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Potent analgesic effects of anticonvulsants on peripheral thermal nociception in rats

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1 Anticonvulsant agents are commonly used to treat neuropathic pain conditions because of their effects on voltage- and ligand-gated channels in central pain pathways. However, their interaction with ion channels in peripheral pain pathways is poorly understood. Therefore, we studied the potential analgesic effects of commonly used anticonvulsant agents in peripheral nociception.

2 We injected anticonvulsants intradermally into peripheral receptive fields of sensory neurons in the hindpaws of adult rats, and studied pain perception using the model of acute thermal nociception. Commonly used anticonvulsants such as voltage-gated Na^+ channel blockers, phenytoin and carbamazepine, and voltage-gated Ca^{2+} channel blockers, gabapentin and ethosuximide, induced dose-dependent analgesia in the injected paw, with ED_{50} values of 0.30, 0.32 and 8, 410 μg per 100 μl, respectively.

3 Thermal nociceptive responses were not affected in the contralateral, noninjected paws, indicating a lack of systemic effects with doses of anticonvulsants that elicited local analgesia.

4 Hill slope coefficients for the tested anticonvulsants indicate that the dose–response curve was less steep for gabapentin than for phenytoin, carbamazepine and ethosuximide.

5 Our data strongly suggest that cellular targets like voltage-gated Na^+ and Ca^{2+} channels, similar to those that mediate the effects of anticonvulsant agents in the CNS, may exist in the peripheral nerve endings of rat sensory neurons. Thus, peripherally applied anticonvulsants that block voltage-gated Na^+ and Ca^{2+} channels may be useful analgesics.
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Abbreviations: DRG, dorsal root ganglion; GABA, γ-amino-butyric acid; HVA, high-voltage activated; LVA, low-voltage activated; NMDA, N-methyl-D-aspartate; PWL, paw withdrawal latency

Introduction

Neuropathic pain states often lead to a long-lasting increase in excitability of neurons in peripheral and central nociceptive pathways (Woolf, 1991; Coderre *et al*., 1993; Baker & Wood, 2001). Pathological pain is typically resistant to conventional pharmacological treatments (e.g. opioids, nonsteroidal anti-inflammatory drugs), and anticonvulsant agents have been used in pain management over the last few decades due to the clinical impression that they are effective in alleviating certain forms of neuropathic pain, especially lancinating and burning pain (McQuay *et al*., 1995). Specifically, systemically administered carbamazepine (tegretol), phenytoin and the newly introduced anticonvulsant agent gabapentin (neurontin) have been widely used in treating various pain disorders (reviewed by Tremont-Lukats *et al*., 2000). The systemic use of anticonvulsants in neuropathic pain is based on the fact that central neuroplasticity plays a prominent role in promoting abnormal pain states, similar to seizure disorders. However, systemic administration of anticonvulsants is often hampered by side effects such as impaired motor and mental functions that may limit their chronic administration. Furthermore, serious side effects such as death from hematological reactions (e.g. agranulocytosis) have been reported (Raynolds, 1993).

During the last two decades, great progress has been made in understanding the cellular targets for anticonvulsant agents. In addition to blocking voltage-gated ion channels in the CNS (e.g. voltage-gated Na^+ and Ca^{2+} channels), these agents can affect the same cellular targets in cell bodies of peripheral sensory neurons that convey nociceptive signals to the spinal cord. For example, therapeutic concentrations of carbamazepine and phenytoin were shown to suppress sustained, repetitive, high-frequency neuronal firing due to their blockade of voltage-gated Na^+ channels in the somata of primary sensory neurons (Macdonald & McLean, 1986). In addition, phenytoin blocks T-type voltage-gated Ca^{2+} currents in acutely dissociated sensory neurons within the same clinically relevant concentrations (Todorovic & Lingle, 1998). More recently, it has been recognized that a new anticonvulsant, gabapentin, is a very useful agent for treating neuropathic pain (Tremont-Lukats *et al*., 2000). Although the cellular mechanisms of gabapentin's actions are not well understood, recent evidence strongly suggests alteration of GABA-ergic transmission in the CNS and blockade of voltage-gated Ca^{2+} channels (Taylor *et al*., 1998) in both central (Stefani *et al*., 2001) and peripheral neurons (Sutton *et al*., 2002). Ethosuximide, an

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anticonvulsant used to treat petit-mal seizures, blocks thalamic T-type Ca^{2+} channels (Coulter *et al*., 1990), but it also blocks T-type Ca^{2+} currents in acutely dissociated rat sensory (nociceptive) neurons (Todorovic & Lingle, 1998). Based on the proposal that the peripheral endings of primary sensory neurons possess a repertoire of ion channels similar to these found on their somata in dorsal root ganglia (DRG), we hypothesized that local infiltration of anticonvulsants on peripheral endings of nociceptive neurons may exert an analgesic effect without eliciting the potentially serious side effects seen with systemic administration.

