Meperidine and Lidocaine Block of Recombinant Voltage-Dependent Na⁺ Channels

Evidence that Meperidine is a Local Anesthetic

Larry E. Wagner II, B.S.,* Michael Eaton, M.D.,† Salas S. Sabnis, B.S.,‡ Kevin J. Gingrich, M.D.§

Background: The opioid meperidine induces spinal anesthesia and blocks nerve action potentials, suggesting it is a local anesthetic. However, whether it produces effective clinical local anesthesia in peripheral nerves remains unclear. Classification as a local anesthetic requires clinical local anesthesia but also blockade of voltage-dependent Na⁺ channels with characteristic features (tonic and phasic blockade and a negative shift in the voltage-dependence of steady-state inactivation) involving an intrapore receptor. The authors tested for these molecular pharmacologic features to explore whether meperidine is a local anesthetic.

Methods: The authors studied rat skeletal muscle β1 (RSKM1) voltage-dependent Na⁺ channels or a mutant form heterologously coexpressed with rat brain Na⁺ channel accessory β, subunit in Xenopus oocytes. Polymerase chain reaction was used for mutagenesis, and mutations were confirmed by sequencing. Na⁺ currents were measured using a two-microelectrode voltage clamp. Meperidine and the commonly used local anesthetic lidocaine were applied to oocytes in saline solution at room temperature.

Results: Meperidine and lidocaine produced tonic current inhibition with comparable concentration dependence. Meperidine caused phasic current inhibition in which the concentration-response relationship was shifted to fivefold greater concentration relative to lidocaine. Meperidine and lidocaine negatively shifted the voltage dependence of steady-state inactivation. Mutation of a putative local anesthetic receptor reduced phasic inhibition by meperidine and lidocaine and tonic inhibition by lidocaine, but not meperidine tonic inhibition.

Conclusions: Meperidine blocks Na⁺ channels with molecular pharmacologic features of a local anesthetic. The findings support classification of meperidine as a local anesthetic but with less overall potency than lidocaine. (Key words: Heterologous expression; mutagenesis; receptor.)

MEPERIDINE (ethyl 1-methyl-4-phenylisonipecotate hydrochloride), a phenylpiperidine, is an opioid widely used for analgesia and sedation. In addition, meperidine produces sensory spinal anesthesia that is roughly equipotent with hyperbaric lidocaine,¹⁻⁵ suggesting that it is a local anesthetic (LA). Additional support for this proposal is derived from reports of action-potential block in peripheral nerve⁶⁻⁹ and muscle.¹⁰ However, the ability of meperidine to produce clinical local anesthesia in peripheral nerve remains unclear because meperidine caused local anesthesia in intravenous regional anesthesia¹¹,¹² but failed to produce median nerve blockade using local infiltration.¹³ Classification as an LA requires clinical local anesthesia but also characteristic blockade of voltage-dependent Na⁺ channels involving an intrapore receptor.¹⁴

Voltage-dependent Na⁺ channels are membrane-spanning proteins that form voltage-sensitive, Na⁺ selective pores through the membranes of excitable cells and are essential to action-potential initiation and propagation. The pore is regulated by channel gates. At resting membrane potentials, Na⁺ channels are in a resting state in which the pore is closed by activation gates. Membrane depolarization induces conformational changes that open activation gates, resulting in conduction of Na⁺ ions through the pore and Na⁺ current. Continued depolarization triggers closure of an inactivation gate, occlusion of the channel pore, and current termination. Membrane repolarization returns the channel to the rest-
Local anesthetics are commonly tertiary amines linked through an amide or ester linkage to an aromatic moiety. They exert clinical effects through the blockade of voltage-dependent Na⁺ channels. Key features of LA action are tonic and phasic current inhibition and a negative shift in the voltage dependence of steady-state inactivation. Tonic or "resting" inhibition arises from channel blockade in the absence of recent activity. Phasic or "use-dependent" inhibition is progressive current depression during repetitive stimulation that stems from the accumulation of long-lasting, drug-blocked states. These complex features of LA action are concisely explained by a modulated receptor, which extended earlier mechanistic proposals of LA action. The hypothesis holds that LAs bind to an intrapore receptor with variable affinity that is determined by channel state; those associated with opening (open and inactivated) have high affinity. Furthermore, bound channels are non-conducting and give rise to stabilized, drug-blocked states as reported by a negative shift in the voltage dependence of steady-state inactivation. A recent investigation has begun to identify the structural underpinnings of an intrapore LA receptor.

