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Single sodium channels from human skeletal muscle in planar lipid bilayers: characterization and response to pentobarbital

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Abstract
Purpose. To investigate the response to general anesthetics of different sodium-channel subtypes, we examined the effects of pentobarbital, a close thiopental analogue, on single sodium channels from human skeletal muscle and compared them to existing data from human brain and human ventricular muscle channels.
Methods. Sodium channels from a preparation of human skeletal muscle were incorporated into planar lipid bilayers, and the steady-state behavior of single sodium channels and their response to pentobarbital was examined in the presence of batrachotoxin, a sodium-channel activator. Single-channel currents were recorded before and after the addition of pentobarbital (0.34–1.34 mM).
Results. In symmetrical 500 mM NaCl, human skeletal muscle sodium channels had an averaged single-channel conductance of 21.0 ± 0.6 pS, and the channel fractional open time was 0.96 ± 0.04. The activation midpoint potential was −96.2 ± 1.6 mV. Extracellular tetrodotoxin blocked the channel with a half-maximal concentration ($k_{1/2}$) of 60 nM at 0 mV. Pentobarbital reduced the time-averaged conductance of single skeletal muscle sodium channels in a concentration-dependent manner (inhibitory concentration 50% [IC_{50}] = 0.66 mM). The steady-state activation was shifted to more hyperpolarized potentials (−16.7 mV at 0.67 mM pentobarbital).
Conclusion. In the planar lipid bilayer system, skeletal muscle sodium channels have some electrophysiological properties that are significantly different compared with those of sodium channels from cardiac or from central nervous tissue. In contrast to the control data, these different human sodium channel subtypes showed the same qualitative and quantitative response to the general anesthetic pentobarbital. The implication of these effects for overall anesthesia will depend on the role the individual channels play within their neuronal networks, but suppression of both central nervous system and peripheral sodium channels may add to general anesthetic effects.

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Introduction

General anesthetics have a wide spectrum of actions on sodium channels of the central nervous system. A recent paper [1] showed that isoforms of the general anesthetic ketamine had a voltage-dependent effect on rat neuronal and human skeletal muscle sodium channels, indicating a local anesthetic effect of the ketamines. In the present investigation, we wished to examine whether pentobarbital, another general anesthetic agent, which we showed previously to have no voltage-dependent effects on central nervous system (CNS) sodium channels, in contrast to ketamine, nevertheless has an effect on skeletal muscle sodium channels.

Dysfunctions of skeletal muscle sodium channels have serious clinical implications, as life-threatening complications resulting from severe muscle rigidity during induction of anesthesia have been observed in patients with hereditary sodium channel myopathies [2,3]. The functional expression of a specific subunit of the skeletal muscle sodium channel (SkM2) very likely plays an important role in patients susceptible to malignant hyperthermia [4]. Finally, succinylcholine produced masseter muscle rigidity and activated myotonic discharges, followed by a neuromuscular block, suggesting that either succinylcholine or its metabolites may interfere directly with voltage-operated sodium channels of the sarcolemma [5]. These examples show that modifications of human skeletal sodium channels may have important clinical consequences. Therefore, anesthetic actions on sodium channels from healthy skeletal muscle should be studied, because not only sodium channels from the CNS but also skeletal muscle sodium channels may be involved in important clinical effects

(immobility) and side effects caused by general anesthetics.

This study continues the investigation of the role sodium channels may play in overall anesthetic sensitivity and in the specific clinical profiles of anesthetics. Sodium channels from three different human tissues have been examined so far. Sodium channels from two human heart tissues (atrium and ventricle) and sodium channels from human CNS differed in their electrophysiological characteristics, while their anesthetic responses to a thiopental analogue (pentobarbital) showed little difference [6]. Here, we examine a sodium channel from a fourth human tissue in the lipid bilayer system: the sodium channel from human skeletal muscle.

