N-*Phenylethyl Amitriptyline in Rat Sciatic Nerve Blockade*

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Background: The antidepressant amitriptyline is commonly used orally for the treatment of chronic pain, particularly neuropathic pain, which is thought to be caused by high-frequency ectopic discharge. Among its many properties, amitriptyline is a potent Na^+ channel blocker *in vitro*, has local anesthetic properties *in vivo*, and confers additional blockade at high stimulus–discharge rates (use-dependent blockade). As with other drug modifications, adding a phenylethyl group to obtain a permanently charged quaternary ammonium derivative may improve these advantageous properties.

Methods: The electrophysiologic properties of *N*-phenylethyl amitriptyline were assessed in cultured neuronal GH_3 cells with the whole cell mode of the patch clamp technique, and the therapeutic range and toxicity were evaluated in the rat sciatic nerve model.

Results: In vitro, *N*-phenylethyl amitriptyline at 10 μM elicits a greater block of Na^+ channels than amitriptyline (resting block of approximately 90% *vs.* approximately 15%). This derivative also retains the attribute of amitriptyline in evoking high-degree use-dependent blockade during repetitive pulses. *In vivo*, duration to full recovery of nociception in the sciatic nerve model was 1,932 ± 72 min for *N*-phenylethyl amitriptyline at 2.5 mM (n = 7) *versus* 72 ± 3 min for lidocaine at 37 mM (n = 4; mean ± SEM). However, there was evidence of neurotoxicity at 5 mM.

Conclusion: N-phenylethyl amitriptyline appears to have a narrow therapeutic range but is much more potent than lidocaine, providing a block duration several times longer than any clinically used local anesthetic. Further work in animal models of neuropathic pain will assess the potential use of this drug.

AMITRIPTYLINE and other tricyclic antidepressants are used often orally for management of various types of chronic pain.[1] Amitriptyline is known to exert a variety of effects, among them blockade of multiple ion channels and receptors and inhibition of norepinephrine and serotonin reuptake[2–8]; however, the underlying mechanism by which it relieves pain remains unclear.[9] Recently, amitriptyline was found to have potent local

anesthetic (LA) properties in a rat sciatic nerve block model.[10]

Many types of pain, including postoperative and neuropathic pain, are thought to be caused by a spontaneous high-frequency discharge of neurons.[11] LAs are known to show the phenomenon of use-dependent blockade, *i.e.*, at high-frequency stimulation, additional blockade is achieved at the same drug concentration. Amitriptyline was shown to have LA properties, to exert a high degree of use-dependent block of various Na^+ channel isoforms *in vitro*,[2] and to be a much more potent LA than bupivacaine[10] (clinically the most commonly used LA for long-lasting nerve blockade) in a rat model of sciatic nerve blockade.

We decided to create a phenylethyl derivative of amitriptyline for several reasons: (1) A phenylethyl group has been added to many other drug classes, *e.g.*, fentanyl,[12,13] to increase drug potency. (2) In former experiments, when phenylethyl was added to lidocaine, the intrinsic affinity in blocking Na^+ channels as well as the LA potency greatly increased.[14] (3) Adding a short alkyl group has been unsuccessful. For example, QX-314 was associated with minimal permeability of membranes and therefore had a very limited clinical effect.[15] On the other hand, the addition of penylethyl to amitriptyline creates a quaternary ammonium (QA) in which the charge is more likely shielded by hydrophobic arms and that should at least partially retain the ability to traverse membranes. (4) Amitriptyline is severely limited by its cardiotoxicity.[16,17] Modifying it into a permanently charged drug, and therefore significantly increasing the time to traverse lipid membranes, should greatly decrease the time to and the peak of the plasma concentration, thereby reducing the adverse effect profile. (5) A high degree of use-dependent block, if retained after the addition of this phenylethyl group (as it was the case with lidocaine), should be capable of reducing high-frequency neuronal discharge at low plasma concentrations, and thus further reducing the adverse effect profile.

We hypothesized that derivatizing amitriptyline to the permanently charged QA derivative *N*-phenylethyl amitriptyline (fig. 1) will create an LA drug with higher potency than amitriptyline and an even greater use-dependent blockade *in vitro*. Therefore, we compared the potency and use-dependent block of *N*-phenylethyl amitriptyline with that of amitriptyline. To determine the LA effect and the therapeutic range *in vivo*, we evaluated *N*-phenylethyl amitriptyline at various concentrations (1, 2.5, and 5 mM) for sciatic nerve blockade in rats and compared it with lidocaine, the LA most frequently used clinically. In addition, we performed histopatho-

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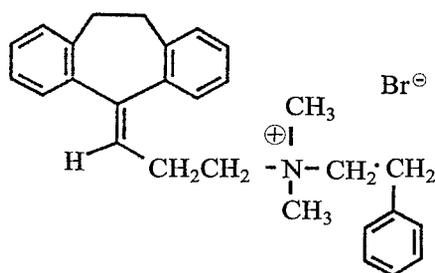
N-phenylethyl amitriptyline bromide

Fig. 1. Chemical structure of *N*-phenylethyl amitriptyline bromide, which is created by adding a phenylethyl group onto the nitrogen atom, yielding a permanently charged molecule. Bromide is the salt form, but bromide itself has no effect on Na^+ channels.

logic studies of sciatic nerve preparations to evaluate neurotoxicity.