We investigated the effects of meperidine and the commonly used LA lidocaine on currents of rat skeletal muscle α₁ subunit (RSkM1) Na⁺ channels expressed heterologously with rat brain β₁ accessory subunit in Xenopus oocytes. The approach allowed study of a homogeneous Na⁺ channel population and examination of the role of an intrapore LA receptor by manipulating channel structure through mutagenesis and expression. A preliminary version of this work has been published in abstract form.

Material and Methods

Molecular Biology

Rat skeletal muscle Na⁺ channel α₁ subunit (RSkM1; provided by Dr. David Yue, Department of Biomedical Engineering, The Johns Hopkins University) was inserted in pBluescript (KS⁻) at EcoRI. Xenopus β-globin untranslated region flanked αWT, αF1579A, and β₁ in pBluescript (KS⁻) to enhance expression. cRNA was synthesized using T3 RNA polymerase after a linearizing cut at Sal I followed by 5' capping.

Oocyte Expression

Xenopus oocytes were obtained from frogs purchased from Nasco (Fort Atkinson, WI). Oocytes were defolliculated in preparation for RNA injection and electrical recording by exposure to collagenase (0.2 mg/ml, type II; Sigma, St. Louis, MO) for 1-3 h at 20°C. Oocytes were injected with 30-50 nl (5-20 ng) of 5' capped cRNA of αWT or αF1579A with β₁ (1:1 ratio by weight), referred to as WT-β₁ and F1579A-β₁, respectively. Na⁺ channel expression in oocytes requires coexpression with β₁ to duplicate in vivo channel function. The oocytes were kept for 1-7 days at 16°C, during which time they were tested for expression using two-electrode voltage clamp.

Two-electrode Oocyte Voltage Clamp

Bath solution contained 100 mM NaCl, 2 mM KCl, 1.8 mM CaCl₂, 1 mM MgCl₂, and 5 mM HEPES, and pH was adjusted to 7.6 with NaOH at 22°C. Oocytes were voltage-clamped using a standard two-microelectrode voltage clamp technique. Electrodes were pulled from borosilicate glass pipettes and filled with 3 M KCl. Electrode resistances were 0.2-0.6 MΩ. Membrane potential was controlled with a voltage clamp amplifier (Model OC-725C, Warner Instruments, Hamden, CT). Only currents < 10 μA were analyzed. A grounded metal shield was inserted between the two electrodes to minimize electrode coupling and speed clamp rise time. Typical charging curves, integral of capacity transient during voltage-clamp depolarization that did not trigger channel activation, were approximated by monoeponential functions with time constants < 0.3 ms.

Voltage commands were generated by a 12-bit digital/analog converter driven by software of our own design written in Axobasic (Axon Instruments, Foster City, CA). Currents were filtered at 1 kHz (~3 dB, 4-pole Bessel) and sampled at > 4 kHz by a 12-bit analog/digital converter. Na⁺ currents were measured using two-electrode voltage clamp (holding potential of −100 mV) 2-7 days after injection. Capacity transients were compensated for using a P/6 protocol in which P/6 pulses were
MEPERIDINE AND LIDOCAINE BLOCK OF RECOMBINANT Na⁺ CHANNELS

applied at least 10 s before data collection to prevent artifact.

