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Antinociceptive efficacy of lacosamide in a rat model for painful diabetic neuropathy

Bettina Beyreuther [a,*], Noëlle Callizot [b], Thomas Stöhr [a]

[a] Schwarz BioSciences GmbH, Department Pharmacology/Toxicology, Alfred-Nobel-Str. 10, 40789 Monheim, Germany
[b] Neurofit, Parc d'Innovation, Rue J Sapidus, 67400 Illkirch, France

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Abstract

Lacosamide was tested in the streptozotocin rat model of diabetic neuropathic pain in comparison to drugs which are commonly used in the treatment of diabetic neuropathic pain, i.e. antidepressants and anticonvulsants. In diabetic rats, lacosamide attenuated cold (10, 30 mg/kg, i.p.), warm (3, 10, 30 mg/kg, i.p.) and mechanical allodynia (30 mg/kg, i.p.). Streptozotocin-induced thermal and mechanical hyperalgesia were reduced by lacosamide at doses of 10 and 30 mg/kg, i.p. Morphine (3 mg/kg) showed similar efficacy on allodynia and hyperalgesia. Amitriptyline (10 mg/kg), venlafaxine (15 mg/kg), levetiracetam (180 mg/kg) and pregabalin (100 mg/kg) exhibited significant effects on thermal allodynia and mechanical hyperalgesia. Only treatment with amitriptyline (30 mg/kg, i.p.) produced full reversal of thermal allodynia comparable to lacosamide. Lamotrigine (45 mg/kg, i.p.) had no effect on both behavioral readouts. Lacosamide's potency and efficacy in reversing pain behavior might be due to its new, yet unknown mechanism of action.

Keywords: Allodynia; Hyperalgesia; Anticonvulsant drug; Diabetic neuropathy; Neuropathic pain; Lacosamide

1. Introduction

The most common precipitating cause of neuropathic pain is diabetes particularly where blood glucose control is poor (Morley et al., 1984). Approximately 20–24% of diabetes patients experience neuropathic pain (Schmader, 2002). Diabetic neuropathic pain can occur either spontaneously, as a result of exposure to normally mildly painful stimuli (i.e. hyperalgesia), or to stimuli that are not normally perceived as being painful (i.e. allodynia) (Brown and Asbury, 1984).

The cause of painful diabetic neuropathy, like other neuropathic pain states, is still unclear (Calcutt, 2002; Sommer, 2003). However, behavioral and physiological studies have revealed indices of sensory dysfunction in animal models of diabetes that include hyperalgesia to mechanical and noxious chemical stimuli and allodynia to light touch.

Currently, the three major classes of drugs recognized as being effective in neuropathic pain treatment are antidepressants, anticonvulsants and opioids (Galer, 1995; McQuay et al., 1996; Sindrup and Jensen, 1999). There remains a clear unmet medical need for drugs that provide greater efficacy/responder rates, with reduced side effects commonly experienced with current therapies.

A number of agents that are effective in the treatment of patients suffering from diabetic neuropathic pain have been shown to partially alleviate mechanical hyperalgesia in the streptozotocin-induced diabetes animal model of painful diabetic neuropathy (Courteix et al., 1994), the most commonly used model in the field of diabetic pain research (Fox et al., 1999).

Lacosamide (*R*-2-acetamido-*N*-benzyl-3-methoxypropionamide, SPM 927, also formerly called harkoseride or ADD 234037) has been shown to be active in animal models for neuropathic and inflammatory pain at doses of 8 mg/kg to 40 mg/kg i.p. (Morrow et al., 2001; Stohr et al., 2006). In addition, oral lacosamide produced analgesia in an open label

* Corresponding author. Tel.: +49 2173 481128; fax: +49 2173 481574.
E-mail address: bettina.beyreuther@schwarzpharma.com (B. Beyreuther).

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study of 25 adult human subjects with resistant neuropathic pain (McCleane et al., 2003).

