia, and joint hyperalgesia in the CFA-induced arthritic rat model. The second aim in the present study, therefore, was to investigate this issue. Antipyrretics (e.g., acetaminophen) and nonsteroidal anti-inflammatory drugs (e.g., indomethacin and diclofenac) are the first line drugs in the treatment of arthritic pain. Antidepressants (e.g., amitriptyline) and antiepileptics (e.g., carbamazepine and gabapentin) have been frequently used in the treatment of chronic pains in addition to their original use. Opioid receptor agonists (e.g., morphine and tramadol) have strong efficacies for various nociceptive pains. Morphine is a prototype opioid receptor agonist although tramadol has two mechanisms of action (opioid and monoaminergic). These different categories of agents were tested in the present study. It has recently been considered that analysis of pain-related parameters in arthritic rats should be conducted in the monoarthritic phase when arthritis is localized around the affected site such as the hind paw, because serious systemic disturbances occur in the polyarthritic phase, making it difficult to attribute the obtained data exclusively to the effect on the nociceptive system (Millan et al., 1988; Stein et al., 1988; Butler et al., 1992). In the present study, the monoarthritic phase was determined based on the balance between the pain parameters and other disease development parameters.

ABBREVIATIONS: CFA, complete Freund’s adjuvant; PID, postinoculation day; NSAID, nonsteroidal anti-inflammatory drug.
Materials and Methods

Animal Preparations. All experiments were performed according to the regulations of the Animal Ethical Committee of Yamanouchi Pharmaceutical Co., Ltd. (Tsukuba, Japan). Male Lewis rats (165–220 g; Charles River, Kanagawa, Japan) were kept under conditions of a 13:11-h day/night cycle at a constant room temperature. The total number of rats used in the study was 340. Food and water were available ad libitum. Arthritis was induced by the CFA inoculation in the rats. Briefly, 100 mg of Mycobacterium butyricum (Difco, Detroit, MI) was thoroughly mixed with 20 ml of paraffin oil. The mixture was then autoclaved for 20 min at 120°C. Each rat was injected in the right footpad (hind paw) with the mixture in a 0.1-ml volume under ether anesthesia. The rats serving as controls were injected with 0.1 ml of saline. In the experiment evaluating the analgesics, eight rats per drug were anesthetized with ether but not treated to serve as naive controls.

Pain Parameters Measurement. Pain and other disease development parameters were measured in the CFA- or saline-treated rats (n = 10 for each group) on postinoculation day (PID) 0 (i.e., just before inoculation) and on PIDs 1, 3, 5, 7, 8, 9, 10, 11, 12, 14, 17, 21, and 28. The measurement for pain parameters was conducted for both hind paws. The measurement of mechanical allodynia was performed with a modified method of Gonzalez et al. (2000). Briefly, the threshold was measured using the von Frey hairs (Semmes-Weinstein Monofilaments, Stoelting Co., IL). The rats were habituated to wire mesh bottom cages before the start of the experiment. Static allodynia was tested in the unrestrained rats by touching the plantar surface of the hind paw with von Frey hairs in ascending order of force (1.2, 1.5, 2.0, 3.6, 5.5, 8.5, 12, 15, 25, and 76 g) for up to 6 s or until a paw withdrawal response was elicited. The lowest amount of force required to elicit a response was recorded as the withdrawal threshold in log g. Thermal hyperalgesia was assessed using the plantar test (model 7370; Ugo Basile, Varese, Italy) and a modified method of Hargreaves et al. (1988). Briefly, the rats were habituated to an apparatus consisting of individual Perspex boxes on an elevated glass table. A mobile radiant heat source was located under the table and focused on the hind paw, and the paw withdrawal latencies were defined as the time taken by the rat to remove its hind paw from the heat source. The cut-off point was set at 15 s to prevent tissue damage. The apparatus was calibrated to give a paw withdrawal latency of approximately 10 s in naive rats. The measurement of joint hyperalgesia was performed by a modification of the previously reported method (Rupniak et al., 1997). The body of rats was held from the back with the left palm, and the bending and extension (one after the other and five times in each direction) of the ankle within its limits of range of motion were performed with the right fingers. The total number of vocalizations emitted after the manipulation (the bending and extension, five times in each direction) was recorded for each paw (the maximum score was 10 for each paw).