Cells were held at −100 mV between infrequent test pulses (−10 mV, 20 ms, > every 10 s). This protocol allowed inactivated channels to return to resting state before delivery of subsequent test pulses. Cells exposed to meperidine or lidocaine (0−20 mM) required approximately 5 min for Na⁺ current magnitudes to stabilize. The currents of cells exposed to > 5 min did not return to control values despite multiple washings with control solutions and intervals up to 30 min. Otherwise, cells were included if currents returned to within 5% of control before drug exposure. Other voltage protocols were delivered infrequently (> every 10 s) or as described in Results with data subjected to the same inclusion criterion.

Statistical and Data Analysis

Normalized current concentration-response relationships were fit with the following logistic equation:

\[ I = \frac{1}{1 + \left( \frac{C}{IC_{50}} \right)^{Slope}} \]

where \( I \) is current magnitude normalized by control, \( C \) is the agent concentration, \( IC_{50} \) is the half blocking concentration, and \( Slope \) is a slope factor related to the Hill coefficient. Normalized current amplitude responses over time were fit with the multieponential function:

\[ I = \sum A_i \cdot \exp(-t/\tau_i) \]

where \( I \) is the normalized current, \( t \) is time, \( A_i \) are the component amplitudes, and \( \tau_i \) is the time constant of the \( i \)th exponential component. Normalized current voltage response relationships were fit with the two-state Boltzmann equation:

\[ I = \frac{1}{1 + \exp(v - v_{50})/Slope_{B}} \]

where \( I \) is the current amplitude normalized by control, \( v \) is membrane voltage, \( v_{50} \) is the voltage at half value, and \( Slope_{B} \) is a slope factor. Equation parameters were estimated using a nonlinear, least-squares algorithm. Goodness of fit was determined by visual inspection. Grouped data are given as mean ± SEM. One-tailed \( P \) values < 0.05 were considered to have statistical significance.

Results

Hallmark features of LA modulation of voltage-dependent Na⁺ channels include tonic and phasic current inhibition and a negative shift of the voltage dependence of steady-state inactivation. These effects are mediated by a putative intrapore LA receptor. We wished to examine meperidine effects in a heterologously expressed Na⁺ channel so that primary protein structure could be manipulated through mutagenesis. The general features of LA action are shared by Na⁺ currents of nervous, skeletal, and cardiac muscle tissue as well as their expressed tissue-specific isoforms. This indicates that fundamental structures mediating LA action are conserved, and observations made in these isoforms have general import. Consequently, we studied rat skeletal muscle Na⁺ channel \( \mu_1 \) α-subunit (RSkM1) because our laboratory is familiar with its heterologous expression, current recording, and molecular manipulation.

We first addressed tonic inhibition, which reflects channel blockade arising from LA binding to resting and possibly open channels. Figure 1A shows a family of Na⁺ currents \( \{I_{Na}\} \) elicited from an individual oocyte expressing wild-type RSkM1 (WT-β₁) Na⁺ channels (see Methods). The control response manifests a typical native \( I_{Na} \) time course that is marked by rapid activation reaching a current peak within milliseconds, followed by current decay caused by fast inactivation. Current-voltage relationships peak at approximately −10 mV (data not shown), which is also consistent with native currents and reports of WT-β₁ expressed in oocytes. Lido-

caine application caused a concentration-dependent reduction of \( I_{Na} \) amplitude, reflecting an increasing proportion of tonically blocked channels. Figure 1B shows an \( I_{Na} \) family elicited from another oocyte expressing WT channels over a range of meperidine concentrations. Interestingly, meperidine also reduced \( I_{Na} \) amplitude in a dose-dependent fashion, marking its ability to induce tonic channel block. A lidocaine concentration-response relationship for normalized current (fig. 1C) reports the fraction of available, unblocked channels versus lidocaine concentration. The relationship was well fit by a logistic equation (see Methods). The fitted \( IC_{50} \) for lidocaine (1.9 ms) is comparable to those reported by Nuss et al. (1.1 ms) and Balser et al. (1.2 ms) for WT-β₁ expressed in oocytes. Remarkably, the concentration-response relationships from grouped data nearly superimpose (fig. 1C), indicating close quantitative potency.