In the present study we examined the effects of lacosamide in comparison to morphine, amitriptyline, venlafaxine, lamotrigine, levetiracetam and pregabalin on allodynia and hyperalgesia in the streptozotocin-induced rat model of diabetic neuropathic pain. All doses of the drugs were chosen according their potency in published pain models. In a set of preliminary control experiments the best time points after streptozotocin-treatment for measurement of allodynia and hyperalgesia were identified. To have a broad description of pain behavior in the streptozotocin model we established assessment of five different pain qualities, i.e. cold, warm and tactile allodynia as well as thermal and mechanical hyperalgesia.

2. Materials and methods

2.1. Animals

All experiments were carried out in accordance with the European Community guidelines for the use of experimental animals, and in accordance to the institutional guidelines of Neurofit and were approved by the responsible institutional committee.

Six week old, male Sprague–Dawley rats (body weight 200–225 g, Janvier, France) were group-housed ($n=5$ per cage) in a room with controlled temperature (21–22 °C), and a reversed light–dark cycle (12 h/12 h), and they had access to food and water ad libitum.

2.2. Development of diabetes in the rat

Diabetes was induced by intravenous (i.v.) injection of buffered solution of streptozotocin (55 mg/kg body weight) in freshly prepared 0.1 mol/l citrate buffer (pH 4.5) in the surgically denuded left saphena magna on day 0. Control animals received an equivalent volume of citrate buffered solution. Blood glucose levels were checked before each phase of behavioral testing on days 10 and 21. Animals with blood glucose levels <14.3 mmol/l (260 mg/dl) were immediately excluded from the study. In this study care was taken during the induction of diabetes in order to avoid illness that was too severe. The body weight and general health was monitored and all animals demonstrated appropriate behavior during the entire study.

2.3. Evaluation of the effect of compounds on nociception

In the first round of experiments the streptozotocin-treated diabetic rats were randomized to five experimental groups ($n=15$ per group) which received the following treatments on the days of pain assessment (days 10 and 21 post-streptozotocin treatment): i.p. injection of saline (vehicle); i.p. injection of 3 mg/kg lacosamide; i.p. injection of 10 mg/kg lacosamide; i.p. injection of 30 mg/kg lacosamide; s.c. injection of 3 mg/kg morphine. The non-streptozotocin-treated control group (control) received an i.p. injection of saline 30 min prior to the pain assessment. Lacosamide and morphine were injected between 30 and 45 min prior to the implementation of behavioral tests, respectively. In addition, four groups of naïve rats ($n=5$ per group) were also used in order to test whether or not the different doses of lacosamide altered the behavioral performance of non-diabetic animals in comparison to the vehicle.

For the testing of the five reference compounds the groups (10–12 animals per group) were divided in three series of experiments each postponed 1 week. Each series was composed of 3–4 animals for each group. Control citrate group (control) received i.p. injection of vehicle (0.25% methylcellulose) 30 min prior to the pain assessment. Amitriptyline, lamotrigine, venlafaxine, pregabalin and levetiracetam were injected (i.p.) 30 to 45 min prior to the implementation of behavioral tests.

Tests for allodynia (cold bath and warm plate at 38 °C) were performed on day 10 after induction of diabetes with streptozotocin and tests for hyperalgesia (paw pressure and hot plate at 52 °C) and dynamic mechanical allodynia (brushing test) were performed on day 21.

2.4. Evaluation of allodynia and hyperalgesia

2.4.1. Cold bath test (thermal allodynia)

Animals were placed on an ice platform submerged approximately 1 cm below the surface of cold water (4 °C), such that the hairy and glabrous skin of the animal feet were in contact with the cold water. The latency before the first reaction (licking, moving the paws, little leaps) was recorded with a cutoff time of 30 s.

2.4.2. Hot plate test (thermal allodynia and hyperalgesia)

Animals were placed into a glass cylinder on a hot plate (Bioblock, France) adjusted to 38 °C (thermal allodynia) or 52 °C (thermal hyperalgesia). The latency of the first reaction was recorded (licking, moving the paws, little leaps or a jump to escape the heat) with a cutoff time of 30 s.

