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Different behavioral and pathological changes between epilepsy-associated depression and primary depression models

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ABSTRACT

Purpose: Comorbid depression is common in patients with epilepsy. However, the epilepsy-associated depression is always atypical and has not been fully recognized by neurologists. This study aimed to compare the behavioral and pathological changes between the chronic lithium chloride-pilocarpine rat epilepsy model (Licl-pilocarpine model) and Chronic Unpredictable Mild Stress rat depression model (CUMS model), trying to find some differences between epilepsy-associated depression and primary depression.
Methods: The Licl-pilocarpine model and CUMS model were established respectively and simultaneously. Spontaneous seizures were recorded by video monitoring. Forced swim test (FST) and sucrose consumption test (SCT) were performed to test depressive behaviors. Immobility time (IMT) and climbing time (CMT) in FST, sucrose preference rate (SPR) in SCT, and weight gain rate (WGR) were adopted to represent severity of depressive behaviors in rats. Immunofluorescent staining was conducted to measure expressions of neuronal specific nuclear protein (NeuN), glial fibrillary acidic protein (GFAP), and CD11b in the hippocampus of Licl-pilocarpine model, CUMS model, and Control group.
Results: Significantly, more prolonged IMT was observed in both Licl-pilocarpine model ($p < 0.05$) and CUMS model ($p < 0.01$) than Control group. But decreased WGR was only seen in CUMS model. The percentage of rats with CMT greater than 100 s was significantly higher in Licl-pilocarpine model than CUMS model ($p < 0.05$). Increased CMT was observed in Licl-pilocarpine model with mild depression subgroup (EMD, IMT ≤ 100 s) even compared with Control group. Neuronal loss was both found in Licl-pilocarpine model and CUMS model when comparing with Control group ($p < 0.05$). However, the number of GFAP and CD11b staining cells was both greater in Licl-pilocarpine model than CUMS model and Control group ($p < 0.05$).
Conclusion: There were some different depressive behavioral and hippocampal pathological changes between Licl-pilocarpine and CUMS models except for some common features. Gliosis and microglial activation might be more involved in the pathophysiology of epilepsy-associated depression than primary depression.

1. Introduction

Psychiatric disorders frequently occur in patients with epilepsy, in which depression is the most common comorbidity, with the prevalence of 20–50% [1–3]. However, the relationship between epilepsy and psychopathology is still poorly understood.

Increased level of plasma corticosterone was found in the Chronic Unpredictable Mild Stress (CUMS)-induced depression model, a promising animal model for primary depression, and had a positive relationship with depressive behaviors [4–6]. Simultaneously, Mazarati et al. [7,8] found that the chronic lithium chloride-pilocarpine rat epilepsy model (Licl-pilocarpine model) which highly mimic temporal lobe epilepsy in humans [9] had elevated plasma corticosterone and depressive behaviors, suggesting that it could be served as a model for the comorbidity of epilepsy and depression. In addition, functional disturbance of the hypothalamus–pituitary–adrenal (HPA) axis and high level circulating corticosterone was also found to contribute to the incidence of depression in patients with epilepsy [10].

Although the high-level serum corticosterone and HPA axis dysfunction might be the common pathophysiological mechanism both in epilepsy-associated depression and primary depression, it could not explain why epilepsy-associated depression is somewhat different from primary depression clinically because the clinical symptoms of depression in patients with epilepsy are always atypical, complex, and easily unrecognized [11–13]. The symptoms of epilepsy-associated depression

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always have relative milder severity that does not meet DSM-IV criteria of major depressive disorder [11]. Suicidal idea, frustration intolerance, irritability, and motor agitation symptoms are unstable and can rapidly alternate with symptom-free periods, so Blumer et al. referred to it as interictal dysphoric disorder [12,13]. In this study, we aimed to compare the depressive-like behavioral and pathological changes between the chronic Licl-pilocarpine rat epilepsy model and CUMS rat depression model, trying to find some similarities and differences in epilepsy-associated depression and primary depression, helping to explain clinical correlations, and guiding diagnosis and treatment for patients with comorbidity of epilepsy and depression.

2. Materials and methods

2.1. Animal care

Male Sprague–Dawley rats (SLRC Laboratory Animal Corporation) weighing about 200–250 g were housed in a room with constant temperature of 22 ± 1 °C, 12 h light–12 h dark cycle, and humidity of 35–40%. The rats were group-housed, and every 5 rats were raised in a 57 × 36 × 14.5 cm cage to avoid isolated effects on their behaviors. The experiment was done in accordance with the policies of the National Institutes of Health. And the study has been approved by Animal Care and Use of Committee of Zhongshan Hospital, Fudan University, China.

