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Local Anesthetic Properties of Prenylamine

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Background: **Local anesthetics that produce analgesia of long duration with minimal impairment of autonomic functions are highly desirable for pain management in the clinic. Prenylamine is a known calcium channel blocker, but its local anesthetic blocking effects on voltage-gated sodium channels have not been studied thus far.**

Methods: **The authors characterized the tonic and use-dependent prenylamine block of native Na^+ channels in cultured rat neuronal GH_3 cells during whole cell voltage clamp conditions and the local anesthetic effect of prenylamine by neurologic evaluation of sensory and motor functions of sciatic nerve during neural block in rats.**

Results: **Prenylamine elicits both use-dependent block of Na^+ channels during repetitive pulses (3 μM prenylamine produced 50% block at 5 Hz) and tonic block for both resting and inactivated Na^+ channels. The 50% inhibitory concentration for prenylamine was 27.6 ± 1.3 μM for resting channels and 0.75 ± 0.02 μM for inactivated channels. Furthermore, *in vivo* data show that 10 mM prenylamine produced a complete sciatic nerve block of motor function, proprioceptive responses, and nociceptive responses that lasted approximately 27, 34, and 24 h, respectively. Rats injected with 15.4 mM bupivacaine, a known local anesthetic currently used for pain management, had a significantly shorter duration of blockade (< 2 h) compared with rats injected with prenylamine.**

Conclusions: **The data presented here demonstrate that prenylamine possesses local anesthetic properties *in vitro* and elicits prolonged local anesthesia *in vivo*.**

TRADITIONAL local anesthetics (LAs) block voltage-gated sodium channels (NaChs) and inhibit the propagation of action potentials in excitable membranes. Voltage-gated NaChs are the main target of LAs. LAs are known to block nerve, skeletal, muscle, and cardiac muscle NaChs, which are primarily responsible for excitability of their respective tissue. LA potency, as Na^+ channel blockers, is governed by channel state, with open and inactivated states being favored over resting states. Voltage-dependent conformational changes of the LA binding site can explain the changes of LA affinity between resting, open, and inactivated states.[1]

There are structural similarities between voltage-gated sodium and calcium channel proteins, even though these two channels differ strongly in their ion selectivity.[2] The homologous domains of the α-subunit of NaChs can be aligned with 32–37% sequence identity with that of the L-type calcium channels.[3] Both α-subunits form a fourfold pseudosymmetry with four repeated domains, each with six transmembrane segments.[3] There are drugs that can block both calcium channels and NaChs.[4,5] It has been reported that there is a correlation between the potencies of calcium channel blockers in preventing neurotoxicity induced by veratridine in brain neuronal cultures and their binding affinity for [H^3]batrachotoxinin-B binding sites.[6] This raises a possibility that some calcium channel blockers may block Na^+ channels with a high affinity.

Few LAs for pain management produce analgesia of long duration. The development and availability of such LAs that can cause reversible blockade of neural functions is desirable and advantageous for certain pain management in the clinic. Prenylamine, a coronary vasodilator, is a calcium channel blocker formerly used in the treatment of angina pectoris but now superseded by safer antianginal drugs.[7–10] The general pharmacologic activities, including surface anesthesia, of prenylamine and some of its cycloalipahtic derivatives have been previously studied.[11] The LA properties of prenylamine on voltage-gated NaChs have not been characterized thus far. We selected prenylamine because it contains large hydrophobic moieties (fig. 1). Previous results indicate that LAs with two large hydrophobic moieties are more potent *in vivo*.[12,13] This study examines the LA properties of prenylamine *in vitro* by electrophysiologic studies of the NaCh on neuronal GH_3 cells and assesses its usefulness as a long-acting LA *in vivo* by neurobehavioral examination of sciatic nerve block in the rat in comparison with the known LA anesthetic bupivacaine.

Materials and Methods

Prenylamine and Bupivacaine

Prenylamine was purchased from Sigma Chemical Co. (St. Louis, MO). Bupivacaine was a gift from AstraZeneca, (Westborogh, MA). For the electrophysiologic experiments, prenylamine and bupivacaine were dissolved in dimethyl sulfoxide at 100 mM and were diluted shortly before the experiments. For sciatic nerve blockade, prenylamine was dissolved in 5% dextrose solution and bupivacaine in 0.9% sodium chloride solution. Prenylamine is insoluble in saline solutions; thus, 5% dextrose was used as the vehicle of transfer for injection. Neither 0.9% sodium chloride nor 5% dextrose solution had any analgesic effect.