We next tested for phasic inhibition using a pulse train (15 Hz) protocol (fig. 2). Figure 2A plots normalized \( I_{Na} \) amplitudes versus pulse number. In control, \( I_{Na} \) amplitudes vary little, indicating high channel availability at each pulse and, therefore, little accumulation of inactiv-
vated channels over the train. Constant lidocaine concentration caused progressive reductions in $I_{\text{Na}}$ amplitudes, which reached an apparent plateau near pulse no. 5. The declining phase of this response can be explained by decreasing channel availability resulting from accumulation of slowly recovering, depolarization blocked channels. In this analysis, the plateau reflects an equilibrium between intrapulse blockade and interpulse recovery and reports the steady-state fraction of available, unblocked channels. This value is approximately 0.3 for lidocaine. Notably, meperidine application caused qualitatively similar effects, thereby marking phasic inhibi-

![Fig. 1. Tonic block of WT-$\beta_1$ Na$^+$ channels. Na$^+$ currents ($I_{\text{Na}}$) recorded from individual Xenopus oocytes expressing WT-$\beta_1$ channels triggered by the indicated voltage protocols over a range of lidocaine (LIDO; A) and meperidine (MEP; B) concentrations (control = CTL), as indicated to left of the respective trace. Channel opening is reflected by a downward current deflection. (C) Concentration–response relationships for $I_{\text{Na}}$ amplitudes normalized by control for meperidine and lidocaine in grouped data ($n = 5-9$). Solid line represents logistic equation fit of lidocaine response with indicated parameters (see Methods).](image)

![Fig. 2. Phasic block of WT-$\beta_1$ Na$^+$ channels. Phasic or “use-dependent” blockade arises from the accumulation of drug-blocked channels induced by a train of depolarizations. Phasic blockade was assayed using the indicated pulse train (15 Hz; top). (A) Plot of $I_{\text{Na}}$ amplitudes for each pulse normalized to that of pulse no. 1 vs. pulse number for control (CTL), 1 mm lidocaine (LIDO), and meperidine (MEP) in grouped data ($n = 5-8$). (B) Concentration–response relationships for the ratio of $I_{\text{Na}}$ amplitudes of pulse nos. 15 to 1 ($I_{\text{Na,15}}/I_{\text{Na,1}}$) in grouped data ($n = 5-8$). Smooth curves represent logistic equation fits of the relationships with indicated parameters.](image)
MEPERIDINE AND LIDOCAINE BLOCK OF RECOMBINANT Na⁺ CHANNELS

Fig. 3. Recovery from depolarization-induced blockade of WT-β1 Na⁺ channels. (Top) The two-pulse protocol used to determine the time course of channel recovery from nonconducting states induced by the prepulse. (A) Plot of the amplitudes of I_{Na}s triggered by the test pulse and normalized to that of prepulse in control and the presence of lidocaine (LIDO, indicated concentration) vs. recovery interval (n = 6). In control, the response was accounted for (see Methods) by a single fast exponential function, whereas in lidocaine, the response was well-fit by a biexponential function (solid lines, parameters indicated). (B) Same as in (A) but for meperidine (MEP, indicated concentration; n = 5); see text for details.

The meperidine response manifests a plateau of approximately 0.6, indicating less steady-state phasic block. We considered the ratio of I_{Na} amplitudes for pulse nos. 15 and 1 (I_{Na,15}/I_{Na,1}) a convenient gauge of plateau value. We examined this indicator over a wide concentration range and constructed concentration-response relationships (fig. 2B). Both relationships were well fit by a logistic equation with comparable slopes. The meperidine relationship is shifted rightward, signifying lower potency. Assuming these agents differ only in the affinity of a target receptor, the differences in IC_{50} values of logistic equations suggest a fourfold lower affinity for meperidine.

