

Chen J, Li H, Luo C, Li Z, Zheng JH. Involvement of peripheral NMDA and non-NMDA receptors in development of persistent firing of spinal wide dynamic-range neurons induced by subcutaneous bee venom injection in the cat. Brain Res 1999a; 844: 98–105.


Chen J, Luo C, Li H-L, Chen HS. Primary hyperalgesia to mechanical and heat stimuli following subcutaneous bee venom injection into the plantar surface of hindpaw in the conscious rat: A comparative study with the formalin test. Pain 1999b; 83: 67–76.


Davidson EM, Gogeshall RE, Carlton SM. Peripheral NMDA and non-NMDA glutamate receptors contribute to nociceptive behaviors in the formalin test. Neuropeptides 1997; 8: 941–946.


Kim YH, Na HS, Yoon YW, Han HC, Ko KH, Hong SK. NMDA receptors are important for both mechanical and thermal allodynia from peripheral nerve injury in rats. Neuroreport 1997; 8: 2149–2153.


Ma PP, Alborne AJ, Woolf CJ. Morphine, the NMDA receptor antagonist MK801 and the tachykinin NK1 receptor antagonist RP67580 attenuate the development of inflammation-induced progressive tactile hypersensitivity. Pain 1998; 77: 49–57.


Neugebauer V, Lücke T, Schaible HG. N-methyl-D-aspartate (NMDA) and non-NMDA receptor antagonists block the hyperexcitability of dorsal horn neurons during development of acute arthritis in rat's knee joint. J Neurophysiol 1993; 70: 1365–1377.


Siuka KA, Jordan HH, Willis WD, Westland KN. Differential effects of N-methyl-D-aspartate (NMDA) and non-NMDA receptor antagonists on spinal release of amino acids after development of acute arthritis in rats. Brain Res 1994; 664: 77–84.


Effects of human placental extract on chemical and thermal nociception in mice

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Several reports indicate that pregnancy and parturition are associated with elevated maternal pain thresholds to noxious stimuli. The objective of this study was to examine whether the human placental extract, a clinically used preparation, can inhibit experimental nociception. Nociception was assessed in mice using acetic acid-induced writhing and hot-plate tests. The human placental extract (200 and 400 mg/kg, i.p.) elicited dose-related antinociception in the acetic acid-induced writhing test. Furthermore, it (200 mg/kg, i.p.) potentiated the morphine-induced antinociception (1.25 mg/kg, s.c.). In the hot-plate test, the human placental extract (100, 200 and 400 mg/kg, i.p.) per se displayed no significant antinociception but potentiated the duration of morphine (10 mg/kg, s.c.) analgesia. The potentiation by the extract of the morphine-induced antinociception in both acetic acid and hot-plate tests was, however, found to be naloxone sensitive. Mice treated with the extract (400 mg/kg, i.p.) neither manifested any overt behavioural change in the open-field test nor demonstrated significant influence on pentobarbital sleeping time, suggesting that it has no central depressant or sedative activity. The data provide evidence to show that the human placental extract has a peripheral analgesic property possibly mediated by an opioid mechanism. © 2000 European Federation of Chapters of the International Association for the Study of Pain

KEYWORDS: placental extract, pregnancy, nociception, opioid mechanism.

INTRODUCTION

Animals and humans manifest an elevated maternal pain threshold to aversive stimuli during gestation and parturition (Ginzler, 1980; Kristal et al., 1985; Cogan and Spinnato, 1986; Sander and Ginzler, 1987; Toniole et al., 1987; Whipple et al., 1990; Jarvis et al., 1997; Pinheiro-Machado et al., 1997). It is well established that the placentas of many species produce opioids and contain opioid receptors, suggesting that placental opioids may exert local effects (Nakai et al., 1978; Lemaire et al., 1983; Hon and Ng, 1986; Zhang et al., 1991). The physiological role of placenta-derived opioids and the regulation of their production remain speculative. Placenta-derived β-endorphin, an endogenous opioid agonist, may primarily be a myometrial quiescence-inducing agent and a regulator of the stress response of the fetal-maternal unit. Placental-derived dynorphin, another endogenous κ-opioid agonist may also directly affect the placenta, as the majority of opioid receptors in this tissue are of the κ-type for which dynorphin is the principal ligand (Belisle et al., 1988). Thus, the pregnancy and parturition associated antinociception may, in part, be mediated by the dynorphin/κ-antinociceptive system and partly by the endorphin/μ-opioid system.

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Human placental extract (HPE) has been used clinically for the treatment of vitiligo, gingival hyperplasia and oral submucous fibrosis (Anil and Beena, 1993; Calvarran et al., 1989; Pai et al., 1995). Considering the increases in nociceptive threshold that have been observed during pregnancy and parturition, the present study aimed to verify whether human placental extract can induce antinociception in animal models of nociception. Furthermore, we verified whether this antinociception was mediated via an opioid mechanism by making comparisons with the effects of morphine and naloxone, drugs that stimulate and block opioid receptors, respectively.

MATERIAL AND METHODS

Animals

Male Swiss mice (20–25 g) obtained from the Central Animal House, Federal University of Ceará were used. They were maintained on a 12 h/12 h light-dark cycle under controlled conditions of temperature (25 ± 2°C) and humidity (55–60%) with free access to standard laboratory food (purina chow) and tap water. The experimental protocols were approved by the Animal Care and Use Committee of this University. The animals were randomly assigned to control and experimental groups (n = 8) and were starved overnight for the experimentation. Each animal was tested only once and all tests were conducted between 10:00 and 16:00 h.

Drugs

The drugs used were: naloxone hydrochloride (Sigma, St Louis, MO, USA), morphine sulphate (Dimorf, Crystalia, Brazil), pentobarbitone sodium (Abbott Lab, France) and human placental extract (Placentrex®, Albert David Ltd, India). All drugs were dissolved in normal saline (0.9% NaCl).

Nociceptive tests

Antinociceptive activity of HPE was measured against chemical (acetic acid test) and thermal (hot-plate test) noxious stimuli.

Acetic acid test

The test procedure was carried out as described by Koster et al. (1959). Animals were administered saline (10 ml/kg, i.p.), HPE (100, 200 and 400 mg/kg, i.p.), morphine (1.25 mg/kg, s.c.) or morphine at the same dose in association with HPE (200 mg/kg, i.p.), 30 min prior to an i.p. injection of 0.6% acetic acid (10 ml/kg). The number of abdominal constrictions (writings) manifested by each mouse was registered for 20 min, starting 10 min after acetic acid injection. In a few other experiments, animals were pretreated with naloxone (1 and 5 mg/kg, s.c.) 15 min prior to morphine or HPE (200 mg/kg, i.p.) to verify the possible mechanism of antinociception.

Hot-plate test

The hot-plate test was performed as previously described (Pieretti et al., 1991). Briefly, the hot-plate (Ugo Basile, Italy, 25 × 25 cm) was set at a temperature of 55 ± 0.5°C and each mouse was given two trials, separated by a 30 min interval. The first trial was used to acquaint the animal with the test procedure and the second trial served as the control reaction time (latency in seconds(s) for licking of the hind paw). Mice were preselected, any showing a reaction time greater than 20 s were not used. Immediately after the second trial, the mice were given an injection of saline (0.9% NaCl, 10 ml/kg, i.p.), HPE (100, 200 and 400 mg/kg, i.p.), morphine (10 mg/kg, s.c.) or morphine at the same dose and HPE (400 mg/kg, i.p.). When both drugs were given to an animal they were administered within 10 s. To avoid possible injury, there was a cut off period of 45 s while measuring the reaction time. In a separate experiment, the effects of naloxone (1 mg/kg, s.c., 15 min prior to test drugs) were tested in order to verify a possible involvement of the opioid mechanism in the antinociceptive effects of HPE and morphine.