2.2. Establish Licl-pilocarpine chronic rat epilepsy model

Status epilepticus (SE) induced by Licl and pilocarpine was conducted in accordance with our previous study [14]. Animals received an intraperitoneal (i.p.) injection of Licl (127 mg/kg, dissolved in deionized water, Sigma, St. Louis, MO, USA). Animals were injected i.p. with scopolamine methyl nitrate (1 mg/kg, Sigma) after 24 h and then pilocarpine hydrochloride (40 mg/kg, Sigma) 30 min later. The stages of seizure degree were classified by the Racine scale [15]. After 1 h of seizure onset, rats were injected i.p. with diazepam (10 mg/kg) to terminate further seizures and reduce mortality. Control animals were injected i.p. with the same dose of Licl but used saline instead of pilocarpine. No special high calorie palatable supplements were added for rats after SE.

One week after SE, animals underwent two-week video monitoring for detecting spontaneous seizures. Forced swim test (FST) were performed at the end of two-week monitoring after verifying no seizures had developed for at least 6 h prior the behavioral test.

2.3. CUMS procedures

Rats were subjected to different kinds of stressors for 21 days as previously described [16]. A total of seven stressors were performed in this study. These stressors varied daily and were unpredictable by rats. The schedule and types of stressor were presented in Table 1.

2.4. Sucrose consumption test (SCT)

The SCT was performed in the Licl-pilocarpine and CUMS models before experiment and every week after SE and the onset of CUMS. The aim of SCT is to test for anhedonia on the basis of the innate preference of rodents toward sweets [17]. Before every test, water deprivation was carried out for 24 h. After water deprivation, every rat was supplied with two identical bottles of water, regular water and 1% sucrose water. The volumes of regular and sucrose water intakes were calculated 1 h later (Sucrose preference rate (SPR) = sucrose consumption / (sucrose consumption + water consumption) × 100%). Low sucrose consumption is interpreted as an equivalent of the state of anhedonia.

2.5. FST

Three weeks after SE and the onset of CUMS, FST was conducted in the Licl-pilocarpine and CUMS models. The rat was put into a tank filled with water (60 cm height and 30 cm diameter) maintained at 22–25 °C. Five minutes of swimming behavior was videotaped and analyzed. There are 3 types of swimming behaviors in the modified FST: immobile behavior, climbing behavior, and swimming behavior. The longer time of immobility is indicative of state of despair, while the climbing and swimming behaviors are active behaviors [18,19].

2.6. Histology and immunofluorescent measurements

After FST, saline and 4% paraformaldehyde were used to perfuse the rats. Next, the rats were decapitated, and the brains were put into 4% paraformaldehyde at 4 °C overnight. After that, the brains were dehydrated by 30% sucrose for 2–3 days, embedded in Tissue Freezing Medium (Jung, Nussloch, Germany), and frozen in liquid nitrogen immediately. The 20 μm coronal sections (cut from the bregma −3.24 mm to −3.96 mm [20]) were acquired and incubated with 3% goat serum to block nonspecific signals. Following serum blocking, the sections were incubated with mouse antineuronal specific nuclear protein (NeuN, 1:600, Millipore), glial fibrillary acidic protein (GFAP, 1:400, Boster), and CD11b (1:400, Chemicon) in 1 × PBS containing 0.3% Triton X-100 overnight at 4 °C. Following a 1 × PBS rinse for three times, the sections were incubated with goat antimouse IgG-Cy2 (1:600) for 1 h at room temperature. The stained sections were observed by Olympus fluorescence microscope. Cell counting was conducted in 2 slices in each rat brain. The positive cells of NeuN, GFAP, and CD11b in the CA1, CA3, and dentate gyrus (DG) sectors of hippocampus were counted using ImageJ software combining with visual inspection.

2.7. Statistics

All quantitative data were expressed as mean ± SD. One way analysis of variance (ANOVA) or Student's *t*-test was used to compare means between groups. The correlations between seizure frequency, latency, or average time of sustained seizures and depressive behavioral parameters were analyzed using Pearson correlation analysis. The SPSS 21.0 software was utilized to complete all of the statistics. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Spontaneous recurrent seizures (SRS) observation in Licl-pilocarpine rat model and the correlations with depressive behaviors

Two-week video tapes for all experimental rats were reviewed by the same researcher. Rats with spontaneous seizures reached Racine stages 4–5 (rearing and/or rearing and falling) were regarded as chronic Licl-pilocarpine rat epilepsy model in this study. At last, 23 rats survived SE and had SRS reached stages 4–5. No correlations were found between

Table 1
Schedule of CUMS administered over a 7-day period and repeated for 3 weeks.