Phasic inhibition arises from depolarization-induced, drug-blocked states with slower recovery than control fast inactivation (approximately 20 ms). Therefore, increased lidocaine potency in phasic inhibition can arise from either greater lidocaine potency in depolarization-induced block or slower recovery of resultant blocked states. We used a two-pulse protocol (fig. 3) to explore the recovery time course of depolarization-induced, nonconducting states. Figure 3A plots normalized I_{Na} amplitude versus recovery interval, which conveys the time course of channel availability after the prepulse. We described time courses using multieponential functions (see Methods). In control, short recovery intervals (< 2 ms) resulted in a near-zero response, where most channels were fast inactivated during the prepulse and remained so over these brief recovery periods. Increasing recovery interval caused a rapid monoexponential increase (τ_s = 4.9 ms), reflecting swift channel recovery from fast inactivation. Lidocaine markedly altered this response by introducing a new slow exponential (τ_s = 490 ms), likely representing recovery of drug-blocked channels. The fast component was reduced by roughly fivefold compared with control, indicating fewer exclusively inactivated channels. Meperidine also induced a new slow component (fig. 3B) representing drug-blocked channels that recovered with a similar time constant (τ_s = 628 ms). The smaller magnitude of this component is explained by a twofold lower concentration relative to lidocaine and less sensitivity to depolarization-induced drug block. Therefore, greater lidocaine potency in phasic inhibition arises from higher channel sensitivity to depolarization-induced drug block.

With meperidine tonic and phasic inhibition established, we considered drug-induced alterations in the voltage-dependence of steady-state inactivation using a two-pulse voltage protocol (fig. 4). The 100-ms prepulse is sufficiently long to fix a new steady-state relation between resting and fast inactivated channels. We plotted normalized test I_{Na} versus prepulse voltage (fig. 4A), which charts the voltage-dependence of available resting channels. In control, for largely negative prepulses (< −80 mV), this relationship is nearly one, indicating high channel availability. Increasing depolarization reduces the relationship, which approaches zero near −30 mV. This indicates a shift from available resting channels to the unavailable fast inactivated state. Lido-}
2B), we used a fivefold greater and approximately equipotent meperidine concentration. Notably, meperidine application caused a similar negative shift (approximately 5 mV) characteristic of LA action and consistent with stabilization of nonconducting states.

The main functional component of the Na⁺ channel is a 260-kDa pore-forming a subunit. Its sequence is highly conserved among nervous, cardiac, and skeletal tissues, indicating a common fundamental structure in which the channel is arranged in the membrane as four homologous domains or repeats (I-IV). Each domain contains at least six α-helical transmembrane repeats S1-S6 (fig. 5A). The four domains are thought to come together like staves of a barrel to form the integral ion channel pore. Recently, critical amino acid residues affecting LA block in expressed rat brain IIA Na⁺ channels were identified and proposed to contribute to an intrapore LA receptor. Among these, phenylalanine (F) 1764, when mutated to alanine, produced relative LA insensitivity. Figure 5A shows the extracellular S5-S6 loop, residues of α-helix of domain IVS6, and the location of the homologous residue (F1579) in RskM1. To test for the involvement of the putative intrapore LA receptor in meperidine action, we mutated F1579 to alanine and reexamined meperidine and lidocaine blockade.

