Journal of the Neurological Sciences xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Neuroinflammation and neuronal autophagic death were suppressed via Rosiglitazone treatment: New evidence on neuroprotection in a rat model of global cerebral ischemia

Zi-Qiang Shao *, Zun-Jing Liu

Department of Neurology, China–Japan Friendship Hospital, Beijing 100029, China

ARTICLE INFO

Article history:
Received 19 November 2014
Received in revised form 9 December 2014
Accepted 17 December 2014
Available online xxxx

Keywords:
Rosiglitazone
Global cerebral ischemia
Function recovery
Inflammatory
Autophagy
Rats

ABSTRACT

Ischemic stroke is one of the leading causes of mortality and disability with documented high incidence and relapse rate. Accumulating evidence indicates that autophagy participated in neuronal cell death and functional loss induced following ischemia/reperfusion (I/R) injury. The peroxisome proliferating activating receptor-γ (PPAR-γ) agonist, Rosiglitazone (RSG), is known for its anti-inflammatory actions. Previous studies have demonstrated that RSG can exert neuroprotection in animal models of both chronic brain injuries and acute brain insults. However, whether RSG treatment is involved in the autophagic neuronal death following I/R injury remains totally unclear. The present study aimed to hypothesize that treatment of RSG could induce neuroprotective properties in a rat model of global cerebral ischemia (GCI), and thereby to investigate the underline mechanisms. We found that a single injection of RSG immediately following GCI significantly reduced cerebral infarct volume and brain edema, as well as increased neuron survival rate and function recovery. These effects correlate with a decrease of inflammatory cytokines and autophagy-associated proteins expression in the hippocampus region. Our results provide in vivo evidence that RSG significantly protected rats against I/R injury induced brain injury, and the mechanism might associate with inhibiting the processes of neuroinflammation and thereby attenuated of neuronal autophagic death. All data suggest that RSG can be further developed as a clinical neuroprotective candidate in ischemic stroke.

© 2014 Elsevier B.V. All rights reserved.

1. Introduction

Ischemic stroke is one of the leading causes of mortality and disability with documented high incidence and relapse rate. Thrombolysis therapy plays a critical role in dealing with ischemic cerebrovascular abnormality. However, the blood reperfusion process after thrombolysis may cause a more serious tissue injury, namely ischemic/reperfusion (I/R) injury [1]. It has been proposed that oxidative stress [2], inflammation [3], glutamate release [4], intracellular and mitochondrial calcium-overload [5], and apoptosis [6] may take part in the process of I/R injury. Accumulating evidence indicates that autophagy also plays an important role in the mechanisms underlying I/R-induced neuronal damage [7,8].

Autophagy is a highly regulated process that involves the degradation of a cell's cytoplasmic macromolecules and organelles. Even though the role of autophagy in healthy cells is moderate and physiological, some dying cells exhibit grossly enhanced autophagy, which has led to the identification of 'type 2' or 'autophagic' cell death as a distinct type of cell death. Previous data showed that elevation of microtubule-associated protein 1 light chain 3 (LC3)-II is a reliable marker of autophagy activation [9], and the expression of LC3-II increased greatly within 48 h of reperfusion after 20 min of I/R injury [10]. Beclin-1 is also a crucial value protein that participates in the regulation of neuronal autophagy [11]. Disruption of autophagy may be detrimental in some circumstances, but it is currently unknown whether it promotes or prevents neuronal death in response to I/R [12]. However, pre-treatment with inhibitors of autophagy markedly decreased the infarct area in neonatal and adult rats with middle cerebral artery occlusion [13,14]. Therefore, autophagy is a potential target for neuroprotective strategies in the process of I/R injury.

