Mechanism of Wulan Shisanwei Tangsan in Protecting Against Cerebral Ischemia-reperfusion Injury by Regulating the cGAS-STING Pathway

Yanbin LI, Chunhui LIU*, Hanrui BAI, Wenling CONG, Lifen WANG, Zeyu WU, Qin WANG, Jiawei LIU

College of Traditional Chinese Medicine, Inner Mongolia Medical University, Hohhot 010110, China

Abstract [**Objectives**] To investigate the protective effect of the Mongolian medicine Wulan Shisanwei Tangsan (WL-13) against cerebral ischemia-reperfusion injury (CIRI) and its regulatory mechanism on the cGAS-STING pathway. [**Methods**] An SD rat MCAO/R model and OGD/R-injured astrocytes were adopted, and different doses of WL-13 (0.22, 0.44, 0.88 g/kg/d) were administered for intervention. Cerebral infarct area was assessed by TTC staining. The levels of inflammatory cytokines (TNF-α, IL-6, IL-1β) and cyclic nucleotides (cAMP, cGMP, cGAMP) were measured by ELISA to evaluate the regulatory effects of WL-13 on the cGAS-STING-NF-κB pathway and neuroinflammation. [**Results**] WL-13 reduced cerebral infarct size in MCAO/R rats in a dose-dependent manner and improved neurological deficits. It decreased the levels of TNF-α, IL-6, IL-1β, cGMP, and cGAMP, and increased cAMP levels in hippocampal tissue and astrocyte supernatants. The high-dose group (0.88 g/kg/d) exhibited the most pronounced effects. [**Conclusions**] WL-13 attenuated CIRI by inhibiting the cGAS-STING-NF-κB-mediated neuroinflammatory cascade. This study provides an experimental pharmacological basis for the clinical application of WL-13 and the modern development of Mongolian medicine.

Key words Cerebral ischemia-reperfusion, cGAS-STING, Neuroinflammation, Wulan Shisanwei Tangsan, Mongolian medicine

1 Introduction

In the classification of the Global Burden of Disease (GBD), stroke is the third leading cause of death worldwide. Its high mortality and disability rates severely affect human health and quality of life. Ischemic stroke accounts for 65.3% of new cases and is the predominant form of stroke. Restoring cerebral blood perfusion in time is essential for the treatment of ischemic stroke. However, reperfusion often leads to a series of irreversible pathological damages to brain tissue, namely cerebral ischemia-reperfusion injury (CIRI)[1].

Inflammation is a key pathological driving factor of CIRI, which can exacerbate brain injury, leading to physiological dysfunction and even functional loss[2]. During CIRI, mitochondrial DNA and nuclear DNA fragments from damaged cells are released into the cytoplasm, where they are recognized by cyclic GMP-AMP (cGAMP) synthase (cGAS). cGAS then catalyzes the synthesis of the cyclic dinucleotide cGAMP, which subsequently activates stimulator of interferon genes (STING) and initiates downstream signaling cascades[3-7]. STING recruits and activates the IκB kinase complex (IKKα/β/γ), which then phosphorylates IκBα, leading to the release and nuclear translocation of NF-κB, thereby initiating the transcriptional expression of pro-inflammatory cytokines such as IL-1β and TNF-α[8-9]. Studies have shown that as a key participant in the NF-κB pathway, p65 interferes with the inflammatory response under ischemic conditions. The authors have observed this phenomenon in MCAO animal models (essentially simulating stroke) and in microglia exposed to OGD/R[10-12]. It is noteworthy that astrocytes interact with microglia as important components of the neurovascular unit to jointly influence the progression of neuroinflammation[13]. Therefore, targeting the cGAS-STING pathway in astrocytes may become a potential therapeutic strategy for CIRI.