Pentobarbital sleeping time

Thirty minutes following HPE (400 mg/kg, i.p.) or normal saline (10 ml/kg, i.p.) administration, mice
were given an intraperitoneal dose of pentobarbitalone (50 mg/kg, i.p.) and the sleeping times were determined. The time between loss and subsequent recovery of the righting reflex was taken as the duration of sleeping time (Pieretti et al., 1992).

Open-field test

The effect of HPE on locomotor activity was tested in the open-field test. Mice that received normal saline (10 ml/kg, i.p.) or HPE (100, 200 and 400 mg/kg, i.p.) were individually observed for locomotion by placing them in the centre of an open-field arena (40 cm of diameter) as described by Capaz et al. (1981) and the locomotion frequency (number of floor units the animal entered) was counted for a 4 min period following 30, 60 and 90 min of drug administration.

Statistical analysis

Data are expressed as the means ± SEM and were analysed by one-way analysis of variance (ANOVA) followed by Student Newman Keul's test for multiple comparisons between groups. P values of 0.05 or less were considered significant.

RESULTS

Effects on chemical nociception

HPE (200 and 400 mg/kg) produced a significant dose-dependent reduction in the number of abdominal constrictions (writhes) in the acetic acid test (Table 1). Furthermore, a 200 mg/kg dose of HPE significantly enhanced the antinociception produced by 1.25 mg/kg morphine. Table 2 shows the antagonism by naloxone of the antinociception induced by morphine and HPE. A smaller dose of naloxone (1 mg/kg, s.c.) reversed the antinociceptive effect of morphine (1.25 mg/kg) but not that of HPE (200 mg/kg) which was antagonized only partially by a high dose naloxone (5 mg/kg, s.c.).

Effects on thermal nociception

Intraperitoneal administration of HPE (100, 200 and 400 mg/kg) failed to produce any significant analgesia in the hot-plate test (data not shown). Morphine (10 mg/kg) demonstrated

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of writhes/20 min (mean ± SEM)</th>
<th>Inhibition (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (Saline)</td>
<td>45.25 ± 3.38</td>
<td>-</td>
</tr>
<tr>
<td>Morphine (1.25, s.c.)</td>
<td>16.66 ± 7.53**</td>
<td>63</td>
</tr>
<tr>
<td>Morphine (2.5, s.c.)</td>
<td>0.00 ± 0.00***</td>
<td>100</td>
</tr>
<tr>
<td>HPE (100, i.p.)</td>
<td>45.00 ± 7.59</td>
<td>00</td>
</tr>
<tr>
<td>HPE (200, i.p.)</td>
<td>21.33 ± 5.07*</td>
<td>52</td>
</tr>
<tr>
<td>HPE (400, i.p.)</td>
<td>11.25 ± 5.06***</td>
<td>75</td>
</tr>
<tr>
<td>Morphine (1.25, s.c.) + HPE (200, i.p.)</td>
<td>7.25 ± 3.25***</td>
<td>94</td>
</tr>
</tbody>
</table>

*p < 0.05; ** p < 0.01; *** p < 0.001 vs saline control (n = 8; ANOVA and Student Newman-Keul's test).
antinociception as shown by an increase in the mean latency to 31.93 s at 30 min and 27.32 s at 60 min, which differed significantly from baseline data (Fig. 1). When morphine and HPE (400 mg/kg) were co-administered, the morphine analgesia was significantly enhanced at time points of 60, 120 and 150 min (Fig. 1). The duration of morphine analgesia, in fact, was significantly increased by HPE beyond 150 min (not shown in graph). HPE-induced potentiation of morphine analgesia was, however, reversed by naloxone (1 mg/kg, s.c.), administered 15 min before HPE injection.

**Effects on pentobarbital sleeping time and locomotor activity**

HPE (400 mg/kg) showed no significant effect on sleeping time induced by pentobarbitone in mice (41.67 ± 8.43 min) when compared with the control group response (38.00 ± 7.71 min). Similarly, in the open-field test, HPE did not adversely impair locomotor frequency following its administration for 30, 60 and 90 min (85.83 ± 6.23; 46.66 ± 9.11 and 36.16 ± 6.51 units, respectively) when compared to the control (107.00 ± 10.33; 61.16 ± 5.42 and 57.16 ± 7.71 units).

**DISCUSSION**

The results of the present study indicate that HPE produces peripheral analgesia in the mouse assessed by the acetic acid-induced writhing test. It has also been shown that a 200 mg/kg dose of HPE significantly enhances the antinociception produced by 1.25 mg/kg morphine. These observations correlate well with the available literature describing the capacity of the placenta to secrete opioids and exert local effects (Nakai, 1978; Liotta et al., 1982; Lemaire et al., 1983; Weindl et al., 1983; Zhang et al., 1991). In the acetic acid test, the per se antinociceptive effect of HPE was insensitive to a smaller dose of naloxone (1 mg/kg) but was found to be weakly antagonized by a higher dose of naloxone (5 mg/kg). Over the last 20 years, it has been firmly established that there are three different 'classical' types of opioid receptors μ (mu), δ (delta) and κ (kappa) which have been renamed as OP₁, OP₂ and OP₃ receptors, respectively (Dhawan et al., 1996). Endogenous peptide ligands that activate opioid receptors have been previously described (Hughes et al., 1975; Brownstein, 1993). Since placenta secretes β-endorphins as well as dynorphins (Liotta et al., 1982; Weindl et al., 1983; Dawson-Basea and Gintzler, 1996), it is possible that the relative effectiveness of μ, δ and κ-opioid receptor activation to elicit analgesia and its antagonism to naloxone may vary. Naloxone exhibits some preference to μ-receptors (Herz and Almeida, 1989), however has been shown to bind to κ- and δ-receptors (Herkenham et al., 1986; Sharif & Hughes, 1989). The HPE-induced attenuation of acetic acid nociception and the potentiation of morphine antinociception were found to be naloxone-sensitive, indicating, at least in part, the involvement of an opioid mechanism in the effects of HPE.

Unlike in the acetic acid test, HPE failed to exhibit per se antinociceptive activity in the
Short Communication

Lack of stereoselectivity for the antiallodynic effect of mexiletine in spinally injured rats

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Systemically administered mexiletine, an antiarrhythmic, has been shown to also possess analgesic properties in some conditions of neuropathic pain. It has been suggested that the analgesic effect of mexiletine may be derived from the action of one of its optical isomers, (+)(S)-mexiletine. In the present study, we have compared the effects of systemic (−)-(R)- and (+)-(S)-mexiletine, on chronic mechanical allodynia-like behaviour in spinally injured rats, a model of central neuropathic pain in which racemic mexiletine has been shown to be active. I.p. racemic mexiletine as well as (−)-(R)- and (+)-(S)-mexiletine at 25 mg/kg all produced significant, but brief, alleviation of mechanical allodynia in a similar fashion as assessed with von-Frey hair elicited vocalization in the spinally injured rats. A slight increase in motor impairment was observed in all three groups which reached statistical significance for the racemic mexiletine and (+)-(S)-mexiletine. Our results suggest that both isomers of mexiletine contribute to the antiallodynic effect in this model of central pain. © 2000 European Federation of Chapters of the International Association for the Study of Pain

KEYWORDS: analgesia, central pain, mexiletine, neuropathic pain, stereoselectivity.

INTRODUCTION

In addition to being local anesthetics and antiarrhythmics, the Na⁺ channel blocker lidocaine and related drugs, such as tocainide and mexiletine, are useful analgesics upon systemic administration, particularly for the treatment of neuropathic pain (Lindström and Lindblom, 1987; Deigard et al., 1988; Rowbotham et al., 1991; Kingery, 1997; Jarvis and Coukell, 1998). One of the problems associated with application of this class of drugs is the presence of side-effects and toxicity, leading to a narrow therapeutic window (Kingery, 1997; Jarvis and Coukell, 1998). Traditionally, these drugs were used in clinical and experimental settings as racemic mixtures. It has recently been suggested that the analgesic effect of mexiletine on neuropathic pain may be the action of the (+)-S-isomer (Moseley, 1999). This would open up the possibility of using a chirally pure version of mexiletine for pain treatment with reduced side-effects, as other effects of mexiletine, such as that on Na⁺ channels on skeletal muscles has been shown to be associated with the (−)-R-isomer (De Luca, 1997; Desaphy et al., 1999).