Methods

Chemicals and animals

All drugs were obtained from Sigma Chemical Company (St Louis, MO, U.S.A.) except for gabapentin, which was a kind gift of Parke-Davis (Ann Arbor, MI, U.S.A.). Phenytoin and carbamazepine were prepared as 20 mg cm^{-3} stock solutions in 100% DMSO and diluted to final concentrations the day of the experiment. Ethosuximide and gabapentin were dissolved in normal saline (NS). A total of 162 adult retired female Sprague–Dawley rats (Harlan, weight 290–320 g) were used in this study. Female rats were used because they are less aggressive than adult male rats and, thus, easier to use for behavior pain testing.

Behavioral pain studies

The experiments were approved by the University of Virginia Animal Care and Use Committee (Charlottesville, VA, U.S.A.). The nociceptive response to heat was tested in a commercially available paw thermal stimulation system as described elsewhere (Jevtovic-Todorovic *et al*., 1998; 2003; Todorovic *et al*., 2001; 2002). The device consists of a clear plastic chamber ($10 \times 20 \times 24$ cm) that sits on a clear, elevated glass floor and is temperature regulated at 30°C. Adult female Sprague–Dawley rats were placed in the plastic chamber and given 10–15 min to accommodate. A radiant heat source mounted on a movable holder beneath the glass floor was positioned to deliver a thermal stimulus to the plantar side of the hind paw. When an animal withdraws its paw, a photocell detects interruption of a light reflection and an automatic timer shuts the heat source off. This provides an accurate record of paw withdrawal latency (PWL). The PWL can be measured with this apparatus with a precision of 0.1 s. To prevent thermal injury, the thermal source is automatically discontinued after 20 s if the rat fails to withdraw its paw.

To test the effects of drugs or vehicle in peripheral receptive fields of sensory neurons, we injected 100 μl of each test compound intradermally in the plantar side of the right hind paw. The noninjected side (left hind paw) was used as a control in each animal. All solutions were pH balanced to 7.4 to avoid skin irritation. No signs of skin inflammation, discoloration or irritation were noted at the sites of injection with any of the test compounds. All doses are expressed in μg per 100 μl. Baseline values (*B*) were compared to thermal PWLs of noninjected and injected paws at various time points during the testing as indicated in Figures 1 and 2 (post-treatment values). In the data displayed, every point is an average of at least nine animals and values represent mean $\pm$ standard error (s.e.). Statistical analysis was performed using an ANOVA comparing within-subject variables: paw condition (injected vs noninjected) and test session (prior to drug administration or 10, 20, 60 or 90 min post-treatment). Pairwise comparisons were also conducted and alpha levels were adjusted using the Bonferroni procedure when appropriate.

Dose–response data were fit to the function $PI([DRUG]) = PI_{max}/(1 + (ED_{50}/[DRUG])^n)$, where PI_{max} is the maximal percentage increase in PWLs caused by a drug in the injected vs noninjected paw 10 min following injection, ED_{50} is the dose that produces half-maximal increase in PWLs indicating an analgesic effect and n is the apparent Hill coefficient indicating the slope of the curve. Fitted values are reported with 95% linear confidence limits. Fitting was performed with Origin 7.0 software (Microcal Software, Northhampton, MA, U.S.A.).

