Effects of ketamine on voltage-gated sodium channels in the barrel cortex and the ventral posteromedial nucleus slices of rats

Jianyin Yin,[a,*] Bao Fu,[b,*] Yuan Wang[a] and Tian Yu[a]

Ketamine is commonly used as a dissociative anesthetic with unique actions in the central nervous system. Previous studies have found that the thalamocortical systems play an important role in general anesthetics induced unconsciousness. Whether the voltage-gated sodium channels in the thalamocortical systems are the target of ketamine remain unclear. The present study used a whole-cell patch-clamp technique to observe the effects of ketamine on voltage-gated Na^+ channels in thalamocortical pyramidal neurons. We found that IC50 of ketamine on Na^+ currents in the primary somatosensory barrel cortex pyramidal neurons and the thalamus ventral posteromedial nucleus pyramidal neurons was 686.72 ± 39.92 and 842.65 ± 87.28 μM, respectively. Ketamine accelerated the Na^+ channels inactivation and slowed inactivation of Na^+ channels after recovery but did not affect the activation. We demonstrated the detailed suppression process of neural voltage-gated Na^+ channels by ketamine on thalamocortical slice. This may provide a new insight into the mechanical explanation for the ketamine anesthesia. *NeuroReport* 30: 1197–1204 Copyright © The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

The mechanisms by which general anesthetics induce unconsciousness are still unclear despite over a century of research. While mechanisms are not entirely sure, there has been significant work done on both local and general anesthetic drugs mechanisms of action [1–3]. Facilitation of inhibitory transmission and (or) inhibition of excitatory transmission is considered to be the major neurophysiological effects of general anesthetics on synaptic transmission [4–6], but the cellular and molecular targets for these actions remain unknown. As we known general anesthetics can suppress neurons' activity, the underlying mechanisms are still poorly understood, especially the kinetic changes of voltage-gated Na^+ channels, which are mostly related to neuronal excitability. A previous study had demonstrated that isoflurane and propofol inhibit the voltage-gated Na^+ currents (INa) in nerve terminals isolated from rats [7]. Our previous study also showed that etomidate inhibited INa of primary somatosensory cortex pyramidal neurons [8]. The voltage-gated ion channel modulates neuronal excitability, especially the action potential-conducted neuronal signal transmission [9]. Therefore, voltage-gated Na^+ channels may play a key role in the loss of consciousness induced by general anesthetics.

Ketamine is commonly used as a dissociative anesthetic with unique actions in clinic. A variety of receptors are the targets of ketamine, including nicotinic and muscarinic receptors [10]. Ketamine also attenuates the glutamatergic neurotransmission in the ventral posteromedial nucleus slices of rats [11], and NMDA (N-methyl-D-aspartic acid) receptors for glutamate are the main target of ketamine [12–14]. Previous studies have demonstrated that the thalamocortical systems play an important role in general anesthetics induced unconsciousness [15–17]. Whether voltage-gated Na^+ channels in the thalamocortical systems are the targets of ketamine remain unclear.

The present study used a whole-cell recording technique to observe the effects of ketamine on voltage-gated Na^+ channels on the primary somatosensory barrel cortex (S1BF) pyramidal neurons and the thalamus ventral posteromedial nucleus (VPM) pyramidal neurons in the thalamocortical neural network.

Materials and methods

Animals

All experimental and procedures were approved by Committees on Investigations Involving Animals in Zunyi Medical University, China. All male Sprague-Dawley rats

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(15–20 d) were purchased from animal center of the Army Medical University (Chongqing, China). All animals received humane care in compliance with the 'Guide for the care and use of laboratory animals' in China (No. 14924, 2001). The rats were housed in a standard animal care room with a 12:12-hour light-dark cycle at 22°C.

Brain slice preparation

The thalamocortical slices were prepared as previous described [4,8]. Rats were anesthetized with isoflurane and decapitated. Then, take out the whole brain tissue and use sharp blades to repair brain tissue. The block was affixed with cyanoacrylate to the bottom of a cutting chamber. Slices (300 μm) were cut on a vibrational microtome (HM650V, Thermo, USA) using a sharp blade to produce smooth-surface slices. All the above experimental processes were completed in ice-water mixture. The prepared brain slice was put in an incubation solution at 34°C for 1 hour for recovery before recording. The incubation solution contained (in mM): NaCl 126, $CaCl_2$ 2, KCl 2.5, $NaHCO_3$ 25, $MgSO_4{\cdot}7H_2O$ 2, $NaH_2PO_4{\cdot}2H_2O$ 1.5 and Glucose·H_2O 10, pH 7.35-7.45, continuously saturated with 95% O_2 and 5 % CO_2.