Central neuropathic pain after spinal cord injury is a troublesome clinical condition for which effective treatments are lacking (Boivie, 1994; Bowsher and Nurmikko, 1996; Yezierski, 1996). Systemic local anesthetics remain one of the few options for treating such pain states (Boivie, 1994; Bowsher and Nurmikko, 1996). We have previously shown that systemic...
racemic mexiletine at 15 or 30 mg/kg alleviated chronic mechanical allodynia-like behaviours in spinally injured rats, a model of central pain (Xu et al., 1992a, 1992b). The antiallodynic effect of mexiletine was, however, associated with side-effects at the dose of 30 mg/kg (Xu et al. 1992b). The present study was conducted to examine and compare the effects of chirally pure (+)-S and (-)-R-isomers in alleviating allodynia-like behaviour in spinally injured rats. The behavioural side-effect profiles of the two isomers were also assessed.

METHODS

Twelve female Sprague-Dawley rats (B & K Universal, Sollentuna, Sweden) weighing 180–210 g at the time of spinal cord injury were used. The experiments were carried out according to the Ethical Guidelines of the International Association of the Study of Pain and were approved by the local research ethics committee. An ischaemic spinal cord injury was produced according to methods described previously. We have reported that a subset of spinally injured rats developed a chronic pain syndrome, including marked mechanical and cold allodynia (Xu et al., 1992a; Hao et al., 1996). The rats used in the present study were injured 3–6 months previously and all exhibited allodynia-like behaviours for at least 2 months. The first six rats were administered with (+)-S- or (-)-R-mexiletine and the injection was made in a cross-over fashion 48 h later. Racemic mexiletine paired with saline was administered in the same fashion in a separate group of six rats. The experimenter who conducted the experiment was always blind to the treatments administered.

To examine touch-evoked allodynia, vocalization thresholds to graded mechanical touch/pressure were tested with von Frey hairs. During testing the rats were gently restrained in a standing position and a von Frey hair was pushed onto the skin until the filament became bent. The frequency of the stimulation was about 1/s and the stimuli were applied 5–10 times at each intensity. The stimulation which induced consistent vocalization (>75% response rate) was considered as the pain threshold. The motor function of the animals was examined using a combined motor score assessing performance of rats in several motor tests (open field, righting reflex, incline plane etc. [Hao et al., 1996]).

(+)-S- and (-)-R-mexiletine were kindly provided by Pharmacia & Upjohn. Racemic mexiletine was obtained from Sigma. All drugs were dissolved in 0.9% normal saline and injected i.p. in a volume of 1 ml/kg. The data are expressed as median ± median absolute deviation and were analysed using the Wilcoxon sign-ranked test and Mann-Whitney U test. Values of $p<0.05$ were considered to be statistically significant.

RESULTS

The spinally injured rats used in this study exhibited severe mechanical allodynia-like behaviour with vocalization threshold generally below 5 g upon von Frey hair stimulation (Table 1). Corresponding values in normal rats are usually between 73–95 g (Xu et al., 1992). I.p. administration of racemic mexiletine at 25 mg/kg, but not saline, significantly alleviates the mechanical allodynia-like behaviour for 30 min, which is manifested by an increase in vocalization threshold (Table 1). Both (+)-S- and (-)-R-mexiletine also produced significant alleviation of mechanical allodynia in a fashion similar to racemic mexiletine (Table 1). The antiallodynic effect of (-)-R-mexiletine had somewhat shorter onset and duration of action than its (+)-S-isomer and the racemate, but the magnitude of the maximal effect was similar between the two isomers. No statistical difference could be detected at any time point between the isomers and racemate and between the isomers themselves, although all produced significant antiallodynia compared to their own pre-drug control values (Table 1).

Minor motor impairments were noted in the spinally injured rats, manifested as mild deficits in walking and reduced performance on the incline plant test. I.p. racemic-, (+)-S- and (-)-R-mexiletine produced a small increase in the motor deficits of these spinally injured rats shown by a slowed righting reflex and noticeable
TABLE 1. Effects of systemic (25 mg/kg) racemic, (-)-(R) and (+)-(S) mexiletine and saline on vocalization threshold to mechanical stimulation with von Frey hairs in spinaly injured rats.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>(+)-(R,S)-mexiletine</th>
<th>(-)-(R)-mexiletine</th>
<th>(+)-(S)-mexiletine</th>
<th>Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4.6±0</td>
<td>0.4±0.1</td>
<td>0.62±0.3</td>
<td>4.6±0</td>
</tr>
<tr>
<td>10</td>
<td>39.7±32.6*</td>
<td>37.4±35.8*</td>
<td>3.0±2.7*</td>
<td>4.6±0</td>
</tr>
<tr>
<td>20</td>
<td>72.3±37.2*</td>
<td>36.8±38.0*</td>
<td>36.5±36.8*</td>
<td>4.6±0</td>
</tr>
<tr>
<td>30</td>
<td>11.6±5.9*</td>
<td>1.0±0.8</td>
<td>3.1±2.5*</td>
<td>4.6±0</td>
</tr>
<tr>
<td>45</td>
<td>4.6±1.1</td>
<td>0.5±0.15</td>
<td>1.0±0.5</td>
<td>4.5±0</td>
</tr>
<tr>
<td>60</td>
<td>5.1±1.5</td>
<td>0.5±0.15</td>
<td>1.0±0.5</td>
<td>4.5±0</td>
</tr>
<tr>
<td>90</td>
<td>4.6±0.5</td>
<td>0.4±0</td>
<td>0.67±0.53</td>
<td>4.6±0</td>
</tr>
</tbody>
</table>

The threshold is defined as the pressure (g) exerted by von Frey hairs applied to the allodynic skin area (rostral to the spinal cord injury segment) required to evoked vocalization in <75% of trials. Time 0 represents the vocalization threshold before mexiletine administration. Six rats were included in each group in a blinded fashion. Data are expressed as median ± MAD (median absolute deviation). *= p < 0.05 compared to control value with Wilcoxon signed-ranks test.

deficits in the extension withdrawal reflex (Fig. 1). The motor effect reached statistical significance for the racemate and (+)-S-mexiletine (Fig. 1). Neither isomer of mexiletine produced sedation or other side-effects, whereas vomiting was seen in one rat treated with racemic mexiletine.

DISCUSSION

The present results clearly show that systemic administration of chirally pure isomers of mexiletine produces an antiallodynic effect in this model of central neuropathic pain after spinal cord injury in a fashion similar to racemic mexiletine. No difference in the antiallodynic effect was seen between the (+)-S- and (-)-R-isomers and between these isomers and the racemate at a dose of 25 mg/kg. These results agree with our earlier studies where we showed that racemic mexiletine and tocainide are antiallodynic in this model (Xu et al., 1992a, 1992b). Thus it appears as if both isomers contribute to the antiallodynic effect of racemic mexiletine. This is similar to an earlier study where both isomers of mexiletine produced antifibrillatory as well as convulsant effects in rats (Igwenzie et al., 1992). Our results therefore did not support the notion that the analgesic effect of mexiletine lies in the (+)-(S)-isomer (Moseley, 1999). Neither do our results agree with the conclusion from an earlier

![Figure 1](image_url)  
**FIG. 1.** Motor scores of rats before (time 0) and after i.p. injection with saline (n = 6, open circles in A), 25 mg/kg of racemic mexiletine (n = 6, open squares in A) and (-)-(R)-mexiletine (n = 6, circles in B) and (+)-(S)-mexiletine (n = 6, squares in B). The data are expressed as median ± MAD. *= p < 0.05 compared to control value with Wilcoxon signed-ranks test.
study in which the antinoiceptive action of tocainide, which is structurally closely related to mexiletine, has been shown to be associated with the (−)-R-isomer (Franchini et al., 1993). We believe that the mechanism of action for mexiletine in treating the mechanical allodynia in spinally injured rats lies in its effect on hyperexcitable dorsal horn neurons through blocking the sodium channels. We have previously observed that the abnormal ongoing activity recorded from dorsal horn neurons in the allodynic rats can be abolished by systemic lidocaine (Xu et al., unpublished observation), supporting such a hypothesis.

