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Effects of Intrathecally Administered Lamotrigine, a Glutamate Release Inhibitor, on Short- and Long-term Models of Hyperalgesia in Rats

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Background: **Lamotrigine is a sodium channel blocker that inhibits the neuronal release of glutamate. Systemic administration of lamotrigine induces analgesia in short- and long-term models of hyperalgesia in rats. Considering the key role of N-methyl-D-aspartate receptors in the sensitization of dorsal horn neurons that leads to hyperalgesia, the author hypothesizes that intrathecally injected lamotrigine would be effective in reducing the hyperalgesia.**

Methods: **Short-term hyperalgesia was induced by unilateral intraplantar injection of prostaglandin E_2. Long-term hyperalgesia was produced by treating rats with streptozotocin, which causes diabetic neuropathy and, in a different group of animals, by loose ligation of the sciatic nerve (chronic constriction injury). Hyperalgesia was assessed by measuring withdrawal reaction time after paw pressure, and analgesia was measured by the thermal tail-flick test.**

Results: **In the short-term model, intrathecally administered lamotrigine (12.5, 25.0, and 100.0 μg) produced a dose-dependent increase in the reaction time of the hyperalgesic paw. The highest dose that completely restored the reaction time to control levels (26–29 s) from the hyperalgesic levels (12–15 s) did not affect the reaction time of the normal contralateral paw. In the tail-flick test, a consistent effect could be observed only with doses of 200 μg, which caused transient motor impairment of the hind paws. In the long-term models of hyperalgesia, intrathecally administered lamotrigine produced a dose-dependent and long-lasting (24–48 h) antihyperalgesic effect.**

Conclusions: **Intrathecally administered lamotrigine produced a spinal, dose-dependent, and long-lasting antihyperalgesic effect in short- and long-term neuropathic models of hyperalgesia. (Key words: Long-term constriction injury; paw pressure test; prostaglandin E_2; streptozotocin-induced diabetic neuropathy.)**

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LAMOTRIGINE, a novel antiepileptic drug, is known to block sodium channels in a use-dependent manner[1] and to inhibit glutamate release in the striatum,[2] cortex[3] and hippocampus.[4] Nakamura-Craig and Follenfant have shown that oral lamotrigine induces dose-dependent analgesia in short-term (intraplantar injection of prostaglandin E_2 [PGE_2]) and long-term (streptozotocin-induced diabetes and hind paw ultraviolet radiation) models of hyperalgesia in rat without significant side effects (sedation and motor impairment).[5,6] Thus, the mechanism of action of lamotrigine may be of particular interest for the control of hypersensitivity (hyperalgesia and allodynia) that follows tissue trauma (postoperative pain) or peripheral nerve lesion (neuropathic pain).

The effects of systemic administration of lamotrigine in models of hyperalgesia is suggested to be of central origin, as its local application to the hyperalgesic paw is ineffective.[6] In the last few years, studies have suggested that excitatory amino acids, particularly glutamate acting on the N-methyl-D-aspartate (NMDA) receptors located on the superficial layers of the spinal dorsal horn, are involved in the development of inflammatory and neurogenic hyperalgesia.[7–9] Sodium channel-mediated high-frequency spontaneous discharges may also be involved in the pathogenesis of abnormal pain behavior that follows peripheral nerve damage.[10] Therefore, the purpose of the current study was to examine the effects of intrathecally administered lamotrigine on short- and long-term models of hyperalgesia in rats.

Materials and Methods

The study protocol was approved by the Home Office (London, UK). The experiments were performed according to the ethical guidelines of the International

Association for Study of Pain and Home Office regulation on human use of research animals.

Intrathecal Cannulation

Intrathecal cannulation was performed on male Wistar strain rats (body weight, 300–400 g) anesthetized with sodium pentobarbital (60 mg/kg, intraperitoneally) or isoflurane using a technique modified from Yaksh and Rudy.[11] A polyethylene catheter (PE-10 stretched to yield an outer diameter of 0.32 mm; dead space = 4 μl) was inserted through an incision of the atlantooccipital membrane and advanced 10 cm caudally to leave its tip in the intrathecal space just below the lumbar enlargement. The other tip of the catheter was attached to a polyethylene catheter (PE-20, 2 cm), which was fixed to the neck muscles with one end remaining outside the skin.