2.4.3. Paw pressure withdrawal test (mechanical hyperalgesia)

Nociceptive flexion reflexes were quantified using the Randall–Selitto paw pressure device (Bioseb, France), which applied a linearly increasing mechanical force to the dorsum of the rat's hind paw. The mechanical nociceptive threshold was defined as the force at which the rat withdrew its paw. The cut off pressure was set to 250 g.

2.4.4. Brushing test (dynamic allodynia)

The hair on the legs, flanks, and lower back was sequentially brushed with a cotton-tipped applicator using an oscillating motion (rate of 1–2/s for 30 s). Brushing was done with no more force than required to move the applicator through the hair such that only the pelage was disturbed (Loomis et al., 2001). The number of reactions during the brushing was counted.

2.5. Data analyses

Comparisons of groups of behavioral data and body weight at each individual time point were conducted using Analysis of

Variance (ANOVA) followed by post-hoc analysis (Dunnett's test). Results were presented as means and standard error of the mean (S.E.M.) and analyses revealing P-values ≤ 0.05 were deemed to be statistically significant.

2.6. Drugs

Lacosamide, pregabalin, levetiracetam and lamotrigine were synthesized at Schwarz BioSciences GmbH. Amitriptyline hydrochloride was obtained from Sigma (Germany), venlafaxine from TRC (Canada) and morphine sulfate from Francopia (France). Lamotrigine was solved in 0.25% methylcellulose, the others drugs in saline. Streptozotocin was purchased from Sigma (France). Drug administrations were made in a volume of 10 ml/kg. Drug treatment given to each group was examined blind.

3. Results

3.1. Development of body weight and blood glucose levels in streptozotocin-treated rats

The streptozotocin-treated animals had 17% less body weight than the control rats on day 10 and 24% less on day 20 (Fig. 1). The average blood glucose levels of the streptozotocin-treated animals were 515 mg/dl on day 10 and 551 mg/dl on day 20 compared to 116 mg/dl of the control animals (Fig. 1). The general health was monitored strictly and even though the diabetic rats had a slightly reduced body weight all animals demonstrated normal behavior during the entire study.

3.2. Behavioral tests in naïve animals

The non-diabetic animals had no statistical significant effects on any of the pain parameters measured in comparison with control rats after treatment with 3, 10 and 30 mg/kg lacosamide (Fig. 2).

3.3. Thermal allodynia in the rat

Streptozotocin-treated animals which received the vehicle exhibited a very short mean threshold latency in the cold bath test (approximately 6 s) in contrast to control/vehicle-treated animals (>15 s) which indicates that cold allodynia developed (Fig. 3). Treatment of streptozotocin-animals with lacosamide 10 and 30 mg/kg (i.p.) and morphine 3 mg/kg (s.c.) produced statistically significant increases in the threshold latency ($P<0.05$, Dunnett's test). In fact, lacosamide at these doses produced full reversal of streptozotocin-induced cold allodynia. However, although the threshold latency was greater at the 3 mg/kg dose of lacosamide than that in vehicle-treated streptozotocin-animals, the difference was not statistically significant.

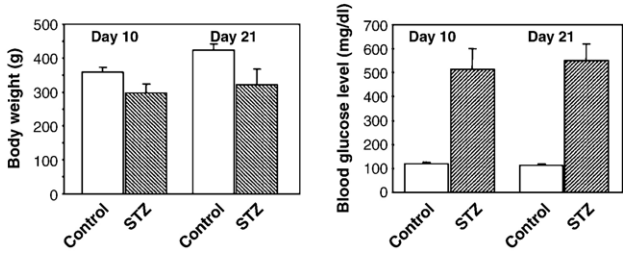

Fig. 1. Body weight and blood glucose levels in control ($n=15$) and streptozotocin (STZ)-treated rats ($n=75$) on days 10 and 20 after STZ-treatment.

