Meperidine Suppression of Spinal Dorsal Horn Neurons

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Background: In addition to local anesthetics, meperidine has been successfully used for local anesthesia. When applied intrathecally, the dorsal horn neurons of the superficial laminae are exposed to high concentrations of meperidine. These cells represent an important point for the transmission of pain information. This study investigated the blocking effects of meperidine on different ionic currents of spinal dorsal horn neurons and, in particular, its impact on the generation of action potentials.

Methods: Using a combination of the patch clamp technique and the entire soma isolation method, the action of meperidine on voltage-gated Na⁺ and K⁺ currents in spinal dorsal horn neurons of rats was described. Current clamp recordings from intact neurons showed the functional relevance of the ion current blockade for the generation of action potentials.

Results: Externally applied meperidine reversibly blocked voltage-gated Na⁺ currents with a half-maximum inhibiting concentration (IC₅₀) of 112 μM. During repetitive stimulation, a slight phasic block occurred. In addition, A-type K⁺ currents and delayed-rectifier K⁺ currents were affected in a dose-dependent manner, with IC₅₀ values of 102 and 52 μM, respectively. In the current clamp mode, single action potentials were suppressed by meperidine. The firing frequency was lowered to 54% at concentrations (100 μM) insufficient for the suppression of a single action potential.

Conclusions: Meperidine inhibits the complex mechanism of generating action potentials in spinal dorsal horn neurons by the blockade of voltage-gated Na⁺ and K⁺ channels. This can contribute to the local anesthetic effect of meperidine during spinal anesthesia.

SYSTEMICALLY applied meperidine is widely used for analgesia and anesthesia. In addition, meperidine produces conduction block when applied locally to peripheral nerve, suggesting that it is a local anesthetic.1,2 Subarachnoid application of meperidine results in spinal anesthesia3,4 including motor blockade5–6 sufficient for surgery of the lower limbs,5 the perineum,6 urologic surgery,5,7 and caesarean delivery.7 Meperidine is also useful for intravenous anesthesia either as a sole agent9,10 or in combination with local anesthetics.11,12

In in vitro experiments, meperidine blocks action potential conduction in peripheral nerves13 and muscle14 by inhibiting voltage-gated Na⁺ and K⁺ channels.

Spinal dorsal horn neurons receive their inputs from primary afferent terminals and therefore participate in processing the sensory information from noxious receptors. In contrast to the peripheral nerve, which only conducts the action potential in the region where local anesthetics are applied during spinal anesthesia, dorsal horn neurons must generate an action potential before transmitting it to supraspinal targets. During spinal and epidural anesthesia, the applied drugs diffuse directly into the spinal cord,15 especially to the superficial neurons in laminae I and II, which are important for the transmission of primary sensory input such as pain and thermoception.16–18 Although most clinical studies regarding the local anesthetic effects of meperidine deal with its effects on the spinal cord,1,3,7,8,19–21 the majority of electrophysiologic studies were performed on peripheral nerves or on artificially expressed ion channels.2,13,22–25 These experiments demonstrated the effects of meperidine on voltage-gated ion channels and on action potential conduction, which is explained by blockade of voltage-gated Na⁺ and K⁺ channels. However, it remains unclear how meperidine influences the generation of action potentials in superficial spinal dorsal horn neurons.

In this study, we investigated the effects of meperidine on the generation of single action potentials and on series of action potentials in spinal dorsal horn neurons of the rat. Furthermore, the effect on voltage-gated Na⁺ and K⁺ channels was investigated.

Materials and Methods

Preparation

Experiments were performed by means of the patch clamp technique26 on 200-μm slices cut from lumbar enlargements (L3–L6) of the spinal cord of 3- to 11-day-old rats.27–29 The animals were rapidly decapitated, and the spinal cords were carefully cut out in ice-cold preparation solution bubbled with 95% O₂-5% CO₂. After removal of the pial membrane with fine forceps, the spinal cord was embedded in a preparation solution containing 2% agar cooled down to 39°C. To accelerate solidification of the agar, the beaker with the preparation was placed in ice-cold water. The agar block containing the lumbar enlargement of the spinal cord was cut out and glued to a glass stage fixed in the chamber of the tissue slicer. The spinal cord was sliced in ice-cold preparation solution under continuous bubbling. The
slices were thereafter incubated for 45 min at 32°C. The procedures of animal decapitation have been reported to the local veterinarian authority and are in accordance with the German guidelines.