Whole-cell voltage-clamp recordings

After recovery, the slice was transferred to a recording chamber that had been perfused with artificial cerebrospinal fluid containing the following (in mM): NaCl 50, Choline chloride 90, KCl 5.4, TEA-Cl 30, EGTA 10, $CaCl_2$ 2, $MgCl_2$ 1, CdCl 0.1, HEPES 10, Glucose 10, pH:7.35-7.45. The micropipette (5–8 MΩ) filled with an intracellular solution, containing (in mM): CsCl 70, CsF 70, TEA-Cl 20, EGTA 10, CaCl2 1, MgCl2 2, Na2ATP 3, HEPES 10, pH: 7.35-7.45. VPM or S1BF pyramidal neurons were visually identified with a BX51WI microscope (Olympus, Japan) equipped with infrared-differential interference contrast optics as described previously [4]. Voltage-gated INa were sampled at 10 kHz and filtered at 2.9 kHz with an EPC10 amplifier and PatchMaster software (HEKA Instruments, Inc., Lambrecht, DE) [4]. The perfusion system was gravity-fed, allowing a routine flow of 0.5≈2 ml/min. Different drug solutions were successively administrated, and INa recording should wait for 2 minutes after every solution exchange (the solution in the recording chamber could be completely exchanged in approximately 1 minute). In order to obtain a stable current, all currents were recorded 2 minutes after cell impaling. The current trace was confirmed as voltage-activated INa by exhibiting complete inhibition with 0.5 mM tetrodotoxin.

Data analysis

IC50 (half-maximal inhibiting concentrations), Na^+ conductance, activation curves, steady-state inactivation curves, and data for INa recovery from inactivation were made according to previous described [8]. Data were analyzed using FitMaster (HEKA Instruments, Inc.) and GraphPad Prism software package version 5.0 (GraphPad Software Inc., San Diego, California, USA). Data are expressed as mean ± SEM. Statistical significance was assessed by ANOVA; $P < 0.05$ was considered statistically significant.

Results

Basic properties of Na^+ currents in primary somatosensory barrel cortex pyramidal neurons

The voltage was clamped at −80 mV, the neuron was given a hyperpolarizing stimulation (60 ms, −120 mV), and then a depolarizing stimulation (80 ms, −10 mV). We could record an inward current as shown in Fig. 1a. Tetrodotoxin (1 μM) can completely block the current reversibly (it was not shown here), indicating that the inward current is voltage-gated INa.

In order to observe the stability of INa in neurons involved in this study, the peak of INa was recorded at 0, 1, 3, 5, and 7 minutes after rupture of membrane. The relationship between recording time and the density of INa was plotted with time as transverse axis and peak current density (peak current/membrane capacitance) as longitudinal axis. The curve (Fig. 1b) shows that the peak INa reaches a stable level at 1 minute after rupture (n = 20). As a result, we began to record currents after a 1 minute period following rupture of membrane in the subsequent experiments.

Effects of ketamine on density of Na^+ current

The neuron was perfused with ketamine (10, 100, 300, 1000, 3000, and 10 000 μM), respectively. The peak current of INa was recorded before and after administration of ketamine. IC50 values were obtained by least-squares fitting of data to the Hill equation: $Y=1/\{1+([Ket]/IC_{50})^h\}$, where Ket is the concentration of ketamine, IC50 was the concentration giving a half-maximum effect and h was the Hill coefficient. Ketamine inhibited INa in a dose-dependent manner. At holding potentials of −80 mV, ketamine -IC50 for peak INa inhibition was 686.72 μM with Hill slopes of 1.27 on S1BF neurons (Fig. 2a), while IC50 was 842.65 with Hill slopes of 1.02 on VPM neurons (Fig. 2b). The result indicates that ketamine inhibits the peak current of INa in S1BF neurons more significantly than that in VPM neurons of rats.

Effects of ketamine on peak Na^+ current

After the whole-cell model was formed, a hyperpolarization stimulation (100 ms, −100 mV) was given firstly, and then a series of INa (Fig. 3a1) were obtained with hyperpolarizing impulses (20 ms voltage steps from −80 to +50 mV in +10 mV increments (Fig. 3a2).

Effects of ketamine on representative current-voltage (I-V) curves of INa in S1BF and VPM neurons were