Results

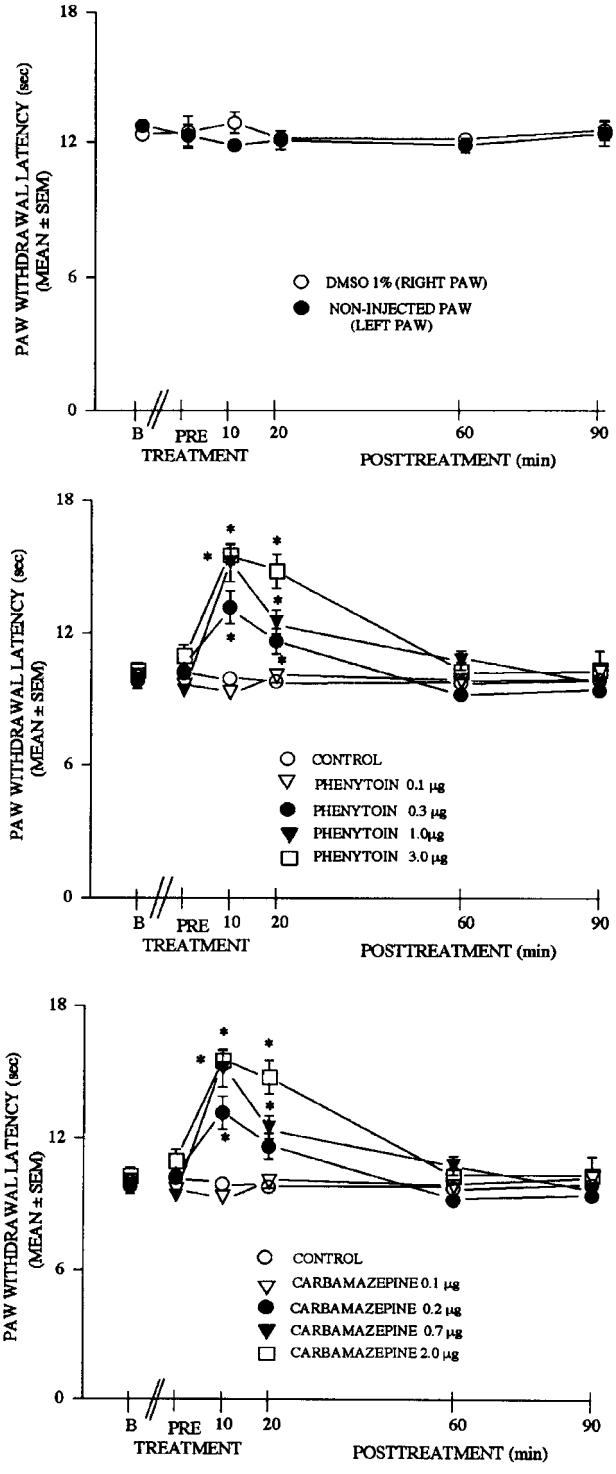
Phenytoin and carbamazepine are anticonvulsants that are potent blockers of voltage-gated Na^+ channels *in vitro*. Figure 1 summarizes the dose-dependent analgesic effects of these two agents when injected *in vivo* in peripheral receptive fields of sensory neurons. When injected into peripheral receptive fields of sensory neurons, phenytoin (from 0.1 to 3.0 μg) induced a dose-dependent increase in PWLs in the injected paws that lasted about 20 min, returning to preinjection level by 60 min (Figure 1, top panel). A maximal increase in PWL was induced at 10 min with the two highest doses – 1.0 and 3.0 μg (about 60% increase from the baseline). A calculated ED_{50} value from the fitted phenytoin dose–response curve (Figure 3) was $0.30 \pm 0.02\mu$g. As seen in Figure 1 (top panel), PWLs were not affected in the contralateral, noninjected side, demonstrating that this potent analgesic effect of phenytoin was not due to systemic absorption. Carbamazepine (Figure 1, bottom panel) induced a similar magnitude of analgesia with a maximal increase of PWLs of about 60% from the baseline. This effect was dose-dependent, with 0.7 and 2.0 μg inducing the maximal analgesic effect after 10 and 20 min with nearly a complete return to baseline PWLs 60 min postinjection. A calculated ED_{50} value from the fitted carbamazepine dose–response curve was $0.32 \pm 0.04\,\mu$g (Figure 3), indicating that carbamazepine is about as potent a local analgesic as phenytoin.

Gabapentin and ethosuximide are anticonvulsants that are presumed to block mainly voltage-gated Ca^{2+} channels *in vitro*. Figure 2 summarizes the dose-dependent analgesic effects of these two agents *in vivo* when injected in peripheral receptive fields of sensory neurons. Note that both agents induced a prolongation of the maximum PWLs on the injected side (about 60% from the baseline) at 10 min, similar to the effect observed with phenytoin and carbamazepine. However, this increase was only about 20% from the baseline at 20 min (compared to about a 40% increase from the baseline recorded with phenytoin and carbamazepine), indicating that the analgesic effect of these two agents is more transient. As with phenytoin and carbamazepine, PWLs were not significantly affected in contralateral paws. Compared to phenytoin and carbamazepine, gabapentin and ethosuximide were less potent analgesics. ED_{50} values from the fitted gabapentin and

ethosuximide dose–response curves were 8.0±1.0 and 410±37 μg, respectively (Figure 3).