Solutions
Preparation solution contained 115 mM NaCl, 5.6 mM KCl, 2 mM CaCl₂, 1 mM MgCl₂, 11 mM glucose, 1 mM NaH₂PO₄, and 25 mM NaHCO₃ (pH 7.4 when bubbled with 95% O₂-5% CO₂). In the experimental chamber, the slices were superfused by low-Ca²⁺ solution to reduce spontaneous synaptic activity and to prevent activation of Ca²⁺ currents and Ca²⁺-dependent K⁺ currents. Low-Ca²⁺ solution was obtained from the preparation solution by setting the concentration of Ca²⁺ to 0.1 mM and increasing the concentration of MgCl₂ to 5 mM (referred to as Ringer’s solution). Tetraethylammonium-containing solution (TEA solution) used for Na⁺ current recordings contained 95 mM NaCl, 5.6 mM KCl, 0.1 mM CaCl₂, 5 mM MgCl₂, 11 mM glucose, 1 mM NaH₂PO₄, 25 mM NaHCO₃, and 20 mM TEA-Cl (pH 7.4 when bubbled with 95% O₂-5% CO₂). The study of K⁺ currents was performed in Na⁺-free choline-Cl solution containing 141 mM choline-Cl, 0.6 mM KCl, 0.1 mM CaCl₂, 5 mM MgCl₂, 11 mM glucose, and 10 mM HEPES; pH 7.4 was adjusted with 1 M KOH. KCl was then added to give a final K⁺ concentration of 5.6 mM.

Meperidine (Dolantin®, Aventis Pharma, Bad Soden, Germany) was directly added to control solutions. The experimental chamber with a volume of 0.4 ml was continuously perfused by external solution at a rate of 2-3 ml/min; the pH of solutions containing drug was tested and corrected to eliminate potential pH-induced effects.

The pipette solution used for K⁺ current recordings from intact neurons contained 5 mM NaCl, 144.4 mM KCl, 1 mM MgCl₂, 3 mM EGTA, and 10 mM HEPES; pH 7.3 was adjusted with 1 M KOH. KCl was then added to give a final K⁺ concentration of 155 mM. The pipette solution used for K⁺ current recordings in experiments with isolated somata contained 5 mM NaCl, 144.4 mM KCl, 1 mM MgCl₂, 3 mM EGTA, and 10 mM HEPES; pH 7.3 was adjusted with 1 M NaOH. NaCl was then added to give a final Na⁺ concentration of 15 mM. In experiments with Na⁺ currents, the pipette solution contained 5.8 mM NaCl, 134 mM CsCl, 1 mM MgCl₂, 3 mM EGTA, and 10 mM HEPES; pH 7.3 was adjusted with 1 M NaOH. NaCl was then added to give a final Na⁺ concentration of 15 mM.

Recording Conditions
Pipettes pulled from borosilicate glass tubes (GC 150; Clark Electromedical Instruments, Pangbourne, United Kingdom) were fire polished to give a final resistance of 3-7 MΩ. The patch clamp amplifier was an Axopatch 200B (Axon Instruments, Foster City, CA). In experiments with Na⁺ currents, the effective corner frequency of the low-pass filter was 5 kHz; K⁺ currents were filtered with 1 kHz. The frequency of digitization was twice that of the filter frequency. In current clamp mode, action potentials were filtered with 5 kHz and sampled at 10 kHz. The data were stored and analyzed using commercially available software (pCLAMP; Axon Instruments). Transients and leakage currents were digitally subtracted in all experiments using records with hyperpolarizing pulses that activated no currents. Offset potentials were nulled directly before formation of the seal. Errors in the clamped potential evoked by the series resistance of the electrode were not corrected. For currents recorded in the isolated somata, voltage errors due to resistance in series in most cases did not exceed 4 mV. All experiments were performed at room temperature of 21–23°C.