Neurologic Evaluation of Sciatic Nerve Block in the Rat

The following protocol, which we and other investigators have used previously for the evaluation of sciatic

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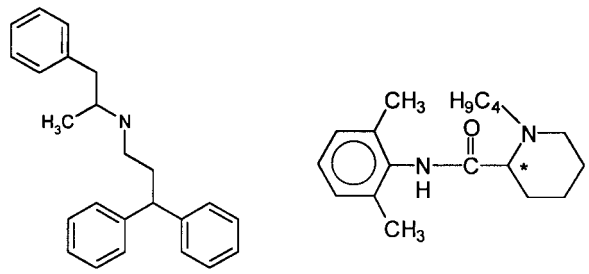

Prenylamine Bupivacaine

Fig. 1. Chemical structures of prenylamine and bupivacaine.

nerve block in the rat,[13,14] was approved by the Harvard Medical Area Standing Committee on Animals (Boston, MA). Male Sprague Dawley rats were purchased from Charles Rivers Laboratories (Cambridge, MA) and used for *in vivo* experiments. Neurobehavioral examination consisted of evaluation of motor function, proprioception, and nocifensive reaction immediately before injection of 0.2 ml of the drug solution and at various timed intervals after injection. Changes of function were estimated as percentage of maximal possible effect (MPE). Motor function was evaluated by measuring the "extensor postural thrust" of the hind limbs by holding the rat upright with the hind limb extended so that the distal metatarsus and toes support the animal's weight and measuring the extensor thrust as the gram force applied to a digital platform balance, the force that resists contact of the platform by the heel. The preinjection control value is considered 0% of the MPE. The reduction in this force, representing reduced extensor muscle contraction caused by motor blockade, was calculated as a percentage of the control force. A force less than 20 g (also referred to as weight of the "flaccid limb") is considered 100% MPE. Proprioception evaluation was based on the resting posture and postural reaction ("tactile placing" and "hopping"). The functional deficit was graded as 3 (normal) or 0% MPE, 2 (slightly impaired), 1 (severely impaired), and 0 (complete) or 100% MPE. Keeping the rat in the normal resting posture with the toes flexed and the dorsi of the feet placed on the supporting surface, we evaluated tactile placing as the ability of the animal to reposition its toes. Lifting the front half of the animal off the ground and then lifting one of its hind limbs at a time off the ground so that the animal moves laterally evokes hopping response. This process normally evokes a prompt hopping with the weight-bearing limb in the direction of movement to keep the animal from falling over. A predominantly motor impairment causes a prompt but weaker-than-normal response. Conversely, with a predominantly proprioceptive blockade, delayed hopping is followed by greater lateral hops so that the animal avoids falling over or, in case of full blockade, in no hopping at all. Nocifensive reaction is evaluated by the withdrawal reflex or vocalization to pinch of a skin fold over the lateral metatarsus (coetaneous pain) and of the distal phalanx of the fifth toe (deep pain). Nocifensive reaction is graded 4 (normal: vocalization and withdrawal of hind limb, or 0% MPE), 3 (more slowly than control, or 25% MPE), 2 (not complete response, or 50% MPE), 1 (weak attempts to withdraw, or 75% MPE), and 0 (absent response, or 100% MPE).

Whole Cell Voltage Clamp Experiments

Rat clonal pituitary GH_3 cells were purchased from the American Type Culture Collection (Rockville, MD). Cell cultures were split twice a week and maintained in Dulbecco modified Eagle medium supplemented with 1% penicillin–streptomycin and heat-inactivated 10% fetal bovine serum (Hyclone Labs, Logan, UT) in a 5% carbon dioxide incubation chamber at 37°C. For recording of Na^+ current, GH_3 cells were replated in a 35-mm culture dish, which was then used as a recording chamber. The whole cell configuration of the patch clamp technique was used to record macroscopic Na^+ currents at room temperatures ranging from 21 to 23°C. Pipette electrodes were fabricated with a tip resistance ranging from 0.8 to 1.2 MΩ. Command voltages were controlled by pCLAMP software (Axons Instruments, Inc., Foster City, CA) and delivered by a List-EPC7 patch clamp amplifier (List-Electronics, Darmstadt/Eberstadt, Germany). After the establishment of whole cell configuration, cells were dialyzed for 20–30 min to equilibrate with the pipette solution before data were acquired. Data were filtered at 5 kHz, sampled at 50 kHz, collected, and stored with pCLAMP software. Voltage error was generally less than 3 mV at +30 mV after series resistance compensation. Leak and capacitance currents were subtracted by P/-4 protocol, which was not applied in the use-dependent block of Na^+ currents. Pipette electrodes were filled with an internal solution containing 100 mM NaF, 30 mM NaCl, 10 mM EGTA, and 10 mM HEPES titrated with CsOH to pH 7.2. The external solution consisted of 85 mM choline Cl, 65 mM NaCl, 2 mM $CaCl_2$, and 10 mM HEPES titrated with tetramethylammonium-hydroxide to pH 7.4.