Figure 5B shows Iₙ₌ elicited from individual oocytes expressing F1579A-β₁ channels. Control responses show typical activation and inactivation time courses, which, in combination with unaltered current–voltage relationships (data not shown), indicate unchanged fundamental channel properties. Lidocaine depressed Iₙ₃ amplitude nearly threefold less than that for WT-β₁ channels, which reports a noticeable reduction in tonic block sensitivity (fig. 1). Given the parallel effects of meperidine and lidocaine heretofore, we were surprised that Iₙ₃ sensitivity to meperidine seemed unchanged from WT-β₁ (fig. 1), suggesting no change in meperidine tonic block. These observations were confirmed in concentration–response relationships from grouped data (fig. 5B). The lidocaine relationship for F1579A-β₁ is rightward-shifted compared with that for WT-β₁, resulting in a threelfold reduction in sensitivity based on changes in IC₅₀ values and consistent with previous reports. However, the meperidine relationship is unchanged from WT-β₁, suggesting that F1579 is uninvolved in meperidine tonic block (see Discussion).

We assayed phasic blockade of F1579A-β₁ using the earlier pulse train protocol (fig. 5C). We constructed concentration–response relationships for the ratio of Iₙ₃ amplitudes for pulse nos. 15 and 1 (Iₙ₃₁₅/Iₙ₃₂), which reports the steady-state fraction of available channels (fig. 5C). The steepness of the lidocaine relationship was dramatically reduced, resulting in a more than fourfold increase at higher concentrations (> 2 mM) relative to WT-β₁. This indicates a marked reduction in phasic block sensitivity consistent with prior results. Importantly, similar striking changes are also observed in the meperidine relationship, which points to a critical role of F1579 in phasic block by meperidine.

**Discussion**

Our primary goal in this study was to determine whether meperidine possesses the molecular pharmacologic properties required for classification as an LA. We...
MEPERIDINE AND LIDOCAINE BLOCK OF RECOMBINANT Na⁺ CHANNELS

Fig. 5. Tonic and phasic block of F1579A-β₁ Na⁺ currents. (A, left) Cartoon of the general putative structure of a pore-forming Na⁺ channel α subunit and the amino acid chains that reside within (membrane-spanning segments) and without the cell membrane (intracellular and extracellular loops). Area enclosed by dashed box is magnified (right) to show individual amino acids of the domain IV membrane-spanning segment S6 and an α-helical structure. Residue F1579 is indicated. Mutation to an alanine (A), as shown, disrupts the associated intrapore LA receptor (see text). (B, top) Individual Iₖ values (−10 mV depolarization, holding = −100 mV) measured in oocytes expressing F1579A-β₁ in control (CTL) and 2 mM lidocaine or meperidine (as indicated). (B, bottom) Concentration–response relationships for Iₖ amplitude normalized by control from oocytes expressing F1579A-β₁ (filled symbols, n = 5–8). WT relationships were replotted from figure 1 for comparison (open symbols). The smooth curve represents the logistic equation fit to lidocaine response (parameters indicated). (C) Concentration–response relationships for the ratio of Iₖ amplitudes of pulse nos. 15 to 1 (Iₖ₆₋₁⁰ / Iₖ₁) elicited by a pulse train (top) in grouped data for F1579A-β₁ (n = 5–8). WT relationships were replotted from figure 2 for comparison (open symbols).

