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ORIGINAL ARTICLE

Propofol protects against impairment of learning-memory and imbalance of hippocampal Glu/GABA induced by electroconvulsive shock in depressed rats

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Abstract
Purpose General anesthetics are believed to induce amnesia. However, propofol can ameliorate cognitive deficits induced by electroconvulsive therapy (ECT), a treatment for mental disorders. This study aimed at investigating the possible molecular mechanism as well as the effects of propofol on learning-memory impairment in depressed rats induced by ECS (electroconvulsive shock, the analog of ECT to animals).
Methods Rats were treated with ECS (or sham ECS) pretreated with intraperitoneal injection of propofol (100 mg/kg) (or normal saline, 0.01 l/kg) after being treated with chronic unpredictable mild stresses to reproduce an animal model of depression. Sucrose preference test, open field test, and Morris water maze were used to assess behavioral changes. Hippocampal glutamate (Glu) and γ-aminobutyric acid (GABA) levels were measured with liquid chromatography, and glutamic acid decarboxylase 65 (GAD65) was assayed immunohistochemically. Additionally, rats undergoing ECS that were pretreated with pentobarbital sodium (45 mg/kg) were included for behavioral tests and electroencephalogram recording for comparison with rats undergoing ECS that were pretreated with propofol or normal saline.
Results ECS rats pretreated with propofol or pentobarbital sodium exhibited similar decreased seizure durations as compared with ECS rats pretreated with normal saline. ECS pretreated with normal saline aggravated learning-memory deficits whereas ECS pretreated with propofol or pentobarbital sodium did not. Rats undergoing ECS pretreated with propofol showed better memory than those undergoing ECS after pretreatment with pentobarbital sodium. ECS pretreated with normal saline downregulated the ratio of Glu/GABA and upregulated GAD65 expression; all these molecular changes were nearly normalized to the level of control group by ECS pretreated with propofol. There were no significant differences of depressive behaviors between groups treated with ECS.
Conclusions The data suggest that propofol alleviated ECS-induced learning-memory impairment without interfering with the antidepressant efficacy of ECS, possibly by inhibiting excessive expression of GAD65 and maintaining the balance between glutamatergic and GABAergic amino acids neurotransmitters in the hippocampus.

Keywords Propofol · Electroconvulsive therapy · Memory · Glutamate · GABA

Introduction

Anesthetic agents have traditionally been assumed to induce amnesia ever since the amnesic effect of nitrous oxide was reported in 1799 [1, 2]. Although anesthesia-induced intraoperative amnesia benefits patients by preventing awareness, anesthetics may also impair cognition, especially learning and memory, causing postoperative cognitive dysfunction (POCD).

Electroconvulsive therapy (ECT) is a highly effective psychiatric therapy frequently used for severe mental disorders, including major depression, mania, and schizophrenia. One of the major adverse effects of ECT is amnesia, which enables electroconvulsive shock (ECS, the analog of ECT to animals) to be a classical method for reproducing animal models of amnesia in research.

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Nowadays, modified ECT (MECT) under general anesthesia is widely used to prevent some of the traditional ECT complications, such as fracture, asphyxia, or cardiovascular instabilities [3]. Interestingly, some general anesthetics [such as propofol (2,6-diisopropylphenol) and ketamine] used in MECT have been found to ameliorate the cognitive deficits induced by ECT in clinical studies [4, 5]. A paradox is that either general anesthetics or ECT can induce amnesia, but the combination of the two in MECT seems to result in relatively better cognition and memory, the mechanism of which remains unclear.

The regulation of learning and memory requires cooperation between excitatory and inhibitory neural systems, the representatives of which are the glutamatergic and γ-aminobutyric acid GABAergic systems, respectively. Besides other aspects including the cyclooxygenase pathway, cholinergic neurotransmission, and nitric oxide pathway, the mechanism of ECT amnesic effects is found to be mainly related to the glutamate-dependent system [6]. Propofol induces anesthetic action predominantly by enhancing the activities of the GABAergic system and related inhibitory neurotransmission. Our previous studies found that propofol exerts its anti-amnesia effects in MECT by regulating glutamate (Glu) and *N*-methyl-D-aspartate receptor 2B (NR2B) in the hippocampus [7]. Whether GABA is involved in the effects of propofol in MECT, and the possible relationship between Glu and GABA therein, are unknown. This study mainly aimed at investigating the excitatory and inhibitory neurotransmitter roles in the effects of propofol on learning and memory dysfunction induced by ECT in an animal model of depression.

Materials and methods

Animals

Ninety healthy male Sprague–Dawley rats (weighing 200–250 g) were obtained from the Laboratory Animal Centre of Chongqing Medical University, housed in standardized laboratory conditions, and acclimatized for 1 week before further experiments. The experimental protocols were approved by the Ethical Committee of Chongqing Medical University and carried out according to international guidelines on the ethical use of laboratory animals.