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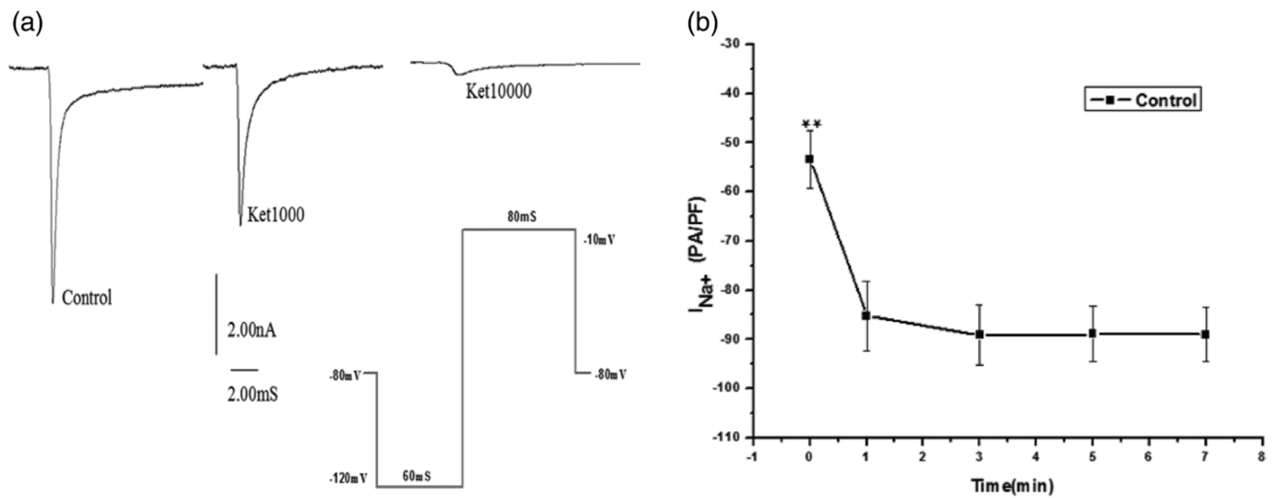
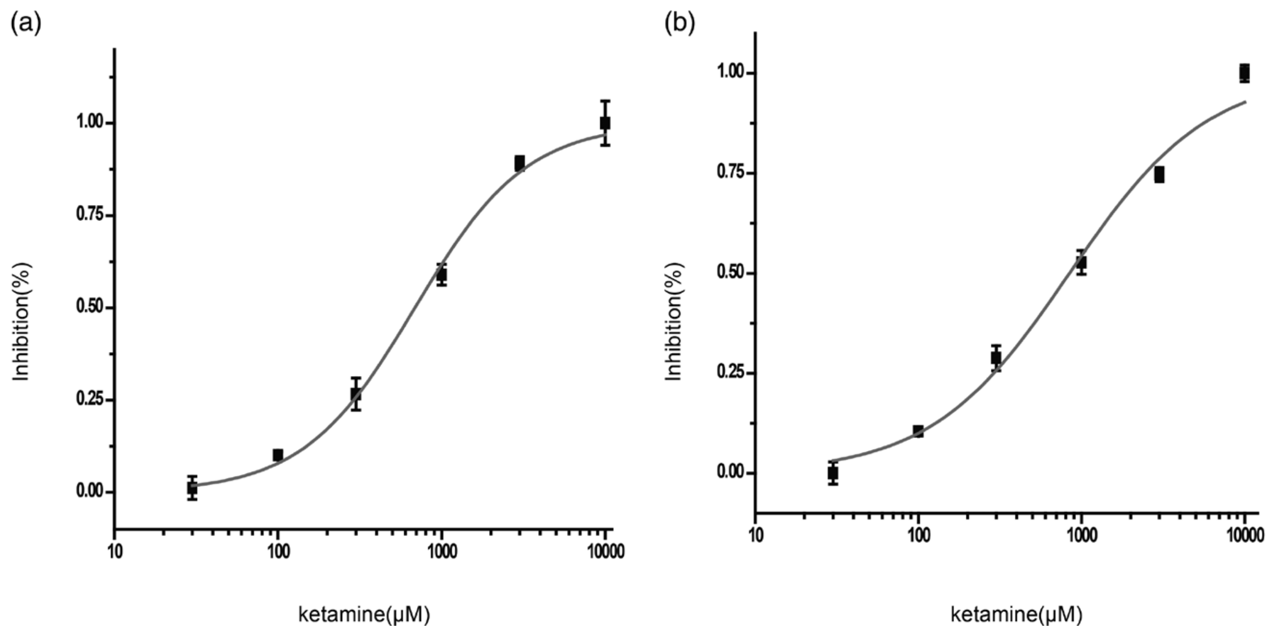
Fig. 1



The voltage-gated INa (a); the relationship between recording time and the density of INa (**$P < 0.01$, n = 20, b). INa, Na^+ current.

Fig. 2



Effects of ketamine on density of INa in S1BF (a) neurons and VPM neurons (b). INa, Na^+ current; S1BF, primary somatosensory barrel cortex; VPM, ventral posteromedial nucleus.

shown in Fig. 3b and c. The threshold of activation potential of INa in S1BF neurons was −40 mV, and it reached the peak at −10 mV (Fig. 3b). However, the threshold of activation potential of INa in VPM neurons was −50 mV, and it reached peak current at −20 mV (Fig. 3c). These results indicate that INa in VPM neurons activate earlier and reach peak values than voltage-gated sodium channels in S1BF neurons. The peak current density of sodium current in S1BF neurons was −91.08 (+8.65 pA/pF) (Fig. 3b, n = 8), and that in VPM neurons was −134.10 (+6.73 pA/pF) (Fig. 3c, n = 8, $P < 0.01$), which indicated that the density of INa in VPM neurons was higher than that in S1BF neurons. From Fig. 3, it can be seen that the peak current density of INa decreases in a concentration-dependent manner with the increase of ketamine concentration (100 and 1000 μM).