Patients, materials, and methods

Preparation

With the approval of the local Committees on Human Rights in Research (the investigation conformed to the principles outlined in the Declaration of Helsinki), human skeletal muscle samples were acquired. After written consent was provided, these samples were obtained from five patients undergoing lower-limb amputation. The muscle tissue was derived from the gastrocnemius muscle of the calf. Samples were taken immediately after amputation and frozen at −80°C. Membrane preparation was as described for canine heart [7].

Bilayer procedures

Most materials and experimental methods are described elsewhere [8,9]; a brief description is given below.

Experiments were conducted in symmetrical Teflon bilayer chambers with 5-ml compartments separated by a Teflon partition bearing a hole of approximately 300-μm diameter in its center. All experiments were conducted at room temperature (22°C–24°C) in symmetrical 500-mM NaCl buffered at pH 7.4 with 10 mM HEPES (4-(2-hydroxyethyl)-1-piperazine ethanesulfonic acid, United States Biochemical, Lleveland, OH, USA); no corrections were made for temperature differences between experiments. Planar bilayers were formed over the aperture from neutral phospholipid solutions containing (4:1) 1-palmitoyl-2-oleoyl-phosphatidylethanolamine and 1-palmitoyl-2-oleoyl-phosphatidylcholine (Avanti Polar Lipids, Birmingham, AL, USA) in decane (5% wt/vol, 99.9% pure; Wiley Organics, Columbus, OH, USA). Tetrodotoxin (TTX) was purchased from Sigma Chemical (St. Louis, MO, USA). Batrachotoxin (BTX) was a gift from Dr. J. Daly, NIH (Bethesda, MD, USA). The incorporation of sodium channels into the bilayer was achieved by adding, with a glass pipette, small amounts of preparation close to the preformed bilayer membrane in the presence of 0.5 μM BTX. In case of fusion of individual channels with the lipid bilayer channel, orientation was determined by channel-gating characteristics. Only experiments with equally oriented channels were included in this study. The electrophysiological sign convention was used for the presentation of the results (i.e., the side to which TTX binds is the reference for the potentials).

Channel currents were recorded under voltage-clamp conditions at holding potentials (as indicated) between −100 mV and +100 mV, using a standard current-to-voltage amplifier (Axopatch 200 and Axon TL-1 DMA Interface; Axon Instruments, Foster City, CA, USA) and filtered at 50 Hz (model 902; Frequency Devices, Haverhill, MA, USA). Current was sampled, and time-averaged conductances were calculated by computer software (pClamp 5.51; Axon Instruments). After the incorporation of a sodium channel into the bilayer, control currents were measured for at least 60 min, using a series of standard protocols with changing membrane potentials (discrete steps of 10 mV or 15 mV, between −100 mV and +100 mV). In one experiment, increasing concentrations of TTX were achieved by adding small amounts from a stock solution to the extracellular side of the channels.

In some experiments, steady-state activation properties were determined as described [9]. In the range of channel activation, channel fractional open time (f_o) could be described by a two-level distribution (Boltzmann distribution) with one open and one closed state:

$$f_o = f_{max}/\{1 + \exp(-z_a F[V - V_a])/RT\}$$

containing as parameter the maximum channel fractional open time (f_{max}), the steady-state midpoint potential (V_a = the potential at which the channel is open $f_{max}/2$), and the valence of the effective gating charge (z_a); (V = membrane potential, F = Faraday constant, R = gas constant, T = absolute temperature).

In a number of experiments, pentobarbital was added from an ethanol stock solution to the aqueous compartment facing either the extracellular or the intracellular side of the channel. Pentobarbital-block ($Block_{[PTB]}$) was calculated according to:

$$Block_{[PTB]} = 1 - g_{[PTB]}/g_{[control]}$$

where $g_{[PTB]}$ is the time-averaged conductance in the presence of pentobarbital and $g_{[control]}$ is the time-averaged conductance in the absence of pentobarbital. The protocol of the control measurements was repeated with increasing concentrations of pentobarbital.

