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The effect of novel anti-epileptic drugs in rat experimental models of acute and chronic pain

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Abstract

The novel anti-epileptic drugs lamotrigine, felbamate and gabapentin were compared in rat experimental models of acute (tail flick) and chronic pain: the chronic constriction injury and spinal nerve ligation models. Lamotrigine (10–100 mg/kg, s.c.), felbamate (150–600 mg/kg, i.p.) and gabapentin (30–300 mg/kg, i.p.) each reversed cold allodynia (chronic constriction injury model) with ED_{50} values of 28, 241 and 103 mg/kg, respectively, 1 h post-dose. However, only gabapentin reversed tactile allodynia (spinal nerve ligation model) with an ED_{50} of 34 mg/kg (i.p.). The established anti-epileptic drugs, carbamazepine (1–30 mg/kg, i.p.) and phenytoin (1–100 mg/kg, s.c.), were ineffective in both models. The anti-allodynic effect of the newer anti-epileptic drugs was observed at doses that were either ineffective or produced only a negligible effect on acute nociceptive function and/or locomotor activity. In conclusion, the data suggest that the newer anti-epileptic drugs appear to have the potential to be effective alternatives to either carbamazepine or phenytoin in the treatment of neuropathic pain. However, only gabapentin ameliorated both cold and touch hyperesthesias.

Keywords: Neuropathic pain; Allodynia; Antinociception; Tail-flick test; Behavior; Electroshock test, maximal; Lamotrigine; Felbamate; Gabapentin

1. Introduction

Chronic abnormal pain syndromes that follow peripheral nerve damage have been found to have a much reduced sensitivity to the two major classes of analgesics, opioids (Arner and Myerson, 1993) and non-steroidal anti-inflammatory drugs (Max et al., 1988). In the search for alternative forms of treatment, anti-convulsants have emerged amongst the more commonly used pharmacological interventions (reviewed by Swerdlow, 1984; McQuay et al., 1995). Carbamazepine and, to a lesser extent phenytoin, have been found to be useful against various types of neuropathic pain conditions (Swerdlow, 1984; McQuay et al., 1995), but appear to have particular utility when there is a paroxysmal, lancinating component, e.g. trigeminal neuralgia (Campbell et al., 1966; Killian and Fromm, 1968). However, pain relief has often been obtained concomitantly with numerous adverse events (Campbell et al., 1966; Killian and Fromm, 1968; Rull et al., 1969) and/or limitations in efficacy (Killian and Fromm, 1968; Saudek et al., 1977; Leijon and Boivie, 1989) which have restricted tolerability of these drugs.

The novel anti-epileptic drugs lamotrigine, felbamate and gabapentin have emerged as agents with the potential for mono-therapy in the treatment of epilepsy, particularly in those types refractory to the established drugs, carbamazepine and phenytoin (for review see Upton, 1994). It has been suggested that this may be due, in part, to the newer anti-epileptic drugs having either alternative or additional mechanisms of action to the frequency-dependent sodium channel blockade attributed to the anti-epileptic action of carbamazepine and phenytoin (Macdonald and Kelly, 1994; Upton, 1994). For example, it has been proposed that lamotrigine, felbamate and/or gabapentin exert either a pre- or post-synaptic modulation of glutaminergic transmission which may contribute to the overall therapeutic profile (Cheung et al., 1992; White et al., 1992; Leach et al., 1986; McCabe et al., 1993; DeSarro et al., 1994; Singh et al., 1996), although only felbamate has been shown to interact directly with any of the glutamate

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receptor sub-types. Both gabapentin (Kocsis and Honmou, 1994) and felbamate (Rho et al., 1994) have also been suggested to potentiate GABAergic function without having any direct interaction with GABA/benzodiazepine sites (Swinyard et al., 1986; Rock et al., 1993; Suman-Chauhan et al., 1993).

