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GLYCYRRHIZIN ATTENUATES ISOFLURANE-INDUCED COGNITIVE DEFICITS IN NEONATAL RATS VIA ITS ANTI-INFLAMMATORY ACTIVITY

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Abstract—Children exposed to general anesthetics such as isoflurane are maybe at an increased risk of cognitive impairment. Recent studies have indicated that this kind of cognitive decline is associated with neuroinflammation in the hippocampus of neonatal rodents. Glycyrrhizin is a naturally available compound for the treatment of inflammatory and neurodegenerative diseases. We therefore aimed to investigate the effects of glycyrrhizin on the isoflurane-induced cognitive deficits and hippocampal neuroinflammation in the neonatal rats. Seven day-old rats were exposed to 1.8% isoflurane for 4 h. Saline and glycyrrhizin solution was injected intraperitoneally 30 min prior to isoflurane or control gas exposure. The effects of isoflurane and glycyrrhizin treatment on memory performance were examined using Morris Water Maze (MWM) task. The protein expression of high-mobility group box 1 (HMGB1), NFκB, Bcl-2, Bax and cleaved (active) caspase-3 were determined by Western blot assay. The protein levels of TNF-α and IL-1β were detected by enzyme-linked immunosorbent assay (ELISA). The combination of ELISA and Western blot results showed that glycyrrhizin attenuated isoflurane-induced increases of pro-inflammatory cytokines (TNF-α and IL-1β) and activation of HMGB1/NFκB signaling pathway in the hippocampus of neonatal rats. Furthermore, glycyrrhizin treatment prevented the deficits in spatial memory induced by neonatal exposure to isoflurane. Consistent with these observations, we found that glycyrrhizin alleviated isoflurane-induced neuroapoptosis and down-regulations of PSD-95 and SNAP-25 in the hippocampus of neonatal rats. These results suggest that glycyrrhizin may be a potential therapeutic agent for developmental neurotoxicity and subsequent cognitive decline induced by neonatal exposure to general anesthetics.
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Key words: glycyrrhizin, hippocampus, HMGB1, isoflurane, NFκB.

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Abbreviations: AD, Alzheimer's disease; EDTA, ethylenediaminetetraacetic acid; ELISA, enzyme-linked immunosorbent assay; HMGB1, high-mobility group box 1; LPS, lipopolysaccharide; MWM, Morris Water Maze.

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INTRODUCTION

General anesthetics such as isoflurane are widely used in pediatric surgery, and their safe uses in children have become a major issue of interest. However, several population studies have demonstrated that children exposed to general anesthetics display learning disabilities during childhood (Wilder et al., 2009). However, the underlying mechanisms are still not clearly understood.

Recently, neuroinflammation has come to be recognized as an important underlying mechanism in general anesthetics-induced cognitive impairments in neonatal rodents (Lu et al., 2010; Shen et al., 2013). *In vitro* studies have demonstrated that isoflurane exposure may cause the activation of classic pro-inflammatory factor NFκB p65 in neuronal and microglia cultures (Zhang et al., 2013). This phenomenon was further supported by animal studies showing that anesthesia with isoflurane or sevoflurane in neonatal mice could result in overproductions of pro-inflammatory cytokines such as TNF-α and IL-1β in the hippocampus, which may contribute to cognitive impairment in the adulthood (Lu et al., 2010; Shen et al., 2013). Thus, the prevention of neuroinflammation might be a new and effective therapeutic approach for isoflurane-induced cognitive impairment in neonatal rodents.

Glycyrrhizin, a triterpenoid saponin compound, is the main component of Glycyrrhiza glabra which possesses potent anti-oxidant, anti-inflammatory and immune-modulatory properties (Lee et al., 2007; Mollica et al., 2007). Glycyrrhizin is capable of inhibiting the chemoattractant activity and mitogenic activity of high-mobility group box 1 (HMGB1) (Mollica et al., 2007; Ohnishi et al., 2011). HMGB1 has been identified as an endogenous danger signal molecule in the brain and the inhibition of HMGB1 activities can provide the brain with protective effects by attenuating neuroinflammation in ischemic injury (Kim et al., 2006; Faraco et al., 2007) and neurodegenerative diseases (Gao et al., 2011; Li et al., 2013a,b). Furthermore, it has also been demonstrated that the treatment with glycyrrhizin can alleviate β-amyloid (Ahn et al., 2006; Zhao et al., 2013) or systemic lipopolysaccharide (LPS)-induced (Song et al., 2013) cognitive impairment via inhibition of neuroflammation.