Drugs and treatment schedule

Part 1

The rats in part 1 were randomly assigned into six groups ($n = 12$ each). Group C was the control group of healthy rats that were not treated. Rats in group D were treated with the chronic unpredictable mild stress (CUMS) procedure and then with sham ECS pretreated with normal saline (0.01 l/kg, i.p.); rats in group P were treated with CUMS and then with sham ECS pretreated with propofol (0.01 l/kg, concentration 0.01 kg/l, equals 100 mg/kg, i.p.; No. Fx061, AstraZeneca, Italy); rats in group E were treated with CUMS and then with ECS pretreated with normal saline (0.01 l/kg, i.p.); rats in group M were treated with CUMS and then with ECS pretreated with propofol (100 mg/kg, i.p.); and rats in group MB were treated with CUMS and then with ECS pretreated with pentobarbital sodium (2%, 45 mg/kg, i.p., No. 060222; Beijing Chem, China). The order of all the treatments (or sham treatments) and tests was as follows: (1) sucrose preference test (SPT) and open field test (OFT); (2) CUMS (group C not being administered); (3) SPT and OFT; (4) ECS (with propofol, normal saline, or pentobarbital sodium) or sham ECS (with propofol or normal saline) according to the group assignment; (5) SPT, OFT, and Morris water maze task; (6) high performance liquid chromatography analysis or immunohistochemistry analysis (except for group MB). The interval between each two behavioral tests (or CUMS, or ECS) was 24 h, respectively; 24 h after the Morris water maze was performed, the hippocampi were prepared according to the requirement for further molecular assays.

Part 2

The rats in part 2 were randomly assigned into three groups ($n = 6$ each): groups E2, M2, and MB2. The rats in groups E2, M2, and MB2 were treated with ECS with the same procedures as groups E, M, and MB in part 1, respectively. An electroencephalogram (EEG) was recorded before, during, and after the administration of ECS.

Chronic unpredictable mild stress procedure

For 3 weeks, rats in part 1 received no CUMS (in group C) or daily stressor stimuli (in the other five CUMS-treated groups) as described before [8]. Briefly, one of the stressor stimuli was randomly applied to the rats in CUMS-treated groups once daily: (1) swimming in cold water at 8–10°C for 5 min; (2) tail pinching for 1 min; (3) food deprivation for 24 h; (4) water deprivation for 24 h; (5) social crowding (24 rats per cage) with cage tilted 30° from horizontal for 24 h; (6) shaking for 20 min (1 shake/s); (7) 24 h continuous lighting; (8) housing in an isolated cage for 24 h; (9) hot stress in oven at 42°C for 5 min; (10) undesirable confinement for 2 h.

Electroconvulsive shock treatments

After being treated with CUMS, rats in part 1 were administered ECS (pretreated with normal saline, pentobarbital

sodium, or propofol 10 min before ECS administration) or sham ECS (pretreated with normal saline or propofol 10 min before ECS administration) every other day for six times according to the group assignment. ECS was conducted using a pulse generator (DX-II; Shanghai Institute of Health Sciences, China; 50 mA, 1 s, 50 Hz, via electrodes at the incidence point of temporal lobe on both sides), and sham ECS was handled identically as ECS without current. The saturation of blood oxygen was monitored with a pulse oximeter (PM-9000; Mindray Medical International Limited, China) to exclude hypoxic rats. ECS in part 2 were performed under EEG recording to evaluate the intensity and duration of ECS seizures.

Sucrose preference test

After a 23-h period of water and food deprivation, rats in part 1 were given free access to two pre-weighed bottles each with 1% (w/v) sucrose solution or water, respectively, for 1 h. Then, both bottles were weighed to measure the consumption of water or sucrose solution. The percentage of sucrose solution in the total liquid consumed indicates sucrose preference, representing a parameter of hedonic behavior, the loss of which indicates depressive disorder [9].

Open field test

The apparatus consisted of an 80-cm-square black wooden box with 40-cm-high boundary walls, divided into 16 equal squares of 20 × 20 cm^2 by lines marked on the floor. The field was lighted with a 40 W bulb fixed 50 cm above it. Each rat in part 1 was placed at the center of the field and its activity was observed for 5 min. Parameters assessed were horizontal ambulation (the number of squares crossed, indicating general locomotor) and the times of rearing (when a rat stood completely erect on its hind legs, indicating exploratory behavior) [10].

Morris water maze

Each rat in part 1 was submitted to four consecutive trials from each one of four quadrants in a pool (150 cm in diameter, 25 ± 1°C) per day for 5 days and trained to find a hidden circular platform (11 cm in diameter, 2 cm beneath the water in the southwestern quadrant). The rat was allowed a maximum of 60 s to reach the platform, and if it could not find the platform within 60 s, it was guided toward the platform. The rat then was left there for another 10 s. Times to reach the platform were recorded and expressed as the means of the data during the last 3 days of training (i.e., evasive latency, indicating learning abilities). On the sixth day, the rats were given a probe trial for 60 s in the absence of the platform. The percent dwell time spent in the southwestern quadrant indicated the rats' spatial memory retention [11].