Statistical Analysis

An unpaired Student *t* test was used to evaluate the significance of drug-induced changes in the rate and the steady state of tonic and use-dependent block. A one-way analysis of variance on ranks was used to assess the significance of differences in the magnitude and durationof functional changes detected by neurologic evaluation after prenylamine and bupivacaine injection. A P value < 0.05 was considered statistically significant.

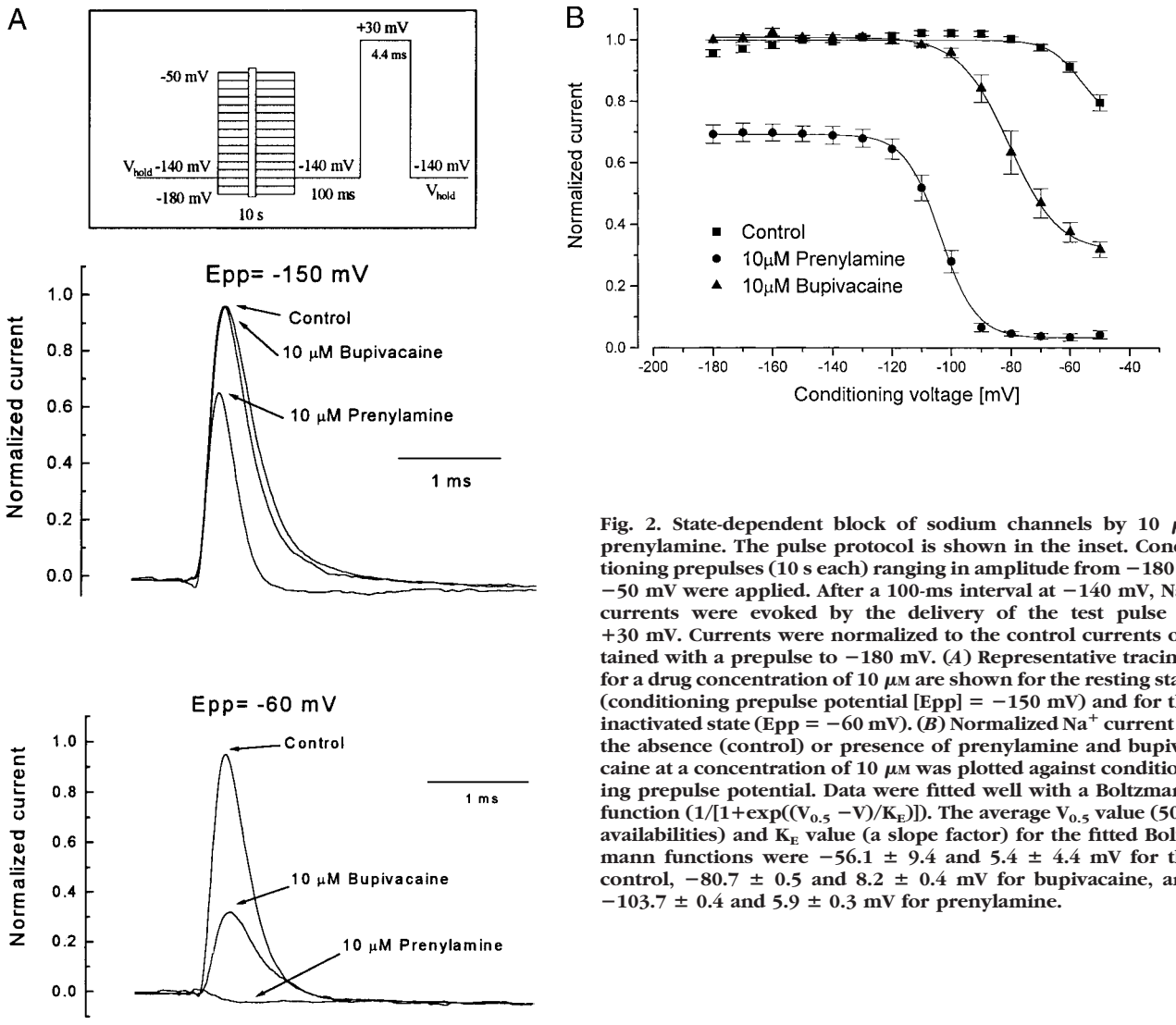

Fig. 2. State-dependent block of sodium channels by 10 μM prenylamine. The pulse protocol is shown in the inset. Conditioning prepulses (10 s each) ranging in amplitude from −180 to −50 mV were applied. After a 100-ms interval at −140 mV, Na^+ currents were evoked by the delivery of the test pulse to +30 mV. Currents were normalized to the control currents obtained with a prepulse to −180 mV. (*A*) Representative tracings for a drug concentration of 10 μM are shown for the resting state (conditioning prepulse potential [Epp] = −150 mV) and for the inactivated state (Epp = −60 mV). (*B*) Normalized Na^+ current in the absence (control) or presence of prenylamine and bupivacaine at a concentration of 10 μM was plotted against conditioning prepulse potential. Data were fitted well with a Boltzmann function ($1/[1+\exp((V_{0.5}-V)/K_E)]$). The average $V_{0.5}$ value (50% availabilities) and K_E value (a slope factor) for the fitted Boltzmann functions were −56.1 ± 9.4 and 5.4 ± 4.4 mV for the control, −80.7 ± 0.5 and 8.2 ± 0.4 mV for bupivacaine, and −103.7 ± 0.4 and 5.9 ± 0.3 mV for prenylamine.

Results

Steady State Tonic Block of Neuronal Sodium Channels by Prenylamine

Local anesthetic binding to NaChs was highly voltage-dependent.[15] The affinity of prenylamine for neuronal NaChs was determined by delivering conditioning pulses of 10 s ranging from −180 to −50 mV and measuring the Na^+ current remaining at a +30 mV test pulse. Conditioning pulses of 10 s were used to allow steady state binding of drug. A 30-s interval separated each conditioning test pulse pair, and a 100-ms interval separated the conditioning and test pulse to allow drug-free