Ion currents were investigated in voltage clamp mode. Na⁺ currents were recorded in external TEA solution using pipettes filled with CsCl solution. They were activated by a voltage step to −20 mV after a 50-ms prepulse to −120 mV. Holding potential was −80 mV. For investigation of use-dependent blockade (30 pulses at 2, 5, and 10 Hz), no hyperpolarizing prepulse was applied. K⁺ currents were recorded in external choline-Cl solution. K⁺ currents were separated on the basis of a procedure described previously. Total K⁺ currents activated by depolarizing steps to +40 mV after a 150-ms prepulse to −120 mV consisted of both rapidly inactivating A-type and delayed-rectifier components. A similar depolarization applied after a 150-ms prepulse to −60 mV (which almost completely inactivates K⁺ current) elicited only a nonactivating component of K⁺ current, considered to be delayed-rectifier current. The amplitudes of the Kdr currents were measured at the end of a 250-ms depolarizing pulse.

Action potentials were recorded in current clamp mode. To make the action potentials or trains of action potentials comparable, we kept the membrane potential at approximately −80 mV in current clamp experiments by injecting sustained depolarizing or hyperpolarizing currents through the recording electrode. The duration of the current pulse was 10 ms for single action potentials and 500 ms for series of action potentials.

To reduce the resistance in series, experiments in voltage clamp mode were performed using the method of entire soma isolation (see The Method of Entire Soma Isolation). The identification of a neuron in the spinal cord slice was followed by the isolation procedure. In isolated somata, the voltage errors due to the resistance in series were smaller than 4 mV.

Identification of Dorsal Horn Neurons
The dorsal horn neurons were identified in spinal cord slices as multipolar cells with a soma (8- to 12-μm diameter) located in laminae I–III. Neurons were distinguished from glial cells in voltage clamp mode on the...
basis of a procedure described previously. In all neurons studied, a large Na⁺ current exceeding 1 nA could be elicited; they were able to generate action potentials and sometimes showed spontaneous synaptic activity. The resting potentials measured in intact neurons lay between −84 and −50 mV.

Method of Entire Soma Isolation

A detailed description of the entire soma isolation method has been given elsewhere. Briefly, in whole cell recording mode, the entire soma of the neuron was isolated from the slice by slow withdrawal of the recording pipette. The isolated structure was classified as soma if it had lost all of its processes during isolation and preserved only 10–20% of original Na⁺ current recorded from the neuron in the slice before its isolation. The isolated structure was classified as soma-plus-axon complex if it contained one process and preserved more than 90% of the original Na⁺ current. The sound physiologic condition of an isolated structure was confirmed by a considerable increase in its input resistance (reflecting a decrease in membrane leakage conductance), by stable or even improved membrane resting potentials, and by the ability of soma-plus-axon complex to be excitable i.e., to generate action potentials.

Statistical Analysis and Fitting

The current study is based on recordings from 20 intact neurons in the spinal cord slice and 61 isolated somata. Numerical values are given as mean ± SEM. The parameters obtained by fitting the data points are given as mean ± SE.

Data points were fitted using a nonlinear least-squares method with the equation: $f(C) = 1 - \text{RES} \times C/(C + IC_{50})$, where C is the blocker concentration, $IC_{50}$ is the half-maximum inhibiting concentration, and RES is the fraction of current that cannot be blocked by meperidine (only needed for the $K_{DR}$ currents). Because the Hill coefficient was less than 1 (0.93 for $I_{Na}$ and $K_{A}$ and 0.75 for $K_{DR}$), in all curves, it was set to 1 to account for a 1:1 binding.

Intergroup differences were assessed by a factorial analysis of variance with post hoc analysis with the Fisher least significant difference test. The Student paired t test was used to compare the relative amplitudes of Na⁺ currents at the 30th pulse before and after 100 $\mu$M meperidine (phasic blockade) and threshold potentials in control and after application of meperidine. P values less than 0.05 were considered significant.