High performance liquid chromatography analysis

At 24 h after the Morris water maze task was performed, hippocampi were obtained from half the rats in every group (in part 1 except for group MB). The levels of Glu and GABA were determined with high performance liquid chromatography (HPLC) as described previously [12]. A model LC-2010A liquid chromatograph (Shimadzu Seisakusho, Kyoto, Japan) and an ODS column (Nagel ODS-C8; 4.6 mm × 150, 5 μm) were used. The wavelength for detection was set at 360 nm. The contents of Glu and GABA were quantified by comparison with the standard curves for each amino acid. The formula for calculating Glu and GABA content in the hippocampus is as follows: Glu or GABA (μg/g) = [concentration of sample (μg/μl) × volume of sample (μl)]/weight of hippocampus (g).

Immunohistochemistry

At 24 h after the Morris water maze task was performed, the other half number of rats in every group (in part 1 except for group MB) were each deeply anesthetized with sodium pentobarbitone (3%, 45 mg/kg, i.p.) and perfused through the ascending aorta with 4% paraformaldehyde (PFA). The brains were postfixed in 4% PFA and cut into sections (5 μm thick). Sections were incubated with rabbit anti-GAD65 polyclonal antibody (Boster, Wuhan, China), then incubated with the secondary antibodies labeled with biotin, added with streptavidin–peroxidase solution and colored with diaminobenzidine. The expression (optical density) of glutamic acid decarboxylase 65 (GAD65) in CA1 and CA3 of the hippocampus was measured with the Image-Pro Plus 6.0 (Media Cybernetics, USA) analysis system.

EEG recording

EEG electrodes were implanted using a stereotaxic instrument under anesthesia with urethane (10%, 1,000 mg/kg) in every rat in part 2. Recording electrodes were implanted in the skull 1 mm posterior to the bregma and 3 mm to the left and right of the midline, respectively. The reference electrode was implanted 2 mm anterior to the bregma. The electrode recording points were located external to the dura mater. The electrodes were fixed in position with dental cement. The rats were then housed singly for 1 week before being treated with ECS. EEG was recorded for 20 s before and immediately after ECS stimulation had been administered for 2 min. Postictal suppression index (PSI, calculated

as the 3-s mean amplitude beginning 0.5 s after seizure termination, divided by the mean 3-s peak amplitude obtained during the seizure, and expressed as percent suppression, as described previously [13]) was used to measure seizure intensity. EEG seizure duration was also measured.

Statistics

All data were expressed as mean ± SEM. Statistical analyses used the SPSS statistical package, version 10.0 (SPSS, Chicago, IL, USA). Statistical significance was determined with repeated-measures analysis of variance (ANOVA) (repeatedly measured behavioral data) and ANOVA for the rest of the data. $P < 0.05$ was considered significant.

Results

Sucrose preference test and open field test

There was no significant difference among groups in the sucrose preference percentage (SPP) initially ($P > 0.05$). After administration of the CUMS procedure, rats in the five CUMS-treated groups exhibited decreased SPP in comparison with either their values at baseline ($P < 0.05$) or those of rats in group C ($P < 0.05$). The values among the five CUMS-treated groups were not significantly different ($P > 0.05$). After rats underwent ECS (or sham ECS), the values of groups E, M, and MB increased significantly from those before ECS ($P < 0.05$), being significantly greater than those of either group D or group P ($P < 0.05$), although they were still less than those of the rats in group C and their base values ($P < 0.05$). Moreover, the differences between the values of groups E, M, and MB were not significant ($P > 0.05$), and the differences between the values of groups D and P also were not significant ($P > 0.05$) (Fig. 1). Changes of either ambulation or rearing times in OFT were the same as those in SPT (Fig. 2a, b).

Morris water maze

There were no significant differences of swimming speed between rats during all procedures ($P > 0.05$). After administration of ECS or sham ECS, evasive latencies (EL) of the five CUMS-treated groups increased and the percent dwell time (PDT) decreased, compared with those in group C ($P < 0.05$); the EL of group E was longer while its PDT was less, in comparison with those of each of the other four CUMS-treated groups (D, P, M, or MB; $P < 0.05$); there were no differences of either EL or PDT among the other four groups (M, D, P, and MB) ($P > 0.05$), except that the PDT of group MB was less as compared with group M ($P < 0.05$) (Fig. 3a, b).