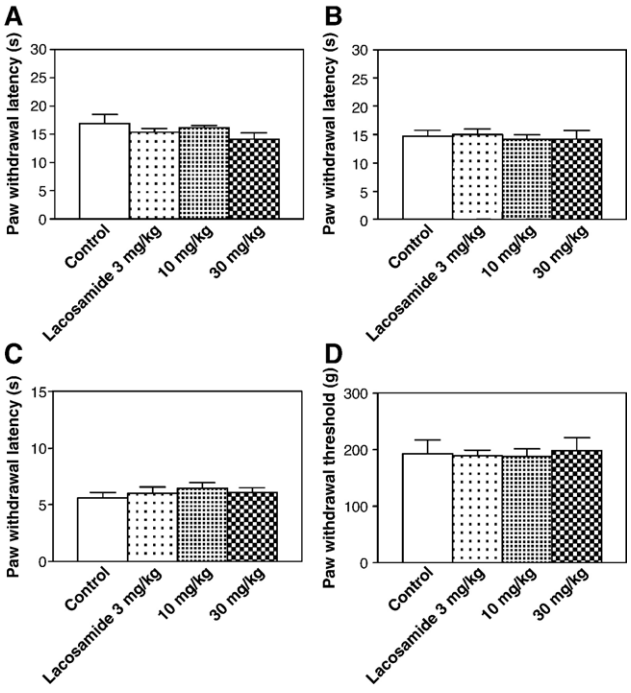

Fig. 2. Behavior of non-diabetic rats after treatment with lacosamide (3, 10 or 30 mg/kg i.p.). Figure A is the cold bath test, B the hot plate test at 38 °C, C the hot plate test at 52 °C and D the paw pressure test. Rats were tested between 30 and 45 min post drug. Data are presented as mean±S.E.M. from 5 animals/group. *$P<0.05$ Dunnett's test versus control/lacosamide-treated animals.

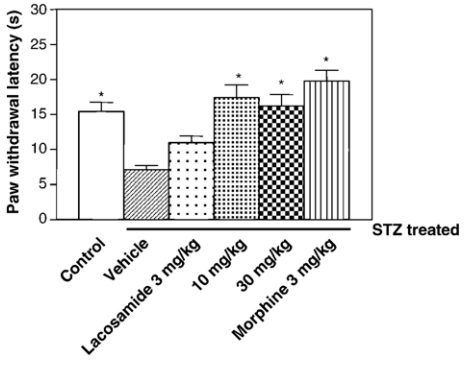

Fig. 3. Effect of lacosamide (i.p.) and morphine (s.c.) on paw withdrawal latency in the cold bath test on day 10 in streptozotocin (STZ)-treated rats. Animals were tested between 30 and 45 min post drug. Data are presented as mean±S.E.M. from 15 animals/group. *$P<0.05$ Dunnett's test versus streptozotocin/vehicle-treated animals.

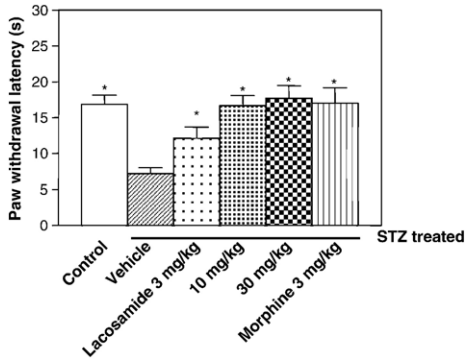

Fig. 4. Effect of lacosamide (i.p.) and morphine (s.c.) on paw withdrawal latency in the warm plate test at 38 °C on day 10 in streptozotocin (STZ)-treated animals. Rats were tested between 30 and 45 min post drug. Data are presented as mean±S.E.M. from 15 animals/group. *$P<0.05$ Dunnett's test versus streptozotocin/vehicle-treated animals.