Neuroprotective therapy during ischemia and reperfusion is considered as a crucial strategy to reduce neuronal damage. Numerous clinical trials of neuroprotective agents in acute stroke have failed after promising results in animal models and the need for clinically effective neuroprotective drugs is still very strong [15]. Rosiglitazone (RSG), a peroxisome proliferating activating receptor-γ (PPAR-γ) agonist, is known for its anti-inflammatory actions via activation of PPAR-γ. Previous studies have demonstrated that RSG can exert neuroprotection in many animal models, including global cerebral ischemia (GCI), Alzheimer's disease, Amyotrophic lateral sclerosis, spinal cord injury, traumatic brain injury and Parkinson's disease [16–21]. Afterwards, a

* Corresponding author at: Department of Neurology, China-Japan Friendship Hospital, No.2, Yinghua East Street, Chaoyang District, Beijing 100029, China. Tel./fax: +86 10 84205259.
E-mail address: shangziqiang126@sina.com (Z.-Q. Shao).

http://dx.doi.org/10.1016/j.jns.2014.12.027
0022-510X/© 2014 Elsevier B.V. All rights reserved.

Please cite this article as: Shao Z-Q, Liu Z-J, Neuroinflammation and neuronal autophagic death were suppressed via Rosiglitazone treatment: New evidence on neuroprotection in a rat model of global cerebral ischemia, J Neurol Sci (2015), http://dx.doi.org/10.1016/j.jns.2014.12.027

recent study suggested that administration of RSG attenuated excessive neuronal apoptosis in a rat model of GCI [22], but whether RSG treatment is involved in the autophagic neuronal death following GCI remains totally unclear. Thus, we designed this study to investigate the hypothesis that RSG could provide neuroprotection post-GCI and determined the potential mechanisms.

2. Materials and methods

2.1. Animals and GCI model

Adult female Sprague Dawley rats weighing 250–300 g, aged 3 months, were used in this study. All procedures were approved by the local legislation for ethics of experiments on animals. All rats were allowed free access to food and water before the operation under optimal conditions (12 h light:12 h darkness cycle, 22 °C). Female rats were bilaterally ovariectomized, and 1 week later, GCI was induced by 4-vessel occlusion. All operations were performed under anesthesia. Briefly, the rats were anesthetized with 10% chloral hydrate (350 mg/kg, i.p.), the vertebral arteries were electrocauterized and the common carotid arteries (CCA) were exposed. After 24 h, the rats were anesthetized using isoflurane anesthesia and the CCA were re-exposed and clipped by artery clips for 10 min followed by reperfusion. Rats that lost their righting reflex within 30 s and whose pupils were dilated and lost response to light during ischemia were selected for the experiments. Rectal temperature was maintained at 37 ± 0.5 °C using a thermal blanket during ischemia. Sham-operated animals underwent the same surgical procedures without occlusion of the CCA. Then the brains were dissected and cut into 5 coronal slices, 2-mm each, and the slices were incubated in 2% 2,3,5-triphenyltetrazo-lium chloride (TTC, Amresco, USA) for 15 min, according to the previous method [23].

2.2. Group and drug administration

Rats were randomly assigned to Sham-operated group (Sham, $n = 60$), GCI received only equal volumes of 25% DMSO solution (Vehicle, $n = 60$), and GCI treated with RSG group (RSG, $n = 60$). RSG (Avandia, GlaxoSmithKline, USA) was dissolved in 25% DMSO and stored at 4 °C. After GCI, RSG was immediately given as an intraperitoneal injection in RSG group following GCI (6 mg/kg body weight) as previously [24]. All tests were run blinded, and the animal codes were revealed only at the end of the behavioral and histologic analyses.

2.3. Hematoxylin and eosin (H&E) stain and neuron count

At 24 h after surgery, rats were again anesthetized as described above, and perfused intracardially with isotonic sodium chloride solution, followed by 4% (*w*/*v*) paraformaldehyde in 0.1 M sodium phosphate buffer (pH = 7.4). The brains were removed and fixed for 48 h in 4% (*w*/*v*) paraformaldehyde. After fixation, brains were embedded in paraffin, and sliced into 4 m coronal sections at the level of bregma and stained with H&E. The surviving and dying neurons in hippocampus per 1 mm were quantified.

2.4. Motor function recovery

At 24 h post-GCI, Bederson's test for neurological deficits was performed as previously described [23].

2.5. Measurement of the brain edema

Rat brains were separated and weighed immediately with a chemical balance to get wet weight (WW). Following drying in a desiccating oven for 24 h at 100 °C, dry tissues were weighed again to get dry weight (DW). The water percentage in the brain was calculated according to the formula: % brain water = (WW − DW) / WW) × 100.