Recent evidence suggests that several key events contribute towards the pathogenesis of abnormal pain states following a peripheral nerve injury. Thus, high frequency spontaneous discharge from ectopic sites in the peripheral nerve (for review see Devor, 1994) following injury causes enhanced spinal glutamate release leading to an increased responsiveness of dorsal horn neurons (Woolf and Wall, 1986) and expansion of the cutaneous receptive field, i.e. central sensitization (Cook et al., 1987). Spinal neuron disinhibition involving a loss of GABAergic function (Sivilotti and Woolf, 1994) contributes to the hyperexcitable state. A prominent manifestation of central sensitization is allodynia, a state in which normally innocuous input is perceived as pain (Campbell et al., 1988; Woolf and Doubell, 1994). Since all of the novel anti-epileptic drugs have been described as having either a direct or indirect influence on glutaminergic or GABAergic transmission, the present study therefore examined the potential anti-allodynic properties of the novel anti-epileptic drugs against tactile and cold allodynia in two rodent models of neuropathic pain. A comparison was made with drug performance in an acute, high threshold test of nociception (tail flick) and on motor coordination.

2. Materials and methods

The following experimental procedures for the surgical preparation and testing of animals were reviewed and approved by the Institute Animal Care and Use Committee at Roche Bioscience.

2.1. Animals

Adult male Sprague-Dawley rats (Harlan) of various weight ranges (see individual experimental procedures) were used in all experiments. Animals were housed two per cage and allowed free access to food and water on a 12 h light/dark cycle in rooms that were temperature and humidity controlled.

2.2. Chronic constriction injury

The chronic constriction injury was produced according to the previously described procedure of Bennett and Xie (1988). Briefly, rats (150–180 g at time of surgery) were anesthetized with sodium pentobarbital (70 mg/kg, i.p., supplemented if required). The common right sciatic nerve was exposed at mid-thigh level and, proximal to the trifurcation of the sciatic, four loose ligatures (4.0 chromic gut) with about 1 mm spacing were tied around the nerve. The desired degree of constriction retarded but did not block circulation through the epineurial vasculature. In every animal, an identical (sham) procedure was performed on the opposite side (left) with the exception that the sciatic nerve was not ligated. All operations were completed by closing the muscle in layers, applying wound clips to close the skin incision and allowing the animals to recover for a period of 5–7 days.

The cold water test has been previously described in detail (Hedley et al., 1995). Each animal is placed onto a metal stage submerged to a depth of 2.5 cm in ice-cold water (0°C) contained within a square Perspex chamber (21×21 cm). The animal responds by lifting the paw on the ligated side out of the water. The latency to paw withdrawal (mean $\pm$ standard error of the mean, S.E.M.) was measured at 6.8 ± 0.8 s ($n = 28$). At no time did any animal withdraw the paw on the sham side from the cold water. This being the case we arbitrarily set a maximum cut-off of 20 s to avoid any possible interference with the sensitivity of the animal to respond to subsequent post-treatment exposure to the cold stimulus. For each experiment, animals were first pre-screened twice with 20 min interval between tests, in order to select for animals displaying clear signs of cold allodynia, i.e. animals with a paw withdrawal latency on the ligated side of < 13 s in both trials. The animals were then randomly assigned to groups consisting of 8–10 animals per group. The latency to paw withdrawal was then determined at 1, 3 and/or 5 h post-treatment.

2.3. Spinal nerve (L5/L6) ligation

Spinal nerve ligation was carried out as previously described (Kim and Chung, 1992). Rats (150–180 g at time of surgery) were anesthetized with sodium pentobarbital (70 mg/kg, i.p., supplemented if required) and the L5 and L6 spinal nerves then tightly ligated (6.0 silk suture) just distal to the dorsal root ganglia. The muscle was then closed in layers, wound clips applied to close the skin incision and the animals allowed to recover for a period of at least 5 days before testing.

Tactile allodynia was evaluated in spinal nerve ligated animals with a calibrated series of eight von Frey filaments as described previously (Chaplan et al., 1994). Briefly, the rats were placed in clear plastic cages (H: 5″, L: 10″, W: 4 5/8″) fitted with a wire mesh floor and allowed to acclimate for 15 min. The following filaments, ($\log_{10}$ of the bending force (g)), were employed to test for allodynia: 0.4, 0.7, 1.2, 2.0, 3.6, 5.5, 8.5 and 15.1 g. Filaments of greater force were not used since these alone would physically lift the paw. Each filament was applied once to the mid-plantar surface of the affected hindpaw. It was applied in a perpendicular fashion and depressed slowly (4–6 s) until bending occurred. From the overall pattern of responses a 50% gram withdrawal threshold was calculated

(see Chaplan et al., 1994; Jett et al., 1996), according to the following formula:

$$50\%\ \text{withdrawal threshold (g)} = \frac{10(10^{[xf-kd]})}{10\,000}$$

where *xf* is the value (in log units) of the final von Frey hair used; *k* is the pattern value and *d* is the mean difference (in log units) between filaments: 0.223.