Disease Development Parameters Measurement. The scoring of mobility was performed by modifying the evaluation scale reported by Butler et al. (1992): score 2, there were restrictions of full range of motion of the ankle in both bending and extension; score 1, there was a restriction of full range of movement of the ankle in bending or extension; and score 0, no restriction. The measurements for paw volume and joint stiffness were conducted for both hind paws. All the time-course observations were performed by one of the authors to avoid interobserver differences. The time-course measurement experiment was carried out by the observer who was not blind to the CFA or saline treatment because the difference between the ipsilateral and contralateral paw was apparent mainly due to the difference in paw volume.

Drugs. Acetaminophen, indomethacin, diclofenac sodium and amitriptyline hydrochloride were obtained from Sigma-Aldrich (St. Louis, MO). Morphine hydrochloride and carbamazepine were purchased from Takeda Chemical Industries (Osaka, Japan) and Wako Pure Chemical Industries (Osaka, Japan), respectively. Cariprazine, which contained 100 mg of tramadol hydrochloride per 2 ml, was purchased from Nippon Shinyaku Co., Ltd. (Kyoto, Japan). Gabapentin was prepared by Yamanouchi Pharmaceutical Co., Ltd. (Ibaraki, Japan). Acetaminophen, diclofenac, and carbamazepine were suspended in 0.5% methylcellulose. Amitriptyline and morphine were dissolved in saline. Gabapentin and indomethacin were dissolved in distilled water and 0.1 M Tris buffer, respectively. Tramadol was diluted with saline. The conditions, under which each drug had proved to exhibit its optimal analgesic effect in other rat pain models, were used for each drug evaluation to evaluate sufficiently the maximum efficacy. Indomethacin was administered at 3 to 30 mg/kg p.o. 1 h before the pain parameter measurement (Okuyama and Alhara, 1984). Diclofenac was administered at 10 to 100 mg/kg i.p. 30 min before measurement (Eichenhofer et al., 1998). Acetaminophen was administered at 100 to 600 mg/kg p.o. 30 min before measurement (Grandon-Soto et al., 1999). Amitriptyline was administered at 3 to 30 mg/kg i.p. 30 min before measurement (Korzeniewska-Rybcka and Plaznik, 1998). Carbamazepine was administered at 20 to 80 mg/kg p.o. 1 h before measurement (Nakamura-Craig and Follenfant, 1995). Gabapentin was administered at 30 to 300 mg/kg p.o. 1 h before measurement (Field et al., 1999). Morphine was administered at 1 to 10 mg/kg s.c. 30 min before measurement (Bertorelli et al., 1999). Tramadol was administered at 9 to 88 mg/kg s.c. 30 min before measurement (Giusti et al., 1997). Drug concentrations were calculated according to the base form.

Analgesic Efficacy Evaluation. Thirty-two rats (eight rats per dose and four doses per drug) treated with the CFA and another eight rats as naive controls were used for each drug evaluation. The analgesic effects were evaluated on PID 9, when mechanical allodynia, thermal hyperalgesia, joint hyperalgesia, and joint stiffness in the ipsilateral paw reached almost the maximum, although those parameters in the contralateral paw changed only slightly and the systemic disturbance (toes shown by the change of mobility score) was small. On the day before evaluation (PID 8), body weight, mechanical allodynia, thermal hyperalgesia, and joint hyperalgesia were measured for the 32 rats that were to be used for drug evaluation. The rats were allocated to four groups (eight rats per group) such that the differences in the averages of those parameters among the groups became small. The behavioral disturbance was small in the CFA-treated rats on PID 9 except that the rats walked being protective only toward the ipsilateral hind paw. During the evaluation of analgesic efficacy, the behavioral abnormalities that might be caused by the nontarget drug effect such as reduction of motion were also checked by observing the animals. All the analgesic effect evaluations and behavioral observations were performed by one of the authors to avoid interobserver differences. All the analgesic effect...
evaluations and behavioral observations were carried out by the observer who was blind to the drug treatment.

