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Effect of gabapentin and lamotrigine on mechanical allodynia-like behaviour in a rat model of trigeminal neuropathic pain

Dennis Christensen, Michèle Gautron, Gisèle Guilbaud, Valérie Kayser*

Unité de Recherches de Physiopharmacologie du Système Nerveux, INSERM U-161, 2 rue d'Alésia, 75014 Paris, France

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Abstract

Injury to the trigeminal nervous system may induce severe pain states. This study examined the antinociceptive effect of the novel anticonvulsants, gabapentin and lamotrigine, in a rat model of trigeminal neuropathic pain produced by chronic constriction of one infraorbital nerve. Responsiveness to von Frey filament stimulation of the vibrissal pad was evaluated 2 weeks post-operation. Hyper-responsive rats received acute and repeated (five injections separated by the half-life of the compound) injections with gabapentin and lamotrigine. 76% of the nerve-injured rats displayed pronounced hyper-responsiveness (median 0.217 g (lower–upper percentiles 0.217–0.217) vs. 12.5 g pre-operative), that was resistant to both single (5–100 mg/kg) and repeated (5–30 mg/kg) injections with i.p. lamotrigine. Repeated (30 and 50 mg/kg), but not single (30–100 mg/kg) injections of i.p. gabapentin partially alleviated the mechanical allodynia-like behaviour. Repeated injections of gabapentin at 50 but not at 30 mg/kg produced motor deficits. The results indicate that gabapentin rather than lamotrigine may be a better therapeutic approach for the clinical management of some trigeminal neuropathic pain disorders. © 2001 International Association for the Study of Pain. Published by Elsevier Science B.V. All rights reserved.

Keywords: Infraorbital nerve injury; Neuropathic pain; Allodynia; Rat; Anticonvulsant

1. Introduction

Sensory nerve damage may induce severe, so-called neuropathic pain. Clinical studies suggest that this chronic pain syndrome occurs more frequently in the trigeminal system than at spinal levels (Sweet, 1984). In addition, pathological painful conditions at the trigeminal level may present with a remarkable broad spectrum of symptoms (Fields, 1996). Idiopathic trigeminal neuralgia presents as brief stabbing pain in the distribution of the trigeminal nerve similar to an electric shock. Pain paroxysms may occur spontaneously but are usually triggered by light mechanical contact, sometimes distant from the region in which the pain is felt. Distinctive from idiopathic trigeminal neuralgia is secondary trigeminal neuralgia, characterized by a burning or aching pain. Pains only follow stimulation of the painful region (Burchiel, 1993; Loeser, 1994).

The anticonvulsants carbamazepine, and to a lesser extent phenytoin and baclofen, are the treatments of choice for idiopathic trigeminal neuralgia (Fields, 1996), although a substantial proportion of patients become refractory or intolerant to these medications (Killian and Fromm, 1968). Secondary trigeminal neuralgia is, however, very poorly controlled by these established drugs. Therefore, attention has been recently drawn on the novel anti-convulsant drugs, gabapentin and lamotrigine and their possible usefulness in trigeminal pain disorders. A growing number of reports suggest a beneficial effect of these compounds on various pain symptoms related to trigeminal nerve disease (Canavero and Bonicalzi, 1997; Lunardi et al., 1997; Zakrzewska et al., 1997; Sist et al., 1997a,b; Khan, 1998; Solaro et al., 1998).

Recently a rat model of trigeminal neuropathic pain produced by chronic constriction injury to the infraorbital nerve (CCI-ION) has been developed. Rats with a CCI-ION consistently display signs of abnormal spontaneous pain-related behaviour (Kryzhanovski et al., 1993) as well as mechanical (Vos et al., 1994; Idänpään-Heikkilä and Guilbaud, 1999) and thermal (Kryzhanovski et al., 1992; Imamura et al., 1997) hypersensitivity. We recently demonstrated that in this model, carbamazepine is devoid of effects at doses that do not induce sedation and baclofen has a moderate anti-allodynic effect after repeated, but not single injections (Idänpään-Heikkilä and Guilbaud, 1999).

In this study we examined the anti-allodynic effect of both single and repeated systemic administration of gaba-

* Corresponding author. Tel.: +33-1-4078-9350; fax: +33-1-4588-1304.
E-mail address: kayser@broca.inserm.fr (V. Kayser).

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pentin and lamotrigine against a mechanical stimulus in this model of trigeminal neuropathic pain.

2. Methods

All experiments were carried out in accordance with the European Communities Council Directive (86/609/EEC) as well as with Ministry of Agriculture regulations. In addition, we adhered to The Recommendations of the Committee for Research and Ethical Issues of the International Association for the Study of Pain (IASP) Ethical Guidelines (1983). In particular, the duration of the experiments was as short as possible and the number of animals used was kept to a minimum.

2.1. Animals

Male Sprague–Dawley rats (Charles River, France, strain Crl:CD(SD)BR), weighing 175–200 g on arrival, were used. The rats were housed five to a cage on a 12:12-h light/dark cycle. The ambient temperature was kept at 22°C, and the rats had free access to standard laboratory food and tap water. The animals were allowed to habituate to the housing facilities for at least 1 week before surgery.

