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European Journal of Pharmacology 473 (2003) 27–33
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Antihyperalgesic effect of levetiracetam in neuropathic pain models in rats

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Received 27 February 2003; received in revised form 28 April 2003; accepted 26 May 2003

Abstract

The purpose of this study was to assess, in rats, the antinociceptive effects of levetiracetam (i.p.), a novel antiepileptic drug, in acute pain tests and in two models of human neuropathic pain. Levetiracetam and carbamazepine contrasted morphine by an absence of effect in the tail flick and hot plate tests. In normal rats, carbamazepine failed to modify the vocalisation thresholds to paw pressure whereas levetiracetam slightly increased this threshold only at the highest dose (540 mg/kg) for 30 min. In the sciatic nerve with chronic constriction injury model, the highest dose of levetiracetam (540 mg/kg) and carbamazepine (30 mg/kg) reversed the hyperalgesia. In streptozocin-induced diabetic rats, levetiracetam dose-dependently increased the vocalization threshold from 17 to 120 mg/kg reaching a similar effect as 10 mg/kg of carbamazepine. These results indicate that levetiracetam induces an antihyperalgesic effect in two models of human neuropathic pain, suggesting a therapeutic potential in neuropathic pain patients.

Keywords: Antiepileptic; Analgesia; Neuropathic pain; Antiepileptic drug; Levetiracetam

1. Introduction

The early report of Blom on the analgesic effect of carbamazepine in patients with trigeminal neuralgia (Blom, 1962) stimulated the use of antiepileptic drugs for the treatment of neuropathic pain syndromes. The clinical efficacy of antiepileptic drugs was later confirmed by several placebo-controlled clinical trials (Tremont-Lukats et al., 2000; Ross, 2000; Backonja, 2000) and a meta-analysis (McQuay et al., 1995). To date, antiepileptic drugs are used primarily in the treatment of trigeminal neuralgia and diabetic or postherpetic neuropathies. They have been reported to be more effective than placebo in several clinical trials (Nicol, 1969) but their use appears associated with several unwanted adverse effects such as drowsiness, dizziness, nausea and skin rash (Rull et al., 1969; Wilton, 1974; Lindstrom and Lindblom, 1987; Tremont-Lukats et al., 2000). Thus, there remains a need for novel antiepileptic drugs with improved tolerability, despite the greater safety margin of certain newly marketed antiepileptic drugs, e.g. gabapentin, for treating neuropathic pain syndromes (Rosenberg et al., 1997; Attal et al., 1998; Solaro et al., 1999, 2000).

The antinociceptive effect of antiepileptic drugs has also been reported in preclinical studies. For instance, it has been shown that carbamazepine is effective in a rat trigeminal pain model, which is produced by stimulation of the tooth pulp with bradykinin (Foong and Satoh, 1983, 1984a,b, 1985; Satoh and Foong, 1983). Likewise, carbamazepine, as well as gabapentin, were shown to possess antinociceptive effects in animal models of continuous pain (Bianchi et al., 1995; Nakamura-Craig and Follenfant, 1995; Singh et al., 1996; Field et al., 1997; Chapman et al., 1998; Jones and Sorkin, 1998; Pan et al., 1999; Kayser and Christensen, 2000).

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doi:10.1016/S0014-2999(03)01933-2

Levetiracetam (KEPPRA®) is a novel antiepileptic drug with a pharmacological profile distinct from other antiepileptic drugs. Levetiracetam lacks anticonvulsant activity in acute animal seizure models, like the maximal electroshock and pentylenetetrazol models, whereas it induces a potent seizure protection and antiepileptogenic activity in animal models of chronic epilepsy (Klitgaard et al., 1998). This particular profile stimulated the present study to explore whether levetiracetam possesses antinociceptive activity in animal models of chronic versus acute pain models since antiepileptic drugs display activity primarily in neuropathic pain conditions (Tremont-Lukats et al., 2000). Thus, the activity of levetiracetam and carbamazepine was compared in rats in the chronic constriction injury and streptozocin-induced diabetes models.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats (Charles River and IFFA Credo, France) initially weighing 200–250 g, were housed four or five per cage under standard laboratory conditions and allowed food and water ad libitum.

