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The Antidepressant Mechanism of JiaWeiWenDan Decoction Regulating p38MAPK-ERK5 Signal Transduction Pathway

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Abstract

Objective: To investigate the anti-depression mechanism of JiaWeiWenDan Decoction in regulating p38MAPK-ERK5 signal transduction pathway. **Methods:** Depression model rats were randomly divided into Blank Control Group, Model Control Group, Chinese Medicine Treatment Group, and Western Medicine Treatment Group (hereinafter referred to as Blank Group, Model Group, Chinese Medicine Group, and Western Medicine Group), with 48 rats in each group. The mice were treated with p38MAPK-ERK5 on the 7th day, 14th day and 21st day, respectively, and the mice were treated for 28 days. The key targets and cytokines in p38MAPK-ERK5 signal transduction pathway were detected. **Results:** Compared with the Blank Group, the expression of p38MAPKmRNA in the hippocampus of the Model Group was increased. The Chinese Medicine Group and Western Medicine Group could reduce the expression of p38MAPK mRNA ($P < 0.05$). Compared with the Blank Group, the expression of ERK5 mRNA in the prefrontal cortex, hippocampus and hypothalamus of the Model Group decreased significantly ($P < 0.05$). The expression level of p38MAPK protein in hippocampus was increased in the Model Group, and the expression level of p38MAPK protein in hippocampus was decreased in the Chinese Medicine Group ($P < 0.05$). The expression levels of ERK protein in amygdala and hypothalamus in the Model Group were higher than those in the Blank Group, but the expression level of ERK protein in hippocampus was lower than that in the Blank Group. Compared with the Blank Group, the contents of NO and iNOS in hippocampus, frontal cortex and serum of the Model Group were significantly increased ($P < 0.05$); There was no significant difference between the Chinese and Western Medicine Groups. **Conclusion:** The anti-inflammatory effect of JiaWeiWenDan Decoction may be related to the regulation of p38MAPK-ERK5 signaling pathway. With the advance of the treatment week, the best effect was obtained when the treatment was

started on the 7th day of modeling.

Keywords

JiaWeiWenDan Decoction, Depression, p38MAPK-ERK5 Signal Transduction Pathway

1. Introduction

In recent years, with the accelerated pace of people's life and work, coupled with the aggravation of various stress factors, the prevalence of depression has increased year by year. Data show that there are more than 350 million patients with depression in the world [1]. In China, patients with depression account for 4% - 8% of the total population, about 55 million people, and the annual economic burden is more than 60 billion yuan [2]. The disease has become a major and common problem faced by the social public health system. However, as a mental disease with multiple causes and heterogeneity, the pathogenesis of depression has not been clarified so far, and the existing antidepressant western drugs, such as fluoxetine and paroxetine, are easy to produce side effects such as nausea and insomnia when taken for a long time, affecting patient compliance [3], resulting in the lack of effective prevention and treatment strategies and intervention drugs in clinical practice. Traditional Chinese medicine has certain advantages in the prevention and treatment of depression, because it is good at the holistic conditioning of body and mind. If we can give full play to the characteristics of traditional Chinese medicine, explore effective treatment and intervention mechanism for the psychosomatic comorbidity of depression, it is of great significance to the clinical prevention and treatment of depression, especially to reduce the suicide rate.

In the past, depression was mainly caused by stress factors acting on the body, causing dysfunction of nervous, endocrine, immune, and other systems, and then affecting signal transduction pathways, resulting in neuronal damage [3]. However, current research believes that inflammation is a common mechanism of many diseases. Inhibiting the activity of inflammatory cytokines and inflammatory signal transduction pathways can improve depression and increase the therapeutic response of antidepressant drugs [4]. ERK5, as an atypical MPAK pathway, is of great significance to the pathophysiological process and development of diseases [5]. Research on central nervous system diseases, especially depression, is still in its infancy [6]. Therefore, combined with previous clinical practice and experiments, this study confirmed that JiaWeiWenDan Decoction, which is composed of regulating the spleen and stomach, can improve the mood, cognitive function, and somatic symptoms of patients with depression without toxic side effects [3]. Previous related experimental studies suggested that: There is a cascade interaction between HMGB1-TLR4-MyD88-NF-κB and NLRP3 path-

way, and the node is NF-κB, which jointly mediates downstream signals, activates downstream inflammatory factors, and leads to inflammatory cascades, and affects the survival and apoptosis of nervous system cells [7] [8]. JiaWeiWenDan Decoction mediates the process of depression by affecting the above reactions and plays a role in relieving depression and anti-inflammatory mechanism. The p38MAPK-ERK5 signaling pathway is involved. Therefore, this study started with the p38MAPK-ERK5 signaling pathway and integrated the previous research results, in order to explore the pathogenesis and intervention mechanism of depression based on the MAPK pathway and provide a new target for the treatment of depression.

