Pakistan J. Zool., pp 1-7, 2023. **DOI**: https://dx.doi.org/10.17582/journal.pjz/20230213200208

Long Term Effects of SSRI Antidepressants on Levels of Different Serum Growth Factors in Patients with Depression

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ABSTRACT

The objective of this study was to investigate the effect of long-term use of SSRI (selective serotonin reuptake inhibitors) antidepressants on serum nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF), vascular endothelial growth factor (VEGF) and insulin-like growth factor 1 (IGF-1) levels. A total of 51 patients with depression who were diagnosed for the first time and did not receive drug treatment in our hospital were selected as the depression group, and 42 healthy people who underwent physical examination in our hospital during the same period were selected as healthy controls. We compared the serum levels of NGF, GDNF, VEGF, and IGF-1 between the two groups. The patients in the depression group were treated with SSRI antidepressants for 8 weeks, and the changes in serum growth factors and Hamilton Depression Scale (HAMD-17) scores were compared before and after treatment. In addition, Spearman's method was used to analyze the correlation between the changes of serum growth factors levels and HAMD-17 score in patients with depression. After treatment, the levels of serum NGF and GDNF in the depression group were raised than those before treatment ($P<0.05$), and the levels of serum VEGF and IGF-1 were reduced than those before treatment ($P<0.05$). After treatment, the total score of HAMD-17 and the scores of sleep factor, cognitive impairment factor, block factor and anxiety somatization factor in the depression group were reduced than those before treatment ($P<0.05$). The change rates of serum NGF and GDNF concentrations in the depression group were positively correlated with the reduction rate of HAMD-17 and the reduction rate of each factor ($P<0.05$). It was concluded that decreased levels of growth factors may be related to the onset of depression in patients, which is a biomarker of depression and can be used as a target for clinical antidepressant therapy.

Article Information
Received 13 February 2023
Revised 25 February 2023
Accepted 27 March 2023
Available online 20 June 2023
(early access)

Authors' Contribution
EZ, MZ and CS collected the samples. WZ and WX analysed the data. ZH and XQ conducted the experiments and analysed the results. All authors discussed the results and wrote the manuscript.

Key words
Depression, SSRI, NGF, IGF-1, VEGF

INTRODUCTION

Depression is a very common psychiatric disorder in life, which is associated with significant costs, responsibility for society and excess mortality (Li *et al*., 2022). It is expected that the prevalence of depression will increase especially in the elderly (Heo *et al*., 2008). In depression, in addition to mood disorders, sometimes a decrease in the speed of executive function and impaired attention are also observed (McDermott and Ebmeier, 2009). As the most common clinical depressive disorder, depression patients are mainly clinically manifested as mental depression, low mood, reticence, decreased will activity, thinking delay and other clinical symptoms. Without timely and effective treatment, it can lead to suicidal behavior, which poses a serious threat to health and safety (Mishra *et al*., 2019).

Depression patients still lack unified treatment methods at present, and selective serotonin reuptake inhibitor (SSRI) antidepressants are the main clinical treatment methods, which are suitable for the treatment of depression and other related depressive disorders (Tanti and Belzung, 2013). Studies have found that effective monitoring of depression patients taking SSRI antidepressants for a long time is of great clinical significance to improve the prognosis of patients, so as to judge the treatment effect and the optimal health of patients (Kaihola *et al*., 2015). An important factor in the growth

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0030-9923/2023/0001-0001 $ 9.00/0

of nerve cells is nerve growth factor (NGF), a cytokine that acts on neurons. Its high expression of nutritive nerves can regulate the differentiation of external nerves and promote the regeneration and differentiation of damaged neurons (Martino *et al*., 2013). Neurotrophic factors, such as glial cell-derived neurotrophic factor (GDNF), promote the growth of neuronal axon fibers, stimulate neuronal regeneration, and inhibit neuronal apoptosis (Brunoni *et al*., 2015). Vascular endothelial growth factor (VEGF) can be used as a neurotrophic factor to nourish nerves and promote the growth and regeneration of nerve cells (Ventriglia *et al*., 2009). Insulin-like growth factor-1 (IGF-1) is a growth promoting cytokine mainly synthesized by liver cells, which plays an important regulatory role in promoting the regeneration of nerve cells and improving nerve function (Levada *et al*., 2020). This study analyzed the effects of long-term use of SSRI antidepressants on the levels of NGF, GDNF, VEGF and IGF-1 in serum of patients with depression, and explored whether the changes in the levels of those growth factors in peripheral blood were correlated with the efficacy of depression and antidepressants. It provides a new research idea for the etiology of clinical depression and the efficacy of antidepressants.

