

Correlation Analysis Between BDNF and Postoperative Cognitive Dysfunction in Aged Rats

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Abstract: *Objective:* To investigate the relationship between BDNF and postoperative cognitive dysfunction among aged rats. *Methods:* 36 SPF healthy aged male SD rats were randomly assigned to a control group and a model group, respectively, with 18 rats in each group. Abdominal exploration was performed on the rats in the model group after anesthesia, while the rats in the control group were not operated on after anesthesia. The escape latency and swimming distance of the two groups were analyzed on a day prior to surgery as well as on the first day, third day, and seventh day following surgery; the expression levels of BDNF protein in the hippocampus of rats in the two groups were compared on the first day, third day, and seventh day following surgery; the correlation between BDNF and escape latency and swimming distance was analyzed. *Results:* The escape latency and swimming distance of the rats in the control group on a day prior to surgery, the first day, third day, and seventh day following surgery did not differ significantly ($p > 0.05$), but those in the model group had significant behavioral difference ($p < 0.05$). On a day prior to surgery, the rats in both groups showed no significant behavioral difference in escape latency and swimming distance ($p > 0.05$), but on the first day, third day, and seventh day following surgery, the escape latency and swimming distance of the rats in the model group were significantly longer than those in the control group ($p < 0.05$). In the control group, there was no significant difference in the protein expression of BDNF in the hippocampus of rats on the first day, third day, and seventh day following surgery, but there was significant difference in the model group. On the first day, third day, and seventh day following surgery, the BDNF protein expression level in the rats' hippocampus of the control group was significantly higher than that of the model group ($p < 0.05$). The data from Pearson correlation analysis confirmed that BDNF protein expression is negatively correlated with escape latency ($r = -0.567, p < 0.001$) and swimming distance ($r = -0.623, p < 0.001$). *Conclusion:* In aged rats, the BDNF protein expression level decreases, and the degree of cognitive dysfunction increases after surgery.

Keywords: BDNF; Aged rats; Postoperative cognitive dysfunction; Escape latency; Swimming distance

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1. Introduction

Postoperative cognitive dysfunction (POCD) is common in the elderly, and elderly patients often have persistent disorders in concentration, attention, memory, learning, and other aspects after surgery. Several risk factors of POCD have been identified, including hypertension, old age, surgery, diabetes, anesthesia, and other factors^[1,2]. However, its pathological and physiological mechanisms are unclear, which will lead to prolonged hospital stay and a reduction in patients' quality of life while increasing the economic burden, social burden, and public health burden on patients^[3,4]. Studies have found that the incidence of cognitive

dysfunction in elderly patients over 60 years old who had undergone extensive non-cardiac surgery is 25.8% one week after surgery and 9.9% three months after surgery^[5,6]. In recent years, with the intensification of population aging and the popularization of surgery for elderly patients, POCD has become a serious social concern. Therefore, clarifying the pathogenesis of POCD in the elderly can better reduce the occurrence of POCD^[7,8]. Brain-derived neurotrophic factor (BDNF) is known to regulate the plasticity of synapses, the proliferation and differentiation of neurons, as well as the release of neurotransmitters^[9,10]. Therefore, this paper analyzes the correlation between BDNF and POCD in aged rats, so as to provide a basis for reducing the occurrence of POCD in elderly people.

2. Materials and methods

2.1. Study population

A total of 36 healthy aged male SD rats of SPF grade, age ranging from 18-20 months and weight ranging from 500-600 g, were purchased from the Animal Center, Xi'an Jiaotong University. According to the random number table method, the rats were randomly divided into two groups: control group (n = 18) and model group (n = 18).

2.2. Reagents and instruments

BDNF antibody was purchased from Biosharp Company, China, Western blot kit was purchased from Wuhan Seville Biotechnology Co., Ltd., and Morris water maze equipment was purchased from Nanjing Calvin Biotechnology Co., Ltd.