It needs to be emphasized that although the duration of action for mexiletine was brief, this should not be seen as a problem for clinical application. In a clinical setting, mexiletine is likely to be given orally over a prolonged period of time (weeks) in order to achieve a stable therapeutic blood concentration. Hence, the brief duration of action for a single injection of mexiletine in rats (which may also differ from humans in terms of the pharmacokinetics of mexiletine) cannot be predictive for the clinical situation.

Some minor differences were noted for the motor effects of the racemic mexiletine and the two isomers. It is possible therefore that the motor effect of mexiletine was mediated primarily by its (+)-(S)-isomer. Thus, by showing that both isomers of mexiletine produced antiallodynia, our results do not entirely rule out the possibility that chirocally pure forms of mexiletine may be useful analgesics with reduced side-effects. It is important to note that technical developments in recent years has enabled large scale production of chirally pure drugs, making such an option both practical and cost-effective (Moody et al., 1994; Stoschitzky et al., 1997).

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REFERENCES


Experimental Note

Tramadol anti-inflammatory activity is not related to a direct inhibitory action on prostaglandin endoperoxide synthases

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The analgesic drug tramadol has been shown to relieve pain in inflammatory conditions, to inhibit the development of experimental inflammation, and to reduce prostaglandin (PGE₁) concentrations in the inflammatory exudate. In this study, we evaluated the putative activity of tramadol to suppress prostaglandin endoperoxide synthase-1 (PGHS-1), and prostaglandin endoperoxide synthase-2 (PGHS-2) activities in human whole blood in vitro. Platelet thromboxane (TX)B₂ production and monocyte PGE₁ production in LPS-stimulated blood were measured in samples incubated with different concentrations (300 ng/ml, 3 μg/ml, 30 μg/ml) of tramadol or its enantiomers. Neither tramadol nor the enantiomers inhibited the formation of arachidonic acid metabolites. Our results indicate that the anti-inflammatory effect of tramadol demonstrated in some models is not related to a direct inhibitory effect on the formation of prostaglandins. © 2000 European Federation of Chapters of the International Association for the Study of Pain

**KEYWORDS:** tramadol, prostaglandin endoperoxide synthase-1, prostaglandin endoperoxide synthase-2, human blood.

INTRODUCTION

Tramadol hydrochloride ([1RS, 2RS]-2-[[dimethylamino]-methyl]-1-(3-methoxyphenyl)]-cyclohexanol hydrochloride induces anti-hyperalgesic and antinociceptive effects in animals (Sacerdote et al., 1997; Bianchi and Panera, 1998), and is increasingly used for the treatment of pain associated with acute and chronic inflammatory conditions in humans (Barnigade and Langford, 1998). This drug is a 1:1 racemic mixture of two enantiomers ((+)- and (−)-tramadol), with different pharmacological properties (Raffa and Friderichs, 1996).

We have recently demonstrated that tramadol inhibited different types of experimental inflammation in rats. In particular, we observed that the acute administration of tramadol significantly reduced the edema and the hyperalgesia induced by yeast injection in the paw. Moreover, in the subcutaneous carrageenin-induced inflammation, we observed that the administration of tramadol at analgesic doses reduced the amount of the exudate, as well as the concentration of PGE₁, but not the concentration of leukotriene (LT)B₄, in the inflammatory exudate (Bianchi et al., 1999a). Similar results have been obtained following the administration of the enantiomers of tramadol in the same experimental conditions (Bianchi et al., 1999b). Although tramadol has been reported not to be active in all...
experimental models of inflammation (Raffa and Friderichs, 1996), we considered it to be of interest to investigate the possibility that tramadol may directly reduce prostaglandin production. Such an effect of tramadol might be relevant for the efficacy and tolerability of this drug in clinical conditions of inflammatory pain. It is well known that arachidonic acid is converted enzymatically into inflammatory prostaglandins (such as PGE₃) by the activity of a key enzyme, PG-endoperoxide synthase (PGHS). It has been demonstrated that two isoforms of PGHS exist, referred to as PGHS-1 and PGHS-2. Both exhibit the cyclooxygenase and peroxidase activities that lead to the formation of different prostanoids (DeWitt, 1991), and play a relevant role in inflammation (Zhang et al., 1997; Smith et al., 1998).

We, therefore, considered it of interest to study tramadol and its enantiomers in relation to their ability to affect PGHS-1, and PGHS-2 activities in vitro. We used the assay system most widely accepted for the characterization of drugs able to exert anti-inflammatory effects (Patrignani et al., 1994; Pairet and van Ryn, 1998; Warner et al., 1999).

METHODS

Blood was drawn from healthy donors that had not taken any NSAIDs during the previous 15 days; 30–50 ml of blood were collected in order to test all different substances on aliquots from the same donor.

Substances to be tested were added in the opportune tubes (glass tubes for PGHS-1 and plastic tubes for PGHS-2 test) and dried in a vacuum dryer (Speed Vac, Savant) to avoid any vehicle interference. We used the following drugs: tramadol hydrochloride (Prodotti Formenti, Milano, Italy), (+)-tramadol, and (-)-tramadol (Grüenthal GmbH, Aachen, Germany), acetylsalicylic acid (ASA, Sigma-Aldrich, Milano, Italy), nimesulide (Helsinn Healthcare, Pambio-Noranco, Switzerland). One millilitre whole blood aliquots were distributed in glass tubes and allowed to clot at 37°C for 1 h, centrifuged for 10 min at 2500 × g and serum assayed for TxB₂ by enzyme immunoassay (EIA) to demonstrate PGHS-1 activity. ASA (50 μM) was used as a reference compound.

PGHS-2 activity was tested in 1 ml heparinized (Na-heparine, 10 U/ml) whole blood aliquots which were incubated for 24 h at 37°C with ASA 50 μM in order to avoid constitutive PGHS-1 contribution, and 10 μg/ml lipopolysaccharide (LPS, Sigma-Aldrich, Milano, Italy) to induce monocyte PGHS-2. The production of PGE₂ was assayed in plasma, after centrifugation at 2500 × g for 10 min. Nimesulide was used as a reference compound. Statistical comparisons were made by analysis of variance.

RESULTS

Average platelet TxB₂ production resulted of 282 ± 87 ng/ml. As expected, the pretreatment with ASA caused a 89.2% inhibition in TxB₂ production. Average PGE₂ production resulted of 94 ± 43 ng/ml. Nimesulide (7 μg/ml, 700 ng/ml, and 70 ng/ml) inhibited PGE₂ production by 94.9%, 57.3%, and 21.5%, respectively.

Tramadol and its enantiomers (300 ng/ml, 3 μg/ml, 30 μg/ml) inhibited neither platelet TxB₂ production, nor monocyte PGHS-2-dependent synthesis of PGE₂ (Table 1).

