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Research Article

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Lithium Carbonate Alleviate Neuronal Apoptosis to Improve Depression Symptoms in Mice by the JNK/c-Jun Signaling Pathway

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Abstract

Objective

To explore lithium alleviate the apoptosis of nerve cells through JNK/ C-Jun signaling pathway and improve the depressive symptoms in depressed mice.

Methods

30 male mice were randomly divided into blank control , model group and drug intervention group. A model of depression was established by Chronic unpredictable mild stress (CUMS). Mice in drug intervention group were given lithium from 4th weekend. The behavior of mice were evaluated and Western blot was used to detect expression levels of related proteins.

Results

Compared with model group, drug intervention group showed a significant decrease depressive symptoms ($P < 0.01$). Western blotting results show that compared with blank control group, protein levels of P-JNK /JNK ,P-C-Jun/C-Jun ,caspase-3 and Bax in PFC of model group were significantly increased ($P < 0.01$), Bcl-2 level significantly decreased ($P < 0.01$);Compared with the model group, the protein levels of nerve cells p-JNK/JNK, P-C-Jun/C-Jun, aspase-3 and Bax in prefrontal cortex of mice in drug intervention group were significantly decreased ($P < 0.01$), Bcl-2 level increased significantly ($P < 0.01$).

Conclusions Lithium improve depression symptoms by reducing apoptosis of prefrontal cortex nerve cells through JNK/ C-Jun signaling pathway in depression-like mice.

Keywords: Depression, Lithium Carbonate, JNK/c-Jun, Cell Apoptosis, Animal Model

1. Background

Depression is a common mental disease, which is mainly characterized by emotional disorders, lack of pleasure, cognitive dysfunction or increased susceptibility to relapse [1]. According to the World Health Organization (WHO) report in 2017, the number of depression patients worldwide reached 322 million, of which the prevalence rate of depression in China reached 4.2%; It is predicted that depression will become the first factor in the global disease burden by 2030 [2]. Depression has become a global neuropsychiatric disease and a major burden on the human

medical system. It is urgent to further explore its pathogenesis and more effective treatment methods. Although there are dozens of antidepressants in clinical application, the treatment of depression still faces many difficulties. The selection of mood stabilizer is also one of the methods. Lithium carbonate is one of the classic mood stabilizers and the gold standard of anti-manic drugs, so it has been used for the treatment of bipolar mania [3]. Lithium salt was first used to treat gout in 1859, and then gradually applied to the treatment of mental diseases due to its beneficial effect on mood [4]. Evidence-based medicine found that lithium is effective in treating acute mania, including accompanying psychiatric symptoms. For the maintenance period, it is effective as a single therapy, mainly used to prevent mania. Its combination increases its therapeutic value. It is equally effective for patients with rapid and non-rapid cycling, accompanying symptoms of obsessive-compulsive symptoms, alcohol and drug abuse, neurocognitive impairment, suicidal ideation, and fatigue. The current review provides support for the effectiveness of lithium in addressing a wide range of clinical issues related to bipolar disorder. It is comparable to that recently developed drugs in efficacy [5]. In other meta-analysis study found that compared with the placebo, lithium performs well in improving manic symptoms (N = 56, n = 14503) similar to other mood stabilizer and atypical antipsychotics. It also found that compared with the placebo, lithium performs well in improving manic symptoms(N = 61, n = 15466)similar to other mood stabilizer and atypical antipsychotics. In summary, these antipsychotic drugs carbamazepine, lithium, tamoxifen, and sodium valproate are effective in treating acute mania [6].

Lithium is a first-line drug and an effective mood stabilizer for bipolar disorder. Until today, lithium salt is still regarded as a classic drug to prevent mania and suicide in bipolar patients [7,8]. Many studies have shown that the clinical efficacy of lithium is related to its neuroprotective effect, but its mechanism is still unclear [9]. Apoptosis is a programmed cell death to maintain the stability of the internal environment. The occurrence and development of depression is usually accompanied by the apoptosis of nerve cells, so how to reduce the apoptosis of nerve cells is an important research direction in the treatment of depression. C-Jun N-terminal kinase (JNK) belongs to a class of kinases in the mitogen-activated protein kinase (MAPK) family [10,11]. A large number of research results show that JNK is activated to different degrees in the events of nerve atrophy, inflammatory reaction, oxidative stress and psychological stress, and these events are closely related to depression, When the JNK pathway is activated, the activated JNK can reactivate a variety of effector proteins, including transcription factors, to produce biological effects. C-Jun is the main downstream factor of JNK [12]. Under activated conditions, JNK phosphorylates c-Jun and induces nerve cell apoptosis. It is worth exploring whether the therapeutic effect of lithium carbonate on depression is related to the nerve cells mediated by JNK/c-Jun pathway. In this study, we discuss whether lithium carbonate can reduce the apoptosis of nerve cells and improve the depressive symptoms of depression-like mice through JNK/c-Jun pathway.