After these procedures, rats were housed individually in cages on a 12-h/12-h light/dark cycle at 22°C. Experiments were performed within 3–10 days after cannulation. Only rats showing no motor impairment were used in these experiments. At the end of the study, Evans blue dye (10 μl) was injected intrathecally, and lumbar and thoracic laminectomies were performed to locate the position of the catheter tip and to analyze the macroscopic aspect of the spinal cord and meninges.

Intrathecal Injections

Intrathecal injections of drugs were given in volumes of 10 μl followed by 4 μl (inside volume of the catheter) saline to flush the catheter at room temperature (22°C). Intrathecal injections of drugs were made at intervals of 3 or 4 days in each animal. The rats injected with carbamazepine received only one injection; the other animals received 2 or 3 injections.

Drugs

Lamotrigine mesylate was supplied by the Wellcome Foundation Ltd (England). Morphine and carbamazepine were purchased from Sigma (England). Lamotrigine and morphine were diluted in physiologic saline (0.9%, vol/weight), and carbamazepine was prepared as a suspension in a vehicle consisting of saline and polyethyleneglycol (50:50, vol%/vol%).

Pain Tests

The paw pressure test was conducted as described by Ferreira *et al.*[12] Reaction time was defined as the time in seconds for hind paw withdrawal from a constant pressure (40 mmHg) applied through a platform (diameter, 1 cm^2) to the dorsal surface of the hind paw positioned between the platform and a bar. The basal reaction time was 25–30 s, but this time was reduced (hyperalgesia) to 12–15 s in hyperalgesic states.

The tail-flick test was performed using an automatic apparatus. Radiant heat was focused on the tail, 2 cm from the tip, and the time between the stimulus presentation and the rapid withdraw of the tail was defined as response latency. Analgesia was defined whenever response latency was higher than 3 SD from the pooled mean pretreatment values (mean ± SD, 2.5 ± 0.5 s). A cutoff time of 10 s was used when no response occurred.

Hyperalgesia

Short-term Hyperalgesia. ***Intraplantar Administration of Prostaglandin E_2.*** Short-term hyperalgesia was induced by intraplantar injection of PGE_2 (100 ng, 0.1 ml) into one of the hind paws. Intrathecal injections were performed 150 min after the PGE_2 injection. The reaction time of the hind paw was measured 15, 30, 60, 120, and 300 min and 24 h after intrathecal injection. In this model, the animals were tested over a period of 5 h after injection because the hyperalgesic effect of intraplantar administration of PGE_2 remains constant up to this time.

Long-term Hyperalgesia. ***Streptozotocin-induced Diabetic Neuropathy.*** Rats were treated with intraperitoneal injections of streptozotocin (Zanosar; Upjohn, France) (75 mg/kg, intraperitoneally) dissolved in distilled water according to a method described elsewhere.[13] The experiments were performed 4 weeks after the induction of diabetes. Blood glucose was measured on the day before the pain tests by tail clip sampling, and only rats with blood glucose levels ≥14 mM and reaction times between 12 and 15 s were used. Reaction time was assessed on the day of streptozotocin injection (normal control), immediately before intrathecal injection (hyperalgesic control) and 1, 2, 5, 24, and 48 h after the intrathecal injection.

Long-term Constriction Injury. Nerve ligation was performed according to the method of Bennett and Xie.[14] The right sciatic nerve was exposed under anesthesia, and a segment 5- to 7-mm long was then dissected. Four loose ligatures (4–0 chromic gut) were made around the dissected nerve with a 1.0- to 1.5-mm interval. Intrathecal cannulation was performed immediately after nerve ligation. Reaction time was measured

before sciatic ligation and repeated immediately before intrathecal injection (3–5 days later) and 30 min and 1, 2, 5, 24, 48, and 72 h after intrathecal injection. Only rats with reaction times between 15 and 12 s were considered hyperalgesic and used in the study.

Any gross behavior, respiratory pattern, and gait changes were recorded. Motor blockade was rated: 0, no noticeable change; 1, slight hind paw weakness; and 2, ataxia of the hind paws. The persons who performed the tests were aware of the drug and the dose injected. A single dose of intrathecally administered morphine (2.5 μg) or carbamazepine (100 μg) was tested in the short-term and in the streptozotocin-induced diabetic neuropathy models.

