Original Article
Effect of telmisartan prevents cerebral ischemia-reperfusion injury-mediated oxidative stress and inflammation in a rat model

Baijing Dong, Qingla Li, Yuwen Song, Li Li, Wanchen Qiao, Jiaxin Zhao, Jiabin Tang, Xiaoqian Liu

Department of Neurosurgery, The Fourth Hospital of Harbin Medical University, Harbin 15001, China

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Abstract: With secure and dependable antihypertensive effects, telmisartan is an antihypertensive drug. Telmisartan was reported showing distinct neuroprotective effect in cerebral IR injury but the underlying mechanisms are still unclear. The aim of this study was to evaluate the effect of telmisartan prevents cerebral ischemia-reperfusion (I/R) injury-mediated oxidative stress and inflammation in model rat to explore possible molecular mechanism. Male Sprague-Dawley (SD) rats were used to induce cerebral I/R injury using middle cerebral artery occlusion. 30 SD rats were randomly and evenly divided into 3 groups: Sham, I/R, telmisartan treated ischemia-reperfusion group. The results showed that telmisartan improved neurological impairments, inhibited apoptosis, resisted oxidative stress and inflammation in hippocampus of cerebral I/R injury rats. However, pretreatment with telmisartan inhibited the activation of adrenocorticotropic hormone (ACTH), vasopressin, catecholamine and natriuretic peptides activities in cerebral IR injury rat. These findings confirm the involvement of telmisartan prevents cerebral ischemia-reperfusion injury-mediated oxidative stress and inflammation in model rat.

Keywords: Telmisartan, cerebral ischemia-reperfusion injury, oxidative stress, inflammation

Introduction
Telmisartan is a kind of selective angiotensin II receptor type I inhibitor with strong effects, which can be used for patients who have primary hypertension and cardiovascular risk but cannot be treated by angiotensin converting enzyme inhibitor (ACEI) [1]. Telmisartan can reduce both the systolic pressure and diastolic blood pressure [2]. Besides, compared with ACEI and other ATI inhibitors, it has less untoward effects and tolerance [3].

Cerebral ischemia-reperfusion injury (cerebral IR injury) is a common and frequently-occurring disease. In particular, healthy injuries and life threats caused by cerebral apoplexy is most serious [4]. Cerebral stroke, also called cerebral apoplexy, has high morbidity, disability and death rates. It can cause visual impairment, loss of verbal ability, paralysis and amentia [5]. For patients themselves, it not only hampers their health and lives, but also evidently lowers their life qualities. Meanwhile, it also brings heavy mental and economic burden is controlled and smokers are largely reduced, incidence of stroke in developed countries is beginning to reduce [6]. However, as aging is serious in developed countries, absolute quantity of stroke patients is still increasing. In developing countries, the morbidity of stroke is obviously increased.

Abnormal secretion of Adrenocorticotropic Hormone (ACTH) caused by function impairment of hypothalamic neuron which is triggered by severe craniocerebral trauma would increase urine sodium output [7]. Therefore, resulting from the increase of water reabsorption by kidney, low sodium and low plasma osmotic pressure occur. Thus, syndrome of inappropriate secretion of antidiuretic hormone (SIADH) happens [8].

Metabolic disorder of energy is an important cause of cerebral IR injury. When cerebral IR injury occurs, barriers of oxidative phosphorylation of chondriosome would cause the decrease of ATP production and produces large numbers of reactive oxygen species and triggers oxida-
Telmisartan and cerebral ischemia-reperfusion injury

Table 1. The Sequence of PCR primers of PCR

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In the study, the cerebral IR injury was modeled by middle cerebral artery occlusion (MCAO). The external carotid artery of every rat was exposed and dissected, 4-0 monofilament nylon was introduced into internal carotid artery for performing MCAO via external carotid artery. MCAO was withdrawn to introduce reperfusion for 2 h.