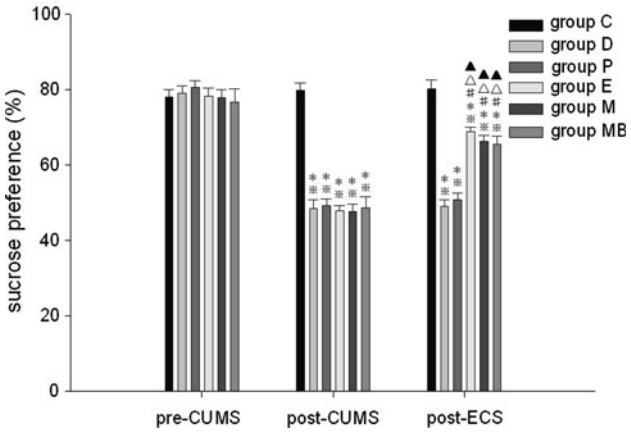

Fig. 1 Propofol did not affect the effectiveness of electroconvulsive shock (ECS) to reverse the decrease of sucrose preference of depressed rats. Data of sucrose preference percentage (%) are presented as mean ± SEM: $^{※}P < 0.05$ compared with pre-chronic unpredictable mild stress (CUMS); $^{*}P < 0.05$ compared with group C; $^{\#}P < 0.05$ compared with group D; $^{\Delta}P < 0.05$ compared with group P; $^{▲}P < 0.05$ compared with post-CUMS. Treatments: CUMS to groups D, P, E, M, and MB; sham ECS with normal saline to group D; sham ECS with propofol to group P; ECS with normal saline to group E; ECS with propofol to group M; ECS with pentobarbital sodium to group MB. $n = 12$ in each group

High performance liquid chromatography analysis

As compared with group C, the content of Glu in group D increased, its GABA content decreased, and the ratio of Glu/GABA in either group D or group P increased ($P < 0.05$). The content of Glu in group E decreased, its GABA content increased, and the ratio of Glu/GABA decreased ($P < 0.05$). The content of Glu, GABA, and ratio of Glu/GABA were not significantly different in group M ($P > 0.05$). Compared with either group D or group P, the content of Glu in group E decreased, the content of GABA increased, and the ratio of Glu/GABA decreased ($P < 0.05$). Compared with group D, the content of Glu in group M decreased, the content of GABA increased, and the ratio of Glu/GABA decreased ($P < 0.05$). Compared with group P, the ratio of Glu/GABA in group M decreased ($P < 0.05$). Compared with group E, the content of Glu in group M increased, the content of GABA decreased, and the ratio of Glu/GABA increased ($P < 0.05$). There was no significant difference of Glu, GABA, or the Glu/GABA ratio between groups D and P ($P > 0.05$) (Fig. 4a–c).

Immunohistochemistry

Compared with group C, decrease in intensity of GAD65 immunoreactive puncta (optical density) was observed in both CA1 and CA3 regions of hippocampus in both group

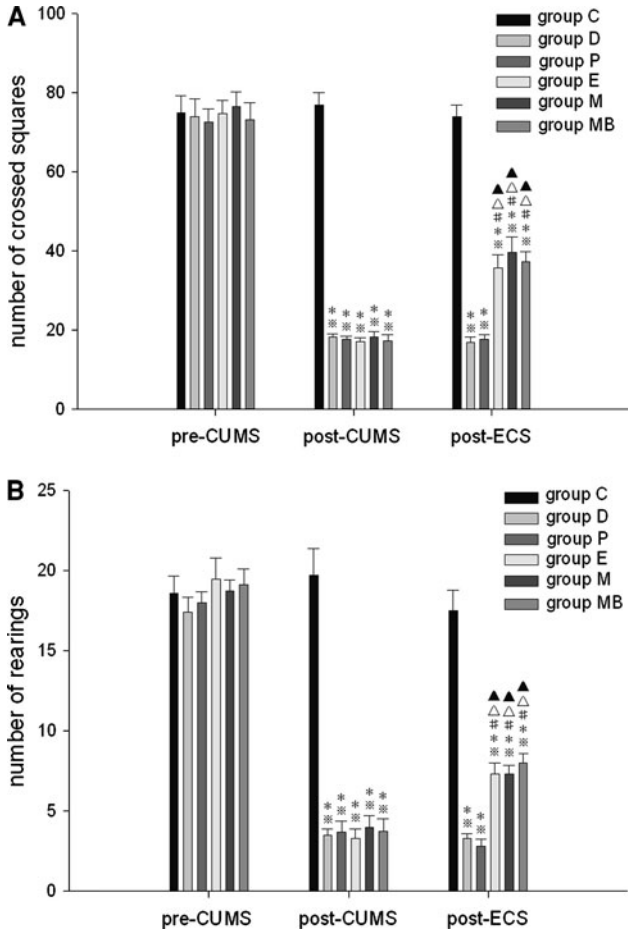

Fig. 2 Propofol did not affect the effectiveness of electroconvulsive shock (ECS) to reverse the decrease of open-field-test parameters of depressed rats. **a** Ambulation scores (number of crossed squares). **b** Rearing scores (number of rearing activities). Data of these scores are presented as mean ± SEM: $^{※}P < 0.05$ compared with pre-chronic unpredictable mild stress (CUMS); $^{*}P < 0.05$ compared with group C; $^{\#}P < 0.05$ compared with group D; $^{\Delta}P < 0.05$ compared with group P; $^{\blacktriangle}P < 0.05$ compared with post-CUMS. Treatments: CUMS to groups D, P, E, M, and MB; sham ECS with normal saline to group D; sham ECS with propofol to group P; ECS with normal saline to group E; ECS with propofol to group M; ECS with pentobarbital sodium to group MB. $n = 12$ in each group