Standard deviations (SD) were used when expressing averages; to examine significance we analyzed our data using a two-step procedure—a Kruskal-Wallis test (non-parametric counterpart of an analysis of variance [ANOVA]), followed by a multiple comparison test (Dunnett, multiple groups vs control). In all tests the data were found to be significantly different under a probability level of 0.05.

Results

In the experimental system of the planar lipid bilayer the incorporation of a sodium channel is a rare event. Table 1 shows the number of overall experiments and the—by comparison—small numbers of successful experiments with single-channel incorporations suitable for pharmacological investigation. As data obtained from individual patients showed no significant differences, they were subsequently pooled.

The typical recordings of a single skeletal muscle sodium channel under our control conditions are shown in Fig. 1a. The skeletal muscle channel stayed open most of the time (96%) and showed only rare and brief closures, of the order of 100 ms or less [10], because BTX impairs channel fast inactivation [11].

Analysis of the transitions between open and closed states revealed a single-channel current-voltage relationship that was symmetrical and independent of membrane potential under symmetrical electrolyte conditions.

Extracellular TTX (but not intracellular TTX, which had no effect at all) blocked sodium channels in an all-or-none manner, manifesting itself as closures of long duration. This block was almost complete at +45 mV when 0.1 μM TTX was added to the extracellular side of the experimental setup. TTX sensitivity was assessed by the addition of increasing concentrations of the toxin to the extracellular side of the incorporated channels. The block could be shown to be voltage-dependent, with block decreasing as the potential across the channel was increasingly depolarized. Subconductance states were observed in none of the experiments with sodium channels from human skeletal muscle.

In 7 out of 12 experiments, single channels were successfully exposed to the general anesthetic pentobarbital. When pentobarbital was added to either side of the sodium channels, these underwent frequent transitions between a fully open and a fully closed state (Fig. 1b, c). As this action became too rapid for full resolution, it was quantified by measuring the current averaged over time (Fig. 2a); from these data, the fractional open times were calculated. Pentobarbital induced a concentration-dependent block of the channels (Fig. 2b).

At membrane potentials more negative than −80 mV, the fractional open time (but not the single-channel conductance) usually became dependent on membrane potential. Below this voltage, the fractional open time decreased successively with increasing negative potentials, until channels were totally closed at a potential below −120 mV. This effect reflects channel deactivation, which—due to BTX modification—is shifted to more hyperpolarized potentials. Only single-channel experiments with more than three successive activation curves were included in this analysis. With increasing concentrations of pentobarbital, the midpoints of activation were shifted to increasingly more negative potentials (Fig. 3). At all examined pentobarbital concentrations, these shifts were significant (340 μM, −7.4 mV; 670 μM, −16.7 mV; 1340 μM, −22.7 mV).

Table 1. Number of experiments, channel incorporations, and membranes included in the study of human skeletal muscle sodium channels in planar lipid bilayers

No. of experiments	49
No. of membranes	302
Average no. of membranes/experiment	6.2
No. of experiments with channels	26
No. of experiments included	12
No. of channels	15
Experiments with single channel	9
Experiments with pentobarbital	7