2.2. Nociceptive test procedures

2.2.1. Thermal acute pain tests

2.2.1.1. Hot plate test. Rats were placed on a metal plate (20 cm in diameter), the temperature of which was maintained at 56 ± 0.5 °C. The reaction time necessary to elicit licking of the forepaws was measured and considered as the nociceptive threshold. A cutoff time of 20 s was used.

2.2.1.2. Tail flick test. A radiant heat source (100 W bulb lamp) calibrated at 16.5 V was focused on the distal half of the tail of the rat. The reaction time of each animal to flick its tail was measured as the nociceptive threshold. A cutoff time of 12 s was used.

2.2.2. Mechanical pain test

2.2.2.1. The paw pressure test. Nociceptive thresholds, expressed in grams, were measured with an Ugo Basile analgesimeter (Bioseb) by applying an increasing pressure to the right hind paw of unrestrained rats until a squeak (vocalization threshold) and/or a struggle was obtained (a cutoff level of 750 g was applied).

2.3. Chronic neuropathic pain models

2.3.1. Chronic constriction injury model

Preliminary vocalization thresholds to paw pressure (the mean of two consecutive stable values which do not differ more than 10%) were determined before surgery. Ligatures were applied around the common sciatic nerve of the right hind paw, according to the method detailed by Bennett and Xie (Bennett and Xie, 1988; Attal et al., 1990). Briefly, rats were anesthetized by intraperitoneal (i.p.) administration of sodium pentobarbital (50 mg/kg) and four chromic gut (5-0) ligatures were tied loosely (with about 1-mm spacing) around the common sciatic nerve. The nerve was only constricted slightly such that circulation through the epineural vasculature was not interrupted. Nociceptive thresholds to paw pressure in rats with chronic constriction injury were determined 2 weeks after surgery and served as pre-injection control values. Only animals with at least 15% decrease of vocalization thresholds were selected.

2.3.2. Diabetic model

Preliminary thresholds to paw pressure (the mean of two consecutive stable values which do not differ more than 10%) were determined before diabetes induction. Animals were intraperitoneally (i.p.) injected with streptozocin (75 mg/kg) (Zanosar*, Pharmacia, France) dissolved in distilled water, according to the method described by Courteix et al. (1993). Diabetes was confirmed one week later by measurement of tail vein blood glucose levels with Ames Dextrostix and a reflectance colorimeter (Ames Division, Miles Laboratories, France). Blood samples were obtained from the tail by pinprick and only animals with a final blood glucose level >14 mM were considered diabetic. This model has been shown to be sensitive to antidepressants, morphine, and several other putative antinociceptive agents such as antagonists of cholecystokinin B receptors (Courteix et al., 1994; Coudore-Civiale et al., 2000). Nociceptive thresholds to paw pressure in diabetic rats were determined 3 weeks after diabetes induction and served as pre-injection control values. Only animals with at least 15% decrease of vocalization thresholds were selected.

2.4. Testing session

The blind experiments were performed in a quiet room by a single experimenter. Specific control groups were used for each experimental series. These were monitored by a local ethical committee. Since a certain amount of suffering might result from these experiments, the guidelines of the Committee for Research and Ethical Issue of the I.A.S.P. (Zimmermann, 1983) were followed. Great care was taken, particularly with regard to housing conditions, to avoid or minimize discomfort to the animals.

2.5. Pharmacological experiments

Rats were randomly injected with the different drugs or saline. Each experiment was performed with different groups of rats.

Table 1
Effect of levetiracetam, carbamazepine and morphine in the hot plate and tail flick tests

Compound	Dose (mg/kg)	Hot plate latency (s)	Tail flick latency (s)
Levetiracetam	0	6.1 (0.2)	1.4 (0.3)
	54	5.8 (0.3)	2.1 (0.5)
	170	6.4 (0.5)	1.2 (0.2)
	540	5.9 (0.7)	2.3 (0.5)
	950	7.8 (1.1)	2.2 (0.6)
Carbamazepine	0	6.0 (0.7)	2.1 (0.7)
	10	6.5 (0.6)	1.2 (0.2)
	30	8.4 (0.7)	1.7 (0.2)
Morphine	0	6.2 (0.5)	3.1 (0.5)
	6	7.9 (0.8)	6.5 (1.1)[a]
	12	15.1 (1.9)[b]	8.0 (0.7)[b]

Results are expressed in terms of means, with S.E.M. in parentheses.
[a] $P<0.05$.
[b] $P<0.01$.