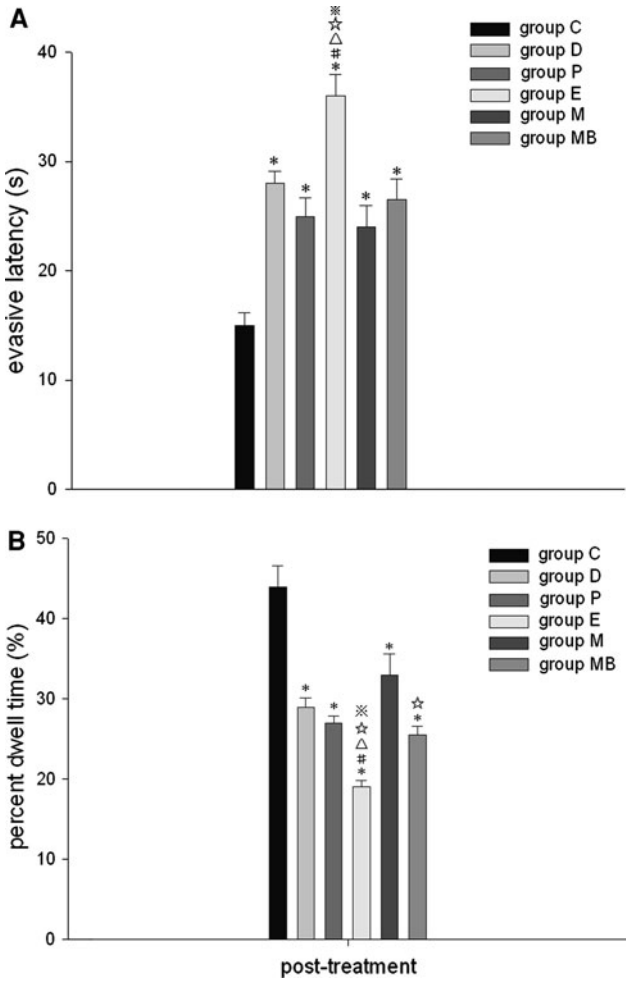

Fig. 3 Propofol reversed the increase of evasive latency and decrease of percent dwell time induced by electroconvulsive shock (ECS) in depressed rats in the Morris water maze task. **a** Evasive latency (s, time to find the platform, indicating learning ability). **b** Percent dwell time (%, time percentage spent in the platform quadrant, indicating memory). Data are presented as mean ± SEM: $^{*}P < 0.05$ compared with group C; $^{\#}P < 0.05$ compared with group D; $^{\Delta}P < 0.05$ compared with group P; $^{☆}P < 0.05$ compared with group M; $^{※}P < 0.05$ compared with group MB. Treatments: chronic unpredictable mild stress (CUMS) to groups D, P, E, M, and MB; sham ECS with normal saline to group D; sham ECS with propofol to group P; ECS with normal saline to group E; ECS with propofol to group M; ECS with pentobarbital sodium to group MB. $n = 12$ in each group

D and group P, and an increase was seen in group E ($P < 0.05$). Compared with either group D or group P, the intensity of both group E and group M increased ($P < 0.05$). The intensity of group M decreased in comparison with group E ($P < 0.05$). There was no significant difference of optical density between groups D and P in either CA1 or CA3 regions ($P > 0.05$) (Fig. 5).

Seizure intensity and duration

There was no significant difference of PSI among groups E2, M2, and MB2 ($P > 0.05$) (Fig. 6a). Compared with group E2, the seizure duration of either group M2 or MB2 significantly decreased ($P < 0.01$, respectively); there was no significant difference between the latter two groups ($P > 0.05$) (Fig. 6b).