2. Materials and Methods

2.1. Materials

2.1.1. Experimental Animals

Male C57BL/6 mice (weighing 22 ± 3 g, 8 weeks old) were used in this study. The mice was provided by Beijing Weitong Lihua Experimental Animal Co., Ltd., the production license number of experimental animals is [SCXK (Beijing) 2019-0011], and it is raised by the Experimental Animal Center of Zhejiang University of Traditional Chinese Medicine. The use license number of experimental animals is [SYXK (Zhejiang) 2019-0022].Mice are allowed to freely obtain food and water during a 12 hour light/dark cycle (with lights on at 09:00) in a room at 24 ± 1 ° C and a relative humidity of 50% -60%.All operations during this experiment comply with the Regulations on the Management of Experimental Animals of the People's Republic of China. This study was approved Animal Care and Use Ethic Committee of Zhejiang Chinese Medical University. The animal ethics number 20200622-04. Thirty mice were randomly divided into three groups, namely blank control group, model group and Lithium carbonate group (model+Lithium carbonate), with 10 mice in each group.

2.1.2. Main Reagents and Drug

Lithium carbonate (Hunan Qianjin Xiangjiang Pharmaceutical Co., Ltd., batch number: H43020372); β- Actin□ β- Actin antibody (Immunoway, batch number: YM3028-100ug), c-Jun N-terminal kinase (JNK) antibody (Hua'an Biological Co., Ltd., batch number: RT1550), phosphorylated c-Jun N-terminal kinase (p-JNK) antibody (Hua'an Biological Co., Ltd., batch number: ET1609-42), c-Jun antibody (Hua'an Biological ,Co., Ltd. batch number: ET1608-3). Phosphorylated c-Jun (p-c-Jun) antibody (SANTA CRUZ, batch number sc-822), cysteine aspartic acid protease-3 (Caspase-3) antibody (Hua'an Biological Co., Ltd., batch number ER30804), B cell tumor/leukemia 2 (Bcl-2) antibody (Hua'an Biological Co., Ltd., batch number ER0602), apoptosis related protein Bcl-2 related X protein (Bax) antibody (Hua'an Biological Co., Ltd., batch number ET1603-34).

2.1.3. Main Instruments

SMART 3.0 Spontaneous Activity Video Analysis System Detection (Panlab/Rivald, Spain), SDS-PAGE Vertical Electrophoresis Tank (MP-8001, Beijing Kaiyuan Bole Biotechnology Co., Ltd.).

2.2. Methods

2.2.1. Model Establishment and Intervention

The chronic unpredictable mild stress (CUMS) program refers to the modeling method proposed by Liu et al. and is slightly modified by methods of stress as following:(1) 12 hours of nighttime illumination; (2) abrosia for 24 hours; (3) binding for 4 hours; (4) wet pad material for 24 hours (200ml of water per cage); (5) swimming in ice water for 5 minutes (4 ℃); (6) water prohibition for 24 hours; (7) horizontal shaking of the rat cage for 10 minutes; (8) pinch the tail for 5 minutes (1cn from the end of the tail); (9) tilt the rat cage for 24 hours (45 °) [13]. Mice were randomly subjected to one of the above stimulation methods at different times every day, and did not continuously apply the same stimulation for two days. They were continuously stimulated for

8 weeks to establish a depression mouse model. The mice in the lithium carbonate group were given 75 mg/kg lithium carbonate by gavage at the end of the fourth week of modeling once a day to the end of eighth weekend. The mice in the model group were given the same amount of normal saline by gavage, while the mice in the control group did not receive any stimulation treatment, and were given the same amount of normal saline by gavage at the same time.

2.2.2. Behavioral Assessment

Behavioral assessment includes classic sugar water preference test(SPT), open field test (OFT). and forced swimming test(FST). The indicator of sugar preference experiment is sugar preference rate, which is sugar consumption/(sugar consumption+pure water consumption)× 100%. The observation indicators of the open field experiment are the number of times (times) of crossing the middle grid and the total distance (cm).The observation indicator of the forced swimming experiment is to record the time of immobility within 5 minutes after swimming by video camera.