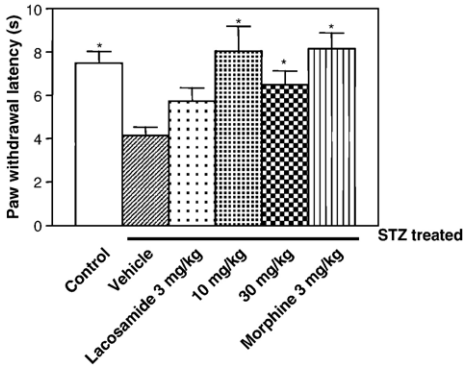

Fig. 6. Effect of lacosamide (i.p.) and morphine (s.c.) on paw withdrawal latency in the hot plate test at 52 °C on day 21 in streptozotocin (STZ)-treated animals. Rats were tested between 30 and 45 min post drug. Data are presented as mean± S.E.M. from 15 animals/group. *$P<0.05$ Dunnett's test versus streptozotocin/vehicle-treated animals.

Treatment with streptozotocin also induced thermal allodynia as evidenced by a significantly shorter threshold latency of streptozotocin/vehicle-animals in the warm plate (38 °C) test as compared to that of control/vehicle-treated animals ($P<0.05$, Dunnett's test) (Fig. 4). Treatment of streptozotocin-rats with lacosamide 3, 10 and 30 mg/kg and morphine 3 mg/kg produced statistically significant increases in the threshold latency ($P<0.05$, Dunnett's test), when compared with streptozotocin/vehicle-treated animals. Full reversal of thermal allodynia was seen with doses of 10 and 30 mg/kg lacosamide. Fig. 5 shows that thermal allodynia developed in response to streptozotocin treatment of the second cohort of rats since the threshold of the withdrawal latency of streptozotocin-animals in the warm plate (38 °C) test was significantly shorter than that of control animals ($P<0.05$, one way ANOVA). Treatment of streptozotocin-rats with amitriptyline at 10 and 30 mg/kg induced a significant ($P<0.05$, Dunnett's test) increase in the threshold of the paw withdrawal latency. At 30 mg/kg, amitriptyline produced full reversal of thermal allodynia. Streptozotocin-rats treated with levetiracetam at 60, 180 and 540 mg/kg showed reduced levels of thermal allodynia although no full reversal was observed with any of the doses tested. Similarly, venlafaxine displayed a significant reduction but no full reversal of thermal allodynia for the 3 tested doses (5, 15 and 45 mg/kg). Pregabalin showed a slight but significant alleviation at 100 mg/kg. Lamotrigine had no effect on the withdrawal latency in the warm plate at any concentration tested (5, 15 and 45 mg/kg).

3.4. Thermal hyperalgesia in the rat

Thermal hyperalgesia, hot plate 52 °C, developed since the paw withdrawal latency of streptozotocin/vehicle-treated animals was statistically significantly shorter than that of control/vehicle-treated animals ($P<0.05$, Dunnett's test; Fig. 6). Treatment of streptozotocin-rats with lacosamide 10 and 30 mg/kg and morphine 3 mg/kg, but not lacosamide 3 mg/kg, induced a statistically significant increase ($P<0.05$, Dunnett's test) in paw withdrawal latency compared to streptozotocin/vehicle-treated animals. Lacosamide at doses of 10 and 30 mg/kg produced full reversal of thermal hyperalgesia.