In sham group, SD rats were administrated with normal saline; in cerebral IR injury group, SD rats were modeled to cerebral IR injury model and administrated with normal saline; in tel + IR group, SD rats were modeled to cerebral IR injury model and administrated with 5 mg/kg of telmisartan for 10 days prior to MCAO.

Material and methods

Animals, cerebral IR injury modeling and treatment

30 Sprague-Dawley (SD) rats were randomly and evenly divided into 3 groups: namely Sham group (Sham), cerebral ischemia-reperfusion injury group (I/R), telmisartan treated ischemia-reperfusion group (tel + IR). This study was approved by the Institutional Research Committee of The fourth hospital of Harbin Medical University and performed at the Surgical Dream Works Laboratory. All SD rats were kept in pairs at room temperature with a 12 h/12 h dark (7:00 h-19:00 h)/light (19:00 h-7:00 h) cycle. All animals received in compliance with the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health.

Neurological deficits determination

A five point scale was used to evaluate the neurological defects after reperfusion. The scale was divided into five grades from 0 to 4. Normal, no neurologic deficit is 0, mild, when lifted by tail, flexion of forelimbs and contralateral torso is 1, moderate, circling to contralateral side but maintaining normal posture is 2, severe, leaning to the contralateral side is 3 and very severe, no spontaneous motor activities is 4.

Western blotting

Harvested hippocampus tissues were homogenized by RIPA lysis buffer system (Beyotime Biotechnology, Jiangsu, China) with protease inhibitor cocktail (Santa Cruz Biotechnology, Inc. USA) on ice. The homogenates were centrifuged at 12000 g for 10 minutes at 4°C and the total protein was measured using BCA method with a BCA Protein Assay kit (Beyotime Biotechnology, Jiangsu, China). 30-50 μg proteins were separated and concentrated using SDS-PAGE gel, and then transferred into PVDF membranes electronically (Millipore, Darmstadt, Germany). 5% defatted milk was blocked...
unspecific binding and specific antibodies against COX-2 (1:4000, Cell Signaling Tech, USA), MMP-2 (1:3000, Cell Signaling Tech, USA), MMP-9 (1:3000, Cell Signaling Tech, USA) and GAPDH (1:5000, Beyotime Biotechnology, Jiangsu, China) were used to incubate the membranes at 4°C for 12 h. PVDF membranes was incubated with the horseradish peroxidase-conjugated secondary antibodies incubation and then detected by using enzymatic chemiluminescence (ECL) kit (Bio-Rad).

Enzyme-linked immunosorbent (ELISA) assay

Whole Blood samples were collected and analyzed using the bedside Triage B-type natriuretic fluorescence immunoassay (Biosite Diagnostics, La Jolla, CA, USA). NF-κB and Tumor necrosis factor-α (TNF-α), Interleukin-1 (IL-1β) and Interleukin-6 (IL-6) levels were measured using ELISA kits (Beyotime Biotechnology, Jiangsu, China).

Quantitative RT-PCR (qRT-PCR)

of caspase-9 and natriuretic peptides (BNP)

Total RNA was prepared from Harvested hippocampus tissues (100 mg) using TRIzol® reagent (Invitrogen Life Technologies, Carlsbad, CA, China). 1 μl of Total RNA was used to synthesize Complementary DNA (cDNA) with a First Strand cDNA Synthesis kit (Thermo Fisher Scientific Inc., Waltham, MA, USA). qRT-PCR was carried out using a Maxima SYBR-Green PCR kit (Thermo Fisher Scientific Inc.). The primers of PCR are shown in Table 1. PCR program was finished as follows: 95°C for 30 sec, 60 or 58°C for 45 sec and extension at 72°C for 30 sec, for 40 cycles.

Adrenocorticotropic Hormone (ACTH) extraction and quantification in tissue

Hippocampus was disrupted with 0.1 M of perchloric acid and disposed with Branson Sonifier 450 (Branson, Danbury, CT, USA) for 30 s. CAT was extracted using activated alumina and quantified with ultraperformance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS).