channels to recover from fast inactivation (fig. 2A, inset). With 10 μM prenylamine, there was a 30% tonic block of peak amplitude with hyperpolarized prepulse voltages of less than −120 mV. However, prepulse voltages greater than −120 mV resulted in a strong block of peak Na^+ currents, reaching a steady state level of approximately 97% blockade between prepulse voltages of −90 and −50 mV (fig. 2B). With 10 μM bupivacaine, there was no difference in peak amplitude with respect to control at hyperpolarized prepulse voltages of less than −110 mV, but there was a block at more depolarized potentials. Figure 2A shows representative traces at low (−150 mV) and high (−60 mV) drug binding affinity states of 10 μM prenylamine as compared with the control (no drug) and 10 μM bupivacaine. Thus, these data show that binding of prenylamine with NaChs is voltage-dependent, with low-affinity binding at more hyperpolarized prepulse voltages from −120 to −180 mV, which may correspond to binding with the resting state of the NaCh, and high-affinity binding at more depolarized prepulse voltages from −90 to −50 mV, which may correspond to the inactivated state. Thus, as shown for traditional LAs,[16] prenylamine also shows this state-dependent binding affinity.

Concentration Dependence of the Block of Resting and Inactivated Neuronal Sodium Channels by Prenylamine

To determine more directly prenylamine potencies in blocking resting and inactivated channels, we measured

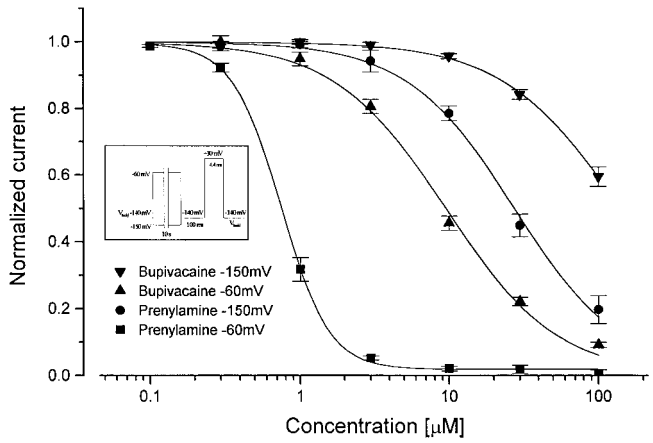

Fig. 3. Concentration–response curves for resting and inactivated sodium channels. The pulse protocol is shown in the inset. The resting affinity for prenylamine in GH_3 sodium channel was measured with a prepulse of −150 mV for 10 s, and the inactivated affinity was measured with a prepulse of −60 mV for 10 s. The peak amplitudes of Na^+ currents, evoked by a test pulse to +30 mV for 4.4 s, were measured at various drug concentrations, normalized with respect to the peak amplitude in control, and plotted against the drug concentration. Data are reported as the mean ± SE (n = 6 for all groups). Solid lines represent fits to the data with the Hill equation.