2.2. Surgery

Rats were anesthetized with pentobarbital (Nembutal, 60 mg/kg i.p.) and the head of the rat was fixed in a Horsley–Clark stereotaxic frame. All surgery was performed under direct visual control using a Zeiss operation microscope (10–25 ×). A midline scalp incision was made, exposing skull and nasal bone. The infraorbital part of the left infraorbital nerve was exposed using a surgical procedure similar to that described by Gregg (1973) and Jacquin and Zeigler (1983). The edge of the orbit, formed by the maxillary, frontal, lacrimal and zygomatic bones, was dissected free. To give access to the infraorbital nerve, the orbital contents were gently deflected with a cotton-tipped wooden rod. The infraorbital nerve was dissected free at its most rostral extent in the orbital cavity, just caudal to the infraorbital foramen. Two chromic catgut (5-0) ligatures (2 mm apart) were loosely tied around the infraorbital nerve. To obtain the desired degree of constriction, a criterion formulated by Bennett and Xie (1988) was applied: the ligatures reduced the diameter of the nerve by a just noticeable amount and retarded, but did not interrupt the epineural circulation. The scalp incision was closed using silk sutures (5-0).

2.3. Nociceptive testing

Rats were placed individually in small (35 × 20 × 15 cm) plastic cages. Before any actual stimulation session rats were adapted to the observation cage and the testing environments for 2 h. During this period the experimenter reached slowly into the cage to touch the walls of the cage with a plastic rod, similar to the ones on which the von Frey filaments are mounted. After the 2 h of habituation rats were in a sniffing/no locomotion state (with four paws placed on the ground neither moving nor freezing) and the stimulation session was started. In rare cases a rat would still be moving/exploring after 2 h and the habituation period was then prolonged to 3 h. Mechanical sensitivity was determined with a graded series of six von Frey filaments (Semmes–Weinstein monofilaments, Stoelting, Wood Dale, IL, USA). The filaments produced a bending force of 0.217, 0.745, 2.15, 4.64 and 12.5 g. The stimuli were applied within the infraorbital nerve territory, near the centre of the vibrissal pad, on hairy skin surrounding the mystacial vibrissae. The filament was applied to the point of bending three times on the contralateral side and then on the nerve-injured side for a total of six applications per rat for each filament, always beginning with the filament producing the lowest force. During one session, the complete series of von Frey hair intensities was presented in an ascending series and either (1) a brisk withdrawal reaction of the head, rat pulls briskly the head backward; (2) escape/attack, rat avoids further contact with the filament either passively by moving its body away from the stimulating object to assume a crouching position against cage wall, sometimes with the head buried under the body, or actively by attacking the stimulus object, making biting and grabbing movements; (3) asymmetric face grooming, rat displays an uninterrupted series of at least three face-wash strokes directed to the stimulated facial area, often preceded by the brisk withdrawal reaction, was considered as nociceptive behaviour and the corresponding filament as the mechanical response threshold. These responses represent the highest scores in the rank-ordered response scoring system, initially described by Vos et al. (1994) and are sensitive to analgesic compounds (Idänpään-Heikkilä and Guilbaud, 1999; Christensen et al., 1999). The filament of 12.5 g was chosen as the cut-off threshold to prevent tissue injury and because the bending force already turned the head of the rat.

Nociceptive behavioural tests were performed 1 day before and 2 weeks after surgery, since at this time postoperatively, the abnormal response to mechanical stimulation in ION-ligated rats is at a stable maximum (Vos et al., 1994; Idänpään-Heikkilä and Guilbaud, 1999) and postoperative modified values in sham-operated rats has returned to values comparable with those seen in normal rats (Idänpään-Heikkilä and Guilbaud, 1999). In the preoperative test, stimulation with the filament of 12.5 g did not induce any nociceptive behaviour in the majority of the rats (~90%) and, in order to avoid non-specific responses, only these rats were included in the study.

Testing sessions, beginning at 09:30 h, were conducted in a quiet room by the same person, blind to the injected solution (vehicle or drug) and the dose used. Rats were randomly assigned in groups of 4–6 for a given series of tests. Each animal received drugs only once and was used in only one experiment. At the end of an experiment rats were killed.

2.4. Motor coordination testing

Locomotor function was tested using the Ugo Basile (Comerio, Italy) accelerating rotarod (model 7750) for rats. This apparatus consists of a base platform and a rotating rod of 3 cm diameter with a non-skid surface. The rod, 50 cm in length, is divided into four equal sections by five disks. Four rats were tested simultaneously. The animals were acclimatized to the revolving drum and habituated to handling in order to avoid stress during testing. The treadmill was set to accelerate from 4 to 40 rev./min in a period of 5 min. The integrity of motor coordination was assessed as the performance time on the rod measured from acceleration start until fall from the drum. The rats were acclimatized to acceleration by three training runs. The mean of the fourth and fifth training run served as control performance time (expressed in seconds).