Statistical Analysis

Differences between drug- and saline-treated rats at each time point were analyzed with by Kruskal-Wallis one-way analysis of variance by ranks followed by pairwise comparisons to the hyperalgesic values using the Mann–Whitney U test. The chi-square test was used to compare the proportions of motor blockade scores among the groups assessed in the tail-flick test that received 100, 150, or 200 μg of lamotrigine intrathecally. The values are reported as mean ± SD. A probability value ≤0.05 was considered significant.

Results

Lamotrigine produced increased latency in the tail-flick test only at doses ≥100 μg (fig. 1). Marked transient (40–60 min) motor blockade of the hind paw could be observed with the doses of 150 and 200 μg (fig. 2). Although the increase in response latency and the extent of motor blockade were dose-related, there was no correlation between response latency and the rate of motor impairment ($r^2 < 0.1$ at 15, 30, 60, and 120 min after intrathecal injection). Some animals remained analgesic after recovery from the motor blockade for as long as 24–48 h after intrathecal injection. In contrast, some animals showed ataxia of the hind paws but still had normal response latency. No changes in the respiratory pattern or behavior of the rats could be observed when the highest dose was used. None of the rats that received two or three doses of intrathecally administered lamotrigine presented any motor or sensory sequels, and the aspects of the spinal cord, meninges, and fiber around the catheter at autopsy were similar in the groups that received saline or lamotrigine.

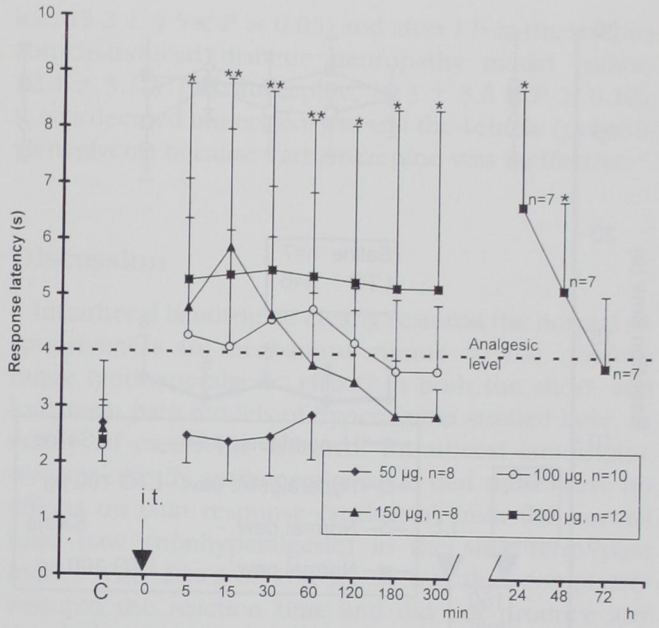

Fig. 1. Effects of intrathecal (it) administration of lamotrigine on the response latency (RL) in the rat tail-flick test. The rats that received 200 μg and exhibited response latency ≥4 s were tested after 24, 48, and 72 h of the it injection. *Significantly different from control ($P \leq 0.05$).

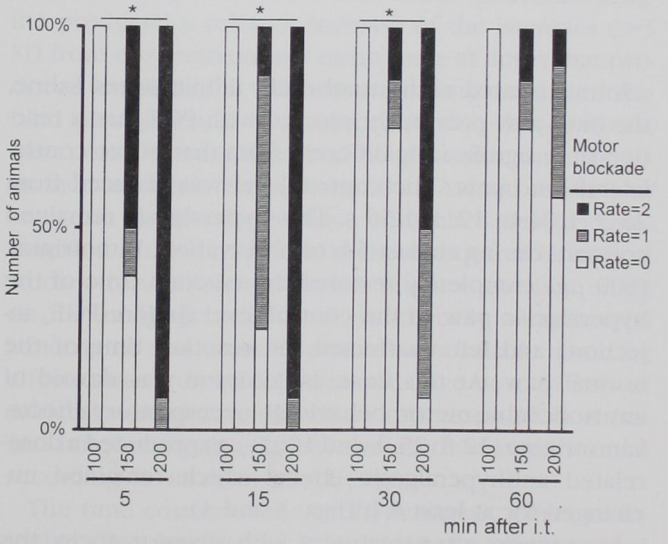

Fig. 2. Motor blockade produced by intrathecal injection of lamotrigine. The percentage of animals showing different rates of motor blockade is indicated for each group at different times of observation. The numbers of rats were 10, 8, and 12 for lamotrigine given at 100, 150, and 200 μg, respectively. Proportions were compared by chi-square analysis. *Significantly different ($P \leq 0.05$).