2. Materials and Methods

2.1. Experimental Animals

Two hundred 8-week-old male Sprague-Dawley rats (purchased from Guangdong Medical Laboratory Animal Center, Laboratory animal license number SYXK (XIANG) (2019-0001), weight 180 ± 20 g, clean grade, were provided by Hunan Sleike Jingda Laboratory Animal Co., LTD. Feeding environment: room temperature 22˚C ± 3˚C, relative humidity 55% ± 3%, 12 h circadian rhythm, free to eat and drink, after 1 week to adapt to the environment began the experiment. There were 5 animals/cage in the blank group, and 1 animal/cage in the other groups.

2.2. Grouping of Animals

According to the random number table grouping method, 192 SD rats with similar behavioral scores were selected from 200 SD rats and randomly divided into blank control group, model control group, Chinese medicine treatment group and western medicine treatment group (hereinafter referred to as blank group, model group, Chinese medicine group and western medicine group), with 48 rats in each group.

2.3. The Depression Rat Model Was Established

Except for the blank group, the rats in the other groups were kept alone and subjected to 21 days of unpredictable stress stimuli from the day of grouping, including 24 h fasting, 24 h water deprivation, overnight lighting, swimming in cold water at 4˚C for 5 min, drying in an oven at 45˚C for 5 min, tail clamped for 1min, high-speed horizontal shaking for 3 min, electric shock to the sole of the foot at 100 volts for 1 min, and tail suspension for 1 min. A total of 9 stimuli were administered, one was randomly arranged to be given daily for 21 days, and each stimulus was presented 2 - 3 times.

2.4. Methods of Administration

The TCM group was given gavage of JiaWeiWenDan Decoction 12 g/(kg·d), the western medicine group was given gavage of fluoxetine 1.8 mg/(kg·d), and the

model group and the blank group were given gavage of normal saline 2 mL/(kg·d), starting at 8:00 am every day for 28 days.

JiaWeiWenDan Decoction composition: Zhishi 10 g, Pinellia 15 g, Poria 20 g, Tangerine 10 g, Codonopsis 10 g, Zhuru 20 g, Rhizoma Cyperi 20 g, Maidong 30 g, Chaihu 30 g, Platycodon grandiflorum 20 g, Licorice 10 g.

2.5. Indicators of Observation

The contents of NO and iNOS were determined by nitrate reduction method, ELISA and enzymatic colorimetry.

The expression of p38MAPK and ERK5 protein and phosphorylated ERK5 in brain regions (frontal cortex and hippocampus) were detected by immunohistochemistry and Western-blotting.

The expression of p38MAPK and ERK5 mRNA in brain regions (frontal cortex, hippocampus) was detected by Real-Time PCR.

2.6. Statistical Methods

The experimental data were expressed as mean ± standard deviation ($\overline{\chi} \pm S$) and analyzed by SPSS 23.0 statistical software. One-Way ANOVA was used for comparison between multiple samples, and q test was used for pairwise comparison. $P < 0.05$ was considered significant.

3. Results of the Experiment

3.1. Expression of p38MAPK and ERK5 mRNA in Each Group

Compared with the blank group, the expression of p38MAPKmRNA in the hippocampus of the model group increased. The Chinese medicine group and western medicine group could reduce the expression of p38MAPK mRNA ($P < 0.05$). Compared with the blank group, the expression of ERK5 mRNA in the prefrontal cortex, hippocampus and hypothalamus of the model group decreased significantly ($P < 0.05$), as shown in Table 1 and Table 2.

3.2. The Protein Expression of p38MAPK and ERK5 in Each Group Was Detected

The expression level of p38MAPK protein in hippocampus was increased in the model group, and the expression level of p38MAPK protein in hippocampus was decreased in the Chinese medicine group ($P < 0.05$). The expression levels of ERK protein in amygdala and hypothalamus in the model group were higher than those in the blank group, but the expression level of ERK protein in hippocampus was lower than that in the blank group, as shown in Table 3 and Table 4.