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
24 h water deprivation	Inescapable foot shock (60 times, 2 s/time)	1 min tail clip	5 min ice water swimming	24 h 45° cage tilt	24 h reversed light/dark	Damp sawdust overnight

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the SRS parameters (seizure frequency, latency, and duration) and depressive behavioral parameters [immobility time (IMT), SPR, and weight gain rate (WGR)] ($p > 0.05$).

3.2. Comparisons of behaviors between Licl-pilocarpine model and CUMS model

3.2.1. Common depressive behaviors in Licl-pilocarpine and CUMS models

The IMT, SPR, and WGR were used to represent depressive behaviors of rats in this study. Eight from ten rats were selected after screening with SCT at the baseline and induced into CUMS depression model after 3 weeks of stressful stimulations. As shown in Fig. 1, IMT was significantly prolonged (Fig. 1A), and SPR was in decreased trend (Fig. 1B) in Licl-pilocarpine and CUMS models relative to Control group. Although IMT was decreased a little in Licl-pilocarpine model compared with CUMS model, there was no statistical difference. Interestingly, only WGR in CUMS model decreased significantly than those in Control group and Licl-pilocarpine model ($p < 0.05$, Fig. 1A).

3.2.2. More active behaviors in Licl-pilocarpine model relative to CUMS model and Control group

According to the previous study by Pineda et al. [21], we set IMT greater than 100 s that accounted for 1/3 of the total swimming time as the severe depressive behaviors in rats (ESD subgroup). Rats with IMT less than or equal to 100 s were regarded as having mild depressive behaviors (EMD subgroup). There were 7 over 23 rats (30.4%) in Licl-pilocarpine model that had IMT greater than 100 s. While in CUMS group, 5 over 8 rats (62.5%) had IMT greater than 100 s, which seemed a little higher than in Licl-pilocarpine group, but without significance ($p > 0.05$). Moreover, behavioral observation showed that 13 over 23 rats (56.5%) with climbing time (CMT) greater than 100 s were found in Licl-pilocarpine group, which was significantly greater than that (1 over 8 rats, 12.5%) in CUMS model ($p < 0.05$). At the same time, CMT was significantly prolonged in EMD subgroup than in Control, ESD, and CUMS groups (Fig. 2).

3.3. Comparisons of pathological changes between Licl-pilocarpine model and CUMS model

Every 6 rats' brains were selected from Control group, EMD and ESD groups of Licl-pilocarpine model, and CUMS model, and every 2 slices with the similar coronal hippocampal areas according to the rat brain atlas were chosen respectively to do further stains.

3.3.1. Similar neuronal loss in Licl-pilocarpine and CUMS models

Neuronal nucleus (NeuN) was stained to represent neurons in the brain. The number of NeuN positive cells in the hippocampus of rats was compared between Control group, Licl-pilocarpine model, and CUMS model to investigate the difference of neuronal loss. The results showed that the number of NeuN positive cells in the CA1 and DG subfields of hippocampus in Licl-pilocarpine and CUMS models both decreased and was significantly less than in Control group ($p < 0.01$). In the CA3 subfield of hippocampus, only neuronal loss in Licl-pilocarpine model had significance when compared with Control group ($p < 0.05$) (Fig. 3A–B).

3.3.2. More obvious gliosis in Licl-pilocarpine model than in CUMS model

Glial fibrillary acidic protein is a marker for astrocytes. The number of GFAP positive cells was used to reflect the gliosis in the hippocampi of rats. As shown in Fig. 4, the number of GFAP positive cells was significantly greater in the CA1, CA3, and DG subfields of hippocampus in Licl-pilocarpine model than in Control group and CUMS model (**$p < 0.01$). Compared with Control group, the gliosis was more obvious in CA1 ($p < 0.01$) and DG ($p < 0.05$) subfields of hippocampus in CUMS group, no statistical difference was found in CA3 subfield of hippocampus (Fig. 4A–B).

