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Influence of miR-155 on behaviors of depression mice through regulating Wnt/β-catenin signaling pathway

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Abstract. – OBJECTIVE: To study the influence of micro ribonucleic acid (miR)-155 on depression-like behaviors of depression mice, and to explore the role of Wnt/β-catenin signaling pathway in behavioral regulation of depression mice.

MATERIALS AND METHODS: The mouse model of depression was established *via* chronic unpredictable mild stress (CUMS). All mice were randomly divided into control group (n=12), model group (n=12), and fluoxetine group (n=12). The expression level of miR-155 in the hippocampus of mice in each group was detected *via* quantitative Polymerase Chain Reaction (qPCR). The changes in the behaviors of mice in each group were evaluated *via* behavioral experiments. The apoptosis level in the hippocampus of mice in each group was detected *via* terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) staining. Moreover, the content of inflammatory factors in the hippocampus of mice in each group was detected using the enzyme-linked immunosorbent assay (ELISA) kits. The expression levels of Wnt/β-catenin signaling pathway-related proteins in each group were detected *via* Western blotting.

RESULTS: The expression level of miR-155 in the hippocampus was significantly higher in model group than that in control group ($p<0.01$). Meanwhile, the expression level of miR-155 was significantly lower in fluoxetine group than that in model group ($p<0.01$). There were no statistically significant differences in the crossing score and rearing score in the open field test among groups ($p>0.05$). Compared with those in control group, the immobility time in tail suspension test and forced swimming test were significantly increased ($p<0.01$), while the sucrose preference degree significantly declined ($p<0.01$) in model group. Fluoxetine could significantly reduce the immobility time in tail suspension test and forced swimming test ($p<0.01$) and increase the sucrose preference degree ($p<0.01$) in model group. The number of TUNEL-positive cells in the hippocampus of mice in model group was significantly larger than that in control group ($p<0.01$). Fluoxetine could effectively reduce the number of TUNEL-positive cells in the hippocampus ($p<0.01$). Compared with those in control group, the content of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-6 in the hippocampus was significantly increased ($p<0.01$), while the content of IL-10 was significantly decreased ($p<0.01$) in model group. Fluoxetine could effectively reduce the content of TNF-α, IL-1β, and IL-6 ($p<0.01$) and increase the content of IL-10 ($p<0.01$). Besides, in model group, the expression levels of dishevelled-1 (DVL-1) and β-catenin in hippocampus remarkably declined ($p<0.01$), while the expression levels of glycogen synthase kinase-3β (GSK-3β) and adenomatous polyposis coli (APC) were remarkably increased ($p<0.01$) compared with those in control group. Fluoxetine could effectively lower the expressions of GSK-3β and APC in the hippocampus ($p<0.01$) and increase the expressions of DVL-1 and β-catenin ($p<0.01$) in model group.

CONCLUSIONS: MiR-155 is involved in regulating the depression-like behaviors of depression mice through promoting the release of inflammatory factors and the apoptosis of hippocampal neurons. Its mechanism may be related to the inhibition of the Wnt/β-catenin signaling pathway.

Key Words
MiR-155, Depression, Neuroinflammation.

Introduction

Depression is a kind of emotional disorder characterized by the long-term persistent depressed mood and retardation of thinking, accompanied by suicidal tendency. According to the data of the World Health Organization, there have been more than 350 million depression patients in the world as of 2017[1]. The pathogenesis of depression remains

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unclear, and there have been no reliable and timely diagnosis means for depression currently, greatly limiting the treatment of depression[2,3]. The anti-depressive drugs developed based on the neurotransmitter hypothesis can effectively increase the content of various monoamine neurotransmitters in the synaptic cleft, thereby alleviating the symptoms of depression. However, these drugs have such deficiencies, such as slow onset of action, low efficiency, and many adverse reactions[4,5]. Schule et al[6] found that 60% of patients have emotional anesthesia and 39% of patients have a suicidal tendency after taking anti-depressive drugs. It is extremely important to further explore the pathogenesis of depression and search the new therapeutic target for depression. There is a lot of research evidence that depression may be closely related to neuroinflammation. Yu et al[7] showed that the phosphodiesterase-4 inhibitor can relieve the pathological process of neuropsychiatric diseases in rats through reducing neuroinflammation, thus improving the depression-like behaviors of depression rats.

Micro ribonucleic acid (miR)-155, as a typical multifunctional gene, is highly expressed in various diseases, which induces apoptosis *via* affecting the expression of inflammatory factors. Yao et al[8] found that the expression level of miR-155 is significantly increased in myocardial cells of patients with acute myocardial infarction, and it is inversely proportional to the survival time of patients. According to Onodera et al[9], the miR-155 overexpression will significantly increase the release of inflammatory factors in vascular endothelial cells, aggravating the vascular endothelial injury. There is no definite research evidence proving that the expression of miR-155 is correlated with depression. Zhang et al[10] have demonstrated that miR-155 can inhibit the Wnt/β-catenin signaling pathway through increasing the expression of adenomatous polyposis coli (APC – an inhibitor of Wnt/β-catenin signaling pathway). In this study, the mouse model of depression was established *via* chronic unpredictable mild stress (CUMS). The aim was to investigate the regulatory effects of miR-155 on depression and its underlying mechanism.