the tonic block at −150 mV for resting-state affinity and at −60 mV for inactivated-state affinity in a concentration-inhibition experiment. The 50% inhibitory concentration (IC_{50}) value for prenylamine and bupivacaine was 27.6 ± 1.3 and 189.6 ± 22.3 μM, respectively, for resting channels and 0.75 ± 0.02 and 9.5 ± 0.6 μM, respectively, for inactivated channels (fig. 3). Prenylamine was 6.9 times more potent in the resting state and 12.7 times more potent in the inactivated state than bupivacaine. The IC_{50} values for both the resting and inactivated channels showed a statistically significant difference ($P < 0.05$) between prenylamine and bupivacaine. The Hill coefficients calculated for prenylamine and bupivacaine were 1.2 ± 0.07 and 0.8 ± 0.07 in the resting state and 2.57 ± 0.19 and 1.11 ± 0.11 in the inactivated state, respectively. Except for the Hill coefficient value of 2.57 for prenylamine in the inactivated state of the NaCh, the Hill coefficients were close to unity for both drugs, suggesting a single binding site for the drugs at the NaCh. A Hill coefficient of 2.57 suggests that there might be at least two binding sites for at least two prenylamine molecules in the inactivated state of the NaCh. On the other hand, such a high Hill coefficient from a steep curve may be a result of experimental error caused by the use of low concentrations of the hydrophobic drug; thus, steady state may not have been fully reached during perfusion of the cell with the drug (see Discussion). The results here show that prenylamine, like traditional LAs, displays a low affinity for the resting state of the NaCh and a high affinity for the inactivated state.

Use-dependent Block of Neuronal Sodium Channels by Prenylamine

Because prenylamine produced tonic inhibition when the cell was stimulated infrequently, we measured the use-dependent inhibition of Na^+ currents when the cell was stimulated at 5 Hz. When GH_3 cells were stimulated repetitively, a strong use-dependent block of Na^+ currents occurred in the presence of 3 μM prenylamine, as compared with that produced by bupivacaine and no drug (control; fig. 4A). In figure 4B, an additional 50% use-dependent block of Na^+ currents was evoked by 3 μM prenylamine at a frequency of 5 Hz. At the same concentration, bupivacaine elicited only approximately 13% of use-dependent block, a value significantly less than that elicited by prenylamine ($P < 0.05$). The rate of use-dependent block by prenylamine was relatively rapid, with a time constant of 2.27 ± 0.04 pulse, whereas the time constant of bupivacaine was 6.0 ± 0.21 pulses. Thus, prenylamine, like the LAs, has the ability to elicit both tonic and use-dependent block.

Development of and Recovery from Prenylamine Block of Inactivated Sodium Channels

To characterize in more detail prenylamine block of neuronal NaChs in the inactivated state, we assessed the time course of development and recovery from block. For the development of drug block of inactivated channels (fig. 5A), the prepulse duration at −70 mV was varied (0–20 s), and the peak current at the test pulse was measured. A 100-ms interpulse at −140 mV was inserted before the test pulse to allow full recovery of fast inactivation. At 3 μM prenylamine, the block developed with a fast time constant of 0.59 ± 0.05 s and a slow time constant of 4.79 ± 0.8 s.

The time course of recovery from the inactivated drug-bound state of the NaCh was measured by a two-pulse protocol. The interpulse duration (after the 10-s conditioning prepulse to −70 mV) at −140 mV was varied (0.7 ms to 50 s), and the peak current at the test pulse was measured. Currents in the absence of drug and in the presence of 3 μM prenylamine recovered with fast and slow time constants (fig. 5B). Fast recovery is caused by the recovery from inactivation of unblocked channels in the presence of prenylamine, whereas the slow recovery is caused by the slow dissociation of prenylamine from channels blocked during the conditioning prepulse. Control currents had fast and slow time constants of 2.9 ± 0.3 ms and 0.06 ± 0.02 s, respectively. In the presence of 3 μM prenylamine, a small portion of the current (1%) recovered with a fast time constant of 1.6 ± 2.8 ms, and a large portion (99%) recovered with a slow time constant of 2.5 ± 0.1 s (n = 6). For comparison, in human heart NaChs in the presence of 10 μM R(+)-bupivacaine, a small portion (23%) of the current recovered with a fast time constant of 7.3 ± 1.1 ms, and a