3.3.3. Greater number of microglia cells in Licl-pilocarpine model than CUMS model and Control group

The CD11b is a marker for microglia cells in the brain. The number of CD11b positive cells was counted to detect inflammatory response in Licl-pilocarpine and CUMS models. The results showed that the number of CD11b positive cells in the CA1, CA3, and DG subfields of hippocampus

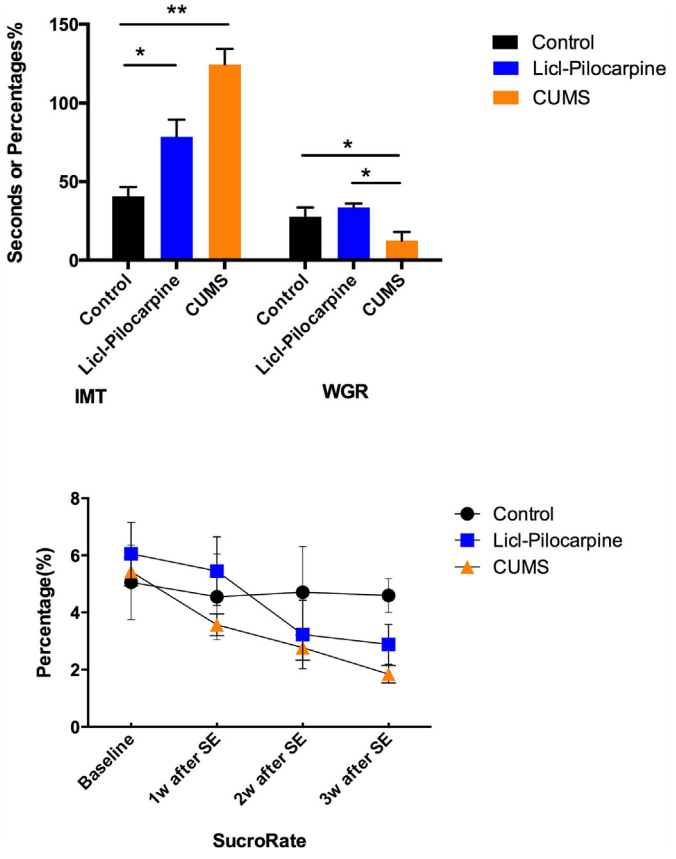

Fig. 1. A) The IMT was significantly prolonged in Licl-pilocarpine and CUMS models compared with Control group (*$p < 0.05$, **$p < 0.01$, $n = 10$ in Control group, $n = 23$ in Licl-pilocarpine model, and $n = 8$ in CUMS model); WGR in CUMS model decreased significantly than those in Control group and Licl-pilocarpine model (*$p < 0.05$). B) SPR was in decreased trend in Licl-pilocarpine and CUMS models relative to Control group. IMT, immobility time; WGR, weight gain rate; SPR, sucrose preference rate; CUMS, Chronic Unpredictable Mild Stress.

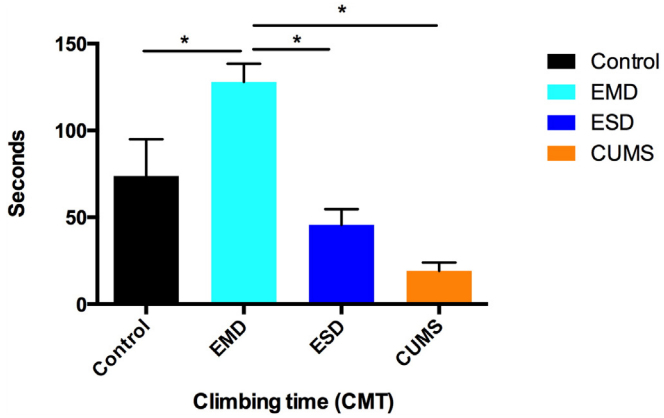

Fig. 2. The CMT was significantly prolonged in EMD subgroup than in Control, ESD, and CUMS groups (*$p < 0.05$, $n = 10$ in Control group, $n = 16$ in EMD subgroup, $n = 7$ in ESD subgroup, and $n = 8$ in CUMS group). CMT, climbing time; EMD, Licl-pilocarpine model with mild depression; ESD, Licl-pilocarpine model with severe depression; CUMS, Chronic Unpredictable Mild Stress.

