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Tonic Blocking Action of Meperidine on Na^+ and K^+ Channels in Amphibian Peripheral Nerves

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Background: **Among opioids, meperidine (pethidine) also shows local anesthetic activity when applied locally to peripheral nerve fibers and has been used for this effect in the clinical setting for regional anesthesia. This study investigated the blocking effects of meperidine on different ion channels in peripheral nerves.**

Methods: **Experiments were conducted using the outside-out configuration of the patch–clamp method applied to enzymatically prepared peripheral nerve fibers of *Xenopus laevis*. Half-maximal inhibiting concentrations were determined for Na^+ channels and different K^+ channels by nonlinear least-squares fitting of concentration–inhibition curves, assuming a one-to-one reaction.**

Results: **Externally applied meperidine reversibly blocked all investigated channels in a concentration-dependent manner, *i.e.,* voltage-activated Na^+ channel (half-maximal inhibiting concentration, 164 μM), delayed rectifier K^+ channels (half-maximal inhibiting concentration, 194 μM), the calcium-activated K^+ channel (half-maximal inhibiting concentration, 161 μM), and the voltage-independent flicker K^+ channel (half-maximal inhibiting concentration, 139 μM). Maximal block in high concentrations of meperidine reached 83% for delayed rectifier K^+ channels and 100% for all other channels. Meperidine blocks the Na^+ channel in the same concentration range as the local anesthetic agent lidocaine (half-maximal inhibiting concentration, 172 μM) but did not compete for the same binding site as evaluated by competition experiments. Low concentrations of meperidine (1 nM to 1 μM) showed no effects on Na^+ channels. The blockade of Na^+ and delayed rectifier K^+ channels could not be antagonized by the addition of naloxone.**

Conclusions: **It is concluded that meperidine has a nonselective inhibitory action on Na^+ and K^+ channels of amphibian peripheral nerve. For tonic Na^+ channel block, neither an opioid receptor nor the the local anesthetic agent binding site is the target site for meperidine block. (Key words: Analgesics; binding site; pain; receptor.)**

LOCAL anesthetic agents are well known to interrupt impulse conduction in peripheral nerve axons when applied locally in high concentrations. The phenylpiperidine opioid meperidine, in addition to its systemic opioid effect, also shows local anesthetic–like action when applied directly to peripheral nerves. Using this effect, *in vivo* studies have demonstrated that intrathecally applied meperidine gives sufficient nerve block to perform surgery of the lower limbs[1] or the perineum,[2] Cesarean section,[3] and urologic surgery.[4,5] Intravenous regional anesthesia also has been conducted with meperidine, either in addition to local anesthetic agents[6] or as the sole agent.[7] Several *in vitro* studies have demonstrated that the local anesthetic–like effect of meperidine is attributable to its ability to block impulse conduction in isolated peripheral nerves[8] or dorsal root axons.[9]

Local anesthetic agents are known to block impulse conduction by inhibiting voltage-dependent Na^+ channels in a reversible and concentration-dependent manner. In addition to the tonic block observed at low-stimulation frequencies, these drugs produce additional block at high-stimulation frequencies called use-dependent or phasic block.[10] In addition, different K^+ channels are inhibited by local anesthetic agents, which may play a role for inhibiting axonal conduction.[11,12] Regarding local anesthetic agents, the underlying mechanism for conduction block by meperidine is its Na^+ channel–blocking property; voltage-dependent K^+ channels also are affected.[13]

Other opioids, such as morphine, fentanyl, and sufentanil, also exert local anesthetic–like effects when administered in high concentrations.[14,15] In addition to a non-

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specific blocking effect, it is postulated that conduction block in peripheral nerve by meperidine is mediated *via* opioid receptors.[16]

The axonal patch–clamp method[17] allows discrimination among different peripheral nerve ion channels and enables pharmacologic studies of each channel type to be performed.[18] Using this method, in the current study, we investigated the blocking potency of meperidine on Na^+ and different K^+ currents of amphibian peripheral nerves on the single channel level.

Materials and Methods

Preparation

The patch–clamp method[19] was applied to sciatic nerves[17] of the clawed toad *Xenopus laevis*. Animals were killed by decapitation. These procedures were reported to the local veterinarian authority and were in accordance with German guidelines. Nerves were dissected and desheathed mechanically and incubated with 3 mg/ml collagenase (Worthington type CLS II; Biochrom, Berlin, Germany) in Ringer's solution for 135 min and subsequently with 1 mg/ml protease (type XXIV; Sigma Chemical Co., St. Louis, MO) in Ca^{2+}-free Ringer's solution for 35 min. The temperature was kept constant at 24°C. Next, the preparation was washed in Ca^{2+}-free Ringer's solution, cut into 3-mm-long segments, and put into a culture dish that had been coated with laboratory grease (Glisseal Blue; Borer Chemie, Solothurn, Switzerland). After 30 min of rest, axons were used for up to 10 h.

