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Research report

Repetitive transcranial magnetic stimulation regulates L-type Ca^{2+} channel activity inhibited by early sevoflurane exposure

Yang Liu [a,1], Huiyun Yang [a,1], Xiaohong Tang [b,c], Wenwen Bai [a], Guolin Wang [b,c,**], Xin Tian [a,*]

[a] School of Biomedical Engineering, Tianjin Medical University, Tianjin, China
[b] Department of Anesthesiology, Tianjin Medical University General Hospital, Tianjin, China
[c] Tianjin Research Institute of Anesthesiology, Tianjin, China

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ABSTRACT

Background: Sevoflurane might be harmful to the developing brain. Therefore, it is essential to reverse sevoflurane-induced brain injury.
Objective: This study aimed to determine whether low-frequency repetitive transcranial magnetic stimulation (rTMS) can regulate L-type Ca^{2+} channel activity, which is inhibited by early sevoflurane exposure.
Methods: Rats were randomly divided into three groups: control, sevoflurane, and rTMS groups. A Whole-cell patch clamp technique was applied to record L-type Ca^{2+} channel currents. The I-V curve, steady-state activation and inactivation curves were studied in rats of each group at different ages (1 week, 2 weeks, 3 weeks, 4 weeks and 5 weeks old).
Results: In the control group, L-type Ca^{2+} channel current density significantly increased from week 2 to week 3. Compared with the control group, L-type Ca^{2+} channel currents of rats in the sevoflurane group were significantly inhibited from week 1 to week 3. Activation curves of L-type Ca^{2+} channel shifted significantly towards depolarization at week 1 and week 2. Moreover, steady-state inactivation curves shifted towards hyperpolarization from week 1 to week 3. Compared with the sevoflurane group, rTMS significantly increased L-type Ca^{2+} channel currents at week 2 and week 3. Activation curves of L-type Ca^{2+} channel significantly shifted towards hyperpolarization at week 2. Meanwhile, steady-state inactivation curves significantly shifted towards depolarization at week 2.
Conclusions: The period between week 2 and week 3 is critical for the development of L-type Ca^{2+} channels. Early sevoflurane exposure inhibits L-type Ca^{2+} channel activity and rTMS can regulate L-type Ca^{2+} channel activity inhibited by sevoflurane.

1. Introduction

During the early development of animals and humans the brain is especially vulnerable to environmental influences, including general anesthesia. Clinical studies have demonstrated that anesthesia and surgery in children younger than 4 years probably increases their probability of developing disabilities in reading, writing, and arithmetic (Alkire et al., 2008). This has raised significant concerns among anesthesiologists, neuroscientists and parents regarding the safety of general anesthetics in infants (Feng et al., 2012a, 2012b).

Sevoflurane (2,2,2-trifluoro-1-[trifluoromethyl]ethyl fluoromethyl ether) is widely used during surgical procedures (Lerman et al., 1994). It is especially suitable for infants and children because of its low blood gas partition coefficient, rapid onset and offset, and low risk of airway irritation. However, recent studies have demonstrated that prolonged exposure to sevoflurane can cause neuron degeneration, abnormal social behaviors like autism, and seizure-like electroencephalogram activity (Cao et al., 2012; Jevtovic-Todorovic et al., 2003; Satomoto et al., 2009; Seubert et al., 2013). Furthermore, sevoflurane can also inhibit neurogenesis and change the synaptogenesis during brain development (Vutskits et al., 2005). Above all, these studies indicate that sevoflurane might be harmful to the developing brain. Therefore, it is important to explore the mechanisms of sevoflurane' effects on the developing brain.

Voltage-gated Ca^{2+} channels have an important role in

* Corresponding author.
** Corresponding author at: Tianjin Medical University General Hospital, Tianjin 300070, China.
E-mail addresses: wangguolinemail@126.com (G. Wang), tianx@tijmu.edu.cn (X. Tian).
[1] These authors contributed equally to this work.

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dendritic development, neuronal survival, and synaptic plasticity (Li et al., 2007). L-type Ca^{2+} channels contribute to approximately 30–50% of all Ca^{2+} channel currents in the hippocampus (Mintz et al., 1991). L-type Ca^{2+} channel activation promotes activation of various transcription factors in cultured neurons, including myocyte enhancer factor 2 (MEF-2) and cAMP response element-binding protein (CREB), and triggers the expression of Ca^{2+}-regulated genes, including brain-derived neurotrophic factor (BDNF), c-Fos and Bcl-2, which are essential to neuronal survival (Bito et al., 1996; Catterall, 2000; Weick et al., 2003; West et al., 2001; Zhou et al., 2004). Moreover, prolonged L-type Ca^{2+} channel blockade leads to apoptosis in cultured neurons (Murphy et al., 1991). Therefore, modulation of L-type Ca^{2+} channel activity may play a crucial role in brain development. Studies have revealed that L-type Ca^{2+} channels can be inhibited by sevoflurane (Eckle et al., 2012; Gibert et al., 2012). However, the role of sevoflurane in regulating L-type Ca^{2+} channel during the period of rapid brain development is still not well understood.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique and that has been used to treat neurological diseases such as Alzheimer's Disease, Parkinson's disease, epilepsy, and depression (Tan et al., 2013a, 2013b; Dayan et al., 2013; Feil and Zangen, 2010; Hallett, 2007; Ridding and Rothwell, 2007; Schulz et al., 2013; Wassermann and Zimmermann, 2012). The magnetic field penetrates the skull painlessly and an electrical current may be induced in the underlying neurons, which can generate action potentials (Platz and Rothwell 2010; Torres et al., 2013). Studies have revealed that rTMS can cause persistent changes in neuronal activity and influence hippocampal synaptic plasticity (Ahmed and Wieraszko, 2006; Kim et al., 2006; Levkovitz and Segal, 2001; Ogiue-Ikeda et al., 2003, 2005).