Discussion

The core findings of this study are that propofol attenuated the impairment of learning and memory, inhibited excessive expression of GAD65, and reversed the imbalance of the ratio of glutamate and GABA in the hippocampus

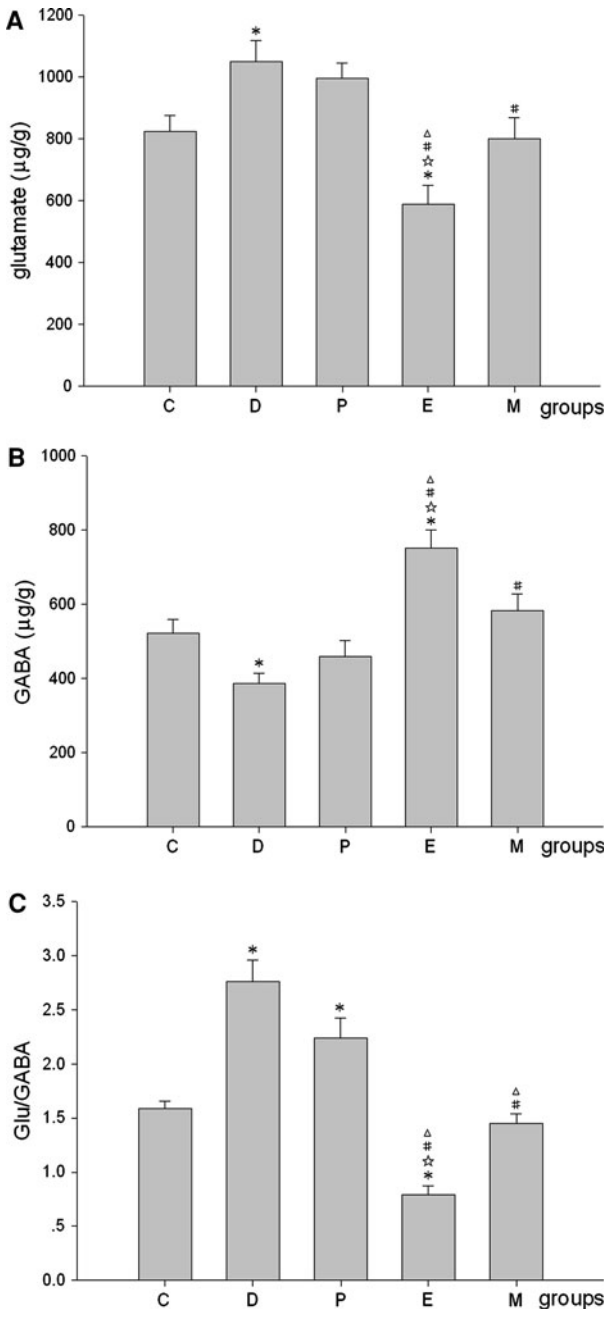

Fig. 4 Propofol reversed the changes of hippocampal glutamate, γ-aminobutyric acid (GABA) level, and their ratio induced by electroconvulsive shock (ECS) in depressed rats. **a** Propofol reversed the decrease of hippocampal glutamate level (Glu, μg/g) induced by ECS in depressed rats. **b** Propofol reversed the increase of hippocampal GABA level (μg/g) induced by ECS in depressed rats. **c** Propofol reversed the decrease of hippocampal glutamate and GABA ratio induced by ECS in depressed rats. Data are presented as mean ± SEM: $^{*}P < 0.05$ compared with group C; $^{\#}P < 0.05$ compared with group D; $^{\Delta}P < 0.05$ compared with group P; $^{\star}P < 0.05$ compared with group M. Treatments: chronic unpredictable mild stress (CUMS) to groups D, P, E, and M; sham ECS with normal saline to group D; sham ECS with propofol to group P; ECS with normal saline to group E; ECS with propofol to group M. $n = 6$ in each group

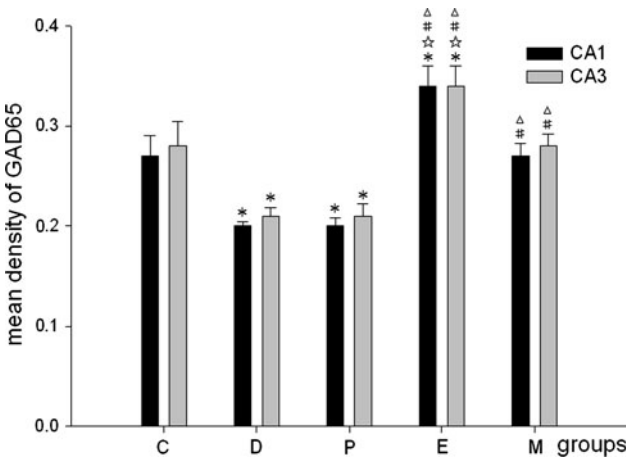

Fig. 5 Propofol reversed the increase of expression of hippocampal glutamic acid decarboxylase 65 (GAD65) induced by electroconvulsive shock (ECS) in depressed rats. Data are presented as mean ± SEM: $^{*}P < 0.05$ compared with group C; $^{\#}P < 0.05$ compared with group D; $^{\Delta}P < 0.05$ compared with group P, $^{\star}P < 0.05$ compared with group M. Treatments: chronic unpredictable mild stress (CUMS) to groups D, P, E, and M; sham ECS with normal saline to group D; sham ECS with propofol to group P; ECS with normal saline to group E; ECS with propofol to group M. $n = 6$ in each group

induced by ECS in depressed rats. Propofol alone did not aggravate the learning and memory deficits in depressed rats. Also, propofol did not compromise the antidepressant effectiveness of ECS.