3.3. Effects of Each Group on the Expression of NO and iNOS in Hippocampus, Frontal Cortex and Serum of Rats

The contents of NO in hippocampus, frontal cortex and serum were measured

by nitrate reductase method. Compared with the blank group, the contents of NO in hippocampus, frontal cortex and serum of the model group were significantly increased ($P < 0.05$). Compared with the model group, the contents of NO in hippocampus, frontal cortex and serum of the Chinese medicine group and the western medicine group were significantly decreased ($P < 0.05$), but there was no significant difference between the Chinese and western medicine groups, as shown in Table 5.

Compared with the blank group, the expression of iNOS in the hippocampus and frontal cortex of the model group was significantly increased ($P < 0.05$); Compared with the model group, the expression of iNOS in the hippocampus and frontal cortex of the Chinese medicine group and the western medicine group was significantly decreased ($P < 0.05$); There was no significant difference between the Chinese and western medicine groups, as shown in Table 6.

Table 1. Comparison of p38MAPK mRNA expression levels in different brain regions of rats in each group ($\overline{\chi} \pm S$).

Group	Prefrontal cortex	Amygdala	Seahorse	Hypothalamus
Blank group	1.000 ± 0.065	1.000 ± 0.097	1.000 ± 0.350	1.000 ± 0.003
Model group	0.919 ± 0.075	0.838 ± 0.124	1.812 ± 0.195 [a]	0.851 ± 0.313
Chinese Medicine Group	0.920 ± 0.160	0.969 ± 0.038	0.52 ± 0.180 [b]	0.908 ± 0.223
Western medicine group	0.936 ± 0.108	0.960 ± 0.356	0.593 ± 0.208 [b]	0.938 ± 0.139

[a]Compared with the blank group, $P < 0.05$; [b]Compared with the model group, $P < 0.05$.

Table 2. Comparison of ERK5 mRNA expression levels in different brain regions of rats in each group ($\overline{\chi} \pm S$).

Group	Prefrontal cortex	Amygdala	Seahorse	Hypothalamus
Blank group	1.000 ± 0.056	1.000 ± 0.082	1.000 ± 0.070	1.000 ± 0.078
Model group	0.700 ± 0.103[a]	0.231 ± 0.006	0.497 ± 0.052[a]	0.407 ± 0.074[a]
Chinese Medicine Group	0.798 ± 0.110	0.267 ± 0.018	0.559 ± 0.085	0.415 ± 0.017
Western medicine group	0.812 ± 0.056	0.215 ± 0.008	0.647 ± 0.132	0.435 ± 0.036

[a]Compared with the blank group, $P < 0.05$.

Table 3. Comparison of p38MAPK protein expression levels in different brain regions of rats in each group ($\overline{\chi} \pm S$).

Group	Prefrontal cortex	Amygdala	Seahorse	Hypothalamus
Blank group	1.145 ± 0.05	0.723 ± 0.02	0.895 ± 0.03	0.881 ± 0.02
Model group	1.375 ± 0.04	0.691 ± 0.02	1.29 ± 0.05 [a]	0.822 ± 0.03
Chinese Medicine Group	0.679 ± 0.02	0.770 ± 0.03	0.521 ± 0.02 [b]	0.741 ± 0.02
Western medicine group	1.367 ± 0.06	1.098 ± 0.04[b]	1.163 ± 0.04	0.990 ± 0.03

[a]Compared with the normal control group, $P < 0.05$; [b]Compared with the model group, $P < 0.05$.

Table 4. Comparison of ERK protein expression levels in different brain regions of rats in each group ($\overline{\chi} \pm S$).

Group	Prefrontal cortex	Amygdala	Seahorse	Hypothalamus
Blank group	0.33 ± 0.18	0.15 ± 0.02	0.33 ± 0.03	0.14 ± 0.02
Model group	0.27 ± 0.02	0.36 ± 0.03 [a]	0.19 ± 0.03 [a]	0.39 ± 0.03 [a]
Chinese Medicine Group	0.13 ± 0.02	0.32 ± 0.02	0.31 ± 0.05 [b]	0.31 ± 0.06
Western medicine group	0.31 ± 0.03	0.33 ± 0.03	0.18 ± 0.04	0.35 ± 0.04

[a]Compared with the blank group, $P < 0.05$; [b]Compared with the model group, $P < 0.05$.

Table 5. Effect of NO expression in hippocampus, frontal cortex and serum of rats in each group.

