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Research Report

Propofol inhibits inflammatory cytokine-mediated glutamate uptake dysfunction to alleviate learning/memory impairment in depressed rats undergoing electroconvulsive shock

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ABSTRACT

Electroconvulsive therapy (ECT) is an effective treatment for major depression, but can result in memory impairment. Several studies have shown that anesthetic propofol can alleviate the impairment of memory induced by ECT. However, the underlying molecular mechanisms remain unclear. We aimed to investigate the effects of propofol and electroconvulsive shock (ECS, analog of ECT in animals) on hippocampal inflammatory cytokines and glutamate uptake in depressed rats. The chronic unpredictable mild stress (CUMS) procedure was adopted to establish a model of depression. Sixty adult Sprague–Dawley rats were randomly divided into 5 groups with the following assignments ($n=12$ for each group): group C: control group without treatment; group D: CUMS+sham ECS; group DE: CUMS+ECS; group DP: CUMS+propofol (80 mg/kg, i.p.); group DPE: CUMS+propofol (80 mg/kg, i.p.)+ECS. Sucrose preference test and Morris water maze were used to assess behavioral changes. Hippocampal glutamate levels were measured with high performance liquid chromatography and the expression levels of IL-1β, TNF-α, GLAST and GLT-1 was quantificational analyzed by real time PCR or Western Blotting. The results demonstrated that ECS increased the levels of IL-1β and TNF-α, down-regulated the expression of GLT-1, GLAST expression remains stable, heightened the concentration of glutamate in the hippocampus and aggravated learning and memory impairment of depressed rats. Propofol suppressed IL-1β and TNF-α production, up-regulated the expression of GLT-1, decreased the concentration of glutamate in the hippocampus and attenuated the impairment of learning and memory induced by ECS. Propofol alleviate the learning and memory impairment induced by ECS could be partly attributed to its anti-inflammatory effects.

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Abbreviations: MDD, major depressive disorder; ECT, electroconvulsive therapy; ECS, electroconvulsive shock; GLAST, glutamate aspartate transporter; GLT-1, glutamate transporter 1

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1. Introduction

Major depressive disorder (MDD) is a common and disabling psychiatric illness that afflicts approximately 17% of the world's population, resulting in enormous personal suffering, as well as social and economic burden (Kessler et al., 2003). However, more than 30% of patients with depression fail to achieve remission to current available antidepressant medications (Rush, 2007).

Electroconvulsive therapy (ECT) is a highly effective treatment for major depression, especially drug-resistant and refractory depression, but can result in learning and memory function impairment (Lisanby, 2007; Semkovska and McLoughlin, 2010). Several studies have shown that propofol can alleviate cognitive deficits induced by ECT in clinical studies and animal model (Butterfield et al., 2004; Li et al., 2012). Our earlier studies indicated that the protective effects of propofol on cognitive function in ECT might be related to increased seizure threshold and decreased stimulus intensity (Li et al., 2012; Luo et al., 2012). However, the underlying molecular mechanisms remain poorly understood.

Glutamate is recognized as the major excitatory neurotransmitter in the mammalian CNS. Multiple lines of evidence suggested that glutamate-mediated excitotoxic injury contribute to the cognitive deficits of several neurodegenerative disorders (Salinska et al., 2005). Excessive activation of glutamate receptors commonly triggers uncontrolled intracellular signaling cascades and therefore results in neuronal toxicity. It is very clear that increased level of extracellular glutamate is the major cause of glutamate-mediated excitotoxicity. However, the clearance of released glutamate is assumed mainly by the glutamate transporters, which are responsible for glutamate uptake and particularly abundantly expressed on astrocytes (Gegelashvili et al., 2001). Hence, glutamate transporters can efficiently control the concentration of glutamate in the synaptic cleft and protect from excitotoxicity. A recent study has shown that ECS (analog of ECT in animals) can increase the level of glutamate in the hippocampus of depressive animal (Biedermann et al., 2012). However, the impact of ECT on expression and activity of glutamate transporters remains unclear.

More recently, inflammation mediators have been shown to influence the efficiency of glial glutamate uptake in pathological conditions (Zhao et al., 2004). Studies indicate that proinflammatory cytokines, especially IL-1β and TNF-α negatively regulate the expression and activity of glial glutamate transporters (Hu et al., 2000; Szymocha et al., 2000). Acute ECS can increase the plasma levels of cytokines including TNF-α and IL-1β (Lehtimaki et al., 2008; Fluitman et al., 2011). Several studies have reported recently that propofol exerts anti-inflammatory effects and efficiently decreases the expression and release of cytokines in rats (Ma et al., 2013; Peng et al., 2014). However, whether or not propofol can reduce neuroinflammation that induced by ECT require further study.

This study mainly aimed to investigate the effects of propofol on learning and memory dysfunction induced by ECT as well as the potential roles of proinflammatory cytokines and glutamate transporters in this process.

2. Result

2.1. Sucrose preference test

After administration of the CUMS procedure, rats in the four CUMS-treated groups (groups D, DE, DP, DPE) exhibited approximately 20% decrease in sucrose preference percentage (SPP) compared with rats in group C (group C: 86.22±5.74%; groups D: 66.13±4.43%; groups DE: 63.45±5.40%; groups DP: 65.38±4.01%; groups DP: 62.03±5.02%, respectively) ($P<0.05$), while the values among the four CUMS-treated groups were not significantly different ($P>0.05$). After rats underwent ECS treatment, the SPP values of the ECS treatment groups (group DE and group DPE) were significantly increased in comparison with those before ECS treatment ($P<0.05$), and exhibited significantly higher SPP compared with group D ($P<0.05$, respectively). However, the values of group DPE were still less than those of the rats in group DE or group C ($P<0.05$). Moreover, There was no significant difference between group D and group DP ($P=1.000$), as well as between group C and group DE ($P=0.935$) (Fig. 1).

2.2. Morris water maze

The swimming speeds of rats were similar between groups during all procedures (data not shown). Before administration of ECS, rats in the four CUMS-treated groups exhibited increased escape latencies (EL) and decreased space exploration time (SET) compared with those of rats in group C ($P<0.05$), while there were no difference in either EL or SET between the four CUMS-treated groups ($P>0.05$). After rats underwent ECS treatment, compared with group D, the ECS treatment groups (group DE and group DPE) showed significantly prolonged EL ($P<0.05$ and $P<0.05$, respectively) and shortened SET ($P<0.05$, respectively). Compared with group DE, the propofol combined with ECS treatment group (group DPE) demonstrated shorter EL and longer SET ($P<0.05$, respectively). There was no difference in either EL or SET between groups D and groups DP ($P=0.129$ and $P=0.307$, respectively) (Fig. 2(A) and (B)).

2.3. Expression levels of IL-1β and TNF-α in hippocampus

The mRNA expression of IL-1β and TNF-α were quantificationally analyzed by real time PCR. Compared to control group (group C), rats in the other four groups (group D, DP, DE, and DPE) displayed a significantly higher expression level of IL-1β ($P<0.05$) and TNF-α ($P<0.05$) in hippocampus. Compared to group D, ECS treatment groups (group DE and group DPE) markedly increased the expression level of IL-1β ($P<0.05$, respectively). The group DE displayed a significantly higher expression level of TNF-α compared to group D ($P<0.05$), but the expression level of TNF-α was no difference between group DPE and group D ($P=0.247$). Propofol efficiently attenuated the increased levels of IL-1β and TNF-α induced by ECS. Compared to group DE, propofol combined with ECS group (group DPE) displayed a significantly lower levels of IL-1β and TNF-α ($P<0.05$, respectively). There was no