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Lacosamide displays potent antinociceptive effects in animal models for inflammatory pain

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Abstract

Lacosamide is a functionalized amino acid which was initially synthesized as an antiepileptic drug. In addition to its broad anti-seizure activity, lacosamide was shown to display efficacy in animal models for neuropathic pain and is currently in phase III clinical development for the treatment of epilepsy and neuropathic pain. In order to further profile its antinociceptive properties, the effects of lacosamide on inflammatory pain in the formalin test, the carrageenan model and the adjuvant-induced arthritis model were investigated.

For the formalin test, mice received an intraplantar injection of formalin and the subsequent licking response was measured over 45 min. Lacosamide was administered 30 min before formalin. For the carrageenan model, mechanical and thermal hyperalgesia were assessed 3 h following an intraplantar injection of carrageenan. Lacosamide was administered to rats 30 min before pain threshold measurements. For the adjuvant-induced arthritis test rats received intraplantar injections of Freund's complete adjuvant into the right hindpaw which lead to the development of arthritic symptoms in all animals tested for antinociception. On day 11 after arthritis induction, mechanical hyperalgesia was assessed by the modified Randall Selitto paw pressure test following acute treatment with lacosamide.

Lacosamide dose-dependently attenuated mechanical hyperalgesia following carrageenan injection and in rats suffering from Freund's complete adjuvant-induced arthritis. Moreover, thermal hyperalgesia induced by carrageenan as well as the formalin-induced licking response were dose-dependently attenuated by lacosamide.

These results suggest lacosamide may be active against various forms of acute and chronic inflammatory pain in humans.

Keywords: Inflammatory pain; Antiepileptic drug; Lacosamide; Arthritis; Formalin test; Carrageenan test

1. Introduction

Lacosamide (*R*-2-acetamido-*N*-benzyl-3-methoxy-propionamide, SPM 927) previously called harkoseride or ADD234037 is a novel anticonvulsant drug. It belongs to a series of functionalized amino acids which have been synthesized as a new class of anticonvulsant agents (Kohn et al., 1991). Lacosamide has shown activity in a wide variety of animal models for epilepsy including the maximal electroshock test, the rat hippocampal kindling model and different models of self-sustaining status epilepticus. In addition, it was shown to be neuroprotective against perforant path stimulation induced hippocampal cell loss (Bialer et al., 2002).

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Lacosamide is currently evaluated in phase III clinical development for the treatment of epilepsy.

Neuropathic pain is a chronic abnormal pain state which is associated with injury to neural tissue, causing normally innocuous stimuli to become painful (allodynia) or increasing the sensitivity to nociceptive input (hyperalgesia). In addition, the nervous system itself can generate and perpetuate pain without any ongoing stimuli from an injury or indeed without the involvement of any injury at all. Various mechanisms for neuropathic pain have been suggested; however, no single one is universally accepted. However, the role of inflammatory mediators has been emphasized for at least part of the painful neuropathies (Sommer, 2003).

The response of neuropathic pain to opioid analgesics is inconsistent, with reports of effect and lack of effect with, for example, morphine (Arner and Meyerson, 1988). It is now accepted that tricyclic antidepressants and antiepileptic drugs have an analgesic effect in neuropathic pain. Carbamazepine, phenytoin (both as phenytoin and fosphenytoin), lamotrigine, and gabapentin have all been shown to possess an analgesic effect (Sindrup Jensen, 1999; Backonja, 2002). However, the response to tricyclic antidepressants and AEDs is inconsistent. Furthermore, side effects may be significant and often limit their use in patients with pain. Thus, there is a need for more effective and better-tolerated drug treatments for patients with neuropathic and chronic inflammatory pain.

In addition to its anti-convulsive properties, lacosamide was shown to be active in animal models for neuropathic pain (Morrow et al., 2001). Lacosamide potently reduced mechanical allodynia and moderately attenuated thermal hyperalgesia in the chronic constriction injury (Bennett-) or the spinal nerve ligature (Chung) model. It was, however, inactive on acute pain as assessed by the tail flick test. In order to further profile the antinociceptive effects of lacosamide we now evaluated lacosamide in rat models for acute and chronic inflammatory pain, i.e., the formalin test, the carrageenan model, and the chronic complete Freund's adjuvant (FCA) induced arthritis model.

Intradermal injections of formalin into the paw induce a biphasic nociceptive response as evidenced by flinching, licking or biting the affected paw (Dubuisson and Dennis, 1977; Wheeler-Aceto et al., 1990). The early response results from a direct stimulation of nociceptors by formalin whereas the late phase response is believed to be due to the development of peripheral inflammation and central sensitization of dorsal horn neurons. This makes the formalin test a well accepted animal model for pain (Tjolsen et al., 1992). The formalin test is a chemically induced tonic pain model in which biphasic changes of nociceptive behavior are assessed and supraspinal plasticity of nociception is considered as a molecular basis for neuropathic pain particularly during the second (=late) phase of the test, during which most clinically used drugs against neuropathic pain are active.

