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Report

The significate of IGF-1 and IGF-1R in reducing PTSD cognitive function symptoms

L'importance de l'IGF-1 et de l'IGF-1R dans la réduction des symptômes de la fonction cognitive du troubles de stress post-traumatique

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ABSTRACT

Objective. – To study the expressions of insulin-like growth factor 1 (IGF-1) and IGF-1 receptor in the hippocampal CA1 region of posttraumatic stress disorder (PTSD) rats.
Methods. – Forty healthy adult male Wistar rats were adopted. The internationally established single prolonged stress (SPS) method was used to set up the PTSD rat model and the immunohistochemical (IHC) method was applied to detect the expressions of IGF-1 and its receptor in the hippocampal CA1 region of PTSD rats.
Results. – After SPS stimulus, the expression of IGF-1 protein in the rat hippocampal CA1 region increased with the development of PTSD and reached the maximum on the 14th day, which is statistically different from that of the control group ($P < 0.05$); While the expression of IGF-1 receptor protein showed no significant difference on the 1st day and 7th day before and after stress ($P > 0.05$), but slightly decreased on the 14th day and 28th day than before ($P < 0.05$).
Conclusion. – After stress, the expression of IGF-1 receptor didn't grow in pace with that of IGF-1 accordingly, but slightly lowered instead. This indicates that IGF-1 receptor may affect the positive role of IGF-1 to some degree and meanwhile involve the pathophysiological process of cognitive changes of PTSD.

Mots clés :
Expérimentation animale
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RÉSUMÉ

Objectif. – Étudier l'expression du facteur de croissance 1 de l'insuline (IGF-1) et du récepteur d'IGF-1 dans la région CA1 de l'hippocampe des rats soumis au syndrome de stress post-traumatique (SSPT).
Méthodes. – Sur quarante rats Wistar adultes adultes sains, la méthode de stress prolongé unique (SPS) établie à l'échelle internationale a été utilisée pour mettre en place le modèle PTSD et la méthode immunohistochimique (IHC) a été appliquée pour détecter les expressions de l'IGF-1 et de son récepteur dans la région CA1 de l'hippocampe des rats PTSD.
Résultat. – Après stimulation SPS, l'expression de la protéine IGF-1 dans la région CA1 de l'hippocampe du rat a augmenté avec le développement du SSPT et a atteint le maximum le 14^{e} jour, ce qui est statistiquement différent de celui du groupe témoin ($p < 0{,}05$). Alors que l'expression de la protéine du récepteur d'IGF-1 n'a montré aucune différence significative le 1er jour et le 7^{e} jour avant et après le stress ($p > 0{,}05$), elle a légèrement diminué les 14^{e} et 28^{e} jours précédents ($p < 0{,}05$).
Conclusion. – Après le stress, l'expression du récepteur de l'IGF-1 n'a pas augmenté par rapport à l'IGF-1 en conséquence, mais a été légèrement diminuée. Cela indique que le récepteur de l'IGF-1 peut affecter le rôle positif de l'IGF-1 dans une certaine mesure et implique le processus pathophysiologique des changements cognitifs du SSPT.

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1. Introduction

As public emergencies like natural disasters, major traffic accidents, violent and terrorist activities increase constantly, the incidence of disorders related with psychological stress is rising year by year. And posttraumatic stress disorder (PTSD) is a kind of stress disorder characterized by the most severe clinical symptoms, worst prognosis and strongest possibility of brain damage. Currently, there is still no consensus regarding PTSD on the mechanism of changes in cognition, emotion and memory and other aspects. Some people hold that the formation of PTSD is influenced by dysfunction of emotional system [2,12,18,22], while some deem that the reason patients appearing symptoms like flashbacks, nightmares, or forcing to recall traumatic situations is simply because of their weakening cognitive control function [13,14,23]. To date, nevertheless, most studies tend to hold that some specific areas of brain, such as over-activation or inhibition of hippocampus and amygdala, result in neuroendocrine disorder and abnormal gene expression, but the mechanism involved mediating stress response remains unclear.

With further research, people began to link insulin with cognition. Most scholars deem that brain insulin has a protective effect on cognitive function [3,7]. Widely distributed in the brain, IGF-1 is overlapped with insulin on molecular structure, receptor and function. They have a high homology and both of them play an important role in cell proliferation, apoptosis and tumorigenesis. IGF-1 is involved in regulating hippocampal neurogenesis and formation of abnormal neural network as well as affecting the excitability of hippocampal neurons [16]. Nakajima et al. [17], in studying the effect of chronic stress on the perception of rat, discovered that chronic stress leads to a high expression of IGF-1 in the brain cortex and liver of rats, suggesting that IGF-1 is involved in the body anti-stress mechanism. Nowadays, the role of IGF-1 as an effective factor in neurogenesis processes associated with central nervous system (CNS) and peripheral nervous system (PNS) has been well known better than before and mechanisms of this factor about how it plays a role in this regard becomes more and more hot [1,4].