MATERIALS AND METHODS

General information

From January 2021 to April 2022, we selected 51 patients with depression who did not receive drug treatment in our hospital, a healthy control group of 42 healthy people underwent physical examinations at our hospital during the same period. The levels of serum NGF, GDNF, VEGF and IGF-1 of the two groups were compared. General data did not differ significantly between the two groups (P>0.05). All subjects signed informed consent, which was approved by the Hospital's Ethics Committee. Inclusion criteria for depression group: (1) Diagnosed as depressed patients according to clinical symptoms, signs and examinations (Latendresse *et al*., 2017); (2) No antidepressant, anxiety and other psychotropic drugs were taken within 2 weeks before enrollment;(3) Patients with complete clinical medical records; (4) 20 years ≤ age ≤75 years. Exclusion criteria: (1) pregnant or lactation women; (2) Those who are allergic to the drugs used in this study; (3) Patients with severe cognitive impairment or aphasia; (4) Serious heart, liver, renal insufficiency; (5) Patients with other mental diseases.

Methods

Fasting peripheral venous blood was taken from all subjects in the morning, and centrifuged at 3500 rpm for 10 min to separate the serum, testing was conducted at -80°C in a refrigerator. ELISA determined serum levels of NGF, GDNF, VEGF, and IGF-1 with kits purchased from Beijing Leadman Biochemical Co., Ltd., instructions were strictly followed during the operation.

Hamilton Depression Scale (HAMD-17) (Kraus *et al*., 2017) was used to judge the severity of elderly patients with depression, including sleep factor, cognitive impairment factor, block factor and anxiety somatization factor. Patients with a higher score have more severe depressive symptoms.

Statistical analysis

SPSS 20.0 was used for statistical analysis, count data was compared by the 2-tailed test, and measurement data was expressed as mean ± standard deviation. The t test was used for comparison, Pearson's method was used for correlation analysis, and P< 0.05 was considered statistically significant.

RESULTS

Among the total 93 members of the sample, three participants were excluded from the study. The sample included 37 females and 53 males aged between 44 and 56 years, with mean age of 50.6 ±1.32 (SD) years (Table I). The demographic variables of the patients who participated in the study was shown in Table I. As the table shows, there are no significant differences between the depression group and the healthy group so it can be concluded that they are homogenous groups.

Table I. Characteristics of the patients.

Group	Gender (n)		Age (year)	Weight (kg)
	Man	Woman		
Depression (n=50)	30	20	44.26±12.30	66.34±9.42
Healthy (n=40)	23	17	45.37±10.86	65.27±8.60
$\chi^2/t/Z$	0.057		-0.448	0.556
P	0.811		0.655	0.579

Comparison of serum indexes between the two groups before treatment has shown in Table II. Before treatment, the levels of NGF and GDNF in depression group were reduced than those in healthy control group (P<0.05), the levels of VEGF and IGF-1 in depression group were raised than those in healthy control group (P<0.05). As the comparison of serum indexes in depression group before and after treatment is shown in Table III, in the depression group, NGF and GDNF levels were raised after treatment (P<0.05), serum VEGF and IGF-1 levels were reduced

than those before treatment (P<0.05). Furthermore, the comparison of depression scores of patients with depression before and after treatment is shown in Table IV. There is a reduction in the total scores of HAMD-17, sleep factor, cognitive impairment factor, block factor, and somatization factor of anxiety in the depression group after treatment (P<0.05). Ultimately, an analysis of the correlation between serum index concentration change and depression score reduction rate of patients with depression was shown in Table V. The serum concentrations of NGF and GDNF decreased positively with HAMD-17 levels and other factors in depression groups (P<0.05), the change rate of serum VEGF and IGF-1 concentration was negatively correlated with the reduction rate of HAMD-17 and other factors (P<0.05).