Further potential antinociceptive efficacy of lacosamide was assessed in a rat experimental model of acute inflammation using a modified Randall and Selitto procedure (Randall and Selitto, 1957). This mechanical paw pressure test has become a standard method for testing the efficacy of new compounds for alleviating acute inflammatory pain. Acute inflammation is induced by injection of carrageenan, a non-specific inflammatory agent, into the plantar surface of one hind paw of the animal.

Finally, lacosamide was evaluated in a model for chronic inflammation, the rat Freund's adjuvant-induced arthritis model. In this model, animals develop a destructive polyarthritis in response to interplantar FCA injection that mimics rheumatoid arthritis in humans and is accompanied by chronic pain (Colpaert et al., 1982; Nagakura et al., 2003).

2. Materials and methods

All experiments were performed in different laboratories according to the Helsinki declaration and the guidelines for pain research in animals of the International Association for the Study of Pain and were approved by the local governmental bodies.

2.1. Experiment 1: Two-phase formalin test in mice

2.1.1. Animals

Male mice of Rj: NMRI strain, 22–26 g body weight range were supplied by Elevage Janvier, 53940 Le Genest-Saint-Isle, France. They were delivered to the laboratory at least 5 days before the experiments and, upon arrival, were housed 10 per cage in macrolon cages ($25 \times 19 \times 13$ cm) with free access to food (UAR 113 – UAR, 91360 Epinay-sur-Orge, France) and tap water (i.e., non-fasted) until tested. The animal house was maintained under artificial lighting (12 h) between 7.00 and 19.00 in a controlled ambient temperature of 22 ± 2 °C, and relative humidity maintained at 40–70%.

2.1.2. Drugs and reagents

Lacosamide (Schwarz BioSciences) and morphine (Coopération Pharmaceutique Française) were dissolved in physiological saline and administered i.p. in a volume of 10 ml/kg body weight. Formaldehyde 30% (Celtipharm) was diluted in physiological saline (5% solution) and was administered in a volume of 25 μl/paw.

2.1.3. Experimental design and statistical analyses

The method, which detects antinociceptive and/or anti-inflammatory activity, follows that described by

Wheeler-Aceto and Cowan (1991). Mice were given an intraplantar injection of 5% formalin (25 μl) into the posterior left paw. This treatment induces paw licking in control animals. The time spent licking was counted for 5 min, immediately, 10, 20, 30 and 40 min after injection of formalin. Ten mice were studied per group. The test was performed blind. Lacosamide was evaluated at the doses of 8, 16, and 32 mg/kg, administered i.p. 30 min before formalin. Morphine (8 mg/kg), administered under the same experimental conditions, was used as reference substance.

The licking response was analyzed by two way repeated measures analysis of variance (ANOVA) with treatment as independent and time as dependent variable. Post hoc comparisons were done with the Fisher least significant difference method where appropriate and $p < 0.05$ was considered statistical significant.

2.2. Experiment 2: Carrageenan-induced mechanical hyperalgesia in rats

2.2.1. Animals

Male Sprague-Dawley rats (Rj:SD, IOPS Han), 195–235 g body weight range were supplied by CERJ, France. They were delivered to the laboratory at least 5 days before the experiments and, upon arrival, were group housed with free access to food (U.A.R., France) and tap water (i.e., non-fasted) until tested. The animal house was maintained under artificial lighting (12 h) between 7.00 and 19.00 in a controlled ambient temperature of 22 ± 2 °C, and relative humidity maintained at $55 \pm 10\%$.

2.2.2. Drugs and reagents

Lacosamide (Schwarz BioSciences) and indomethacin (Sigma, France) were dissolved in physiological saline and administered i.p. in a volume of 10 ml/kg body weight. Carrageenan Lambda type IV (Sigma, France) was suspended in 1% methylcellulose (2% suspension) and was administered in a volume of 0.1 ml/paw.

2.2.3. Experimental design and statistical analyses

Rats were given an intraplantar injection of 2% carrageenan (0.1 ml) into the posterior right paw. Three hours later pain threshold was measured using a mechanical nociceptive stimulation (modified Randall Selitto paw pressure test). Therefore. the inflamed and the non-inflamed hind paw were exposed to an increasing force until the nociceptive reaction (vocalization or paw withdrawal) was reached. Ten rats were studied per group. The test was performed blind. Lacosamide was evaluated at the doses of 10, 20, and 40 mg/kg, administered i.p. 30 min before pain threshold measurement. Indomethacin (10 mg/kg), administered under the same experimental conditions, was used as reference substance.

