Background: The mechanism underlying the protective effect of propofol on electroconvulsive therapy (ECT) induced learning and memory function impairment remains largely unknown. The present study aimed to explore the effect of propofol on the expression of N-methyl-D-aspartic acid (NMDA) receptor subunit NR2A/2B and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor subunit glutamate receptor 1 (GluR1) in the hippocampus of rat depression model undergoing electroconvulsive shock (ECS, analog of ECT in animals) in order to uncover the mechanism underlying the damaging effect of ECS on the learning and memory function, and the mechanism underlying the protective effect of propofol on the learning and memory function in ECS treatment.

Methods: This study was designed as a longitudinal study. Establishment of depression model was conducted with the application of chronic unpredictable mild stress (CUMS) in Sprague-Dawley rats. All 50 rats were randomly assigned into 5 groups (N=10): one control group (group C, 10 healthy rats) and four groups exposed to CUMS treatments for 28 days to construct the rat model of depression (group D, P, E, PE). Rats in group C were treated with intraperitoneal injection of 8 ml/kg normal saline and sham ECS (without the administration of current). Rats in group C were treated with intraperitoneal injection of 8 ml/kg normal saline and then sham ECS. Rats in group P received intraperitoneal injection of propofol 80 mg/kg and then sham ECS, while rats in group E were treated with intraperitoneal injection of normal saline 8 ml/kg and then ECS. Rats in group PE were treated with intraperitoneal injection of propofol 80 mg/kg and then ECS. The treatments were conducted once a day for 7 consecutive days. The sucrose preference test was performed to assess the depression behavior. Learning and memory function of rats was evaluated with Morris water maze. Western-blot assay was applied to determine the expression levels of NR2A/2B subunit and GluR1 subunit in the hippocampus.

Results: Sucrose preference percentage of the rats in group E and group PE increased compared with rats in group D. Compared with group D, rats in group E showed increased escape latency, decreased space exploration time, as well as increased expression of GluR1, and decreased NR2A/2B expression. Shorter escape latency, longer space exploration time, and higher level of NR2A/2B expression were showed in rats in group PE than in group E.

Conclusions: ECS treatment up-regulated the expression of GluR1 receptor while down-regulated the expression NR2A/2B receptors in rat hippocampus. Propofol mitigating learning and memory function impairment in depression model rats undergoing ECS may via alleviating the inhibitory effect induced by ECS on the NMDA receptor NR2A/2B subunit expression.

ABSTRACT

Protective Effect of Propofol on Electroconvulsive Shock Induced Learning and Memory Function Impairment Involves Up-Regulation of NMDA Receptor NR2A/2B Subunit in A Rat Model of Depression

Xue-Chao Hao, Xian-Lin Zhu, Ping Li, Jing Chen, Feng Lv, and Su Min
Major depressive disorder (MDD) is widely distributed in the population as the leading cause of disability predicted by the World Health Organization (1). Besides mental depression, the high level of disability in depressed patients is associated with cognitive deficits (2). Electroconvulsive therapy (ECT) is considered to be the most effective tool for treatment of depression, including severe and refractory forms (3). Nevertheless, ECT clinical application is limited for the concern about its adverse effect, the cognitive function impairment. The therapeutic antidepressant effect and cognitive impairment adverse effect is tightly connected, as shown by reports that while higher dose of stimulation is delivered for getting better antidepressant efficacy, greater cognitive impairment emerges as well (4).

Modified ECT (MECT) is performed with the using of general anesthetic and muscle relaxant to reduce the adverse effect of traditional ECT, including hemodynamic fluctuation and fracture. Although it remains controversial about the influence of anesthetics on the antidepressant efficacy of ECT (5-7), MECT performed under propofol anesthesia is found with attenuated cognitive deficit in both clinical and basic studies (8-10). In addition, the influence of propofol on the antidepressant effect and cognitive deficit are both performed in a manner of dosage dependent, shown as the results that with the higher dose of propofol, the better cognition outcomes, and the weaker antidepressant effect in rats (data not published). These discoveries demonstrated the close relation between the ECT antidepressant effect and its cognitive deficits.