Methods

Cell Culture

Rat clonal pituitary GH_3 cells were purchased from the American Type Culture Collection (Rockville, MD). Cells were split twice a week and maintained in Dulbecco modified Eagle medium (Hyclon Labs, Logan, UT) supplemented with taurin (1%), penicillin–streptomycin (1%), hydroxyethylpiperazineethane sulfonic acid, HEPES (20 mM), and heat-inactivated fetal bovine serum (10%), as described previously.[18] The 35-mm culture dishes in which the cells were grown also were used as recording chambers.

Whole Cell Voltage Clamp Experiments. The whole cell configuration of the patch clamp technique was used to record macroscopic Na^+ currents at room temperature (21–23°C). The pipette electrodes had a 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-Electronic, Darmstadt–Eberstadt, Germany). After the whole cell configuration was established, cells were dialyzed for 30 min before data were acquired. Data were filtered at 5 kHz, sampled at 50 kHz, collected, and stored with pCLAMP software. Leak and capacitance currents were subtracted by the P/-4 protocol. The P/-4 protocol was not applied in the use-dependent block of Na^+ currents, as the affinity for LAs is strongly voltage dependent. Whole cell recordings were maintained for more than 1 h in this preparation with little or no run-down of the Na^+ current. 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 150 mM choline Cl and 10 mM HEPES titrated with TMA-OH to pH 7.4. These solutions create an outward Na^+ gradient and current, further reducing potential problems associated with series resistance errors.

Chemicals

Lidocaine hydrochloride and amitriptyline hydrochloride were purchased from Sigma Chemical Company (St. Louis, MO); *N*-phenylethyl amitriptyline (fig. 1) was synthesized by RBI (Natick, MA). The purity was greater than 98% by high-performance liquid chromatography, the lot contained 0.25 moles of water, and the molecular weight was 462.47 (anhydrous). For the electrophysiologic experiments, amitriptyline and *N*-phenylethyl amitriptyline were dissolved in dimethyl sulfoxide at 100 mM and were diluted shortly before the experiments. *N*-phenylethyl-amitriptyline at the highest concentration used for the *in vivo* experiments (2.5 and 5 mM) needed to be heated to approximately 50°C to dissolve completely, but once dissolved did not precipitate when allowed to cool to room temperature. The heating process itself should not affect the stability of this compound as the synthesis of QA compounds requires heating to 80–90°C.

Rat Sciatic Nerve Block and Neurobehavioral Evaluation

The protocol for animal experimentation was reviewed and approved by the Harvard Medical Area Standing Committee on Animals. Male Sprague-Dawley rats were purchased from Charles River Laboratory (Wilmington, MA) and kept in the animal housing facilities at Brigham and Women's Hospital, with controlled humidity (20–30% relative humidity) at room temperature (24°C), and a 12-h (6:00 AM to 6:00 PM) light– dark cycle. Rats were handled before the procedure to familiarize them with the experiment and to minimize stress-induced analgesia. At the time of injections, animals weighed 300–350 g and showed no signs of neurobehavioral impairment.

Sciatic nerve blockade was performed as follows: rats were lightly anesthetized by inhalation of sevoflurane, and the landmark (greater trochanter) of the left hind limb was localized. Either 0.2 ml lidocaine at 37 mM (n = 4) or 0.2 ml *N*-phenylethyl amitriptyline at various concentrations—1 mM (n = 5), 2.5 mM (n = 7), and 5 mM (n = 12)—was injected in immediate proximity to the sciatic nerve with a 27-gauge hypodermic needle attached to a tuberculin syringe as described previously,[19] and the rat was observed for development of sciatic nerve blockade, indicated by paralysis of the hind limb. The right hind limb was used as a control.