The nociceptive thresholds (g of contact pressure) of the inflamed and the non-inflamed paw were analyzed by one way ANOVA with treatment as independent variable. Post hoc comparisons were done with the Fisher least significant difference method where appropriate and $p < 0.05$ was considered statistical significant.

2.3. Experiment 3: Carrageenan-induced thermal hyperalgesia and paw edema in rats

2.3.1. Animals

Male rats of Rj: Wistar (Han) strain, 200–335 g body weight range were supplied by Elevage Janvier (France). Animals were delivered to the laboratory at least 5 days before the experiments and, upon arrival, were group housed with free access to food (UAR, France) and tap water (i.e., non-fasted) until tested. The animal house was maintained under artificial lighting (12 h) between 7.00 and 19.00 in a controlled ambient temperature of 21 ± 1 °C, and relative humidity maintained at 40–70%.

2.3.2. Drugs and reagents

Lacosamide (Schwarz BioSciences), acetylsalicylic acid (Sigma, France) and morphine-hydrochloride (Coopération Pharmaceutique Française) were dissolved in physiological saline and administered i.p. in a volume of 10 ml/kg body weight. Carrageenan (Laserson and Sabetay) was suspended in physiological saline and was administered in a volume of 50 μl/paw.

2.3.3. Experimental design and statistical analyses

The method, which detects antinociceptive activity in rats suffering from inflammatory pain, follows that described by Winter et al. (1962). Rats were given an intraplantar injection of 0.75 mg carrageenan (50 μl) into the lower surface of posterior right paw. Two hours later rats were submitted to thermal stimulation of both, the inflamed and the non-inflamed hindpaws. For thermal stimulation, the apparatus (Ugo Basile, Reference: 7371) consisted of 6 individual Plexiglas boxes ($17 \times 11 \times 13$ cm) placed upon an elevated glass floor. Rats were placed in the box and left free to habituate for 10 min. Then, a mobile infrared radiant source (setting 20) was focused under the inflamed and non-inflamed hindpaws and the paw-withdrawal latencies were automatically recorded. Paw-withdrawal interrupts the reflected radiation and switches off the counter and the light source. In order to prevent tissue damage, if no reaction was noted, the test was terminated after 45 s. For measurement of edema (after the behavioral measures), the animals were sacrificed by decapitation and the non-inflamed and inflamed paws sectioned and weighed. Ten rats were studied per group. The test was performed blind. Lacosamide was evaluated at the doses of 8, 16, and 32 mg/kg, administered i.p. 30 min before thermal stimulation. Morphine (8 mg/kg) and

acetylsalicylic acid (256 mg/kg), administered under the same experimental conditions, were used as reference substances.

Withdrawal latencies and weights of the inflamed and the non-inflamed paw were analyzed by one way analysis of variance (ANOVA) with treatment as independent variable. Post hoc comparisons were done with the Fisher least significant difference method where appropriate and $p < 0.05$ was considered statistical significant.

2.4. Experiment 4: Mechanical hyperalgesia during adjuvant-induced arthritis in rats

2.4.1. Animals

Female Wistar rats (Charles River, Germany) weighing 80–90 g at the beginning of the experiments were group housed with free access to food and water.

2.4.2. Drugs and reagents

Lacosamide (Schwarz BioSciences) and morphine (Arzneimittelwerk Dresden, Germany) were dissolved in water and administered i.p. Freund's complete adjuvant (Impfstoffwerk Dessau, Germany) was suspended in paraffin oil.

2.4.3. Induction of adjuvant arthritis

Rats received an intraplantar injection into the right hindpaw of 0.1 ml Freund's complete adjuvant (5 mg heat-killed mycobacterium tuberculosis) on day 0. On day 11, the degree of arthritis development was evaluated by visual inspection and only rats which showed clear signs of arthritis such as redness, swelling and impaired motility of the injected paw were included in the further experiment.