For each experiment, animals were first pre-screened in order to select for animals displaying clear signs of tactile allodynia, i.e. animals with a 50% gram paw withdrawal threshold of < 4 g on the ligated side. The animals were then randomly assigned to groups consisting of 8–10 animals per group. The 50% gram paw withdrawal threshold was then determined 60 min post-treatment.

The above procedure was carried out solely in spinal nerve ligation animals after preliminary experiments had determined that application of the von Frey filaments to chronic constriction injury animals in a similar manner failed to elicit a tactile allodynic response.

2.4. Tail flick

Rats (180–220 g), 8–10 animals per group, were loosely wrapped, individually, in a thin cotton towel with the head covered and tail exposed. Each animal was then placed on a platform with the tail positioned in a specialized shallow groove and a focused beam of light directed at the tail from above, approximately 2.5 cm from the tip. Movement of the tail from the groove allows the beam of light to hit a sensor, formerly covered by the tail, which then automatically switches off the beam and stops the timer. The duration of time required for the tail response after exposure to the thermal stimulus was considered the tail response latency time. The maximum time allowed was 10 s in order to prevent tissue damage. Rats were tested once to determine the pre-dose tail response latency following which they were then dosed and again tested for their tail response latency at 60 min post-dose.

2.5. Maximal electroshock seizure test

Each rat (80–130 g) received a single, electroconvulsive shock stimulus (99 mA), evoked using orbital electrodes, for a duration of 2 s (ECT unit, Ugo Basile, Milan, Italy). The criterion for the occurrence of seizure activity was the tonic extension of hind limbs. Vehicle or drugs were administered 60 min prior to electroshock to groups of 10 animals and the number protected (%) by each dose of drug recorded.

2.6. Spontaneous locomotor activity

The motor activity boxes consisted of 14 standard Perspex transfer cages. Each cage is surrounded by an Automated Cage Activity System (San Diego Instruments) containing a 1 inch band of photobeams and photosensors numbering three per box. The number of photobeam breaks was analyzed by PC computer using PAS software. In order to assess drug action against optimal locomotor and exploratory behavior, at a time convenient to the operator, rats (200–250 g) were housed under reversed 12 h light/dark cycle conditions and tested in an enclosed room illuminated with only dim red light. Vehicle or drug was administered to groups of eight rats and motor activity assessed, 1 h post-drug administration, by placing the rats in the computerized cages for a period of 15 min. Rats were not previously habituated to the cage as this would have compromized the analysis of drug action. The number of activity counts, i.e., two or more beams broken in succession, was then recorded for each rat and the mean $\pm$ S.E.M. calculated for each group. The treatment groups were balanced across the 14 activity boxes and across all of the test sessions.

2.7. Drugs

Drugs were administered either intraperitoneally (gabapentin, felbamate and carbamazepine) or subcutaneously (lamotrigine and phenytoin) in a dose volume of either 2 ml/kg (all except felbamate) or 1 ml/kg (felbamate). Historical and preliminary examination of these drugs determined the route of administration in each individual case. Gabapentin was dissolved in distilled water, felbamate in 1-methyl 2-pyrrolidinone and carbamazepine in 40% polypropylene glycol : 10% ethanol : 5% sodium benzoate/benzoic acid : 2% benzyl alcohol). Lamotrigne and phenytoin were administered as a homogenous suspension consisting of 0.5% carboxymethylcellulose : 0.4% Tween 80 : 0.9% benzyl alcohol in saline.

2.8. Statistics

All group comparison data were analyzed using a Kruskal-Wallis one-way analysis of variance (ANOVA) followed by a pairwise comparison between vehicle and each drug-treated group using a Dunnett's *t*-test on the ranked data. Drug effects were considered to be statistically significant only if they were different from both the pre-dose data and the vehicle data (at that time point) at the $P < 0.05$ level.