2.2.3. Sample Collection

After the last behavioral test , mice were sacrificed by cervical dislocation. The brain tissue was removed and placed in pre-cooled PBS buffer. After washing off residual blood, the prefrontal cortex was quickly removed on the ice surface. The prefrontal cortex was separated and cut according to the three-dimensional localization map of the mouse brain, and stored in liquid nitrogen for subsequent Western Bolt testing.

2.2.4. Western Bolt Test

The preparation of total protein in the prefrontal cortex of mice in each group was carried out using 1 ml of cold RIPA buffer and supplemented with 1% PMSF (phenylmethanesulfonyl flfluoride,Beyotime ST505), a protease inhibitor and phosphatase inhibitors. Before obtaining the protein supernatants, probes were ground and centrifuge at 12000 rpm at 4 ° C for 30 minutes. BCA assay was used the protein concentration was determined.20ug protein was transferred to polyvinylidene difluoride(PVDF) membrane after electrophoretic on 10% SDS-PAGE gel. Then, membranes were incubated with primary antibodies overnight at 4 ° C after blocking with 5% nonfat milk in TBS Tween 20, as follows: Phosphorylated c-Jun (p-c-Jun) antibody (SANTA CRUZ, batch number sc-822), Cysteine aspartic acid protease-3 (Caspase-3) antibody (Hua'an Biological Co., Ltd., batch number ER30804), B cell tumor/leukemia 2 (Bcl-2) antibody (Hua'an Biological Co., Ltd., batch number ER0602), apoptosis related protein Bcl-2 related X protein (Bax) antibody (Hua'an Biological Co., Ltd., batch number ET1603-34).The membrane was washed three times with TBS-Tween 20 (5 minutes each time) before incubating with the secondary antibody goat antirabbit IgG antibody (Biker, 1:5000) and goat anti-mouse IgG antibody (Biker, 1:50000) at room temperature for 2 hours.After the final washing step, an enhanced chemiluminescence reaction was performed on the membrane, and the bands were quantified by a densitometry (Quantity One 4.2, Bio Rad, Hercules, CA). Standardize the density value of the marker to the GAPDH level were normalized . Each experiment should be conducted at least three times. Image Studio Ver2.0 software was used for detection and quantification of each band.

2.2.5. Statistical Analysis

Statistical analysis was completed by Graph Pad Prism8 0 software. All data are mean ± standard deviation ($\bar{x}$ ± s). Single factor analysis of variance was used for overall comparison between multiple groups, and t-test was used for mean comparison between the two groups, with P<0 05 representing a statistically significant difference.

3. Results

3.1. Effect of Lithium Carbonate on Behavior of Depressed Mice

The results of the mouse sugar preference experiment showed that compared with the blank control group, the model group showed a significant decrease in sugar preference (P<0.01); Compared with the model group, the preference for sugar water in the Lithium carbonate group increased significantly (P<0.01) (see Figure 1 and Table1).

Note: The sugar preference in each group were statistically analyzed($F = 4.96$, $P = 0.032$).Compared with the normal control group, * $P < 0.05$,** $P < 0.01$; Compared with the stress group, ## $P < 0.01$.

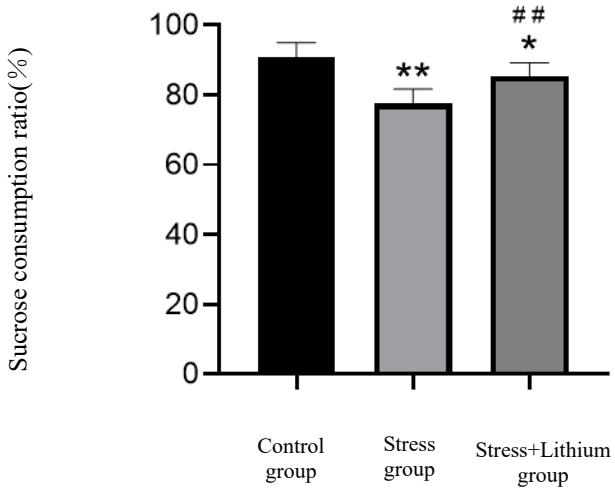

Figure 1: Effect of Lithium carbonate on behavior of depressed mice

The results of the mouse sugar preference experiment showed that compared with the blank control group, the model group showed a significant decrease in sugar preference (P<0.01); Compared with the model group, the preference for sugar water in the Lithium carbonate group increased significantly (P<0.01).