2.4.4. Experimental design and statistical analyses

Rats were treated on day 0 with either Freund's complete adjuvant or solvent (healthy control group). On day 11 rats which developed primary and/or secondary arthritis were randomly assigned to receive vehicle, lacosamide (20, 30 or 40 mg/kg) or morphine (10 mg/kg i.p.). Morphine served as positive control substance. Mechanical hyperalgesia was measured according to the modified Randall-Selitto test (Fa. Ugo Basile, Italy). Therefore the right hind paws were exposed to an increasing force until vocalization occurred or the maximal force (5.3 MPa) was reached, whatever occurred first. Measurements were taken on day 11 at 0 min (before drug injection/baseline value) and 15, 30, 60 min, and 24 h thereafter. All data are expressed as the percentage of maximum possible effect (%MPE) = [postdrug threshold − baseline threshold]/[maximal possible threshold − baseline threshold] * 100. Statistical analysis was performed by using two way repeated measures ANOVA with treatment as independent and time as dependent variable. Post hoc comparisons were done with the Fisher least significant difference method where appropriate and $p < 0.05$ was considered statistical significant. Another analysis was performed in order to demonstrate that FCA-treated rats displayed mechanical hyperalgesia. Therefore, the threshold pressure at baseline of FCA-treated groups was compared to that of the healthy control group by Student's t test. Furthermore, in order to get an estimate of effect size the mean percent change from baseline during the 15–60 min time period was calculated for each treatment group and compared to that of the FCA-treated vehicle group by means of Student's test.

3. Results

3.1. Experiment 1: Two-phase formalin test in mice

Formalin induced a clear nociceptive response ($F[4,249] = 12.34$, $p < 0.001$)] which was dose-dependently attenuated by lacosamide ($F[4,45] = 8.38$, $p < 0.001$; Fig. 1). The lower doses of lacosamide (i.e., 8 and 16 mg/kg) were only active at 40–45 min after formalin administration, the time at which the maximal nociceptive response induced by formalin was observed. SPM 927 at a dose of 32 mg/kg attenuated nociceptive behavior throughout the observation period and displayed similar antinociceptive efficacy as the reference compound morphine (8 mg/kg).

3.2. Experiment 2: Carrageenan-induced mechanical hyperalgesia in rats

Carrageenan induced marked mechanical hyperalgesia as evidenced by reduced nociceptive threshold of the injected as compared to the non-injected paw (Fig. 2).

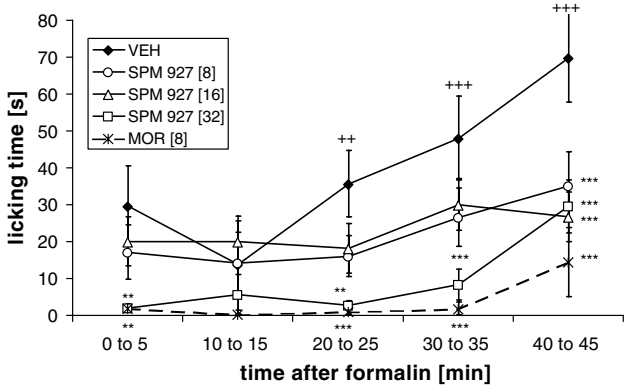

Fig. 1. The effects of lacosamide (SPM 927) on the formalin-induced nociceptive response in mice. Licking times (means ± SEM) during 5 min observation periods following the injection of formalin are shown. Lacosamide or morphine, administered 30 min before formalin attenuated the licking response. Doses are indicated in brackets and given as mg/kg bodyweight. $^{++,+++}p < 0.01/0.001$ versus observation period 10–15 min within vehicle group. $^{**,***}p < 0.01$, 0.001 treatment groups versus vehicle control group.

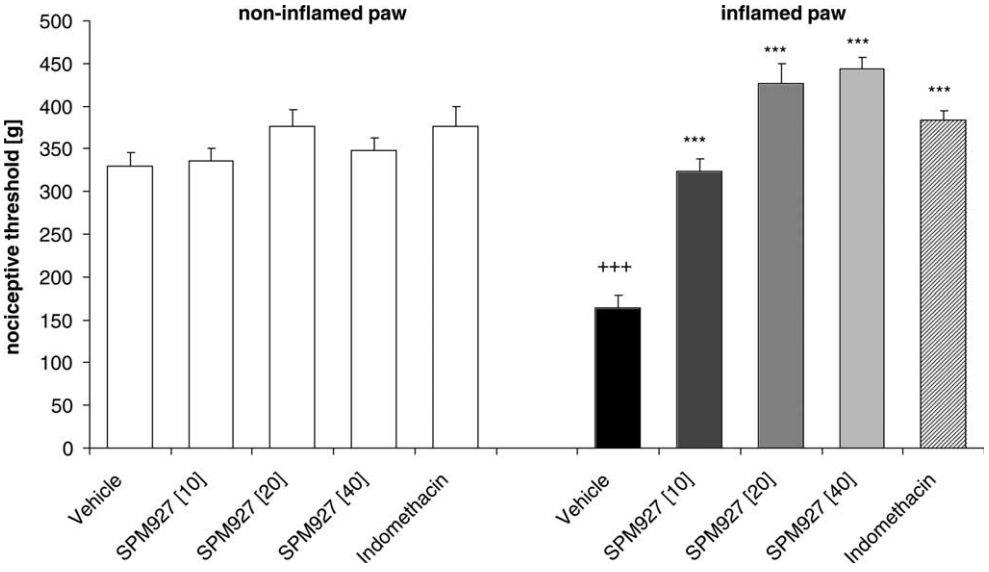

Fig. 2. The effects of lacosamide (SPM 927) on carrageenan-induced mechanical hyperalgesia in rats. Nociceptive thresholds in grams (means ± SEM) 3 h following the injection of carrageenan are shown. Lacosamide or indomethacin, administered 30 min before measurement reversed carrageenan-induced decrease of threshold pressure. Doses are indicated in brackets and given as mg/kg bodyweight. $^{+++}p < 0.001$ versus non-inflamed paw. $^{***}p < 0.001$ treatment groups versus vehicle control group.