Solutions

Experiments were performed with different external solutions containing (in mM) 110 NaCl, 2.5 KCl, 2 $CaCl_2$, 5 BES (N,N-bis[2-hydroxyethyl]-2-aminoethanesulfonic acid; Ringer's solution), and either 100 nM tetrodotoxin (Ri-TTX; Sigma, Deisenhofen, Germany) or 10 mM tetraethylammoniumchloride (Ri-TEA), all adjusted to *p*H 7.4 with tris[hydroxymethyl]aminomethane (TRIS) base. In some experiments, an external solution with an increased concentration of K^+ has been used (105 mM K_o), containing 105 KCl, 13 NaCl, 2 $CaCl_2$, 5 BES, and 100 nM TTX.

The internal solution contained (in mM) 105 KCl, 13 NaCl, 5 BES, 3 EGTA adjusted to *p*H 7.2 with TRIS base (KCl_i) or CsCl instead of KCl for the investigation of Na^+ current ($CsCl_i$). Meperidine was obtained as a commercial preparation (Dolantin; Hoechst, Bad Soden, Germany) that did not contain other ingredients except water. Lidocaine was obtained from Sigma (Deisenhofen, Germany). Control solution and different test solutions were applied to excised outside-out patches by a multiple barrel perfusion system.

Electrophysiologic Recording

All experiments were performed using outside-out patches formed from the membrane of partially demyelinated axons. Patch pipettes were pulled from borosilicate glass tubes (GC 150; Clark Electromedical Instruments, Pangbourne, United Kingdom), coated with Sylgard 184 (Dow Corning, Seneffe, Belgium), and fire-polished before the experiment. The pipettes had a resistance of 4–20 MΩ. Voltage clamp was performed by an EPC 7 patch–clamp amplifier (List, Darmstadt, Germany). Voltage-dependent currents were filtered at 3 kHz with a four-pole low-pass Bessel filter, digitized at 10 kHz with a Labmaster TM-40 analog-digital/digital-analog board (Scientific Solutions, Solon, OH) and stored on the hard disk of an IBM-compatible computer. Traces of voltage-independent currents were stored on videotape using a modified PCM-501ES pulse code modulation unit (Sony, Tokyo, Japan) and processed offline later. Recordings were made at 14 ± 1°C. Membrane potentials (E) are given for the inner side with respect to the outer side of the membrane.

Na^+ currents were investigated in outside-out patches formed from the membrane of the nodal region of the axon. Ri-TEA was used as the external and $CsCl_i$ as the pipette solution. In voltage–clamp mode, the membrane holding potential was set to −90 mV. To remove fast inactivation of the Na^+ channels completely, a 50-ms prepulse to −130 mV was applied before a 50-ms depolarizing test pulse to −40 mV elicited Na^+ currents. To reduce noise originating from random channel openings in subsequent traces, 20 traces of Na^+ currents were averaged before the peak Na^+ current was measured to quantify fractional block in given drug concentrations. These data were used to construct concentration–inhibition curves, which were then fitted with equation 1 to obtain half-maximal inhibiting concentration (IC_{50}) values.

For the investigation of voltage-dependent K^+ currents (K_{DR}), Ri-TTX was used as the bath and KCl_i as the pipette solution. Holding potential was −90 mV; a 50-ms test pulse to 0 mV elicited K^+ currents. Twenty traces were averaged, and the steady-state K^+ outward current was measured during the last 20 ms of the averaged

trace. Concentration–effect relations were evaluated similarly for Na^+ channels.

The calcium-dependent K^+ channel (K_{Ca}) was investigated in outside-out patches at a holding potential of +40 mV. At this potential, other K_{DR} inactivated after 1 min and thereafter made no contribution to the current. The bath solution was Ri-TTX, and the pipette solution was KCl_i, which contained 100 μM $CaCl_2$ to activate K_{Ca} currents. For analysis, current traces of at least 30 s in control solution and in different concentrations of drug were filtered at 1 kHz and digitized at 5 kHz offline from videotape. The mean current of a trace was then calculated as the average of all sample points in the trace. Dividing the mean current in drug by the mean current in control solution and subtracting the result from 1 yields fractional block.

To study flicker K^+ background channels (K_{fli}), outside-out patches were formed on thin axons ($\approx$5 μm outer diameter). The holding potential was −90 mV, and no test pulse was applied. The bath solution was 105 mM K_o, and the pipette solution was KCl_i. Fractional block was measured as described earlier.