2.6. Morris water maze

The spatial learning and memory of the rats were evaluated by Morris water maze as described previously [25]. Each rat was allowed to find the submerged platform within 90 s, and rest on it for 20 s. If the rat failed to find the hidden platform within 90 s, it was guided to the platform and placed on it for 20 s. The procedure was repeated for all

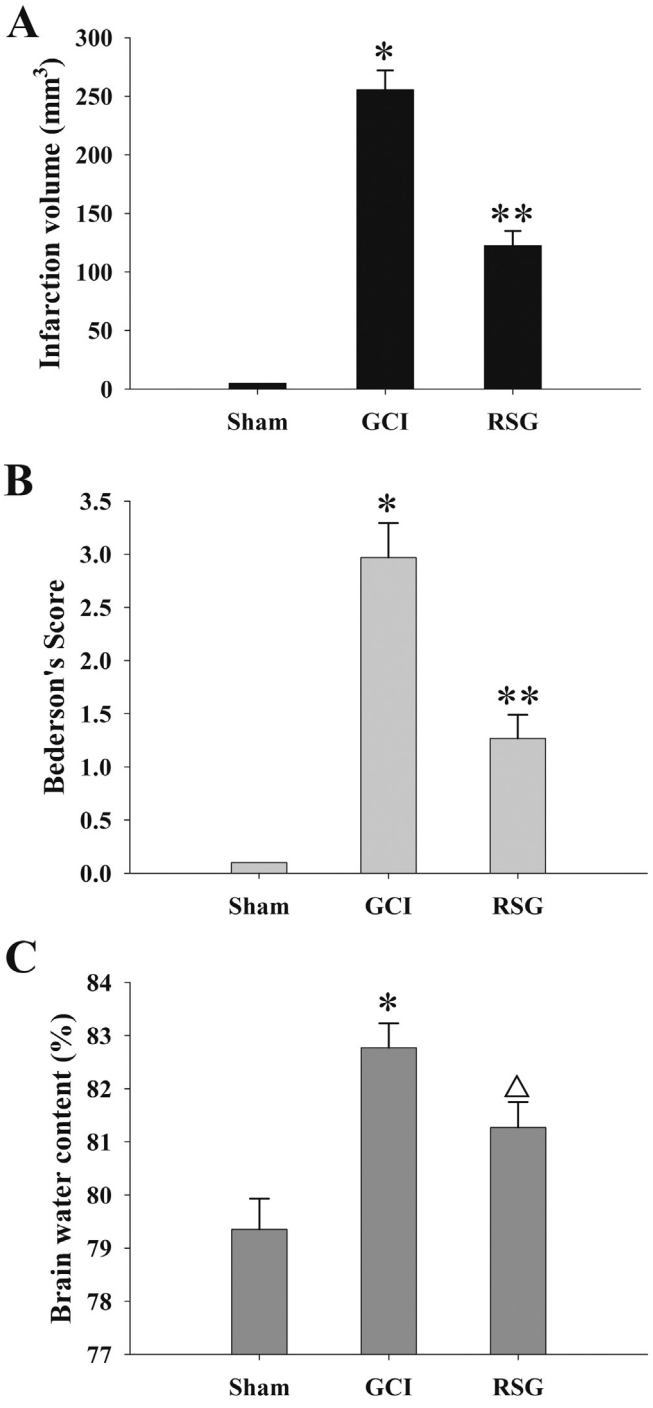

Fig. 1. The neuroprotective effect of RSG on GCI. The changes in infarction volume (A), Bederson's score (B) and brain water content (C) of the rat were determined at 24 h following GCI. Bars represent mean ± standard error ($n = 5$, per group). $^{*}P < 0.01$ vs. Sham group, $^{**}P < 0.01$ vs.GCI group and $\triangle P < 0.05$ vs.GCI group.

Please cite this article as: Shao Z-Q, Liu Z-J, Neuroinflammation and neuronal autophagic death were suppressed via Rosiglitazone treatment: New evidence on neuroprotection in a rat model of global cerebral ischemia, J Neurol Sci (2015), http://dx.doi.org/10.1016/j.jns.2014.12.027

Download English Version:

https://daneshyari.com/en/article/8276407

Download Persian Version:

https://daneshyari.com/article/8276407

Daneshyari.com