Therefore, we hypothesized that IGF-1 and its receptor may be involved in the incidence, development and prognosis of PTSD [21] and thereby the increase or decrease of their expression may be one of the mechanisms leading to the cognitive, emotional and memory changes in PTSD. Thus in this study, to explore the possible pathological mechanism of PTSD, animal model was adopted to study the expression of IGF-1 and its receptor in the hippocampal CA1 region of PTSD rats as well as their relationship with cognitive, emotional and memory changes.

2. Methods and materials

2.1. Experimental animal

The protocol for this study was approved by the institutional animal care and use committee of Shihezi University and all animal treatments were carried out at Shihezi University. All experiments were performed in accordance with the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research. Forty 6-week-old male Wistar rats (weighing 180g ± 25 g) provided by the Experimental Animal Center of Xinjiang Medical University were used. All animals revealed no abnormality through general physical examination. They were fed in animal room under a regulated temperature of 20 to 23°C and a humidity of 50% to 60% and had free access to food and water. The feeding box was paved with soft sawdust inside to reduce foot irritation. Before the experiment, rats were provided 12/12 hour controlled light strictly, stroked daily for 3 minutes and helped to adapt to environment for one week. During the experiment, unnecessary suffering was minimized for experimental animals.

2.2. Methods

2.2.1. Experiment grouping

All rats were randomly divided into five groups, namely: post-stress 1d group (the 1st day, 8 rats), post-stress 7d group (the 7th day, 8 rats), post-stress 14d group (the 14th day, 8 rats), post-stress 28d group (the 28th day, 8 rats) and normal control group (normal, 8 rats).

2.2.2. The establishment of PTSD rats model

Based on the reference, the internationally mature SPS method [6,11] was employed to set up the animal model, which is specifically as below. The rats were first wrapped completely from head to tail and then bound with tape for 2 hours so that its body cannot move, but 3–5 holes were reserved near the nose to facilitate breath. After a break of two minutes, the rats were forced to swim for 20 minutes in a transparent rectangular tank made of food-grade plastics (400mm × 200mm × 350 mm, water depth 300 mm, water temperature 22 ± 2°C). Then, following a 15-minute break, the rats were placed in a box with an appropriate amount of 99.5% ether until they showed such symptoms as shortness of breath, staggering and loss of consciousness. Afterwards, they were removed to a well-ventilated cage (not the one for feeding) until their consciousness was recovered before being put back to the original feeding cage. And this method was the criterion for the animal affected with PTSD in this study.

2.2.3. Preparation of Brain Specimens

Rats from the 1st day, 7th day, 14th day, 28th day and normal groups were taken for heart perfusion to draw their brains.

First, 1.5 mL 0.1% chloral hydrate anesthesia was injected into the rats and then their abdominal cavity was cut open to expose their heart. The perfusion needle was inserted from cardiac apex into the left ventricle and to the aorta end. Then, the right atrial appendage was cut open and 250 mL ice saline (4°C) was infused rapidly until incision effluent from the right atrial appendage becomes crystal clear and liver pale. Then, 250 mL 4% precooled paraformaldehyde solution (4°C) was infused. The total infusion time was controlled around 1.5 hours. Brains were surgically removed from the rats and rapidly frozen in liquid nitrogen and stored at −80°C until use.

2.2.4. Detection of the Expressions of IGF-1 and IGF-1 Receptor in Hippocampal CA1 Region by Immunohistochemsy

Some samples of corresponding brain regions were taken out and placed in the 4% paraformaldehyde solution (4°C) for 24 hours. After dehydration, transparency, wax dipping, paraffin embedding and wax block precooling, the brain tissue was subject to serial coronal sectioning with a thickness of 3 μm. All brain slices were selected at regular intervals. Six hippocampal slices were taken from about the same position of each rat. These brain slices were dried and saved for the subsequent immunohistochemistry.

After dewaxing, de-xylene, removal of endogenous peroxidase activity and antigen retrieval successively, the selected paraffin sections were dripped primary antibody (Rabbit Anti-Rat IGF-1 and Rabbit Anti-Rat IGF-1 Receptor) respectively. The blank control group (only adding phosphate buffer) and antibody specificity control group (adding primary antibody or secondary antibody (Goat Anti-Rabbit IgG) only) were established. All sections were conducted immunohistochemical staining simultaneously. After added with primary antibody, sections were placed into a wet box overnight under 4 °C and in the next day incubated at 37 °C for 30 minutes after being rewarmed at 37 °C, washed with PBS for

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