2.8.1. Parameter estimation

The percent maximum possible effect was calculated for each animal in the form of $100 \times [(\text{post-dose} - \text{pre-dose})/(\text{cutoff} - \text{pre-dose})]$. ED_{50} values (mean with 95% confidence limits) were estimated using the following sigmoidal model: % maximum possible effect $= min + (max - min)/\{1 + \exp[(ED_{50} - \text{dose})/N]\}$, where ED_{50} is the concentration for the compound to achieve half of the

maximum response in the dose-response curve, *N* is the curvature parameter, *max* is the maximum response and *min*, the minimum response. In most cases, *max* extrapolated to 100% with the exception of the gabapentin curve in the tactile allodynia model where *max* was constrained to the mean value of the highest dose (300 mg/kg) group with respect to % of the maximum possible effect in the model. Nonlinear curve fitting was carried out using SAS (Cary, NC, USA).

3. Results

3.1. Effects of anti-epileptic drugs on neuropathy-induced cold allodynia

Animals with the chronic constriction injury to the sciatic nerve displayed cold allodynia by lifting only the ligated leg out of the pool of ice-cold (0°C) water with a latency (mean ± S.E.M.) of 6.8 ± 0.8 s ($n = 28$). The cut-off latency for the test was 20 s.

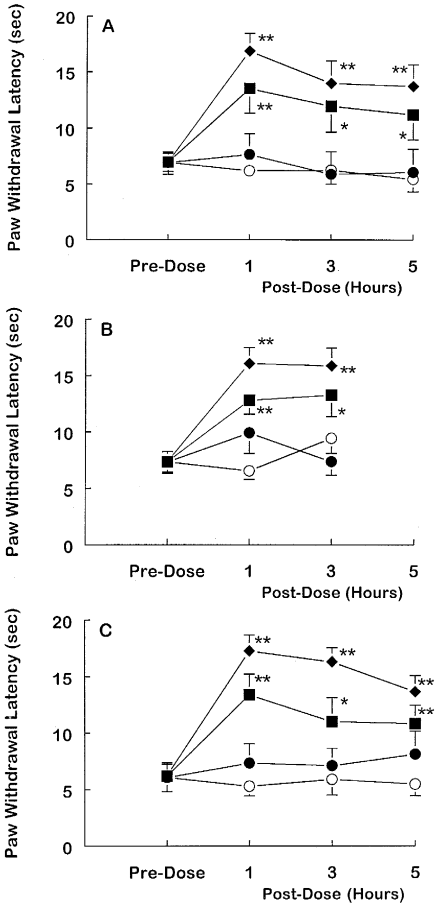

Fig. 1. Effect of (A) lamotrigine at 10 (●), 30 (■) and 100 (♦) mg/kg, s.c., (B) felbamate at 150 (●), 300 (■) and 600 (♦) mg/kg, i.p., and (C) gabapentin at 30 (●), 100 (■) and 300 (♦) mg/kg, i.p., on cold water-induced allodynia in rats with a chronic constriction injury to the sciatic nerve. The open circles in each case represent the vehicle control. Each bar represents the mean latency to paw withdrawal (s) ± S.E.M., of 8–10 animals per group. Level of statistical significance from pre-dose control and vehicle control groups at each time point is denoted by either the single ($P < 0.05$) or double ($P < 0.01$) asterisks.

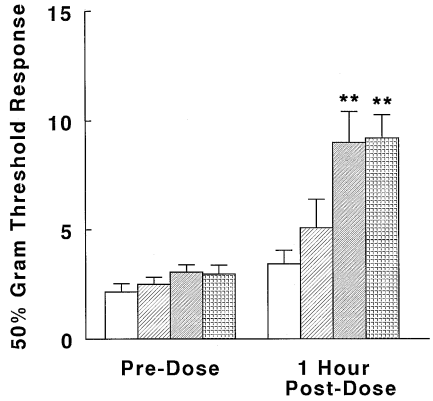

Fig. 2. Effect of gabapentin on the tactile allodynic response to a series of von Frey filaments in spinal nerve (L5/L6) ligated rats. Vehicle (white) or gabapentin at 30 (diagonal lines), 100 (dots) or 300 (stippled) mg/kg (i.p.) was administered intraperitoneally 1 h before testing. Each bar represents the mean latency to paw withdrawal (50% gram threshold) ± S.E.M., of 8–10 animals per group. Level of statistical significance from pre-dose control and vehicle control groups at each time point is denoted by the double ($P < 0.01$) asterisks.