DISCUSSION

We have recently demonstrated that the analgesic drug tramadol is able to reduce experimental inflammation in rats. In these previous studies we examined the effects of tramadol in two

**TABLE 1.** Effects of tramadol and its enantiomers ((+)-tramadol, and (−)-tramadol) on TxB₂ production in human platelets and PGE₂ production by human whole blood incubated with LPS. The table reports the data obtained with the drug concentration of 3 μg/ml; similar results were obtained with lower (300 ng/ml) and higher (30 μg/ml) concentrations. Values are reported as mean ± SEM from three experiments.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>TxB₂ (ng/ml)</th>
<th>PGE₂ (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>282 ± 87</td>
<td>94 ± 43</td>
</tr>
<tr>
<td>Tramadol</td>
<td>383 ± 72</td>
<td>99 ± 41</td>
</tr>
<tr>
<td>(+)-Tramadol</td>
<td>291 ± 110</td>
<td>100 ± 44</td>
</tr>
<tr>
<td>(−)-Tramadol</td>
<td>303 ± 101</td>
<td>77 ± 22</td>
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</tbody>
</table>

*European Journal of Pain (2000), 4*
classical preclinical tests for inflammation and inflammatory pain, such as carrageenan-induced oedema, and yeast-induced paw inflammation (Bianchi et al., 1999a; Bianchi et al., 1999b). Both of these models are frequently used for the experimental evaluation of nonsteroidal anti-inflammatory drugs, in order to predict their clinical potency (Mukherjee et al., 1996).

The present data demonstrate, even at concentrations significantly higher than those reported as effective in the human (Sunshine, 1994), tramadol does not directly affect PGHS-1 nor PGHS-2 activities, indicating that the drug exerts its anti-inflammatory action without directly affecting the enzymes involved in the generation of arachidonic acid metabolites.

Tramadol exerts a dual mechanism of action: binding to mu-opioid receptors and potentiation of the monoaminergic system (Raffa and Friderichs, 1996). It has been demonstrated that both opioids and drugs enhancing serotoninergic and noradrenergic transmission reduce inflammatory oedema in several experimental conditions (Bianchi et al., 1994; Bianchi et al., 1995; Bianchi & Panerai, 1996; Sacerdote et al., 1996; Stein et al., 1997). It can, therefore, be proposed that the anti-inflammatory action of tramadol is not related to a direct interaction with PGHS, but it could be primarily due to the anti-oedema effect of the drug via the same mechanisms involved in the analgesic action. This hypothesis is also consistent with the data presented in an extensive review on the pharmacological properties of tramadol, where it has been reported that the inhibition of kaolin-induced paw oedema was not accompanied by an anti-inflammatory action in the cotton pellet granuloma test in rats (Raffa and Friderichs, 1996). The pharmacodynamic profile of tramadol is therefore completely different from that of anti-inflammatory drugs, including the new COX-2 inhibitors. These findings may help to explain the good gastric and renal tolerability of tramadol when used in humans (Bamigbade and Langford, 1998).

REFERENCES


Bianchi M, Rossoni G, Panerai AE. tramadol reduces inflammatory edema in rats: additive action of the (+) and (−) enantiomer. Abstracts 9th World Congress on Pain, 1999b; 522–523.


Bulletin Board

Interdisziplinärer Arbeitskreis
‘Muskeltonus und Schmerz’
2001 ‘Muscle Pain’ Research Award

The Interdisziplinärer Arbeitskreis ‘Muskeltonus und Schmerz’ (Interdisciplinary Working Group ‘Muscle Tone and Pain’) announces its ‘Muscle Pain’ Research Award (€10,000.-) for the year 2001. The award is intended to acknowledge major achievements in basic or clinical research on pathogenesis, diagnosis and management of muscle pain including alterations of muscle tone and spasticity. The 2001 award is sponsored by grants from Aventis Pharma Deutschland GmbH, Novartis Pharma GmbH, Deutschland, and Sanofi-Synthelabo GmbH.

Manuscripts accepted or published in 1999/2000 issues of reviewed scientific journals can be submitted and will be evaluated by an independent scientific committee. Research groups that have a continuous record of successful research in the field of muscle pain will also be considered for the award.

Submission deadline: April 30, 2001

For more information please contact:
Interdisziplinärer Arbeitskreis ‘Muskeltonus und Schmerz’, Dr Michel Spaeth MD, Friedrich-Baur-Institut, Medizinische Klinik, Klinikum der Universität, Innenstadt, Ziemssenstraße 1, D-80336 Munich, Germany. Tel: +49-89-51607557; FAX: +49-89-51604750; E-mail: Michael.Spaeth@lrz.uni-muenchen.de
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| J Brennum | S Grond | R Maldonado | B A Simpson |
| E Bruera | J-X Hao | M Marsala | P Sjogren |
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| B J Collet | P Heuts | R Melzack | S Stewart |
| J G Collins | R Hill | N Memran-Pourcher | A Stubhaug |
| D Cottrell | A Holdcroft | S Mense | H Takahashi |
| M Cousins | R Jamison | R A Meyer | R-D Treede |
| G Crombez | T S Jensen | B A Meyerson | P Vergara |
| B Crul | R W Johnson | K Mizumura | J W S Vlaeyen |
| V Chapman | E Kalso | S Morley | Z Wiesendhelm-Hallin |
| P Dellemijin | V Kayser | R B North | A C de C Williams |
| P K Eide | T Kawamata | J L Ochoa | X Xu |
| J Eisenach | U E Kongsgaard | P-O Ostergren | R P Yezierski |
# Contents of Volume 4

**Volume 4 Number 1 2000**

---

**Editorial**
Fernando Cervero 1

---

**Guest Editorial**
Beware somatization
Harold Merskey 3

---

**Review Article**
Wind-up and the NMDA receptor complex from a clinical perspective
Per K. Eide 5

Commentary: the peripheral mechanisms of abnormal temporal summation
Paolo Marchettini and Antonio Barbieri 15

---

**Original Articles**

Neuronal inhibitory effects of methadone are predominantly opioid receptor mediated in the rat spinal cord *in vivo*
Katherine J. Carpenter, Victoria Chapman and Anthony H. Dickenson 19

Citalopram in patients with fibromyalgia—a randomized, double-blind, placebo-controlled study
Ulla Maria Anderberg, Ina Marteinsdottir and Lars von Knorring 27

The emotional stroop task and chronic pain: what is threatening for chronic pain sufferers?
Geert Crombez, Dirk Herman and Hugo Adriaensen 37

The DSM-IV nosology of chronic pain: a comparison of pain disorder and multiple somatization syndrome
Wolfgang Hiller, Jörg Heuser and Manfred M. Fichter 45

The influence of pain intensity on somatosensory perception in patients suffering from subacute/chronic lateral epicondyalgia
Ann-Sofie Leffler, Eva Kosek and Per Hansson 57