DISCUSSION

Depression patients often show clinical symptoms such as silence, emotional disorders, low mood, decreased will activity, mental retardation and so on. If the initial onset of depression is not paid enough attention and effective treatment, the repeated course of disease will gradually worsen, seriously affecting the daily life and work quality of patients (Veldman *et al*., 2021). At present clinical mainly by adopting the method of drug treatment of depression patients, SSRI antidepressants is the drug of choice for clinical treatment of depression patients, such as fluvoxamine, sertraline, paroxetine and fluoxetine, SSRI antidepressants can have specificity on serotonin reuptake inhibition, thus increases the synaptic cleft serotonin levels, it can reduce sympathetic excitability, and thus play a good role in anti-anxiety and anti-depression (Dimitriadis *et al*., 2019). A long-term monitoring of depression patients taking SSRI antidepressants is critical to improving their prognosis, so as to judge the treatment effect and the optimal health of patients (Aleksovski *et al*., 2018). In recent studies, genetics, stress theory, central neurotransmitter hypothesis, neuronal injury, hypothalamic-pituitary-gonadal (HPG) axis dysfunction have been linked to the development and occurrence of depression, but the pathogenesis remains unclear (Tiger *et al*., 2020). According to the modified theory, depression is attributed

Table II. Serum indexes between the two groups before treatment.

Group	n	NGF (ng/L)	GDNF (pg/ml)	VEGF (ng/ml)	IGF-1 (ng/ml)
Depression	50	10.18±3.52	371.12±89.37	72.34±20.60	22.40±6.32
Healthy	40	28.12±2.48	749.45±180.45	52.25±16.57	14.62±4.48
t		-27.259	-12.980	5.006	6.573
P		0.000	0.000	0.000	0.000

NGF, nerve growth factor; GDNF, glial cell line-derived neurotrophic factor; VEGF, Vascular endothelial growth factor; IGF-1, insulin-like growth factor 1.

Table III. Serum indexes in depression group before and after treatment.

Group	n	NGF (ng/L)	GDNF (pg/ml)	VEGF (ng/ml)	IGF-1 (ng/ml)
Before treatment	50	10.18±3.52	371.12±89.37	72.34±20.60	22.40±6.32
After treatment	50	42.25±9.57	791.62±202.48	56.34±17.62	15.64±5.50
t		-22.239	-13.434	4.174	5.705
P		0.000	0.000	0.000	0.000

For abbreviations see, Table II.

Table IV. Depression scores of patients before and after treatment.

Group	n	Total score of HAMD-17	Sleep factor	Cognitive impairment factor	Block factor	Somatization factor of anxiety
Before treatment	50	20.41±5.86	4.56±1.64	3.44±1.52	5.43±1.58	6.33±2.43
After treatment	50	13.02±3.01	2.32±0.80	2.08±1.04	3.92±0.75	3.75±1.12
t		7.932	8.680	5.222	6.105	6.818
P		0.000	0.000	0.000	0.000	0.000

For abbreviations see, Table II.

Table V. An analysis of the correlation between serum index concentration change and depression score reduction rate of patients with depression.

Indicators	NGF		GDNF		VEGF		IGF-1	
	r	P	r	P	r	P	r	P
Decrease rates of HAMD-17	0.320	0.000	0.481	0.000	-0.361	0.000	-0.394	0.026
Decrease rates of Sleep factor	0.364	0.000	0.324	0.004	-0.350	0.000	-0.432	0.005
Decrease rates of Cognitive impairment factor	0.399	0.000	0.369	0.000	-0.427	0.000	-0.182	0.026
Decrease rates of Block factor	0.335	0.000	0.318	0.012	-0.428	0.000	-0.227	0.005
Decrease rates of Somatization factor of anxiety	0.515	0.000	0.595	0.000	-0.356	0.000	-0.353	0.000

For abbreviations see, Table II.

to changes in neurotransmitters such as 5-serotonin and norepinephrine, in addition to these factors, neurotrophic factors such as NGF, GDNF, VEGF, and IGF-1 may also be involved in the pathophysiological process of depression (Hisaoka-Nakashima *et al*., 2019).

Neurotrophic factors are secreted by astrocytes and neurons, which support the development, growth and functional integrity of neurons, and play critical role in maintaining the normal function of neurons, regulating the growth of neurons, nerve plasticity and synaptic formation (Liu *et al*., 2012). Both NGF and GDNF are important members of the neurotrophic factor family. Compared to healthy controls, the depression group had lower levels of serum NGF and GDNF before treatment, as a result of treatment, serum levels of NGF and GDNF in those with depression were raised than those before treatment. A positive correlation was found between the change rate of serum NGF and GDNF concentration and the decrease rate of HAMD-17 and the decrease rate of each factor in the depression group. These results suggest that the synthesis and release of neurotrophic factor NGF and GDNF decreased significantly during depressive episode, and the use of SSRI antidepressants can improve the levels of neurotrophic factor NGF and GDNF to achieve the effect of treatment for depressive patients, and the decrease of neurotrophic factor NGF and GDNF may be associated with the onset of depressive patients. It is a biomarker of depression and can be used as a new target for clinical antidepressant treatment (Sun *et al*., 2013). Studies have found that the lack of neurotrophic factor tends to increase the vulnerability of astrocytes and neuronal cells and even lead to cell death, while the abnormal function of astrocytes and neuronal cells leads to the damage of structural plasticity and neurotransmission block, which may be the pathophysiological mechanism of affective disorders (Brunoni *et al*., 2018).