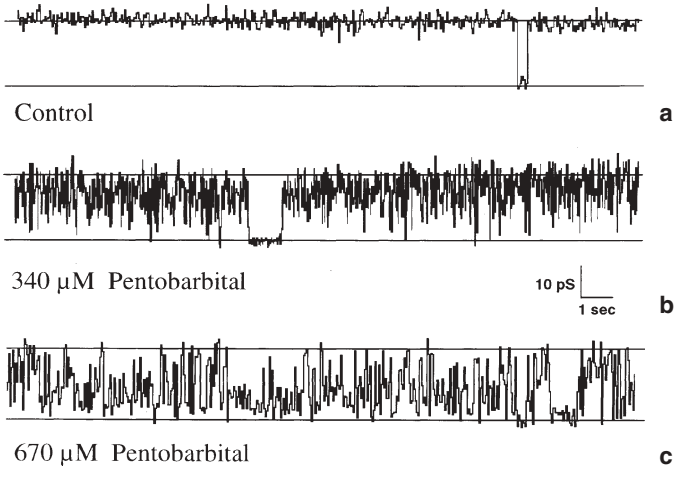

Fig. 1. **a** Recordings of a single sodium channel from human skeletal muscle. Membrane potential was kept at 45 mV. The channel is open most of the time. This trace was deliberately chosen to show one closing event. **b** Same channel as in **a**, but with 340 μM pentobarbital. Again, this trace was deliberately chosen to show the fully closed state usually not seen. **c** Same channel as in **a**, with 670 μM pentobarbital

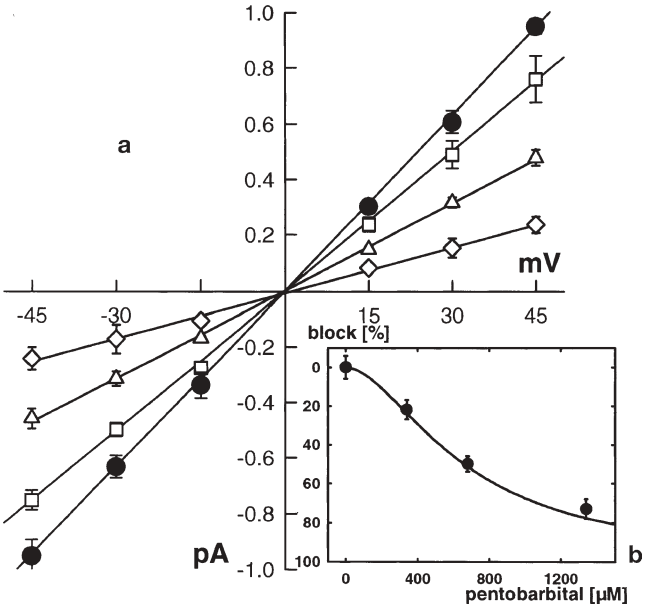

Fig. 2. a Pentobarbital effect on single-channel time-averaged currents of batrachotoxin (BTX)-modified skeletal muscle sodium channels as a function of membrane potential. *Filled symbols* represent control data, and *open symbols* represent increasing concentrations of pentobarbital (*squares*, 340 μM pentobarbital; *triangles*, 670 μM pentobarbital; *diamonds*, 1340 μM pentobarbital). *Error bars* denote SD; *lines* represent the respective linear regression. **b** Concentration-response curve of the pentobarbital block on fractional open time of human skeletal muscle sodium channels. Data were fitted with a rectangular hyperbola. An inhibitory concentration 50% (IC_{50}) value of 662 μM was estimated, with a maximal suppression of 100% (fit, 107.2%); the Hill coefficient was 1.76. *Error bars* denote SD