2.5.1. Experiment 1: effect of levetiracetam in thermal acute pain tests

2.5.1.1. Hot plate and tail flick tests. Three experimental series were performed. In the first, rats received an i.p. administration of vehicle (saline) or levetiracetam (54, 170, 540 and 950 mg/kg) and were tested 30 min afterwards. In the second, rats received an i.p. injection of vehicle (saline) or morphine (6 and 12 mg/kg) and were submitted to the test 30 min later. In the third, rats received an i.p. injection of vehicle (hydroxypropyl methylcellulose, 1%) or carbamazepine (10 and 30 mg/kg) and were submitted to the test 30 min later. $N=8$ in each treated group.

2.5.2. Experiment 2: effect of levetiracetam in a mechanical acute pain test

Preliminary thresholds to paw pressure (the mean of two consecutive stable values which do not differ more than 10%) were determined. Rats ($n=8$) received i.p. vehicle (saline), levetiracetam (17, 54, 92.5, 120, 170 and 540 mg/kg) or carbamazepine (10 and 30 mg/kg). They were submitted to the paw pressure test between 0.25 and 3 h after the injection.

2.5.3. Experiment 3: effect of levetiracetam in chronic pain models

2.5.3.1. CCI model. After determining pre-injection control values to the ligated paw pressure test, rats ($n=8$) received i.p. vehicle (saline), levetiracetam (17, 54, 92.5, 120, 170 and 540 mg/kg) or carbamazepine (10 and 30 mg/kg). They were submitted to the paw pressure test between 15 and 180 min after this injection.

2.5.3.2. Diabetic model. After determination of a pre-injection control value to the paw pressure test (right paw), rats ($n=8$) received i.p. vehicle (saline), levetiracetam (17, 54, 92.5 and 120 mg/kg) or carbamazepine (10 and 30 mg/kg). They were submitted to the paw pressure test between 15 and 180 min after this injection.

2.6. Expression of results and statistical analysis

Results are expressed as means ± S.E.M. (hot plate or tail flick latency expressed in seconds and vocalization threshold expressed in grams). Statistical comparisons were made by a one-way analysis of variance (ANOVA) followed by Dunnett's test for the hot plate and tail flick mean latency data. A two-way ANOVA followed by Dunnett's test was used to examine the time course after the various treatments