At 1 h post-dose, lamotrigine (10–100 mg/kg, s.c.), felbamate (150–600 mg/kg, i.p.) and gabapentin (30–300 mg/kg, i.p.) produced a dose-dependent increase in the latency to paw withdrawal from the cold water stimulus with ED_{50} (mean with 95% confidence limits) values of 28 (18, 38), 241 (146, 337) and 103 (66, 140) mg/kg, respectively (Fig. 1). At the highest dose tested, lamotrigine (100 mg/kg, s.c., $P < 0.01$), felbamate (600 mg/kg, i.p., $P < 0.01$) and gabapentin (300 mg/kg, i.p., $P < 0.01$) all produced a significant and sustained (> 3 h) elevation in the paw withdrawal latency to the cold water stimulus (Fig. 1). For lamotrigine ($P < 0.01$) and gabapentin ($P < 0.01$) there was still a significant anti-cold allodynic effect at 5 h post-dose (Fig. 1).

The established anti-convulsants, carbamazepine (1–30 mg/kg, i.p.) and phenytoin (1–100 mg/kg, s.c.) were found to be ineffective at all doses tested (data not shown). At the highest dose of carbamazepine tested (30 mg/kg, i.p.), the latency to paw withdrawal at 1 h post-dose was 13.3 ± 2.1 s (vs. 9.8 ± 2.3 s for the vehicle; $P > 0.05$). For phenytoin at the highest dose tested (100 mg/kg, s.c.), the latency to paw withdrawal at 1 h post-dose was 13.3 ± 2.1 s (vs. 9.8 ± 2.3 s for the vehicle; $P > 0.05$).

3.2. Effects of anti-epileptic drugs on neuropathy-induced tactile allodynia

Spinal nerve (L5/L6) ligated animals displaying tactile allodynia responded to the von Frey filaments on the ligated side with a 50% gram threshold of 2.1 ± 0.3 g ($n = 17$). The normal side failed to respond to any filament up to the maximum of 15.1 g.

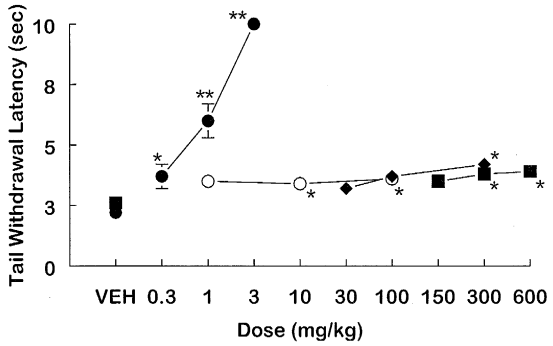

Fig. 3. Effect of felbamate (■), gabapentin (♦) and phenytoin (○), 1 h post-drug administration, on rat tail withdrawal latency from a water bath held at a constant temperature of 52°C. Vehicle range for the anti-epileptic drug treatment groups was 3.0–3.1 s. Morphine (●) was used as a positive control. Each bar represents the mean latency to tail withdrawal (s) ± S.E.M. of 8 animals per group. In most cases the S.E.M. is occluded by the symbol area. Level of statistical significance from vehicle control for each treatment group is denoted by either the single ($P < 0.05$) or double ($P < 0.01$) asterisks.

Gabapentin, at 1 h post-dose, produced a dose-dependent anti-tactile allodynic effect with an ED_{50} value (50% of the maximal drug effect) of 34 (2, 66) mg/kg (i.p.) and a maximal effect that extrapolated to 51% of the maximum possible effect for the test (15.1 g) at 100 and 300 mg/kg (Fig. 2). Both felbamate (150–600 mg/kg, i.p.) and lamotrigine (10–100 mg/kg, s.c.) were completely ineffective in reducing tactile allodynia as was carbamazepine (1–30 mg/kg, i.p.) up to the highest doses permissible in each case, i.e., 600, 100 and 30 mg/kg, respectively (data not shown). Thus, at 1 h post-dose, the 50% gram threshold response for lamotrigine (100 mg/kg) was 1.6 ± 0.4 g (vs. 1.8 ± 0.2 g for vehicle; $P > 0.05$) and for felbamate (600 mg/kg) was 3.3 ± 0.6 g (vs. 3.9 ± 1.5 g for vehicle; $P > 0.05$). For carbamazepine (30 mg/kg, i.p.), the 50% gram threshold for paw withdrawal at 1 h post-dose was 5.1 ± 1.3 g (vs. 5.6 ± 1.6 g for the vehicle, $n = 9$; $P > 0.05$).