Statistical Analysis. Data were expressed as the mean ± S.E.M. The time-course curves for mechanical allodynia, thermal hyperalgesia, joint hyperalgesia, body weight, and paw volume were subjected to two-way repeated measures analysis of variance with post hoc t test. In experiments for drug evaluation, the difference in scores between the vehicle-treated and naive control groups was analyzed by Student’s t test to confirm significant changes in the pain parameters in the ipsilateral paw. The analgesic effects were analyzed by Dunnett’s t test, and in each case, the drug-treated groups were compared with the vehicle-treated group. In each statistical analysis, the comparison was conducted for paws on the corresponding side. P < 0.05 was considered statistically significant.

Results

Time Courses of Pain Parameters. The time-course curves for mechanical allodynia were significantly different between the CFA- and saline-treated rats in both hind paws (two-way repeated measures analysis of variance). The thresholds in both hind paws in the saline-treated rats remained stable over the observation period. The threshold in the ipsilateral paw in the CFA-treated rats decreased progressively during the first 7 days and reached a plateau that lasted throughout the rest of the observation period. The differences in the ipsilateral threshold between the CFA- and saline-treated rats were statistically significant on PIDs 1 to 28 (post hoc t test). The threshold in the contralateral paw in the CFA-treated rats remained almost stable until PID 9, decreased progressively from PID 10 to 14 and reached a plateau. The differences in the contralateral threshold between the CFA- and saline-treated rats were statistically significant on PIDs 10 to 28. The decrease of threshold in the ipsilateral paw was significantly larger in magnitude than that in the contralateral paw (Fig. 1A). The time-course curves for thermal hyperalgesia were significantly different between the CFA- and saline-treated rats in the ipsilateral hind paw, although those were not between the CFA- and saline-treated rats in the contralateral paw. The latencies in both paws in the saline-treated rats and in the contralateral paw in the CFA-treated rats remained, apart from fluctuations of a small magnitude, stable throughout the observation period. The latency in the ipsilateral paw in the CFA-treated rats decreased markedly on PID 1, showed a rebound on PID 3, and remained decreased during the rest of the observation period. The differences in the ipsilateral latency between the CFA- and saline-treated rats were statistically significant on PIDs 1 to 28 (Fig. 1B). The time-course curves for the joint hyperalgesia were significantly different between the CFA- and saline-treated rats in both hind paws. The numbers of vocalization in both paws in the saline-treated rats remained almost zero throughout the observation period. The numbers of vocalization in the ipsilateral paw in the CFA-treated rats increased progressively during the first 8 days and reached a plateau. The differences in the ipsilateral number of vocalization between the CFA- and saline-treated rats were statistically significant on PIDs 1 to 28. The numbers of vocalization for the contralateral paw in the CFA-treated rats remained almost zero until PID 9, increased progressively from PID 10 to 17 and reached a plateau. The differences in the contralateral number of vocalization between the CFA- and saline-treated rats were statistically significant on PIDs 11 to 28 (Fig. 1C).