Anesthesiology, V 91, No 5, Nov 1999
studied currents of heterologously expressed Na⁺ channels, which provided a homogeneous channel population, thus likely eliminating other confounding channels and possible modulatory pathways.10 This powerful approach was essential in examining the role of an intrapore LA receptor because it allowed manipulation of channel structure using mutagenesis. Our results, for the first time, indicate that meperidine blocks voltage-dependent Na⁺ channels with hallmark features of LAs, including tonic and phasic blockade and a negative shift in the voltage dependence of steady-state inactivation. These effects were observed at millimolar concentrations roughly similar to lidocaine in this study and meperidine concentrations achieved during typical clinical dosing for subarachnoid administration.16 Our data also show that disruption of the putative LA receptor through the F1579A mutation markedly reduced sensitivity to phasic block but not to tonic block. This apparent contradiction can be explained by an emerging picture of intrapore LA blocking effects (rapid and discrete) of currents from single Na⁺ channels lacking fast inactivation; this suggests LA binding within the Na⁺ channel pore blocks ion flow and involves two distinct binding domains.39 The possibility of dual separate binding domains finds additional support in recent observations. F1579A selectively eliminates discrete block in single RSKM1 channels lacking fast inactivation, suggesting F1579 contributes primarily to a binding domain mediating discrete block.40 Discrete block may result when the aromatic tail of an LA molecule binds to a lipophilic binding pocket partly formed by F157940 or through π electron interactions between aromatic rings.21,41 In addition, introduction of negative charge on the selectivity filter enhanced tonic block by tertiary amine but not neutral LAs.12 F1579A and the homologous mutation in rat brain IIA profoundly impairs phasic inhibition, thereby pointing to a critical role of discrete block. If discrete block is mediated by shallow lipophilic amino acid residues (i.e., F1579), then rapid block may arise from interactions of the positively charged tertiary amine head with deep negatively charged structures on or adjacent to the selectivity filter. Assuming some form of these drug-channel configurations exist in resting channels, then interactions with a rapid binding domain may predominate in meperidine tonic inhibition. Therefore, meperidine tonic inhibition would be little changed by alteration of a discrete binding domain by mutation F1579A. Decreased meperidine interactions with a discrete binding domain accord with lower meperidine potency in phasic inhibition. In contrast, lidocaine may interact with the discrete domain in both tonic and phasic inhibition. Overall, these observations suggest a complex molecular picture for LA binding within the Na⁺ channel pore. Further structural and pharmacologic studies are required for a deeper understanding of these pore interactions and LA inhibition.

The salient structural features of LAs include a tertiary amine linked to an aromatic group through an amide or ester bond. At physiologic pH, the tertiary amine is frequently protonated because its pKₐ is approximately 8, resulting in a net positive charge. At a simple level, the molecular arrangement can be envisaged as a linear structure with a charged hydrophilic quaternary amine head and an aromatic lipophilic tail. Interestingly, these primary features are shared by meperidine, where the tertiary amine (pKₐ = 8.5) on the piperidine ring serves as the charged head, and a phenyl group serves as the lipophilic tail.13 If these features figure prominently in LA binding with its receptor, then these shared qualities are consistent with meperidine being an LA.

In addition to meperidine, several other opioids induce LA effects. Morphine seems to inhibit sodium conduction of nerves and muscle in a manner that involves a direct LA effect10,44-46 as well as an indirect opioid receptor-mediated pathway.10,45-47 Methadone blocks peripheral mammalian nerves.7,48 In addition, both fentanyl and sufentanil block nerve conduction.9,49 It will prove interesting to determine whether these agents may qualify as LAs.