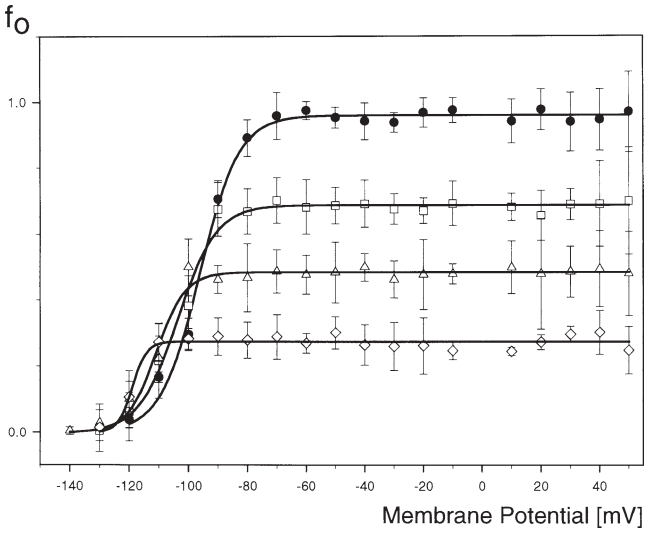

Fig. 3. Averaged fractional open times (f_o) as functions of membrane potential. The graph illustrates the activation behavior of single sodium channels from human skeletal muscle under control conditions (*filled circles*) and under the influence of three concentrations of pentobarbital (340 μM, *squares*; 670 μM, *triangles*; 1340 μM, *diamonds*). Membrane potential was changed in steps of 10 mV in the hyperpolarizing direction. The channels were clearly open most of the time at −50 mV and above; the channels closed successively with more hyperpolarized potentials, until they were closed at −120 mV and below. *Lines* represent Boltzmann fit of the data under each pentobarbital condition. *Control*, V_a = −96.2 mV, z_a = 6.6, F_{max} = 0.96; *340 μM*, V_a = −103.6 mV, z_a = 6.6, F_{max} = 0.69; *670 μM*, V_a = −110.9 mV, z_a = 4.9, F_{max} = 0.48; *1340 μM*, V_a = −118.9 mV, z_a = 2.4, F_{max} = 0.27. V_a, z_a, and F_{max}; potential at which the channel is open $f_{max}/2$, valence of the effective gating charge, and maximum channel fractional open time, respectively

Discussion

The lipid bilayer technique provides stable experimental conditions needed for pharmacological studies. Individual sodium channels can be observed for several hours, making it possible to distinguish steady-state properties (e.g., an intrinsic variability) from a natural run-down of the preparation [12], a consideration that is particularly important in the study of drug actions [10,11]. In addition, data are not only sampled in a true steady-state but also different pharmacological situations (such as increasing concentrations of a drug) can be explored sufficiently and repeatedly with the same channel. Because pharmacological agents may act by causing changes in the physiochemical properties of the lipid membrane, the option to modify and control the lipid environment of the channel is important.

When pharmacological effects on sodium channels from different tissues are compared, one must allow for the possibility that differences in sensitivity may not only arise from changes in the amino-acid sequence of the ion channel proteins [7,13,14] but also from post-translational modification [15]. Thus, differences in potency may not become apparent when sodium channels are expressed heterologously in foreign cells using molecular–biological methods. In contrast to the patch-clamp method, native human sodium channels are reconstituted into planar lipid bilayers. The main advantages of the bilayer system are that the protein is kept in a well-characterized lipid environment and that the complete channel with all its subunits and associated structures can be investigated.

The number of successful experiments in this study was small but typical, and not different from other experimental series with human sodium channels. The sodium channel of human skeletal muscle examined in this study had the qualitative biophysical characteristics expected for BTX-modified sodium channels in planar lipid bilayers (Table 2). Comparing the sodium channels of three human tissues with other channels revealed different electrophysiological properties, although they shared many similarities.

Table 2. Comparison of properties of sodium channels from skeletal muscle, heart, and central nervous system (CNS) preparations incorporated into planar lipid bilayers

Sodium channels	Reference no.	Channel conductance	Fractional open time	Steady-state activation midpoint	IC_{50} (pentobarbital) on channel conductance	Effect on channel conductance (%) at clinical concentration	Shift in steady-state activation for 670 μM pentobarbital
Human skeletal muscle ($n = 12$)	This study	21.0 ± 0.6 pS	0.96 ± 0.04	−96.2 mV ± 1.6 mV	662 μM	8.4%	−16.7 mV ± 0.8 mV
Human CNS	[19]	25.8 ± 0.6 pS ($n = 19$)	0.93 ± 0.05 ($n = 15$)	−84 mV ± 10 mV ($n = 187$)	660 μM [10]	10.3%	−16.3 mV ± 2.3 mV
Human heart ventricle ($n = 13$)	[6,18]	24.7 ± 1.2 pS	0.85 ± 0.04	−99.5 mV ± 3.1 mV	690 μM	8.3%	−10.9 mV ± 0.8 mV[a]
Human heart atrium ($n = 15$)	[17]	23.8 ± 1.6 pS	0.83 ± 0.06	−98.0 mV ± 2.3 mV	714 μM	9.8%	−10.6 mV ± 2.4 mV[a]
Eel electroplax (muscle-derived)	[28]	23.8 pS	0.96 ± 0.02	−79 mV	583 μM	9.9%	−5.7 mV ± 2.8 mV[a]
Rat skeletal muscle, 200 mM NaCl	[7]	20.0 ± 1.1 pS	>0.9				