3.3. Tail flick

The anticonvulsant drugs were tested for possible effects on normal sensory nociceptive function in the rat tail flick test. Pre-dose baseline tail flick latencies did not differ between the vehicle groups (range of 2.6–2.9 s) and any of the treatment groups (range of 2.4–2.9 s). In addition, vehicle latencies, at 1 h post-administration, also did not significantly differ between treatment groups (range of 3.0–3.1 s; Fig. 3). As a positive control, morphine produced a dose-dependent, robust increase in tail flick response latency with 3 mg/kg (s.c.) producing a maximal response latency of 10 s in all rats tested (Fig. 3). In comparison, felbamate (at 300 and 600 mg/kg, i.p.), gabapentin (only at 300 mg/kg, i.p.) and phenytoin (at 10 and 100 mg/kg, s.c.), 1 h post-administration, significantly increased tail flick latency (Fig. 3). However, the magnitude of the antinociceptive effect, although statistically significant ($P < 0.05$ in each case), was small, extrapolating to maximum increases in the threshold latency of 16%, 20% and 15%, respectively. Moreover, for each anti-epileptic drug, the dose-response relationship was very flat through a dose-range that covered at least an order of magnitude (cf. morphine). In the case of phenytoin the antinociceptive effect did not even appear to be dose related (Fig. 3). Carbamazepine (1–30 mg/kg, i.p.; 3.3 ± 0.1 s at 30 mg/kg vs. 3.0 ± 0.1 s for vehicle) and lamotrigine (10–100 mg/kg, s.c.; 2.4 ± 0.1 s at 100 mg/kg vs. 3.0 ± 0.1 s for vehicle) produced no significant ($P > 0.05$) change in tail flick latency (data not shown).

3.4. Maximal electroshock seizure test

Lamotrigine showed a marked dose-dependent anticonvulsant action in the maximal electroshock seizure test in rats with a mean ED_{50} (with 95% confidence limits) of 5.0 (3.7, 6.8) mg/kg (s.c.). The anticonvulsant potency of lamotrigine was equipotent to that of carbamazepine which had an ED_{50} of 4.9 (3.5, 7.0) mg/kg (i.p.). Gabapentin also demonstrated a dose-dependent anticonvulsant effect in this test with an ED_{50} of 17.3 (9.3, 32.3) mg/kg (i.p.). The potency of gabapentin was therefore 3- to 4-fold less than that of carbamazepine and lamotrigine but similar to phenytoin (ED_{50} = 15.6 (12.0, 20.4) mg/kg, s.c.). Felbamate also produced dose-dependent protection of hind limb extension, but was the least potent drug tested with an ED_{50} value of 48.5 (39.1, 60.2) mg/kg.

3.5. Spontaneous locomotor activity test

Lamotrigine (10–100 mg/kg, s.c.), felbamate (150–600 mg/kg, i.p.) and gabapentin (30–300 mg/kg, i.p.) were all analysed for potential sedative/ataxic properties using

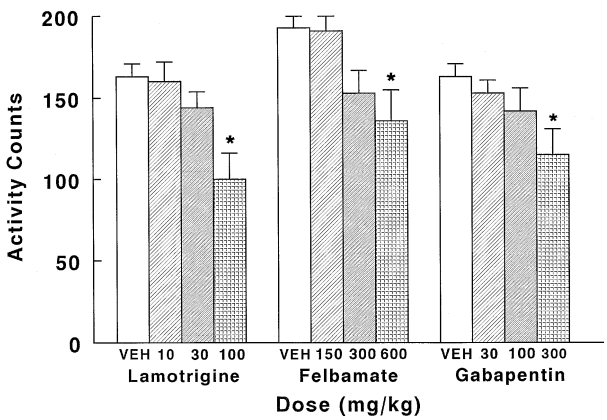

Fig. 4. Effect of lamotrigine, felbamate and gabapentin, 1 h post-drug administration, on rat locomotor activity. Each bar represents the mean number of activity counts (two or more photobeams broken in succession) ± S.E.M. of 8 animals per group. Level of statistical significance from vehicle control for each treatment group is denoted by a single ($P < 0.05$) asterisk.

a computerized locomotor activity monitoring system (Fig. 4). Lamotrigine (100 mg/kg), felbamate (300 and 600 mg/kg) and gabapentin (300 mg/kg) all caused a significant ($P < 0.01$) decrease in activity counts (two or more photobeams broken in succession) as compared to vehicle. Carbamazepine (1–30 mg/kg, i.p.) and phenytoin (1–100 mg/kg, s.c.) produced no significant ($P > 0.05$) effect on locomotor activity at any dose (data not shown).