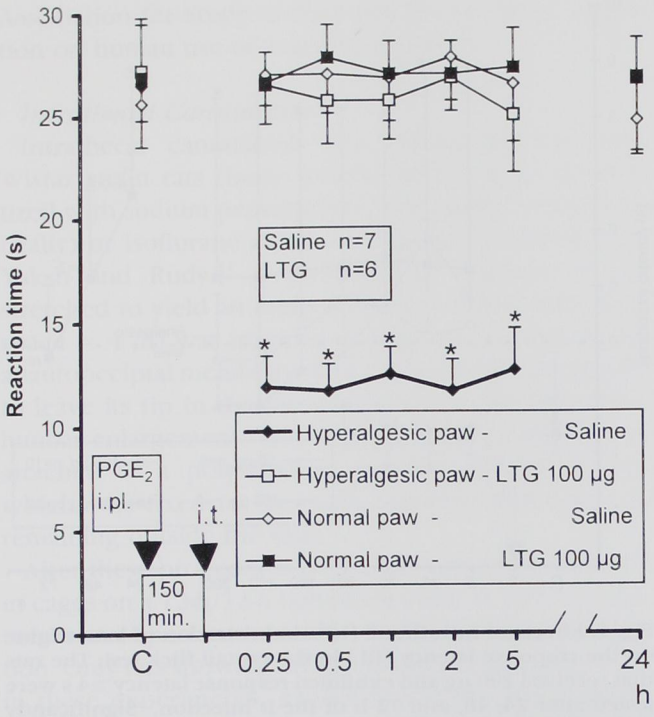

Fig. 3. Effects of intrathecal (it) administration of lamotrigine (LTG) or saline on reaction time in the paw pressure test, measured in the normal hind paw and in the hind paw made hyperalgesic by intraplantar (i.pl.) injection of prostaglandin E_2 (PGE_2). *Significantly different from control ($P \leq 0.05$). The normal paw was always tested before the hyperalgesic paw.

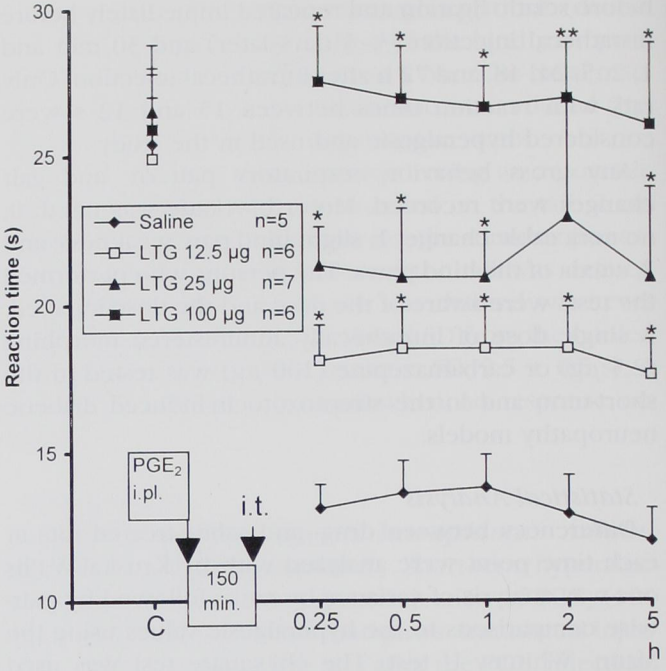

Fig. 4. Effects of intrathecal administration of lamotrigine (LTG) on reaction time in the rat paw pressure test. Short-term hyperalgesia was induced by intraplantar (i.pl.) injection of prostaglandin E_2 (PGE_2). *Significantly different from saline ($P \leq 0.05$).