Statistical analysis

Data acquired in this study were expressed in a (mean ± SD) manner and analyzed by SPSS, Inc., (version 21.0; IBM Corp., Armonk, NY, USA). One-way analysis of variance (ANOVA) was used to analyze the differences between groups. P<0.05 were considered to indicate a statistically significant difference.

Results

Effect of telmisartan prevents cerebral ischemia-reperfusion injury-mediated neurological impairments in model rat

The chemical structure of telmisartan (≥98% HPLC, Sigma-Aldrich Co. USA) was showed in Figure 1. We first evaluated the effects of
Telmisartan and cerebral ischemia-reperfusion injury

Figure 4. Effect of telmisartan prevents cerebral ischemia-reperfusion injury-mediated oxidative stress in model rat. Effect of telmisartan prevents cerebral ischemia-reperfusion injury-mediated MDA (A) and SDO (B) in model rat. Sham, Sham group; I/R, cerebral ischemia-reperfusion injury group; tel + IR, telmisartan treated ischemia-reperfusion group. **P<0.01 compared with 0 μM group, ***P<0.01 compared with 0 μM group.

Figure 5. Effect of telmisartan prevents cerebral ischemia-reperfusion injury-mediated inflammation in model rat. Effect of telmisartan prevents cerebral ischemia-reperfusion injury-mediated IL-1β (A), IL-6 (B), TNF-α (C) and NF-κB (D) in model rat. Sham, Sham group; I/R, cerebral ischemia-reperfusion injury group; tel + IR, telmisartan treated ischemia-reperfusion group. **P<0.01 compared with 0 μM group, ***P<0.01 compared with 0 μM group.

Figure 6. Effect of telmisartan prevents cerebral ischemia-reperfusion injury-mediated COX-2 in model rat. Effect of telmisartan prevents cerebral ischemia-reperfusion injury-mediated COX-2 protein expression using western blotting assays (A), statistical analysis of COX-2 protein expression in model rat (B). Sham, Sham group; I/R, cerebral ischemia-reperfusion injury group; tel + IR, telmisartan treated ischemia-reperfusion group. **P<0.01 compared with 0 μM group, ***P<0.01 compared with 0 μM group.

telmisartan prevents cerebral ischemia-reperfusion injury-mediated neurological impairments in model rat. After MCAO, telmisartan treated could reduce the cerebral ischemia-reperfusion injury-induced neurological impairments in model rat (Figure 2).
Telmisartan and cerebral ischemia-reperfusion injury

Effect of telmisartan prevents cerebral ischemia-reperfusion injury-mediated caspase-3 in model rat

As demonstrated in Figure 3, cerebral ischemia-reperfusion injury-induced caspase-3 activity was remarkably tested, compared with the sham group. Telmisartan treated effectively inhibited the cerebral ischemia-reperfusion injury-induced caspase-3 activity in model rat (Figure 3).

Effect of telmisartan prevents cerebral ischemia-reperfusion injury-mediated oxidative stress in model rat

As shown in Figure 4A, cerebral ischemia-reperfusion injury could increase the MDA activity comparing with sham group, in which was effectively reduced by treatment with telmisartan. However, sham group rats showed SOD activity was increased, compared with cerebral ischemia-reperfusion injury model rat (Figure 4B). Cerebral ischemia-reperfusion injury induce the inhibition of SOD activity was effectively recovered following telmisartan treatment (Figure 4B).

Effect of telmisartan prevents cerebral ischemia-reperfusion injury-mediated inflammation in model rat

We found that the activities of IL-1β, IL-6, TNF-α and NF-κB in cerebral ischemia-reperfusion injury rats were increased significantly inhibited in sham group (Figure 5A-D). We also found that telmisartan treatment effectively reduced the cerebral ischemia-reperfusion injury-induced IL-1β, IL-6, TNF-α and NF-κB activities in rat (Figure 5A-D).