4. Discussion

The newer anti-epileptic drugs, lamotrigine, felbamate and gabapentin, all produced a pronounced anti-cold allodynic effect in the chronic constriction injury model at doses that did not appear to be compromized by overt behavioral events. This ability to acutely reverse a prominent manifestation of neuronal sensitization demonstrates the potential of these drugs as analgesics for the relief of chronic pain following tissue/nerve injury. Moreover, the negligible effect of these drugs against an acute, high threshold thermal noxious stimulus suggests a selective interaction with pathways associated with pathophysiological events rather than with normal sensory nociceptive function. Gabapentin, however, was the only anti-epileptic drug that produced a reversal of the tactile allodynic response in the spinal nerve (L5/L6) ligation model which, if predictive of the clinical experience, implies that only this drug of the group tested will be able to provide relief against both cold and touch pain associated with a peripheral nerve injury.

The performance of lamotrigine, felbamate and gabapentin against cold allodynia supports and extends previous observations in experimental models of nerve injury and/or inflammation. Thus, lamotrigine, over a similar dose range, was recently reported to reverse both prostaglandin E_2- and streptozotocin-induced mechanical hyperalgesia (Nakamura-Craig and Follenfant, 1995). In the case of felbamate and gabapentin, the data were relatively consistent with previous reports of effects of these drugs against additional measures of sensory dysfunction in the chronic constriction injury model; mechanical (felbamate only) and thermal hyperalgesia (Imamura and Bennett, 1995; Xiao and Bennett, 1995). Interestingly, felbamate was recently found to be also effective against tactile allodynia in the chronic constriction injury model (Imamura and Bennett, 1995). While the reason for this discrepancy is unclear it is possible that it may reflect a differential sensitivity between the chronic constriction injury and spinal nerve ligation models. However, in contrast to felbamate, the potency and limited efficacy of gabapentin against tactile allodynia in the spinal nerve ligation model was almost identical to that previously reported in the chronic constriction injury model (Xiao and Bennett, 1995), i.e. gabapentin not only exhibited a similar potency but also produced only a partial (51%) reversal of the tactile allodynic response in both models.

The anti-cold allodynic effectiveness of all three newer anti-epileptic drugs in this model of nerve injury was clearly superior to both carbamazepine and phenytoin in a dose range up to an order of magnitude higher than the anticonvulsant dose. The relative lack of potency of the established drugs at doses not associated with side-effects correlates closely with previous observations in other experimental models of peripheral nerve injury and inflammation (Xu et al., 1992; Nakamura-Craig and Follenfant, 1995; Koch et al., 1996). It is also not dissimilar to the clinical experience with carbamazepine and phenytoin in which sufficient and sustained relief has only been consistently obtained against those types of pain with a prominent paroxysmal (lancinating) component (Swerdlow, 1984).

Despite intense speculation (Macdonald and Kelly, 1994; Upton, 1994) there have been no firm conclusions, at least for felbamate and gabapentin, as to the primary mechanism(s) of action that contribute towards the anticonvulsant and now anti-hyperalgesic/anti-allodynic effects of these drugs. However, while lamotrigine, felbamate and gabapentin all showed an increased anti-convulsant potency relative to anti-cold allodynia the difference was only approximately 6-fold, i.e. within an order of magnitude. It is possible that this could reflect a difference in the primary mechanisms underlying the action of each drug in each test. Alternatively, it may simply reflect a difference in the stimulus strength that each drug has to overcome in order to produce an effect.