Results

$Na^{+}$ Currents

$Na^{+}$ currents were recorded from isolated somata of dorsal horn neurons in external TEA solution using pipettes filled with Cs⁺ containing solution. Externally applied meperidine at concentrations ranging from 10 to 1,000 $\mu$M reversibly blocked the peak $Na^{+}$ current in a concentration-dependent manner (fig. 1A). Figure 1B depicts currents of 13 experiments normalized to control solution ($I_{0}$).

Fig. 1. Effect of meperidine on the inactivating $Na^{+}$ current. (A) Recordings of the tetrodotoxin-sensitive $Na^{+}$ current in control solution and in the presence of $10, 100, 300$, and $1,000 \mu$M meperidine. The currents were activated by a voltage step to −20 mV after a 50-ms prepulse to −120 mV. Holding potential was −80 mV. (B) Concentration dependence of the $Na^{+}$ current suppression by meperidine (13 somata). The $IC_{50}$ value for $Na^{+}$ currents was $118 \pm 5 \mu$M. The currents ($I$) were normalized by the amplitude of the corresponding current recorded in control solution ($I_{0}$).

To investigate the use dependence of $Na^{+}$ current block by meperidine, $Na^{+}$ currents were activated at a frequency of 2 Hz first in control solution and then in the presence of 100 $\mu$M meperidine. The current in control and several consecutive currents recorded in 100 $\mu$M meperidine are shown in figure 2A. Figure 2B shows the
peak amplitudes of the Na\(^+\) currents in control and after addition of 100 \(\mu M\) meperidine normalized to the amplitude of the first current recorded in control solution (\(n = 8\)). In the absence of meperidine, the amplitude of the 30th current was reduced by 25\%, probably because of the insufficient recovery of Na\(^+\) channels from slow inactivation. In the presence of 100 \(\mu M\) meperidine, the relative amplitude was reduced from 0.75 to 0.37 \((P < 0.001)\) at the 30th pulse. This corresponds to a current reduction of 49\% caused by slow recovery from inactivation and by use dependent blockade. A similar effect could be observed at frequencies of 5 and 10 Hz (table 1).

**K\(^+\) Currents**

K\(^+\) currents were recorded from isolated somata of spinal dorsal horn neurons in external choline-Cl solution using pipettes filled with high-K\(^+\) solution. Meperidine was applied externally at concentrations ranging from 10 to 3,000 \(\mu M\). Fast inactivating K\(_A\) currents were blocked by externally applied meperidine (fig. 3A). The corresponding half-maximum inhibiting concentration was 102 ± 5 \(\mu M\) (\(n = 34\); fig. 3B). A slightly higher sensitivity to meperidine could be observed in K\(_{DR}\) currents (fig. 4A). The dose–response curve was fitted with the Hill equation, giving an IC\(_{50}\) value of 52 ± 10 \(\mu M\) (\(n = 31\); fig. 4B). Even at high concentrations of meperidine (3,000 \(\mu M\)), the blockade of K\(_{DR}\) currents was not

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**Table 1. Use-dependent Blockade of Sodium Currents at Frequencies of 2, 5, and 10 Hz**

<table>
<thead>
<tr>
<th>Frequency, Hz</th>
<th>Control</th>
<th>100 (\mu M) Meperidine</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.75 ± 0.04</td>
<td>0.37 ± 0.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5</td>
<td>0.57 ± 0.04</td>
<td>0.25 ± 0.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>10</td>
<td>0.46 ± 0.04</td>
<td>0.16 ± 0.02</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values represent the relative amplitudes of the 30th pulse in control solution and after application of 100 \(\mu M\) meperidine compared with the first pulse in control solution. Sodium currents are activated by a voltage pulse to –20 mV (10 ms); holding potential was –80 mV. Data are given as mean ± SEM.
Action Potentials