Injections of the highest used concentration of DMSO (1%) or NS were given to controls and did not have a significant effect on thermal nociception ($N=9$–12 animals for each, Figures 1 and 2 top panels).

The calculated Hill slope coefficient for thermal analgesia is larger than 1 for phenytoin–2.8, carbamazepine–2.1 and ethosuximide–2.5, which indicates steep dose–response relationships. In contrast, gabapentin has a more shallow dose–response curve with a Hill slope coefficient of 0.9. (Figures 3).



Discussion

Our study demonstrates that anticonvulsant agents that are voltage-gated Na^+ channel blockers–phenytoin and carbamazepine–and voltage-gated Ca^{2+} channel blockers–gabapentin and ethosuximide–are very effective local analgesics.

Phenytoin and carbamazepine are potent Na^+ channel blockers *in vitro*. In this study, the locally administered ED_{50} s for phenytoin and carbamazepine required to attenuate peripheral nociception *in vivo* were in the low submicrogram range (0.30 and 0.32 μg 100 μl^{-1}, respectively). By comparison, the commonly used doses of lidocaine, a well-known and widely used local anesthetic that also blocks voltage-gated Na^+ channels, are more than 3000–6000 times higher (1–2% solution, or 1000–2000 μg 100 μl^{-1}). Based on this, it would seem that locally applied anticonvulsants could be very useful in treating conditions that require local infiltration and regional nerve blockade, especially in cases where this route of administration may be beneficial in pain states where abnormal thermal nociception is associated with acute tissue injury (e.g. sunburns, surgical thermocoagulation, nerve plexus injury).

Although a model of local injection into the peripheral receptive field is an excellent method for assessing direct pharmacological effects on peripheral nerve endings, its limitation (small volume that could be injected, inability to apply vasoconstrictors) results in alterations of nociception that are relatively short lived (Hargreaves *et al*., 1988; Jackson *et al*., 1995; Zhou *et al*., 1996; Alley *et al*., 1998; Carlton & Zhou, 1998; Carlton *et al*., 1999; Todorovic *et al*., 2001). In clinical practice, longer-lasting effects of local anesthetics in regional anesthesia are achieved by injecting large volumes (e.g. 40–50 ml) and adding vasoconstrictors like epinephrine to slow down absorption from the site of injection. Thus, in spite of the relatively transient nature of the responses in our

Figure 1 Phenytoin and carbamazepine induce analgesia in thermal PWL testing. Upper panel: Injections of 1% DMSO in saline (open symbols), which was used as a vehicle for experiments with phenytoin and carbamazepine, did not significantly change PWLs in the injected side in comparison to the noninjected side (filled symbols). Middle panel: Phenytoin induces a dose-dependent increase in thermal PWL. Phenytoin (0.3, 1.0 and 3.0 μg) significantly increased PWLs (*, $F(1, 22)=13.51$, $P=0.001$; $F(1, 22)=119.83$, $P=0.000$; and $F(1, 20)=24.53$, $P=0.000$, respectively) at 10 min and (*, $F(1, 22)=9.97$, $P=0.005$; $F(1, 22)=24.327$, $P=0.000$; and $F(1, 20)=28.4$, $P=0.004$, respectively) at 20 min postinjection when compared to the noninjected paw (control, open circles). PWLs returned to control values by 60 min following injection; control (noninjected) sides are grouped together. Lower panel: Carbamazepine induces a dose-dependent increase in thermal PWL. Carbamazepine (0.2, 0.7 and 2.0 μg) significantly increased PWLs (*, $F(1, 16)=19.02$, $P=0.000$; $F(1, 16)=65.08$, $P=0.000$; and $F(1, 16)=25.16$, $P=0.000$, respectively) at 10 min and the two highest doses (0.7 and 2.0 μg) significantly increased PWLs (*, $F(1, 16)=12.80$, $P=0.003$ and $F(1, 16)=14.30$, $P=0.002$, respectively) at 20 min postinjection when compared to the noninjected paw (control, open circles). Again, PWLs returned to control values by 60 min following injection.

experiments, we believe that local administration of anticonvulsants like phenytoin and carbamazepine could be potentially useful in clinical use (e.g. regional nerve block) given the high potency they exhibited in our behavior paradigms.