Injection of hypertonic saline into musculus infraspinatus resulted in referred pain and sensory disturbances in the ipsilateral upper arm
Ann-Sofie Leffler, Eva Kosek and Per Hansson 73
<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descending facilitatory modulation of a behavioral nociceptive response by stimulation in the adult rat anterior cingulate cortex</td>
<td>83</td>
</tr>
<tr>
<td>Amelita A. Calejesan, Susan J. Kim and Min Zhuo</td>
<td></td>
</tr>
<tr>
<td>The anticonvulsant remacemide and its metabolite AR-R12495AA attenuate spinal synaptic transmission and carrageenan-induced inflammation in the young rat</td>
<td>97</td>
</tr>
<tr>
<td>A. U. R. Asghar, S. S. Hasan and A. E. King</td>
<td></td>
</tr>
<tr>
<td>Clinical Note</td>
<td></td>
</tr>
<tr>
<td>The effects of exogenous analgesia in a patient with borderline personality disorder (BPD) and severe self-injurious behaviour</td>
<td>107</td>
</tr>
<tr>
<td>Norbert J. Thürauf and Heike A. Washeim</td>
<td></td>
</tr>
<tr>
<td>Experimental Note</td>
<td></td>
</tr>
<tr>
<td>Lumbar catheterization of the subarachnoid space with a 32-gauge polyurethane catheter in the rat</td>
<td>111</td>
</tr>
<tr>
<td>Esther M. Pogaizki, Peter K. Zahn and Timothy J. Brennan</td>
<td></td>
</tr>
<tr>
<td>Volume 4 Number 2 2000</td>
<td></td>
</tr>
<tr>
<td>Editorial</td>
<td>115</td>
</tr>
<tr>
<td>Fernando Cervero</td>
<td></td>
</tr>
<tr>
<td>Guest Editorial</td>
<td>117</td>
</tr>
<tr>
<td>Time to re-evaluate golden standards?</td>
<td></td>
</tr>
<tr>
<td>Jürgen Linder</td>
<td></td>
</tr>
<tr>
<td>Review Article</td>
<td>121</td>
</tr>
<tr>
<td>Substance P</td>
<td></td>
</tr>
<tr>
<td>Dirk G. Snijderaar, Ris Dirksen, Rob Slappendel and Ben J. P. Crul</td>
<td></td>
</tr>
<tr>
<td>Original Articles</td>
<td>137</td>
</tr>
<tr>
<td>The symptom check-list, SCL-90-R: its use and characteristics in chronic pain patients</td>
<td></td>
</tr>
<tr>
<td>Jochen Hardt, Hans U. Gerbershagen and Petra Franke</td>
<td></td>
</tr>
<tr>
<td>Psychological predictors of the effectiveness of radiofrequency lesioning of the cervical spinal dorsal ganglion (RF-DRG)</td>
<td>149</td>
</tr>
<tr>
<td>Han Samwel, Robert Slappendel, Ben J. P. Crul and Victor F. Voerman</td>
<td></td>
</tr>
<tr>
<td>Gender differences in regional brain response to visceral pressure in IBS patients</td>
<td>157</td>
</tr>
<tr>
<td>Steven Berman, Julie Munakata, Bruce D. Naliboff, Lin Chang, Mark Mandelkern, Dan Silverman, Edward Kovalik and Emeran A. Mayer</td>
<td></td>
</tr>
</tbody>
</table>
Pain and quality of life in patients with critical limb ischaemia: results of a randomized controlled multicentre study on the effect of spinal cord stimulation
G. H. Spincemaille, H. M. Klomp, E. W. Steyerberg, J. D. F. Habbema 173

Low frequency TENS is less effective than high frequency TENS at reducing inflammation-induced hyperalgesia in morphine-tolerant rats
Kathleen A. Sluka, Mary A. Judge, Michele M. McColley, Pauley M. Reveiz and Bethany M. Taylor 185

Plasma levels after peroral and topical ibuprofen and effects upon low pH-induced cutaneous and muscle pain
Astrid E. Steen, Peter W. Reeh, Gerd Geisslinger and Kay H. Steen 195

No effect of preoperative paracetamol and codeine suppositories for pain after termination of pregnancies in general anaesthesia
Vegard Dahl, Frode Fjellanger and Johan C. Raeder 211

Evidence-Based Medicine
Five easy pieces on evidence-based medicine (1)
Eija Kalso 217

Correspondence
Letter to the Editor
Elon Eisenberg, Ana Kleiser, Arielle Dortort, Tamar Haim and David Yarnitsky 221

Bulletin Board 223

Volume 4 Number 3 2000

Guest Editorial
Psychosocial stress and chronic pain
Boudewijn Van Houdenhove 223

Original Articles
Abnormalities of somatosensory perception in patients with painful osteoarthritis normalize following successful treatment
Eva Kosek and Gunnar Ordeberg 229

Brain somatic representation of phantom and intact limb: a fMRI study case report
Miguel Condés-Lara, Fernando A. Barrios, Juan Romero Romo, Rafael Rojas, Perla Salgado and Julian Sánchez-Cortazar 239
<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intratheca]ly administered endotoxin or cytokines produce allodynia,</td>
<td></td>
</tr>
<tr>
<td>hyperalgesia and changes in spinal cord neuronal responses to nociceptive stimuli in the rat</td>
<td>247</td>
</tr>
<tr>
<td>Alison J. Reeve, Sadhana Patel, Alyson Fox, Katherine Walker and Laszlo Urban</td>
<td></td>
</tr>
<tr>
<td>Validation of the German version of the Fear-Avoidance Beliefs Questionnaire (FABQ)</td>
<td>259</td>
</tr>
<tr>
<td>Michael Pfingsten, Birgit Kröner-Herwig, Eric Leibing, Uta Kronshage and Jan Hildebrandt</td>
<td></td>
</tr>
<tr>
<td>Autonomic responses and pain perception in Alzheimer's disease</td>
<td>267</td>
</tr>
<tr>
<td>Innocenzo Rainero, Sergio Vighetti, Bruno Bergamasco, Lorenzo Pinessi and Fabrizio Benedetti</td>
<td></td>
</tr>
<tr>
<td>The development and validation of a Greek version of the short-form McGill Pain Questionnaire</td>
<td>275</td>
</tr>
<tr>
<td>George Georgoudis, Paul J. Watson and Jacqueline A. Oldham</td>
<td></td>
</tr>
<tr>
<td>Perceived future in chronic pain: the relationship between outlook on future and empirically derived psychological patient profiles</td>
<td>283</td>
</tr>
<tr>
<td>Christina Hellström, Bengt Jansson and Sven G. Carlsson</td>
<td></td>
</tr>
<tr>
<td>Age-related changes in nociception and effect of morphine in the Lou rat</td>
<td>291</td>
</tr>
<tr>
<td>D. Jourdan, S. Boghossian, A. Alloui, C. Veyrat-Dubreuil, M. A. Coudore, A. Eschalier and J. Alliot</td>
<td></td>
</tr>
<tr>
<td><strong>Experimental Note</strong></td>
<td></td>
</tr>
<tr>
<td>Capillary blood sampling: the pain of single-use lancing devices</td>
<td>301</td>
</tr>
<tr>
<td>Heinrich Fruhstorfer</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Notes</strong></td>
<td></td>
</tr>
<tr>
<td>Acute abstinence syndrome following abrupt cessation of long-term use of tramadol (Ultram®): a case study</td>
<td>307</td>
</tr>
<tr>
<td>E. Freye and J. Levy</td>
<td></td>
</tr>
<tr>
<td>Post stroke shoulder pain: more common than previously realized</td>
<td>313</td>
</tr>
<tr>
<td>Giles E. Gamble, Elisa Barberan, David Bowsher, Pippa J. Tyrrell and Anthony K.P. Jones</td>
<td></td>
</tr>
<tr>
<td><strong>Invited Commentary</strong></td>
<td></td>
</tr>
<tr>
<td>Spinal cord stimulation in limb ischemia – time for revival?</td>
<td>317</td>
</tr>
<tr>
<td>B. Linderoth and B. A. Meyerson</td>
<td></td>
</tr>
<tr>
<td><strong>Evidence-Based Medicine</strong></td>
<td></td>
</tr>
<tr>
<td>Five easy pieces on evidence-based medicine (2)</td>
<td>321</td>
</tr>
<tr>
<td>Eija Kaiso and R. Andrew Moore</td>
<td></td>
</tr>
</tbody>
</table>
Volume 4 Number 4 2000

Editorial
Ulf Lindblom 325

Original Articles
Relationship between mechanical sensitivity and postamputation pain: a prospective study
Lone Nikolajsen, Susanne Ilkjær and Troels S. Jensen 327

Does failure hurt? The effects of failure feedback on pain report, pain tolerance and pain avoidance
Johanna H.C. van den Hout, Johan W.S. Vlaeyen, Madelon L. Peters, Iris M. Engelhard and Marcel A. van den Hout 335