Wulan Shisanwei Tangsan (WL-13) is a classic compound formula in Mongolian medicine, recorded in Chapter 5 of *The Observer's Delight* (*Guanzhe Zhi Xi*). It is composed of *Inula helenium*, *Sophora flavescens*, *Rubus* spp., *Kaempferia galanga*, *Terminalia chebula*, *Melia toosendan*, *Gardenia jasminoides*, *Rubia cordifolia*, *Eriobotrya japonica*, lacca, *Trollius chinensis*, oak nut, and *Lithospermum erythrorhizon*. The formula is cool in nature and is considered an effective remedy for treating blood-heat disorders. It is a composite of three formulas: Chagan Tang, Shari Tang, and Sihong Tang, with the addition of *T. chinensis* and oak nut. The combination of these three formulas is effective against various febrile conditions. In Mongolian medicine, it is believed to clear blood-heat and is mainly used for treating headaches, red eyes, hypertension, and other conditions caused by excessive blood-heat[14-16]. Modern pharmacological studies have shown that WL-13 can inhibit excessive autophagy in neural cells, improve neurological deficits, lower blood pressure and lipid levels, and regulate hepatic fibrosis. Our previous research has confirmed that WL-13 promotes angiogenesis in CIRI and regulates neuronal autophagy and apoptosis[17-19]. However, the anti-inflammatory mechanism of WL-13 is not completely clear, and whether it inhibits

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Yanbin LI, master's degree. * Corresponding author. Chunhui LIU, professor.

neuroinflammation by regulating cGAS-STING pathway remains to be clarified.

In this study, a MCAO/R rat model and OGD/R-injured astrocytes were used to observe the neuroprotective effects of WL-13 on CIRI and to explore its regulatory mechanism on the cGAS-STING-NF-κB signaling pathway and downstream inflammatory factors, with the aim of providing new theoretical evidence and drug targets for the treatment of ischemic stroke.

2 Materials and methods

2.1 Animals Adult male Sprague-Dawley (SD) rats (weighing 250 – 280 g, $n = 100$) were purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd. [License No. SCXK (Jing) 2021-0006]. All animals were reared in a barrier environment at a temperature of (25 ± 1) ℃ and a relative humidity of 50%, with five rats per cage, and they had free access to food and water. Because estrogen exerts a protective effect against ischemic stroke, only male rats were selected in this study[20]. All animal experiments were approved by the Animal Ethics Committee of Inner Mongolia Medical University (Approval No. YKD202001071).

According to previous research methods[17 – 19], the rats were randomly divided into seven groups: negative control group (NC), sham-operated group (Sham), ischemia-reperfusion model group (I/R), nimodipine group (NMP, 10.8 mg/kg/d), and Wulan Shisanwei Tangsan low-dose (WL-13-L, 0.22 g/kg/d), medium-dose (WL-13-M, 0.44 g/kg/d), and high-dose (WL-13-H, 0.88 g/kg/d) groups. An additional 30 adult male SD rats of the same strain were used for the preparation of drug-containing serum.

2.2 Cells Rat astrocytes (RA) were purchased from Hohhot Zehao Biotechnology Co., Ltd. in Inner Mongolia (Catalog No. BNCC342351) and used for *in-vitro* OGD/R model establishment.

2.3 MCAO Surgery The MCAO/R model was established according to the method of Longa *et al.*[21]. Rats were anesthetized with 5% isoflurane for induction and 2.5% isoflurane for maintenance. After shaving and disinfection of the neck area, a midline cervical incision was made. The right common carotid artery (CCA), external carotid artery (ECA), and internal carotid artery (ICA) were carefully isolated. A microvascular clip was temporarily placed on the CCA and ICA. After the thermal coagulation of the branches of the ECA, a small incision was made, and a monofilament suture (Wuhan Servicebio Technology Co., Ltd.) was inserted through the incision into the ECA. The microvascular clip on the ICA was then released, and the suture was advanced into the ICA until it reached the beginning of the middle cerebral artery and occluded blood flow. The entrance of the ECA was ligated to prevent suture detachment, and the incision was sutured, leaving the distal end of the suture exposed externally. After 90 min of ischemia, the suture was gently withdrawn to achieve reperfusion. In the sham-operated group, the neck vessels were exposed and the incision was sutured without suture insertion.

2.4 Neurological Evaluation Twenty-four hours after MCAO surgery, neurological function was assessed using the Zea-Longa test[21]. The scoring criteria were as follows: 0 point, no neurological deficit; 1 point, failure to fully extend the contralateral forepaw; 2 points, rotating to the contralateral side when walking; 3 points, leaning to the contralateral side when walking; 4 points, unable to move independently. Animals with scores of 1 – 3 points were selected for subsequent experiments. Scoring was performed independently by experimenters who were unaware of the grouping.