Time Courses of Other Disease Development Parameters. The time-course curves for body weight between the CFA- and saline-treated rats were significantly different. The CFA-treated rats showed a decreased rate of body weight gain compared with the saline-treated rats. The difference in body weight between the CFA- and saline-treated rats grew almost constantly from PID 3 to 28. The differences in body weight between the CFA- and saline-treated rats were significant on PIDs 10 to 28. The decrease of threshold in the contralateral paw in the CFA-treated rats remained, apart from fluctuations of a small magnitude, stable throughout the observation period. The threshold in the ipsilateral paw in the CFA-treated rats decreased progressively from PID 10 to 14 and reached a plateau. The differences in the contralateral threshold between the CFA- and saline-treated rats were statistically significant on PIDs 10 to 28. The decrease of threshold in the ipsilateral paw was significantly larger in magnitude than that in the contralateral paw (Fig. 1A). The time-course curves for thermal hyperalgesia were significantly different between the CFA- and saline-treated rats in the ipsilateral hind paw, although those were not between the CFA- and saline-treated rats in the contralateral paw. The latencies in both paws in the saline-treated rats and in the contralateral paw in the CFA-treated rats remained, apart from fluctuations of a small magnitude, stable throughout the observation period. The latency in the ipsilateral paw in the CFA-treated rats decreased markedly on PID 1, showed a rebound on PID 3, and remained decreased during the rest of the observation period. The differences in the ipsilateral latency between the CFA- and saline-treated rats were statistically significant on PIDs 1 to 28 (Fig. 1B). The time-course curves for the joint hyperalgesia were significantly different between the CFA- and saline-treated rats in both hind paws. The numbers of vocalization in both paws in the saline-treated rats remained almost zero throughout the observation period. The numbers of vocalization in the ipsilateral paw in the CFA-treated rats increased progressively during the first 8 days and reached a plateau. The differences in the ipsilateral number of vocalization between the CFA- and saline-treated rats were statistically significant on PIDs 1 to 28. The numbers of vocalization for the contralateral paw in the CFA-treated rats remained almost zero until PID 9, increased progressively from PID 10 to 17 and reached a plateau. The differences in the contralateral number of vocalization between the CFA- and saline-treated rats were statistically significant on PIDs 11 to 28 (Fig. 1C).
Efficacies of Analgesics. Nonsteroidal anti-inflammatory drugs (NSAIDs) indomethacin and diclofenac did not significantly reduce mechanical allodynia (Fig. 3, A and B). They significantly reduced thermal hyperalgesia at 30 mg/kg p.o. for indomethacin (Fig. 3C) and 100 mg/kg i.p. for diclofenac (Fig. 3D). They significantly reduced joint hyperalgesia at 10 and 30 mg/kg p.o. for indomethacin (Fig. 3E) and 100 mg/kg i.p. for diclofenac (Fig. 3F). Neither indomethacin nor diclofenac affected scores in the contralateral paw (Fig. 3, A–F). Neither of them influenced the behavior of rats, at least, during the observation period. An antipyretic acetaminophen did not significantly improve any pain parameter tested. It did not affect scores in the contralateral paw (Fig. 4, A, C, and E). It did not influence the behavior of rats, at least, during the observation period. An antidepressant amitriptyline failed to improve mechanical allodynia (Fig. 4B). It, however, significantly and fully reduced thermal hyperalgesia (Fig. 4D) and significantly reduced joint hyperalgesia (Fig. 4F) at 30 mg/kg i.p. It did not affect mechanical threshold (Fig. 4B) or numbers of vocalization in the contralateral paw (Fig. 4F), although it significantly increased latency of response to the thermal stimulation in it (Fig. 4D) at 30 mg/kg i.p. It caused reduction of motion in rats at the dose (30 mg/kg i.p.) that showed significant analgesic effects. Antiepileptics carbamazepine and gabapentin did not reduce mechanical allodynia (Fig. 5, A and B). Carbamazepine significantly reduced thermal hyperalgesia at 80 mg/kg p.o. (Fig. 5C). Gabapentin failed to affect thermal hyperalgesia (Fig. 5D). Neither gabapentin nor carbamazepine reduced joint hyperalgesia (Fig. 5, E and F). Neither carbamazepine nor gabapentin affected scores in the contralateral paw (Fig. 5, A–F). Carbamazepine induced reduction of motion in rats at the dose (80 mg/kg p.o.) that showed a significant effect on thermal hyperalgesia. Opioid receptor agonists morphine and tramadol improved all the pain parameters tested. They recovered all the pain parameters to naive control level at higher doses (Fig. 6, A–F). Morphine significantly increased

![Diagram](attachment:image.png)

Fig. 2. Time course of disease development parameters (A, body weight; B, mobility; C, paw volume; D, joint stiffness). The parameters were measured on PID 0, or on the verge of the adjuvant or saline inoculation into the right hind paw, and on PIDs 1, 3, 5, 7, 8, 9, 10, 11, 12, 14, 17, 21, and 28. The scoring of mobility was performed by modification of the evaluation scale reported by Butler et al. (1992). The paw volume was measured by volume displacement of an electrolyte solution in a plethysmometer and represented in milliliters. The scoring of joint stiffness was performed by the evaluation scale reported by Butler et al. (1992). All results were expressed as the mean ± S.E.M. in 10 rats per group. In A and B, an open or closed circle represents the mean in the saline- or adjuvant-treated rats. In C and D, an open circle or square represents the mean in the right (ipsilateral) or left (contralateral) hind paw, respectively, in the saline-treated rats, and a closed circle or square represents the mean in the ipsilateral or contralateral hind paw, respectively, in the adjuvant-treated rats.
mechanical threshold and latency of response to the thermal stimulation in the contralateral paw (Fig. 6, A and C), although tramadol significantly increased only the latency of response to the thermal stimulation in it (Fig. 6D). Both morphine and tramadol produced reduction of motion in rats at the doses (10 mg/kg s.c. for morphine, 88 mg/kg s.c. for tramadol) that showed full efficacies in the ankle flexion test.