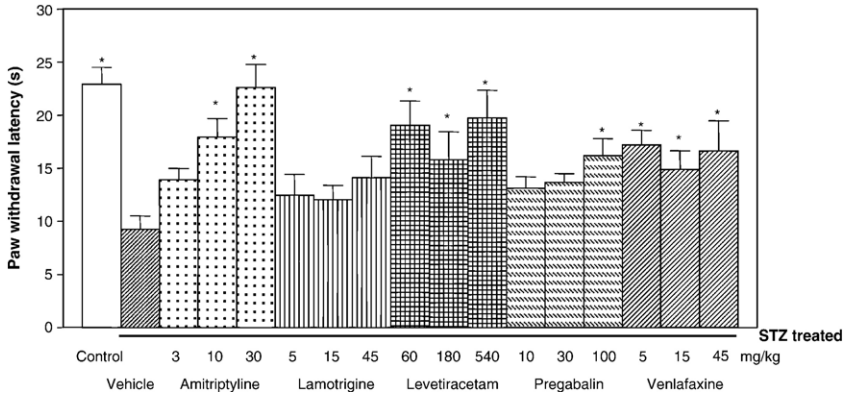

Fig. 5. Effect of amitriptyline, venlafaxine, lamotrigine, levetiracetam and pregabalin, all administered i.p., on paw withdrawal latency in the warm plate test at 38 °C on day 10 in streptozotocin (STZ)-treated animals. Rats were tested between 30 and 45 min post drug. Data are presented as mean±S.E.M. from 10–12 animals/group. *$P<0.05$ Dunnett's test versus streptozotocin/vehicle-treated animals.

3.5. Dynamic allodynia in the rat

Dynamic allodynia developed since the number of reactions during brushing was clearly elevated after streptozotocin treatment. Statistically significant lower scores than in the streptozotocin/vehicle-treated animals in the brushing test were noted for lacosamide (30 mg/kg) and morphine (3 mg/kg, $P<0.05$, Dunnett's test) (Fig. 7). However, reductions in the lacosamide 3 and 10 mg/kg groups approached P values of $P=0.05$ and $P=0.06$ versus streptozotocin/vehicle, respectively.

3.6. Mechanical hyperalgesia in the rat

There was a marked mechanical hyperalgesia as evidenced by a reduction in the paw pressure withdrawal thresholds in the streptozotocin/vehicle-treated animals compared to control/vehicle-treated animals ($P<0.05$, Dunnett's test) (Fig. 8). Treatment of streptozotocin-rats with lacosamide 10 and 30 mg/kg and morphine 3 mg/kg, but not lacosamide 3 mg/kg, induced a significant increase ($P<0.05$, Dunnett's test) in paw pressure withdrawal threshold compared to streptozotocin/vehicle-treated animals. Lacosamide at 10 and 30 mg/kg induced partial reversal of mechanical hyperalgesia. Efficacy, however, was comparable to that of morphine. Similarly, in the second cohort of rats vehicle-treated streptozotocin-animals demonstrated a marked decrease in the paw withdrawal threshold as compared to control animals, i.e. mechanical hyperalgesia developed (Fig. 9). Treatment of streptozotocin-rats with amitriptyline at doses of 3, 10 and 30 mg/kg, induced a significant increase ($P<0.05$, Dunnett's test) in paw withdrawal threshold as compared to vehicle-treated animals. Similarly, treatment of streptozotocin-rats with 180 and 540 mg/kg levetiracetam induced a significant ($P<0.05$, Dunnett's test) increase in paw withdrawal threshold as compared to vehicle-treated animals. Comparable results were recorded with venlafaxine at 15 mg/kg and 10 mg/kg of pregabalin. Surprisingly, higher doses of pregabalin were without effect. None of the test compounds provided full reversal of mechanical hyperalgesia. Lamotrigine had no effect on paw withdrawal threshold at any concentration tested (i.e. 5, 15 and 45 mg/kg).

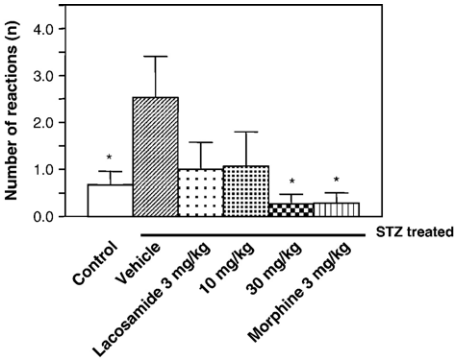

Fig. 7. Effect of lacosamide (i.p.) and morphine (s.c.) on the number of behavioral reactions resulting from brushing on day 21 in streptozotocin (STZ)-treated animals. Rats were tested between 30 and 45 min post drug. Data are presented as mean±S.E.M. from 15 animals/group. *$P<0.05$ Dunnett's test versus streptozotocin/vehicle-treated animals.