2.5. Drugs

Gabapentin (30, 50 or 100 mg/kg, SigmaAldrich, St. Quentin, France) was diluted in sterile physiological saline and administered i.p. in a volume of 1 ml/kg. Lamotrigine (5, 15, 30, 60 or 100 mg/kg, GlaxoWellcome, Evreux, France) was administered i.p. in a volume of 2 ml/kg as a homogeneous suspension consisting of 0.5% carboxymethylcellulose/0.4% Tween-80/0.9% benzyl alcohol in saline. In addition to single injections, the drugs were injected repeatedly five times using the half-life ($t_{1/2}$) of each molecule as the injection interval: gabapentin 30 or 50 mg/kg × 5 ($t_{1/2}$ = 1 h 40 min; Radulovic et al., 1995); lamotrigine 5, 15 or 30 mg/kg × 5 ($t_{1/2}$ = 10 h; Walker et al., 1996). In each group the control rats received the same volume of vehicle.

2.6. Statistical analysis

Data on nociceptive testing are expressed as median (lower-upper percentiles) and analyzed by the nonparametric Kruskal–Wallis one-way analysis of variance. The Wilcoxon rank sum test (Mann–Whitney *U*-test) was used for individual comparisons. Data from the experiment on motor coordination are expressed as mean ± standard deviation (SD) and analyzed by one-way analysis of variance. The areas under the time curves (AUCs) were calculated using the trapezoidal rule. The *t*-test was used to compare overall effects (AUCs) between two groups. All procedures were carried out using a computer program (Statgraphics Plus, Manugistics, Rockville, MD, USA). The observed differences were regarded as being significant when the *P* values were less than 0.05.

3. Results

Two weeks after surgery 78 of 104 (76%) infraorbital nerve constricted rats presented a markedly increased responsiveness to mechanical stimulation of the territory of the ligated nerve. The mechanical response threshold was reduced from the pre-operative value of ≥ 12.5–0.217 g and occasionally 0.745 g (median threshold = 0.217 (0.217–0.217) g). In accordance with previous studies (Christensen et al., 1999; Idänpään-Heikkilä and Guilbaud, 1999) these rats showed a parallel increase in the responsiveness to stimulation of the territory of the contralateral infraorbital nerve (median threshold = 0.217 (0.217–0.217) g). In the remaining 25 of 104 (24%) infraorbital nerve-injured rats the median mechanical response threshold of the nerve-injured (12.5 (12.5–12.5) g) and the contralateral (12.5 (12.5–12.5) g) side was not modified.

3.1. Effect of lamotrigine

Single (5, 15, 30, 60, 100 mg/kg, n = 5–7 in each group) and repeated (5, 15, 30 mg/kg × 5, n = 5–7 in each group) injections of lamotrigine and vehicle were devoid of effects on the mechanical hyper-responsiveness. A single injection of 100 mg/kg as well as repeated injections at 30 mg/kg resulted in pronounced motor deficits and the animals were unable to perform the rotarod test.

3.2. Effect of gabapentin

Single i.p. injections of saline or the doses 30 or 50 mg/kg of gabapentin (n = 5–7 in each group) had no effect on the mechanical response threshold. At the dose 100 mg/kg a tendency towards an antinociceptive effect was observed after 90–150 min (Fig. 1A). However, at this dose gabapentin reduced the motor performance in the rotarod test (Fig. 1B). Repeated i.p. injections of saline did not modify either the mechanical response threshold (Fig. 2A,B) or the rotarod performance time (Fig. 2C). In contrast to single injections, repeated administration of gabapentin at both 30 and 50 mg/kg × 5 gradually increased the mechanical response threshold of both the nerve-injured and the contra-lateral side. At the dose 30 mg/kg an anti-allodynic effect was found already after the second injection. The maximal increase in the response thresholds of both the nerve-injured (2.15 (2.15–4.14) g) and the contralateral (2.15 (1–2.15) g) side was reached at 30 min after the third injection, and after the fifth and last injection the effect lasted up to 2 h (Fig. 2A,B). Repeated injections of gabapentin at 30 mg/kg was devoid of effects on motor coordination compared with saline-treatments (P = 0.23, Fig. 2C). At the dose 50 mg/kg, repeated injections of gabapentin also resulted in significant effects. Peak effects for both the nerve-injured (4.64 (2.6–4.64) g) and the contralateral (4.64 (2.6–4.64) g) side was reached at 30 min after the fifth injection, and after this last injection the effect lasted up to 2 h (Fig. 3A,B). However, repeated injections of the dose 50 mg/kg was associated with motor disturbances in comparison with saline-treated animals ($P < 0.01$, Fig. 3C). The overall anti-allodynic effect of repeated i.p injections of the dose 30 mg/kg and 50 mg/kg did not differ (P = 0.48).