Effect of telmisartan prevents cerebral ischemia-reperfusion injury-mediated COX-2 in model rat

Firstly, we found that the COX-2 protein expression was activated in cerebral ischemia-reperfusion injury model compared with sham (Figure 6A, 6B). Telmisartan administration suppressed the activation of COX-2 protein expression in rat, compared with model rats (Figure 6A, 6B).

Effect of telmisartan prevents cerebral ischemia-reperfusion injury-mediated MMP-2 and MMP-9 in model rat

Compared with sham group, there was a prominent increase in the MMP-2 and MMP-9 protein expression of cerebral ischemia-reperfusion injury model group (Figure 7A-C). Moreover, telmisartan inhibited cerebral ischemia-reperfusion injury-induced MMP-2 and MMP-9 protein expression in rats (Figure 7A-C).

Effect of telmisartan prevents cerebral ischemia-reperfusion injury-mediated ACTH in model rat

Figure 8 demonstrated the ACTH level of cerebral ischemia-reperfusion injury rat was observably reduced compared with sham rats. We found that administration of telmisartan effectively increased the inhibition of ACTH level in cerebral ischemia-reperfusion injury rat (Figure 8).

Effect of telmisartan prevents cerebral ischemia-reperfusion injury-mediated BNP in model rat

As shown in Figure 9, cerebral ischemia-reperfusion injury-mediated BNP was markedly increased compared with sham rats (Figure 9). In contrast, telmisartan treatment effectively inhibited cerebral ischemia-reperfusion injury-mediated BNP expression in rat (Figure 9).

Discussion

As an acute disease, cerebral IR injury is a result of ischemia, anoxia or sudden rupture hemorrhage of brain blood vessels caused by blockade of blood vessels. It has two types, i.e. ischemic cerebral apoplexy and hemorrhagic stroke. The former one occupies approximately 87%. Cerebral IR injury may cause necrosis of tissues in ischemic nuclear zone in ischemic penumbra [4]. Together they could make loss of brain functions. More than a half patients admitted into hospital for dysneuria is caused by ischemic cerebral apoplexy. Primary challenges of ischemic apoplexy are that its therapeutic time window is short, which makes patients with stroke cannot be treated in time. In this present study, we firstly investigated the effect of telmisartan prevents cerebral ischemia-reperfusion injury-mediated neurological impairments and caspase-3 activity in model rat. In addition, Pang et al. reported that Telmisartan protects against nutrient deprivation-induced apoptosis through activation of caspase-3 pathway [13].

Oxidative stress is cellular damage caused by unbalance of oxidative functions and antioxi-
Telmisartan and cerebral ischemia-reperfusion injury

Figure 7. Effect of telmisartan prevents cerebral ischemia-reperfusion injury-mediated MMP-2 and MMP-9 in model rat. Effect of telmisartan prevents cerebral ischemia-reperfusion injury-mediated MMP-2 and MMP-9 protein expression using western blotting assays (A), statistical analysis of MMP-2 and MMP-9 protein expression in model rat (B and C). Sham, Sham group; I/R, cerebral ischemia-reperfusion injury group; tel + IR, telmisartan treated ischemia-reperfusion group. **P<0.01 compared with 0 μM group, ##P<0.01 compared with 0 μM group.

Figure 8. Effect of telmisartan prevents cerebral ischemia-reperfusion injury-mediated ACTH in model rat. Sham, Sham group; I/R, cerebral ischemia-reperfusion injury group; tel + IR, telmisartan treated ischemia-reperfusion group. **P<0.01 compared with 0 μM group, ##P<0.01 compared with 0 μM group.

Figure 9. Effect of telmisartan prevents cerebral ischemia-reperfusion injury-mediated BNP in model rat. Sham, Sham group; I/R, cerebral ischemia-reperfusion injury group; tel + IR, telmisartan treated ischemia-reperfusion group. **P<0.01 compared with 0 μM group, ##P<0.01 compared with 0 μM group.