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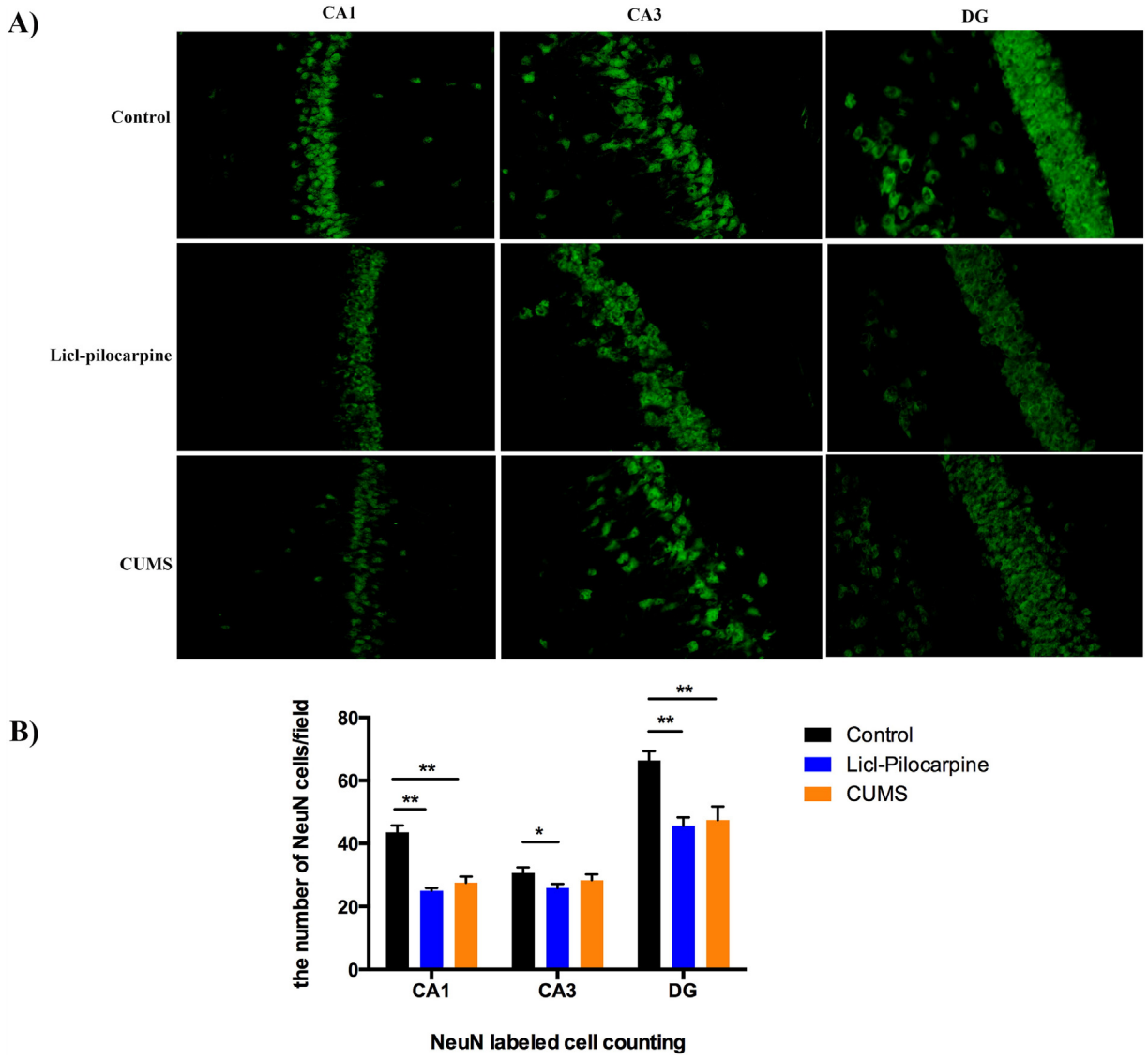

Fig. 3. A) 20× magnification immunofluorescence micrographs show NeuN positive cells in the CA1, CA3, and DG subfields of hippocampus in Control group, Licl-pilocarpine model, and CUMS model respectively; B) the number of NeuN positive cells in the CA1 and DG subfields of hippocampus in Licl-pilocarpine and CUMS models both decreased and was significantly less than in Control group (**$p < 0.01$). In the CA3 subfield of hippocampus, only neuronal loss in Licl-pilocarpine model had significance when compared with Control group (*$p < 0.05$).

was significantly greater in Licl-pilocarpine model than in CUMS model and Control group (*$p < 0.05$, **$p < 0.01$). No statistical difference was found between Control group and CUMS model ($p > 0.05$) (Fig. 5A–B).