Note: Compared with the normal control group, * $P < 0.05$, ** $P < 0.01$; Compared with the model group, ## $P < 0.01$.

	Sugar preference(%)	Total distance of motion(cm)	Crossing times	Immobility time(s)
Control group	92.5±4.4	2928.6±255.5	161.5±15.3	175.3±12.5
Stress group	75.5±5.1**	1624.8±175.6**	117.3±13.5**	212.5±17.2**
Stress+Lithium group	81.3±3.8*#	2607.1±250.2*#	126.1±11.2*#	190.6±14.6*#

Table1: Comparison of Behavioral Index Among Three Groups

Sugar preference: F = 4.96, P = 0.032; Total distance of motion: F = 4.71, P = 0.045; Crossing times: F = 5.06, P = 0.026; Immobility time: F = 5.01, P = 0.026.

Compared with the normal control group, * $P < 0.05$, ** $P < 0.01$; Compared with the stress group, #$P < 0.01$.

3.2. Effects of Lithium Carbonate on the Total Distance of Exercise and the Number of times of Crossing in Depressed Mice

The open field experiment includes two parts: the total distance of movement and the number of passes. The total exercise distance of mice showed a significant decrease in the model group compared to the blank control group (P<0.01);Compared with the model group, the total distance of exercise in the Lithium carbonate group increased significantly (P<0.01) ; shows that the number of times of passing through the grid in the model group is significantly lower than that in the normal group (P<0.01). After treatment with Lithium carbonate, the number of times of passing through the grid in the Lithium carbonate group is significantly higher than that in the model group (P<0.01).see Figure 2A, Figure 2B and Table1.

Note: The open field experiment in each group were statistically analyzed (F = 4.71, P = 0.045, Figure A; F = 5.06, P = 0.026,Figure B). Compared with the normal control group, * $P < 0.05$, ** $P < 0.01$; Compared with the stress group, ## $P < 0.01$.

Figure 2 Influence of lithium carbonate on total distance of exercise in open field experiment of CUMS mice: A. Statistical chart of total distance of mice in each group; B. Statistical chart of the number of lattice penetration of mice in each group.

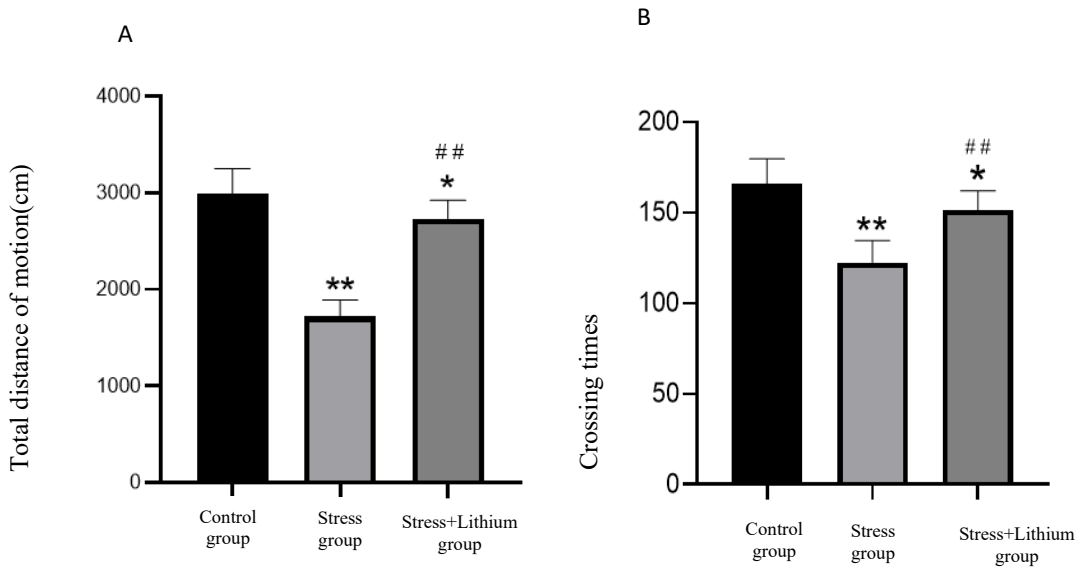

Figure 2: Effects of Lithium carbonate on the total distance of exercise and the number of times of crossing in depressed mice

The open field experiment includes two parts: the total distance of movement and the number of passes.The total exercise distance of mice showed a significant decrease in the model group compared to the blank control group (P<0.01);Compared with the model group, the total distance of exercise in the Lithium carbonate group increased significantly (P<0.01) (Figure 2A); Figure 2B shows that the number of times of passing through the grid in the model group is significantly lower than that in the normal group (P<0.01). After treatment with Lithium carbonate, the number of times of passing through the grid in the Lithium carbonate group is significantly higher than that in the model group (P<0.01).