The neurobehavioral examination focused on motor function, proprioception, and nociception. Motor func-
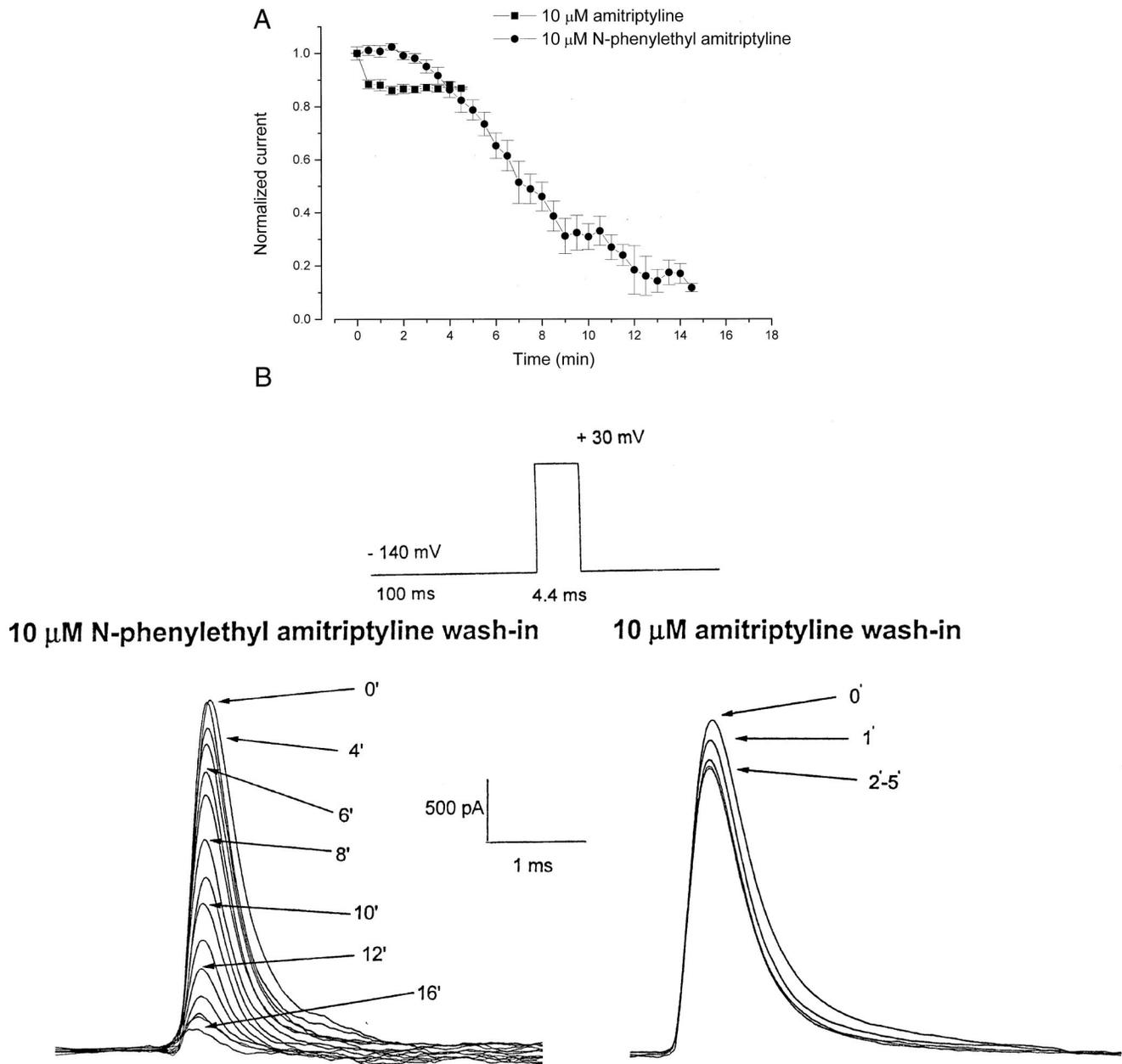
Fig. 2. Tonic inhibition of Na$^+$ currents by amitriptyline and *N*-phenylethyl amitriptyline in neuronal GH$_3$ cells. (*A*) Time course of wash-in. The peak amplitudes of Na$^+$ currents, evoked by a test pulse, were measured at a concentration of 10 μM, normalized with respect to the peak amplitude in the control and plotted against time. Data are reported as mean ± SEM (n = 6). The wash-in time for *N*-phenylethyl amitriptyline, because it is a quaternary ammonium derivative, is greatly prolonged. In addition, the percentage of channel block is approximately six times higher than that of the parent structure. (*B*) Representative tracings of wash-in. The pulse protocol is shown in the inset. The holding potential was −140 mV for 100 ms, followed by a test pulse to 30 mV for 4.4 ms; the start-to-start interval was 30 s.

tion was tested by holding the rat by three legs and allowing the control–study limb to push against the platform of a scale, which records the force applied in grams ("extensor postural thrust"). The test for proprioception was based on resting posture and postural reactions ("hopping" and "tactile placing"). Nociception was evaluated by the withdrawal reflex or vocalization to a pinch of the fifth toe of the hind limbs. All examinations were graded and repeated three times and the average

was used. Details of the neurobehavioral examination can be found elsewhere.[19]

Because amitriptyline is known to cause sedation, especially at higher doses, close attention was paid to the general appearance of the animals, particularly those injected with *N*-phenylethyl amitriptyline. In brief, grooming, food intake, responsiveness to environmental stimuli, and exploratory activity were closely monitored.