4. Discussion

Studies found that the clinical presentations of depression in patients with epilepsy were always atypical, and quite a few patients failed to meet the DSM axis categories [22]. Kanner et al. suggested that depressive disorders in many patients with epilepsy were different from those of patients without epilepsy [23]. Based on this point, we compared the depressive behaviors associated with epilepsy in Licl-pilocarpine model with CUMS model that represented behaviors of primary depression. We found that Licl-pilocarpine model and CUMS model both had more prolonged IMT and decreased SPR relative to Control rats. However, they still had other different behaviors, such as the following: 1) CUMS model had lower WGR than Licl-pilocarpine model; 2) over 60% of rats in CUMS model had severe depressive behavior (IMT > 100 s) while only about 1/3 of rats in Licl-pilocarpine model had severe depression; and 3) more rats in Licl-pilocarpine model had active behaviors compared with CUMS model and Control group, especially the part of rats with mild depressive behaviors (IMT ≤ 100 s).

There are three types of behaviors in FST: the swimming behavior, the climbing behavior, and the immobile behavior. Increased IMT can be interpreted as an experimental correlate of a state of despair. Climbing behavior is a type of active behavior consisting of upward directed movements of the forepaws along the side of the swim chamber [18]. In our study, more rats had IMT greater than 100 s and lower WGR in CUMS model indicated more distinct depressive behaviors in CUMS model than Licl-pilocarpine model. And more rats with greater CMT in Licl-pilocarpine model than CUMS model and Control rats might indicate that there were other behavioral impairments such as irritability in Licl-pilocarpine model, as other studies demonstrated that Licl-pilocarpine rat epilepsy model had aggressive behaviors [24]. This finding for different depressive behaviors in Licl-pilocarpine model and CUMS model implied that the underlying pathophysiology for epilepsy-associated depression might be partly different from that of primary depression.

Hippocampal neuronal loss is determined to be involved in the process of epileptogenesis [25] and also contribute to depressive behaviors [26]. So the characteristic of hippocampal neuronal loss was compared between Licl-pilocarpine model and CUMS model to see if there were

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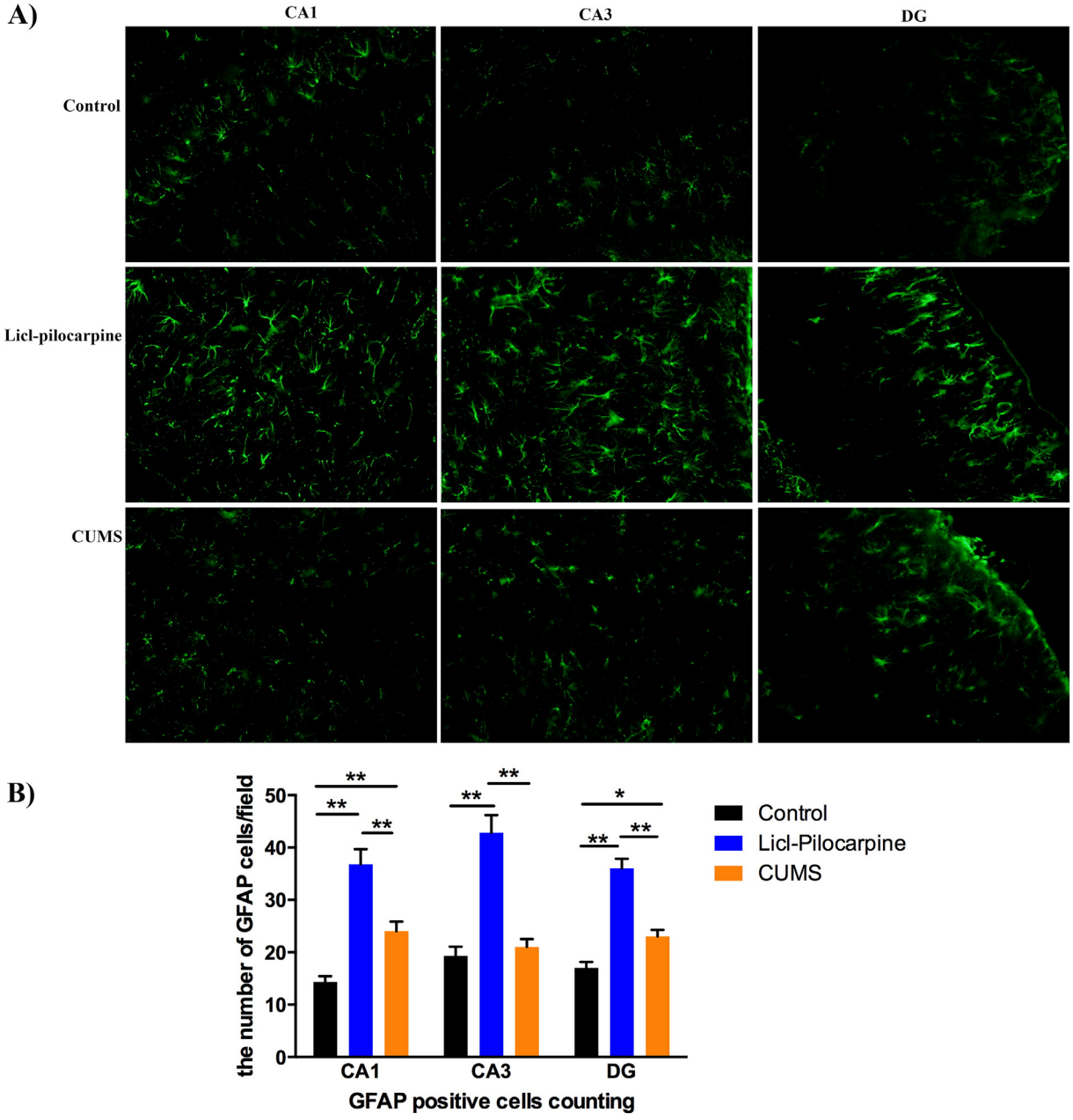