This carrageenan-induced mechanical hyperalgesia was dose-dependently and fully reversed by lacosamide ($F[5,59] = 40.16$, $p < 0.001$). The reference compound indomethacin also fully restored mechanical hyperalgesia. Both drugs, at the doses tested did not affect nociceptive thresholds of the non-injected paw ($F[4,49] = 1.47$ n.s.).

3.3. Experiment 3: Carrageenan-induced thermal hyperalgesia and paw edema in rats

Carrageenan induced marked thermal hyperalgesia as evidenced by reduced nociceptive threshold of the injected as compared to the non-injected paw (Fig. 3). This carrageenan-induced thermal hyperalgesia was

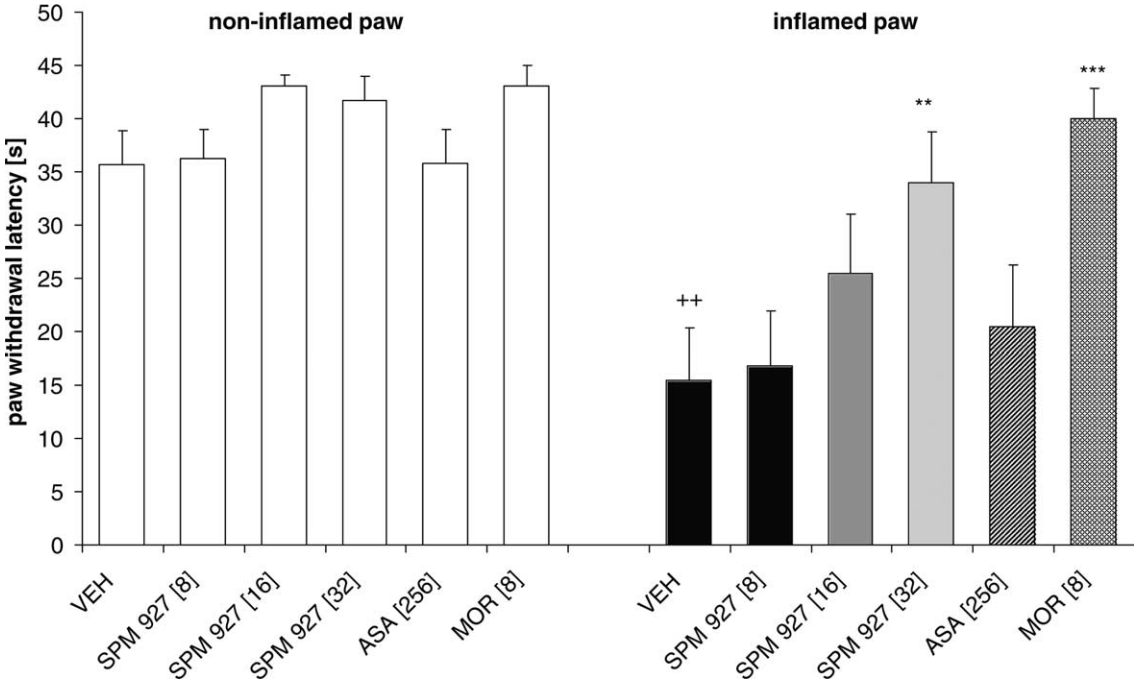

Fig. 3. The effects of lacosamide (SPM 927) on carrageenan-induced thermal hyperalgesia in rats. Paw withdrawal latencies in seconds (means ± SEM) 2 h following the injection of carrageenan are shown. Lacosamide, morphine and acetylsalicylic acid, administered 30 min before measurement reversed carrageenan-induced decrease of paw withdrawal latencies of the inflamed paw. Doses are indicated in brackets and given as mg/kg bodyweight. $^{++}p < 0.01$ versus non-inflamed paw $^{**,***}p < 0.01$, 0.001 treatment groups versus vehicle control group.

dose-dependently attenuated by lacosamide ($F[6,69] = 4.36$, $p < 0.001$). The reference compound morphine fully restored thermal hyperalgesia whereas acetylsalicylic acid was ineffective. All three drugs, at the doses tested did not affect nociceptive thresholds of the non-injected paw ($F[5,59] = 2.18$ n.s.).