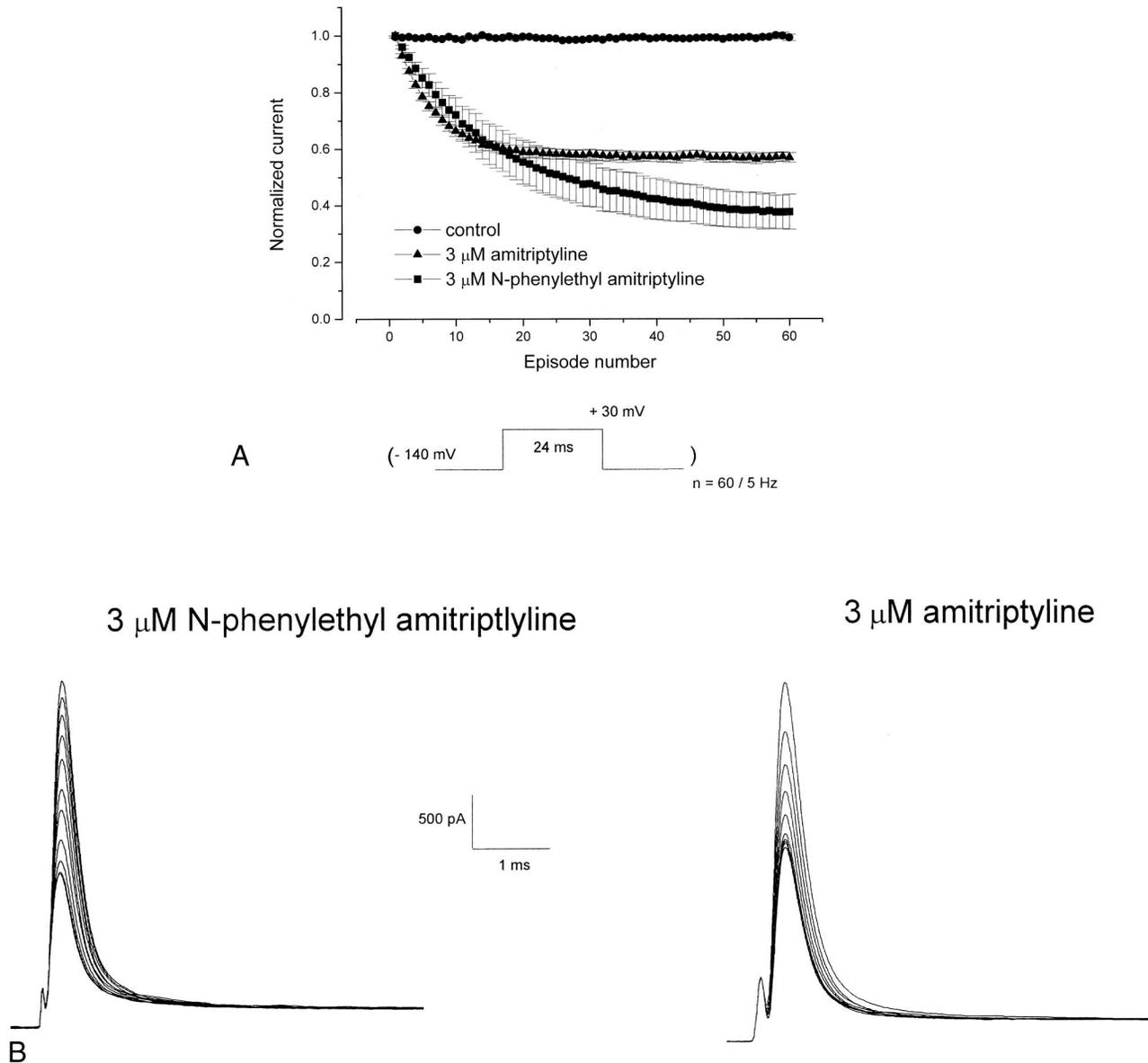As the highest concentration is naturally associated

Fig. 3. Use-dependent blockade of amitriptyline *versus* **that of** *N***-phenylethyl amitriptyline at concentrations of 3** μM **in neuronal GH$_3$ cells.** (*A*) The peak amplitude of each data set was normalized with respect to the peak amplitude of the first pulse of the set. The normalized current was plotted against pulse number. Data were well fitted by a single exponential function with a time constant of 5.92 ± 0.05 pulse for amitriptyline and 15.95 ± 0.18 pulse for *N*-phenylethyl amitriptyline. No effect is seen with the control (no drug); 50.3 ± 0.1% additional blockade with amitriptyline and 66.8 ± 0.3% (SEM, n = 5) with *N*-phenylethyl-amitriptyline (*P* < 0.05). (*B*) Representative tracings and pulse protocol. From the holding potential of −140 mV, a test pulse of +30 mV was evoked for 24 ms. A total of 60 pulses were delivered at 5 Hz. The tracings shown were obtained after pulse numbers 1, 3, 5, 7, 10, 15, 20, 30. . .60 for control, amitriptyline, and *N*-phenylethyl amitriptyline at identical concentrations. The current was normalized without leak subtraction.

with the greatest risk of toxicity, we selected more animals (n = 12) for the concentration of 5 mM.

Pathology

Morphologic changes of the sciatic nerves at the higher doses (2.5 and 5 mM) were evaluated by killing rats by administering an overdose of sevoflurane 2 weeks after the injection. A neuropathologist experienced in peripheral neurotoxicity who was blinded to the study groups evaluated sciatic nerves from each of the following groups: 2.5 and 5 mM *N*-phenylethyl amitriptyline

(n = 7 and 12, respectively) and 37 mM lidocaine (n = 4) for the control group. The sciatic nerves were excised and placed in 4% glutaraldehyde in 0.1 M cacodylate buffer. After fixation, cross-sections of the sciatic nerves were embedded in paraffin and stained with hematoxylin and eosin, as previously described.[20]

Statistical Analysis

A one-way analysis of variance was used to calculate the significance of the difference in the inhibition of Na$^+$ current between amitriptyline and *N*-phenylethyl ami-