In the case of lamotrigine, the anti-cold allodynic action could be explained by its previously reported block of voltage-dependent sodium channels leading to stabilization of the pre-synaptic neuronal membrane and a subsequent reduction in neurotransmitter release, in particular, the excitatory amino acids glutamate and aspartate (Leach et al., 1986; Cheung et al., 1992). Moreover, any such interaction would be predicted to resemble that of the local anesthetics lidocaine and mexiletine since, in contrast to carbamazepine and phenytoin, these drugs produce an anti-cold allodynic effect in this model (Hedley et al., 1995). However, lamotrigine was ineffective against tactile allodynia which contrasts with the effectiveness of the local anesthetics in this test (Jett et al., 1996). The present study, therefore, cannot preclude the putative additional mechanism of action, linked with its anti-convulsant profile (Upton, 1994), from playing a role in the anti-cold allodynic action of lamotrigine.

Felbamate has been associated with a number of different mechanisms any one of which, either individually or in combination, could be responsible for suppression of the cold allodynic response. Thus, felbamate has been reported to interrupt glutaminergic function through an antagonist interaction at the *N*-methyl-D-aspartate (NMDA)/glycine modulatory site (McCabe et al., 1993; DeSarro et al.,

1994) and/or α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)/kainate receptors (White et al., 1992; DeSarro et al., 1994). It also has been shown to potentiate GABAergic function (Rho et al., 1994) as well as having the potential to block voltage-dependent sodium currents (White et al., 1992). A prominent NMDA antagonist action, however, would help explain the lack of activity in the tactile allodynia test as mechanical stimuli appear less sensitive to compounds interacting directly with the NMDA/glycine complex (Meller, 1994).

The anti-convulsant/anti-allodynic effect of gabapentin may also be the consequence of an individual mechanism or the product of a multiplicity of mechanisms. At present the most intriguing possibility is a specific binding site in rat brain (Suman-Chauhan et al., 1993) that may be associated with the $\alpha_2\delta$ sub-unit of the calcium channel (Gee et al., 1996). Stereoselectivity exhibited by some GABA analogs for the binding site appears to correlate with anti-convulsant activity suggesting that it may play a role in the anti-convulsant action of gabapentin (Suman-Chauhan et al., 1993). It remains to be seen what contribution this site may make towards the analgesic action of gabapentin in rodent experimental models of chronic pain. In addition to this specific binding site, gabapentin has been reported to exert a physiological modulation of glutaminergic (Singh et al., 1996) and GABAergic (Kocsis and Honmou, 1994) function without appearing to bind directly to any known site associated with these receptor/channel complexes (Suman-Chauhan et al., 1993).

The potential clinical utility of lamotrigine, felbamate and gabapentin for the treatment of neuropathic pain is further supported by the clear separation obtained between doses producing a robust anti-allodynic effect and changes in overt behavioral performance. Indeed, for all three of the newer anti-epileptic drugs, the highest dose tested was associated with no overt behavioral effects while being shown to almost completely suppress the cold allodynic response. All three drugs were found to produce a significant reduction in the computerized locomotor activity test. However, in each case this effect appeared to have little impact on the ability of the animal to perform the hindpaw withdrawal reflex to the cold water stimulus. Thus, in order to test for normal reflex behavior in the presence of drug, a noxious mechanical (pin-prick) stimulus was applied to the plantar surface on the sham-operated side of animals with a chronic constriction injury (Koch et al., 1996; J. McGuirk, personal communication) and resulted in an unimpaired reflex response (0.1–0.2 s).

In conclusion, the overall profile of the newer anti-epileptic drugs used in this study suggests that these drugs could provide an effective alternative to either carbamazepine or phenytoin in the treatment of neuropathic pain. However, only gabapentin appears to have suitable efficacy to treat a wider spectrum of conditions. Each of these drugs might be expected to have an improved margin of safety despite the potential need for higher doses than those required for anti-convulsant activity. In the case of gabapentin this has recently been confirmed by a preliminary, unblinded study in patients with refractory reflex sympathetic dystrophy in which gabapentin (900–2400 mg/day) produced satisfactory and sustained pain relief when administered over a 2–6-month period (Mellick and Mellick, 1995). However, in contrast, felbamate was recently withdrawn from the anti-convulsant market by the Food and Drugs Administration of the USA. This was in response to the increasing incidence of reports of aplastic anaemia and acute liver toxicity. Fatalities have been recorded from both conditions and physicians have been advised by the FDA to discontinue therapy when possible.

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