Materials and Methods

Experimental Animals and Design

A total of 36 male C57BL/6 mice weighing (20±2) g were purchased from Medical Laboratory Animal Center of Guangdong Province [license No.: SCXK (Guangdong, China) 2016-0041]. These mice were fed adaptively for 1 week before the experiment under the temperature of (24±2)°C and humidity of (50±10)% in line with the circadian rhythm and had free access to food and water. The 36 mice were randomly divided into control group (n=12), model group (n=12), and fluoxetine group (n=12). The depression model was established *via* CUMS in model group and fluoxetine group. After successful modeling, fluoxetine (10.0 mg/kg) was intraperitoneally injected into the mice in fluoxetine group, while an equal volume of normal saline was injected into the mice in control group and model group. After drug administration for 3 consecutive weeks, the depression-like behaviors of mice in each group were evaluated *via* behavioral experiments. After that, the mice were executed immediately, and hippocampus was isolated and stored in a refrigerator at -30°C for subsequent researches. All experimental operations were performed in accordance with the relevant regulations of the NIH Guide for the Use of Laboratory Animal. The experimental protocol was reviewed and approved by the Laboratory Animal Ethics Committee of Jinan University Animal Center.

Establishment of CUMS Model

The mouse model of depression was established *via* different stress every day, and the stress methods should be different every day for at least 4 consecutive weeks and not interrupted. The specific stress methods was as follows: soaking of padding in water and cage wetting for 24 h, electric shock against foot for 10 s, swimming in ice water (4°C) for 3 min, body binding with a centrifuge tube of the right size for 2 h, food deprivation for 24 h, cage tilt (45°) for 24 h, water deprivation for 24 h, tail clamping with binder clips of the right size for 2 min, swimming in warm water (56°C) for 3 min. Whether the mouse model of depression was established successfully was verified *via* behavioral experiments.

Evaluation of Depression-Like Behaviors of Mice Via Behavioral Experiments

The depression-like behaviors of mice were evaluated using open field test, sucrose preference test, tail suspension test, and forced swimming test. The specific operations were as follows:

Open field test: an open box with a square bottom (60 cm × 60 cm × 20 cm) was equally divided into 36 equal-sized grids. After the odor in the experimental space was removed using alcohol, the mice were placed in the center of each quadrant.

Table I. Primer sequences.

Gene	Forward primer	Reverse primer
miR-155	5'-TTAATGCTAATCGTGATAGGGG-3'	5'-GCTTCGGCAGCACATATACTAAAAT-3'
GAPDH	5'-CTGAACGGGAAGCTCACTGG-3'	5'-TCCGATGCCTGCTTCACTAC-3'

The crossing score (the number of grids stridden over by hind legs) and the rearing score (the times of forelimb standing) of mice in each group in the box within 5 min were recorded.

Sucrose preference test: the sucrose intake training was conducted for the mice in each group at 1 d before the test. Each mouse was fed in a separate cage, and had free access to water (20 mL 10% sucrose water contained in 2 bottles). After 24 h, one of the sucrose water bottles was replaced with 20 mL pure water in the same container, and the new one was placed for 24 h. At the beginning of the test, each mouse was fasted for water for 24 h. 2 bottles containing 20 mL sucrose water and 20 mL pure water were placed in the cage (the total weight of each bottle was measured before the test). After 2 h, the weight of each bottle was measured again, and the sucrose preference degree in each group was calculated.

Tail suspension test: the end of the tail was fixed on a hook using the medical tape with the head downwards to ensure that the body could not be turned over. The immobility time of mice with the tail suspended within 6 min was recorded.

Forced swimming test: the mice were placed in a transparent plastic barrel with an appropriate amount of water (the limbs of mice could not touch the bottom of the barrel) at an appropriate temperature. The experimental images of mice were recorded for 6 min, and the immobility time in the last 4 min was measured.