Voltage-gated Ca^{2+} channels play a major role in the control of cellular excitability and transmitter release in central and peripheral neurons. This family of channels consists of several distinct subtypes that may play distinct roles in nociception. Currents arising from these channels are subdivided into two major classes based on the membrane potential at which they become activated: high-voltage activated (HVA) or sustained currents which are further divided into L, P, Q, N and R subtypes and low-voltage activated (LVA) or transient (T-type) Ca^{2+} currents (reviewed by Miller, 1998). It is relatively well established that N-type voltage-gated Ca^{2+} channels play a crucial role in central nociceptive transmission (Woolf, 1991; Coderre *et al*., 1993). Although *in vitro* studies have shown that peripheral sensory neurons are particularly rich in N, L and T types of these channels (Scroggs & Fox, 1992; Todorovic & Lingle, 1998), peripheral local administration of L- and N-type antagonists did not cause antinociceptive effects in normal rats (White & Cousins, 1998).

Currently, highly potent and selective blockers of T-type Ca^{2+} channels are not available, which impedes progress in understanding the role of these channels in sensory transmission. However, the role of peripheral T-type Ca^{2+} channels in nociception is recently suggested since redox agents that modulate these currents *in vitro* can modulate thermal nociception *in vivo* (Todorovic *et al*., 2001). Furthermore, mibefradil, a peripherally acting antihypertensive agent and preferential T-type channel blocker, has antinociceptive effects when administered systemically (Todorovic *et al*., 2002). Ethosuximide is thought to be a relatively selective, although not very potent, blocker of T-type voltage-gated Ca^{2+} channels in both thalamic (Coulter *et al*., 1990; Huguenard & Prince, 1994) and peripheral sensory neurons (Todorovic & Lingle, 1998). In another study with thalamic slices, it was shown that ethosuximide blocks slowly inactivating voltage-gated Na^+ currents, as well as Ca-dependent K^+ currents, and this was suggested as the main mechanism of its anticonvulsant activity (Laresche *et al*., 1998). It is not known whether ethosuximide-sensitive voltage-gated Na^+ and K^+ currents exist in sensory neurons; however, given the recently proposed role of T channels in peripheral nociception (Todorovic *et al*., 2001; 2002), blockade of T-type Ca^{2+} channels in sensory neurons by ethosuximide could contribute to attenuation of thermal nociception in our *in vivo* experiments.

The mechanisms of gabapentin's anticonvulsant and analgesic effects are not well understood. Even though the subtype of voltage-gated Ca^{2+} channel is not identified, it is well established that gabapentin has high affinity for the $\alpha 2\delta$ subunit of voltage-gated Ca^{2+} channels (Taylor *et al*., 1998; Tremont-Lukats, 2000). Our study shows that gabapentin is more potent than ethosuximide (50-fold lower ED_{50}) in