Current clamp experiments were performed in intact neurons in the spinal cord slice using Ringer's solution as bath and pipettes filled with high-K+ solution. Single action potentials were elicited using a 10-ms depolarizing current pulse of increasing amplitude (fig. 5 and table 2; n = 12). A concentration of 10 µM meperidine had little effect on the shape of a single action potential. Only a slight reduction of the repolarizing velocity was observed. The addition of 100 µM meperidine caused marginal changes in a single action potential. The overshoot potential was slightly reduced, and the width of the action potential increased. Most noticeably, the hyperpolarizing afterpotential disappeared. These effects were more pronounced with 300 µM meperidine. The application of 1,000 µM meperidine resulted in disappearance of the action potential; the membrane response was only passive to the stimulus current. A detailed analysis of different action potential parameters is given in table 2.

Series of action potentials were elicited using a depolarizing current pulse with a duration of 500 ms. The recording in control solution at different current pulses was followed by the application of 100 µM meperidine, a concentration that produced only slight effects on a single action potential. Figure 6 shows the effect of 100 µM meperidine on the firing frequency of series of action potentials. Compared with control recordings in eight neurons, the maximum firing frequency was re-
duced to 54 ± 8% (n = 8). At strong current pulses eliciting the maximum firing frequency in control solution, the neuron in the meperidine containing solution lost its ability to produce series of action potentials.

**Discussion**

In addition to local anesthetics in clinical practice, numerous other drugs, such as opioids,

and clonidine,

and ketamine,

among opioids, meperidine takes an exceptional position and has already successfully been used in spinal anesthesia, where it produces a strong sensory and motor blockade comparable to that of lidocaine.

To understand the action of intrathecally applied meperidine, it is necessary to consider its effects on different sites: (1) mixed nerves after their passage through the intervertebral foramina, (2) dorsal root ganglion, and (3) spinal cord. Many investigators have studied the action of meperidine on peripheral nerve.

In contrast, little is known about the local anesthetic action of meperidine on the spinal cord or the dorsal root ganglia. However, in numerous clinical studies, meperidine has been administered intrathecally.

In this article, we investigated the effects of meperidine on voltage-gated ion channels and on action potentials in spinal dorsal horn neurons. The major findings of this study are as follows: (1) At clinical concentrations of meperidine, voltage-gated Na⁺ and K⁺ channels are inhibited. (2) In the current clamp mode, the firing frequency of trains of action potentials is decreased at concentrations insufficient for the suppression of a single action potential (100 μM). (3) Single action potentials are suppressed by meperidine (1,000 μM).

Meperidine at clinically relevant concentrations during local anesthesia exhibits both tonic and a slight use-dependent block of Na⁺ currents in sensory neurons of laminae I and II of the spinal cord. The IC₅₀ value for tonic block is 118 ± 5 μM. This value is in the same range as described for local anesthetics. Similar values were reported for single Na⁺ channels in frog nerve fibers. Briu et al.

found an IC₅₀ value of 164 μM. Significantly higher concentrations were reported for the α subunit of Na⁺ channels expressed heterologously with rat brain β₃ accessory subunit in Xenopus oocytes (IC₅₀ = 1.9 mM). In our experiments, the fraction of blocked ion channels increased during repetitive stimulation from 30% in control to 63% in 100 μM meperidine (2 Hz). This use-dependent blockade is usually explained by a higher affinity of the drug to open or inactivated Na⁺ channels compared with affinity to the resting state. The blockade of Na⁺ currents and of single action potentials cannot be reversed by different concentrations of naloxone, indicating that the electrophysiologic effects de-

![Fig. 5. Effects of meperidine on single action potentials. Recordings of action potentials in control solution (left) and after application of 10, 100, 300, and 1,000 μM meperidine (n = 12). The membrane potential was adjusted to −80 mV by injecting a sustained current through the recording pipette. The impulse protocol is noted below the corresponding traces. (Right) All traces superimposed with a different time scale.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931200/)