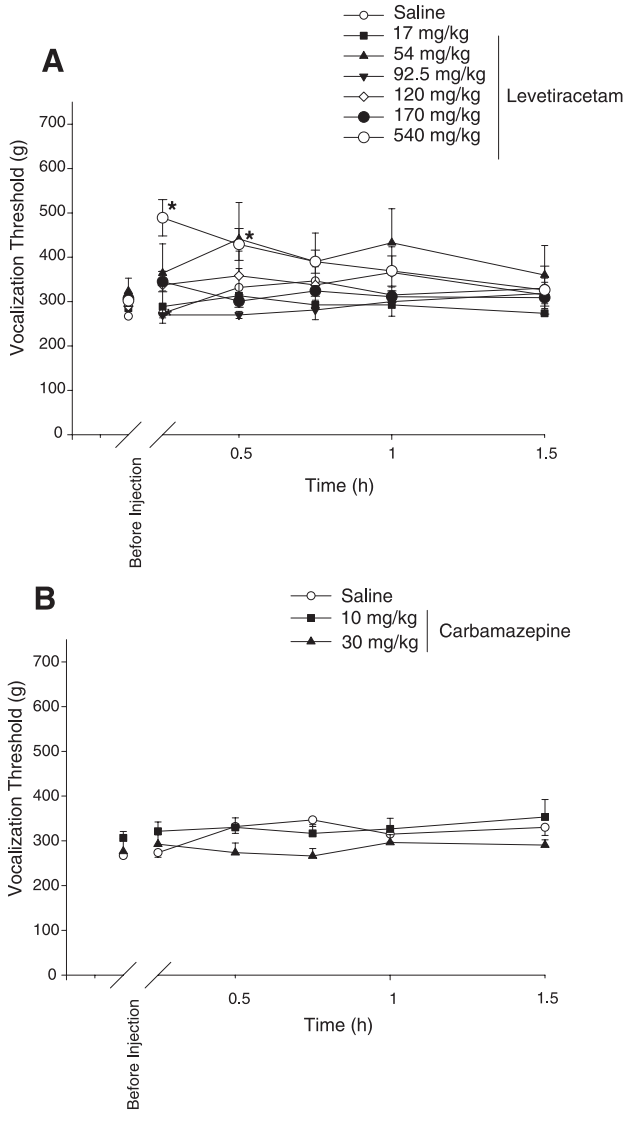

Fig. 1. Effect of levetiracetam (17, 54, 92.5, 120, 170 and 540 mg/kg, i.p.) (A) and carbamazepine (10 and 30 mg/kg, i.p.) (B) on the vocalisation response to a paw pressure in normal rats. Results are expressed by the time-course curve of the means ± S.E.M. vocalisation threshold expressed in grams. *$P<0.05$ versus time-matched control saline treated value, Dunnett's test.

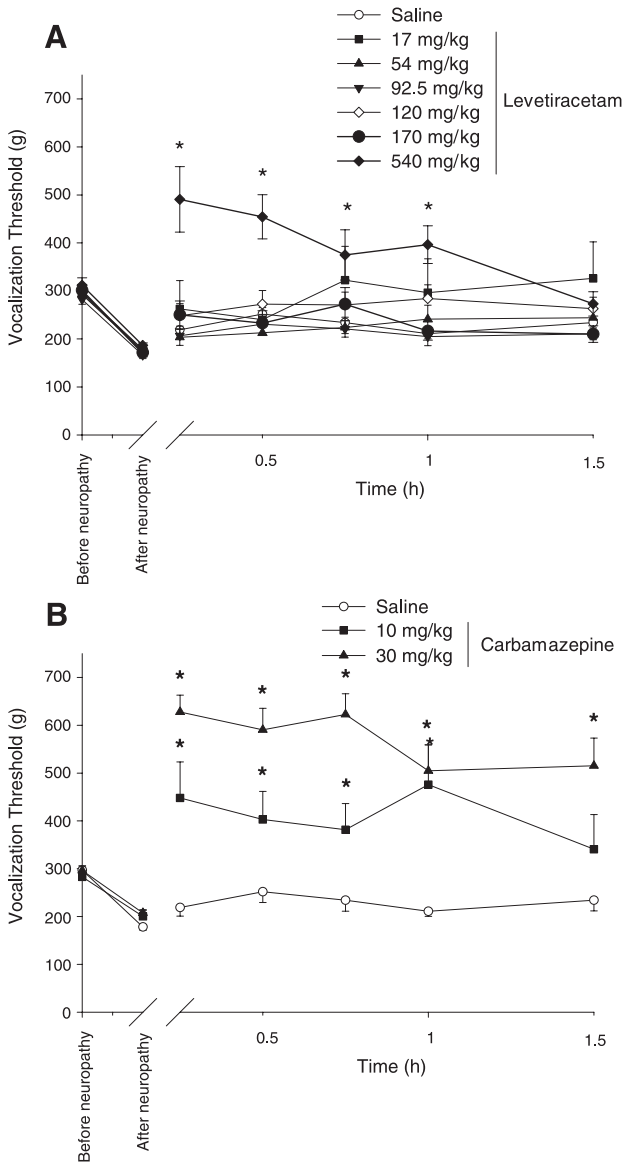

Fig. 2. Effect of levetiracetam (17, 54, 92.5, 120, 170 and 540 mg/kg, i.p.) (A) and carbamazepine (10 and 30 mg/kg, i.p.) (B) on the vocalisation response to a paw pressure in mononeuropathic rats. Results are expressed by the time-course curve of the means ± S.E.M. vocalisation threshold expressed in grams. *$P < 0.05$ versus time-matched control saline treated value, Dunnett's test.

in the paw pressure test. In all cases, the significance level was 0.05.

2.7. Drugs

Levetiracetam (UCB Pharma, Belgium) and morphine sulfate (FEDERA) were dissolved in a saline solution. Carbamazepine was dissolved in hydroxypropyl methylcellulose (1%). Drugs were injected in a total volume of 5 ml/kg (hot plate and tail flick) or 1 ml/kg (paw pressure test in normal rats, chronic constriction injury and diabetic models).