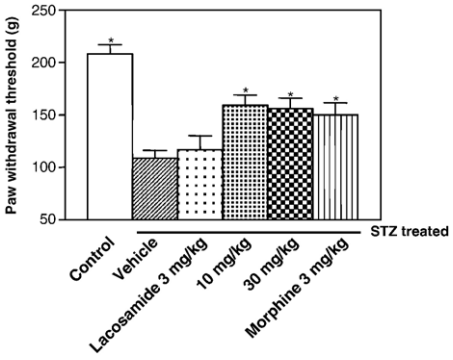

Fig. 8. Effect of lacosamide (i.p.) and morphine (s.c.) on paw pressure withdrawal threshold on day 21 in streptozotocin (STZ)-treated animals. Rats were tested between 30 and 45 min post drug. Data are presented as mean±S.E.M. from 15 animals/group. *$P<0.05$ Dunnett's test versus streptozotocin/vehicle-treated animals.

4. Discussion

The results of the current study have confirmed previous findings (Courteix et al., 1998) that hyperglycaemia induced by diabetes in rats alters pain sensitivity by producing both allodynia and hyperalgesia. Although one tries to mimic the symptoms and etiology associated with neuropathic pain in patients, it is difficult to assess and thus predict the clinical efficacy of novel drugs in rat models. By assessing as many primary preclinical end points as possible, even though they might not be primary contributors to reduced quality of life in the clinic, one can try to understand the potential efficacy and mechanism of action of new drugs especially in comparison to drugs known to be effective in patients.

Lightly stroking the surface of the skin is a readout which is used in patients with peripheral neuropathy (Samuelsson et al., 2005). Trying to mimic the clinical situation we performed the brush-evoked allodynia readout developed by Loomis et al. (2001) who characterized hair deflection in naïve rats as well as in rats treated with strychnine or bicuculline. Our study is the first describing brush-evoked allodynia in STZ-treated rats. Nevertheless, Field et al. (1999) described dynamic allodynia in STZ-treated rats after stroking the plantar surface of the rats hind paw concluding that Abeta- and small diameter nociceptive fibres mediate the dynamic allodynia. Lacosamide at the highest dose tested completely reversed brush-evoked dynamic allodynia. Additionally it was demonstrated that lacosamide fully reversed thermal allodynia and hyperalgesia and attenuated mechanical hyperalgesia comparable to morphine. As expected, lacosamide had no acute antinociceptive effects on normal animals indicating specific antihyperalgesic and anti-allodynic effects under conditions of neuropathic pain.

The antinociceptive efficacy of lacosamide in this study was consistent with its effects on a broad spectrum of antinociceptive behaviors in models of neuropathic and inflammatory pain

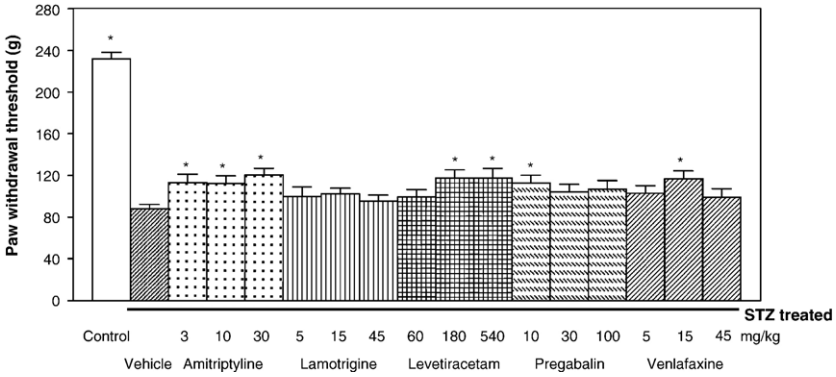

Fig. 9. Effect of amitriptyline, venlafaxine, lamotrigine, levetiracetam and pregabalin, all administered i.p., on paw pressure withdrawal threshold on day 21 in streptozotocin (STZ)-treated animals. Rats were tested between 30 and 45 min post drug. Data are presented as mean ± S.E.M. from 10–12 animals/group. *$P<0.05$ Dunnett's test versus streptozotocin/vehicle-treated animals.

in rats (Morrow et al., 2001; Stohr et al., 2006) and with the results of a clinical trial (McCleane et al., 2003) which indicates that a large-scale controlled trial of lacosamide in patients with neuropathic pain, particularly diabetic neuropathy, is warranted.