Expression Level of MiR-155 in Hippocampus of Mice

Hippocampus tissues were taken in each group, weighed, added with an appropriate amount of TRIzol (Invitrogen, Carlsbad, CA, USA), homogenized with a manual homogenizer, transferred into a new centrifuge tube, shaken for 10 min, and placed for 10 min. Then, the RNA was extracted from the hippocampus in each group strictly according to the instructions of the RNA extraction kit (Nanjing Vazyme Biotech Co., Ltd., Nanjing, China), and the absorbance $(A)_{260}/A_{280}$ and optical density (OD) value of RNA were determined. The reverse transcription system was prepared in strict accordance with the instructions of the reverse transcription kit (TaKaRa, Otsu, Shiga, Japan). The polymerase chain reaction (PCR) parameters were adjusted as follows: 37°C for 15 min, and 85°C for 5 min, followed by reverse transcription. The quantitative polymerase chain reaction (qPCR) system (TaKaRa, Otsu, Shiga, Japan) was also prepared, and the qPCR parameters were set up on the qPCR instrument: pre-denaturation at 95°C for 30 s, PCR at 95°C for 5 s, and at 60°C for 34 s, a total of 40 cycles. The qPCR primers (Invitrogen, Carlsbad, CA, USA) were designed and synthesized, and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as an internal reference. The sequences are shown in Table I. The relative expression level of miR-155 was calculated using $2^{-\Delta\Delta Ct}$ based on the Ct value of the amplification result and expressed as miR-155/GAPDH.

Detection of Number of Apoptotic Cells Via Terminal Deoxynucleotidyl Transferase-Mediated dUTP Nick End Labeling (TUNEL) Staining

The TUNEL-positive cells in the hippocampus were detected using the TUNEL staining kit (Beyotime, Shanghai, China). The mice in each group were executed immediately after behavioral experiments, and the whole brain was taken out and cut into 40 μm-thick brain slices using a freezing microtome. Then, these brains were treated with freshly-prepared 3% hydrogen peroxide for 10 min and washed with phosphate-buffered saline (PBS) for 3 times strictly according to the instructions of the kit. The slices were observed and photographed under a confocal fluorescence microscope, and the number of TUNEL-positive cells in the hippocampus was calculated in each group. The yellow-green fluorescence indicated the positive cells, namely apoptotic cells.

Determination of Content of Inflammatory Factors

The expression levels of inflammatory factors in hippocampus of mice in each group were detected using the enzyme-linked immunosorbent assay (ELISA) kits of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, and IL-

10 (Wuhan Boster Biological Technology Co., Ltd., Wuhan, China): the hippocampus tissues were taken, weighed, added with an appropriate amount of PBS, homogenized on ice with a homogenizer, and centrifuged at 12,000 rpm and 4°C for 10 min. The supernatant was collected. The standard solution of TNF-α, IL-1β, IL-6, and IL-10 was prepared for plotting the standard curves. 100 μL standard solution or sample solution was added into a 96-well plate taken from the kit, sealed and incubated at 37°C for 1.5 h. After the residual liquid was patted dry, 100 μL biotin-labeled antibody was added for incubation at 37°C for 1 h. After the residual liquid was patted dry, 250 μL washing solution and 100 μL ABC working solution were added, followed by incubation at 37°C for 30 min. After the plate was washed, it was added with 90 μL tetramethylbenzidine (TMB) developing solution and sealed (Thermo Fisher Scientific, Waltham, MA, USA), followed by incubation in a dark place at 37°C for 20 min. Next, the TMB stop buffer was added and mixed evenly, and the absorbance was detected at a wavelength of 450 nm using a microplate reader. The standard curves were plotted using CurveExpert 1.4 software, and the concentrations of TNF-α, IL-1β, IL-6, and IL-10 in each sample were calculated.

Detection of Protein Expression Via Western Blotting

The hippocampus tissues were taken, weighed, added with 1 mL radioimmunoprecipitation assay (RIPA) lysis buffer (Beijing TDY Biotech Co., Ltd., Beijing, China) per 100 mg and 1% protease inhibitor, homogenized on ice with the homogenizer and centrifuged at 12,000 rpm and 4°C for 10 min. The supernatant was collected as the total protein. The protein was quantified using the bicinchoninic acid (BCA) protein quantification kit (Pierce, Rockford, IL, USA). An appropriate number of protein samples were taken in each group to prepare the loading buffer in the same concentration. The sodium dodecyl sulfate-polyacrylamide gel electrophoresis gel was prepared, followed by electrophoresis. Then, the protein was transferred onto a polyvinylidene difluoride (PVDF) membrane (Millipore, Billerica, MA, USA) and sealed with the freshly-prepared 5% skim milk powder for 1 h. The target band was cut and incubated with the corresponding primary antibodies, including dishevelled-1 (DVL-1) (1:1000, CST, Danvers, MA, USA), β-catenin (1:1000, CST, Danvers, MA, USA), glycogen synthase kinase-3β (GSK-3β) (1:1000, CST, Danvers, MA, USA), APC (1:1000, CST, Danvers, MA, USA) and GAPDH (internal reference antibody, 1:1000, CST, Danvers, MA, USA), at 4°C overnight. After the band was washed with Tris-Buffered Saline-Tween 20 (TBST 20) for 3 times, the horseradish peroxidase (HRP)-labeled goat anti-rabbit secondary antibody (1:5000, Shanghai Yihyson Biological Co., Ltd., Shanghai, China) was added for incubation at room temperature for 2 h. After the band was washed again with TBST for 3 times, the enhanced chemiluminescence (ECL) solution (Thermo Fisher Scientific, Waltham, MA, USA) was added for image development and exposure in a dark room. Finally, the expression levels of related proteins were calculated after image processing with ImageJ.