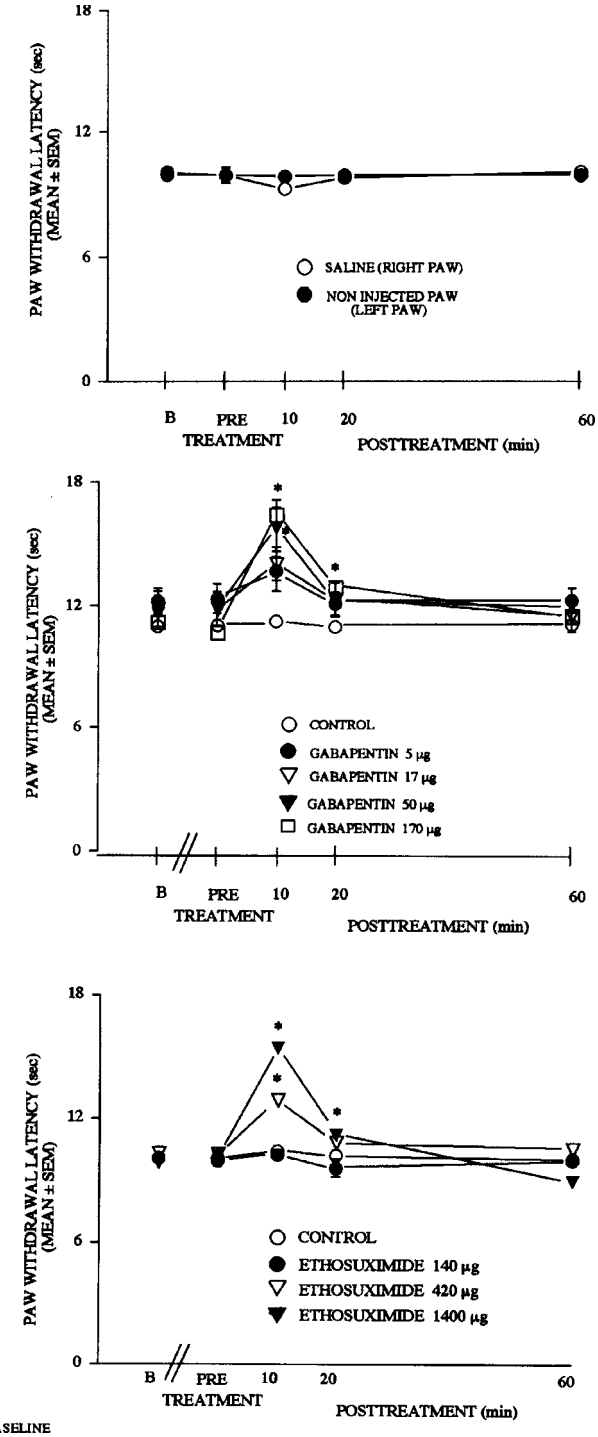


Figure 2 Gabapentin and ethosuxamide induce analgesia in thermal PWL testing. Upper panel: Injections of saline alone (open symbols) did not significantly change PWLs when compared to noninjected paws (filled symbols). Middle panel: Gabapentin induces a dose-dependent increase in thermal PWL. Gabapentin (50 and 170 μg) significantly increased PWLs (*, $F(1, 16) = 5.56$, $P = 0.031$ and $F(1, 16) = 138.14$, $P = 0.000$, respectively) at 10 min and the highest dose (170 μg) significantly increased PWLs (*, $F(1, 16) = 38.64$, $P = 0.000$) at 20 min postinjection when compared to the noninjected paw (control, open circles). PWLs returned to control values by 60 min following injection. Lower panel: Ethosuxamide induces a dose-dependent increase in thermal PWL. Ethosuxamide (420 and 1400 μg) significantly increased PWLs (*, $F(1, 16) = 22.74$, $P = 0.000$ and $F(1, 22) = 175.81$, respectively) at 10 min and the highest dose (1400 μg) significantly increased PWLs (*, $F(1, 16) = 8.54$, $P = 0.010$) 20 min postinjection when compared to the noninjected paw (control, open circles). PWLs returned to control values by 60 min following injection.

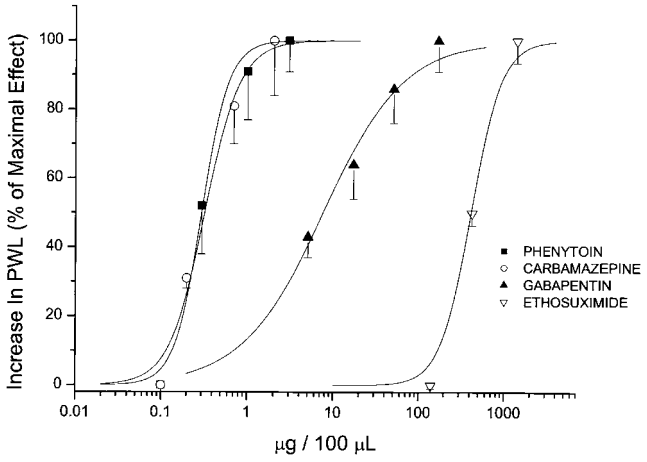


Figure 3 Dose-dependent local thermal analgesia following local injections of anticonvulsants. Average dose–response curves for local analgesia indicated by maximal increase in thermal PWLs on injected side vs noninjected side 10 min after injection (y-axis) and dose of anticonvulsant expressed in $\mu g\,100\,\mu l^{-1}$ (x-axis). All points are normalized to the maximal effect seen with a particular agent from data presented in Figures 1 and 2 and are averages of at least nine experiments. Solid lines are best fits of the Hill equation (see Methods) and downward vertical lines indicate s.e.m. Fits were constrained to 100% block with ED_{50} and h values of $0.30\pm0.02\,\mu g$ ($h=2.8\pm0.9$), $0.32\pm0.04\,\mu g$ ($h=2.1\pm0.4$), $8\pm1\,\mu g$ ($h=0.9\pm0.1$) and $410\pm37\,\mu g$ ($h=2.5\pm0.7$) for phenytoin, carbamazepine, gabapentin and ethosuximide, respectively.