2.5 TTC staining for infarct area detection Rats in the MCAO groups were euthanized 14 d after administration. Blood was flushed by perfusion through the left ventricle with normal saline. Brain tissues were collected and frozen at – 20 ℃ for 30 min. The frozen brain tissues were cut into 2 mm coronal sections and stained with TTC staining solution (Wuhan Servicebio) in the dark at 37 ℃ for 15 – 20 min.

2.6 ELISA detection of inflammatory factors The concentrations of inflammatory factors per mg of protein were quantitatively determined using ELISA kits, including TNF-α (BY-ER331063, BYabscience, Nanjing), interleukin-6 (IL-6) (BY-ER330219, BYabscience, Nanjing), interleukin-1β (IL-1β) (BY-ER330206, BYabscience, Nanjing), cyclic adenosine monophosphate (cAMP) (BY-JZF0192, BYabscience, Nanjing), cyclic guanosine monophosphate (cGMP) (BY-JZF0311, BYabscience, Nanjing), and cyclic GMP-AMP (cGAMP) (Enzymlinked, MM-71994R1, China).

2.7 Statistical analysis Data are presented as mean ± standard deviation (SD) based on three or more independent experiments. Comparisons among multiple groups were conducted using one-way analysis of variance (ANOVA). GraphPad Prism 10.5.0 and Hiplot were employed for statistical analyses and network plot analyses.

3 Results and analysis

3.1 Effects of WL-13 on cerebral infarct volume Cerebral infarct area was evaluated 14 d after reperfusion (Fig. 1). No infarct area was detected in either the NC group or the Sham group. Compared with the I/R group, the infarct area was significantly reduced in all WL-13 dose groups and the NMP group ($P < 0.01$). Further comparison revealed that the infarct area in the WL-13-H group was significantly smaller than that in the WL-13-L and WL-13-M groups. These data indicated that, compared with low- and medium-dose WL-13, high-dose WL-13 (0.88 g/kg/d) exerted the most significant ameliorative effect on the increase in infarct area caused by cerebral ischemia, providing a basis for dose optimization of WL-13 in the treatment of CIRI.