The mechanisms underlying the antidepressant effect of ECT is still unclear. Studies have shown that the antidepressant effect of ECT is associated with the increase in synaptic transmission efficacy mediated by up-regulated transcription of glutamate receptor 1 (GluR1), increased synapses in hippocampus, hippocampal mossy fiber sprouting, and long-term potentiation (LTP)-like changes (11-13). However, these positive findings--potentiation in synaptic efficacy--could hardly explain the tightly accompanying negative effect, the cognitive deficit. In view of the tight relation between the antidepressant effect and the cognitive deficit in ECT, it’s not clear whether the mechanisms listed above for a certain issue would be an appropriate explanation for the two contradictory sides of the ECT. It is plausible that the ECT induced LTP-like changes would lead to a stage of LTP saturation which impairs cognition in return (14, 15). However, what is the mechanism underlying the LTP saturation, and what is the effect of propofol on LTP saturation is poorly understood.

Synaptic plasticity, including LTP, is the biological basis of learn and memory. α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor, especially GluR1, which is the most abundantly expressed subunit of AMPA receptor in hippocampus (16), is an important participant in the N-methyl-D-aspartic acid (NMDA) receptor-dependent synaptic plasticity (17-19). Calcium influx through activated NMDA receptor mediates the plasticity expression by activating protein kinase or protein phosphatase cascade (17). NR2A and NR2B are the predominant regulatory subunits for the regulation of NMDA receptor calcium permeability in the forebrain (20).

Therefore, based on these findings, and for those intriguing questions, the study was designed to explore in rats whether the electroconvulsive shock (ECS) and propofol would alter the expression of GluR1 and NR2A/2B subunits, thus influence the mechanism that the synaptic plasticity as well as the learning and memory function relying on.

MATERIALS AND METHODS

Animals
Healthy male adult Sprague-Dawley rats (weighting 200-250 g) were obtained from the Experimental Animal Center of Chongqing Medical University. All the rats were housed in standard laboratory room conditions (12/12-hour light/dark cycle, lights turned on at 08:00 a.m.) with a constant temperature of 22 ± 2°C and humidity of 62 ± 3%. The rats had free access to food and water except for the chronic unpredictable mild stress (CUMS) procedure. It took a week before experimental procedure for the rats to be adaptive to the surroundings. All the procedures were approved by the Ethical Committee of...
Chongqing Medical University, and were performed in accordance with the animal care guidelines of the National Institutes of Health and the standards of the ethical care and use of laboratory animals issued by the State Committee of Science and Technology of China.

**Experimental Groups and Treatments**

A total of 50 rats, 10 normal rats and 40 depression model rats were used with respect in the current study, and these rats were randomly assigned into 5 groups (N= 10): one control group (group C, 10 healthy rats) and four groups exposed to CUMS treatment for 28 days to construct the rat model of depression (group D, P, E, PE). After the establishment of depression model, the behavioral test was conducted to evaluate the depression and the learning and memory function in all rats. The sucrose preference test (SPT) and the open field test (OFT) were conducted to evaluate the severity of the depression on days 29 and 30, respectively. The Morris water maze (MWM) was conducted on days 31- 36. The ECS treatments were conducted once a day for seven consecutive days following different protocols for each group: C group received normal saline (8 ml/kg, intraperitoneal [i.p.]) and sham ECS; D group received normal saline (8 ml/kg, i.p.) and then sham ECS treatment; P group received propofol (80 mg/kg, i.p.) and sham ECS; E group received normal saline (8 ml/kg, i.p.) and then ECS treatment; Group PE received propofol (80 mg/kg, i.p.) and then received ECS treatment. After the treatments were accomplished, behavioral test was performed sequentially in all rats. Then, all rats were decapitated under anesthesia to prepare the hippocampus for biological assays. The experimental time line is shown in figure 1.