Table 1. Duration of Complete Blockade and Full Recovery of Lidocaine Compared with *N*-Phenylethyl Amitriptyline

| | Complete Blockade of Functions (min) | | | | Full Recovery of Functions (min) | | | |
| | Lidocaine | *N*-Phenylethyl Amitriptyline | | | Lidocaine | *N*-Phenylethyl Amitriptyline | | |
	37 mM	1.0 mM	2.5 mM	5.0 mM	37 mM	1.0 mM	2.5 mM	5.0 mM
Proprioception	28 ± 1	—	379 ± 40	1393 ± 90	87 ± 3	22 ± 2	2160 ± 50	4053 ± 200
Motor	28 ± 1	—	338 ± 36	1380 ± 87	69 ± 8	90 ± 0	2568 ± 72	4733 ± 233
Nociception	28 ± 1	—	319 ± 17	1740 ± 130	72 ± 3	13 ± 2	1932 ± 72	4627 ± 203

Duration of complete blockade and time to full recovery for proprioceptive, motor, and nociceptive functions (mean ± SEM) for lidocaine at 37 mM (n = 4) and *N*-phenylethyl amitriptyline at 1 (n = 5), 2.5 (n = 7), and 5 mM (n = 12). Of note, none of the rats in the 1.0 mM group had complete blockade of any function tested.

triptyline at the 60th pulse. An unpaired student *t* test was used to detect significant differences among the proprioceptive, motor, and sensory–nociceptive functions of the animals after *N*-phenylethyl amitriptyline or lidocaine injection (Origin; Microcal Software, Inc., Northhampton, MA). Statistical significance was defined as $P < 0.05$.

Results

Voltage Clamp Experiments

Wash-in. *N*-phenylethyl amitriptyline is a potent Na^+ channel blocker with a slow wash-in rate (figs. 2A and B). Wash-in of amitriptyline was much faster, reaching its maximal blockade (approximately 15%) at 2 min, as opposed to that of *N*-phenylethyl amitriptyline, which reached maximal blockade of approximately 90% but took 15 min to achieve this block of Na^+ currents. Therefore, a QA derivative of amitriptyline, like a QA derivative of lidocaine,[14] is much more potent than the parent drug.

Use-dependent Blockade. Once steady state was reached after perfusion of the drug was started, the use-dependent protocol was initiated. The high amount of use-dependent blockade by amitriptyline (approximately 50%), known to be of a degree much greater than that of bupivacaine or lidocaine at an equipotent concentration,[10,21] is even surpassed by *N*-phenylethyl amitriptyline, which provides approximately 66% of an additional blockade at an identical concentration (3 μM). Steady state is still not reached at episode 60 (figs. 3A and B). For comparison, lidocaine reached approximately 20% use-dependent blockade at a concentration of 100 μM.[14]

Rat Sciatic Nerve Blockade

All rats developed sciatic nerve blockade after injection of *N*-phenylethyl amitriptyline or lidocaine. No signs of sedation or any other type of neurobehavioral abnormalities were detectable at any time. All rats in the lidocaine and 1- and 2.5-mM *N*-phenylethyl amitriptyline groups recovered completely without any clinically detectable neurologic deficits. However, 2 of 12 rats in the 5-mM group did not recover completely, only to approximately 50% of baseline. These two rats were excluded

from the graph, but a detailed description including histopathologic results is provided.

Duration of Complete Blockade. In the 37-mM lidocaine group, the duration of complete blockade was rather short, and no differential blockade was observed (28 ± 1 min for proprioception, nociception, and motor blockade, n = 4, table 1). A significantly longer duration of blockade for all qualities was observed in the *N*-phenylethyl amitriptyline group at 2.5 mM: duration of complete blockade was 379 ± 40, 319 ± 17, and 338 ± 36 min for proprioceptive, nociceptive, and motor function, respectively (n = 7, table 1). For comparison, in previous studies the duration of complete blockade for amitriptyline at the same concentration–dosage injected during identical conditions was 176 ± 7, 218 ± 19, and 169 ± 8 min, respectively.[10] Of note, rats with the concentration of 1 mM *N*-phenylethyl amitriptyline did not reach complete block for any function tested.

Duration to Full Recovery. As with complete blockade, the time until all functions tested were fully recovered was greatly prolonged in the *N*-phenylethyl amitriptyline group. Some differential blockade was observed, but only in the lidocaine group, in which the time to proprioceptive recovery (87 ± 3 min) was significantly prolonged compared with nociceptive recovery (72 ± 3 min) but not with motor recovery (69 ± 8 min). With *N*-phenylethyl amitriptyline at 2.5 mM, the time to full recovery of functions was 1,932 ± 72 min for nociception, 2,568 ± 72 min for motor function, and 2,160 ± 50 min for proprioception (table 1).

The detailed time course of onset and recovery after injection of 1, 2.5, and 5 mM *N*-phenylethyl amitriptyline is shown in figure 4. For comparison, as mentioned previously for the duration of complete blockade, the time for full recovery of all functions tested for amitriptyline at 5 mM was 255 ± 11, 353 ± 12, and 270 ± 14 min, respectively.

Histopathology

Lidocaine 37 mM (Control, n = 4). All control animals showed normal peripheral nerve histology, with only rare (< 0.1%) fibers in active stages of axonal degeneration.

