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Effects of Psychological Stress on Central Dopaminergic Neurons

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Abstract: *Objective — To evaluate the effects of psychological stress on central dopaminergic neurons. Methods — A test group of 90 rats was subjected to psychological stress for 30 minutes a day for 14 days. The rats were divided into three groups, and treated with tyrosine 250mg/kg, 500mg/kg, 1000mg/kg per day, 30 rats as psychological stress group and 30 rats as control group. After stress, TH and fos protein immunohistochemical staining were carried out on the relevant brain tissue sections of VTA (lateral tegmental area), Nac (nucleus accumbens) and mPFC (prefrontal cortex), and the results of TH immunohistochemical staining, Fos protein immunohistochemical staining and Fos/TH double staining were analyzed. Results — In VTA, the number of TH positive neurons in stress group was lower than that in control group (P<0.05), and the number of TH positive neurons in 500mg/kg and 1000mg/kg tyrosine groups was higher than that in stress group (P<0.05). The expression of Fos protein in VTA, mPFC and Nac of control group was lower than that of stress group, and the expression of Fos protein in VTA, mPFC and Nac of 500mg/kg and 1000mg/kg tyrosine groups was lower than that of stress group (P<0.05). Conclusion — Repeated psychological stress can damage central dopaminergic neurons, decrease the number of TH positive neurons and increase the expression of Fos protein. Tyrosine, the precursor of dopamine, can effectively control the damage.*

Keywords: *psychological stress, central dopaminergic neurons, effect*

1. Introduction

At present, the research on the effect of psychological stress on central dopaminergic neurons is limited. First, the current research is mostly the analysis of dopamine transmitter level, but there is no research on receptor level and the regulation of receptor level to transmitter level. Second, there is a lack of systematic research on the dopamine mechanism of cognitive deficits caused by psychological stress, especially how and how psychological stress affects VTA-NAc-mPFC system is still unclear. Third, the simulation of psychological stress factors adopts physical stress means, such as electric shock, restraint, forced swimming, cold and hot stress, etc., and no pure psychological stress is simulated.

In addition, tyrosine, as a precursor of catecholamine in vivo, has been shown to prevent stress-induced cognitive decline, but the dose and effect of Tyr administration, the relationship between Tyr administration and VTA-NAc- mPFC system, and whether Tyr administration has protective effect on DA neurons in vitro have not been reported. Psychological stress discomfort the body with a maladaptive response. TH (tyrosine hydroxylase) is a non-heme ferritin mainly distributed in brain dopaminergic neurons [1]. TH is a rate-limiting enzyme for DA synthesis because of its strong specificity of a catalytic substrate, weak activity, fast synthesis speed, and low content. In addition, tyrosine is a precursor for the synthesis of catecholamine transmitters. Therefore, tyrosine supplementation during stress can enhance the synthesis and release of dopamine in the rat brain [2].

Studies have shown that an adequate supply of tyrosine does not affect the function of dopamine neurons in the mPFC (prefrontal cortex) under normal physiological conditions[3]. Tyrosine dose with higher energy quickly promotes the increase of TH level, and the corresponding increase of dopamine level in neurons is mainly generated due to the feedback of TH substrate[4]. Small doses of tyrosine can control TH activity without significantly impacting endogenous dopamine levels. This study mainly evaluates the related effects of psychological stress on central dopaminergic neurons.

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2. Exploration

2.1. Data

A total of 90 rats in the experimental group were subjected to psychological stress for 30 minutes every day for 14 days. The rats were divided into three groups and fed with tyrosine intervention of 250mg/kg, 500mg/kg, and 1000mg/kg daily. The body weight of the rats in the experimental group was 215.63g±21.12, with 62 males and 28 females. The weight of rats in the stress group was 215.45g±25.67, with 17 males and 13 female rats. The body weight of rats in the control group was 217.58g±23.45, with 18 males and 12 females. There was no significant difference in primary data (P>0.05).

2.2. Methods

(1) All rats were fed in a single cage in a soundproof room at a room temperature of about 23℃, with a light-dark cycle of 12 hour/12 hour.