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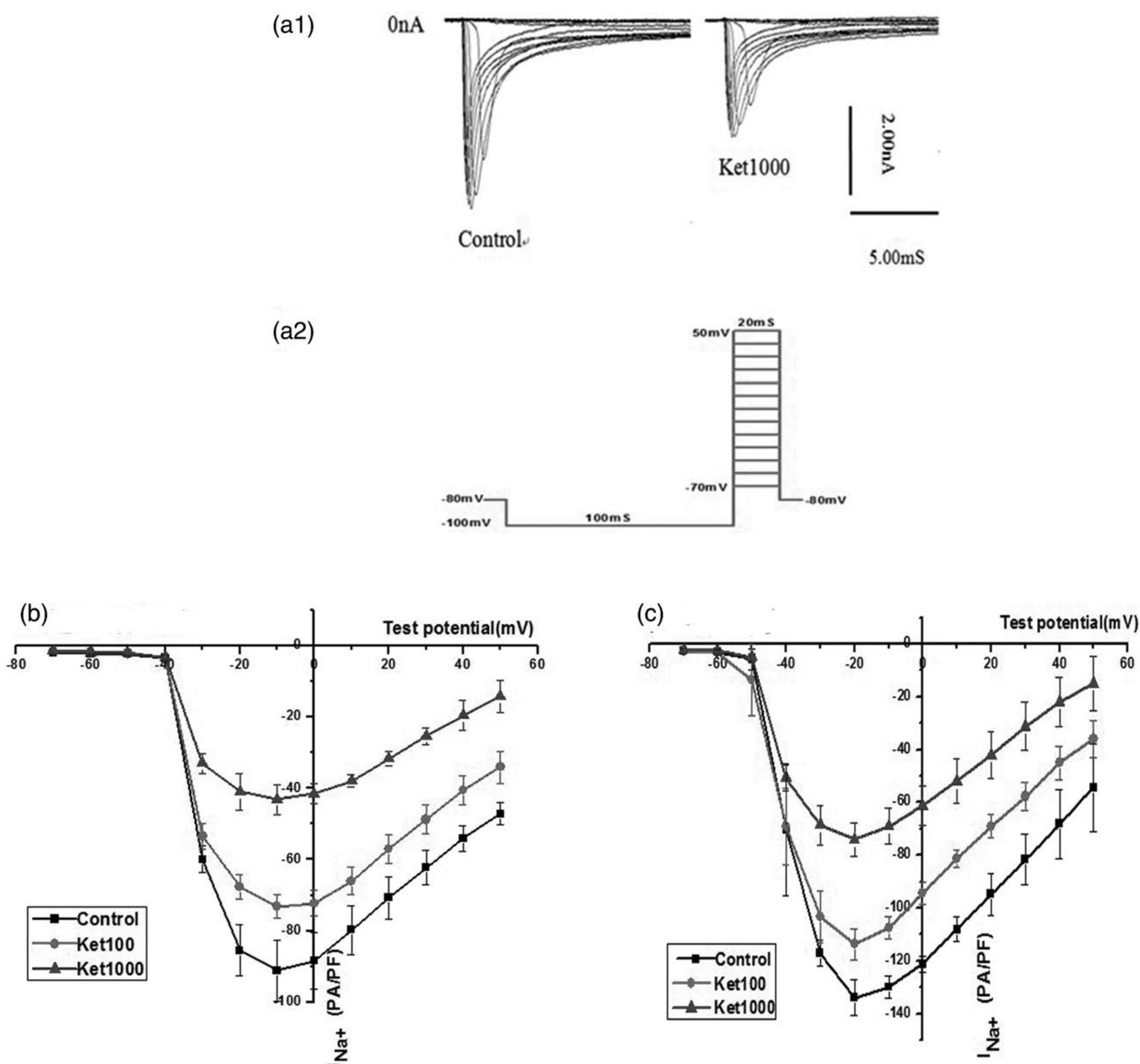
Fig. 3



Representative INa traces in a primary S1BF pyramidal neuron (a1) and the hyperpolarization stimulation (a2); effects of ketamine on representative I-V relationships of INa in S1BFneurons (b) and VPM neurons (c). I-V, current-voltage; INa, Na^+ current; S1BF, primary somatosensory barrel cortex; VPM, ventral posteromedial nucleus.