**Table 2. Effect of Increasing Concentrations of Meperidine on Properties of Single Action Potentials**

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Peak, mV</th>
<th>AHP, mV</th>
<th>Threshold, mV</th>
<th>Duration, ms</th>
<th>Maximum Positive Slope, V/s</th>
<th>Maximum Negative Slope, V/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>46.5 ± 3.9</td>
<td>-87.8 ± 2.8</td>
<td>-39.2 ± 1.3</td>
<td>1.9 ± 0.1</td>
<td>114.1 ± 9.2</td>
<td>-91.7 ± 6.2</td>
</tr>
<tr>
<td>10 μM</td>
<td>41.0 ± 4.3</td>
<td>-82.7 ± 2.7</td>
<td>-40.7 ± 1.1*</td>
<td>2.2 ± 0.1</td>
<td>102.9 ± 10.6</td>
<td>-75.1 ± 6.9*</td>
</tr>
<tr>
<td>100 μM</td>
<td>27.1 ± 5.0†</td>
<td>-77.2 ± 1.3†</td>
<td>-41.9 ± 1.1†</td>
<td>3.2 ± 0.4</td>
<td>68.5 ± 10.4†</td>
<td>-45.0 ± 5.2†</td>
</tr>
<tr>
<td>300 μM</td>
<td>9.9 ± 6.7‡</td>
<td>-74.8 ± 1.2‡</td>
<td>-43.5 ± 1.4‡</td>
<td>5.3 ± 0.6‡</td>
<td>40.6 ± 9.3‡</td>
<td>-23.9 ± 4.0‡</td>
</tr>
<tr>
<td>1,000 μM</td>
<td>-14.6 ± 4.8‡</td>
<td>-73.4 ± 1.7‡</td>
<td>-42.7 ± 0.8‡</td>
<td>10.3 ± 1.4‡</td>
<td>16.4 ± 4.1‡</td>
<td>-10.1 ± 1.9‡</td>
</tr>
</tbody>
</table>

AHP is the maximum hyperpolarization after the action potential, durations of action potentials were measured at the half-maximum amplitude. Positive and negative slopes are the corresponding maximum values after differentiation of the action potentials. Values are given as mean ± SEM. Significance levels are given as *P < 0.05, †P < 0.01, and ‡P < 0.001.
scribed in this article are not mediated via opioid receptors. This is in accord with observations in peripheral nerve.24

K⁺ channels play an important role in regulating the firing patterns of different neurons. In our experiments, meperidine exhibits a tonic blocking action on K_A and on K_DR currents with IC₅₀ values of 102 and 52 μM, respectively. In contrast, local anesthetics such as lidocaine, bupivacaine, and mepivacaine affected K_DR currents in an ambivalent manner; low concentrations (1–10 μM) enhance and higher concentrations (1 mM) block K_DR current in spinal dorsal horn neurons.40 The incomplete block of K_DR currents seems to be a common feature of meperidine and local anesthetics.41 The same effect of meperidine with a similar residuum was observed in amphibian peripheral nerves.24 It might result from a diversity of K⁺ channels contributing to this current; some subtypes may not be sensitive to meperidine. Another explanation is that meperidine or local anesthetics are not completely effective in blocking these currents. Local anesthetics such as lidocaine, bupivacaine, and mepivacaine block K_A currents with similar IC₅₀ values ranging between 109 and 236 μM.30

Single action potentials are suppressed by meperidine in a concentration-dependent manner. Low concentrations (10–300 μM) of meperidine reduce the overshoot potential, and the width of the action potential is increased. The slight reduction in the repolarization velocity and the decrease in the threshold potential is probably due to the higher sensitivity of K⁺ channels to meperidine. At high concentrations (1,000 μM) of meperidine, total Na⁺ current blockade causes a complete suppression of the action potential. Lower concentrations of meperidine (100 μM; IC₅₀ for Na⁺ currents) insufficient for suppression of a single action potential reduce the maximum firing frequency to 54%. A selective blockade of approximately 50% of the K_DR current by 10 μM tetroethylammonium reduces the firing frequency in spinal dorsal horn neurons to 72%. A similar reduction in firing frequency (to 68%) was caused by 100 μM droperidol, blocking voltage-gated sodium channels and K_DR to approximately 50%. An exclusive blockade of voltage-gated Na⁺ currents by tetrodotoxin was insufficient to produce a reduction in firing frequency. Olschewski et al.42 observed no reduction in firing frequency when 10 nM tetrodotoxin was applied to block