2.3. Study design

The rats in the model group were anesthetized with 0.3 ml/100g of 10% chloral hydrate intraperitoneally. In order to prevent the rats from regaining their righting reflex, they were placed in a supine position. Their abdominal skin was disinfected, and a longitudinal incision of about 3cm was made 0.5 cm below the ribs along the abdominal midline. Abdominal exploration of the stomach, liver, large intestine, and small intestine was then performed every 5 minutes. The operation time was set to 20 minutes, and their abdominal cavities were closed thereafter. The rats in the control group were not subjected to surgery after anesthesia.

2.4. Observation indicators

- (1) For the water maze test^[11], the two groups of rats were subjected to a positioning navigation test five days before surgery and trained four times a day. The water maze was divided into four quadrants, maintaining the water temperature at 25°C. The rats were placed 0.7 cm underwater in the first quadrant and were fixed on the escape platform; the reference objects around the platform were kept constant. By using the camera at the pool, the moving images of the rats were analyzed, and the escape latency was recorded. The rats were randomly placed into the water from four quadrants after adapting to the platform for 30 seconds, and the time taken by the rats from the entering the water to standing on the platform was recorded. The swimming distance of the rats was also recorded, taking the total length of the route from entering the water to swimming across the platform. If the rats were unable to locate the platform within 1 minute, they were then led to the platform and kept there for 10 seconds before the next training. The water maze test was performed again on the first, third, and seventh day after surgery, in which the escape latency and swimming distance of the two groups were recorded.
- (2) In both the groups, BDNF protein expression in the hippocampus was determined by Western blot. After completing the water maze on the seventh day, the rats in the two groups were killed, with their hippocampus separated, brain tissues homogenized and grounded, and protein lysate added. After

centrifugation, electrophoresis was performed. Following electrophoretic separation, it was then transferred to a PVDF membrane and subsequently to a plate containing blocking solution for 2 hours. BDNF antibody was added, and it was incubated at room temperature for 2 hours. The membrane with buffer solution was washed three times, for 5 minutes each time. Secondary antibody was then added, and it was incubated at room temperature for another 2 hours. The membrane was washed three times, for 5 minutes each time. The membrane was placed into a developing solution and analyzed and scanned with an imaging system. The relative expression of BDNF was then measured.

(3) The correlation between BDNF and escape latency and swimming distance was analyzed.

2.5. Statistical analysis

The measurement data were expressed in $\bar{x} \pm s$. Comparisons between groups were conducted using one-way ANOVA, whereas pairwise comparisons were conducted using LSD-t tests; the analysis of variance of repeated measurements was conducted to compare the data of water maze at each point of time after surgery. Pearson correlation analysis was performed to analyze the correlation. $p < 0.05$ indicated that the difference was statistically significant.

3. Results

3.1 The escape latency and swimming distance of the rats in the two groups on a day prior to surgery, the first day, third day, and seventh day following surgery

The escape latency and swimming distance of the rats in the control group did not differ significantly on a day prior to surgery, the first day, third day, and seventh day following surgery, $p > 0.05$, while those in the model group had significant behavioral difference, $p < 0.05$. On the day prior to surgery, the escape latency and swimming distance showed no significant difference between the two groups, $p > 0.05$; however, on the first day, third day, and seventh day following surgery, the escape latency and swimming distance of the rats in the model group were significantly higher than those in the control group, $p < 0.05$.

Table 1. The escape latency and swimming distance of the two groups of rats on a day prior to surgery, the first day, third day, and seventh day following surgery (n = 18, $\bar{x} \pm s$)