Carrageenan induced a marked paw edema as evidenced by increased weight of the injected as compared to the non-injected paw (Fig. 4). This carrageenan-induced paw edema was attenuated by the reference compound acetylsalicylic acid but not by lacosamide or the reference compound morphine ($F[6,69] = 27.53$, $p < 0.001$). All three drugs, at the doses tested did not affect weights of the non-injected paw ($F[5,59] = 0.58$ n.s.).

3.4. Experiment 4: Mechanical hyperalgesia during adjuvant-induced arthritis in rats

Visual inspection revealed that by day 11 after FCA injection a clear primary arthritis had developed in all rats as evidenced by redness, swelling and impaired motility of the injected paw. In addition, secondary arthritis has developed in most of the rats which included the same inflammatory symptoms at other parts of the body including the non-injected limbs. This was also evident by clear development of hyperalgesia in all FCA-treated animals at baseline (threshold pressure for healthy control group 152 ± 23; FCA-vehicle group 68 ± 11; FCA-LCM 20 mg/kg group 88 ± 16; FCA-LCM 30 mg/kg group 56 ± 9; FCA-LCM 40 mg/kg group 76 ± 13; FCA-morphine group 59 ± 7; all $p < 0.01$ versus healthy control group).

Lacosamide induced dose-dependent antinociceptive effects in arthritic rats (Fig. 5). This effect was most prominent during the first 60 min of testing and was, for the 40 mg/kg dose of lacosamide comparable to that of morphine (10 mg/kg). The ANOVA revealed main effects of group ($F[9,129] = 7.52$, $p < 0.001$) and time ($F[3,129] = 47.6$, $p < 0.001$) as well as a significant interaction of both factors ($F[27,387] = 5.37$, $p < 0.001$).

An additional analysis was performed on percent change for the 15–60 min time period to baseline within each group. Average percent change from baseline was $99 \pm 12\%$ for the healthy control group, $156 \pm 21\%$ for the FCA-vehicle group; $102 \pm 26\%$ for the FCA-LCM 20 mg/kg group, $292 \pm 44\%$ for the FCA-LCM 30 mg/kg group, $313 \pm 61\%$ for the FCA-LCM 40 mg/kg group, and $402 \pm 63\%$ for the FCA-morphine group. The effects of lacosamide at the doses of 30 and 40 mg/kg and those of morphine were significantly larger than those of vehicle ($p > 0.05$).

4. Discussion

The current experiments show that lacosamide is active in different models for acute and chronic inflammatory pain. Lacosamide attenuated the late-phase formalin-induced nociceptive response starting at