Previous studies using the streptozotocin-rat model demonstrated the efficacy of morphine, amitriptyline, lamotrigine and pregabalin on static allodynia (Field et al., 1999; Ulugol et al., 2002). Additionally, morphine, venlafaxine, amitriptyline and lamotrigine were able to inhibit mechanical hyperalgesia in the same model (Courteix et al., 1994; Marchand et al., 2003; Nakamura-Craig and Follenfant, 1995). These findings were reproduced in this study except for the effect of lamotrigine, which was inactive in reducing pain behavior in our streptozotocin-rat model. Animal models performed by different laboratories reflect differences in their characteristics, like differences in the induction of hyperalgesia (Fox et al., 1999; Malcangio and Tomlinson, 1998). The effect of lamotrigine on reducing mechanical hyperalgesia was measured as paw withdrawal threshold during a constant pressure (40 mm Hg) by Nakamura-Craig and Follenfant (1995). In our study the weight at which the rats withdrew their paw was recorded and no effect of lamotrigine was seen.

Because studies in which different drugs are compared in parallel in the same model are rare we decided to do so by using the main antidepressant and anticonvulsant drugs described as useful for neuropathic pain treatment. On thermal allodynia only amitriptyline showed comparable efficacy to lacosamide and morphine. On mechanical hyperalgesia again amitriptyline at 30 mg/kg was the most active drug of the antidepressant and anticonvulsant drugs tested with 22% inhibition of the nociception, but lacosamide achieved even 52% inhibition at 10 mg/kg.

In vitro experiments demonstrate that the mechanism of action of lacosamide appears to be novel. Lacosamide does not bind to a range of receptors, ion channels, transporters or enzymes. Lacosamide may act in a manner unlike currently available anticonvulsants and antidepressants (Bialer et al., 2002; Hovinga, 2003). A novel mode of action may be responsible for the results of this study which suggest that lacosamide may be more potent and/or more efficacious in animal models of polyneuropathy than the other anticonvulsants studied: lamotrigine (sodium channel inhibitor, Nakamura-Craig and Follenfant, 1995), levetiracetam (neuronal synchronization modulator, Ardid et al., 2003), antidepressants like amitriptyline (tricyclic reuptake inhibitor of noradrenaline and serotonin, Courteix et al., 1994; Field et al., 1999; Ulugol et al., 2002), pregabalin (calcium channel modulator, Ben-Menachem, 2004; Chen et al., 2001; Wallin et al., 2002) and venlafaxine (serotonin- and weak noradrenalin reuptake inhibitor, Marchand et al., 2003).

However, there has been some debate over whether the changes seen in nocifensive reflexes in the streptozotocin-induced model of painful diabetic neuropathy are genuinely indicative of peripheral neuropathy (Fox et al., 1999). Some discrepancies have been noted, e.g. clinical efficacy against neuropathic pain has been noted with tricyclic antidepressants but they have been found to be ineffective in the streptozotocin-diabetic rat in one study (Fox et al., 1999) but not in others (Courteix et al., 1994; Field et al., 1999; Ulugol et al., 2002). Care should also be exercised in extrapolating results of in vivo pharmacological studies in diabetic rats to the clinical setting (Calcutt, 2002). In particular, different distribution kinetics and clearance rates that occur in polydipsic diabetic animals (Courteix et al., 1998) may suggest apparently different relative drug potencies between control and diabetic animals.

Overall, lacosamide in this study exhibited potent and broad spectrum antinociceptive efficacy on neuropathic pain-like behaviors in an animal model for painful diabetic neuropathy.

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