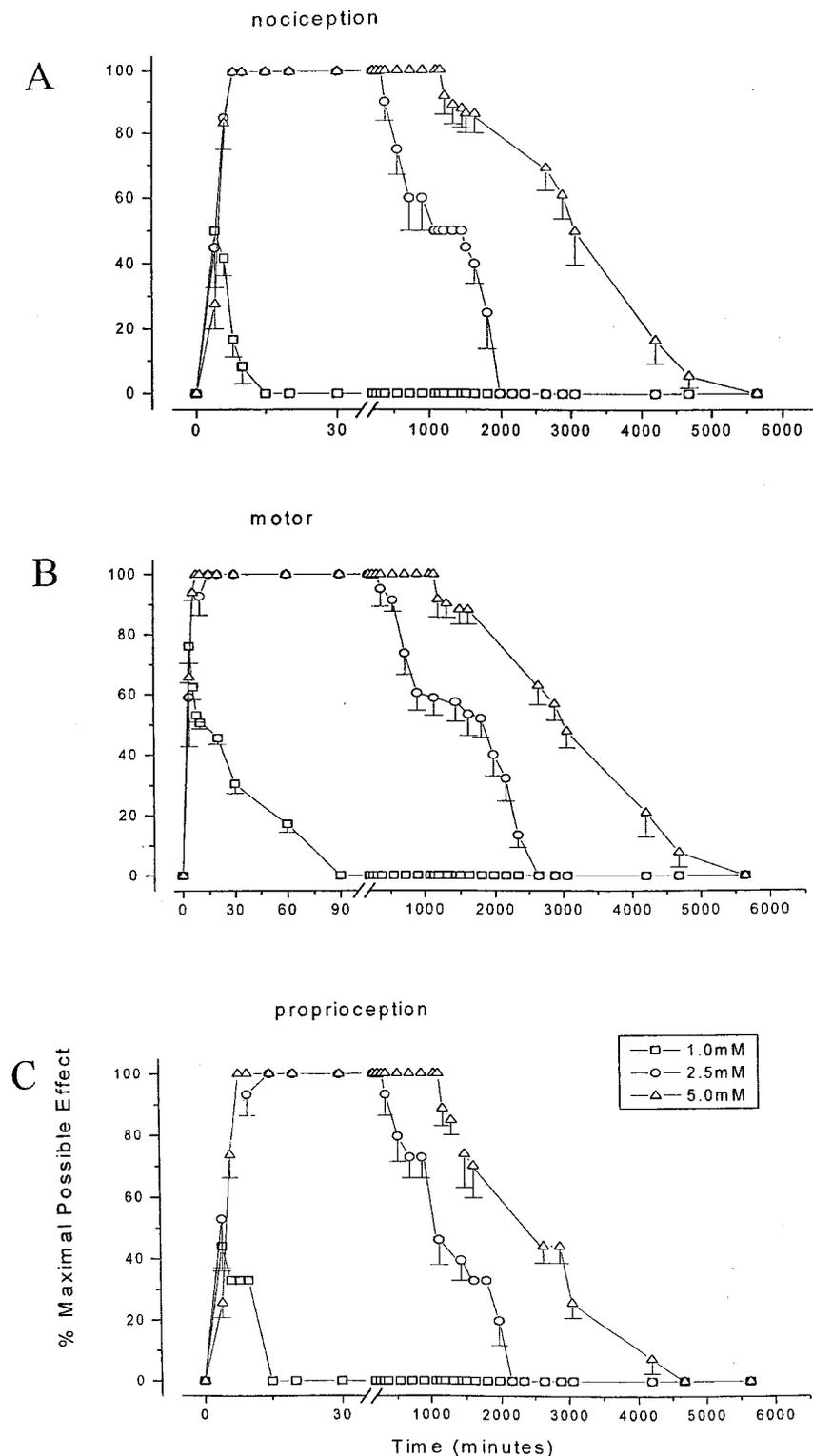**N-phenylethyl Amitriptyline 2.5 mM (n = 7).** All nerve sections studied were comparable to the control.

Fig. 4. Detailed time course of blockade onset and recovery for nociceptive (*A*), motor (*B*), and proprioceptive (*C*) functions (mean ± SEM). Rat sciatic nerve blockade with 0.2 ml *N*-phenylethyl amitriptyline at 1 (n = 5), 2.5 (n = 7), and 5 mM (n = 12). Of note, rats at a concentration of 1 mM reached only approximately 45–75% of maximal possible effect. Two rats in the 5-mM group did not recover completely and are not included in the graphs.

N-phenylethyl Amitriptyline 5 mM (n = 12). No significant change was detectable compared with the control or the lower concentration *N*-phenylethyl amitriptyline group. However, the two animals that did not recover completely showed severe axonal degeneration affecting approximately 30% of the cross-sectional area, localized as a crescent at the periphery of the nerve fascicle.

Discussion

We have shown that *N*-phenylethyl amitriptyline, despite its being a permanently charged QA, traverses neuronal membranes and confers long-acting LA properties.

Such a potent Na^+ channel-blocking drug with a high degree of use-dependent blockade could be useful for

the management of various types of acute and chronic pain. All of the currently available LAs have a rather short duration of action (< 24 h) and are accompanied by a more or less unwanted blockade of motor and sympathetic fibers in addition to sensory–nociceptive blockade. Although we were able to show that 0.2 ml amitriptyline at a concentration of 5 mM causes a significantly longer blockade of nociceptive function than of motor and proprioceptive function in the rat sciatic nerve model,[10] this characteristic of differential blockade could be neither prolonged nor maintained by adding a phenylethyl group to amitriptyline. Nociceptive blockade mostly recovered before other functions (fig. 4, table 1), but this effect may be specific for this rat model, because no differential blockade was detectable with bupivacaine during identical conditions,[10] which is in contradiction to the clinical impression.