Group	Prefrontal Cortex (umol/g)	Serum (mol/mL)	Seahorse (umol/g)
Blank group	35.86 ± 2.05	56.64 ± 12.28	44.81 ± 2.35
Model group	52.56 ± 3.76a	76.20 ± 11.79 [a]	62.10 ± 2.54 [a]
Chinese Medicine Group	39.13 ± 2.75 [b]	59.72 ± 14.83[b]	46.49 ± 3.78 [b]
Western medicine group	33.02 ± 1.54	56.07 ± 13.47	44.86 ± 12.37

[a]Compared with the blank group, $P < 0.05$; [b]Compared with the model group, $P < 0.05$.

Table 6. Effect of rats in each group on iNOS expression in hippocampus, frontal cortex and serum (pg/mL).

Group	Prefrontal Cortex	Serum	hippocampus
Blank group	32.34 ± 2.08	23.62 ± 11.94	32.86 ± 12.38
Model group	49.09 ± 2.82 [a]	25.98 ± 13.48	44.97 ± 11.84 [a]
Chinese Medicine Group	33.48 ± 2.51 [b]	23.3 ± 11.92	31.30 ± 12.14 [b]
Western medicine group	31.24 ± 1.55	30.51 ± 11.32	30.93 ± 12.09

[a]Compared with the blank group, $P < 0.05$; [b]Compared with the model group, $P < 0.05$.

4. Discussion

In 1995, Maes *et al.* [9] reported that the acute phase protein in plasma of patients with severe depression was positive and the content was significantly increased during the attack, while the acute phase protein concentration decreased, and the plasma indexes were negative during the remission period. According to the results, it is speculated that depression is related to inflammatory response, and the theory of inflammatory response in depression is proposed. Recently, the study of inflammatory response has become one of the research hotspots in the pathogenesis of depression. Clinical studies have found that cytokines closely related to inflammatory response, namely inflammatory cytokines, are closely related to depression [10]. Inflammatory cytokines are involved in multiple systems of the body. The body releases inflammatory cytokines to activate peripheral immunity, which leads to immune system or neuroendocrine system disorders and depression. Benrichk J *et al.* [11] observed the effect of inflammatory

cytokine IL-6 on CRH secretion and proposed that inflammatory cytokines lead to excessive activation of HPA axis by regulating the negative feedback inhibition of HPA axis by peripheral glucocorticoids. Constant *et al.* [12] found in animal experiments that inflammatory cytokines such as IL-6 can enhance the activities of neuronal transmitters 5-HT and DA. This change can accelerate the reuptake of monoamine neurotransmitters and reduce their synaptic concentration, suggesting that inflammatory cytokines play an important role in the transformation of depression. The theory of inflammatory response provides a theoretical basis for the treatment of depression and provides a new direction for the clinical treatment of depression [13] [14]. Whether anti-depression can be exerted by interfering with the level, expression and activity of inflammatory factors has become one of the research directions of antidepressant drugs.

Mitogen-activated protein kinase (MAPK), a signal transduction pathway closely related to inflammatory response, is an important signal system used by eukaryotic cells to transact extracellular information into cells, thereby causing cell proliferation, differentiation, transformation and apoptosis. At present, based on sequence homology and functional differences, at least: extracellular signal- regulated kinase 1/2 (ERK1/2) pathway, c-Jun N-terminal kinase (JNK) pathway, p38 mitogen-activated protein kinase (p38 MAPK) pathway and extracellular signal-regulated kinase 5 (ERK5) pathway have been identified [3]. A total of 4 MAPK signal transduction pathways, the first two pathways have been confirmed in the previous study of the project group. This study investigated the role of key factors in the p38MAPK-ERK5 signaling pathway in the development of depression, and the results showed that: JiaWeiWenDan Decoction can improve the mRNA and protein levels of p38MAPK and ERK5 in the hippocampus of depression model rats, regulate the expression of NO and iNOS in the hippocampus, frontal cortex, and serum, and the content of inflammatory factors IL-6, IL-1β, and IL-2. The mechanism may be related to the regulation of p38MAPK-ERK5 signaling pathway. However, whether JiaweiWendan Decoction has an overall network regulation mechanism remains to be explored. Since Chinese medicine has multiple targets and an overall regulation mechanism, it is different from western medicine. Therefore, it is of great value to explore the mechanism of Chinese medicine compound in the intervention of depression for the prevention and treatment of the disease.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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