Effects of ketamine on Na^+ current activation

The effects of ketamine on the activation of INa in S1BF pyramidal neurons and VPM neurons are shown in Supplementary Tables 1 and 2, Supplementary digital content 1, *http://links.lww.com/WNR/A551*. Ketamine (100 and 1000 μM) did not significantly alter the $V_{1/2}$ of activation of Na^+ conductance from holding potentials of −80 mV, consistent with no shift in the I-V curve in S1BF pyramidal neurons (Fig. 4a) and VPM neurons (Fig. 4b).

Effects of ketamine on Na^+ current inactivation

Steady-state inactivation curves for INa in the absence or presence of ketamine were determined with standard two-pulse protocols (Fig. 5a). Ketamine led to a negative shift of INa-inactivation but not affected the slope factor (κ) at −80 mV both in S1BF neurons (Fig. 5b) and VPM neurons (Fig. 5c). The specific changes are shown in Supplementary Tables 1 and 2, Supplementary digital content 1, *http://links.lww.com/WNR/A551*.

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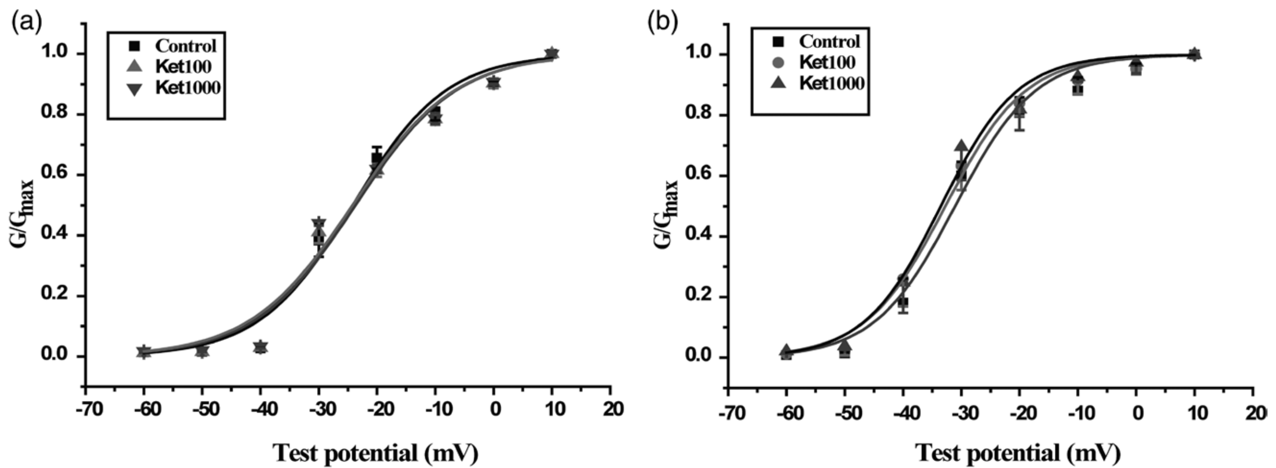
Fig. 4



Voltage-dependent activation curves of Na^+ channels in S1BF neurons (a) and VPM neurons (b) in the absence or presence of ketamine. S1BF, primary somatosensory barrel cortex; VPM, ventral posteromedial nucleus.

Effects of ketamine on the recovery time from Na^+ current inactivation

The effects of ketamine on the de-inactivation (recovery) of voltage-gated Na^+ channel in S1BF neurons are shown in Fig. 6. Representative de-inactivation traces of INa were investigated using a standard two-pulse protocol with varying interpulse intervals (t) from 2 to 20 ms (Fig. 6a). De-inactivation curves of INa were fitted by a single exponential function in S1BF neurons (Fig. 6b) and VPM neurons (Fig. 6c). In S1BF neurons, the recovery time from inactivation of INa was prolonged by the application of ketamine (control 3.58 ± 0.15 vs 4.67 ± 0.13 ms 100 μM; control 3.58 ± 0.15 vs 8.19 ± 0.41 ms 1000 μM; $P < 0.05$). In VPM neurons, the recovery time from inactivation of INa was also prolonged by ketamine (control 4.22 ± 0.10 vs 4.81 ± 0.89 ms 100 μM; control 4.22 ± 0.10 vs 9.85 ± 0.43 ms 1000 μM; $P < 0.05$).

Discussion

Ketamine is a dissociative anesthetic and has been in clinical use for more than four decades. A previous study has shown that ketamine blocks peripheral and central nervous system Na^+ channels [10]. The blockade of different types of voltage-gated Na^+ channels during regional anesthesia by local anesthetic-like drugs has been studied extensively [18]. Ketamine reversibly causes loss of consciousness, but the mechanism remains unclear. More studies demonstrated that thalamocortical system is essential for information integration in the brain [19,20]. Our previous study showed that etomidate enhances GABAergic transmission and attenuates glutamatergic transmission in S1BF and VPM neurons [4]. Therefore, in consideration of VPM and S1BF are the two main brain area in the thalamocortical loop, we attempt to observe the effects of ketamine on voltage-gated Na^+ channels in S1BFand VPM neurons by using whole-cell patch-clamp recordings.