Statistical Analysis

Current records were analyzed using pClamp 5.5.1 software (Axon Instruments, Burlingame, CA). Data points and error bars are given either as mean ± SEM or as fitted values ± SE (standard error of fit). Statistical analysis, fits, and preparation of the figures were accomplished with Fig.P 6.0 software (Biosoft, Cambridge, United Kingdom).

To quantify block, concentration–effect curves were constructed by measuring the fractional block (fb) in dependence of certain drug concentrations (c). A nonlinear least-squares fit of the data points to

$$fb = b_{max} \cdot c/(c + IC_{50}) \quad (1)$$

was then performed to obtain the IC_{50} values and the maximal achievable block (b_{max}).

To determine whether meperidine and lidocaine act at the same binding site on the Na^+ channel, we performed competition experiments with these two agents.[20] In these experiments, Na^+ channels were preblocked with certain concentrations of lidocaine (c_{lido}). Concentration–effect relations with the partially blocked channels reveal apparent IC_{50} values for meperidine ($IC_{50,meperidine,app}$) depending on the fraction of channels blocked previously by lidocaine and on the number of binding sites. Competition for the same binding site results in a shift of the $IC_{50,meperidine,app}$ value according to

$$IC_{50,meperidine,app} = IC_{50,meperidine} \cdot (1 + c_{lido}/IC_{50,lido}) \quad (2)$$

where $IC_{50,lido}$ and $IC_{50,meperidine}$ are the IC_{50} values for lidocaine and meperidine, respectively, as evaluated from concentration–inhibition relations. If the two substances act at different binding sites, no shift should occur; however, possible allosteric interactions have not been considered in this model.

Results

With outside-out patches, formed at the nodal membrane of partially demyelinated axons, voltage-dependent Na^+ currents were investigated after blocking K^+ currents with external TEA and internal Cs^+. The Na^+ peak inward current in response to a test pulse was in the range of 20–150 pA, corresponding to approximately 20–150 channels simultaneously open at the peak.[17] Random openings of the small number of Na^+ channels present in the outside-out patches resulted in fluctuations in amplitude of successive traces, which had to be smoothed by averaging procedures before measurement of peak current. This hindered investigation of use-dependent (phasic) block, which is measured as an increase of Na^+ current inhibition during successive membrane depolarizations at high frequency. We therefore were able to measure tonic block at only low depolarization frequencies.

Meperidine reduced the peak amplitude in a concentration-dependent manner (fig. 1A) in the same concentration range as the local anesthetic agent lidocaine (fig. 1B). The block was always fully reversible for both substances. To compare the potencies of meperidine and lidocaine, fractional block of the peak amplitude was plotted against the concentration of blocker (fig. 1C). Concentrations of meperidine ranged from 1 nM to 3 mM to investigate its effect in a broad range. Fitting equation 1 to the data revealed IC_{50} values of 164 ± 14 μM (n = 10) for meperidine and 172 ± 9 μM (n = 5) for lidocaine. Block was complete at high concentrations of meperidine and lidocaine (maximal block [f_{bmax}] fixed to 1 for fitting).

Local anesthetic block is most likely mediated by binding to specific receptors on voltage-gated Na^+ channels.[21] Meperidine has a similar Na^+ channel–blocking effect in the same concentration range as local anesthetic agents, and therefore it can be postulated that