**Chronic Unpredictable Mile Stress Procedure**

The CUMS process was performed according to a previous study (5). Rats in group C were not exposed to stressor. All the rats in other groups were exposed to a stressor once daily. Briefly, one of the 10 stressors was delivered to CUMS-treatment rats once daily during 9:00 a.m. to 12:00, except for the 24-hour duration ones. All the 10 CUMS stressors were administered randomly to CUMS-treatment rats for 28 consecutive days, and none stressor would be administered in 2 contiguous days, in order to avoid the adaption of rats. The procedure consisted of the following stressors: 5 minutes of swimming in cold water at 4°C, pinching the tail for 1 minute, 24 hours of water deprivation, social crowding (25 rats per cage) with the cage being tilted to 30° from the horizontal for 24 hours, 24 hours of food deprivation, shaking for 20 minutes (1 shake/second), 24 hours of continuous lighting, caged in a soiled cage for 24 hours, hot stress in oven at 45°C for 5 minutes, and undesirable confinement for 2 hours. Each of these 10 stressors was administrated three times except for the ahead listed 2 stressors, which was delivered two times, respectively. Apart from satisfying the need of the study, all efforts were made to minimize animal suffering and to reduce the number of animals used.

**ECS Treatments**

After intraperitoneal treatment with propofol (8 ml/kg, 10 mg/ml) or normal saline (8 ml/kg), ECS was performed via bilateral ear clip electrodes using a Niviqure ECT system (Niviqure Meditech, Bangalore, India) with parameters as bidirectional square wave pulses, 0.8 A in amplitude, 1.5 ms in width, 125 Hz and 0.8 seconds in duration (5, 21). ECS was delivered once daily for 7 consecutive days. The saturation of blood oxygen (SpO₂) and the color of claws of each rat were monitored until the rat regains consciousness. Oxygen was administered to each rat during treatment through a mask. Rats with the value of SpO₂ being less than 95% were excluded. Rats in group C and group E were treated with normal saline, while rats in other groups were treated with propofol. Rats in group C, group D, and group P were treated with sham ECS which was performed with the
same procedure without the administration of current.

Sucrose Preference Test
Anhedonia is the core symptom of depression, which is defined as disability to experience pleasure from activities previously found enjoyable. Sucrose is a pleasure food for rats, and it has been used to evaluate the reward enjoyment of food. The reduction of sucrose preference is a core indication of depressive disorder in rats.

The SPT was carried out as described in previous report (5). After food and water deprivation for 23 hours, each rat was given free access to a bottle filled with water and a bottle filled with 1% sucrose solution for 30 minutes. Then the position of these two bottles was exchanged to avoid place preference, and carried on the SPT for 30 minutes. Each bottle was weighted before and after the 1 hour. The amount of consumption of water and sucrose solution were recorded and the sucrose preference percentage (SPP) was calculated using the following formula: SPP (%) = sucrose solution consumption/(water consumption + sucrose solution consumption) × 100%. The SPT was administered 3 times: before the CUMS exposure, 24 hours after the CUMS exposure and 24 hours after the whole course of ECS was completed.

Morris Water Maze
Each time after delivery of SPT, the Morris water maze was applied to evaluate the learning and memory function with the apparatus for data recording and analysis (ZH0065; Zhenghua Instruments, Chengdu, China). Each rats was submitted to 4 navigation trials semi-randomly from each 1 of 4 quadrants in a pool (150 cm in diameter, with water temperature at 23 ± 2°C) per day for 5 consecutive days. During the 5 days, the platform (10 cm in diameter) was placed in the center of the southeast quadrant and was submerged 1.5 cm below the surface of the water. Time length that each rat took for the location of the platform was recorded as escape latency (EL). There was a maximum of 60 seconds for each rat to locate the platform. If rat could not find the platform within 60 seconds, it would be guided toward the platform, and the EL would be recorded as 60 seconds. Each rat was allowed to stay on the platform for 10 seconds at the interval of trials. The mean EL of each rat performed in the last 3 days was recorded as the value of leaning. On the sixth day, the rat was submitted to a 60-second probe trial with the platform removal from the pool. The percentage of the time that each rat spent in the southeast quadrant was recorded as space exploration time (SET), which indicated the rat spatial memory retention.