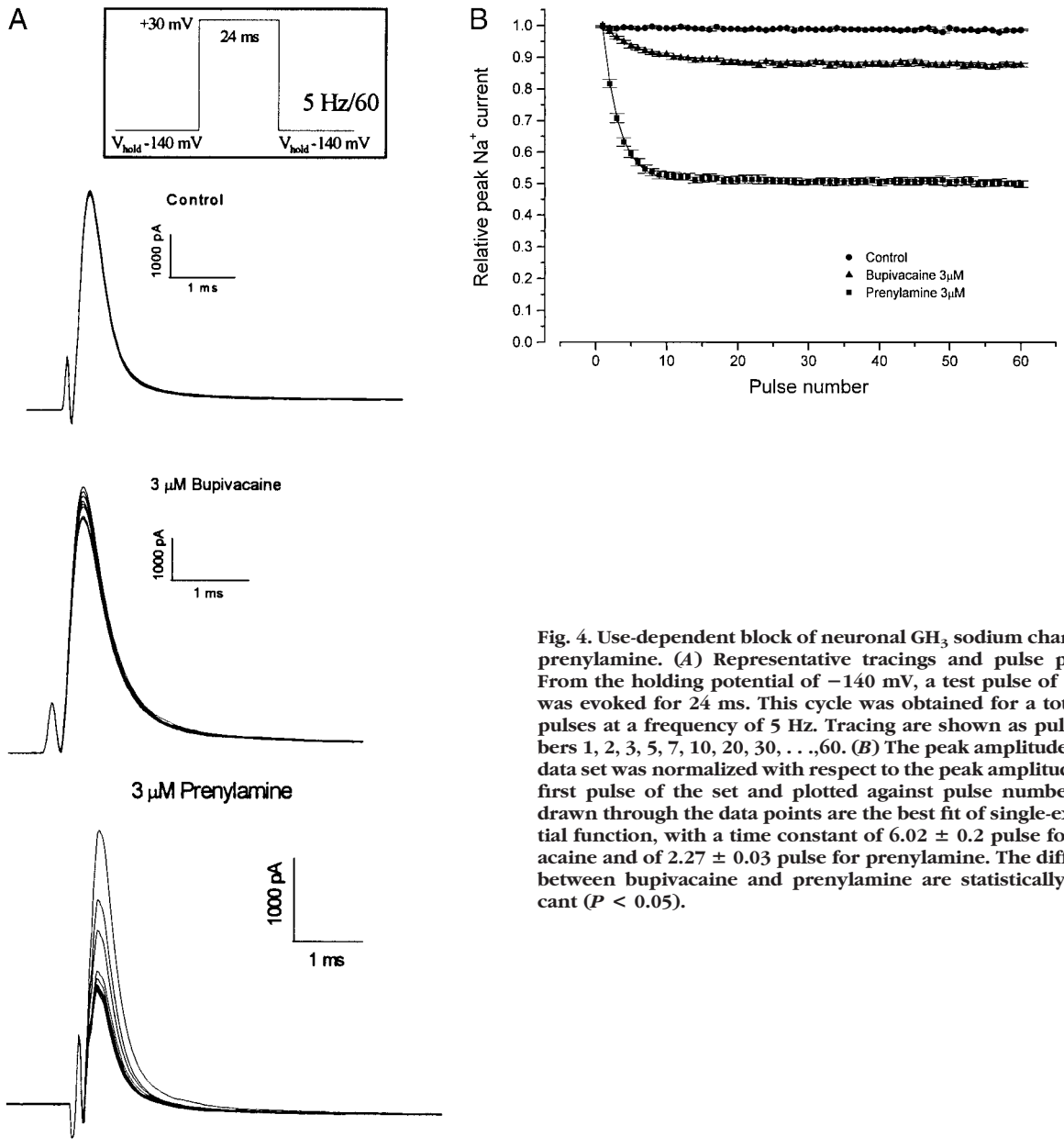

Fig. 4. Use-dependent block of neuronal GH_3 sodium channels by prenylamine. (*A*) Representative tracings and pulse protocol. From the holding potential of −140 mV, a test pulse of +30 mV was evoked for 24 ms. This cycle was obtained for a total of 60 pulses at a frequency of 5 Hz. Tracing are shown as pulse numbers 1, 2, 3, 5, 7, 10, 20, 30, . . .,60. (*B*) The peak amplitude of each data set was normalized with respect to the peak amplitude of the first pulse of the set and plotted against pulse number. Lines drawn through the data points are the best fit of single-exponential function, with a time constant of 6.02 ± 0.2 pulse for bupivacaine and of 2.27 ± 0.03 pulse for prenylamine. The differences between bupivacaine and prenylamine are statistically significant ($P < 0.05$).

large portion (77%) recovered with a slow time constant of 2.1 ± 0.1 s.[16]

Sciatic Nerve Block by Prenylamine

Because prenylamine demonstrated a strong block of NaChs *in vitro*, prenylamine was evaluated *in vivo* on sciatic nerve of rats. Rats were injected at the sciatic notch with 200 μl of 5 and 10 mM prenylamine and with 15.4 mM bupivacaine as a control, and the duration of blockade was evaluated. No animals died, and no major impairments were detected in the injected or noninjected leg. A few rats in the 10-mM prenylamine group showed a slight irritation of the toes, which was seen as a minor swelling and bleeding of the injected leg. This irritation may have been caused during complete blockade of responses when the rat may not have been aware of its toes, injuring itself as a result. All neurobehavioral changes were completely reversible. All rats had complete blocks of motor function, proprioceptive activity, and nociceptive activity within 13 min after receiving the injection (table 1). Rats injected with prenylamine recovered fully from proprioception, nociception, and motor block at a significantly ($P < 0.05$) longer time after injection than rats injected with bupivacaine. Thus, prenylamine elicited at least partial blockade of proprioceptive, motor, and nociceptive responses for 14.4, 14.5, and 17.3 h, respectively, for the 5-mM group and 53.5, 85.0, and 47.9 h, respectively, for the 10-mM group. Bupivacaine-injected rats had a partial block of approximately 2.6 h for all responses (table 1). Furthermore, complete blockade of functions, with the maximal possible block, lasted approximately 2 h for all responses in