In this study, meperidine produced tonic inhibition comparable to lidocaine, but meperidine was fivefold less potent in phasic inhibition. Phasic inhibition likely plays a critical role in Na⁺ blockade by some antiepileptic and antiarrhythmic drugs as well as in local anesthesia.50-52 In these situations, impulses occurring with high frequency produce phasic inhibition that leads to action-potential refractoriness and impulse blockade. Therefore, our data suggest that meperidine is a weaker local anesthetic overall relative to lidocaine. Lower meperidine potency may provide insight into the results of clinical studies examining the ability of meperidine to induce local anesthesia of peripheral nerve, a requirement for classification as an LA. Oldroyd et al.11 compared 40 ml of 0.1% and 0.2% pethidine (meperidine) to 0.5% prilocaine in intravenous regional anesthesia (40 ml) of the upper extremity. Meperidine (0.2%) produced sensory
and motor blockade, but less profoundly than lidocaine. The authors concluded that pethidine has LA action on peripheral nerve but also observed dizziness, nausea, dry mouth, and respiratory depression exclusively in the meperidine group. Acalovschi and Cristea performed a similar study of intravenous regional anesthesia (40 ml), except they compared meperidine (0.25%) with lidocaine (0.5%). Meperidine produced similar degrees of motor and sensory block but with slower onset than lidocaine. There was a significant increase in the incidence of dizziness, nausea, and pain at the injection site in the meperidine group. These studies indicate that meperidine induces clinical local anesthesia of peripheral nerve, although with increased incidence of undesirable side effects. Flanagan et al. studied the effects of median nerve block (5 ml) with meperidine (0.5% and 1.5%) or lidocaine (0.25%) on compound motor action potentials and sensory nerve action potentials in humans. Lidocaine (0.25%) prolonged latencies of both responses consistent with a local anesthetic effect. In contrast, even 1.5% meperidine failed to alter latencies but did cause vertigo, nausea, and flushing in all subjects. Overall, these clinical findings are accounted for by weak LA potency and significant opioid activity of meperidine. Therefore, doses necessary for peripheral nerve block by meperidine may lead to serum anesthetic effects only 1.5% meperidine, as a sole agent, to patients allergic to LAs or as a supplement to traditional LAs. Our conclusion that meperidine is a weak LA has implications in sensory spinal anesthesia. Here, meperidine is roughly equipotent with hyperbaric lidocaine, suggesting differences in LA mechanism for central and peripheral nerves. This may be explained by inhibition of other ion channels in the central nervous system not present peripherally. Alternatively, this may result from differential LA sensitivity among voltage-dependent Na+ channel isoforms in different tissues. Understanding these divergent meperidine effects awaits further pharmacologic investigations of the central and peripheral nervous systems.

In summary, we report that meperidine blocks recombinant voltage-dependent Na+ channels with molecular pharmacologic features characteristic of an LA. The findings lead us to classify meperidine as a weak LA.

References

22. Eaton MP, Wagner LW II, Tran S, Gingrich KJ: Meperidine
induces tonic and phasic blockade of voltage-dependent sodium channels (abstract). ANESTHESIOLOGY 1998; 89:A715
27. Nuss HB, Lomasseli GF, Marban E: Cardiac sodium channels (hH1) are intrinsically more sensitive to block by lidocaine than are skeletal muscle (mu1) channels. J Gen Physiol 1995; 106:1193-1209
28. Armstrong CM, Bezamilla F: Charge movement associated with the opening and closing of the activation gates of the Na channels. J Gen Physiol 1974; 63:533-52
32. Wang DW, Nie L, George Al, Jr, Bennett PB: Distinct local anesthetic affinities in Na+ channel subtypes. Biophys J 1996; 70: 1700-8
33. Nuss HB, Chiamvimonvat N, Perez-Garcia MT, Tomasseli GF, Marban E: Functional association of the beta 1 subunit with human cardiac (hH1) and rat skeletal muscle (mu1) sodium channel alpha subunits expressed in Xenopus oocytes. J Gen Physiol 1995; 106: 1171-91
40. Kimbrough J, Gingerich KJ: Mutation in the putative local anesthetic receptor in IVS6 of rat skeletal muscle mu1 Na+ channels alters single channel interactions (abstract). Biophys J 1999; 7: A32
41. Wright SN, Wang SY, Wang GK: Lysine point mutations in Na+ channel D4-S6 reduce inactivated channel block by local anesthetics. Mol Pharmacol 1998; 54:733-9
42. Sunami A, Dudley SC, Fozard JA: Sodium channel selectivity filter regulates antiarhythmic drug binding. Proc Natl Acad Sci USA 1997; 94:14126-31
43. Cousins MJ, Mather LE: Intrathecal and epidural administration of opioids. ANESTHESIOLOGY 1984; 61:276-310
53. Armstrom PJ, Morton CP, Minno AP: Pethidine has a local anesthetic action on peripheral nerves in vivo. Addition to prilocaine 0.25% for intravenous regional anaesthesia in volunteers. Anaesthesia 1995; 48:382-6