Note: Compared with the normal control group, * $P < 0.05$, ** $P < 0.01$; Compared with the model group, ## $P < 0.01$.

3.3. Effect of Lithium Carbonate on Immobility time in Forced Swimming of Depressed Mice

The immobility time of the model group mice was significantly longer than that of the blank control group (P<0.01); However, after treatment with Lithium carbonate, the immobility time of mice in the Lithium carbonate group was significantly shorter than that in the model group (P<0.01) ,see Figure 3 and Table1.

Note: The immobility time in each group were statistically analyzed(F=5.01,P=0.026). Compared with the normal control group, * $P < 0.05$, ** $P < 0.01$; Compared with the stress group, ## $P < 0.01$.

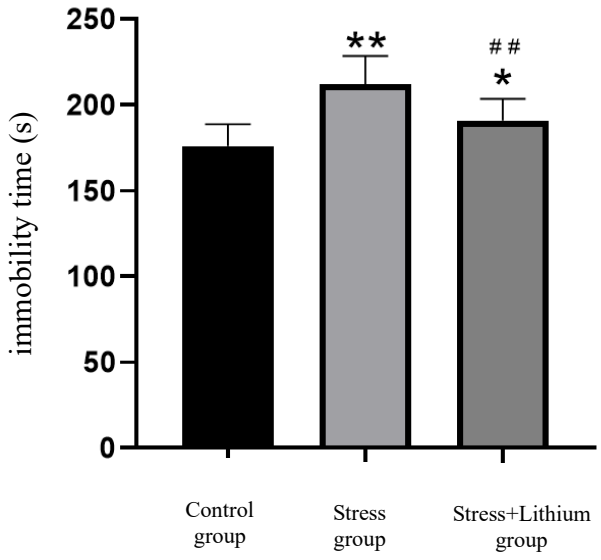

Figure 3: Effect of Lithium carbonate on immobility time in forced swimming of depressed mice

The immobility time of the model group mice was significantly longer than that of the blank control group (P<0.01); However, after treatment with Lithium carbonate, the immobility time of mice in the Lithium carbonate group was significantly shorter than that in the model group (P<0.01) .

Note: Compared with the normal control group, * $P < 0.05$,** $P < 0.01$; Compared with the model group, ## $P < 0.01$.

3.4. Lithium Carbonate on p-JNK/JNK、p-c-Jun/c-Jun in Depressed Mice

As shown in Figure 4, the p-JNK/JNK and p-c-Jun/c-Jun ratios in each group were statistically analyzed. The results showed that compared with the normal group, the p-JNK/JNK, p-c-Jun/c-Jun ratios in the prefrontal cortex of the model group mice were significantly increased (P<0 01), JNK, c-Jun phosphorylation levels increase; Compared with the model group, p-JNK/JNK, p-c-Jun/c-Jun in the prefrontal cortex of mice in the Lithium carbonate group decreased (P<0 01).see Figure4 and Table2.

Note: The p-JNK/JNK and p-c-Jun/c-Jun ratios in each group were statistically analyzed($F = 6.01$, $P = 0.001$).Compared with the normal control group, * $P < 0.05$, ** $P < 0.01$; Compared with the stress group, ## $P < 0.01$.