Dant functions [14]. ROS and increase of free radical production such as reactive nitrogen species are major causes of oxidative stress [15]. As second signal module, ROS can change expressions of genes and proteins to influence inter-cellular cascade of distinct events [16]. Although oxidative stress is necessary for maintaining normal physiological functions, they can bring cellular damages and diseases [17]. We also investigated telmisartan treatment inhibited oxidative stress in cerebral ischemia-reperfusion injury-induce rat. Together, Arab et al. reported that telmisartan attenuates attenuates colon inflammation and oxidative stress, and suppressed caspase-3 activity in a rat model of experimental inflammatory bowel disease [3].

Inflammatory factors of cerebral IR injury such as TNF-a, IL-1 and IL-6 could induce expressions of adhesion molecules and further promote
leukocyte infiltration and development of inflammatory response. Thus, cerebral injuries are worsened [18]. However, inflammatory response at early phase could promote organisms to produce self-protective responses and stimulate ischemic peripheral regions to generate neurotrophic factors [19]. Cerebral IR injury can delay neuron damage after ischemia by large amounts of expressions of above-mentioned neurotrophic factors. Studies demonstrated that acute inflammatory reaction plays a role in secondary brain injury triggered by ischemia reperfusion [20]. Cellular damage process mediated by inflammatory cells is more close to occurrence time when delayed neuron died [20]. In the present study, we found that telmisartan treatment effectively reduced IL-1β, IL-6, TNF-α and NF-κB activities, and suppressed COX-2, MMP-2 and MMP-9 protein expression in cerebral ischemia-reperfusion injury-induce rat. Guerra et al. showed that telmisartan decreases inflammation through TNF-α and NF-κB in a rat model of ulcerative colitis [21]. Araújo et al. confirmed the telmisartan inhibited levels of IL-1 and TNF-α, and down-regulated COX-2, MMP-2, MMP-9 in an experimental periodontitis model [1].

Cerebral IR injury is a major pathological mechanism of cerebral arterial thrombosis. Persistent activation of HPA axis after cerebral IR injury would aggravate neurocytes injuries after ischemia reperfusion [22]. Chief regulatory materials of HPA axis are CRF, ACTH and GC. HPA axis is transported to hypophyseal portal system by CRF and promotes the release of ACTH. ACTH would facilitate adrenal cortex to secrete GC which would elaborate its regulatory functions through a series of biological effects. In this study, we found that administration of telmisartan effectively increased the inhibition of ACTH level in cerebral ischemia-reperfusion injury rat. Miesel et al. reported that telmisartan suppressed ACTH level, regulated body weight and glucose homeostasis [23].

It has been found that plasma natriuretic peptides can secrete in heart chamber and tissue organs such as the brain [24]. After severe brain trauma and complications including cerebral IR injuries, natriuretic peptides are evidently increased, which is considered as a poor indicator for prognosis of traumatic brain injury [24]. On one hand, it will worsen hypothalamus injuries and promote the secretion of natriuretic peptides [25]. On the other hand, large dose of dehydration drugs could cause absolute or relatively inadequacy of circulating blood. Then concentration of natriuretic peptides in circulation would increase [12]. This study showed that telmisartan effectively inhibited BNP expression of cerebral ischemia-reperfusion injury rat. Shimada et al. reported that telmisartan effectively inhibited ambulatory blood pressure monitoring and plasma brain natriuretic peptide in hemodialysis patients [26]. Aoki et al. emerged that long-term effects of telmisartan could decrease natriuretic peptide (hANP) concentration and reduced blood pressure [27].

In summary, the present study showed the effect of telmisartan prevents cerebral ischemia-reperfusion injury-mediated oxidative stress and inflammation in model rat through COX-2, MMP-2/9 and ACTH/BNP. In conclusion, telmisartan may be one potential beneficial drug for treating on cerebral ischemia-reperfusion injury.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Xiaoqian Liu, Department of Neurosurgery, The Fourth Hospital of Harbin Medical University, 37 Yiyuan Street, Nangang District, Harbin 15001, China. Tel: +86-451-82576888; Fax: +86-451-82576888; E-mail: kbtxiaoqianliu@163.com

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