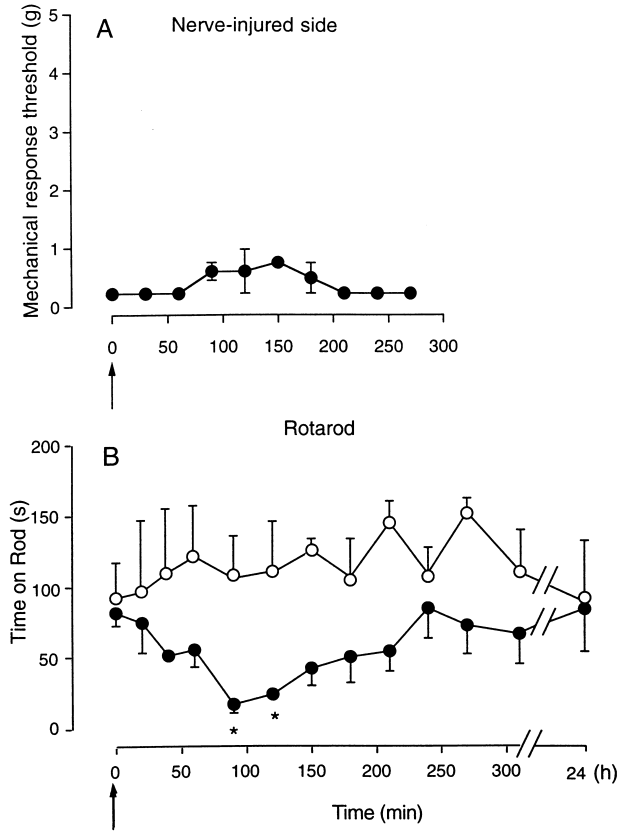

Fig. 1. Time course of the effect of a single injection (↑) of gabapentin (●, 100 mg/kg i.p.) or vehicle (○) on (A) the mechanical response threshold in rats with a CCI-ION and (B) rotarod performance. Each circle represents the median (A) or mean (B) of 6–9 animals. Vertical lines show lower and upper percentiles (A) or SD (B). *$P < 0.05$, **$P < 0.01$ vs. pre-injection control.

4. Discussion

Two weeks after surgery 76% of the animals displayed pronounced abnormal pain sensitivity. The mechanical hyper-responsiveness was observed not only on the lesioned but also on the contralateral, non-lesioned side as previously reported in both behavioural (Vos et al., 1994; Imamura et al., 1997; Christensen et al., 1999; Idänpään-Heikkilä and Guilbaud, 1999) and related electrophysiological (Benoist et al., 1999; Vos et al., 2000) studies. Increasing evidence indicates that following unilateral nerve lesion important changes occur in contralateral non-lesioned structures possibly via signalling in commissural interneurons in the spinal cord and brainstem (Koltzenburg et al., 1999).

The responses in 24% of the nerve-injured rats were not modified. Similar ratios (70–80%) of thermal (Bennett and Xie, 1988) and mechanical (Xu et al., 1999) allodynia-like behaviour are reported after injury to nerves of spinal origin. However, in contrast to the CCI to the sciatic nerve model in which different degrees of pain-related behaviour are observed (Attal et al., 1989, 1990), the present model displays a large separation between animals which exhibit

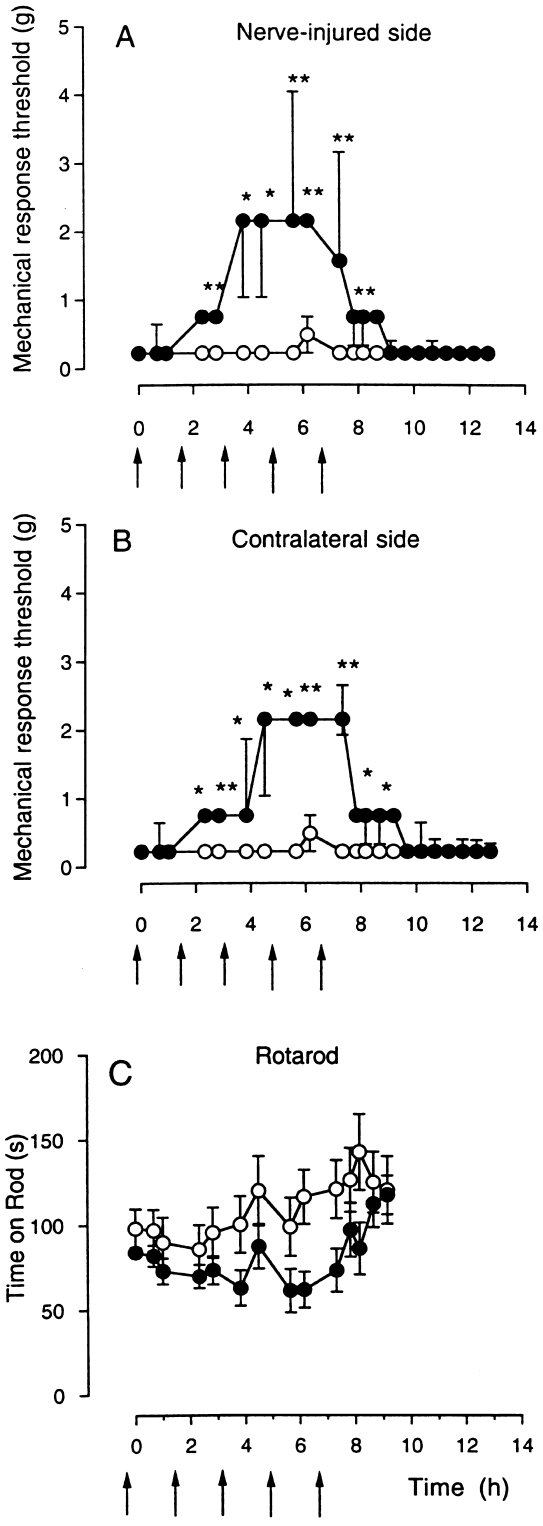

Fig. 2. Time course of the effect of repeated injections (↑) of gabapentin (30 mg/kg i.p., ●) or vehicle (○) on the mechanical response threshold of (A) the nerve-injured and (B) the contralateral side of rats with a CCI-ION, and on (C) rotarod performance. Each circle represents the median (A,B) or mean (C) of 6–9 animals. Vertical lines show lower and upper percentiles (A,B) or SD (C). *$P < 0.05$, **$P < 0.01$ vs. pre-injection control.