Group	Escape latency (s)				F/p	Swimming distance (cm)				F/p
	Pre-operation	Post-operation				Pre-operation	Post-operation			
		1d	3d	7d			1d	3d	7d	
Control	24.71 ± 3.67	24.91 ± 4.67	24.81 ± 3.02	24.82 ± 3.09	0.009/ 0.999	353.10 ± 78.09	356.02 ± 82.34	360.99 ± 82.36	358.99 ± 77.67	0.033/ 0.992
Model	24.92 ± 4.02	46.31 ± 5.21	43.31 ± 7.61	34.67 ± 6.03	48.406/ < 0.001	352.89 ± 81.02	729.89 ± 106.56	658.02 ± 105.77	526.56 ± 87.62	52.936/ < 0.001
t	-0.164	-12.977	-9.587	-6.168		0.008	-11.779	-9.401	-6.075	
p	0.871	< 0.001	< 0.001	< 0.001		0.994	< 0.001	< 0.001	< 0.001	

3.2. BDNF protein expression in the rats' hippocampus of the two groups on the first day, third day, and seventh day following surgery

In the control group, there was no significant difference in BDNF protein expression in the hippocampus on the first day, third day, and seventh day following surgery, $p > 0.05$. However, there was a significant difference in the model group, $p < 0.05$. The expression level of BDNF protein in the hippocampus of rats in the control group was significantly higher than that in the model group on the first day, third day, and seventh day following surgery, $p < 0.05$.

Table 2. Comparison of BDNF protein expression in the hippocampus of rats in the two groups on the first day, third day, and seventh day following surgery (n = 18, $\bar{x} \pm s$)

Group	Post-operation 1d	Post-operation 3d	Post-operation 7d	F/p
Control	148.02 ± 15.81	149.02 ± 14.88	148.99 ± 15.45	0.025/0.975
Model	89.16 ± 8.25	99.03 ± 10.23	105.76 ± 9.23	14.596/< 0.001
t	14.003	11.745	10.191	
p	< 0.001	< 0.001	< 0.001	

3.3. Correlation between BDNF and escape latency and swimming distance

According to Pearson correlation analysis, BDNF expression was found to be negatively correlated with escape latency ($r = -0.567$, $p < 0.001$) and swimming distance ($r = -0.623$, $p < 0.001$).

4. Discussion

In the past, POCD was mostly associated with cardiac surgery. However, in recent years, the incidence of postoperative cognitive dysfunction caused by non-cardiac surgery has also increased [12,13]. Its prevalence has further grown due to population aging. Consequently, it is crucial to prevent and reduce the occurrence of postoperative cognitive dysfunction in clinical practice [14,15]. In the effort to reduce and prevent its occurrence, it is first necessary to understand its mechanism. Therefore, the correlation between BDNF and POCD in aged rats was analyzed in this study.

The results showed that there was no significant difference in the escape latency, swimming distance, and BDNF protein expression in the hippocampus of rats in the control group on a day prior to surgery, the first day, third day, and seventh day following surgery. However, they were statistically significant in the model group. Compared to the control group, the model group had a significantly longer escape latency and swimming distance on the first day, third day, and seventh day following surgery. A significant difference was found between the control group and the model group in the expression of BDNF protein in the hippocampus on the first day, third day, and seventh day following surgery, implying that cognitive dysfunction does occur after surgery. Furthermore, the levels of BDNF protein in the hippocampus of rats decreased significantly, indicating that BDNF protein expression may have a certain correlation with postoperative cognitive dysfunction. This may be attributed to the fact that BDNF is a neurotrophic protein, which is a smaller, alkaline protein found in the cortex and hippocampus, and it may have mediated effects on the survival of neurons. Moreover, it is also known to regulate synaptic transmission and plasticity as well as improve memory, learning, and cognitive functions. Therefore, with reduced BDNF levels in aged rats after surgery, cognitive dysfunction occurs [16-18]. The expression level of BDNF was found to be negatively correlated with the escape latency and swimming distance of rats, which further implies that BDNF protein expression in the brain is negatively correlated with the cognitive function related to escape latency and swimming distance. Consequently, POCD is more severe if the escape latency and swimming distance are longer, indicating that BDNF protein expression in the brain of rats is positively correlated with the severity of cognitive dysfunction.

In conclusion, in aged rats, the level of BDNF decreases and the degree of cognitive dysfunction increases following surgery.

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Disclosure statement

The authors declare no conflict of interest.

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