Statistical Analysis

The data in this study were expressed as mean ± standard deviation. Statistical Product and Service Solutions (SPSS) 19.0 software (SPSS Inc., Chicago, IL, USA) was used for data processing. The analysis of variance was used for the comparison among groups. The Bonferroni's method was adopted for pairwise comparison in the case of homogeneity of variance, while Welch's method was adopted in the case of heterogeneity of variance. $p<0.05$ suggested that the difference was statistically significant.

Results

Expression Level of MiR-155 in Hippocampus

The expression level of miR-155 in the hippocampus of mice in each group was detected *via* qPCR. As shown in Figure 1, the expression level of miR-155 in the hippocampus of mice was significantly higher in model group than that in control group ($p<0.01$), while it significantly declined in model group after treatment with fluoxetine ($p<0.01$).

Evaluation of Depression-Like Behaviors of Mice

To eliminate the influence of the changes in autonomic activities on the immobility time of mice, the open field test was performed to evaluate the autonomic activities of mice in each group. As shown in Figure 2, there were no statistically significant differences in the crossing score and rearing score in the open field test among groups

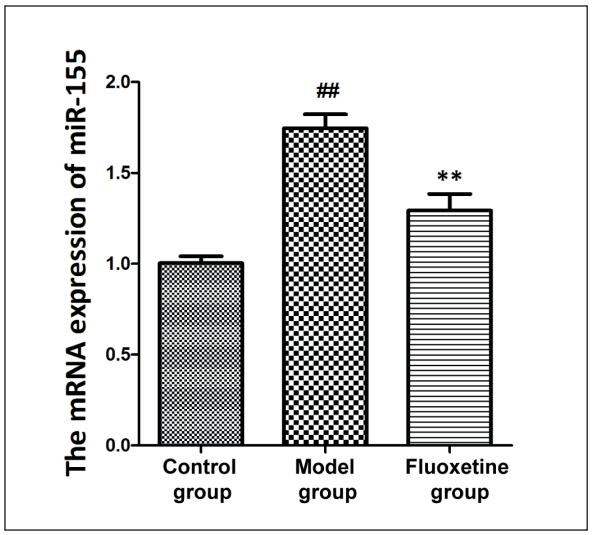

Figure 1. Expression level of miR-155 in the hippocampus of mice in each group. The expression level of miR-155 in the hippocampus of mice was significantly higher in model group than that in control group, and it was significantly lower in fluoxetine group than that in model group. $^{\#\#}p<0.01$ *vs.* control group, $^{**}p<0.01$ *vs.* model group.

($p>0.05$). The depression-like behaviors of mice in each group were further evaluated *via* sucrose preference test, tail suspension test, and forced swimming test. As shown in Figure 3, compared with those in control group, the sucrose preference degree significantly declined ($p<0.01$), while the immobility time in tail suspension test and forced swimming test was significantly increased ($p<0.01$, $p<0.01$) in model group. Fluoxetine could significantly increase the sucrose preference degree ($p<0.01$) and significantly reduce the immobility time in tail suspension test and forced swimming test ($p<0.01$, $p<0.01$) in model group.

Apoptosis Level in Hippocampus

The apoptosis level in the hippocampus of mice in each group was detected *via* TUNEL staining. The results revealed that there were no TUNEL-positive cells in the hippocampus of mice in control group. The number of TUNEL-positive cells in the hippocampus of mice in model group was significantly larger than that in control group ($p<0.01$). Fluoxetine could effectively reduce the number of TUNEL-positive cells in the hippocampus ($p<0.01$) (Figure 4).

Content of Inflammatory Factors in Hippocampus

The content of inflammatory factors in the hippocampus of mice in each group was detected using the ELISA kits. The results showed that compared with those in control group, the content of TNF-α, IL-1β, and IL-6 in the hippocampus was significantly increased ($p<0.01$), while the content of IL-10 was significantly decreased ($p<0.01$) in model group. Fluoxetine could significantly reduce the content of TNF-α, IL-1β, and IL-6 ($p<0.01$) and significantly increase the content of IL-10 ($p<0.01$) (Figure 5).

