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Protective effects of mangiferin on cerebral ischemia–reperfusion injury and its mechanisms

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ABSTRACT

The aim of our study was to investigate the protective properties of mangiferin, a natural glucosyl xanthone found in both mango and papaya on the cerebral ischemia–reperfusion injury and the underlying mechanism. Wistar male rats were subjected to middle cerebral artery occlusion for 2 h followed by 24 h of reperfusion. Mangiferin (25, 50, and 100 mg/kg, ig) or 0.5% carboxymethyl cellulose sodium was administered three times before ischemia and once at 2 h after the onset of ischemia. Neurological score, infarct volume, and brain water content, some oxidative stress markers and inflammatory cytokines were evaluated after 24 h of reperfusion. Treatment with mangiferin significantly ameliorated neurologic deficit, infarct volume and brain water content after cerebral ischemia reperfusion. Mangiferin also reduced the content of malondialdehyde (MDA), IL-1β and TNF-α, and up-regulated the activities of superoxide dismutase (SOD), glutathione (GSH) and IL-10 levels in the brain tissue of rats with the cerebral ischemia–reperfusion injury. Moreover, mangiferin up-regulated the expression of nuclear factor erythroid 2-related factor 2 (Nrf2) and its downstream anti-oxidant protein heme oxygenase-1 (HO-1). The results indicate that mangiferin can play a certain protective role in the cerebral ischemia–reperfusion injury, and the protective effect of mangiferin may be related to the improvement on the antioxidant capacity of brain tissue and the inhibition of overproduction of inflammatory cytokines. The mechanisms are associated with enhancing the oxidant defense systems via the activation of Nrf2/HO-1 pathway.

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1. Introduction

Cerebral ischemia is the chief cause of handicap and the third cause of death worldwide following cardiovascular diseases and cancer, and its incidence rises with the increase of age (Simerabet et al., 2008; Margaill et al., 2005). One of the principles of the cerebral ischemic injury treatment in clinic is to restore the blood reperfusion as early as possible, which will help reduce cerebral ischemic injury and make some irreversible damage restored at least in function. However, reperfusion after cerebral ischemia can also cause brain injury, leading to cerebral edema, brain hemorrhage, and neuronal death. This phenomenon is termed as cerebral ischemia/reperfusion (I/R) injury.

The pathological process of cerebral ischemia–reperfusion injury is rather complex and not clear yet. Multiple mechanisms are involved in it, like the damage and inflammation caused by free radicals (Stephenson et al., 2000), the energy metabolism disorder of brain tissues, the toxicity of excitatory amino acid, the overload of intracellular calcium (Siesjö, 1986; Siesjö and Ann, 1988), the cytotoxic effect of NO (Zhang et al., 1993) and the blood abnormal opening of blood–brain barrier. Recent data support the idea that oxidative stress is also a powerful mediators of cerebral ischemia/reperfusion injury (Chen et al., 2014; Rodrigo et al., 2013). Oxidative stress is closely related to the damage caused by the excessive production of inflammatory cytokines, in which the oxidative stress results in the increased production of reactive oxygen species (ROS) and pro-inflammatory cytokines, and the production of inflammatory cytokines, such as IL-s and TNF-α, etc., is one of the key regulating factors in the mechanism of inflammation induced by ischemia–reperfusion (Liu et al., 2011; Hou et al., 2012). Thus, effective prevention and control of oxidative stress in cerebral ischemia/reperfusion injury are of great clinical value. More and more evidence have indicated that stimulation of endogenous antioxidant systems might be an important strategy for achieving neuroprotection on cerebral ischemia/reperfusion injury (Jung and Kwak, 2010). Nuclear factor erythroid 2-related factor 2 (Nrf2), the inducible transcription factor, regulates multiple lines of cellular antioxidant systems that limit oxidative stress during cerebral ischemia/reperfusion injury (Alfieri et al., 2011). Under normal conditions, Nrf2 is degraded by Kelch-like ECH-associated protein-

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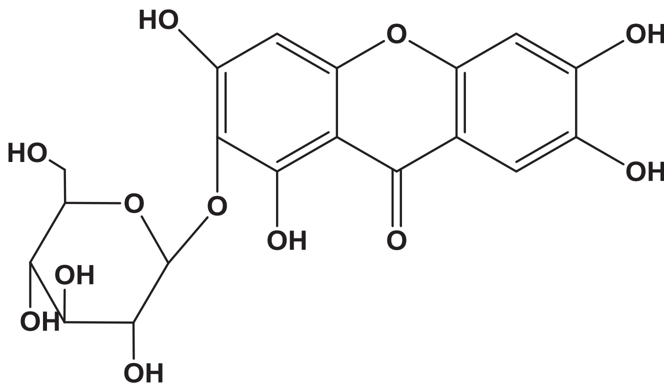

Fig. 1. The chemical structure of Mangiferin.