Tissue Preparation and Western Blot
After the completion of behavior tests, 6 randomly assigned rats were decapitated with respect under the anesthesia administered with sodium pentobarbital (0.5%, 50 mg/kg, i.p.). Briefly, after decapitation, the brains were removed rapidly from the skull. The hippocampus was swiftly isolated on dry ice and stored at -80°C for further western blot assay.

The hippocampus specimens were homogenized in protein lysis buffer with complete protease inhibitors. After centrifugation with 12000 rpm at 4°C for 15 minutes, the supernate was collected. The bicinchoninic acid (BCA) assay kit (Pierce Biotechnology Inc, Rockford, IL, USA) was used to measure the total protein concentration. The samples were boiled and then separated through electrophoresis with β-actin as internal standard. After electrophoresis, the proteins were transferred to polyvinylidene fluoride membranes (Millipore Inc, Darmstadt, Germany). The membranes were blocked with 5% skim milk overnight in Tris-buffered saline (TBS) at 4°C. The blots were then incubated with mouse anti-GluR1 monoclonal antibody (Santa Cruz Inc, Dallas, TX, USA), rabbit anti-NR2A&B polyclonal antibody (Millipore Inc, Darmstadt, Germany), and rabbit anti-β-actin polyclonal antibody (Santa Cruz Inc, Dallas, TX, USA) for 2 hours at room temperature. After washed with TBS containing 0.3% Tween-20, the membranes were incubated with a mixture of horse radish peroxidase (HRP)-conjugated anti-mouse IgG and HRP-conjugated anti-rabbit IgG (Zhongshan-Golden Bridge, Beijing, China) for 1 hour at room temperature. After the membrane rinsed with TBS, the immunoreactive protein bands were visualized on the films by ECL reagent (Pierce Biotechnology Inc, Rock-
ford, IL, USA). Densitometry quantification of the band intensities was performed with the application of Image-ProPlus 6.0 software (Media Cybernetics Inc, Silver Spring, MD, USA).

**Statistical Analysis**

Statistical analysis was performed with the application of SPSS version 17.0 (SPSS Inc, Chicago, IL, USA). All results values were expressed as means ± standard deviation (SD). The behavioral data values of rats in group C were applied mainly as the standard, and based on the absence of pretreatment difference among the randomly assigned groups exposed to CUMS, the statistical analysis for pretreatment or posttreatment comparisons were conducted separately. The pretreatment or posttreatment behavioral data and the values of receptor expression were subjected to one-way analysis of variance for determination of statistical significance. Student-Newman-Keuls q test was applied to detect statistical significant difference between groups. Difference was considered as statistically significant when \( P < 0.05 \).

**RESULTS**

**Sucrose Preference Test**

After treated with CUMS for modeling, the SPPs of the rats exposed to CUMS decreased with significant difference compared with that before CUMS (57.9% vs. 78.4%, \( P < 0.05 \)), and the SPPs of rats in groups D, P, E, and PE decreased compared with group C (\( P < 0.05 \)), and no difference was found among groups D, P, E, and PE (\( P > 0.05 \). After the experimental treatment, statistically significant increased SPPs in rats of group E and group PE were found compared with those in group D and group P (\( P < 0.05 \)). Results of SPT were presented in figure 2A.

**Morris Water Maze**

After treated with CUMS for modeling, the EL increased and SET decreased in groups D, P, E, and PE compared with group C (\( P < 0.05 \), and no difference was found among groups D, P, E, and PE (\( P > 0.05 \). After the experimental treatment, statistically significant increased SPPs in rats of group E and group PE were found compared with those in group D and group P (\( P < 0.05 \). Results of SET and EL were presented in figure 2B and 2C.