Expression levels of related proteins in Wnt/β-catenin signaling pathway in the hippocampus of mice

The expression levels of related proteins in the Wnt/β-catenin signaling pathway in the hippocampus of mice in each group were detected *via* Western blotting. As can be seen from Figure 6, in model group, the expression levels of DVL-1 and β-catenin in the hippocampus remarkably declined ($p<0.01$), while the expression levels of GSK-3β and APC were remarkably increased

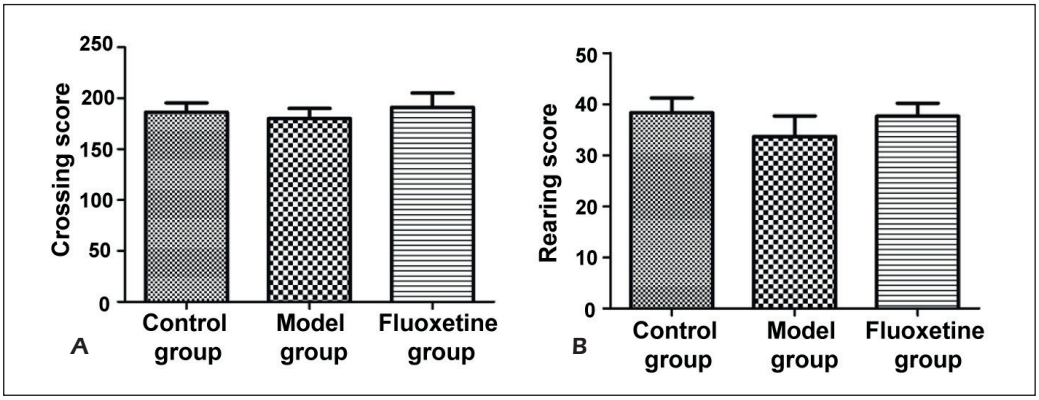

Figure 2. Autonomic activities of mice in each group evaluated via open field test. **A**, Crossing score; **B**, Rearing score. There were no statistically significant differences in the crossing score and rearing score in the open field test among groups.

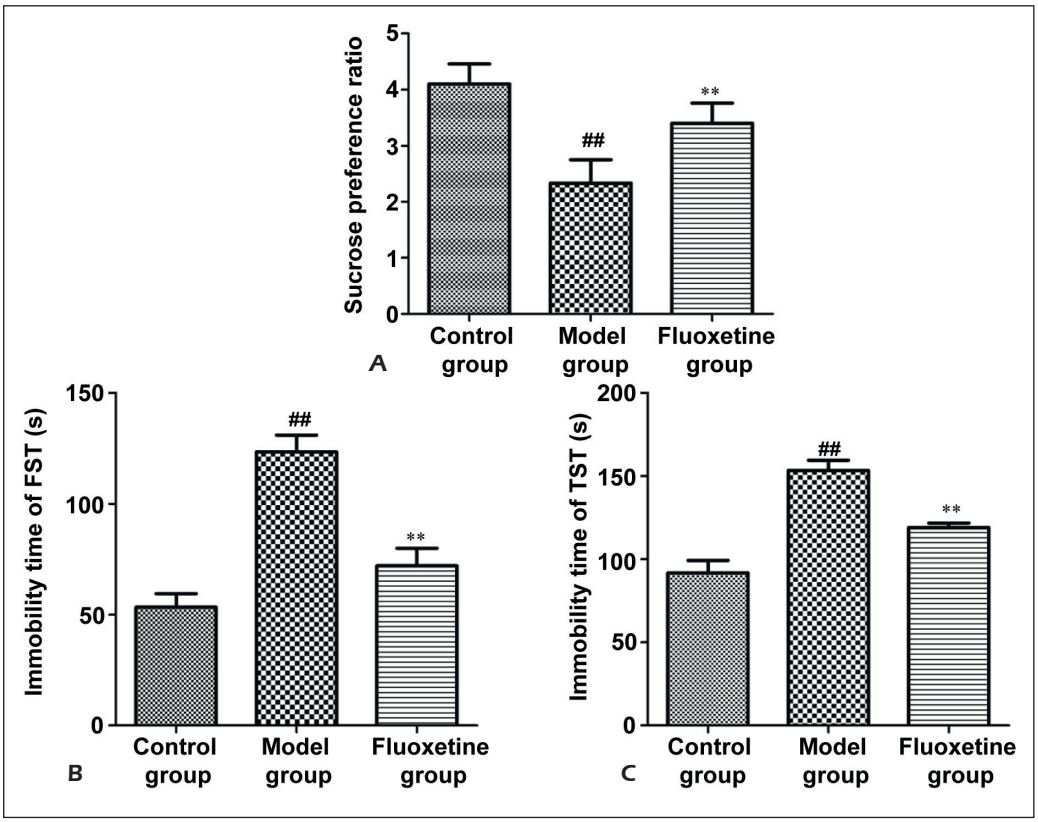

Figure 3. Depression-like behaviors of mice in each group evaluated via behavioral experiments. **A**, Sucrose preference test; **B**, Tail suspension test; **C**, Forced swimming test. The sucrose preference degree was significantly lower in model group than that in control group, while the immobility time in tail suspension test and forced swimming test was significantly longer in model group than that in control group. The sucrose preference degree was significantly higher in fluoxetine group than that in model group, while the immobility time in tail suspension test and forced swimming test was significantly shorter in fluoxetine group than that in model group. $^{\#\#}p<0.01$ *vs.* control group, $^{**}p<0.01$ *vs.* model group.