In our study, the results represent the effects of ketamine on the voltage-gated Na^+ channels on S1BF neurons and VPM neurons. Ketamine (100 and 1000 μM) did not significantly alter the V1/2 of activation of Na^+ conductance or the slope factor (κ) at −80 mV but led to a negative shift of INa-inactivation both in S1BF neurons and VPM neurons. The Na^+ channel is the main molecular basis of action potential firing and modulates neuronal excitability, especially the action potential-conducted neuronal signal transmission [9]. Previous study has showed that propofol and isoflurane inhibit Na^+ channels in isolated rat neurohypophysial nerve terminals [7]. Etomidate also inhibits voltage-gated Na^+ channels in rat primary sensory cortex pyramidal neurons [8]. Ketamine has a high liposolubility and a low plasma protein binding rate, so it is easy to penetrate the blood-brain barrier. Concentration-effect curves for the Na^+ peak current revealed for tonic block half-maximal inhibiting concentrations (IC50) of 269 μM for R (−)-ketamine in superficial dorsal horn neurons [21]. In the present study, ketamine -IC50 for peak INa inhibition was 686.72 μM with Hill slopes of 1.27 on S1BF neurons, while IC50 was 842.65 with Hill slopes of 1.02 on VPM neurons at holding potentials of −80 mV. The result suggests that S1BF neurons are more sensitive to ketamine than VPM neurons. Therefore, S1BF may be the main brain area of ketamine action.

From the I-V curves of INa in the two brain regions, we can see that voltage-gated Na^+ channels are activated earlier and reach their peak earlier in VPM neurons than in S1BF neurons, and the density of INa in VPM neurons is higher than that in S1BF neurons. The earlier the voltage-gated Na^+ channel is activated, the lower the

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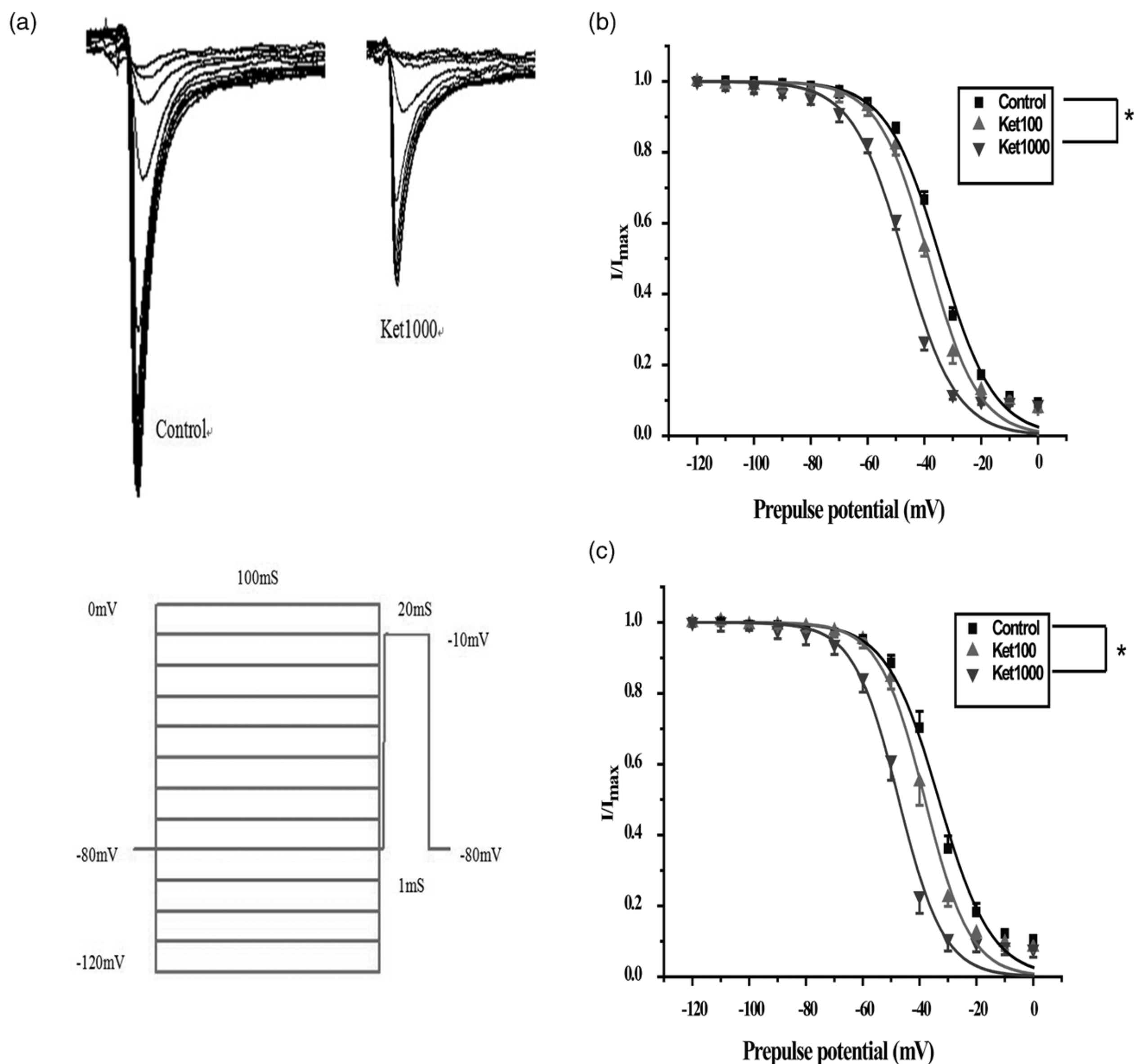
Fig. 5