IC_{50}, inhibitory concentration 50%
[a] Difference from this study is statistically significant

Compared with all other (BTX-modified) human sodium channels in planar lipid bilayers, the single-channel conductance of the skeletal muscle sodium channel was smaller (Table 2; channel conductance). Other authors reported similar differences between sodium channels from skeletal muscle and cardiac muscle in lipid bilayers [7,16].

Only brief closures, of the order of 100 ms or less, could be seen. This resembles sodium channels from human brain and it is in contrast to cardiac channels from human atrium and ventricle, which show longer closures (up to seconds) [17]. This observation was supported by the analysis of the fractional open time (Table 2), which was lower in cardiac sodium channels than in channels from skeletal muscle or brain.

Subconductance states were not detected in the 12 experiments with skeletal muscle sodium channels. This is different from findings in human heart ventricular sodium channels [18] and human brain sodium channels [9] in lipid bilayers where, apart from the predominant single-channel conductance level, we also observed smaller current transitions.

BTX caused sodium channels from human skeletal muscle to stay open 96% of the time by practically abolishing fast inactivation [11]. A similar fractional open time (0.94) has been reported previously for human brain sodium channels [19]. In contrast, the fractional open time of human heart sodium channels was clearly less (0.85) [18], resulting from a population of longer-lasting closing events (longer than 100 ms).

High sensitivity to the specific sodium-channel blocker TTX is one of the main characteristics of neuronal and muscle sodium channels, while cardiac sodium channels demonstrated less sensitivity [20]. We found the same pattern in lipid bilayers, with a tenfold difference in sensitivity (Fig. 4) for brain and skeletal muscle sodium channels compared to human cardiac sodium channels of ventricle [18] and of atrium [17]. The voltage-dependence of the TTX block, another characteristic of BTX-modified sodium channels in bilayers [19,21,22], was similar in all human sodium channels (Fig. 4).

The steady-state activation midpoint of human skeletal muscle sodium channels was not different from that of the two human cardiac channels (Table 2). However, the activation midpoints of these three muscle-type sodium channels were some −10 mV more negative compared to human brain sodium channels (Table 2). Activation midpoint potentials that were more negative for skeletal muscle and cardiac sodium channels than for neuronal sodium channels have been consistently reported by other groups working with expression systems and with native cells [23–25].

Pentobarbital has been used as a reference substance to characterize the response of sodium channels to gen-