3. Results

The experimenter did not observe any overt behavioral modification or impairment in motor performance in the drug-treated animals in any of the experiments.

3.1. Experiment 1: effect of levetiracetam in thermal acute pain tests

3.1.1. Hot plate test

Levetiracetam (54, 170, 540 and 950 mg/kg) and carbamazepine (10 and 30 mg/kg) administered i.p. did not modify the hot plate latency. In contrast, morphine significantly increased the latency to react, with the highest dose

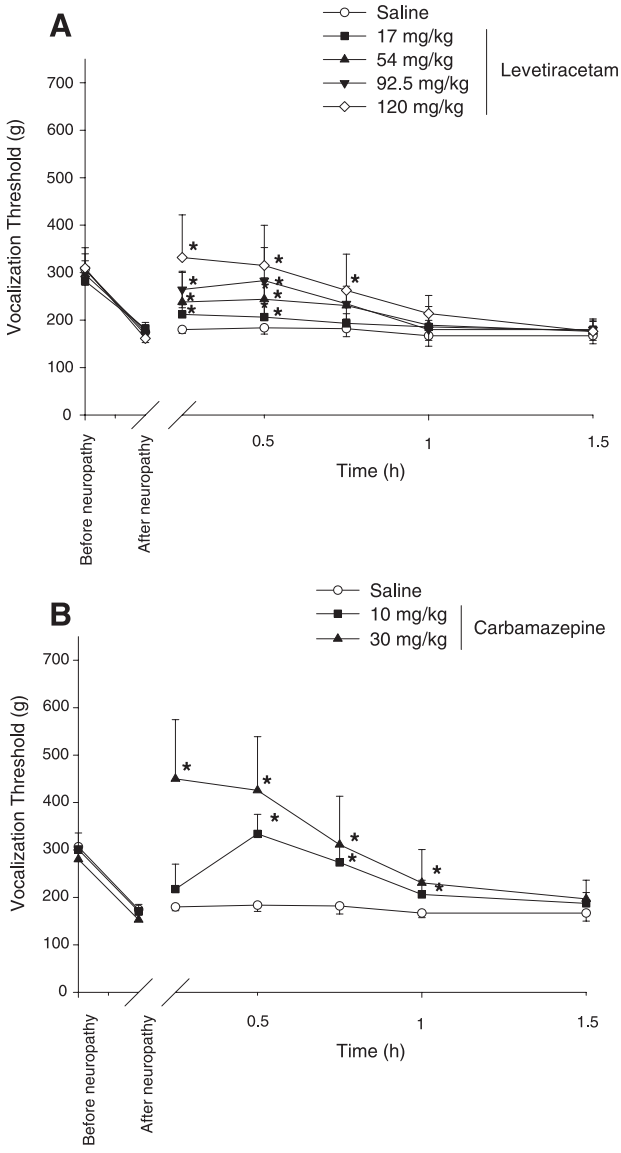

Fig. 3. Effect of levetiracetam (17, 54, 92.5 and 120 mg/kg, i.p.) (A) and carbamazepine (10 and 30 mg/kg, i.p.) (B) on the vocalisation response to a paw pressure in diabetic rats. Results are expressed by the time-course curve of the means ± S.E.M. vocalisation threshold expressed in grams. *$P < 0.05$ versus time-matched control saline treated value, Dunnett's test.

of 12 mg/kg producing significant difference from controls (Table 1).

3.1.2. Tail flick test

None of the doses of levetiracetam and carbamazepine modified the tail flick latency. In contrast, both doses of morphine induced a significant increase in tail flick latency (Table 1).

3.2. Experiment 2: effect of levetiracetam in mechanical acute pain test

As observed in Fig. 1A and B, levetiracetam (17, 54, 92.5, 120 and 170 mg/kg, i.p.) and carbamazepine (10 and 30 mg:kg, i.p.) did not modify the vocalization threshold to hind paw pressure in healthy rats. Levetiracetam (540 mg/kg) induced a slight but significant increase of the vocalization thresholds 15 and 30 min after its injection.