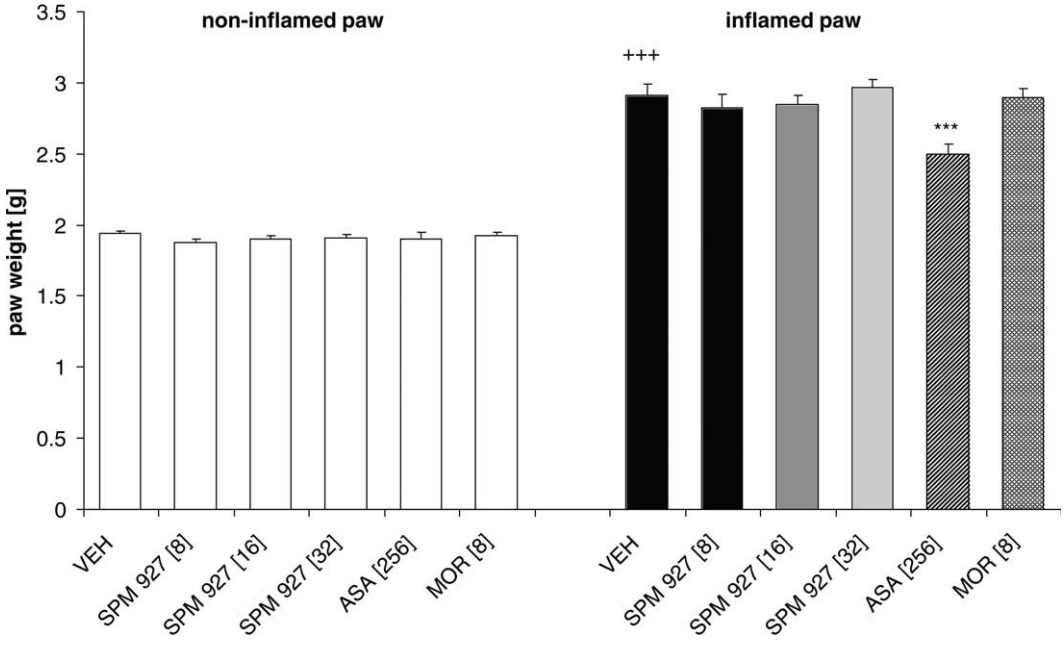

Fig. 4. The effects of lacosamide (SPM 927) on carrageenan-induced paw edema in rats. Paw weight in grams (means ± SEM) 2 h following the injection of carrageenan are shown. Acetylsalicylic acid but not lacosamide or morphine, administered 30 min before measurement reversed carrageenan-induced paw edemas. Doses are indicated in brackets and given as mg/kg bodyweight. $^{+++}p < 0.001$ versus non-inflamed paw. $^{***}p < 0.001$ treatment groups versus vehicle control group.

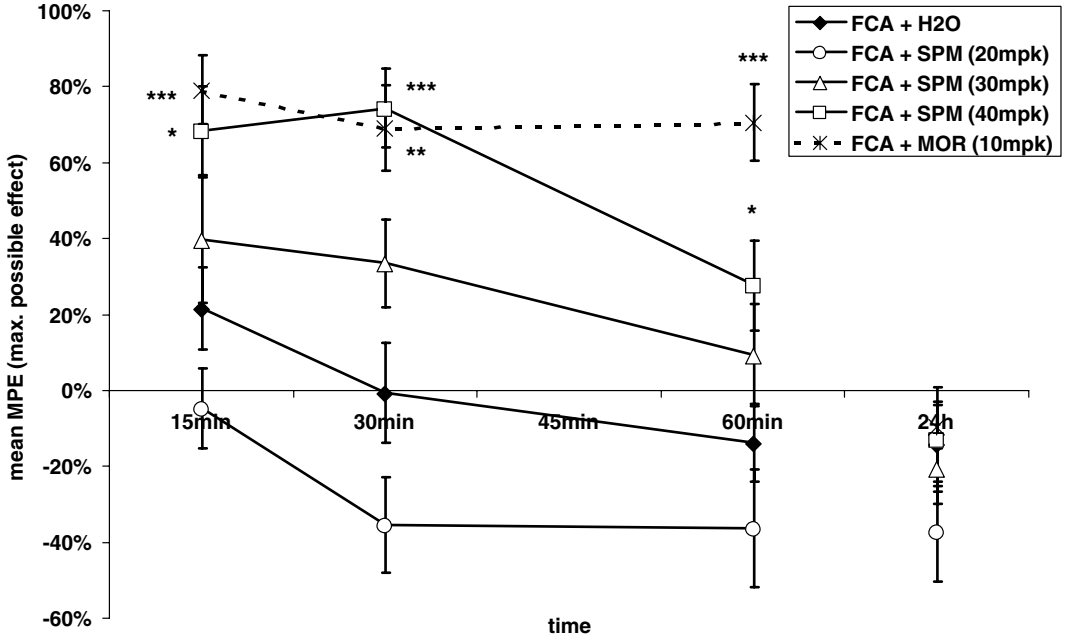

Fig. 5. The effects of lacosamide (SPM 927) on Freund's complete adjuvant-induced mechanical hyperalgesia. Mechanical hyperalgesia (expressed as mean MPE ± SEM) 11 days following the injection of FCA are shown. Lacosamide or morphine, administered immediately before measurement reversed FCA-induced mechanical hyperalgesia. Doses are indicated in brackets and given as mg/kg bodyweight. $^{*,**,***}p < 0.05$, 0.01, 0.001 treatment groups versus vehicle control group.

8 mg/kg, the lowest dose tested. At the highest dose tested (i.e., 32 mg/kg) there was full efficacy which is comparable to the effect of morphine at the dose tested (8 mg/kg). The early phase response was not affected by the lower doses of lacosamide (i.e., 8 and 16 mg/kg) suggesting a specific effect on chronic as compared to acute inflammatory pain. This is in line with earlier experiments showing no effect of lacosamide in another model of acute pain – the tail-flick assay (Morrow et al., 2001). In addition, lacosamide reversed Carrageenan-induced hyperalgesia but not the carrageenan-induced inflammatory response (edema) suggesting that antinociception induced by lacosamide is mediated by interfering with pain transmission rather than with providing anti-inflammatory effects. It was more potent against mechanical hyperalgesia (lowest active dose 8 mg/kg) as compared to thermal hyperalgesia (lowest active dose 32 mg/kg). At the highest dose tested (i.e., 32 mg/kg) the efficacy was comparable to that of morphine but somewhat larger than that of the non-steroidal anti-inflammatory drugs acetylsalicylic acid and indomethacin at the doses tested (i.e., 256 and 10 mg/kg, respectively). Finally lacosamide showed activity against FCA-induced mechanical hyperalgesia albeit at the highest dose only (i.e., 40 mg/kg). However, at this dose the maximal efficacy was comparable to that of morphine at the dose tested (i.e., 10 mg/kg).