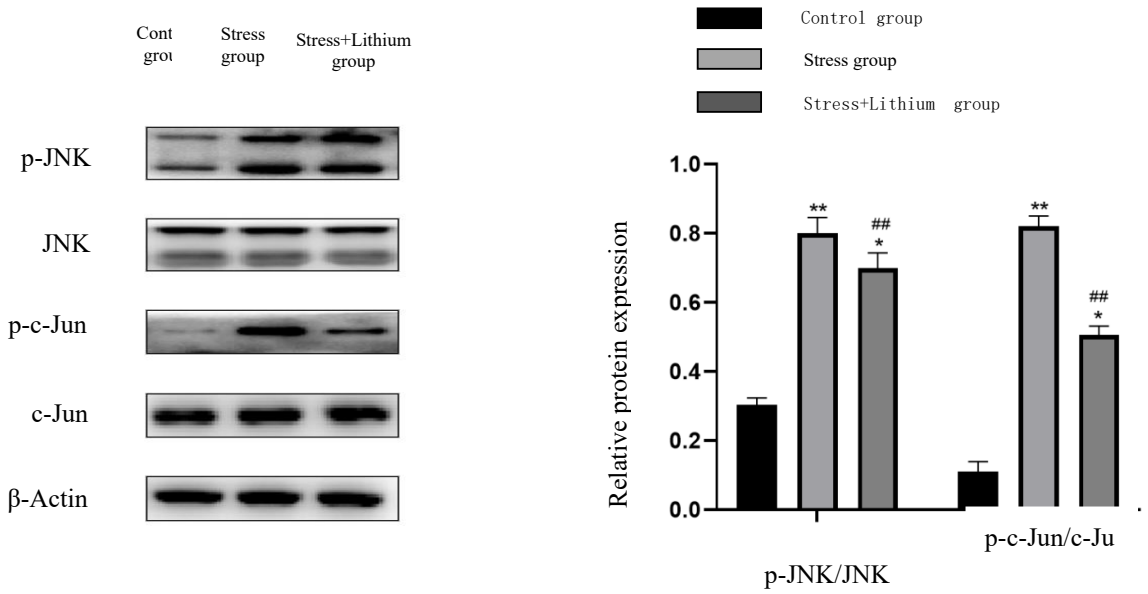

Figure 4: Lithium carbonate on p-JNK/JNK,p-c-Jun/c-Jun in depressed mice

As shown in Figure 4, the p-JNK/JNK and p-c-Jun/c-Jun ratios in each group were statistically analyzed. The results showed that compared with the normal group, the p-JNK/JNK, p-c-Jun/c-Jun ratios in the prefrontal cortex of the model group mice were significantly increased (P<0 01), JNK, c-Jun phosphorylation levels increase; Compared with the model group, p-JNK/JNK, p-c-Jun/c-Jun in the prefrontal cortex of mice in the Lithium carbonate group decreased (P<0 01).

Note: Compared with the normal control group, * $P < 0.05$, ** $P < 0.01$; Compared with the model group, ## $P < 0.01$.

	p-JNK/JNK	p-cJun/c-Ju
Control group	0.29±0.01	0.11±0.05
Stress group	0.77±0.06**	0.78±0.04**
Stress+Lithium group	0.67±0.05*#	0.48±0.03*#

Table 2: Comparison of p-JNK/JNK and p-cJun/c-Ju expression among three groups(%)

p-JNK/JNK:F = 6.01, P = 0.001;p-cJun/c-Ju: F = 6.66 = 0.001

Compared with the normal control group, * $P < 0.05$, ** $P < 0.01$; Compared with the model group, #$P < 0.01$.

3.5. Effect of Lithium Carbonate on Apoptosis Protein in Depressed Mice

Compared with the normal group, the expression of Bcl-2 protein in the model group decreased while the levels of Bax and

Caspase-3 increased (P<0. 05) 01); Compared with the model group, the expression of Bcl-2 protein in the Lithium carbonate group increased, and the levels of Bax and Caspase-3 decreased (P<0.01).see Figure5 and Table3

Note: Bcl-2, Bax and Caspase-3 in each group were statistically analyzed(F = 6.01, P = 0.001).Compared with the normal control group, * P < 0.05, ** P < 0.01; Compared with the stress group, ## P < 0.01.