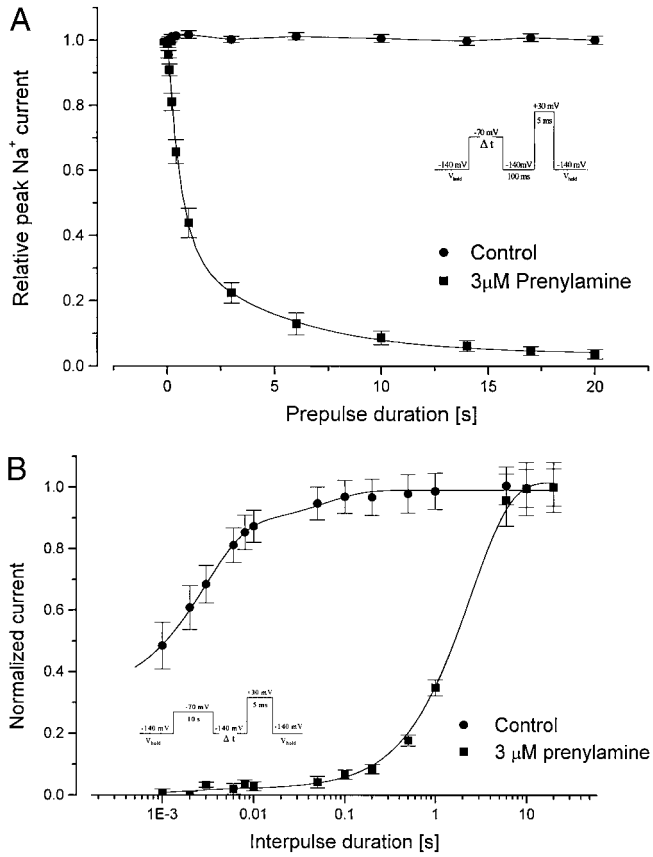

Fig. 5. Development of and recovery from prenylamine block of inactivated sodium channels. For the development of inactivated-state block, the prepulse duration at −70 mV was varied, and the peak current at the test pulse was measured, normalized to the initial peak amplitude (t = 0), and then plotted against the prepulse duration (*A*). The data for 3 μM prenylamine were well fitted by a double-exponential function. For recovery from the inactivated-state block, the interpulse duration at −140 mV was varied, and the peak current at the test pulse was measured, normalized with respect to the peak amplitude without the prepulses, and plotted against the interpulse duration (*B*). The data were well fitted by a double-exponential function.

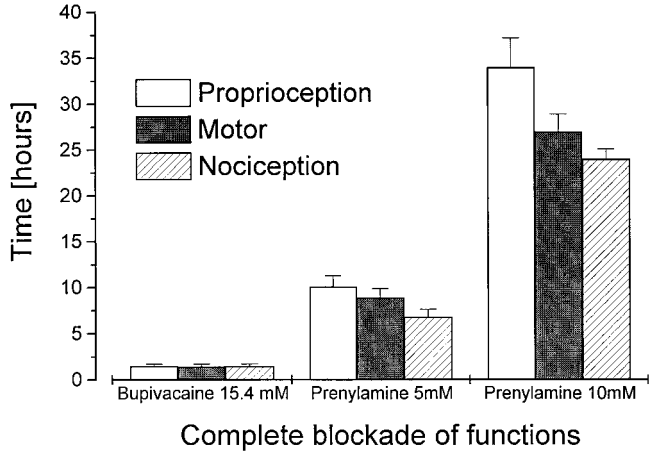

Fig. 6. Sciatic nerve block by prenylamine. Rats were injected with 200 μl of 5 mM (n = 8) and 10 mM (n = 8) prenylamine and 15.4 mM bupivacaine (n = 8), and the duration of complete functional blockade was measured. Values are reported in mean (hours) ± SE. The block of all responses by both 5 and 10 mM prenylamine is statistically significant as compared with the block in the bupivacaine group ($P < 0.05$). In no instance did drug injection lead to death or any other severe complications in the control or injected limbs except for the observable signs of analgesia in the injected limb only.

the bupivacaine-injected group but lasted for 7–10 h for the 5-mM prenylamine group and 25–34 h for the 10-mM prenylamine group (fig. 6). Therefore, prenylamine-induced block lasted at least three times longer at 5 mM and 12 times longer at 10 mM than the block induced by 15.4 mM bupivacaine. Thus, the data suggest that prenylamine induces a strong dose-dependent block of sciatic-nerve responses in rats that is of long duration.