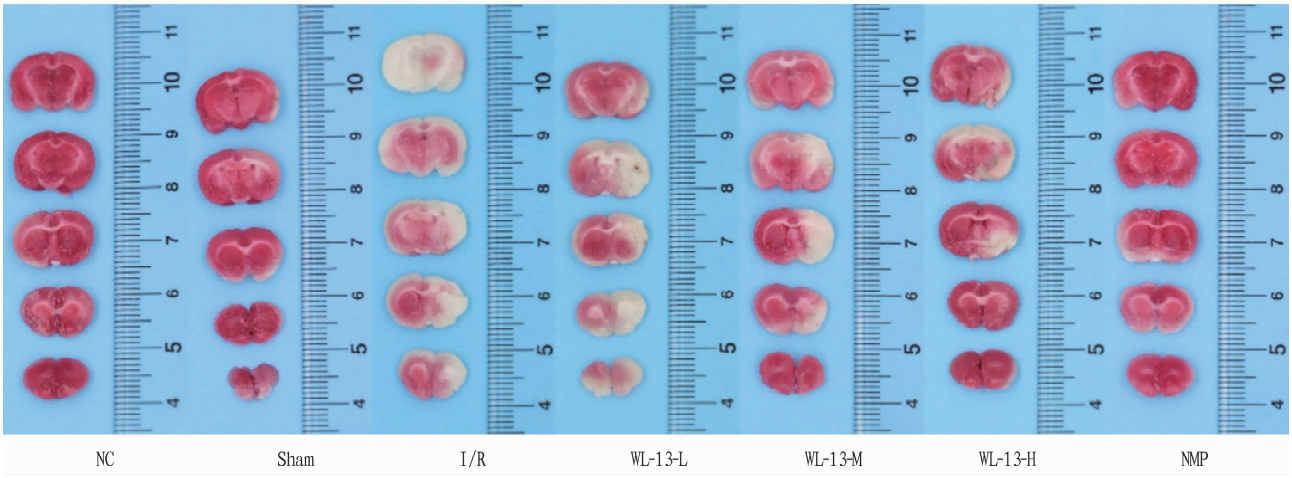


Fig. 1 Representative TTCstained brain sections of rats in various groups

3.2 Effects of WL-13 on inflammatory cytokines and cyclic nucleotide levels in hippocampal tissue of MCAO/R rats The ELISA results are shown in Table 1. Compared with the NC and Sham groups, the levels of TNF-α, IL-6, IL-1β, cGMP, and cGAMP in hippocampal tissue increased significantly in the I/R group ($P<0.01$), while cAMP levels decreased significantly ($P<0.01$). Compared with the I/R group, all treatment groups showed significantly decreased levels of the above inflammatory cytokines as well as cGMP and cGAMP, and significantly increased cAMP levels ($P<0.01$). Intergroup comparisons showed that the degrees of improvement in all indicators in the WL-13-H group were superior to those in the WL-13-L and WL-13-M groups ($P<0.05$). However, compared with the NMP group, the levels of TNF-α and IL-6 in the WL-13-H group remained higher ($P<0.05$).

Table 1 Levels of various factors in the hippocampal region of the affected side of rats ($n=8$)

Group	cAMP // nmol/g	cGAMP // pg/g	cGMP // nmol/g	IL-1β // pg/g	IL-6 // pg/g	TNF-α // pg/g
NC	0.156 ± 0.010	109.88 ± 24.91	0.072 ± 0.006	125.36 ± 7.62	765.83 ± 51.11	628.57 ± 78.11
Sham	0.173 ± 0.009	94.09 ± 23.11	0.071 ± 0.005	161.79 ± 7.11	820.00 ± 52.11	691.95 ± 92.11
I/R	0.060 ± 0.003**	134.28 ± 28.41**	0.204 ± 0.009**	437.61 ± 23.11**	1 727.89 ± 72.11**	3 999.98 ± 148.11**
WL-13-L	0.072 ± 0.005##	122.18 ± 22.11##	0.133 ± 0.010##	373.52 ± 16.11##	1 475.02 ± 71.11##	3 056.02 ± 161.11##
WL-13-M	0.091 ± 0.004##	115.37 ± 30.11##	0.121 ± 0.007##	302.18 ± 14.11##	1 271.23 ± 47.11##	1 998.66 ± 101.11##
WL-13-H	0.130 ± 0.008##	104.23 ± 33.11##	0.108 ± 0.007##	247.56 ± 13.11##	994.89 ± 37.11##	2 063.69 ± 131.11##
NMP	0.123 ± 0.004##	108.33 ± 31.91##	0.085 ± 0.007##	212.43 ± 15.11##	795.27 ± 38.11##	1 060.87 ± 127.11##

NOTE **Compared with the NC group and Sham group, $P<0.01$; ##Compared with the I/R group, $P<0.01$.

3.3 Effects of WL-13 drug-containing serum on inflammatory cytokines and cyclic nucleotide levels in OGD/R-injured astrocytes As shown in Table 2, compared with the NC group, the OGD/R group exhibited significantly decreased cAMP levels in the cell supernatant, while TNF-α, IL-6, IL-1β, cGMP, and cGAMP levels significantly increased. Compared with the OGD/R group, both the WL-13 and NMP groups showed significant regulatory effects on the above factors: decreased levels of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β), cGMP, and cGAMP, and increased cAMP levels. Compared with the NMP group, the WL-13 group showed slightly weaker improvements in all indicators, but the differences were not statistically significant except for TNF-α ($P>0.05$).

Table 2 Levels of various factors in rat astrocyte supernatant ($n=3$, $\bar{x}\pm s$)

Group	cAMP // nmol/g	cGAMP // pg/g	cGMP // nmol/g	IL-1β // pg/g	IL-6 // pg/g	TNF-α // pg/g
NC	142.86 ± 3.65	51.34 ± 0.42	2.22 ± 1.58	144.30 ± 7.59	131.06 ± 14.87	637.61 ± 4.95
OGD/R	88.77 ± 1.31**	64.87 ± 2.22**	103.88 ± 0.93**	251.07 ± 2.55**	295.03 ± 5.52**	1204.33 ± 29.05**
WL-13	105.35 ± 5.24##	51.27 ± 0.76##	46.10 ± 1.16##	212.98 ± 9.13##	261.93 ± 7.88##	1076.38 ± 2.65##
NMP	125.80 ± 1.27##	50.67 ± 0.02##	14.95 ± 0.96##	175.07 ± 1.30##	217.34 ± 7.24##	747.90 ± 3.30##

NOTE **Compared with the NC group, $P<0.01$; ##Compared with the OGD/R group, $P<0.01$.