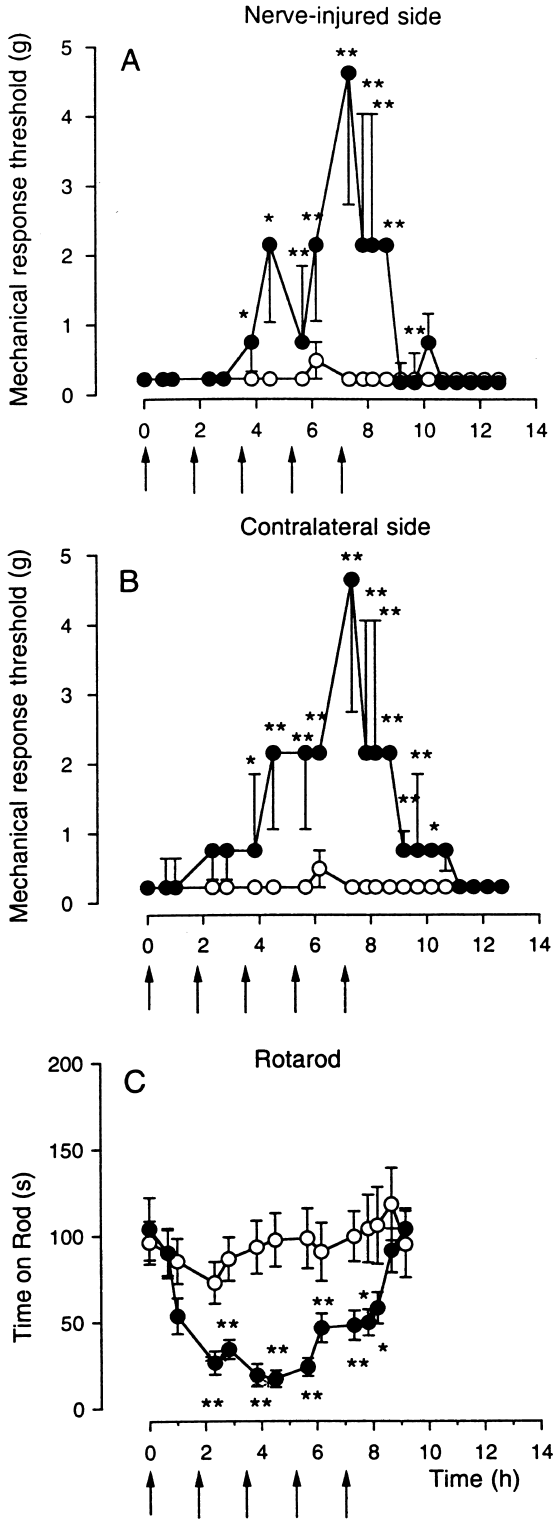

Fig. 3. Time course of the effect of repeated injections (↑ of gabapentin (50 mg/kg i.p., ●) or vehicle (○) on the mechanical response threshold of (A) the nerve-injured and (B) the contralateral side of rats with a CCI-ION, and on (C) rotarod performance. Each circle represents the median (A,B) or mean (C) of 6–9 animals. Vertical lines show lower and upper percentiles (A,B) or SD (C). *$P < 0.05$, **$P < 0.01$ vs. pre-injection control.

and which do not exhibit allodynia-like behaviour. CCI-ION seems to either profoundly alter the mechanical sensory processing in the trigeminal system producing a marked hyper-responsiveness or to have no effect. It may reflect some anatomo-physiological particularities of the trigeminal nerve system. While nerves of spinal origin are mixed, containing a significant motor component, the ION is purely sensory and processes in contrast to spinal nerves, distinct modalities of sensory information independently and from a well-defined and restricted region of the face (Dodd and Kelly, 1991).

Lamotrigine probably acts by stabilizing the slow inactivated conformation of a subtype of sodium channels (Cheung et al., 1992), but modulation of calcium and potassium currents has also been reported (Grunze et al., 1998). This may result in a reduced release of both excitatory (aspartate and glutamate) and inhibitory (GABA) amino acids (Leach et al., 1986; Teoh et al., 1995). In vivo, both systemic (Boyce et al., 1999) and intrathecal (Klamt, 1998) administration of lamotrigine is effective against a paw pressure-induced stimulus in the CCI to the sciatic nerve model. Similarly, in the streptozotocin-induced diabetic neuropathy model, systemic lamotrigine reduces paw pressure-induced hyperalgesia (Nakamura-Craig and Follenfant, 1995). However, in the spinal nerve (L5/L6) ligation model, lamotrigine had no effect against von Frey filament-induced mechanical allodynia-like behaviour (Hunter et al., 1997). In the present study both single and repeated injections of lamotrigine were devoid of effects on von Frey filament-induced hypersensitivity. A common pattern in these behavioural studies seems to be a stimulus-dependent effect of lamotrigine. A recent randomized controlled clinical trial failed to demonstrate any analgesic effect of lamotrigine on neuropathic pain (McCleane, 1999). The results from the present study further indicate that the status of lamotrigine as a potential analgesic in persistent pain states remains unclear.