However, high-frequency rTMS may cause stroke, seizure, and other adverse effects (Kotova and Vorobeva, 2007). The safety profile of low-frequency rTMS has been evaluated in healthy rats and humans (Vernieri et al., 2014). Whether low-frequency rTMS could regulate L-type Ca^{2+} channels inhibited by sevoflurane is not yet known.

To demonstrate the effects of early sevoflurane exposure on L-type Ca^{2+} channel activity, and whether rTMS can regulate L-type Ca^{2+} channel activity inhibited by sevoflurane, we applied a whole-cell patch clamp technique to record L-type Ca^{2+} channel currents in hippocampal CA1 pyramidal neurons. To assess the effects of early sevoflurane exposure on early brain development and rTMS on L-type Ca^{2+} channel activity, current-voltage (I-V) curves, steady-state activation curves and inactivation curves of L-type Ca^{2+} channels were analyzed.

2. Results

2.1. Properties of L-type Ca^{2+} channel in the developing CA1 pyramidal neurons

Whole-cell recordings were obtained from hippocampal CA1

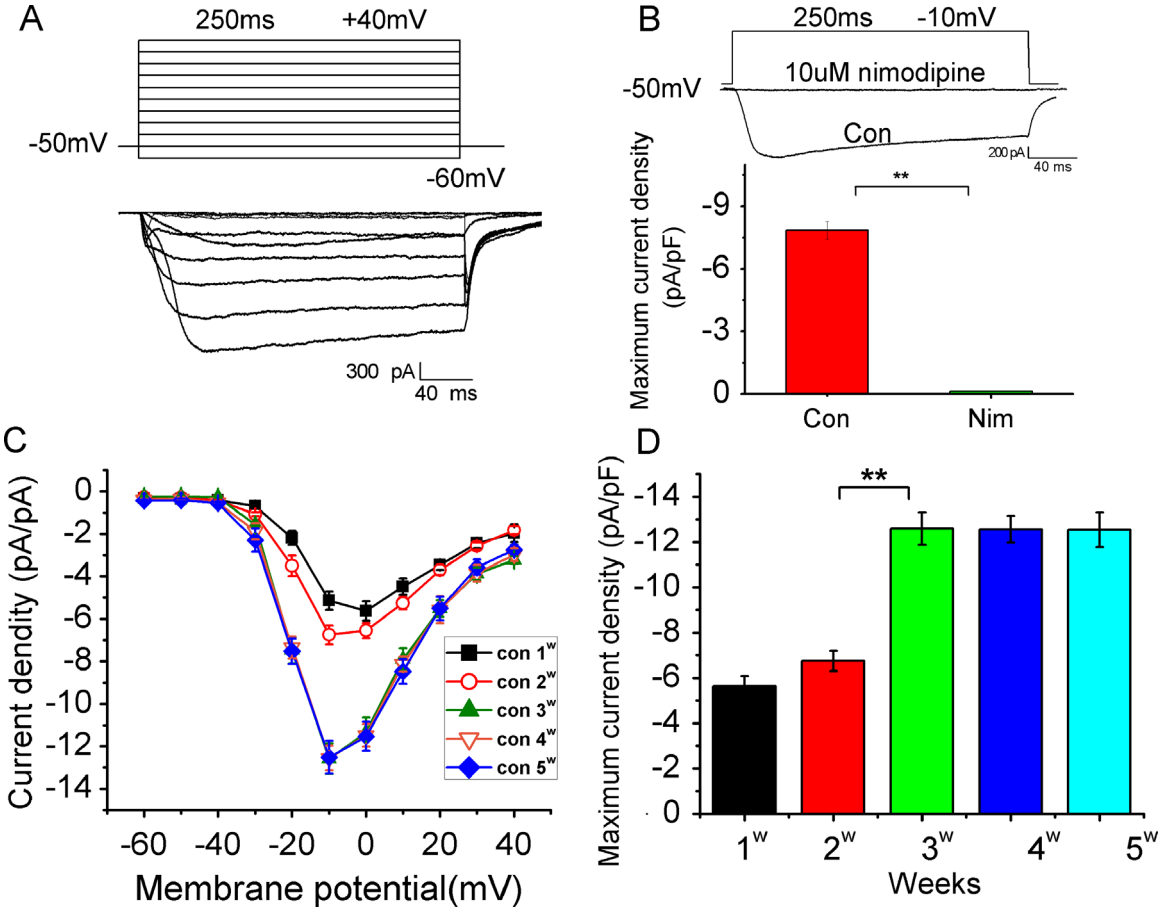

Fig. 1. Current-voltage (I-V) relation of L-type Ca^{2+} channel during brain development in the hippocampal CA1 pyramidal neurons. A. The pulse protocols for recording L-type Ca^{2+} channel currents and Ca^{2+} current traces elicited by step depolarized potentials from −60 mV to +40 mV with an increment of 10 mV. B. The holding potential is −50 mV, the whole-cell L-type Ca^{2+} channel currents evoked by a stimulation pulse at −10 mV for 250 ms. A sample of L-type Ca^{2+} channel currents in the presence and absence of 10 μM nimodipine. C. Current-voltage (I-V) curves of L-type Ca^{2+} channels in con 1^w, con 2^w, con 3^w, con 4^w, and con 5^w groups. D. The maximum current density of L-type Ca^{2+} channels in con 1^w, con 2^w, con 3^w, con 4^w, and con 5^w groups. The data were expressed as mean ± SEM, $^*P < 0.05$, $^{**}P < 0.01$. Shown are mean values obtained for 10 neurons recorded in 6 rats, represented by n (n = 10).