(2) Psychological stress intervention was given to them once a day, for 30 minutes each time, for a total of 14 days.

(3) The content of common feed in the stress group was 0.53%. No electrical stimulation was given to the stress device in the control group.

(4) After stress, related brain tissue sections of VTA (lateral tegmental area), Nac (nucleus accumbens), and mPFC (prefrontal cortex) were performed according to conventional methods, and immunohistochemical staining for TH (tyrosine hydroxylase) and fos proteins was performed.

(5) Four to six units of fos protein were randomly selected by computer image analysis system, that is, 134.553um2, and the number density of each group was determined respectively.

(6) The number of related positive cells in each section of TH immunohistochemistry was observed under a light microscope

2.3. Observation indicators

The results of TH immunohistochemical staining, fos protein immunohistochemical staining and Fos/TH double staining were observed and analyzed.

2.4. Data Analysis

SPSS 22.0 software was used to carry out statistical research. Measurement data were calculated as "t" and represented as "$\chi \pm S$". Data for counting were verified by "χ^2" and expressed as (%). $P < 0.05$ shows the difference with statistical significance.

3. Results

3.1. TH immunohistochemical staining results

Table 1: Number of TH-positive neurons in VTA region ($\chi \pm S$)

Groups	Cases (n)	Distance of section from anterior fontanelle (mm)				
		4.5	4.8	5.1	5.4	5.7
Control group	30	76.52±11.14	135.92±12.34	168.56±23.14	192.56±35.45	155.62±21.47
Group with psychological stress	30	53.25±8.25*	95.46±14.25*	108.44±12.68*	135.46±20.28*	111.29±12.25*
Tyrosine group of 250mg/kg	30	55.81±7.63	101.23±15.64	135.20±15.44	144.25±18.95	140.15±20.64
Tyrosine group of 500mg/kg	30	69.31±9.22	105.16±13.08	158.37±18.75△	180.52±25.45△	144.23±19.32△
Tyrosine group of 1000mg/kg	30	69.60±11.05	122.27±15.98△	162.14±22.12△	178.95±17.46△	147.12±23.65△

Note: Compared with the control group, *P<0.05 is presented; Compared with stress group, △P<0.05 is presented.

The cytoplasm and fibers of TH-labeled neurons were brown and yellow, and most were in the VTA region. The relative arrangement of TH-positive neurons was relatively disordered for the

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psychological stress group, and there was a light coloring of cell bodies. Still, the coloring of axons was not obvious. For the mPFC region, most of them are the related distribution of nerve fibers. Anterior fontanelle 5.1mm posterior. In VTA, the number of TH-positive neurons in the stress group was lower than in the control group (P<0.05). On the other hand, the number of TH positive neurons in 500mg/kg and 1000mg/kg tyrosine groups was higher than that in stress group (P<0.05). See Table 1.

3.2. Immunohistochemical staining of Fos protein

The Fos protein immunoreactive material is located in the nucleus of the nerve, which is mainly blue-black granular with strong expression in VTA, mPFC and Nac. The Fos protein expression levels in the control group's VTA, mPFC and Nac were lower than those of the stress group (P<0.05). In addition, the Fos protein expression levels in VTA, mPFC and Nac of the 500mg/kg and 1000mg/kg tyrosine groups were lower than those of the stress group (P<0.05). Are shown in Table 2.

Table 2: Comparison of Fos protein immunoreactants prime number density in VTA, mPFC and Nac ($\chi \pm S$)

Groups	Cases (n)	mPFC	Nac	VTA
Control group	30	5.23±1.52	7.05±2.14	5.32±1.57
Group with psychological stress	30	15.44±4.68*	15.52±4.61*	15.61±4.58*
Tyrosine group of 250mg/kg	30	11.62±3.44	14.55±4.37	11.45±2.57
Tyrosine group of 500mg/kg	30	9.65±2.14△	13.98±3.45	9.72±2.15△
Tyrosine group of 1000mg/kg	30	10.23±1.91△	10.89±2.54△	10.38±1.79△

Note: Compared with the control group, *P<0.05 is presented; Compared with stress group, △P<0.05 is presented.