Repeated, but not acute gabapentin was effective against the hyper-responsiveness to mechanical stimulation and partially alleviated the allodynia-like behaviour already after doses that were devoid of effects on motor coordination. The reason for the injection frequency-dependence of the effect is unknown. Interestingly, a recent study on spinal cord injured rats showed similar results. The hyper-responsiveness to von Frey filament stimulation was not modified by a single i.p. injection of gabapentin at the dose of 30 mg/kg, but repeated injections with the same dose alleviated allodynia-like behaviour after the third injection (Hao et al., 2000). Since repeated administration induces changes neither in gabapentin metabolism nor in pharmacokinetics (Radulovic et al., 1995; Vollmer et al., 1986), it has been suggested that build-up of the anti-allodynic effect of gabapentin may develop through a time-dependent mechanism or alternatively through a gradual accumulation of the effective concentration of the drug in the nervous system (Hao et al., 2000). It may be that damage to the trigeminal system

and spinal cord produces persistent pain that is less sensitive to gabapentin than the pain-related behaviour of the CCI to the sciatic nerve and related models of injury to nerves of spinal origin, in which a single injection of gabapentin is effective (Hunter et al., 1997; Pan et al., 1999; Kayser and Christensen, 2000).

The mechanism of action of gabapentin is unknown. Although the compound is structurally related to the neurotransmitter γ-aminobutyric acid (GABA) it does not interact with GABA receptors or GABA metabolism. However, gabapentin increases brain GABA in animals (Loscher et al., 1991) and man (Petroff et al., 1996), and enhances GABA release from various brain structures (Gotz et al., 1993; Kocsis and Honmou, 1994), modifications that may reinforce descending inhibitory pathways that modulate incoming pain signals. Note that repeated but not single injections of the $GABA_B$ receptor agonist, baclofen, also alleviate the allodynia-like behaviour in the CCI-ION model of trigeminal neuropathic pain (Idänpään-Heikkilä and Guilbaud, 1999). Alternatively, it has been shown that gabapentin blocks a subunit of calcium channels on neurons (Gee et al., 1996; Stefani et al., 1998) which may be relevant to antinociception considering the central role of intracellular calcium accumulation in the neuronal excitability associated with neuropathic pain (Goodchild, 1997). Finally, in rat brains gabapentin inhibits the synthesis of glutamate (Goldlust et al., 1995), an excitatory amino acid involved in pain transmission, but seems not to interact directly with the corresponding *N*-methyl-D-aspartate receptor (Suman-Chauhan et al., 1993). Whatever the mechanisms are, several animal studies (Hunter et al., 1997; Hwang and Yaksh, 1997; Chapman et al., 1998; Field et al., 1999; Pan et al., 1999) as well as recent randomized, controlled clinical trials (Backonja et al., 1998; Rowbotham et al., 1998) suggest that gabapentin is useful in neuropathic pain after damage to nerves of spinal origin. The present results support data from a number of case reports indicating that gabapentin may be beneficial also against pain associated with disease in the trigeminal nerve system (Sist et al., 1997a,b; Khan, 1998; Solaro et al., 1998). Our experiments do, however, also suggest some limitations to the use of gabapentin. The antinociceptive effect did not appear until the 2nd–3rd doses and disappeared about 2 h after the last dose, and the therapeutic window appeared narrow.

In conclusion, the present results suggest that gabapentin rather than lamotrigine may be a better therapeutic approach for the clinical management of some trigeminal neuropathic pain disorders.

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References

Attal N, Kayser V, Jazat F, Guilbaud G. Behavioural evidence for a bidirectional effect of systemic naloxone in a model of experimental neuropathy in the rat. Brain Res 1989;494:276–284.

Attal N, Kayser V, Guilbaud G. The bidirectional dose-dependent effect of systemic naloxone is also related to the intensity and duration of pain-related disorders: a study in a rat model of peripheral mononeuropathy. Brain Res 1990;525:170–174.

Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, Hes M, LaMoreaux L, Garofalo E. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. J Am Med Assoc 1998;280:1831–1836.

Bennett GJ, Xie YK. A peripheral mononeuropathy in rat that produces abnormal pain sensation like those seen in man. Pain 1988;33:87–107.

Benoist J-M, Gautron M, Guilbaud G. Experimental model of trigeminal pain in the rat by constriction of one infraorbital nerve (IoN): changes in neuronal activities in the Sm1 cortices corresponding to the IoN. Exp Brain Res 1999;126:383–398.