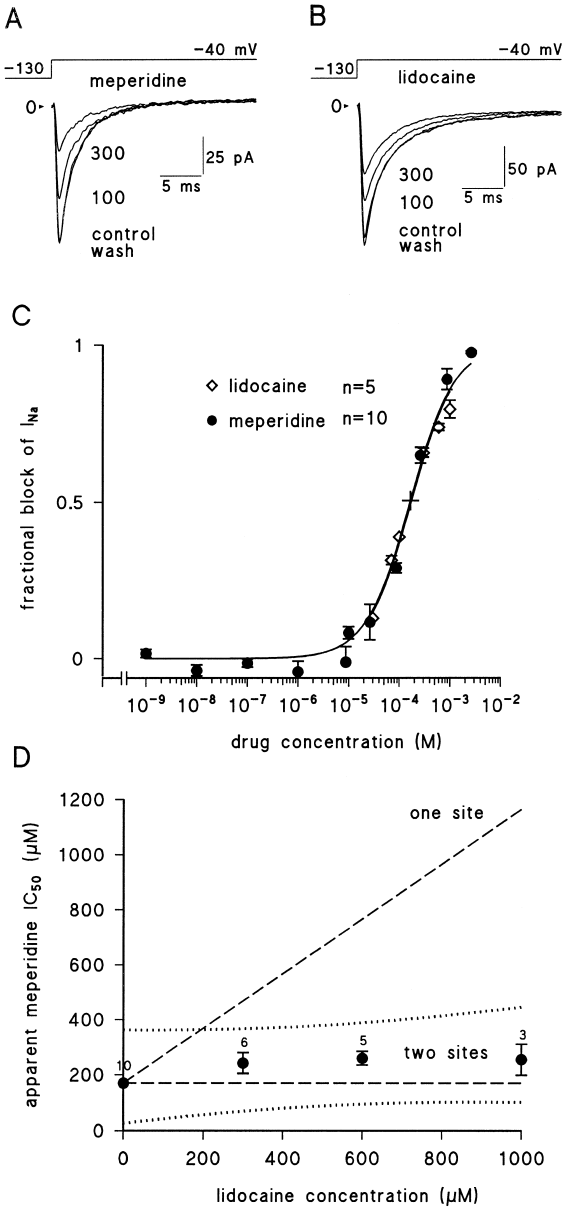

Fig. 1. Effects of meperidine and lidocaine on axonal Na^+ currents. Traces show multiple channel Na^+ currents recorded in (*A*) control and 100 and 300 μM meperidine, and (*B*) control and 100 and 300 μM lidocaine and after wash. The pulse protocol is given in text. Traces represent averages of 20 recordings. Holding potential was set to −90 mV, and a 50-ms prepulse to −130 mV was applied to remove fast inactivation, followed by a 50-ms test pulse to −40 mV. Bath, Ri-TEA; pipette, Cs_{CI}. (*C*) Concentration dependence of Na^+ channel block by externally applied meperidine (circles) and lidocaine (diamonds) were derived from experiments as shown in *A* and *B*. Fractional block was obtained by measuring the reduction of peak current and is plotted *versus* concentration of meperidine and lidocaine, respectively. The cross marks half-maximal concentration (IC_{50}). (*D*) Simultaneous application of meperidine and lidocaine. Ordinate gives apparent IC_{50} values of meperidine obtained from concentration–effect experiments for meperidine during which various concentrations of lidocaine (abscissa) were present. Dashed lines show the theoretical change of the apparent meperidine IC_{50} in dependence of the simultaneously present concentrations of lidocaine assuming models of either competition of both drugs for one binding site (equation 2) or of two independent binding sites (no change). Dotted lines give 95% confidence intervals for the data. (*C* and *D*) Error bars show SEM if larger than symbol size, and the number of experiments is given above each data point.

meperidine acts at the same binding site. To address this question, we performed competition experiments. Concentration–effect curves for lidocaine and for meperidine after lidocaine preincubation were constructed as described in Materials and Methods and in figure 1. IC_{50} values found for meperidine without and with lidocaine incubation are plotted against concentration of lidocaine (fig. 1D). The apparent potency of meperidine is clearly independent of the concentration of lidocaine, suggesting that there is no competition for a common binding site on the Na^+ channel. These results imply that meperidine acts on the peripheral nerve Na^+ channel *via* a different molecular mechanism than local anesthetic agents do.

There is great diversity in K^+ channels in the axonal membrane,[22] and the effect of meperidine on some of these channels was investigated in the present study. K_{DR} of the peripheral nerve have been studied in outside-out patches formed at the nodal or paranodal region of the peripheral nerve. A test pulse to 0 mV from a holding potential of −90 mV elicited K_{DR}. Similar to Na^+ currents, K_{DR} were reversibly blocked in a concentration-dependent manner (fig. 2), but block was not complete even at high concentrations of meperidine. The IC_{50} was evaluated as 194 ± 24 μM (n = 8), and an f_{bmax} value of 0.83 ± 0.03 was reached. We did not perform further investigation of subtypes of K_{DR}.

To investigate K_{Ca}, 100 μM $CaCl_2$ was added to the pipette solution, and the membrane potential was maintained continuously at +40 mV to activate the channels. After inactivation of the K_{DR} (1–2 min), single K_{Ca}s were observed. Meperidine also had a blocking effect on these channels at high concentrations as demonstrated in figure 3A. The fast flickery block of this channel produced by meperidine indicates rapid binding (blocked) and unbinding (unblocked) of the drug in the microsecond range. Because the flickering is too fast to be resolved by