3.3. Experiment 3: effect of levetiracetam in chronic pain models

3.3.1. Chronic constriction injury model

A clear antihyperalgesic effect, characterized by a significant increase in the vocalization threshold 15–60 min after administration of levetiracetam, was obtained at the highest dose tested (540 mg/kg) (Fig. 2A). Carbamazepine induced a significant increase of the vocalization threshold 15–60 min after 10 mg/kg i.p. and from 15 to 90 min after 30 mg/kg (Fig. 2B).

3.3.2. Diabetic model

All four doses of levetiracetam (17, 54, 92.5 and 120 mg/kg, i.p.) significantly increased the vocalization threshold to hind paw pressure (Fig. 3A). This was observed for 30 min after administration of 17, 54 and 92.5 mg/kg and for 45 min after administration of 120 mg/kg. Carbamazepine also significantly increased the vocalization thresholds for 60 min at the two doses tested (10 and 30 mg/kg, i.p.) (Fig. 3B).

4. Discussion

The main finding of the present study was the discovery that levetiracetam induces an aetiology-dependent antihyperalgesic effect in rat models of neuropathic pain. Interestingly, levetiracetam was more potent in the diabetic than in the chronic constriction injury model, which is in line with the view that different pathophysiological mechanisms are involved in the two conditions. This may suggest that levetiracetam could act preferentially in specific neuropathic pain conditions in man.

Levetiracetam was devoid of activity, even at a dose of 950 mg/kg, in healthy rats submitted to an acute noxious thermal (tail flick and hot plate tests), in which morphine was effective. In similar conditions, carbamazepine was also devoid of activity at 10 and 30 mg/kg. In the paw pressure test, however, levetiracetam was induced a small, albeit significant, effect at a dose of 540 mg/kg. This effect was observed up to 30 min after injection. In the same conditions, carbamazepine was found to be inactive at 10 and 30 mg/kg. These results are in accordance with previous findings in animal studies showing a general lack of efficacy of most antiepileptic drugs in acute pain conditions. Indeed, lamotrigine, felbamate, gabapentin, carbamazepine and phenytoin were all reported to be inactive in the tail flick test (Hunter et al., 1997). This has been confirmed in several other studies testing carbamazepine and gabapentin in different acute pain tests (Shimoyama et al., 1997; Mashimoto et al., 1998). The only exception was a recent report by Ipponi et al. (1999) showing that tiagabine reveals antinociceptive effects in the hot plate test.

The reported lack of efficacy of antiepileptic drugs in these acute pain models has limited their preclinical examination in these conditions. On the contrary, positive results generally involve animals with sustained or chronic pain. In 44 studies non-exhaustively referenced between 1982 and 2001, only 4 were done with acute pain tests. Other studies have used acute pain stimulation but in chronic pain models. One example is a study reporting the efficacy of gabapentin in a test where an acute thermal pain stimulus was applied after inducing thermal hyperalgesia in animals (Jun and Yaksh, 1998).

The present study observed that both levetiracetam and carbamazepine possess significant antihyperalgesic activity against sustained neuropathic pain. This is in accordance with several reports showing activity of AEDs in different neuropathic pain models in the rat. For example, a reduction of hyperalgesia and allodynia by felbamate has been shown in the chronic constriction injury model (Imamura and Bennett, 1995). Furthermore, carbamazepine and gabapentin were shown to be effective against allodynia in the 'Chung' model after both systemic (Chapman et al., 1998; Abdi et al., 1998; LaBuda and Fuchs, 2000) and intrathecal administration (Hwang and Yaksh, 1997; Chen et al., 2000).

Our study also revealed a distinct activity of levetiracetam and carbamazepine in the two models used. Thus, carbamazepine appears to be equally active in both models at the two doses of 10 and 30 mg/kg whereas levetiracetam was more potent in the diabetic model (first active dose was 17 mg/kg) than in the chronic constriction injury model (first active dose was 540 mg/kg). These data suggest that levetiracetam may have distinct effects according to the etiology of the neuropathic pain syndromes. This could be of clinical importance when treating neuropathic pain conditions. Indeed, McQuay (2002) has calculated number needed to treat (NNT) for at least 50% pain relief for antiepileptic drugs and observed a NNT of 2.7 in the treatment of diabetic neuropathy and a NNT of 3.2 in the treatment of postherpetic neuralgia. This suggests an ab-

sence of any clear difference in the magnitude of the effect of currently used AEDs (e.g. carbamazepine and gabapentin) among different sustained pain syndromes. Levetiracetam may differ in this respect and could represent the first antiepileptic drug with specific activity according to the neuropathic pain syndrome.