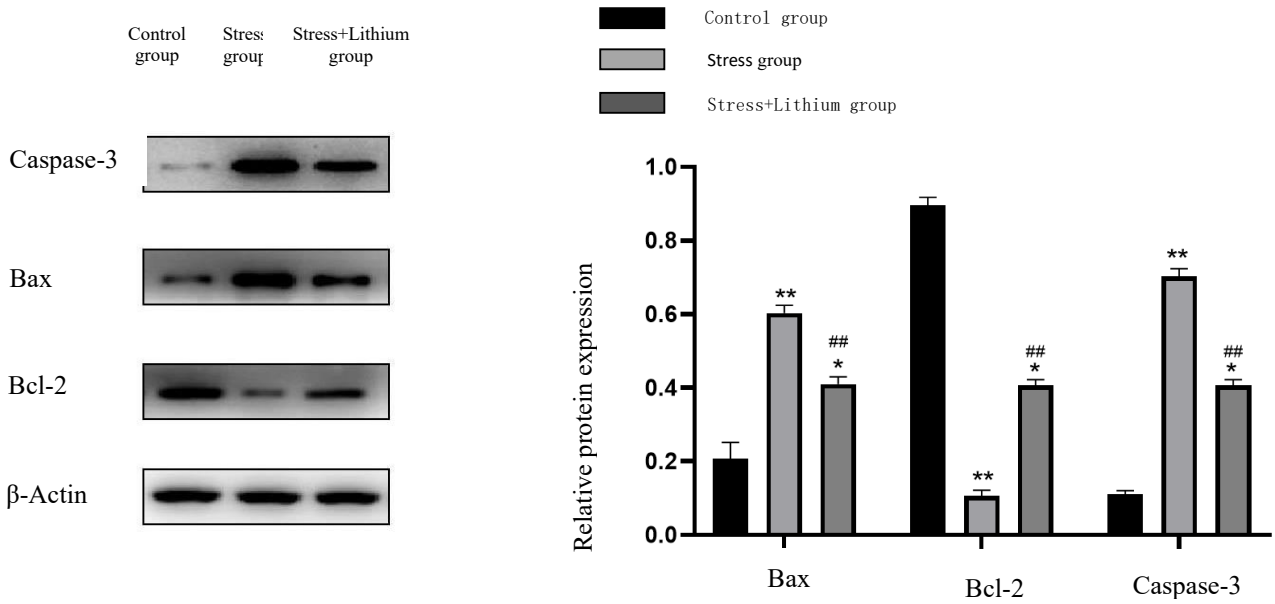

Figure 5: Effect of Lithium carbonate on apoptosis protein in depressed mice

Compared with the normal group, the expression of Bcl-2 protein in the model group decreased while the levels of Bax and Caspase-3 increased (P<0. 05) 01); Compared with the model group, the expression of Bcl-2 protein in the Lithium carbonate group increased, and the levels of Bax and Caspase-3 decreased (P<0.01).

Note: Compared with the normal control group, * P < 0.05, ** P < 0.01; Compared with the model group, ## P < 0.01.

	Bax	Bcl-2	Caspase-3
Control group	0.22±0.0.4	0.92±0.04	0.12±00.1
Stress group	0.61±0.03**	0.10±0.02**	0.71±0.04**
Stress+Lithium group	0.49±0.03*#	0.42±0.07*#	0.41±0.03*#

Table 3: Comparison of apoptotic protein expression among three groups(%)

Bax: F = 5.67, P = 0.018; Bcl-2: F = 6.21, P = 0.001; Caspase-3: F = 5.21, P = 0.011p-cJun/c-Ju

Compared with the normal control group, * P < 0.05, ** P < 0.01; Compared with the model group, #P < 0.01.

4. Discussion

Depression is one of the most common and prominent mental disorders in the world[13]. At present, the incidence rate of depression is increasing year by year, which has become a research hot spot. In the research process, a reasonable animal model of depression is the key, mainly including environmental stress model, social stimulation model, surgical preparation model, Genetically modified animal model and postpartum depression model [14]. Chronic Unpredictable Mild Stress (CUMS) is one of the classic methods for establishing depression models. Through long-term relatively mild and unpredictable human stimuli, animals exhibit depressive like behavior, and its etiology and pathological mechanism are similar to human depression. It has been widely accepted and applied in the establishment of depression animal models [15,16]. Depression like behavior can be detected through behavioral experiments such as sucrose preference test (SPT), open field test (OFT), and forced swimming test (FST) [17,18]. The prefrontal cortex is one of the brain regions that cause mood disorders, and its functional changes play an important role in the pathogenesis of depression [15].