**Western-Blot Assay of NR2A/2B and GluR1**

Compared with group C, the expression levels...
of NR2A/2B and GluR1 decreased in group D (P < 0.05). Compared with group D, the expression of NR2A/2B decreased further in group E (P < 0.05). The expression level of NR2A/2B was higher in group PE than in group E (P < 0.05). The expression levels of NR2A/2B and GluR1 were presented in figure 3 and figure 4.

**DISCUSSION**

The present study demonstrated that ECS produced both antidepressant efficacy and learning and memory impairment in depressed rats with up-regulating GluR1 expression, but down-regulating NR2A/2B expression in the hippocampus. Propofol attenuated the learning and memory impairment caused by ECS, and up-regulated the expression of NR2A/2B. In addition, the dose of anesthetic propofol used in the present study showed no significant influence on ECS antidepressant efficacy or GluR1 expression.

After exposed to CUMS, rats manifested significant decline in SPP compared with rats in control group. Furthermore, as described by previous studies, the declined performance in SPP of these rats was reversed by a week of ECS, but not by the sham ECS (5, 22). These outcomes indicated the successful establishment of depressive behavior model in rats. The rats exposed to CUMS demonstrated learning and memory function deterioration shown by their prolonged EL and shortened SET in MWM test. This cogni-
tive function deterioration was not remitted along with the alleviation of depressive behavior after ECS treatment, on the contrary, even worsened by ECS.

The glutamatergic excitatory synaptic transmission is predominantly mediated by NMDA receptor and AMPA receptor. Numbers of studies have been contributed to uncover the latent role of glutamatergic system in depression, especially the NMDA receptor and AMPA receptor (23, 24). AMPA receptor possesses high Na⁺ permeability, mediates the postsynaptic depolarization, and accounts more for the glutamate synaptic transmission than NMDA receptor (25). Although NMDA receptor contributes less to glutamate synaptic transmission, due to its unique properties that voltage-dependent magnesium blockade and calcium permeability, it plays an more outstanding role in detecting the pre- and post-synaptic activation and calcium-dependent synaptic plasticity (25, 26). The NMDA receptor mediated GluR1 expression increase is one form of LTP.

In this study, the decreased expression of GluR1 which indicated the deficiency in glutamatergic system was postulated to be one of the possible therapeutic targets of depressive behavior. The up-regulatory effect of ECS on the expression of the GluR1 which is consistent with previously reported LTP-like changes induced by ECS, maybe involved in ECS therapeutic mechanism.

Furthermore, the down-regulation in GluR1 and NR2A/2B expression could at least partly explain the declined learning and memory function in depressed rats exposed to CUMS. It is well established that neuron excitability, postsynaptic depolarization and calcium influx play a key role in the induction of synaptic plasticity, and the reduction in neuron excitability can impair learning (27, 28). The GluR1 containing AMPA receptor mediates the rapid ion influx, hence the post synaptic depolarization. The decreased GluR1 and NR2A/2B may lead to lower neuronal excitability and calcium influx, thus to the declined learning and memory function in depressed rats.

The ECS lead to two seemed opposite effect in the glutamatergic system. Accompanied with elevated GluR1 expression and remission of depressive behavior, in ECS-treated rats, reduction in NR2A/2B and deterioration in learning and memory function were demonstrated. The LTP-induction impairment was proposed to be the explanation of ECS induced cognitive deficit (13). Furthermore, Harney et al. (29) found that the intracellular free calcium concentration would influence the direction and extent of synaptic plasticity. Given the great importance of the NR2A/2B-mediated calcium influx in synaptic plasticity, the present study showed the important role of the reduction of NR2A/2B expression in cognitive deficit both for depressed rats and ECS-treated rats. It could be postulated that contradictory influence of ECS to GluR1 and NR2A/2B expression in hippocampus may be the cause of paradoxical effect on depressive and cognitive behavior.