Do epidemiological results replicate? The prevalence and health-economic consequences of neck and back pain in the general population
Steven J. Linton and Marianne Ryberg 347

The analgesic efficacy of topical capsaicin is enhanced by glyceryl trinitrate in painful osteoarthritis: a randomized, double blind, placebo controlled study
Gary McCleane 355

Leg edema from intrathecal opiate infusions
J. Antonio Aldrete and J. M. Couto da Silva 361

Improving the quality of postoperative pain relief
Timo E. Salomäki, Tuula M. Hokajärvi, Pirjo Ranta and Seppo Alahuhta 367

Reciprocal connections between the medullary dorsal reticular nucleus and the spinal dorsal horn in the rat
Armando Almeida, Isaura Tavares and Deolinda Lima 373

Secondary heat, but not mechanical, hyperalgesia induced by subcutaneous injection of bee venom in the conscious rat: effect of systemic MK-801, a non-competitive NMDA receptor antagonist
Hui-Sheng Chen and Jun Chen 389

Effects of human placental extract on chemical and thermal nociception in mice
Luíma A. Gurgel, Flávia A. Santos and Vietla S. N. Rao 403

Short Communication
Lack of stereoselectivity for the antiallodynic effect of mexiletine in spinaly injured rats
Wei-Ping Wu, Jan Nordmark, Zsuzsanna Wiesenfield-Hallin and Xiao-Jun Xu 409
Experimental Note
Tramadol anti-inflammatory activity is not related to a direct inhibitory action on prostaglandin endoperoxide synthases
Carola Buccellati, Angelo Sala, Rossana Ballerio, Mauro Bianchi 413

Bulletin Board 417

Acknowledgements 419
Index to Volume 4

acidosis, pH-induced cutaneous and muscle pain 195
adaptive coping 283
Adriaensen, H 37
age-related changes in nociception, morphine effects, Lou rat 291
Akaluhta, S 367
Aiárete, JA 361
algesimetry, ibuprofen, pH-induced cutaneous and muscle pain 195
Alliot, J 291
allodynia
  endotoxin and cytokines, intrathecal catheterization 247
  musculoskeletal pain 73
Alloui, A 291
Almeida, A 373
Alzheimer's disease, autonomic responses and pain perception 267
amputation, preamputation pain, and mechanical hyperalgesia 327
analgesia
  central and neuropathic pain, mexiletine 409
  pH-induced cutaneous and muscle pain 195
Anderberg, UM 27
anterior cingulate cortex, descending facilitation, rat 83
anticonvulsants, remacemide, AR-R12495AA 97
antidepressants, fibromyalgia clinical study 27
anxiety, SCL-90-R 137
Asghar, AUR 97
asymmetric synapses, spino–fugal pathways 373
autonomic responses, Alzheimer's disease 267
back pain, prevalence, health-care utilization 347
Ballerio, R 413
Barberan, E 313
Barrios, FA 239
bee venom model, mechanical hyperalgesia, effect of systemic MK-801 389
Benedetti, F 267
Bergermaseo, B 267
Berman, S 157
Bianchi, M 413
blood pressure, Alzheimer's disease 267
Boghossian, S 291
borderline personality disorder (BPD), self-injury 107
Bowsher, D 313
brain somatotopic representation, phantom limb, fMRI 239
Brennan, TJ 111
Buccellati, C 413
Calefesan, AA 83
capillary blood sampling, single-use lancing devices 301
capsaicin, topical, enhanced by glyceryl trinitrate, osteoarthritis 355
Carlsson, SG 283
Carpenter, KJ 19
carrageenan inflammation, synaptic transmission in rat 97
central hyperexcitability 229
central pain, mexiletine, stereoselectivity 409
Chang, L 157
Chapman, V 19
Chen, H-S 389
Chen, J 389
cholera toxin, subunit B, spino–bulbo–spinal loop 373
citalopram, fibromyalgia clinical study 27
codeine, preoperative, termination of pregnancies 211
cognitive–behavioral treatment, DSM-IV and ICD-10 systems 45
Condés-Lara, M 239
Coudore, MA 291
Couto da Silva, JM 361
Crombez, G 37

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Cruel, BJP 121, 149
cytokines, intrathecal catheterization 247

Dahl, V 211
depression, SCL-90-R 137
descending facilitation, anterior cingulate cortex, rat 83
diagnostic techniques, symptom checklist SCL-90-R 117, 137
Dickenson, AH 19
Dirksen, R 121
Dortort, A 221
drug delivery
intrathecal catheterization, subarachnoid space, rat 111
transdermal, ibuprofen 195
DSM-IV and ICD-10 systems, cognitive-behavioral treatment 45

economics, epidemiological results, health-care utilization 347
edema, intrathecal opiate infusions 361
Eide, PK 5
Eisenberg, E 221
emotional stroop task, pain-related information giving 37
endotoxin, intrathecal catheterization 247
Engelhard, IM 335
epicondylalgia, subacute/chronic lateral, somatosensory perception 57
epidemiological results, health-care utilization 347
Eschalier, A 291
evidence-based medicine 217, 321

failure feedback, effects on pain report, pain tolerance and pain avoidance 335
fear—avoidance beliefs questionnaire (FABQ), German version, validation 259
fibromyalgia, citalopram, clinical study 27
Fichter, MM 45
Fjellanger, F 211
fMRI, phantom limb, brain somatotopic representation 239
Fox, A 247

Franke, P 137
Freye, E 307
Fruhstorfer, H 301
Future Scale, perceived future 283

Gamble, GE 313
Geisslinger, G 195
gender differences in regional brain responses to visceral pressure, IBS patients 157
gender-related changes in nociception, morphine effects, Lou rat 291
Georgoudis, G 275
Gerbershagen, HU 137
glycerel trinitrate, enhancing topical capsaicin, osteoarthritis 355
Gurgel, LA 403

Habbe, JDF 173
Haim, T 221
Hansson, P 57, 73
Hardt, J 137
Hasan, SS 97
heart rate, Alzheimer's disease 267
Hellström, C 283
Hermans, D 37
Heuser, J 45
Hildebrandt, J 259
Hiller, W 45
Hokajärvi, TM 367
hyperalgesia, mechanical
bee venom model 389
phantom limb 327
hypoaesthesia, musculoskeletal pain 57, 73

ibuprofen, plasma levels, pH-induced cutaneous and muscle pain 195
ICD-10 and DSM-IV systems, cognitive-behavioral treatment 45
Ilkjaer, S 327
inflammation-induced hyperalgesia
endotoxin/cytokines, rat 97
LF-TENS vs HF-TENS, rat 185
synaptic transmission, rat 97
infusions, opiates, causing leg edema 361
interleukin-1beta, intrathecal catheterization 247
intrathecal catheterization
endotoxin or cytokines, allodynia,
hyperalgesia and spinal cord neuronal
responses, rat 247
opioid infusions, leg edema 361
subarachnoid space, rat 111
irritable bowel syndrome, gender differences in
regional brain responses to visceral
pressure 157

Jansson, B 283
Jensen, TS 327
Jones, AKP 313
Jourdan, D 291
Judge, MA 185

Kalso, E 217
Kim, SJ 83
King, AE 97
Kleiser, A 221
Klomp, HM 173
Kosek, E 57, 73, 229
Kovalik, E 157
Kröner-Herwig, B 259
Kronshage, U 259

lancing pain, capillary blood sampling 301
Leffler, A-S 57, 73
Leibing, E 259
Levy, J 307
Lima, D 373
limb edema, intrathecal opiate infusions 361
limb ischemia, spinal cord stimulation 173, 317
Linder, J 117
Linderoth, B 317
Linton, SJ 347
lipopolysaccharide endotoxin, intrathecal
catheterization 247
Low/C/Jall rat, morphine effects, age-related
changes in nociception 291
lumbar catheterization of subarachnoid space,
rat 111

