Original Article

Ginsenoside Rb1 Attenuates Isoflurane/surgery-induced Cognitive Dysfunction *via* Inhibiting Neuroinflammation and Oxidative Stress

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Abstract

Objective Anesthetic isoflurane plus surgery has been reported to induce cognitive impairment. The underlying mechanism and targeted intervention remain largely to be determined. Ginsenoside Rb1 was reported to be neuroprotective. We therefore set out to determine whether ginsenoside Rb1 can attenuate isoflurane/surgery-induced cognitive dysfunction *via* inhibiting neuroinflammation and oxidative stress.

Methods Five-months-old C57BL/6J female mice were treated with 1.4% isoflurane plus abdominal surgery for two hours. Sixty mg/kg ginsenoside Rb1 were given intraperitoneally from 7 days before surgery. Cognition of the mice were assessed by Barnes Maze. Levels of postsynaptic density-95 and synaptophysin in mice hippocampus were measured by Western blot. Levels of reactive oxygen species, tumor necrosis factor-α and interleukin-6 in mice hippocampus were measured by ELISA.

Results Here we show for the first time that the ginsenoside Rb1 treatment attenuated the isoflurane/surgery-induced cognitive impairment. Moreover, ginsenoside Rb1 attenuated the isoflurane/surgery-induced synapse dysfunction. Finally, ginsenoside Rb1 mitigated the isoflurane/surgery-induced elevation levels of reactive oxygen species, tumor necrosis factor-α and interleukin-6 in the mice hippocampus.

Conclusion These results suggest that ginsenoside Rb1 may attenuate the isoflurane/surgery-induced cognitive impairment by inhibiting neuroinflammation and oxidative stress pending future studies.

Key words: Ginsenoside Rb1; Isoflurane; Surgery; Cognitive dysfunction; Synapse; Neuroinflammation; Oxidation stress

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INTRODUCTION

Postoperative cognitive dysfunction (POCD) is one of the most common postoperative complications[1], and is associated with poor short-term and long-term outcomes[2]. POCD diminishes the quality of the patient's life and adds costs to hospitalization and out-of-hospital care[3]. POCD has received considerable attention over the past 15 years[1]. Postoperative cognitive dysfunction syndromes include postoperative delirium (POD) and postoperative cognitive dysfunction (POCD). POD is an acute, transient and fluctuating decline in cognitive functioning in the early postoperative period, whereas POCD is a chronic impairment with more-subtle deterioration in memory, attention and speed of information processing following anaesthesia and surgery. The precise pathogenesis

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of POCD is not known and may involve perioperative as well as patient-related factors. However, there is still a lack of effective treatments for POCD, and many studies aim to find new and novel drugs to treat and/or prevent POCD.

Recent animal studies have strongly suggested the role of neuroinflammation in the development of cognitive dysfunction after surgery under volatile anesthetics[3-5]. These previous studies have shown that anesthetics/surgery increase the expression of inflammatory cytokines in the brain[3,6]. It has been postulated that neuroinflammation response to the oxidative stress may lead to the synapse dysfunction, which can result in cognitive dysfunction[7].

Ginseng is the root of Panax ginseng C. A. Meyer (Araliaceae family) and has been used as a tonic remedy in traditional Chinese medicine for a long time[8-9]. Currently, ginseng is one of the most commonly used herbal medicines in the world[8-10]. Ginsenosides are thought to be the main active components of ginseng with multiple pharmacological activities including anti-inflammation, anti-aging, anti-tumor, anti-oxidation, and anti-fatigue[11-16]. Modern science has identified more than 50 kinds of ginsenosides. Ginsenoside Rb1 has been frequently used to reduce inflammatory process in various diseases[17-21]. However, the relationship between ginsenoside Rb1 and postoperative cognitive dysfunction is unknown.

We therefore assessed whether ginsenoside Rb1 could attenuate the isoflurane/surgery-induced cognitive impairment in mice and the related mechanism. Since the postsynaptic density 95 (PSD-95)[22] and synaptophysin (SVP)[23] are markers of synapse, we compared the levels of hippocampus PSD-95 and SVP as parts of the mechanistic investigation. Elevation of inflammatory cytokine tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) levels has been reported to be associated with the neuroinflammation and contribute to the cognitive impairment induced by surgery under anesthesia[3,7,24-25]. Oxidative stress is defined as an imbalance between production of free radicals and reactive metabolites, reactive oxygen species (ROS) could activate inflammatory pathways leading to over express of inflammatory cytokines[26]. Taken together, we assessed the effects of the ginsenoside Rb1 on isoflurane/surgery induced neuroinflammation (the levels of TNF-α and IL-6), oxidative stress (the levels of ROS) and synapse function (the levels of PSD-95 and SVP) in the hippocampus of mice, as well as the cognitive function (Barnes Maze Test) in the mice.

METHODS

Mice Anesthesia/surgery and Treatment

All animal procedures were approved by the Ethical Committee of Beijing Friendship Hospital, Capital Medical University (Beijing, China), and were performed in accordance with the Guidelines for Animal Experimentation of the International Association in Research and Teaching. Efforts were made to minimize the number of animals used. To avoid selection bias, we assigned animals randomly to different experimental groups by a computer-generated randomization list.

Wide-Type C57BL/6J mice (5-months-old, female) were housed in a controlled environment (20-22 °C, 12 h of light/dark on a reversed light cycle) for seven days prior to the studies. The mice were randomly assigned to the isoflurane/surgery group or the control condition group with ginsenoside Rb1 or normal saline (the vehicle of ginsenoside Rb1) pretreatment. A simple laparotomy was performed under isoflurane anesthesia using the methods described in previous studies[27]. Specifically, anesthesia was induced and maintained with 1.4% isoflurane in 100% oxygen in a transparent acrylic chamber. Fifteen minutes after the induction, the mouse was moved out of the chamber, and anesthesia was maintained *via* a cone device. One 16-gauge needle was inserted into the cone near the nose of the mouse to monitor the concentration of anesthesia. A longitudinal midline incision was made from the xiphoid to the 0.5 centimeter proximal pubic symphysis on the skin, abdominal muscles and peritoneum. Then, the incision was sutured layer by layer with 5-0 Vicryl thread. At the end of the procedure, 2.5% lidocaine and 2.5% prilocaine cream was applied to the incision wound, and then every eight hours for two days to treat the pain associated with the incision. The temperature of the anesthetizing chamber was controlled (DC Temperature Control System; FHC, Bowdoinham, Maine) to maintain the rectal temperature of the mice at 37 ± 0.5 °C during the isoflurane/surgery. After recovering from the anesthesia, each mouse was returned to a home cage with food and water available *ad libitum*. The mice in the control group were placed in their home cages with room air for two hours, which was consistent with the condition of non-surgery patients. Ginsenoside Rb1 was at