Fig. 4. A) 20× magnification immunofluorescence micrographs show GFAP positive cells in the CA1, CA3, and DG subfields of hippocampus in Control group, Licl-pilocarpine model, and CUMS model respectively. B) The number of GFAP positive cells was significantly greater in the CA1, CA3, and DG subfields of hippocampus in Licl-pilocarpine model than in Control group and CUMS model (**$p < 0.01$). Compared with Control group, the gliosis was more obvious in CA1 (**$p < 0.01$) and DG (*$p < 0.05$) subfields of hippocampus in CUMS group.

some different pathological changes. Both of the Licl-pilocarpine and CUMS models had neuronal loss in comparison with Control group. However, we did not find any difference of hippocampal neuronal loss between Licl-pilocarpine model and CUMS model. This finding is consistent with the previous studies that stress not only causes down regulation of hippocampal neurogenesis but also promotes neuronal apoptosis [27]. Hippocampal neuronal loss in Licl-pilocarpine model might not merely be due to stress, as the direct injury by seizures was also observed in epilepsy models [28]. Moreover, reduced hippocampal volume or hippocampal neuron dysfunction in patients with epilepsy was also shown to be related to both seizure severity and depression [29,30], implying the hippocampal neuronal loss was probably involved in epileptogenesis and psychopathology of depression. However, depressive behavior was also observed in the rapid kindling model with the absence or just minimal extent of neuronal injury in the study by Mazarati et al., indicating neuronal plastic changes associated with kindling also took part in the development of depressive behavior in epilepsy [31].

Except for acting as extracellular matrix to support neurons, glial cells are involved in diverse neuronal functions such as modulate synaptic plasticity, regulate extracellular microenvironment, and enforce cellular immunity in the brain [32]. The GFAP is one of the specific markers for reactive astrocyte that is involved in mechanisms of many neurological diseases and central nervous system insults [33]. Many studies have found reactive gliosis in epileptic foci and mesial temporal sclerosis of temporal lobe epilepsy [34,35]. It indicated that reactive gliosis facilitated seizures and epileptogenesis by increasing neuronal excitability and inflammation by glia–neuron communications [36]. Glial dysfunction was also observed in CUMS depression model and patients with major depressive disorder [37,38], which