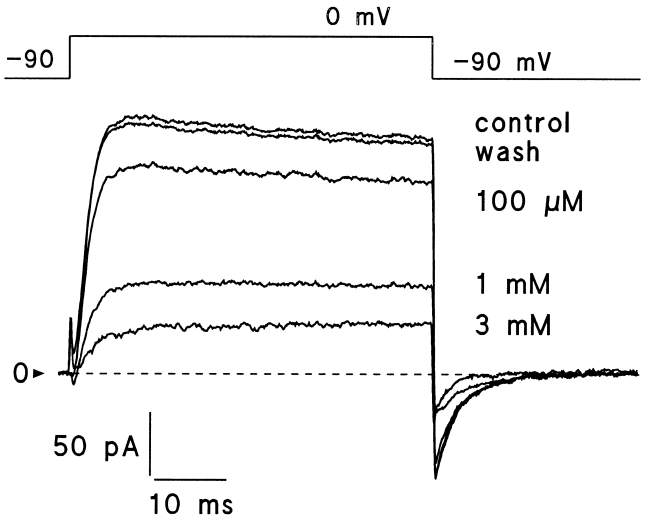

Fig. 2. Effects of meperidine on voltage-activated K^+ currents. Multiple channel K_{DR} currents in an outside-out patch responding to a test pulse to 0 mV from a holding potential of −90 mV. The pulse protocol is given above the traces. Traces show averages of 20 recordings of the K_{DR} current in control solution and 100 μM, 1 mM, and 3 mM meperidine and after wash. Bath, Ri-TTX; pipette, K_{Cli}.

the system (because of filtering), it manifests as a reduction in amplitude of the channel trace (fig. 3A).

Figure 3B shows the effect of meperidine on single voltage-independent (background) K^+ channel found mainly in thin myelinated nerve fibers.[23] Because of its flickery appearance in control solution, the channel was termed flicker K^+ channel. This channel shares features with the cloned K^+ channel rTASK,[24] which belongs to a group of recently discovered two-pore domain background K^+ channels. A noteworthy feature of the flicker K^+ channel is its high sensitivity to lipophilic amide local anesthetic agents, such as ropivacaine and bupivacaine, which might play a role in differential nerve block.[12] Block of this channel by meperidine is concentration dependent and reversible and appears as a reduction in single channel amplitude as seen in amplitude histograms. Flickering block by meperidine overlaps the intrinsic flickering of the channel (fig. 3B).

The concentration–effect relations of meperidine for the Na^+ channel and all K^+ channels investigated are plotted in figure 4. IC_{50} values as derived from nonlinear least-squares fit were 194 ± 24 μM (n = 8) for K_{DR}, with b_{max} = 0.83 ± 0.03. The flicker K^+ and the K_{Ca} were blocked completely at high concentrations of meperidine (b_{max} fixed to 1), with IC_{50} values of 139 ± 15 μM (n = 6) and 161 ± 18 μM (n = 5), respectively.

Meperidine block of Na^+ channels and K_{DR} has been tested for antagonism by naloxone. In these experiments, partial block of Na^+ channels and K_{DR} was induced by 100 and 1,000 μM meperidine, respectively. Addition of naloxone did not influence meperidine block of both channel types (fig. 5).

Discussion

Among clinically used opioids, meperidine exerts the strongest local anesthetic-like effect[25] and has been used successfully for local anesthesia.[1–7] In spinal anesthesia, meperidine produces a segmental motor and sensory block comparable to lidocaine.[1,26] In *in vitro* experiments on rabbit vagal nerves, meperidine inhibited compound action potentials of A and C fibers with IC_{50} values of ≈100 μg/ml (350 μM).[8] Single dorsal root axons required ≈700 μM meperidine to achieve conduction block in ≈60% of the fibers.[9] The IC_{50} value of 164 μM for axonal Na^+ channel block in this study is in good agreement with the earlier observations of compound action potentials block if one takes into account that, because of the conduction safety factor, ≈80% of the Na^+ channels have to be blocked before loss of conduction occurs in a peripheral nerve fiber.

In voltage-clamp experiments, potencies of meperidine and other opioids for peripheral nerve impulse blockade have been evaluated.[27] Highly potent opioids, however, including fentanyl and sufentanil, failed to block nerve conduction in several experimental studies, even at high concentrations.[9,28,29] Electrophysiologic effects of opioids on the central and peripheral nervous system have been reviewed by Duggan and North.[30]

There is a diversity of opioid receptors in the central nervous system.[31] In the sensory peripheral nervous system, the existence of opioid binding sites has been proved in cell somata, *i.e.*, rat dorsal root ganglion neurons, and in the central terminals of these afferent fibers.[32] Further, the amount of μ-, δ-, and κ-receptor encoding mRNA expressed in dorsal root ganglion cells has been found to be intense.[33] However, there seems to be no electrophysiologic importance of opioid receptors in the soma of dorsal root ganglion neurons.[34] Opioid receptors have been shown in sensory peripheral nerve axons,[33] and axons are known to convey opioid receptors by axonal transport into inflamed tissues.[35]

In frog sciatic nerve, Hunter and Frank[16] demonstrated the contribution of opioid receptors to Na^+ current block. In their experiments, naloxone partially antagonized a morphine-induced conduction block. In con-