Therefore, we hypothesize that glycyrrhizin protects against isoflurane-induced cognitive impairment in neonatal rats via its anti-inflammatory property. In the present study, we report that, after neonatal exposure to isoflurane, glycyrrhizin reduces apoptosis and restores

synaptic protein synthesis in the hippocampus of neonatal rats by inhibiting HMGB1/NFκB signaling pathway-dependent pro-inflammatory cytokine production, resulting in improvement of cognitive functions.

EXPERIMENTAL PROCEDURES

Animals

In the present study, mother Sprague–Dawley rats (n = 28) with litters containing male pups (n = 158, from the Center of Experimental Animal of Tongji Medical College) were cross-fostered before starting the experiment. When pups were 7 days old (weighting 11–16 g), they were divided into four experimental groups (defined in the section "Experimental groups") and subjected to corresponding treatment. After experimental treatment, the four groups were distributed equally among litters. All rats were kept under standard lab housing with 12-h light/dark cycle. All experimental protocols and animal handling procedures were performed in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80–23) revised 1996 and the experimental protocols were approved by the committee of experimental animals of Tongji Medical College.

Isoflurane exposure

Rats randomized to the anesthesia group received isoflurane (1.8%, approximate 1 MAC for P7 rats) (Stratmann et al., 2009) flushed with 60% oxygen (balanced with air) for 4 h. Rats in the control group received control gas (60% oxygen, balanced with air) in a similar chamber for 4 h. The size of the anesthesia chamber in the study was 20 × 20 × 10 cm. The chamber was kept in a homeothermic incubator to maintain the experimental temperature at 37 °C. An infrared probe (OhmedaS/5 Compact, Datex-Ohmeda, Louisville, CO, USA) was adopted to continuously monitor the concentrations of oxygen, carbon dioxide and isoflurane in the exhalant gas. After exposure to isoflurane or control gas, all rats were returned to mother female rats. To determine adequacy of ventilation, arterial blood was sampled at the end of isoflurane anesthesia by obtaining a single sample (100 μl) via cardiac puncture. PH, arterial oxygen, and carbon dioxide tensions, base excess, and blood glucose was analyzed by a blood gas analyzer (Kent Scientific Corp., Torrington, CT, USA).

Experimental groups

All neonatal rats were randomly divided into four groups: (1) control group (CON): rats were intraperitoneally injected with 100 μl of saline followed by control gas exposure for 4 h; (2) isoflurane group (ISO): rats were intraperitoneally injected with100 μl of saline followed by 1.8% isoflurane exposure for 4 h; (3) glycyrrhizin group (Gly): rats were intraperitoneally injected with 20 mg/kg glycyrrhizin (100 μl) followed by control gas exposure for 4 h; (4) isoflurane + glycyrrhizin group (ISO + Gly): rats were intraperitoneally injected with 20 mg/kg of glycyrrhizin (100 μl) followed by 1.8% isoflurane exposure for 4 h. The regimen of glycyrrhizin treatment was selected based on a previous study (Ohnishi et al., 2011). Glycyrrhizin was prepared with sterile saline. Saline and glycyrrhizin solution was injected intraperitoneally (i.p.) 30 min prior to isoflurane or control gas exposure. The number of animals used for each experimental group is provided in Table 1.

MWM

MWM test was performed as described in our previous work (Li et al., 2013a,b). The rats (n = 10 per group) prepared for MWM were weaned at P22 and started the training at P31. The training protocol for the task of MWM test consisted of three trials (60 s maximum; interval 20 min) each day for five consecutive days. The probe trial was performed 1 h after the end of the fifth-day training and

Table 1. Study population

Animals	Groups	Sample size	Read-out (number of rats)
P7 rats (n = 158)	CON	n = 49	WB (30) ELISA (5) MWM (10) Blood gas analysis (4)
	ISO	n = 49	WB (30) ELISA (5) MWM (10) Blood gas analysis (4)
	Gly	n = 19	WB (10) ELISA (5) Blood gas analysis (4)
	ISO + Gly	n = 41	WB (22) ELISA (5) MWM (10) Blood gas analysis (4)

CON, control group; ELISA, enzyme-linked immunosorbent assay; Gly, glycyrrhizin group; ISO, isoflurane group; ISO + Gly, Isoflurane + glycyrrhizin group; MWM, Morris Water Maze; P7, postnatal day 7; WB, Western blot analysis.

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