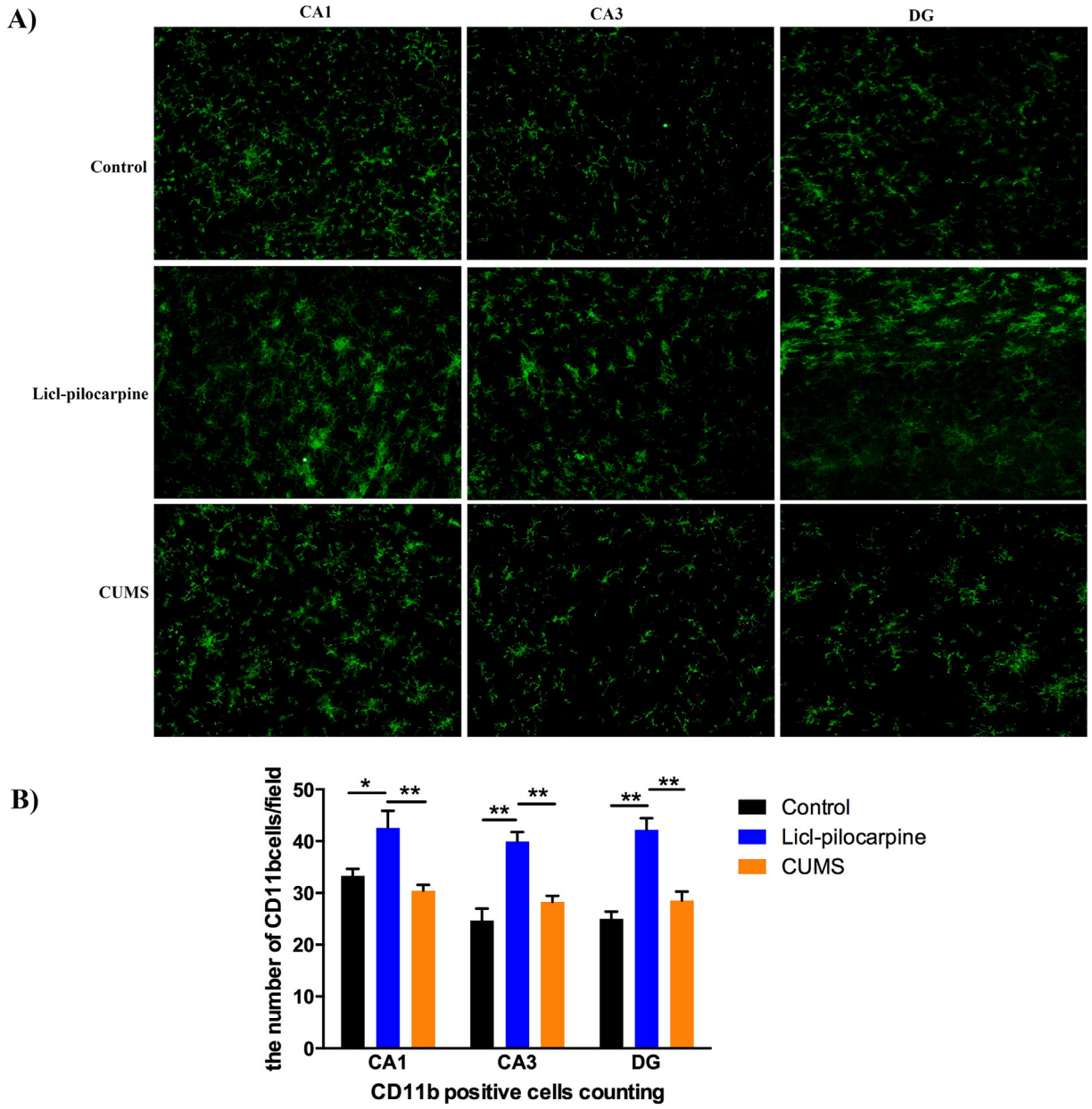

Fig. 5. A) 20× magnification immunofluorescence micrographs show CD11b positive cells in the CA1, CA3, and DG subfields of hippocampus in Control group, Licl-pilocarpine model, and CUMS model respectively. B) The number of CD11b positive cells in the CA1, CA3, and DG subfields of hippocampus was significantly greater in Licl-pilocarpine model than in Control group and CUMS model (**$p < 0.01$,*$p < 0.05$). No statistical difference was found between Control group and CUMS model ($p > 0.05$).

might alter glutamate neurotransmission and then induce neuronal loss [39]. In our study, the reactive gliosis was more obvious in Licl-pilocarpine model than CUMS model and Control group.

As astrocyte and microglia often work together to generate inflammatory process in many neurological diseases [36], we observed the changes of CD11b expression in Licl-pilocarpine and CUMS models at the same time. It showed that microglial cells increased more greatly in Licl-pilocarpine model than CUMS model and Control group, which was in accordance with the changes of astrocytes. These results indicated that gliosis and microglial cells mediated inflammation in the hippocampus might be more greatly involved in the pathophysiology of epilepsy-associated depression rather than primary depression.

5. Conclusions

In this study, we used Licl-pilocarpine model and CUMS model to represent epilepsy-associated depression model and primary depression model respectively, and we found that these two models had some different depressive behavioral and hippocampal pathological changes except for some common features. They both had prolonged IMT compared with Control group, but the decreased WGR was only seen in CUMS model, and Licl-pilocarpine model seemed to have more active behaviors even than Control rats. These two models both had hippocampal neuronal loss. However, more prominent gliosis and microglial activation were found in Licl-pilocarpine model than in CUMS model, indicating that gliosis and microglial cell-mediated inflammatory process might be more greatly involved in epilepsy-associated depression than primary depression.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Disclosures of conflicts of interest

None of the authors has any conflict of interest related to this manuscript.

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