**Fig. 6.** Effects of meperidine on series of action potentials. Series of action potentials were evoked by 500-ms current pulses. The maximum firing frequency in control solution (left) was compared with that after application of 100 μM meperidine (middle; n = 8). The current pulse applied in the upper traces evoked the maximum firing frequency in meperidine containing solution. The current pulse applied in the lower traces evoked the maximum firing frequency in the control solution. The effects of meperidine on series of action potentials are completely reversible (right).

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approximately 50% of Na⁺ channels in spinal dorsal horn neurons. We conclude that the unexpected strong reduction in firing frequency by meperidine could originate from an additional block of Kᵢ currents.

It is difficult to correlate the blockade of Na⁺ and K⁺ currents with the effects on action potentials. There are different safety factors for the different channel types, meaning that only a fraction of the available ion channels are required to produce a single action potential. Madeja et al.⁴³ have demonstrated different IC₅₀ values for the blockade of sodium currents by tetrodotoxin (IC₅₀ = 6.4 nmol) and the reduction of action potential amplitude by tetrodotoxin (IC₅₀ = 104 nmol). At 100 µM meperidine, the action potential duration was not significantly increased, even though K⁺ currents were significantly inhibited in isolated somata. This might be due to a preferred dendritic localization of KDR currents,⁴⁴ which are unlikely involved in the repolarization of the axon hillock where the action potentials are generated.²⁹ Unfortunately, little is known about the safety factors for K⁺ currents in spinal dorsal horn neurons.

In comparison with other opioids, meperidine exhibits the strongest local anesthetic action at clinical concentrations.⁴⁵,⁴⁶ This could be because of its low affinity for opioid receptors allowing the application of high concentrations of meperidine.²⁴ Most opioids in clinical practice have much higher affinities to opioid receptors. Therefore, they have to be applied at relatively low doses that do not exert a local anesthetic effect.¹³,²³ However, they will act as local anesthetics at concentrations exceeding those used in clinical settings. Fentanyl²²,⁴⁷ and sufentanil²⁷ applied at unusually high concentrations (in the micromolar range) were also able to block nerve conduction in rabbit vagus nerve. When applied intrathecally, the usual dose of meperidine is 0.5–1 mg/kg.⁴⁻⁶,⁸ Assuming that the volume of distribution after application of meperidine is 13 ml/kg,²¹ the maximum cerebrospinal fluid concentration can be calculated at 310 µM (1 mg/kg meperidine). This concentration is in the range needed to block voltage-gated Na⁺ and K⁺ currents or single action potentials; a strong inhibiting effect on the generation of series of action potential can be expected. Because the plasma concentrations of intravenously applied meperidine are in the range of 1.3–2 µM,³⁸,⁴⁹ it is unlikely that its systemic effects are mediated by an interaction with ion channels. For this reason, the local anesthetic effect of a single dose of subarachnoid meperidine can be explained by the local anesthetic effect of meperidine. However, an additional analgesic action of meperidine by its interaction with different transmitter systems, opioid receptors, or other ion channels could also contribute to the local anesthetic effect of meperidine.

In conclusion, we have shown that meperidine at concentrations reached after intrathecal application in the cerebrospinal fluid suppresses both voltage-gated Na⁺ and K⁺ (Kᵢ and KᵢDR) currents. In current clamp mode, single action potentials are suppressed in a dose-dependent manner. Concentrations insufficient for blockade of a single action potential produce a strong reduction in firing frequency of spinal dorsal horn neurons. Neuronal firing was also suppressed by blockade of voltage-gated K⁺ channels. Therefore, block of pain transmission by meperidine should be considered a complex interaction that includes effects on different ion channels.

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