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Influence of simvastatin on dopaminergic neurons of lipopolysaccharide-induced rat model of Parkinson's disease

Tan Wang[1,2], Xue-Bin Cao[3], Xiao-Wu Chen[2], Pei-Pei Huang[3], Tian Zhang[2], Zhi-Bin Chen[2*△], Bei-Sha Tang[1*△]

[1]*Department of Neurology, Xiangya Hospital, Central South University, Changsha 410008, China*
[2]*Department of Neurology, Affiliated Hospital of Hainan Medical College, Haikou 570102, China*
[3]*Department of Neurology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 43022, China*

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ABSTRACT

Objective: To investigate the neuroprotective effects of simvastatin on lipopolysaccharide (LPS)-induced rat model of Parkinson's disease (PD) and the mechanisms involved. **Methods:** Hemiparkinsonian rat models were induced by stereotaxieal injection of LPS in the right substantia nigra compacta. After 2 weeks of simvastatin treatment, rotational behavior test was performed after the intraperitoneal injection of apomorphine. Expression of tyroxine hydroxylase (TH) and glial fibrillary acidic protein were analyzed through immunohistochemical staining of substantia nigra and striatum, and the level of TNF-α was evaluated using enzyme-linked immunosorbent assay. **Results:** Comparing with untreated group, behavioral symptoms of the rats were significantly less in the rats that received simvastatin treatment. The TH positive cell count in substantia nigra and striatum were significantly increased ($P<0.05$) and TNF-α expression was significantly decreased ($P<0.05$) in simvastatin group compared to untreated group. **Conclusions:** Simvastatin could effectively inhibit the activation of astrocytes, reduce TNF-α expression, and exert anti-inflammatory effects, and thus protect the dopaminergic neurons in substantia nigra and striatum of the rat model of PD.

1. Introduction

Parkinson's disease (PD) is a degenerative disease of the central nervous system, which has become one of the most important diseases that severely influence humans especially aged people. Pathological characteristics of PD include absence of substantia nigra dopaminergic neuron and formation of Lewy body, which could occur several years before the appearance of typical motor symptoms[1]. Conventional treatment with levodopa could remit clinical symptoms but could not prevent the disease progression; in addition, long-term drug therapy could also induce severe adverse effects[2]. Statins is widely used in clinical practices in treating hyperlipemia. Clinical studies demonstrated that statins could remit motor and non-motor symptoms of patients with PD, and delay the progression of disease[3]. In the present study, the protective effect of simvastatin (simv) on neurons of rats with lipopolysaccharide (LPS)-induced PD was investigated.

2. Materials and methods

2.1. Animals

Forty-five male adult Sprague-Dawley (SD) rats, weighing 230-250 g (Laboratory Animal Centre of Tongji Medical

*Corresponding author: Zhi-Bin Chen, Department of Neurology, Affiliated Hospital of Hainan Medical College, Haikou 570102, China
E-mail: chenzb3801@126.com
Bei-Sha Tang, Department of Neurology, Xiangya Hospital, Central South University, Changsha 410008, China.
E-mail: bstang7398@163.com
△Both authors contributed equally to this work.

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College, Huazhong Science and Technology University, China), were divided into 3 groups, namely control group, LPS group, and LPS+simv group (15 rats in each group).

2.2. Regents and equipment

LPS and apomorphine were purchased from Sigma-Aldrich (America), enzyme-linked immunosorbent assay (ELISA) Kit for tumor necrosis factor-alpha (TNF-α) was purchased from Elabscience Biotechnology Co., Ltd. (Wuhan, China), monoclonal antibody of tyrosine hydroxylase (TH) was purchased from Abcam (America), and glial fibrillary acidic protein (GFAP) polyclonal rabbit anti rat antibody was purchased from Bioss Biotechnology Co., Ltd. (Beijing, China). Rat stereotactic instrument was purchased from Ruiward Company (Shenzhen, China).

2.3. Model induction and treatment

Two μL of LPS (5 μg/μL) was stereotaxically injected into the right substantia nigra pars compacta (SNpc) to induce hemiparkinsonian rat model. Intraperitoneal injection of simvastatin (5 mg/kg) was performed for the rats in the LPS+simv group at 5 pm each day (1 hour before the operation), while intraperitoneal injection of same volume of normal saline was performed for the rats in the control and LPS groups. Intraperitoneal injection of 10% chloral hydrate (3.5 mL/kg) was given for anesthesia, and then the rats were horizontally fixed in the stereotactic instrument with the ear bar parallel to the line connecting bilateral ears, and the height of incisor bar of -3.3 mm. Bregma was considered as origin of coordinates, and the coordinate of substantia nigra was A-5.0 mm, R-2.0 mm, and DV-7.6 mm. For the rats in the LPS and LPS+simv groups, 2 μL of LPS was stereotaxically injected into the right SNpc, while 2 μL of normal saline was injected into the right SNpc for the rats in the control group; the injection speed was 0.4 μL/min, and the needle was retained for 10 min and then retreated slowly.

2.4. Behavioral test

Apomorphine (0.05 mg/kg) was subcutaneously injected. Two weeks later, the time taken to rotate the head to the side contralateral to destruction was recorded and the rotation cycles were recorded every 5 min for 30 min.

2.5. Immunohistochemical examination

Striatum and substantia nigra were collected according to Paxinos and Franklin atlas. Paraffin sections of the tissues were performed of 5 μm thickness. One section was selected from each 6 continuous sections, and 2 sections were selected for each rat. The TH (1:200 dilution) and GFAP (1:100 dilution) staining were performed. Six visual fields of striatum or substantia nigra were selected on the left and right sides of each section (with 3 visual fields on each side), observed, and photographed at same amplification factor (× 20/100/200/400) and at same light intensity. Image-Pro Plus 6.0 software was used to analyze the mean optical density (OD) of TH positive regions of striatum, TH positive cell count at substantia nigra, and mean OD of GFAP positive regions of substantia nigra.

2.6. TNF-α expression at substantia nigra

TNF-α expression at substantia nigra was determined using ELISA. In brief, the rats were decapitated and the brains were collected, and then the substantia nigra was collected on ice, homogenated, and centrifuged at 4 ℃, 12 000 rpm for 10 minutes. Supernatant was collected, and then the TNF-α level was determined according to the instructions of radioimmunoassay kit.

2.7. Statistical analysis

The SPSS software, Version 17.0, was used for the statistical analyses. Data were described as means and standard divisions, and compared using t-test or analyses of variances. A $P<0.05$ was considered statistically significant.

3. Results

3.1. Effects of simvastatin on rotational behavior of the rats

Two weeks after the intraperitoneal apomorphine administration, no rotational behavior was found for the rats in the control group, while increased rotation cycles were found for the rats in the LPS group [mean: (146.8± 7.2) cycles/30 min, $P<0.01$]. However, in LPS+simv group (rats received 14 continuous days of treatment with 5 mg/kg simvastatin), the rotational behavior of the rats significantly decreased as compared with the rats in the LPS group [(79.5± 9.4) cycles/30 min, $P<0.05$].

3.2. Immunohistochemical staining result of TH

The TH positive cell count in the injection region of substantia nigra or striatum, as well as OD in striatum in the control group was not significantly different from LPS group or LPS+simv group ($P>0.05$). In contrast, TH positive neurons

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