Effects of ketamine on INa-inactivation. Currents were elicited by a 40 ms test pulse to −10 mV after a prepulse ranging from −120 to −10 mV in 10 mV increments (a). The effects of ketamine on INa-inactivation curves in S1BF neurons (b) and VPM neurons (c). Data shown as mean ± SEM (n = 8). *$P < 0.05$ vs control by the unpaired *t*-test. INa, Na^+ current; S1BF, primary somatosensory barrel cortex; VPM, ventral posteromedial nucleus.

threshold of action potential, and the higher the excitability of neurons. Therefore, it can be inferred that the excitability of VPM neurons in rats is higher than that of S1BF neurons. In our study, ketamine did not affect slope factor of voltage-gated Na^+ channel currents in two brain regions, but significantly shift the steady-state inactivation curve to the left, decreased the half of the inactivation voltage, and prolonged the recovery time of Na^+ channel inactivation in a concentration-dependent manner. It can be concluded that the inhibition of ketamine on voltage-gated INa in S1BF and VPM neurons is mainly due to ketamine enhancing the inactivation of Na^+ channel and delaying the recovery from inactivation.

The effects of ketamine on inactivation, which was mainly induced by a short prepulse, suggest that t ketamine affects inactivation, which is consistent with greater anesthetic affinity for the inactivated state of the channel and similar to the actions of local anesthetics [22]. The prolonged time of recovery from inactivation indicates either slow anesthetic dissociation from the inactivated state or slowed conversion of channels from the

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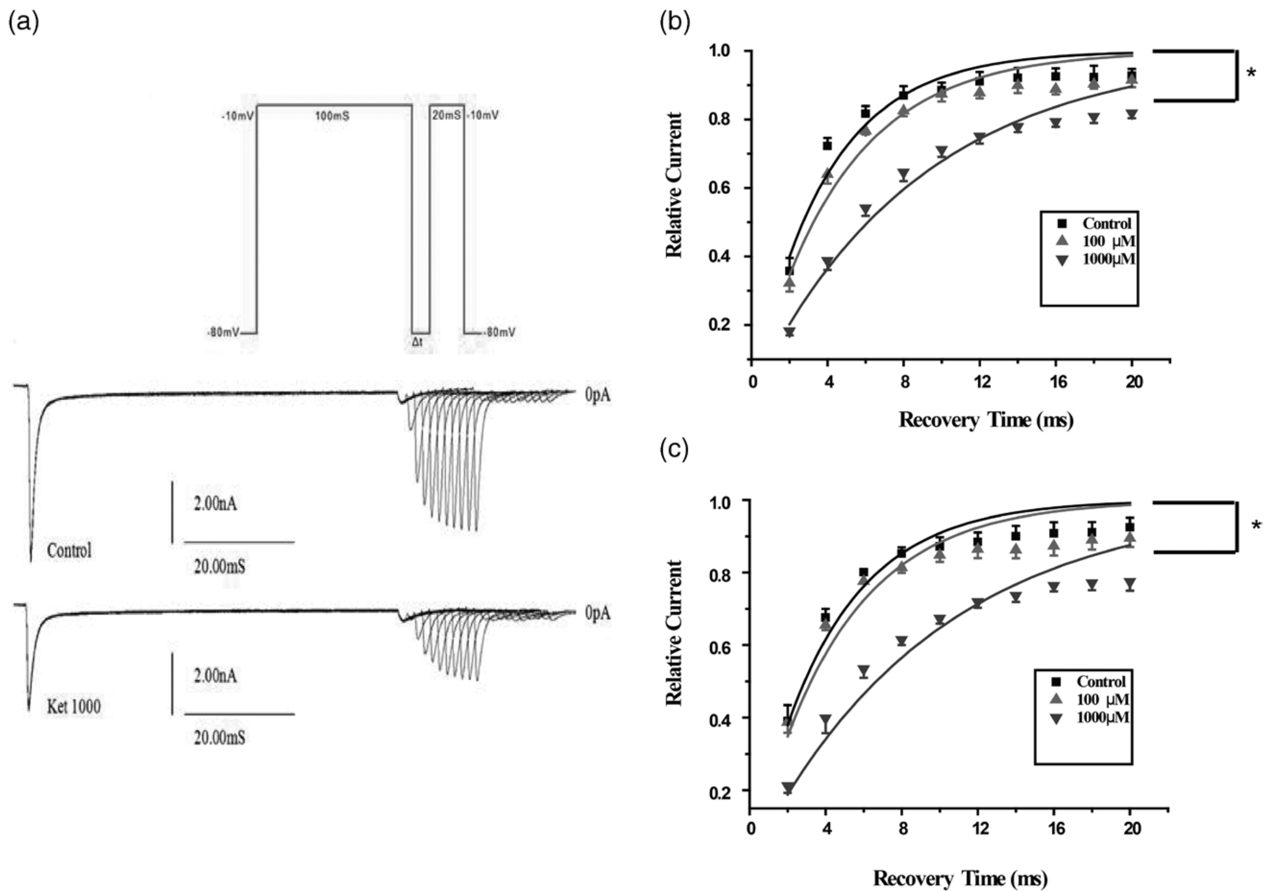
Fig. 6