This specificity could relate to the original pharmacological profile and mechanism of action of levetiracetam (Klitgaard et al., 1998; Margineanu and Klitgaard, 2002). Levetiracetam is devoid of anticonvulsant activity in classical seizure models (Klitgaard et al., 1998). This contrast with a potent protection in animal models of chronic epilepsy, involving genetically determined epileptic (Gower et al., 1995) and kindled animals (Löscher and Hönack, 1993; Klitgaard et al., 1998). The selective action in animals with "epileptogenic brains" together with a high safety margin markedly distinguish levetiracetam from classical and other new antiepileptic drugs which have nearly equipotent effects in normal and genetic/kindled animals (Klitgaard et al., 1998).

In the diabetic model, levetiracetam is effective in a range of doses (17–120 mg/kg, i.p.) comparable to those effective in epilepsy models (Klitgaard et al., 1998). This suggests that levetiracetam can be used in chronic pain patients at the dose used for antiepileptic treatment. In the same model and using the same test Nakamura-Craig and Follenfant (1995) showed that lamotrigine (10, 20 and 40 mg/kg, p.o.) and carbamazepine (40 and 80 mg/kg, p.o.) were effective, but not phenytoin (20–100 mg/kg, p.o.). On the other hand, Field et al. (1999) demonstrated the antiallodynic effect of gabapentin in this model. In the partial or complete nerve ligature models, results obtained with other antiepileptic drugs are also conflicting. In fact, Hunter et al. (1997) did not find any effect of carbamazepine and phenytoin on tactile and cold allodynia, and lamotrigine and felbamate were only effective on cold allodynia whereas gabapentin was effective on the two tests. An antiallodynic effect of gabapentin was observed after intrathecal or systemic administration (Hwang and Yaksh, 1997; Abdi et al., 1998; Pan et al., 1999; Chen et al., 2000).

The mechanism of action of levetiracetam does not involve the main cellular mechanisms associated with classical antiepileptic drugs (Margineanu and Klitgaard, 2002). However, recent findings indicate that levetiracetam reduces high voltage-activated Ca^{2+} currents in rat hippocampus (Niespodziany et al., 2001), specifically the N-type calcium channels (Lukyanetz et al., 2002). The possible mechanism by which levetiracetam exerts antihyperalgesic effects may actually relate to its blocking of N-type calcium channels (Lukyanetz et al., 2002). These channels appear essential for the development of neuropathic pain (Saegusa et al., 2001) and N-type calcium channel blockers have been shown to reduce hyperalgesia (Malmberg and Yaksh, 1994) and allodynia (Yaksh et al., 1995). Ziconotide, a selective N-type calcium channel blocker, has been demonstrated to be effective in postoperative as well as in neuropathic pain in humans (Brose et al., 1997).

In summary, the findings of the present study suggest that levetiracetam may possess a therapeutic potential for the treatment of neuropathic pain in man. The antihyperalgesic effect observed with levetiracetam appeared from a dose of 540 mg/kg in the chronic constriction injury model and at a dose of 17 mg/kg in the diabetic rat model. This indicates that levetiracetam possesses efficacy in both models but exerts its most potent action in the diabetic rat model. The higher dose tested, i.e. 540 mg/kg, was devoid of behavioural and psychotomimetic effects but induced a small, albeit significant, analgesic effect in healthy rats submitted to a paw pressure test. This dose was approximately two times lower than the TD50 value for impairment of rotarod performance in rats, i.e. 1060 mg/kg (Klitgaard et al., 1998). This reveals a wide safety margin for levetiracetam which appears to be of paramount importance, since it is established that first-generation antiepileptic drugs, like carbamazepine for example, produce adverse effects at therapeutic doses (Ross, 2000). In conclusion, these results suggest that levetiracetam might provide therapeutic effects at well-tolerated doses in patients suffering from neuropathic pain.

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