In rats treated with intrathecally administered saline, the hind paw previously injected with PGE_2 had a reaction time significantly different from that of the contralateral hind paw. The control level was reduced from 26 ± 1.04 to 12 ± 1.56 s. This hyperalgesia remained constant during at least 5 h of observation. Lamotrigine (100 µg) completely restored the reaction time of the hyperalgesic paw to the control level (before PGE_2 injection) and left unaffected the reaction time of the normal paw. At this dose, lamotrigine was devoid of any noticeable motor, behavioral, or respiratory effects. Lamotrigine (12.5, 25.0, and 100.0 µg) produced a dose-related antihyperalgesic effect, which remained unchanged for at least 5 h (figs. 3 and 4).

Four weeks after treatment with streptozotocin, the rats exhibited symptoms of a diabetic state (weight loss, large belly, and muscle atrophy) with hyperglycemia (plasma glucose, 16.3 ± 1.4), and marked hyperalgesia (reaction time < 15 s). The results for rats with streptozotocin-induced diabetes are shown in figure 5. In-

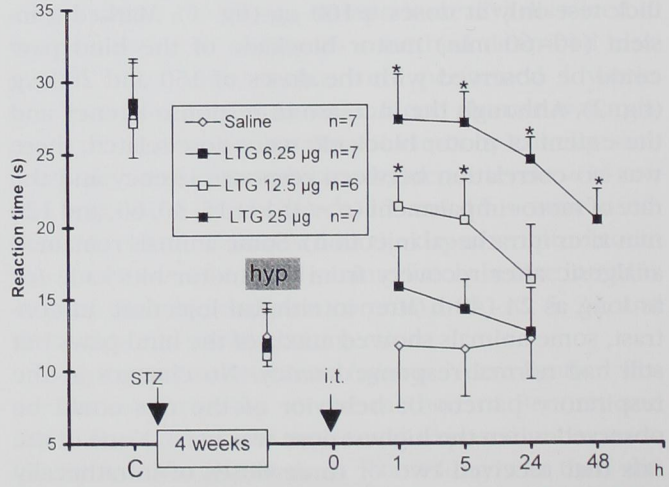

Fig. 5. Effects of intrathecal administration of lamotrigine (LTG) on reaction time in the rat paw pressure test. Long-term hyperalgesia (hyp) was induced by administration of streptozotocin (SZT) (streptozotocin-induced diabetic neuropathy). *Significantly different from saline ($P \leq 0.05$).

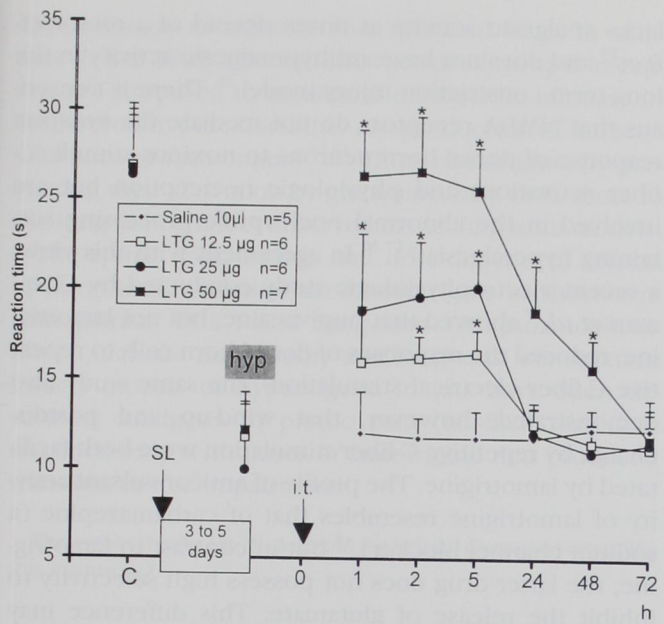

Fig. 6. Effects of intrathecal administration of lamotrigine (LTG) on the reaction time in the paw pressure test. Long-term hyperalgesia (hyp) was induced by loose sciatic ligation (SL) (long-term constriction injury). *Significantly different from saline ($P \leq 0.05$).

trathecally administered saline (10 μl) did not change the intensity of hyperalgesia during the observation period. Lamotrigine (6.25–25.00 μg) produced a dose-dependent increase in reaction time. The effect lasted longer with increasing doses of the drug. Lamotrigine (25 μg) completely restored the reaction time to control levels, and the antihyperalgesic effects were still significant 24 and 48 h after intrathecal injection.