Boyce S, Wyatt A, Webb JK, O'Donnell R, Mason G, Rigby M, Sirinathsinghji D, Hill RG, Rupniak NM. Selective NMDA NR2B antagonists induce antinociception without motor dysfunction: correlation with restricted localisation of NR2B subunit in dorsal horn. Neuropharmacology 1999;38:611–623.

Burchiel KJ. Trigeminal neuropathic pain. Acta Neurochir Suppl (Wien) 1993;58:145–149.

Canavero S, Bonicalzi V. Lamotrigine control of trigeminal neuralgia: an expanded study. J Neurol 1997;244:527.

Chapman V, Suzuki R, Chamarette HL, Rygh LJ, Dickenson AH. Effects of systemic carbamazepine and gabapentin on spinal neuronal responses in spinal nerve ligated rats. Pain 1998;75:261–272.

Cheung H, Kamp D, Harris E. An in vitro investigation of the action of lamotrigine on neuronal voltage-activated sodium channels. Epilepsy Res 1992;13:107–112.

Christensen D, Gautron M, Guilbaud G, Kayser V. Combined systemic administration of the glycine/NMDA receptor antagonist, (+)-HA966 and morphine attenuates pain-related behaviour in a rat model of trigeminal neuropathic pain. Pain 1999;83:433–440.

Dodd J, Kelly JP. Trigeminal system. In: Kandel ER, Schwarz JH, Jessel TM, editors. Principles of neural science, vol 3. New York: Elsevier, 1991, pp. 701–710.

Field MJ, McCleary S, Hughes J, Singh L. Gabapentin and pregabalin, but not morphine and amitriptyline, block both static and dynamic components of mechanical allodynia induced by streptozocin in the rat. Pain 1999;80:391–398.

Fields HL. Treatment of trigeminal neuralgia. N Engl J Med 1996;334:1125–1126.

Gee NS, Brown JP, Dissanayake VU, Offord J, Thurlow R, Woodruff GN. The novel anticonvulsant drug, gabapentin (Neurontin), binds to the alpha2delta subunit of a calcium channel. J Biol Chem 1996;271:5768–5776.

Goldlust A, Su TZ, Welty DF, Taylor CP, Oxender DL. Effects of anticonvulsant drug gabapentin on the enzymes in metabolic pathways of glutamate and GABA. Epilepsy Res 1995;22:1–11.

Goodchild CS. Nonopioid spinal analgesics: animal experimentation and implications for clinical developments. Pain Rev 1997;4:33–58.

Gotz E, Feuerstein TJ, Lais A, Meyer DK. Effects of gabapentin on release of gamma-aminobutyric acid from slices of rat neostriatum. Arzneimittelforschung 1993;43:636–638.

Gregg JM. A surgical approach to the opthalmic maxillary nerve trunk in the rat. J Dent Res 1973;52:392.

Grunze H, von Wegerer J, Greene RW, Walden J. Modulation of calcium and potassium currents by lamotrigine. Neuropsychobiology 1998;38:131–138.

Hao JX, Xu X-J, Urban L, Wiesenfeld-Hallin Z. Repeated administration of

systemic gabapentin alleviates allodynia-like behaviors in spinally injured rats. Neurosci Lett 2000;280:211–214.

Hunter JC, Gogas KR, Hedley LR, Jacobson LO, Kassotakis L, Thompson J, Fontana DJ. The effect of novel anti-epileptic drugs in rat experimental models of acute and chronic pain. Eur J Pharmacol 1997;324:153–160.

Hwang JH, Yaksh TL. Effect of subarachnoid gabapentin on tactile-evoked allodynia in a surgically induced neuropathic pain model in the rat. Reg Anesth 1997;22:249–256.

Idänpään-Heikkilä JJ, Guilbaud G. Pharmacological studies on a rat model of trigeminal neuropathic pain: baclofen, but not carbamazepine, morphine or tricyclic antidepressants, attenuates the allodynia-like behaviour. Pain 1999;79:281–290.

Imamura Y, Kawamoto H, Nakanishi O. Characterization of heat-hyperalgesia in an experimental trigeminal neuropathy in rats. Exp Brain Res 1997;116:97–103.

Jacquin NF, Zeigler HP. Trigemial arosensation and ingestive behaviour in the rat. Behav Neurosci 1983;97:62–97.

Kayser V, Christensen D. Antinociceptive effect of systemic gabapentin in mononeuropathic rats, depends on stimulus characteristics and level of test integration. Pain 2000;88:53–60.

Khan OA. Gabapentin relieves trigeminal neuralgia in multiple sclerosis patients. Neurology 1998;51:611–614.

Killian JM, Fromm GH. Carbamazepine in the treatment of neuralgia. Use of side effects. Arch Neurol 1968;19:129–136.

Klamt JG. Effects of intrathecally administered lamotrigine, a glutamate release inhibitor, on short- and long-term models of hyperalgesia in rats. Anesthesiology 1998;88:487–494.

Kocsis JD, Honmou O. Gabapentin increases GABA-induced depolarization in rat neonatal optic nerve. Neurosci Lett 1994;169:181–184.

Koltzenburg M, Wall PD, McMahon SB. Does the right side know what the left is doing? Trends Neurosci 1999;22:122–127.