Discussion

The present study revealed that there were differences in the time courses among the pain parameters measured. Thermal hyperalgesia in the ipsilateral paw reached the maximum even on PID 1. It is unlikely that the hyperalgesia on PID 1 is caused mainly by progression of arthritis because ankle stiffness score remains almost normal on that day. It is possible that the hyperalgesia is attributable mainly to the CFA-induced acute inflammation in the ipsilateral paw because paw volume in the ipsilateral paw largely increases on PID 1 despite the absence of increase of ankle stiffness. In contrast to the rapid progression of thermal hyperalgesia in the ipsilateral paw, the degrees of mechanical allodynia and joint hyperalgesia in it remain small on PID 1. Because the time courses of mechanical allodynia and joint hyperalgesia in the ipsilateral paw were tuned in to that of joint stiffness in it, it is possible that the development of arthritis is needed to produce full mechanical allodynia and joint hyperalgesia.

There were also differences in the time courses and maximum pain scores between the ipsilateral and contralateral paws. Thermal hyperalgesia never occurred in the contralateral paw even though paw volume and joint stiffness scores in it increased progressively from PID 11 to 17. On the other hand, the time courses of mechanical allodynia and joint hyperalgesia in the contralateral paw concurred with the progression of the paw volume and joint stiffness in it. The absence of thermal hyperalgesia in the contralateral paw in the CFA-induced arthritic rats is in accordance with the result of the previous study (Bertorelli et al., 1999). The reason for the absence in the contralateral paw remains to be clarified, although the inflammation induced directly by the CFA may have a critical role in the induction of thermal hyperalgesia that occurs only in the ipsilateral paw.
maximum scores of joint hyperalgesia and joint stiffness were almost equal between the ipsilateral and contralateral paws, suggesting that the CFA-induced conralateral arthritis has a potential to cause full joint hyperalgesia without the inflammation induced directly by the CFA. On the other hand, the maximum score of mechanical allodynia in the contralateral paw was apparently smaller than that in the ipsilateral paw. It is unlikely that the degree of inflammation is responsible for the difference because there exists a clear difference in the mechanical allodynia score even when paw volume scores are almost equal between the ipsilateral and contralateral paws (for example, PID 9 in the ipsilateral paw versus PID 17 in the contralateral paw). It is possible that some factors involved in the CFA-induced direct inflammation have a critical role also in the induction of full mechanical allodynia.

An antipyretic acetaminophen, the first line drug in the treatment of arthritic pain, unexpectedly had rather small efficacies in reducing allodynia or hyperalgesia in the present study. The weak effect on mechanical allodynia may reflect the recently published report that shows that acetaminophen is poorly active, giving only maximum 30% reversal of mechanical hyperalgesia assessed with the paw pressure test in the CFA-induced arthritic rats (Burgess et al., 2000). The weak effect on thermal hyperalgesia is in accordance with the previous report that shows that efficacy of acetaminophen in reducing thermal hyperalgesia measured with the plantar test is very small at 300 mg/kg p.o. in the CFA-induced arthritic rats (Bertorelli et al., 1999). Because acetaminophen has been reported to be effective in the test using electrical stimulation to the foot in the CFA-induced arthritic rats (Okuyama and Aihara, 1984), its effect seems test (stimulation)-dependent. The present study, however, suggested that the acute dosing of acetaminophen was not so effective in reducing mechanical allodynia, thermal hyperalgesia, or joint hyperalgesia in the CFA-induced arthritic rats. NSAIDs, other first line drugs in the treatment of arthritic pain, were also unexpectedly ineffective in reducing mechanical allodynia in the present study. This result is inconsistent...
with the previous report that shows that NSAIDs are effective in reducing mechanical hyperalgesia assessed with the paw pressure test in the CFA-induced arthritic rats (Attal et al., 1988; Chau and Weichman, 1989). This discrepancy may be attributable to the different methods used to measure mechanical thresholds, i.e., the paw pressure test stimulates joints and surrounding deep tissues, whereas the von Frey hairs used in the present study excite mainly cutaneous tissues. The limited efficacy of NSAIDs in the plantar test and ankle flexion test observed in the present study is in accordance with results of the previous studies, in which indomethacin partially reduces number of vocalization in the ankle flexion test at 10 mg/kg p.o. (Rupniak et al., 1997) or reduces thermal hyperalgesia measured with the plantar test at 3 mg/kg i.p. with limited efficacy (Bertorelli et al., 1999) in the CFA-induced arthritic rats. The limited efficacies of antipyretic and NSAIDs observed in the present study may reflect the clinical situation that their efficacies are not fully satisfactory although they are preferred analgesics for the management of arthritic pain. It should, however, be noted that they are chronically used in the clinic and their anti-inflammatory actions are considered to contribute to their therapeutic effects. Because the anti-inflammatory effect has not been evaluated in the present study, the results obtained may underestimate their potential in the treatment of arthritic pain.