ameliorating thermal nociception. In one animal model of neuropathic pain, locally applied gabapentin inhibited ectopic nerve discharges (Pan *et al*., 1999). In another study, locally applied gabapentin (6–600 μg) ameliorated formalin-induced nociceptive responses in rats (e.g. flinches and lifting/licking), but did not ameliorate mechanical nociception in rats not injected with formalin (Carlton & Zhou, 1998). This indicates that locally applied gabapentin may be more effective in ameliorating thermal than mechanical nociception, and it may affect different manifestations of pain in different pathological conditions.

In our study, blockers of voltage-gated Ca^{2+} channels were less potent than blockers of voltage-gated Na^+ channels. Similar observations have been made with systemic administration of these agents for the treatment of pain states and seizure disorder. For example, the therapeutic plasma concentrations of systemically administered gabapentin and ethosuximide were shown to be over 100 times higher than the therapeutic plasma concentrations of systemically administered phenytoin and carbamazepine (Macdonald & McLean, 1986; McQuay *et al*., 1995; Taylor *et al*., 1998). This suggests that the lesser potency of locally applied voltage-gated Ca^{2+} channel blockers parallels their lower potency in systemic administration. Based on our findings, one could possibly conclude that the voltage-gated Na^+ channels play a more important role in peripheral nociception than voltage-gated Ca^{2+} channels. However, more potent blockers of voltage-gated Ca^{2+} channels might be more potent local analgesics as well.

It is also obvious from Figures 1 and 2 that higher doses of phenytoin and carbamazepine have longer-lasting effects than higher doses of gabapentin and ethosuximide. This could be related to higher lipophilicity and tissue partitioning of carbamazepine and phenytoin or, alternatively, more prolonged channel block. Precise mechanisms of Ca^{2+} channel blockade by ethosuximide and gabapentin in sensory neurons are not known, but both Na^+ channel blockers used here exhibit prominent use-dependent aspects of Na^+ channel blockade *in vitro* (Macdonald & McLean, 1986), which presumably contributes to longer-lasting effects *in vivo*.

Some anticonvulsants act by dampening the excitation of CNS neurons by blocking N-methyl-D-aspartate (NMDA) receptors or augmenting inhibitory effects of GABA (MacDonald & McLean, 1986). These two neurotransmitter systems are also implicated in central analgesic effects of some anticonvulsants (Tremont-Lukats *et al*., 2000). However, it is interesting that anticonvulsants that act predominantly on GABA or NMDA ligand-gated channels did not exhibit analgesic activity in similar models of peripheral nociception. We reported that local administration of noncompetitive antagonists of NMDA receptors such as ketamine and MK-801, as well as competitive NMDA antagonists like D-APV, did not affect peripheral thermal nociception in rats (Todorovic *et al*., 2001). Surprisingly, the GABA agonist muscimol, which produces anticonvulsant effects in CNS neurons (Kohane *et al*., 2002), when locally injected in receptive fields of rat sensory neurons, induced thermal hyperalgesia (Carlton *et al*., 1999). These data suggest that anticonvulsants that inhibit the activity of CNS neurons *via* blockade of NMDA receptors or enhancement of the inhibitory function of GABA are not effective in the peripheral receptive field of sensory neurons in conditions associated with acute pain. However, inhibition of peripheral NMDA (Jackson *et al*., 1995; Lawand *et al*., 1997) and potentiation of GABA (Carlton *et al*., 1999) receptors as a mechanism of antinociception may play a more prominent role in conditions associated with pathological pain due to chronic inflammation.

In conclusion, our data demonstrate that peripherally applied anticonvulsants that block voltage-gated Na^+ and Ca^{2+} channels may be used as effective analgesics to ameliorate thermal nociception, and strongly suggest that cellular targets similar to those that mediate the effects of these anticonvulsant agents in the CNS may also exist in peripheral endings of sensory neurons.

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