Kryzhanovski GN, Reshnyak VK, Dolgikh VG, Gorizontova MP, Speranskaya TV. Trigeminal neuralgia of neuropathic origin. Bull Exp Biol Med (English version) 1992;112:1059–1062.

Kryzhanovski GN, Dolgikh VG, Gorizontova MP, Mironova IV. Formation of a pathological system in rats with neuropathic trigeminal neuralgia. Bull Exp Biol Med (English version) 1993;115:623–625.

Leach MJ, Marden CM, Miller AA. Pharmacological studies on lamotrigine, a novel potential antiepileptic drug: II. Neurochemical studies on the mechanism of action. Epilepsia 1986;27:490–497.

Loeser JD. Tic douloureux and atypical face pain. In: Wall PD, Melzack R, editors. The textbook of pain, 3rd ed. London: Churchill-Livingstone, 1994, pp. 699–711.

Loscher W, Honack D, Taylor CP. Gabapentin increases aminooxyacetic acid-induced GABA accumulation in several regions of rat brain. Neurosci Lett 1991;128:150–154.

Lunardi G, Leandri M, Albano C, Cultrera S, Fracassi M, Rubino V, Favale E. Clinical effectiveness of lamotrigine and plasma levels in essential and symptomatic trigeminal neuralgia. Neurology 1997;48:1714–1717.

McCleane G. 200 mg daily of lamotrigine has no analgesic effect in neuropathic pain: a randomised, double-blind, placebo controlled trial. Pain 1999;83:105–107.

Nakamura-Craig M, Follenfant RL. Effect of lamotrigine in the acute and chronic hyperalgesia induced by PGE2 and in the chronic hyperalgesia in rats with streptozotocin-induced diabetes. Pain 1995;63:33–37.

Pan HL, Eisenach JC, Chen SR. Gabapentin suppresses ectopic nerve discharges and reverses allodynia in neuropathic rats. J Pharmacol Exp Ther 1999;288:1026–1030.

Petroff OA, Rothman DL, Behar KL, Lamoureux D, Mattson RH. The effect of gabapentin on brain gamma-aminobutyric acid in patients with epilepsy. Ann Neurol 1996;39:95–99.

Radulovic LL, Turck D, von Hodenberg A, Vollmer KO, McNally WP, DeHart PD, Hanson BJ, Bockbrader HN, Chang T. Disposition of gabapentin (neurontin) in mice, rats, dogs, and monkeys. Drug Metab Dispos 1995;23:441–448.

Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. J Am Med Assoc 1998;280:1837–1842.

Sist T, Filadora V, Miner M, Lema M. Gabapentin for idiopathic trigeminal neuralgia: report of two cases. Neurology 1997a;48:1467.

Sist TC, Filadora VA, Miner M, Lema M. Experience with gabapentin for neuropathic pain in the head and neck: report of ten cases. Reg Anesth 1997b;22:473–478.

Solaro C, Lunardi GL, Capello E, Inglese M, Messmer UM, Uccelli A, Mancardi GL. An open-label trial of gabapentin treatment of paroxysmal symptoms in multiple sclerosis patients. Neurology 1998;51:609–611.

Stefani A, Spadoni F, Bernardi G. Gabapentin inhibits calcium currents in isolated rat brain neurons. Neuropharmacology 1998;37:83–91.

Suman-Chauhan N, Webdale L, Hill DR, Woodruff GN. Characterisation of [^{3}H]gabapentin binding to a novel site in rat brain: homogenate binding studies. Eur J Pharmacol 1993;244:293–301.

Sweet WH. Deafferentation pain after posterior rhizotomy, trauma to a limb, and herpes zoster. Neurosurgery 1984;15:928–932.

Teoh H, Fowler LJ, Bowery NG. Effect of lamotrigine on the electrically-evoked release of endogenous amino acids from slices of dorsal horn of the rat spinal cord. Neuropharmacology 1995;34:1273–1278.

Vollmer KO, von Hodenberg A, Kolle EU. Pharmacokinetics and metabolism of gabapentin in rat, dog and man. Arzneimittelforschung 1986;36:830–839.

Vos BP, Strassman AM, Maciewicz RJ. Behavioral evidence of trigeminal neuropathic pain following chronic constriction injury to the rat's infraorbital nerve. J Neurosci 1994;14:2708–2723.

Vos BP, Benoist J-M, Gautron M, Guilbaud G. Changes in neuronal activities in the two ventral posterior medial thalamic nuclei in an experimental model of trigeminal pain in the rat by constriction of one infraorbital nerve. Somat Motor Res 2000;17:109–122.

Walker MC, Perry H, Tomg X, Patsalos PN. Cerebro-spinal fluid and blood kinetics of lamotrigene in rat. Epilepsia 1996;37:214.

Xu M, Kontinen VK, Kalso E. Endogenous noradrenergic tone controls symptoms of allodynia in the spinal nerve ligation model of neuropathic pain. Eur J Pharmacol 1999;366:41–45.

Zakrzewska JM, Chaudhry Z, Nurmikko TJ, Patton DW, Mullens EL. Lamotrigine (lamictal) in refractory trigeminal neuralgia: results from a double-blind placebo controlled crossover trial. Pain 1997;73:223–230.