In our present study, we found that lithium carbonate treatment for 4 weeks alleviated depression-like behaviors via decreased the protein levels of nerve cells p-JNK/JNK, P-C-Jun/C-Jun,caspase-3 and Bax and increased Bcl-2 level significantly in the prefrontal cortex of CUMS mice. This means that in addition to the role of lithium in regulating other neurotransmitters, regulating autophagy and JNK/C-Jun signaling pathways may be another mode of action of lithium. Lithium carbonate is a classic emotional stabilizer. For a long time, lithium has been one of the main drugs for treating bipolar disorder. However, there is not yet a good understanding of the etiology or drug treatment mechanisms of this disease[19]. In addition to its current use in patients with bipolar disorder, lithium can also be used to treat acute brain injury, such as stroke and chronic progressive neurodegenerative diseases. Chuang found that lithium in primary neurons can induce cell proliferation near the injury site, accompanied by the loss of proliferating cells in the subventricular area, and some of these proliferating cells show the phenotype of neurons or astrocyte [20]. Tushar Dwivedi et al. confirmed the mechanism of lithium mediated BDNF protection in rat hippocampal neurons [21]. The loss of proximal prefrontal cortex volume in bipolar disorder patients receiving lithium carbonate therapy was suppressed [22]. Since the neuroprotective effect of lithium may be related to clinical improvement, Lithium carbonate is closely related to its neuroprotective effect and improvement of depressive symptoms, which is worth studying.

In this experiment, mice were found to experience of anhedonia after being modeled by CUMS, characterized by a significant decrease in the sugar preference index of the model mice; In open field experiments, there is a decrease in autonomous activity, shorter movement distance, and a decrease in the number of grid crossings; In the forced swimming experiment, the time of immobility was prolonged. But these indexes all increased after the treatment with Lithium carbonate, which indicated that Lithium carbonate could improve the depressive symptoms of depressed mice. At the molecular level, JNK signaling pathway is a member of the Mitogen activated protein kinase (MAPK) family, and can participate in cell proliferation, differentiation, apoptosis, intracellular and extracellular signal transduction and other processes [23]. The activation of JNK is common in various neurodegenerative diseases, and recent studies have gradually confirmed the important role of JNK activation in the regulation of depressive behavior [24].YU et al. showed that Curcumin can inhibit cell apoptosis by inhibiting JNK/c-Jun signaling pathway, down regulating caspase-3 protein expression [25]. In recent years, its use in antidepressant treatment has been carried out in clinic or experiment. Evidence-based medicine has more evidence to confirm the antidepressant effect of Curcumin with great effect size[26],which has been considered as a potential antidepressant [27]. In many studies, curcumin has shown efficacy in regulating neurotransmitter concentration, inflammatory pathways, excitotoxicity, neural plasticity, hypothalamic pituitary adrenal disorders, insulin resistance, oxidative and nitrous stress, and endogenous cannabinoid systems, all of which can participate in the pathophysiology of MDD[28]. One of more anti-depession mechanism is the activation of JNK.

This study show that lithium carbonate has potential points of action on the JNK/c-Jun pathway. Compared with the control group, the expression levels of apoptotic protein Bax and caspase-3 in the model group were significantly increased, and the level of anti-apoptotic protein Bcl-2 was decreased, which all reversed after treatment with Lithium carbonate. The levels of apoptotic protein Bax and caspase-3 were decreased, and the level of anti-apoptotic protein Bcl-2 was increased by lithium carbonate.These results indicate that the antidepressant mechanism of Lithium carbonate is partly through inhibiting JNK/c-Jun, reducing the expression of pro apoptotic protein Bax and Caspase-3, and increasing the level of anti-apoptotic protein Bcl-2 that produce reducing neuronal apoptosis.In fact, the effect of Lithium carbonate on depressive symptoms is also reliable in clinical practice [29]. This study also has the following aspects of insufficient. Firstly,as an antidepressant effect study of drugs, a control group of antidepressants should be set up. Unfortunately, this control group was not set up.Secondly,as an antidepressant effect study of mood stabilizer, a control group of a mood stabilizer should be set up. Unfortunately, this control group was also not set up.Thirdly,to study the therapeutic effects of drugs, it is necessary to investigate the differences in effects under different doses. Unfortunately, such a research design has not be designed.

Declaration

Ethics Approval and Consent to Participate

This study was approved Ethic Committee About Animal Study of Zhejiang Chinese Medical University(20200622-04).

Consent to Publication

All authors agree to publish our paper and no conflict in any interests.

Availability of Data and Material

The data used to support the findings of this study are available from the corresponding author upon request.

Competing Interests

There were not any financial and non-financial competing interests.

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Author's Contribution

Our authors have different contributions to this article and study. Prof.JWD participated in project design, some laboratory work, most statistical analysis, writing papers, and seeking funding. Dr.JHY participated in behavior observation work, part statistical analysis, research reference.Dr.CFP and Dr.LJ participated in some behavior observationsl, most laboratory test.Prof.SFL participated

in part project design, some laboratory work and some writings and final review of article.

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