($p<0.01$) compared with those in control group. Fluoxetine could effectively lower the expressions of GSK-3β and APC in the hippocampus ($p<0.01$) and increase the expressions of DVL-1 and β-catenin ($p<0.01$) in model group.

Discussion

The pathogenic factors and pathological mechanism of depression, a complex refractory emotional neuropsychiatric disease, have not been clarified yet[11]. At present, it is argued in the mainstream view that the pathological mechanism of depression is mainly divided as follows: monoamine neurotransmitter hypothesis[12], neuroinflammation hypothesis, etc.[13]. Most first-line anti-depressive drugs used clinically are developed based on the monoamine neurotransmitter hypothesis. These drugs alleviate depression symptoms through increasing the levels of 5-hydroxytryptamine in synaptic cleft, dopamine, and norepinephrine. However, even though the drugs can raise the level of monoamine neurotransmitter in synaptic cleft in a short term, several weeks or more is often needed in relieving depression symptoms and the treatment rate is low[14,15]. Currently, a large amount of research evidence shows that the occurrence of depression may not be based on the disorder of neurotransmitter level or not just depend on the decline in neurotransmitter level in the synaptic cleft. The pathogenesis of depression remains to be further explored, and there are certain difficulties in improving depression only through increasing the neurotransmitter.

MiRNAs exert a variety of biological effects in the human body through affecting the expression of key genes. Yoon et al[16] found that miR-155 can inhibit the expression of connective tissue growth factor and anti-angiogenic platelet-1 in

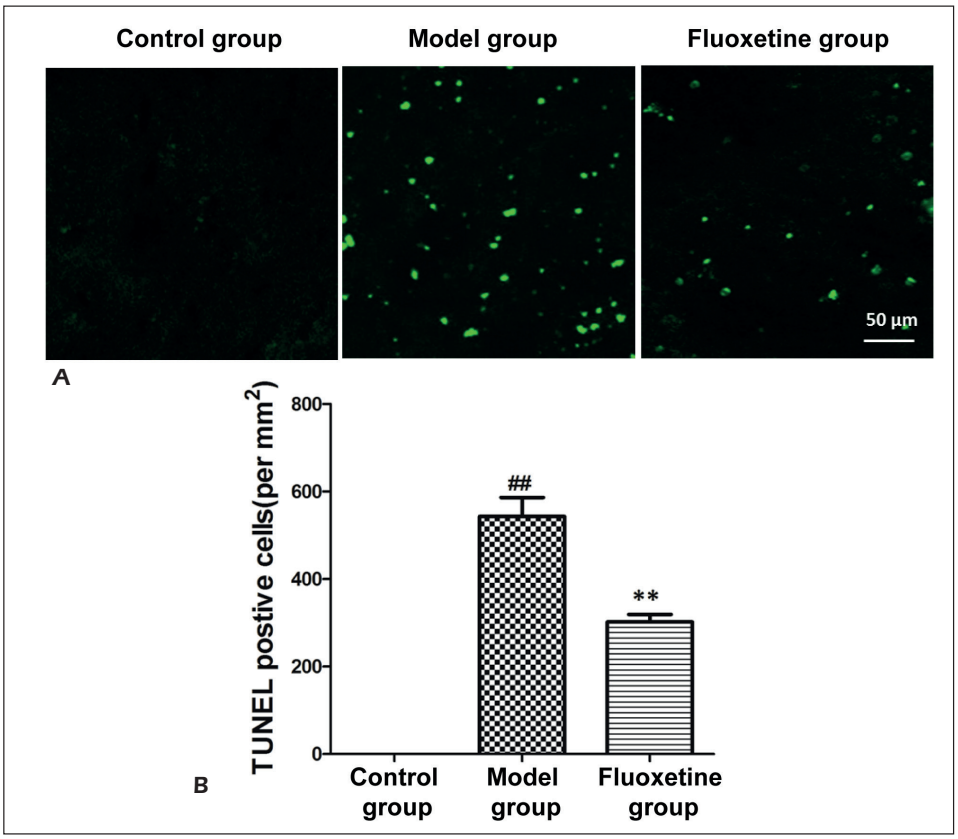

Figure 4. Apoptosis level in the hippocampus of mice in each group detected via TUNEL staining. **A**, Micrograph; **B**, statistical graph (scale bar = 50 μm). The number of TUNEL-positive cells in the hippocampus of mice in model group was significantly larger than that in control group, and it was significantly smaller in fluoxetine group than that in model group. $^{\#\#}p<0.01$ *vs.* control group, $^{**}p<0.01$ *vs.* model group.