Chronic unpredictable mild stress is one of the generally accepted methods to reproduce the animal model of depression. In this study, the behavioral data of CUMS-treated rats significantly decreased as compared with the control group, indicating the successfully induced depressive behavior of these animals.

Propofol (100 or 150 mg/kg) was found to induce amnesia in the rodent [14], and a nonsedative dose of propofol (9 mg/kg) also impaired memory in rats [15]. However, Lee et al. [16] reported that spatial memory was unimpaired in aged rats after anesthesia with propofol. Our results also indicate that propofol is not always negative to cognition and may even be beneficial for learning and memory in some pathophysiological conditions or specific therapeutic procedures.

Propofol was found to be associated with an earlier return of cognitive function or reduced cognitive impairment after ECT, as compared with methohexital and thiopental [5, 17]. However, Avramov et al. [18] discovered that the rates of cognitive recovery were similar when propofol was compared with methohexital and etomidate, which indicated controversy as to the possible benefits of propofol. Based on etomidate anesthesia in ECT, it was found that additional propofol (0.5 mg/kg) prevented the cognitive decrements induced by ECT [19]. The present study confirmed and emphasized that propofol itself had a

definite anti-amnesia effect when used as the sole anesthetic in ECS. Both the learning and memory deficits induced by ECS were significantly alleviated in the propofol-administered group (group M) compared with the group administered normal saline (group E), even to a level that was not significantly different from the sham ECS-treated depressed groups administered normal saline or propofol (groups D and P). These results indicated that propofol could totally antagonize the learning and memory impairment caused by ECT. Moreover, there were not any significant differences of learning and memory between group D and group P, indicating that repeated administration of propofol (six times, every other day) did not induce or aggravate learning and memory impairment.

The induced seizures are responsible for both the therapeutic effectiveness and the adverse effects of ECS. Seizure quality is related to its intensity and duration, for which the currently accepted method of measurement is the EEG recording [20]. In the present study, based on the EEG data, we found that without affecting ECS seizure intensity, both propofol and another anesthetic, pentobarbital sodium, could reduce the seizure duration of ECS to a similar extent, which may contribute to the attenuation by both drugs of ECS-induced learning and memory impairment. However, interestingly, compared with pentobarbital sodium, propofol was found to exert better protection against memory impairment induced by ECS, indicating that the effect of propofol may not only be related to the general anticonvulsive property as an anesthetic, but also results from its more specific intrinsic effects.

The hippocampus is one of the essential brain regions activated in learning and memory. A certain balance of neuronal transmission between the major excitatory neurotransmitter glutamate and the inhibitory substance GABA is required to maintain normal functions of brain, including learning and memory [21]. The decrease of glutamate or increase of GABA (i.e., reduction of the ratio of Glu/GABA) can lead to impairment of learning and memory [22]. The sole path to produce GABA in the brain is with Glu as the substrate and glutamic acid decarboxylase (GAD) as the catalyst, one representative form of which is GAD65. In this study, propofol was found to attenuate cognitive impairment in the behavioral tests whereas it inhibited excessive expression of GAD65 and normalized fluctuations of hippocampal glutamate and GABA at the molecular level.

ECS-induced amnesia arises from pathologically upregulating the glutamatergic system and its excitotoxicity [23]. A seizure can remove the blockage of magnesium on the NMDA receptor, resulting in an influx of cations and water into the cell, oxidative stress, and saturation of hippocampal long-term potentiation [6]. Low serum GABA levels of depressive patients increased after a completed