These antihyperalgesic effects are well in line with other results (Morrow et al., 2001) that indicate that lacosamide is active in animal models for neuropathic pain such as the chronic constriction injury or the spinal nerve ligature model with higher potency for the mechanical allodynia as compared to the thermal hyperalgesia response.

Other anticonvulsant drugs have shown activity in animal models for chronic inflammatory pain. Gabapentin was active during the late but not the early phase of the rat formalin test with minimally effective doses of 20–100 mg/kg (Singh et al., 1996; Field et al., 1997). Other anticonvulsant drugs such as lamotrigine and carbamazepine similarly attenuated the late but not the early phase antinociceptive response to formalin at doses of 15–30 and 20 mg/kg for lamotrigine and carbamazepine, respectively. Phenytoin, another antiepileptic drug was without effect up to a dose of 40 mg/kg (Blackburn-Munro et al., 2002). Thus, the ability of lacosamide to selectively attenuate the late-phase formalin-induced nociceptive response is shared with some but not all anticonvulsant drugs. However, lacosamide seems to be more potent than other anticonvulsant drugs widely used for the treatment of neuropathic and chronic inflammatory pain such as gabapentin.

Gabapentin reversed carrageenan-induced hyperalgesia with minimally effective doses of 20–30 mg/kg for thermal hyperalgesia and of 10 mg/kg for mechanical hyperalgesia (Field et al., 1997; Hurley et al., 2002; Villetti et al., 2003). Pregabalin was active on carrageenan-induced mechanical and thermal hyperalgesia with minimal effective doses of 3 and 6 mg/kg, respectively (Field et al., 1997; Hurley et al., 2002). Lacosa-

mide was thus similarly potent in this model for acute inflammatory pain as compared to gabapentin and pregabalin.

In contrast to the carrageenan test which is a model for acute inflammatory pain can the rat FCA test be considered a model for chronic inflammatory pain. This test can be regarded a model with face and predictive validity for arthritic pain (Nagakura et al., 2003). Lacosamide at the highest dose tested displayed full efficacy against mechanical hyperalgesia at a time when the arthritic condition fully developed. In contrast, gabapentin and carbamazepine were not active against FCA-induced mechanical hyperalgesia when tested 9 days after arthritis induction by FCA (Nagakura et al., 2003). Similarly, acute or chronic gabapentin was only weakly active against FCA-induced hyperalgesia when tested 24 h after FCA injection (Patel et al., 2001). Lacosamide is thus the first anti-convulsive drug to display full antinociceptive efficacy in the rat FCA-induced arthritis model. However, spinally administered gabapentin reduced secondary thermal hyperalgesia of knee joint inflammation induced by intra articular injection of kaolin and carrageenan – a model for acute arthritic pain (Lu and Westlund, 1999). In the same model intrathecal lamotrigine, a sodium channel blocker displayed antihyperalgesic effects showing a higher efficacy for reversal of mechanical allodynia as compared to thermal hyperalgesia (Lee et al., 2002).

In summary, lacosamide showed full efficacy in three different models of inflammatory pain whereas other antiepileptic drugs were not or only partially effective especially in the chronic FCA model. These results demonstrate a unique antinociceptive effectiveness of lacosamide under conditions of chronic inflammatory pain when compared to other antiepileptic drugs.

For the time being, no conclusive molecular mode of action to explain these in vivo antinociceptive effects can be presented. Although lacosamide has been tested in radioligand binding experiments on more than 100 receptors, ion-channels and enzymes, no significant displacement of binding could be detected at a concentration of 10 μM. Lacosamide did not modulate voltage-gated sodium-channels (TTX-sensitive or insensitive), calcium-channels (L-, N-, P- or T-type), or potassium channels (delayed rectifyer, KCNQ2/3). In additional, in vitro functional experiments using mouse cortical neurons it was shown that at low concentrations lacosamide enhanced GABA-evoked currents and attenuated glutamate-evoked currents. However, these results do not suggest a specific molecular mechanism. Furthermore, additional preclinical but preliminary data suggest a multi-modal mode of action.

In summary, lacosamide displayed antihyperalgesic effects in different models for acute and chronic inflammatory pain with similar or even higher potency and efficacy as compared to other anticonvulsant drugs. The effectiveness of lacosamide in these models suggests that it might have clinically relevant effects in patients suffering from pain conditions such as rheumatoid or secondary osteoarthritis. This is currently under investigation in a more relevant animal disease model for arthritis.

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