An anti-depressant amitriptyline induced a full recovery of thermal hyperalgesia and partially attenuated joint hyperalgesia only at the sedative dose, although it was ineffective for mechanical allodynia. There are few reports concerning the analgesic efficacy after single administration of antidepressants in the CFA-induced arthritic rats, although it has been reported that chronic (4 weeks) administration of amitriptyline or imipramine does not modify the mechanical threshold measured with the paw pressure test (Butler et al., 1985). When the survey is extended to other inflammatory pain models, it has been reported that intrathecal amitriptyline reverses thermal hyperalgesia measured with the plantar test in the carrageenan-induced inflamed rats (Eisenach and Gebhart, 1995). Most animal studies concerning analgesic effects of antidepressants have been performed in acute pain models such as tail-flick test and acetic acid-induced writhing test, and it has been shown that antidepressants are most potent in the chemical test such as the rat acetic acid-induced writhing test, but ineffective in tests using thermal or mechanical stimuli with some exceptions (Korzeniewska-Rybicka and Plaznik, 1998). It was interesting that amitriptyline was most sensitive to the plantar test, which used thermal stimulus in the previous study, being different from the results in the acute pain models. The reason for this discrepancy remains to be studied.

A conventional antiepileptic carbamazepine or new generation one gabapentin was almost completely ineffective in all of the pain parameters tested. These negative results contradict results of the previous studies that have shown that gabapentin attenuates mechanical hyperalgesia measured with the paw pressure test in the carrageenan-induced inflamed rats (Field et al., 1997) or reduces thermal hyperalgesia measured with the plantar test in the kaolin/carrageenan-induced inflamed rats (Lu and Westlund, 1999). One possible reason for this discrepancy is the difference of animal models used. The CFA-induced arthritic pain model, a chronic inflammatory pain model, was used in the present study, although acute inflammatory pain models such as the carrageenan-induced inflamed rat model were used in the previous study. It has recently been reported that gabapentin is only weakly active against mechanical hyperalgesia measured with the paw pressure test even at flaccidity-inducing doses in the CFA-induced arthritic rats (Patel et al., 2001). It is conceivable that different pain mechanisms underlie the CFA-induced arthritis model and acute inflammatory pain models.

Opioid receptor agonists morphine and tramadol fully recovered all the pain parameters tested to the naive control level in the present study. Morphine has proved to exert strong analgesic effects in the CFA-induced arthritic rats when assessed, in most cases, with the plantar test (Bertorelli et al., 1999; Fraser et al., 2000) or paw pressure test (Maldonado et al., 1994; Burgess et al., 2000). The present study further showed that morphine exerted strong analgesic effects also on mechanical allodynia and joint hyperalgesia and that a less potent opioid receptor agonist tramadol, like morphine, exerted full efficacies in all the pain parameters tested. The present study suggested that opioid receptor agonists had full efficacies in reducing mechanical allodynia, thermal hyperalgesia, and joint hyperalgesia in the CFA-induced arthritic rats. It should be noted, however, that both morphine- and tramadol-induced reduction of motion in rats at the doses that showed full efficacies. This might reflect the clinical situation that the efficacy of opioid receptor agonists is strong for various nociceptive pains, although their side effects are the limits of their usability.

In conclusion, the present study provided integrated information about the time course of pain and other disease development parameters in the CFA-induced arthritic rats, and clarified acute efficacies of different categories of analgesics in reducing the allodynia and hyperalgesia by the evaluation on PID 9 (monoarthritic phase).

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