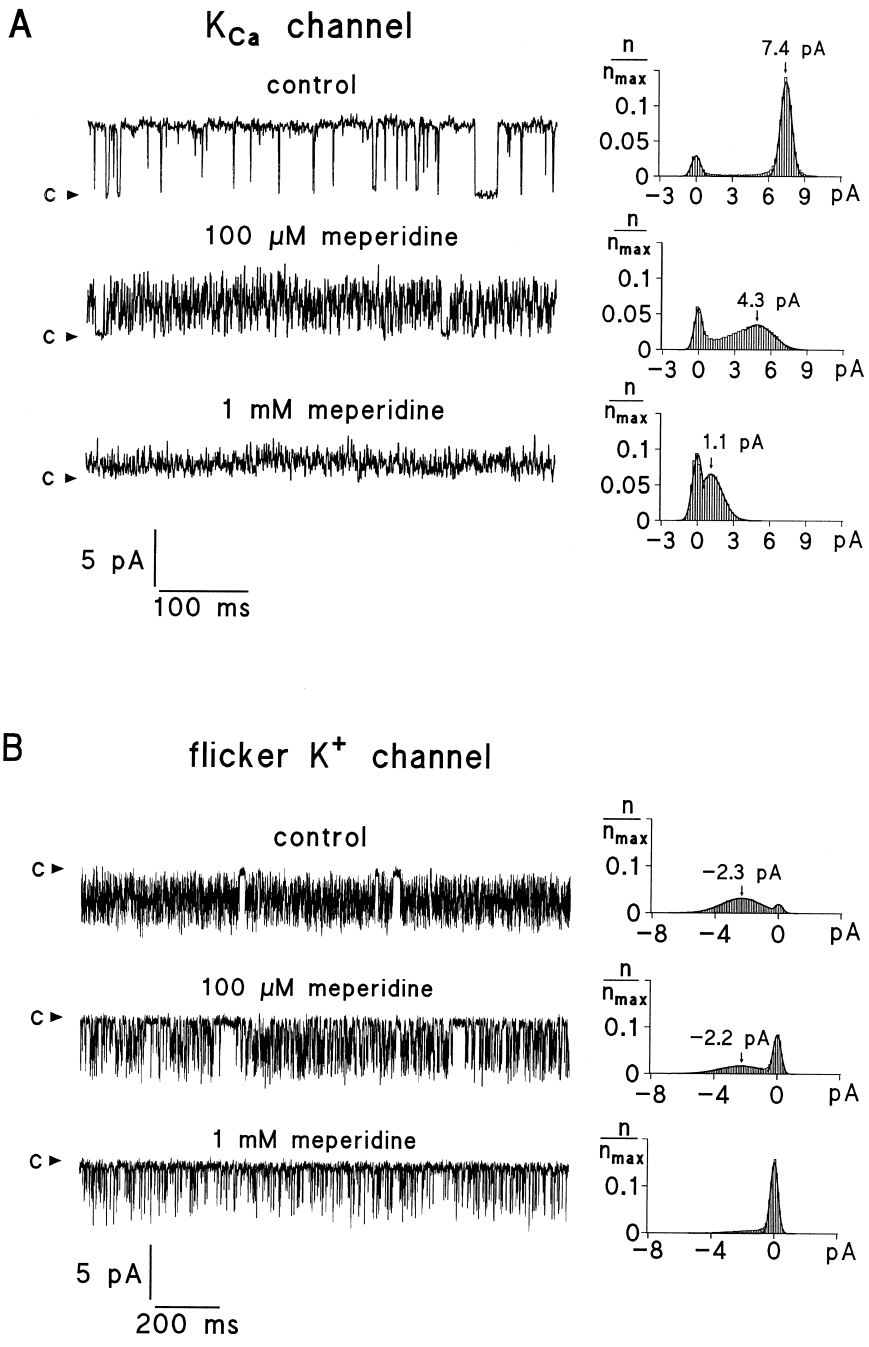

Fig. 3. Effects of meperidine on axonal background K^+ channels. (*A*) Single channel recording from an outside-out patch containing one Ca^{2+}-activated K^+ channel. Traces show current in control solution and after application of 100 μM and 1 mM meperidine. Holding potential was +40 mV. Bath, 105 mM K_o; pipette, K_{Cli} without EGTA but with 100 μM Ca^{2+}. (*B*) Recordings from an outside-out patch containing one flicker K^+ channel. Single channel current is shown in control solution and in 100 μM and 1 mM meperidine. Holding potential was −90 mV. Bath, 105 mM K_o; pipette, K_{Cli}. (*A* and *B*) Closed levels of the channels are marked by an arrowhead and the letter c. Point amplitude histograms from 30-s recordings were fitted with two Gaussian to give single channel amplitudes (indicated above the open channel level) and are plotted to the right of each recording.