4 Discussion

CIRI is a secondary injury occurring after reperfusion therapy for cerebral infarction. It is a serious pathological process characterized by neuronal damage that is paradoxically exacerbated upon

restoration of blood flow, through mechanisms such as mitochondrial dysfunction, oxidative stress, and sterile inflammation[24]. The inflammatory response plays an indispensable role in this process and cannot be overlooked. The cGAS-STING pathway, as a key signaling pathway of the innate immune system, induces inflammatory responses and triggers the activation of downstream pro-inflammatory factors in the pathological progression of various diseases, including colitis, aging-related inflammation, and retinal inflammation[24-26]. The core of this process is the "mtDNA-cGAS-STING-cytokine axis". In specific, ischemia leads to the opening of the mitochondrial permeability transition pore (mPTP), resulting in excessive production of mitochondrial reactive oxygen species (mtROS) and subsequent leakage of mitochondrial DNA (mtDNA) into the cytoplasm[27]. Cytoplasmic mtDNA activates cyclic GMP-AMP synthase (cGAS), producing cyclic dinucleotides such as cGAMP, which in turn promote the dimerization of STING protein[29]. Activated STING enhances the transcription of type I interferons (IFN-α/β) and pro-inflammatory cytokines[24,28].

The Mongolian medicine Wulan Shisanwei Tangsan (WL-13) exerts multi-target neuroprotective effects. Studies have shown that molecular docking experiments confirmed that geniposide can protect neurons from I/R injury by inhibiting inflammation[29]. *T. chebula* extract can protect neurons from cerebral damage caused by transient cerebral ischemia[30]. Matrine in *S. flavescens* exhibits neuroprotective effects[31]. *R. cordifolia* extract exerts antioxidant effects on OGD/R-simulated CIRI model cells, ameliorating oxidative stress injury and reducing neuronal death[32]. Shikonin possesses antioxidant activity and neuroprotective effects against CIRI[33]. In Mongolian medicine, stroke is referred to as "Sa disease". According to Mongolian medical theory, Sa disease is caused by external factors that disrupt the balance of the three roots and seven essential substances in the body, leading to an excessive surge of "Qisu" and "Xila" to the brain (the sea of white vessels), resulting in damage to the white vessels. Alternatively, it may be caused by the predominance of "Badagan" and "Heyi", leading to blockage of cerebral blood vessels by viscous Badagan, thereby causing damage to the black vessels of the brain[34]. In summary, this formula is highly consistent with the Mongolian medical theory of "regulating the balance of Heyi-Xieri", reflecting the wisdom and charm of traditional Mongolian medicine.

The present study has certain limitations. Stroke generally occurs in middle-aged and elderly patients. However, establishing the model while ensuring the survival of middle-aged and elderly rats is very difficult. Therefore, all animal models adopted in this study were adult male healthy rats. In addition, from the perspective of treatment efficacy at different doses, the therapeutic effect of WL-13 showed an increasing trend from low dose to high dose. However, the highest dose set in this animal study was 0.88 g/kg/d, which showed certain limitations compared with the intervention effect of nimodipine in some experiments. In future studies, higher concentrations of WL-13 could be tested to explore the maximization of its therapeutic effects. In addition, the efficacy and pathways of individual herbs in the formula against CIRI remain incompletely understood and require further in-depth study.

5 Conclusions

This study verified the neuroprotective effects of WL-13 on CIRI in both *in-vivo* and *in-vitro* experiments, and revealed its mechanism of alleviating neuroinflammation by inhibiting the cGAS-STING-NF-κB signaling pathway and reducing the secretion of pro-inflammatory cytokines for the first time. Continuous administration of WL-13 (0.88 g/kg/d) for 14 d significantly reduced cerebral infarct size and improved neurological function in MCAO/R rats, and drug-containing serum also attenuated the inflammatory response in OGD/R-injured astrocytes. These results indicate that WL-13 is a promising candidate drug for CIRI, providing an experimental pharmacological basis for its clinical application and the modern development of Mongolian medicine.

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