Rats with loose ligation of the sciatic nerve showed a marked reduction of reaction time 3–5 days after surgery. In these rats, lamotrigine (12.5, 25.0, and 50.0 μg) induced a dose-dependent increase in reaction time. This effect remained constant for at least 5 h, and the effect of the highest dose was still significant 24 and 48 h after intrathecal administration (fig. 6).

Morphine and carbamazepine were tested in the short-term and streptozotocin-induced diabetic neuropathy models (data not shown). Intrathecally injected morphine was used as positive control and completely restored the reaction time to control levels at a dose of 2.5 μg. Intrathecally injected carbamazepine, a drug pharmacologically related to lamotrigine, produced only a slight increase in reaction time after 30 min in the short-term model (saline, 12.1 ± 2.4 s; carbamazepine, 15.2 ± 4.5 s; $P \leq 0.05$) and after 1 h in the streptozotocin-induced diabetic neuropathy model (saline, 12.4 ± 3.1 s; carbamazepine, 13.3 ± 3.6 s; $P > 0.10$). It was deemed unnecessary to test the vehicle (polyethyleneglycol) because carbamazepine was ineffective.

Discussion

Intrathecal lamotrigine clearly restored the normal responsiveness to mechanical stimuli to the noxious range (antihyperalgesic effect) in both the short- and long-term pain models of hyperalgesia studied here. In nearly all cases, the effect of intrathecal lamotrigine was specifically antihyperalgesic in that there were no effects on pain response (analgesia) from the normal hind paw (nonhyperalgesic) in the short-term pain model with doses of 100 μg or less that completely restored the reaction time and did not produce any detectable motor impairment. The effects were dose-dependent in all models and had a long duration in the long-term models. A significant antihyperalgesic effect could be observed in the long-term models of hyperalgesia for as long as 48 h after intrathecal injection of lamotrigine. The effect of intrathecally administered lamotrigine in the tail-flick test was examined in a preliminary screening for effectiveness. In this model, lamotrigine produced a relevant increase of the latencies (>3 SD from the pretreatment mean) only at doses that produced transient but marked motor impairment of the hind paw. Because of its inconsistency, this analgesic effect was not explored, although some animals remained analgesic for as long 48 h. Animal studies on analgesic agents should have controlled designs (randomized and blind) similar to those required in clinical studies. Nevertheless, because this was the first study on the analgesic activity of intrathecally administered lamotrigine and no information was available about its effectiveness (dose range and effective dose in 50% of subjects) or adverse effects in rats assessed in short- and long-term pain models, this study was performed according to an open-label design.

The time course of the antihyperalgesic effect of intrathecally administered lamotrigine was characterized by a short onset, followed by a plateau of at least 5 h and a gradual decline in the short- and long-term pain models. The long duration is the most impressive feature of the effect of lamotrigine. To date, data concerning the pharmacokinetics of lamotrigine in the cerebro-

spinal fluid that could correlate with the time course of its effects are not available, and measurement of its plasma concentration time course in rats receiving doses that produce antihyperalgesic effects also has not been performed. Lamotrigine is almost completely absorbed after oral administration (bioavailability, 97.6%),[15] and the oral doses that produce antihyperalgesic effects in the short-term and diabetes models are similar to those obtained with 100 μg injected intrathecally are 40- and 80-fold higher, respectively.[5,6] Therefore, the antihyperalgesic effects of intrathecally administered lamotrigine were very probably due to its action on the spinal cord. In addition, lamotrigine (100 μg) injected into the hyperalgesic paw is ineffective in the short-term pain model and does not prevent the development of sustained hyperalgesia.[6] Although the long-lasting antihyperalgesic effects and the motor impairment produced by lamotrigine were completely reversible, they could be indicative of drug-induced spinal cord lesion. To date, there have been no studies concerning the spinal cord neurotoxicity of lamotrigine; however, lamotrigine is considered to be a neuroprotective drug.[4] Therefore, a neurotoxic effect of lamotrigine is unlikely to determine its antihyperalgesic property.