N-phenylethyl amitriptyline was compared with amitriptyline *in vitro* because it is more appropriate to compare the derivative with the parent drug than with lidocaine. In addition, the potency of lidocaine during similar conditions has already been established (IC_{50} of 569 μM).[21] Similarly, for the *in vivo* experiments, we chose lidocaine as the control because it is the LA most frequently used clinically, a huge body of literature exists pertaining to lidocaine toxicity that can be used for comparison, and data on rat sciatic nerve blockade by bupivacaine and amitriptyline have been published previously.[10,22]

Toxicity

The parent drug amitriptyline, by being uncharged, has some significant disadvantages. To decrease the incidence and severity of adverse effects, the initial dosage usually is 25 mg orally once a day, and the dose is titrated up slowly to the maximal-tolerated dosage, which is around 100 mg/day. The maximal pain-relieving effect of amitriptyline is often limited by its adverse effects: neurotoxicity beginning with sedation followed by seizure and coma and cardiac toxicity, presenting initially with QRS complex widening and eventual cardiac arrest.[17,23] Theoretically, the charged *N*-phenylethyl amitriptyline, even orally administered, could be better tolerated than amitriptyline because of the greater amount of use-dependent blockade and slower traversing of membranes.

Histologic evaluations of nerve sections of animals that received *N*-phenylethyl amitriptyline at a concentration of 2.5 mM (n = 7) were identical with those of control sections (lidocaine at a concentration of 37 mM, n = 4), with fewer than 0.1% of nerve fibers showing axonal degeneration. In light of the absence of clinical signs of neurologic deficits, this concentration of *N*-phenylethyl amitriptyline is probably safe in the specified rat model.

However, the therapeutic range appears narrow; in the 5-mM *N*-phenylethyl amitriptyline group, 2 of 12 rats did not fully recover and showed corresponding degenerative histopathologic changes.

Toxicity of LAs, even the most common used clinically, remains difficult to assess. For some years now, case reports of cauda equina syndrome caused by relatively low doses of intrathecal lidocaine have appeared frequently,[24,25] and more recently case reports of accidental injection of lidocaine, mepivacaine, or bupivacaine into the spinal cord associated with interscalene block revealed their catastrophic consequences (loss of cervical spinal cord function and radiologic evidence of severe spinal cord damage). Although the neurotoxic potential of bupivacaine at clinically most often used concentrations of approximately 15 mM (which corresponds to a concentration of 0.5%) remains controversial, it is probably not useful to attempt to prolong blockade by increasing the dosage. In our own pilot studies, a fivefold concentration prolonged rat sciatic nerve blockade only to several hours, and a 10-fold concentration caused either seizure and death within minutes or irreversible nerve blockade (n = 6).

In addition, animal experiments have shown that neurobehavioral testing and histopathologic methods may not be sensitive enough to detect subtle changes.[26] Similarly, histopathologic observations do not necessarily correlate with clinical findings and *vice versa*. For example, degenerative histopathologic changes may be present without detectable clinical abnormalities.[27,28] The crescent form-like degeneration located at the periphery of a nerve fasciculus in the two rats that did not recover could also suggest direct needle trauma, but in the absence of evidence this remains speculative. As with any new drug or mode of application, utmost scrutiny must be applied to detect neurotoxicity,[29] and we therefore conclude that there is evidence of neurotoxicity at a concentration of 5 mM.

In summary, we have shown that *N*-phenylethyl amitriptyline is much more potent than amitriptyline or any clinically used LA *in vitro* and *in vivo*, but the therapeutic range of *N*-phenylethyl amitriptyline is narrower than that of currently used LAs. The high degree of use-dependent block by *N*-phenylethyl amitriptyline is pharmacologically interesting for the treatment of all types of pain caused by afferent nerve fibers that fire action potentials at a high frequency, particularly postoperative and neuropathic pain.[30] Theoretically, a drug with such a high degree of use-dependent and frequency-dependent blockade could selectively filter out a high-frequency spectrum but leave conduction of the basic–normal action potential intact. Further studies in models of acute and neuropathic pain will clarify this potentially beneficial effect.

References

1. Bryson HM, Wilde MI: Amitriptyline: A review of its pharmacological properties and therapeutic use in chronic pain states. Drugs Aging 1996; 8:459–76

2. Pancrazio JJ, Kamatchi GL, Roscoe AK, Lynch C III: Inhibition of neuronal Na+ channels by antidepressant drugs. J Pharmacol Exp Ther 1998; 284:208–14

3. Eisenach JC, Gebhart GF: Intrathecal amitriptyline acts as an N-methyl-D-aspartate receptor antagonist in the presence of inflammatory hyperalgesia in rats. ANESTHESIOLOGY 1995; 83:1046–54

4. Sanchez C, Hyttel J: Comparison of the effects of antidepressants and their metabolites on reuptake of biogenic amines and on receptor binding. Cell Mol Neurobiol 1999; 19:467–89

5. Galeotti N, Ghelardini C, Bartolini A: Involvement of potassium channels in amitriptyline and clomipramine analgesia. Neuropharmacology 2001; 40:75–84