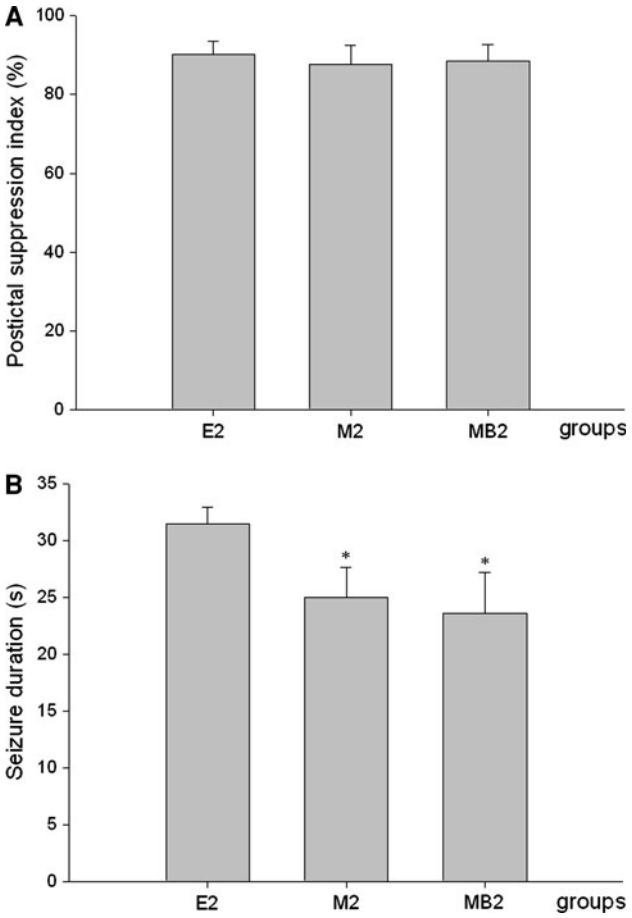

Fig. 6 Propofol or pentobarbital sodium could reduce the EEG seizure duration of electroconvulsive shock (ECS), but did not affect EEG postictal suppression index (PSI). **a** PSI. **b** Seizure duration. Data are presented as mean ± SEM: $*P < 0.01$ compared with group E2. Treatments: ECS with normal saline to group E2; ECS with propofol to group M2 and ECS with pentobarbital sodium to group MB2. $n = 6$ in each group

ECT course, and ECT seemed to increase brain GABA levels as well as GABA activity [24]. It was found that the increased Glu/GABA ratios in the hippocampus of depressed rats decreased after undergoing ECS [25]. In this study, we found in depressed rats that the Glu/GABA ratio decreased whereas the GABA level increased, but the glutamate level decreased after undergoing ECS. We also found that GAD65 in the hippocampus increased after the administration of ECS, which explains the decreased glutamate level from the metabolic aspect. The changes of GAD65 in our study are consistent with a recent stereology-based study [26].

Although more potential effective targets in the brain have been discovered recently [27], classical evidence shows that propofol acts mainly via activating the GABA system to exert anesthetic effects and brain protection, etc. [28, 29]. Propofol inhibits the action of glutamate on rat synaptosomes [30], protects cultured rat hippocampal

neurons against glutamate toxicity [31], and exerts protection through glutamate clearance mechanisms in brain during oxidative stress [32]. In a study in humans tested with magnetic resonance spectroscopy, Glu was downregulated while GABA was upregulated in the propofol-induced unconscious state in normal brain [33]. Propofol was also found to inhibit K^+-evoked glutamate release from rat brain slices, which is mediated by activation of GABAA receptors, revealing the interplay between GABAergic and glutamatergic transmission in propofol anesthetic effects [34]. Kubo et al. [35] found that GAD65(−/−) mice show a diminished response to propofol, indicating the importance of GAD65-mediated GABA synthesis in the action of propofol. Our data indicated that propofol can reverse ECS effects on glutamate, GABA, their ratio, and GAD65, normalizing these parameters to a level similar to those of the control group. Also, repeated administration of propofol alone did not aggravate the increase of the hippocampal Glu/GABA ratio and the decrease of GAD65 in depressed rats.

Additionally, in the present study, compared with group C, the behavioral data of group M were partially reversed, although not to the level of that of group C (see Figs. 1, 2, 3), but the molecular data were completely reversed and normalized (see Figs. 4, 5). The differences between the two levels may be related to the changes in molecular level being more rapid than those in behavior. As a final reflection on the whole subject, these changes in behavioral level may be more easily influenced by other factors and may be delayed. A similar tendency to change in the behavioral data and molecular data has shown consistent effects of ECS at both behavioral and molecular levels, which indicates preliminarily the influence of propofol on ECS effectiveness. Given the limitations of the present study, the potential time–effect relationship of these treatments on different indices will be included in further studies.

Furthermore, propofol was found not to compromise patient psychiatric or behavioral outcome after ECT, as compared with thiopental [36], and it even facilitated significantly better clinical effectiveness than methohexital or etomidate [37]. Based on the behavioral data, our results further confirmed that propofol neither affected depression (no differences were found between groups D and P) nor influenced the antidepressant effectiveness of ECT by itself (no differences were found between groups E and M; see Figs. 1, 2). The apparent conflict of our results (that propofol reduced ECS seizure duration whereas it did not interfere with the antidepressant effects of ECS) indicated that seizure duration might not be the essential predictor of treatment response, which is consistent with the results of other studies [13].

In conclusion, this study showed that, without interfering with the antidepressant efficacy of ECS, propofol alleviated ECS-induced learning-memory impairment, possibly by inhibiting excessive expression of GAD65 and maintaining the balance between glutamatergic and GABAergic amino acids neurotransmitters in hippocampus. Moreover, based on the beneficial effects of propofol in ECT, a perspective hypothesis is that anesthetics may participate in clinical psychiatric therapy, contributing to its safety without compromising efficacy.

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