The mechanism underlying the antihyperalgesic effect of intrathecally administered lamotrigine can only be speculated about. Lamotrigine probably exerts its anticonvulsant effects by blocking voltage-dependent sodium channels, thus stabilizing the presynaptic neuronal membrane and preventing the release of excitatory neurotransmitters, predominantly glutamate.[3] By this mechanism, intrathecally administered lamotrigine could prevent the activation of the glutamate receptors involved in pain transmission and central sensitization, *i.e.,* AMPA (2-amino-3 hydroxy-5-methyl-4-isoxazole-propionic acid), NMDA, and metabotropic receptors. The profile of the effects of lamotrigine on phasic pain (tail-flick test and the reaction time of the normal paw) and on hyperalgesia resembles the effects of glutamate antagonists acting spinally through the NMDA receptor. Typically, NMDA receptor antagonists injected intrathecally are more effective in the suppression of the hyperalgesic phase (second phase) than of the first phase (phasic pain) of the formalin paradigm[16–20] and can reduce phasic pain only at doses that cause motor impairment.[21–24] The motor blockade is suggestive of a local anesthetic activity of intrathecal lamotrigine. In contrast to lamotrigine, however, intrathecally injected lidocaine, a well-studied reversible sodium channel blocker, lacks analgesic activity at doses devoid of a motor effect[25] and does not have antihyperalgesic activity in the long-term constriction injury model.[26] There is consensus that NMDA receptors do not mediate the synaptic response of dorsal horn neurons to noxious stimuli (C-fiber activation) and physiologic nociception but are involved in the abnormal nociceptive processing sustaining hyperalgesia.[9,17,20] In agreement with this view, a recent electrophysiologic study conducted by Chapman *et al.*[27] showed that bupivacaine, but not lamotrigine, reduced the responses of dorsal horn cells to repetitive C-fiber electrical stimulation. The same study also demonstrated, however, that wind-up and postdischarge by repetitive C-fiber stimulation were both facilitated by lamotrigine. The profile of anticonvulsant activity of lamotrigine resembles that of carbamazepine (a sodium channel blocker),[15] but in contrast to lamotrigine, the latter drug does not possess high selectivity to inhibit the release of glutamate. This difference may explain the lack of antihyperalgesic activity of intrathecally administered carbamazepine in the short- and long-term (diabetic neuropathy) pain models of hyperalgesia used in the current study. In agreement with the low effectiveness observed after oral administration,[6] intrathecal injection of carbamazepine produced a small effect in the short-term model and was ineffective in the streptozotocin-induced diabetes model.

Spinal NMDA receptors are clearly involved in long-term constriction injury-evoked pain.[7,8,28,29] In this case, NMDA receptors are involved in development and sustenance of the abnormal sensations; therefore, the ability of lamotrigine to inhibit the release of glutamate was the major contribution to the antihyperalgesic effect reported here. Little information is available concerning the neurochemical mechanisms involved in the enhancement of the nociceptive reaction in the diabetes model. In this respect, a systemic substance P antagonist is capable of completely relieving the long-term hyperalgesia.[30] Studies addressing the participation of glutamate and NMDA receptors in this model of neuropathic hyperalgesia are not available, however, especially considering that lamotrigine can inhibit the evoked release of glutamate while having no effect on substance P release in rat isolated spinal cord.[31] Recently, it was shown that spinal substance P contributes to the generation but not to the maintenance of inflammatory hyperalgesia,[32] supporting the idea that substance P acting at the neurokinin (NK-1) receptor level mainly facilitates activation of NMDA receptors but is

not necessary to maintain this activated state. In addition to the NMDA receptors, the metabotropic receptors are supposed to mediate the long-term increase in the neuron hyperexcitability *via* production of intracellular second messengers.[32,33] Thus, lamotrigine, by preventing their activation by glutamate, may contribute to the long-lasting effect observed in the long-term models.

The spinal, long-lasting, and dose-dependent effects of intrathecally administered lamotrigine in short-term (intraplantar PGE_2) and long-term (streptozotocin-induced diabetic neuropathy and long-term constriction injury) models of hyperalgesia in rats have been described. Analgesia to phasic pain (tail-flick test) was obtained only with doses of lamotrigine that produced transient motor impairment.

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