6. Ghelardini C, Galeotti N, Bartolini A: Antinociception induced by amitriptyline and imipramine is mediated by alpha2A-adrenoceptors. Jpn J Pharmacol 2000; 82:130–7

7. Di Matteo V, Di Mascio M, Di Giovanni G, Esposito E: Acute administration of amitriptyline and mianserin increases dopamine release in the rat nucleus accumbens: Possible involvement of serotonin2C receptors. Psychopharmacology (Berl) 2000; 150:45–51

8. Malatynska E, Miller C, Schindler N, Cecil A, Knapp A, Crites G, Rogers H: Amitriptyline increases GABA-stimulated 36Cl- influx by recombinant (alpha 1 gamma 2) GABAA receptors. Brain Res 1999; 851:277–80

9. Abdi S, Lee DH, Chung JM: The anti-allodynic effects of amitriptyline, gabapentin, and lidocaine in a rat model of neuropathic pain. Anesth Analg 1998; 87:1360–6

10. Gerner P, Mujtaba M, Sinnott CJ, Wang GK: Amitriptyline versus bupivacaine in rat sciatic nerve blockade. ANESTHESIOLOGY 2001; 94:661–7

11. Devor M: Neuropathic pain and injured nerve: Peripheral mechanisms. Br Med Bull 1991; 47:619–30

12. Llama EF, del Campo C, Capo M: New heteroaryl derivatives of fentanyl. J Pharm Pharmacol 1991; 43:68–9

13. Lu YF, Xu H, Liu-Chen LY, Chen C, Partilla JS, Brine GA, Carroll FI, Rice KC, Lai J, Porreca F, Sadee W, Rothman RB: Opioid peptide receptor studies: 7. The methylfentanyl congener RTI-4614–4 and its four enantiomers bind to different domains of the rat mu opioid receptor. Synapse 1998; 28:117–24

14. Wang GK, Quan C, Vladimirov M, Mok WM, Thalhammer JG: Quaternary ammonium derivative of lidocaine as a long-acting local anesthetic. ANESTHESIOLOGY 1995; 83:1293–301

15. Strichartz GR: The inhibition of sodium currents in myelinated nerve by quaternary derivatives of lidocaine. J Gen Physiol 1973; 62:37–57

16. Harrigan RA, Brady WJ: ECG abnormalities in tricyclic antidepressant ingestion. Am J Emerg Med 1999; 17:387–93

17. Sasyniuk BI, Jhamandas V, Valois M: Experimental amitriptyline intoxication: Treatment of cardiac toxicity with sodium bicarbonate. Ann Emerg Med 1986; 15:1052–9

18. Cota G, Armstrong CM: Sodium channel gating in clonal pituitary cells: The inactivation step is not voltage dependent. J Gen Physiol 1989; 94:213–32

19. Thalhammer JG, Vladimirova M, Bershadsky B, Strichartz GR: Neurologic evaluation of the rat during sciatic nerve block with lidocaine. ANESTHESIOLOGY 1995; 82:1013–25

20. Wang GK, Vladimirov M, Quan C, Mok WM, Thalhammer JG, Anthony DC: N-butyl tetracaine as a neurolytic agent for ultralong sciatic nerve block. ANESTHESIOLOGY 1996; 85:1386–94

21. Gerner P, Nakamura T, Quan CF, Anthony DC, Wang GK: Spinal tonicaine: Potency and differential blockade of sensory and motor functions. ANESTHESIOLOGY 2000; 92:1350–60

22. Grant GJ, Vermeulen K, Zakowski MI, Sutin KM, Ramanathan S, Langerman L, Weissman TE, Turndorf H: A rat sciatic nerve model for independent assessment of sensory and motor block induced by local anesthetics. Anesth Analg 1992; 75:889–94

23. Cerda SE, Tong C, Deal DD, Eisenach JC: A physiologic assessment of intrathecal amitriptyline in sheep. ANESTHESIOLOGY 1997; 86:1094–103

24. Drasner K: Lidocaine spinal anesthesia: A vanishing therapeutic index? ANESTHESIOLOGY 1997; 87:469–72

25. Schneider MC, Birnbach DJ: Lidocaine neurotoxicity in the obstetric patient: Is the water safe? Anesth Analg 2001; 92:287–90

26. Hashimoto K, Hampl KF, Nakamura Y, Bollen AW, Feiner J, Drasner K: Epinephrine increases the neurotoxic potential of intrathecally administered lidocaine in the rat. ANESTHESIOLOGY 2001; 94:876–81

27. Li DF, Bahar M, Cole G, Rosen M: Neurological toxicity of the subarachnoid infusion of bupivacaine, lignocaine or 2-chloroprocaine in the rat. Br J Anaesth 1985; 57:424–9

28. Takenami T, Yagishita S, Asato F, Hoka S: Neurotoxicity of intrathecally administered tetracaine commences at the posterior roots near entry into the spinal cord. Reg Anesth Pain Med 2000; 25:372–9

29. Eisenach JC, James FM III, Gordh T Jr, Yaksh TL: New epidural drugs: Primum non nocere (letter). Anesth Analg 1998; 87:1211–2

30. Cummins TR, Dib-Hajj SD, Black JA, Waxman SG: Sodium channels and the molecular pathophysiology of pain. Prog Brain Res 2000; 129:3–19