Effects of ketamine on INa recovery. (a) De-inactivation traces of INa. Currents were elicited by test pulses (100 ms) followed by a 20 ms conditioning step to −10 mV with recovery times (t) of 2–20 ms. Effects of ketamine on the recovery from inactivation of INa in S1BF neurons (b) and VPM neurons (c). Relative currents were calculated as the peak INa elicited by test pulse versus that elicited by conditioning pulse from 80 mV in each sweep; these values were normalized to control values in the absence of anesthetics. *$P < 0.05$ vs control by the unpaired *t*-test. INa, Na^+ current; S1BF, primary somatosensory barrel cortex; VPM, ventral posteromedial nucleus.

inactivated to resting states [8]. Similar to etomidate [8], our results showed that ketamine produces distinct effects on Na^+ channel, which may involve multiple targets on Na^+ channels and on its modulators. Unlike etomidate [8], ketamine led to a negative shift of INa-inactivation but not affected the slope factor (κ) at −80 mV both in S1BF neurons and VPM neurons. Whether this is related to ketamine-induced segregation anesthesia remains to be further studied. A previous study showed that ketamine reversibly depressed sodium currents of frog myelinated nerve fiber, but ketamine did not induce a negative shift of steady-state sodium inactivation-voltage curves [23]. Therefore, the pharmacological effects of ketamine may be different in different neurons.

Propofol inhibits INa on nerve terminals isolated from rat neurohypophysis and isoflurane also inhibits INa on isolated neurohypophysial nerve terminals and spinal neurons of rats [7,24]. These similar effects of general anesthetics suggest that Na^+ channels may be the target of general anesthetics. Therefore, inhibition of voltage-gated Na^+ channels may contribute to the presynaptic effects of general anesthetics on nerve terminal excitability and neurotransmitter release, which may be one of the mechanisms by which general anesthetics lead to loss of consciousness.

The inactivation of Na^+ channel is an active process, and the mechanism of inactivation may be mainly due to the blocking of the channel entrance by ‘spheres’ formed by the intracellular rings connecting repetitive regions III and IV [25]. Phenylalanine residues in the IFM power region located at 1489 are important for rapid inactivation and the outward movement of region IV S4 promotes rapid inactivation by closing inactivation gates [25]. In the present study, ketamine only affects the inactivation and recovery of voltage-gated sodium channels, which can be inferred that ketamine action sites may located in regions III and IV. The present study has several limitations. First, the IC50 in the somatosensory cortex and thalamic

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VPM is higher than used in clinically. In this study, isolated brain slices were used, and drug diffusion may be affected. Second, in this study, patch-clamp technique was used to select the characteristics of voltage-gated sodium channels and action potentials in rat somatosensory cortex and thalamic VPM neurons, but no correlation study was made between the two brain regions. Finally, although we find a complex effect of ketamine on activation and deactivation of voltage-gated sodium currents, the deeper mechanism of these effects still needs to be further explored.

In conclusion, ketamine accelerated the Na^+ channels inactivation and slowed inactivation of Na^+ channels after recovery while did not affect the activation. We demonstrated the detailed suppression process of neural voltage-gated Na^+ channels by ketamine on thalamocortical slice. This may provide a new insight into the mechanical explanation for the ketamine anesthesia.

Acknowledgements

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Conflicts of interest

There are no conflicts of interest.

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