Discussion

The data presented here demonstrate that prenylamine is a potent NaCh blocker during voltage clamp conditions *in vitro* and a long-acting LA when injected into rats for blockage of sciatic nerve *in vivo*.

Prenylamine In Vitro

Like LAs, prenylamine elicits both tonic and use-dependent block activities. Binding of prenylamine with neuronal NaChs is state-dependent. The resting affinity for prenylamine is between voltages −180 and −120 mV, and the inactivated affinity is between voltages −90 and −50 mV. The resting affinity (IC_{50} at −150 mV) for prenylamine in neuronal NaChs is 27.7 ± 1.3 μM, whereas the inactivated affinity (IC_{50} at −60 mV) is 0.75 ± 0.02 μM—a 37-fold difference. In the inactivated state, the NaCh displays not only a strong affinity for prenylamine but also a nonunity stoichiometry in binding with prenylamine (Hill coefficient of approximately 3). A possible explanation is that at −60 mV, multiple prenylamine binding sites are present. Alternatively, it is

Table 1. Onset of and Recovery from Prenylamine and Bupivacaine Block of Functional Responses in Rats after Injection

	Onset of Full Block (min)			Full Recovery from Block (h)		
	Bupivacaine	Prenylamine		Bupivacaine	Prenylamine	
	15.4 mM	5 mM	10 mM	15.4 mM	5 mM	10 mM
Proprioception	3.3 ± 1.0	5.0 ± 0.4	7.4 ± 2.0	2.6 ± 0.2	14.4 ± 1.3	53.5 ± 8.5
Motor	3.7 ± 0.8	8.1 ± 1.1	12.8 ± 2.3	2.7 ± 0.1	14.5 ± 1.3	85.0 ± 5.8
Nociception	3.7 ± 0.8	9.5 ± 3.1	8.0 ± 1.1	2.6 ± 0.2	12.3 ± 1.2	47.9 ± 8.9

possible that there is a nonlinear relation between the aqueous concentration of prenylamine and the effective concentration near the binding site if the effective prenylamine concentration increases more than the aqueous prenylamine concentration in a nonlinear manner.[17] Thus, as previously reviewed, Hill coefficients of greater than 1 are difficult to interpret and may not reflect the number of binding sites.[18] Overall, similar to the LA, binding of prenylamine to the NaCh, particularly in the inactivated state, is highly voltage-dependent.

In addition to eliciting a tonic block, prenylamine elicits a profound use-dependent block of Na^+ currents at 3 μM. Approximately 50% of the Na^+ currents are inhibited after 60 pulses, which is 3.8 times more than that elicited by bupivacaine. Previously, we and other investigators have suggested that channel activation has a role in use-dependent block of LAs, in that the inactivation gate potentiates the use-dependent effect of LAs but is not required to generate those effects.[19,20] Whether this is the case with prenylamine is unclear. However, like other LAs, prenylamine has both tonic and use-dependent block characteristics.

Prenylamine In Vivo

Prenylamine completely blocked prociceptive, nociceptive, and motor activity in both the 5- and 10-mM groups significantly longer than in the 15.4 mM bupivacaine control group. Prociceptive responses were blocked completely longer than motor and nociceptive responses, although motor responses in the 10-mM group took longer to fully recover to normal (85 h). Furthermore, prenylamine at 10 mM induced complete blockade of functions approximately three times longer than did prenylamine at 5 mM. The group that received 15.4 mM bupivacaine did, however, have a faster time of onset of complete blockade compared with the prenylamine groups. Factors such as permeability of the neural sheath to these drugs and their adsorption–diffusion in the surrounding tissue may play a role in their differences in time of onset. However, similarly to LAs, prenylamine blocks neurobehavioral responses after single injection, but with greater potency.

The current study addresses the question of LA properties of prenylamine, a calcium channel blocker, with respect to its effect on NaCh pharmacology *in vitro* and *in vivo*. Prenylamine has potent analgesic effect *in vivo* as an LA and can block NaChs *in vitro*. LAs that produce minimal impairment of autonomic functions with low toxicity and analgesia of long duration are highly desirable in the clinic. Although prenylamine formerly was used orally for the treatment of angina pectoris and was discontinued because of its side effects, such as causing torsade de pointes in some patients,[8] its side effects when used as a LA should be minimal because it will be injected locally and usually only as a single dose. Furthermore, prenylamine can be chemically modified to make it safer but still retain its potent analgesic activity.

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