Recent studies unfolded that some changes taking place in the synaptic plasticity process would in return influence the ability of the synapses for subsequent synaptic plasticity, termed metaplasticity. Thus, metaplasticity is the plasticity of synaptic plasticity (27, 30). It is postulated that foregoing LTP in synapses would elevate the threshold for subsequent LTP, and inhibit the LTP induction, which otherwise facilitates the LTD induction. Previous studies have demonstrated the metaplasticity-like changes in ECS that the ECS-mediated LTP-like changes in hippocampus was accompanied with impairment in LTP induction (13, 14), which was assumed to be the 'LTP saturation'. We speculated that the assumed 'LTP saturation' maybe the presentation of metaplasticity changes in hippocampus synapses. An emerging role of metaplasticity is being realized in behavior and disease (27). And a growing body of studies has been contributing to the elucidation of the mechanisms underpinning metaplasticity as well, emphasizing the role of AMPA receptor and NMDA receptor (31-34). In addition, in view of the intimate relation between LTP-like changes and LTP-induction impairment, as well as the antidepressant efficacy and cognitive deficit, metaplasticity may be the mechanism underlying the contradictory effect of ECS on depressive and cognitive behavior. But for the limitation from the methodology, we did not confirm the role of metaplasticity in the ECS effect on the depression.
Propofol Up-Regulates NMDA Receptor NR2A/2B Subunit

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Propofol up-regulates NMDA receptor NR2A/2B subunit and the cognitive function with the application of electrophysiology assay, as well as the effect of propofol on ECS.

In this present study, it was demonstrated that propofol attenuated the cognition impairment caused by ECS, as well as restoring the down-regulated NR2A/2B expression. Propofol showed no significant effect on both GluR1 expression and antidepressant efficacy of ECS. Our previous study also found that LTP induction in hippocampal slices from control rats has no difference with that from rats treated with ECS under propofol anesthesia (35). Due to its inhibitory effect on neuron activity, propofol could impair the LTP induction in mouse hippocampus (36). Nevertheless, in the context of ECS, the inhibitory effect of propofol could inhibit the LTP-like synaptic plasticity caused by ECS, and then the metaplastic change following synaptic plasticity, consistent with the demonstration that antagonizing neuron activity in visual cortex by dark rearing could inhibit the metaplastic changes including LTP attenuation caused by light rearing (37). This may partly explained the effect of propofol on cognitive behavior and NR2A/2B expression.

Another notable phenomenon is that the proposed inhibitor of propofol for neuron activity did not significantly reduce the GluR1 expression. In addition, reports from Hanines and Wang revealed that both the low and the anesthetic doses of propofol could increase the phosphorylation in serine 845 of GluR1 (38, 39). This indicated that besides its inhibitory effect on synaptic activity, propofol per se possesses some more effect on ECS that need to be explored.

Given the important role of NMDA receptor in the regulation of Ca\(^{2+}\) influx, the disruption in homostasis of intracellular Ca\(^{2+}\) may be a critical component in the mechanism of the ECS induced learning and memory function impairment. Recent studies showed that general anesthetic influence the intracellular Ca\(^{2+}\) via modulating the Ca\(^{2+}\) release channel, such as inositol trisphosphate receptor (40, 41). The regulatory effect of propofol on the homostasis of intracellular Ca\(^{2+}\) may be another target for study of its protective effect in the context of ECS. In addition, metabotropic glutamate receptors have been shown to be associated with the depression and cognitive deficits (42, 43), and roles of these receptors in the protective effect of propofol would be further studied.

In conclusion, the present study demonstrated that the contradictory effect of ECS on depressive behavior versus cognitive function may be caused by its opposite effect on glutamate receptor subunits expression, shown as up-regulating the GluR1 expression versus down-regulating the NR2A/2B expression. This protective effect of propofol may be performed via reversing the reduction in NR2A/2B expression caused by ECS. Furthermore, metaplasticity may open a new potential area for the investigation of the efficacy of ECS and pharmacological attenuation of ECS-induced cognitive deficits, and ECS may provide a new disease model for the exploration of metaplasticity in vivo.

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