McClean, G 355
McColley, MM 185

McGill Pain Questionnaire, Greek translation 275
Mandelkern, M 157
Marieinsdottr, I 27
Mayer, EA 157
mechanical hyperalgesia
bee venom model, effect of systemic MK-801
389
phantom limb 327, 327
medullary dorsal reticular nucleus, and spinal
dorsal horn, reciprocal connections 373
Merskey, H 3
metabotropic glutamate receptor, rat 83
methadone, neuronal inhibitory effects, opioid
receptor-mediated in rat 19
mexiletine
effects on spinally injured rats 409
stereoselectivity, neuropathic pain 409
Meyerston, BA 317
morphine
in borderline personality disorder (BPD) 107
effects, age-related changes in nociception, rat
291
morphine-tolerance, inflammation-induced
hyperalgesia, LF-TENS vs HF-TENS, rat 185
Multidimensional Pain Inventory (MPI),
perceived future 283
Munakata, J 157
musculoskeletal pain
hyperalgesia 73
hypoesthesia 57, 73

Naliboff, BD 157
neck pain, prevalence, health-care utilization 347
neurologic examination, sensory deficit 313
neuropathic pain, mexiletine, stereoselectivity 409
neuropeptides, substance P 121
Nikolajisen, L 327
NMDA antagonists 221
NMDA receptor complex, temporal summation
and wind-up 5
NMDA receptors, bee venom model,
mechanical hyperalgesia 389
Nordmark, J 409

Oldham, JA 275
opioid infusions, causing leg edema 361

European Journal of Pain (2000), 4
opioid mechanism, pregnancy nociception, mice 403
opioid receptor-mediated neuronal inhibitory effects of methadone, rat 19
Ordeberg, G 229
osteoarthritis abnormal somatosensory perception 229
topical capsaicin enhanced by glyceryl trinitrate 355
pain tolerance, pain avoidance, and pain report, negative affect 335
paracetamol, preoperative, termination of pregnancies 211
Patel, S 247
perceived future, Multidimensional Pain Inventory (MPI) 283
Peters, ML 335
Pfingsten, M 259
phantom limb brain somatotopic representation, fMRI 239
mechanical hyperalgesia 327
Pinesi, L 267
placental extract, chemical and thermal nociception, mice 403
Pogatski, EM 111
postoperative analgesia 367
termination of pregnancies 211
pregnancy, chemical and thermal nociception, mice 403
pregnancy termination, preoperative paracetamol/codeine 211
prostaglandin endoperoxide synthases, and tramadol 413
psychological predictors, RF-DRG effectiveness 149
psychosocial stress 225
quality of life, critical limb ischemia, spinal cord stimulation study 317
quantitative sensory testing musculoskeletal pain 57
somatosensory perception 229
questionnaires fear–avoidance beliefs (FABQ) 259
McGill short form, Greek version 275
radiofrequency lesioning, cervical spinal dorsal ganglion, psychological predictors 149
Racder, JC 211
Rainero, I 267
Ranta, P 367
Rao, VSN 403
rat, morphine effects, age-related changes in nociception 291
Rech, PW 195
Reeve, AJ 247
referred pain hypoalgesia 73
somatosensory perception 57
regional brain response, gender differences in IBS patients, visceral pressure 157
Revez, PM 185
Rojas, R 239
Romo, JR 239
rostral ventromedial medulla, descending facilitation, rat 83
Ryberg, M 347
Sala, A 413
Salgado, P 239
saline, referred pain, sensory disturbances 73
Salomäki, TE 367
Samwel, H 149
Sánchez-Cortazar, J 239
Santos, FA 403
SCL-90-R see symptom checklist SCL-90-R
self-injury, borderline personality disorder (BPD) 107
sensory deficit, neurologiel examination 313
shoulder pain, incidence post stroke 313
Silverman, D 157
single-use devices, capillary blood sampling 301
Slappendel, R 121, 149
Shuka, KA 185
Snijder, DG 121
somatization disorder 3 multiple somatization syndrome 45
SCL-90-R 137
somatosensory perception, subacute/chronic lateral epicondylalgia 57
somatotopic representation, phantom limb, fMRI 239
spinal cord
critical limb ischaemia, stimulation effects 173, 317
intrathecal catheterization of subarachnoid space, rat 111
neuronal responses, endotoxin/cytokines, intrathecal catheterization 247
synaptic transmission, carrageenan inflammation, rat 97
spinal dorsal ganglion, radiofrequency lesioning (RF-DRG) 149
Spincemaille, GH 173
spinobulbo–spinal loop, cholera toxin 373
spino–fugal pathways, asymmetric synapses 373
Steen, AE 195
Steen, KH 195
Steyerberg, EW 173
stress, psychosocial 225
stroke, shoulder pain incidence 313
stroof task, pain-related information giving 37
stump pain, and preamputation pain 327
subaeute/chronic lateral epicondylalgia, somatosensory perception 57
substance P 121
symptom checklist SCL-90-R, re-evaluation 117, 137
synaptic transmission, spinal cord 97
tail-flick reflex, anterior cingulate cortex, rat 83
Tavares, I 373
Taylor, BM 185
temporal summation commentary 15
NMDA receptor complex 5
Thürn, NJ 107
tramadol
cessatostaglandin endoperoxide synthases 413
and prostaglandin endoperoxide synthases 413
transcutaneous electrical nerve stimulation (TENS), LF-TENS vs HF-TENS, rat 185
transdermal drug delivery, ibuprofen 195
trauma, capillary blood sampling 301
Tyrrell, PJ 313

Urban, L 247

van den Hout, JHC 335
van den Hout, MA 335
Van Houdenhove, B 225
Veyrat-Durex, C 291
Vigiletti, S 267
visceral pressure, IBS patients, gender differences in regional brain response 157
Vlaeyen, JWS 335
Voerman, VF 149
von Knorring, L 27

Walker, K 247
Washewna, HA 107
Watson, PJ 275
Weisenfeld-Hallin, Z 409
wind-up
inflammation, rat 97
NMDA receptor complex 5
Wu, W-P 409

Xu, X-J 409

Yarnitsky, D 221

Zahn, PK 111
Zhao, M 83
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European Federation of Chapters of the International Association for the Study of Pain (EFIC)

EFIC was formed by the Presidents of the European Chapters of the International Association for the Study of Pain (IASP) at a meeting held during the 7th World Congress on Pain in Paris in August 1993.

Aims
These are in general those of IASP, i.e. to promote research, education and the clinical management of pain. The specific aim is to create a forum for European collaboration on pain issues and to encourage communication at a European level between IASP Chapters, and also with other bodies interested or involved in the fields of pain research and therapy such as the European societies or federations of medical specialties (anaesthesiology, neurology, headache, palliative care etc.), institutions of the European Community, European and national educators and legislators.

Constitution
The affairs of EFIC are conducted by its Council, which consists of the Presidents of the European IASP Chapters, and five elected officers who form the Executive Committee. The Council meets once a year while the Committee manages affairs between meetings. EFIC is being established as a charitable foundation in Belgium.

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EFIC’s Position in Relation to IASP
The bylaws of the IASP (section V) provide that national pain societies and associations may constitute Chapters of the IASP in their country. EFIC acts as a European grouping of these, so that they will benefit from the wider perspectives offered by a transnational organization while allowing for the sociocultural diversity of European nations and regions. Many of the societies have a large percentage of members who are not members of the IASP; they are nonetheless members of EFIC and will benefit from the wider perspectives offered by a transnational organization.

Specific Programmes
EFIC co-operates in the organization of Congresses, such as that in Verona, Italy, in May 1995 and that in Barcelona, Spain, in September 1997. It produces newsletter which is distributed by the Chapters to all their members and is involved with the production of the European Journal of Pain. Under its auspices, task forces are working on aspects of pain research and management, and their findings will be used to improve education and training throughout Europe.
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