trast, Hu and Rubly[14] proposed that the blocking effect of morphine on Na^+ and K^+ currents in frog sciatic nerve is not mediated by opioid receptors. In their experiments, high concentrations of opioids were needed to achieve nerve block. Intravenous application of opioids, which results only in low concentrations in nervous tissues, does not have an effect on peripheral nerve C fibers.[29]

In our experiments, a Na^+ channel–blocking effect mediated *via* opioid receptors is unlikely for two reasons. First, the potency of meperidine in blocking Na^+ channels is low. The IC_{50} value of 164 μM as found in this

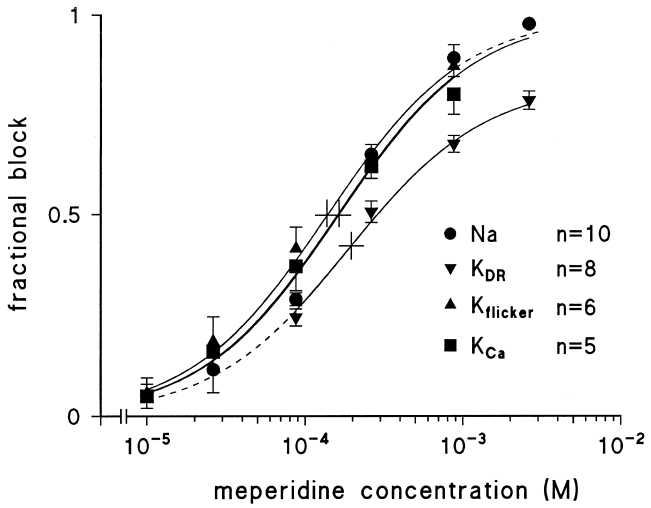

Fig. 4. Concentration dependence of Na^+ (for comparison superimposed from fig. 1), K_{DR}, K_{fli}, and K_{Ca} channel block by externally applied meperidine. Fractional block (fb) is obtained either by measuring reduction of peak current (Na^+ channels), steady-state current (K_{DR} channels), or mean current (K_{fli} and K_{Ca} channel) and is plotted *versus* concentration (c) of meperidine. Data points represent means; error bars represent SEM if larger than symbol size. Curves were obtained by nonlinear least-squares fits of the data points to function 1; crosses mark IC_{50} values, which are given in the text. The maximal achievable block (b_{max}) with high concentrations of meperidine was fitted as 0.83 for K_{DR} and set to 1 for all other channels investigated.

study was 80 times higher than concentrations in plasma needed to achieve postoperative analgesia mediated *via* opioid receptors, which is ≈500 ng/ml (2 μM).[36] An effect on peripheral Na^+ channels in this low concentration range has not been observed for meperidine in our experiments. Second, meperidine block of Na^+ channels could not be antagonized by naloxone, a drug that displaces opioids from the binding site at the opioid receptor. The lack of antagonizing ability by naloxone is interpreted as an nonopioid receptor–mediated effect.

Opioid action on ion channels is mediated *via* intracellular second messenger systems. In neurons of the locus coeruleus and plexus submucosus, it has been shown that μ- and δ-opioid receptors can activate inward rectifier K^+ channels by intracellular second messenger systems, thus hyperpolarizing the cell.[37] In substantia gelatinosa neurons of guinea pigs, μ- and κ-receptors produce an increase in K^+ conductance.[38] Calcium channels are regulated by G_o proteins coupled to opioid receptors, which leads to a reduction of excitability and transmitter release.[39]

In our studies, however, only direct interactions of opioids with ion channels without emphasis on intracellular second messenger mechanisms have been investigated. An activating effect on K^+ channels has not been observed in a broad concentration range in our experiments.

Meperidine has a blocking effect on Na^+ channels in a similar concentration range as lidocaine, which explains the local anesthetic potency of this opioid. Competition experiments between the two agents, however, demonstrated different mechanisms in blocking Na^+ channels.