3.3. Double staining with Fos/TH

The cytoplasm and fiber of Fos/TH double-labeled neurons are brown, and the nucleus is blue and black, mainly located in VTA. Positive products were not seen in the Fos protein and TH immunohistochemical staining antibody replacement test.

4. Discussion

In this study, the number of TH-positive neurons in the stress group was lower than in the control group at the VTA site (P<0.05). The number of TH-positive neurons in the 500mg/kg and 1000mg/kg tyrosine groups was higher than that in the stress group (P<0.05). The Fos protein expression levels in the VTA, mPFC, and Nac of the control group were lower than those in the stress group (P<0.05). The Fos protein expression levels in VTA, mPFC, and Nac of 500mg/kg and 1000mg/kg tyrosine groups were lower than those of the stress group (P<0.05). Favorable products were not seen in the Fos protein and TH immunohistochemical staining antibody replacement test.

The results showed that the main factors for the decrease of TH-positive neurons were that reactive oxygen species inactivated TH and reduced its infectivity. Furthermore, the decrease of TH expression will increase the amount of dopamine synthesis in the short term and regulate TH activity. When stress factors are continuously presented, TH substrate tyrosine will be in short supply, and long-term regulation will reduce TH expression[5]. Currently, c-Fos in the nervous system can play the role of the third messenger in the nuclear response process to exogenous and endogenous signals and is closely related to the secretion of neuroendocrine hormones such as CRF and HPA axis during psychological stress. The c-Fos are characterized by quick responses. Within several tens of minutes after neuron stimulation, the relevant Fos mRNA in the cell will accumulate and reach the peak value, and the FOS protein appears later[6].

In this study, Fos protein expression levels were increased in three brain regions in the stress group, mainly related to acute stress response and slow and continuous expression. 500mg/kg and 1000mg/kg tyrosine can control the degree of psychological stress damage to TH-positive neurons and reduce Fos protein expression level. The likelihood can be that tyrosine-related intervention can increase TH substrate concentration and thus increase TH expression or that the amount of dopamine synthesis in the VTA-NAc-mPFC system increases. The transmitter pathway affects neuroendocrine activity and reduces the stress response and Fos protein expression level[7-8].

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In 1976, some scholars first found a significant increase in central dopamine conversion in the prefrontal cortex of rats under acute stress. Since then, the related effects and mechanisms of psychological stress on the function of central dopamine system have been continuously discovered.

Under stress, the content and activity of central dopamine neurons increased, mainly in the mPFC region, followed by NAc and VTA, while stress basically had no effect on the related nigral striatum region of the dopamine system. For controllable related stress, the increase of dopamine in the mPFC region can reach 80%, for the NAc region, the increase in dopamine is about 45%, while with regard to the striatum, the dopamine concentration basically does not change.

The activation effect of stress on dopamine mainly changes according to the specific severity, controllable degree and severity of stressors, the characteristics of dopamine receptors in different brain regions and the relationship between other neurotransmitters. Tyrosine is an amino acid needed by the body, and it is a precursor of catecholamine transmitter synthesis. Studies have shown that tyrosine hydroxylase increases in cold stress, which can prevent memory loss caused by cold stress.

Studies have shown that small doses of tyrosine can feedback control the activity of tyrosine hydroxylase and have no significant effect on endogenous dopamine levels. Dopamine synthesis of dopamine neurons representing mPFC is more easily affected by precursors, but dopamine levels are regulated by terminal metabolites and supply sufficient tyrosine under normal physiological conditions. It will not affect the function of dopaminergic neurons in mPFC.

5. Conclusion

Psychological stress is a situation in which the dynamic balance system where psychological, biological, and other factors interact with each other is affected by some factors and is out of balance. Psychological stress will affect the central dopaminergic neurons and cause some discomfort. The reasonable use of tyrosine can control the degree of injury. Therefore, researchers should strengthen the analysis of the patient's psychological stress, and tyrosine intervention should be standardized and reasonably applied to reduce the degree of adverse effects caused by psychological stress.

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