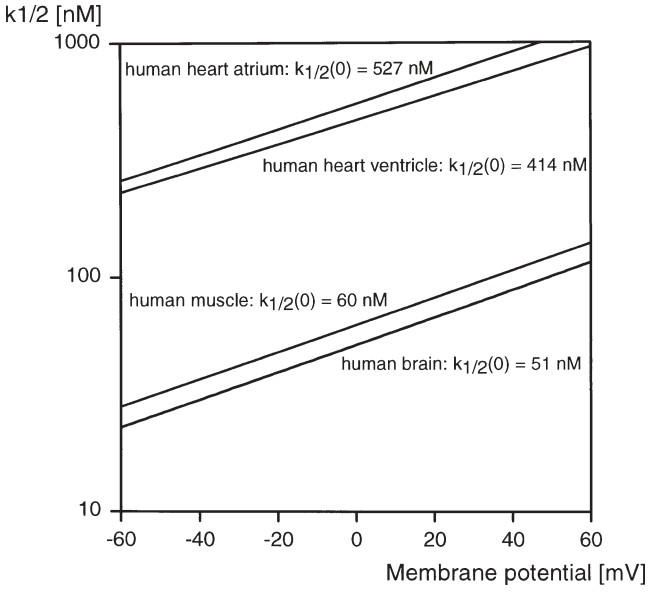

Fig. 4. Voltage-dependence of human sodium channel block by tetrodotoxin (TTX). The half-maximal concentration ($k_{1/2}$) of the TTX block was fitted by linear regression to the equation $k_{1/2}(V)/k_{1/2}(0) = \exp[aFV/(RT)]$, where a = fraction of the applied potential that affects the TTX block; F = Faraday constant; V = membrane potential; R = gas constant; and T = absolute temperature. *Human heart atrium*, the linear regression fit of the experimental points yields a $k_{1/2}$ of 526 nM at 0 mV. The fraction of the applied potentials that effects TTX block, a, is 0.43; $n = 6$ [17]. *Human heart ventricle*, $k_{1/2}(0)$ = of 414 nM, a = 0.45; $n = 5$ [18]. *Human skeletal muscle*, $k_{1/2}(0)$ = 60 nM, a = 0.43; $n = 1$. *Human brain*, $k_{1/2}(0)$ = 51 nM, a = 0.54 [9]

eral anesthetic agents in lipid bilayers [6,10,11]. At a free clinical concentration of 88 mM pentobarbital, our conductance block was 8.4%, which is a significant effect. This block in fact seems small, but it is not known if a suppression of 50 % is needed to induce clinical anesthesia. The clinical concentration for the suppression of a status epilepticus, on the other hand, is much closer to our inhibitory concentration 50% (IC_{50}) (~400 mM) [26]. Considering the electrophysiological differences between sodium channels from different tissue sources, it is surprising that almost no significant difference in anesthetic actions could be found (Table 2). The IC_{50} values for conductance suppression were almost identical, while the hyperpolarizing shifts in the steady-state activation caused by pentobarbital were slightly different.

Among other targets, sodium channels are considered to be very likely targets involved in anesthetic immobility, which is considered to be one of the essential components of anesthesia [27]. In this article, we show that pentobarbital at a clinical concentration also affects a peripheral human sodium channel, the skeletal muscle channel, in addition to its previously reported effects on sodium channels from the human CNS [10]. Considering human sodium channels, immobility may not only be a response of the CNS but even peripheral sodium channels may play a part in the full anesthetic effects.

Still, considering today's sketchy knowledge of the underlying neuronal networks, it is not possible to make conclusive statements about the specific role that sodium channels play in overall anesthesia. Too little is known about the effects that changes in the function of a single type of ion channel have within a complex neuronal network, as these networks have not yet been identified. The location of a molecular structure inside this network may be of greater importance to the overall anesthetic effects than the absolute anesthetic suppression of this molecular structure. Besides, CNS and skeletal muscle sodium channels are only two of many molecular players affected at clinical concentrations of anesthetics. Knowledge of all other molecular participants affected by anesthesia, as well as the network that connects them, is required before a more complete picture of the mechanisms of anesthesia can be obtained.

In conclusion, the general anesthetic pentobarbital has been shown to affect sodium channels of human skeletal muscle at clinical concentrations, and in a concentration-dependent manner. Despite their electrophysiological differences, human sodium channel subtypes show only small differences in their qualitative and quantitative anesthetic responses. The importance of these effects for overall anesthesia can only be fully evaluated when the neuronal networks in which these channels function have been identified. However, as sodium channels are considered likely targets for anesthetic actions causing immobility, this study shows that even peripheral sodium channels may contribute to overall anesthetic effects.

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