Angiogenesis is involved in many physiological and pathological processes, such as inflammation, tumor development, wound healing, embryogenesis and so on. A variety of cytokines participate in vascular formation synergistically, such as VEGF, basic fibroblast growth factor (bFGF), matrix metalloproteinase, platelet-derived growth factor (PDGF) and other factors interact to promote vascular formation. Clinical studies have confirmed that VEGF, bFGF and matrix metalloproteinases, PDGF, and Parkinson's, Alzheimer's disease and vascular cognitive impairment, epilepsy and other central nervous system disease development, can be used as evaluating state, degree and prognosis of index (Edvinsson *et al*., 2017). VEGF is not only a pro-angiogenic factor, but also a neurotrophic factor. It can not only bind to vascular endothelial receptors and promote the proliferation of endothelial cells, induce angiogenesis and nourish nerves, but also promote the differentiation, growth and regeneration of nerve cells, protect nerve cells and enhance synaptic plasticity. Therefore, VEGF is generally considered to have antidepressant effects in clinical practice (Castillo *et al*., 2020). Our results showed that, before treatment, serum VEGF levels in patients with depression were raised than those in healthy controls, while it was reduced after treatment. There was a negative correlation between the change rate of serum VEGF concentration and the reduction rate of HAMD-17 and each factor in the depression group. These results suggest that VEGF synthesis and release are significantly reduced during depressive episodes, and the decreased VEGF level may be associated with the onset of depression, which is a biomarker of depression and can be used as a new target for clinical antidepressant treatment. Scholars have found that the increased plasma VEGF level in depression patients is related to the neuroprotective effect of VEGF caused by trauma and oxidative stress (Viikki *et al*., 2010).

IGF-1 is a growth promoting cytokine synthesized and secreted by liver, which can promote cell differentiation,

participate in wound repair, promote growth, promote bone anabolism, dilate blood vessels, participate in endocrine and metabolic regulation, etc. (Mueller *et al*., 2018). Studies have found that IGF-1 can pass the blood-brain barrier, bind to receptors in the thalamic nucleus and hippocampus, and promote neuron regeneration, nerve signal transmission, neural plasticity and other neural cell activities, which is related to the occurrence of depression, and its serum expression level is positively correlated with depression severity (Rosso *et al*., 2016). This study indicated that, before treatment, serum IGF-1 level in patients with depression was raised than that in healthy controls. After treatment, the level of IgF-1 in patients with depression was reduced than before treatment. The change rate of serum IGF-1 concentration was negatively correlated with the decrease rate of HAMD-17 and the decrease rate of each factor in the depression group. It suggests that the synthesis and release of IGF-1 are reduced during depressive episode, and the use of SSRI antidepressants can achieve the effect of treating depressive patients by increasing the level of IGF-1. The decrease of IGF-1 level may be associated with the onset of depressive patients, and is a biomarker of depressive state, which can be used as a target for clinical antidepressant treatment (Kondo *et al*., 2018).

CONCLUSSION

NGF, GDNF, VEGF and IGF-1 levelsin serum of patients with depression are reduced, and the use of SSRI antidepressants can achieve the effect of treating depression by up-regulating NGF, GDNF, VEGF and IGF-1. The decreased levels of NGF, GDNF, VEGF and IGF-1 may be associated with the onset of depression, which is a biomarker of depression and can be used as a target of clinical antidepressant treatment.

Funding

The research is supported by Wuhu Scientific and technological Achievements Transformation Project (No. 2021cg31).

IRB approval

This study was approved by the Advanced Studies Research Board of the Fourth People's Hospital of Wuhu City, Wuhu, 241002, Anhui Province, China.

Ethical approval

The study was carried out in compliance with guidelines issued by ethical review board committee of the Fourth People's Hospital of Wuhu City, Wuhu, 241002, Anhui Province, China. The official letter would be available on fair request to corresponding author.

Statement of conflict of interest

The authors have declared no conflict of interest.

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