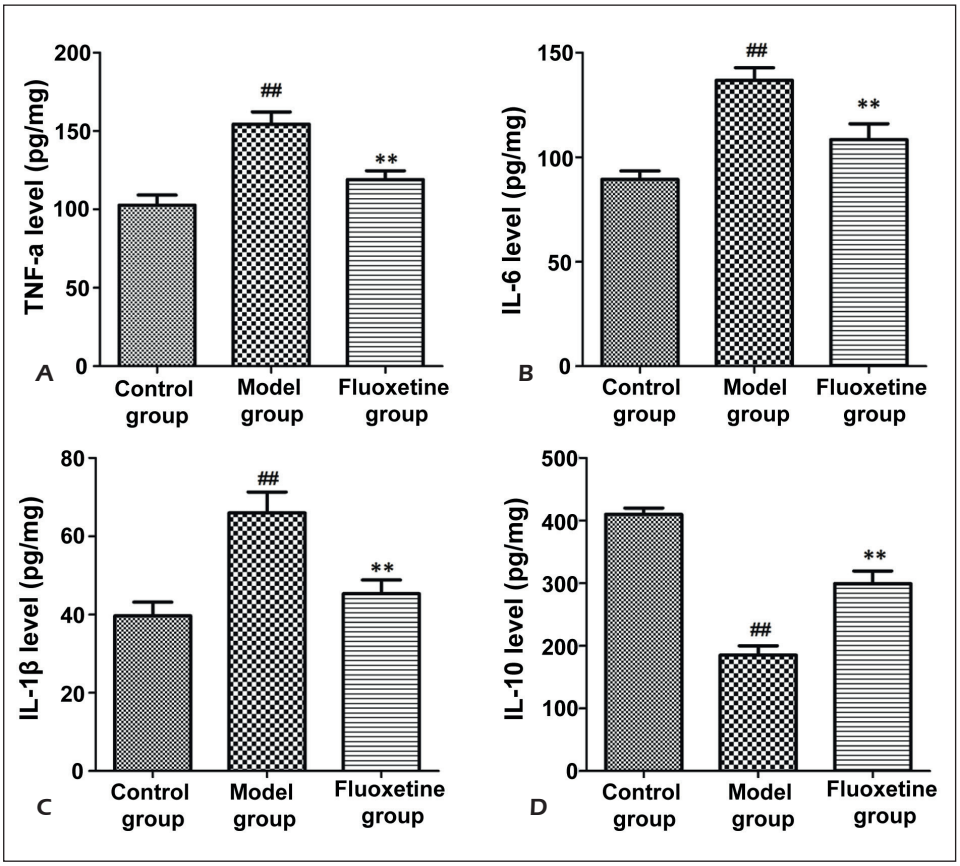

Figure 5. Content of inflammatory factors in the hippocampus of mice in each group. The content of TNF-α, IL-1β, and IL-6 in the hippocampus of mice was significantly higher in model group than that in control group, while the content of IL-10 was significantly lower than that in control group. The content of TNF-α, IL-1β, and IL-6 in the hippocampus of mice was significantly lower in fluoxetine group than that in model group, while the content of IL-10 was significantly higher than that in model group. $^{\#\#}p<0.01$ *vs.* control group, $^{**}p<0.01$ *vs.* model group.