Meperidine shows no selectivity in blocking different peripheral nerve ion channels (all channels are blocked in a similar concentration range). Similarly, high concentrations of morphine were able to block Na^+ and K^+

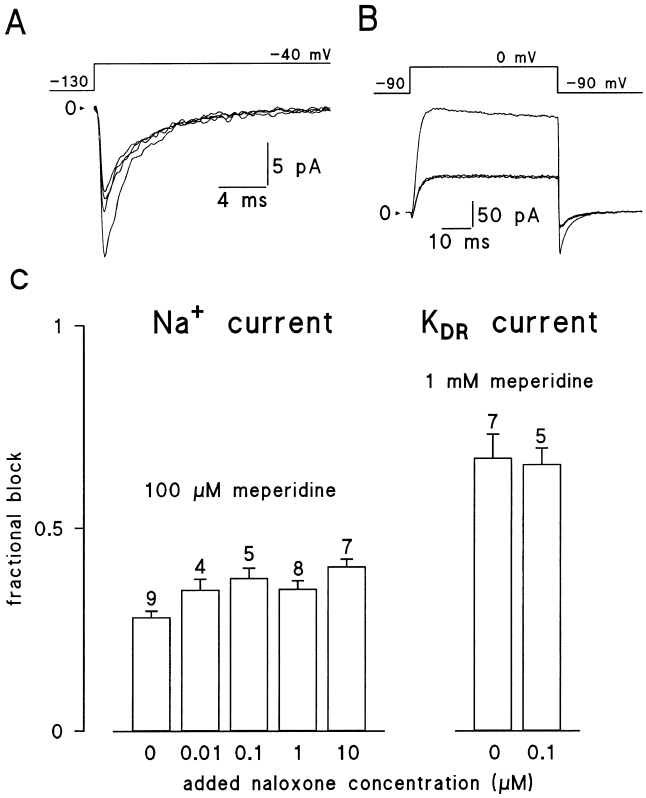

Fig. 5. Simultaneous application of meperidine and naloxone. (*A*) Multiple channel Na^+ currents are recorded in control solution, 100 μM meperidine, 100 μM meperidine plus 10 nM naloxone, and 100 μM meperidine plus 1 μM naloxone (traces from bottom to top). (*B*) Traces show multiple channel K_{DR} currents recorded in control, 1 mM meperidine, and 1 mM meperidine plus 100 nM naloxone (from top to bottom). (*A* and *B*) Pulse protocols are given above the traces; each trace represents an average of 20 recordings. (*C*) Na^+ and K_{DR} channel antagonism by naloxone. Voltage-dependent Na^+ and K_{DR} currents have been blocked by 100 μM and 1 mM meperidine, respectively, before different concentrations of naloxone were added (given on abscissa). Bars indicate fractional block of peak Na^+ (*left*) and steady-state K_{DR} current (*right*) induced by given concentrations of meperidine and naloxone. Error bars show SEM; the number of experiments is given above each bar.

currents equipotently in the squid giant axon[40] and myelinated nerve.[14] The maximal achievable block of K_{DR} of 83% is probably a result of the ion channel diversity contributing to this current,[17,41] and certain channel subtypes may not be sensitive to meperidine. We did not further discriminate between distinct types of K_{DR} in this study, however.

In contrast, local anesthetic agents inhibit different channel types at different concentrations. They generally have higher potencies in blocking voltage-dependent Na^+ channels than K_{DR} in peripheral nerves.[18,42] This selectivity for Na^+ channel block also has been demonstrated by the axonal patch–clamp method for other substances that have a local anesthetic effect, such as ketamine[43] and droperidol (Bräu ME, unpublished data, 1997). For droperidol, competition with lidocaine has been shown in these experiments, revealing a common blocking mechanism for these two agents. Furthermore, lipophilic amide-linked local anesthetic agents, such as bupivacaine and ropivacaine, have much higher potencies in blocking flicker K^+ channels[12] than voltage-sensitive Na^+ channels.

The exact physiologic role of axonal flicker K^+ channels remains unresolved; however, it is speculated that these channels set the resting membrane potential in thin myelinated nerve fibers.[23] Block of flicker K^+ channels may enhance block of Na^+ channels in small axons by depolarizing the resting membrane potential and thus driving more Na^+ channels into their inactivated state.[12]

The successful use of meperidine for local anesthesia is probably attributable to its low affinity to opioid receptors. Because of this, commercial preparations of meperidine are highly concentrated—50 mg/ml (176 mM)—compared with 0.05 mg/ml (0.15 mM) for fentanyl. Therefore, local application of the preparation of meperidine yields sufficiently high concentrations of drug at the nerve for Na^+ channel blockade, whereas potent opioids such as fentanyl do not. Concentrations in plasma achieved during local anesthesia with meperidine, however, are too low to have an analgesic effect.[44]

The opioid meperidine has a local anesthetic–like activity because of its Na^+ channel–blocking potency. Its affinity to peripheral nerve Na^+ channels is comparably low, as for the local anesthetic agent lidocaine. Its action, however, is mediated by a different binding site on the Na^+ channel but not *via* opioid receptors. Current through different K^+ channels of the peripheral nerve is also inhibited by meperidine; inhibiting concentrations are all in a similar range, suggesting a nonselective blocking effect. Nonspecific binding to membrane proteins or nonspecific membrane effects therefore may be the mechanism of action of meperidine on nerve excitability.

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