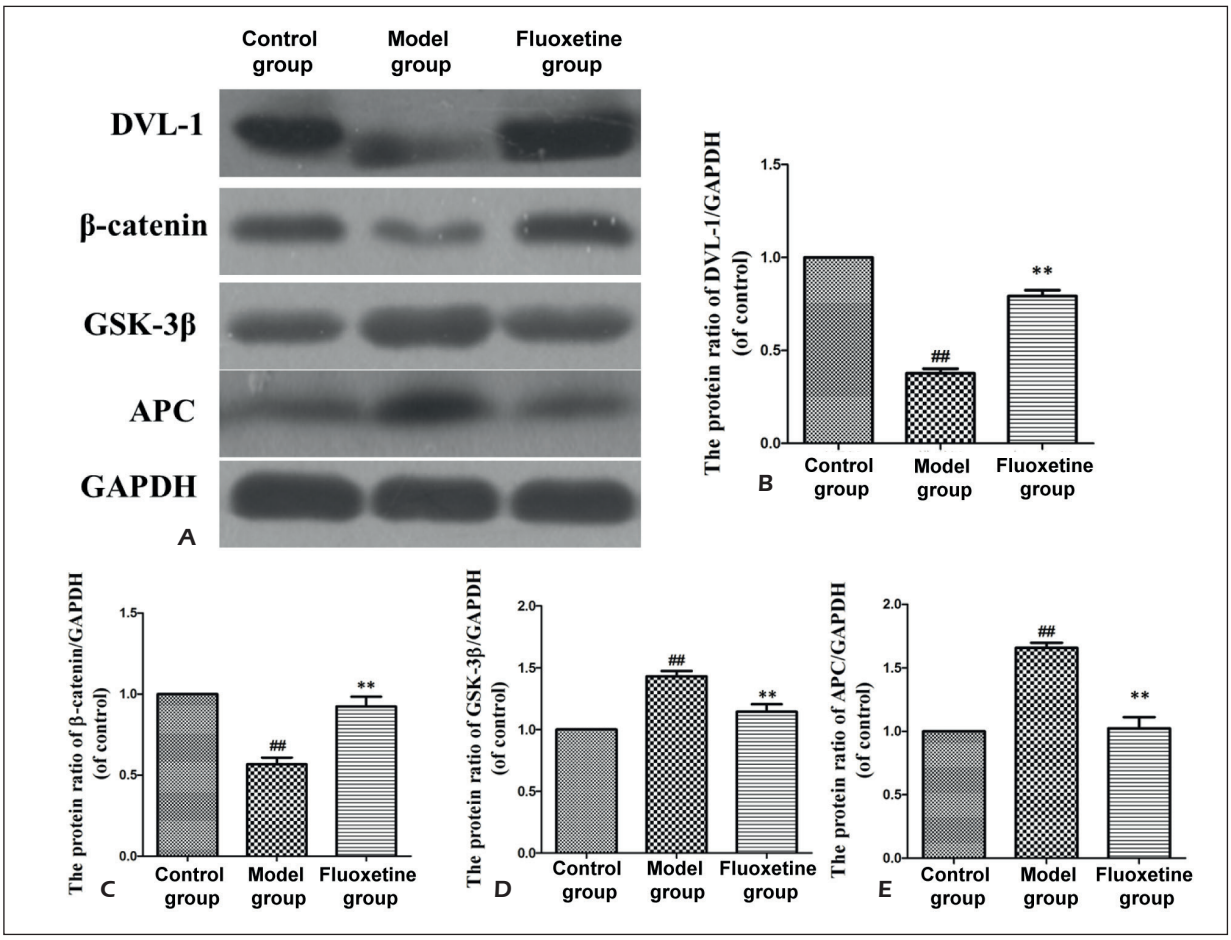

Figure 6. Expression levels of related proteins in hippocampus of mice in each group. **A**, Protein band; **B**, DVL-1; **C**, β-catenin; **D**, GSK-3β; **E**, APC. The expression levels of DVL-1 and β-catenin in the hippocampus of mice in model group were remarkably lower than those in control group, while the expression levels of GSK-3β and APC were remarkably higher than those in control group. Compared with those in model group, the expression levels of DVL-1 and β-catenin were significantly increased, while the expression levels of GSK-3β and APC were significantly decreased in fluoxetine group. $^{\#\#}p<0.01$ *vs.* control group, $^{**}p<0.01$ *vs.* model group.

colon cancer cells, leading to the increased expression of VEGF and promoting the angiogenesis. Wei et al[17] found that miR-155 can be involved in regulating the renal tubular interstitial fibrosis through the Wnt/β-catenin signaling pathway. We found that the expression level of miR-155 in the hippocampus of depression model mice was significantly increased, and it significantly declined after treatment with fluoxetine. Moreover, the depression-like behaviors of mice with the reduced expression level of miR-155 were significantly improved. Our results also showed that the number of apoptotic cells in the hippocampus in model group was significantly increased. The content of inflammatory factors (TNF-α, IL-1β, and IL-6) in the hippocampus was significantly increased, while the content of anti-inflammatory factor (IL-10) was significantly decreased in model group. After treatment with fluoxetine, the apoptosis in the hippocampus was effectively inhibited, the content of TNF-α, IL-1β, and IL-6 was reduced, while the content of IL-10 was increased. The above results indicate that miR-155 may be closely related to the occurrence and treatment of depression. According to Vidal et al[18], the stress state can inhibit the Wnt/β-catenin signaling pathway in the hippocampus of depression model mice, promote the production of hippocampal neurons, and effectively protect the hippocampal neurons. The expression level of β-catenin, an important molecule in the Wnt signaling pathway, has close correlations with the activation and inhibition of Wnt pathway[19]. Li et al[20] found that, after the Wnt/β-catenin signaling pathway is inhibited,

the expression level of β-catenin is significantly decreased, and the expression levels of β-catenin and DVL-1 decline in the absence of Wnt, thereby increasing the expressions of APC and GSK-3β. In this work, the expressions of DVL-1 and β-catenin in the hippocampus of mice in model group were significantly decreased, while the expressions of GSK-3β and APC were significantly increased. After treatment with fluoxetine, the expressions of DVL-1 and β-catenin were significantly increased, while the expressions of GSK-3β and APC were decreased. The above data suggested that the Wnt/β-catenin signaling pathway is involved in the occurrence and treatment of depression.

Conclusions

Altogether, miR-155 may reduce the release of inflammatory factors and the apoptosis of hippocampal neurons through inhibiting the Wnt/β-catenin signaling pathway, thus improving the depression-like behaviors of depression mice.

Conflict of Interests

The authors declare that they have no conflict of interest.

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