1(Keap1)-dependent pathway. Once activated, Keap1-Nrf2 binding is disturbed and Nrf2 transactivate antioxidant response element (ARE)-driven genes in the nucleus including SOD, GSH and heme oxygenase-1 (HO-1) (Jung and Kwak, 2010).

Mangiferin (MF; 1, 3, 6, 7-tetrahydroxyxanthone C_2-β-D-glucoside; Fig. 1), a natural glucosyl xanthone found in both mango and papaya, is known to exhibit numerous pharmacological activities, including anti-inflammatory, antioxidant/antiradical, antibacterial, hepatoprotective, anticarcinogenic, antiapoptotic, antidiabetic and antiviral action (Das et al., 2012; Wang et al., 2011; Garcia-Rivera et al., 2011; Tang et al., 2012; Li et al., 2010; Garrido et al., 2004; Chae et al., 2011; Marquez et al., 2012; Leiro et al., 2003). Remarkably, mangiferin has a strong antioxidant activity in the biological peroxidation system, which might result from the action of scavenging free radicals, e.g., OH^- and O_2^- associated with initiation of lipid peroxidation (Leiro et al., 2003). Because of the confirmed physiological and pharmacological activities, and the advantage of low toxic and side effects, mangiferin is considered to be greatly potential to be applied in the clinic, and much attention has been paid to it. However, the protective effect of mangiferin against cerebral I/R injury has not been fully evaluated yet. The underlying mechanism of its beneficial effect remains unknown. Therefore, the aim of the present study was designed to investigate the protective effects and possible mechanism of mangiferin on cerebral ischemia–reperfusion injury in rats.

2. Materials and methods

2.1. Materials and chemicals

MF ($C_{19}H_{18}O_{11}$, FW=422.34, purity $\geq$95%) was purchased from Nanjing ZeLang Medical Technology Co. Ltd. (Nanjing, China). SOD, GSH and MDA test kits were obtained from Nanjing Jiancheng Bioengineering Institute (Nanjing, China). IL-10, IL-1β and TNF-α levels were determined using an ELISA kit of R&D system Inc. (MN, USA). All the other chemical reagents were of analytical reagent grade.

2.2. Animals

The animals were used in accordance with the procedure approved by the Animal Ethics Committee of Shanghai Jiao-Tong University, Shanghai, China. Male Wistar rats weighing 220–250 g were kept in polypropylene cages in an air-conditioned room at 22 ± 0.5 °C and maintained on a standard laboratory feed and water ad libitum. Animals were acclimatized for 1 week before the experiments under a controlled light/dark cycle.

2.3. Experimental design

Wistar rats were randomly divided into six groups: SHAM control group (n=8), MODEL group (ischemia/reperfusion group, n=8), three different doses for MF-treated groups and Nimodipine-treated group (15 mg/kg/day, as the positive control). MF was dissolved in 0.5% carboxymethyl cellulose sodium administered (i.g.) at doses of 25 mg/kg (L-25 group), 50 mg/kg (M-50 group) and 100 mg/kg (H-100 group) respectively once a day for three times before the middle cerebral artery occlusion operation. The animal number of each group was eight. Rats in SHAM-operated and MODEL group were administered (i.g.) with 0.5% carboxymethyl cellulose sodium in the same volume, once a day for three consecutive days. After 1 h of the last administration, the focal cerebral ischemia–reperfusion rat model was induced using the method of intraluminal vascular occlusion as previously reported with slight modifications (Hua et al., 2009). Briefly, rats were anesthetized with chloral hydrate (400 mg/kg, i.p.). Body temperature was regulated at 37 °C by homoisothermy bench. Following the skin incision, the left common carotid artery, the external carotid artery and the internal carotid artery were carefully exposed and dissected away from adjacent nerves. Microvascular aneurysm clips were applied to the left common carotid artery and the internal carotid artery. A silicon rubber-coated 6-O monofilament was introduced into an arteriotomy hole, fed distally into the internal carotid artery and advanced 18–20 mm (Tao et al., 2015) from the carotid bifurcation. Regional cerebral blood flow (rCBF) was measured at 1 mm posterior and 4 mm lateral to the bregma with laser-Doppler flowmetry (PF5010; Perimed Co. Ltd., Sweden). Changes in rCBF were expressed as a percentage of the average of 2 or 3 baseline values, a drop in rCBF of $\geq$80% was considered to be a successful occlusion. The internal carotid artery clamp was removed and focal cerebral ischemia started. After ischemia for 2 h, the filament was gently removed (Zhang et al., 2013). The collar suture at the base of the external carotid artery stump was tightened. The skin was closed, anesthesia discontinued, and the animals were returned to the pre-warmed cages. Animals in the Sham group underwent neck dissection and coagulation of the external carotid artery, but no occlusion of middle cerebral artery.

2.4. Evaluation of neurological deficit

After 24 h of reperfusion, neurological deficit was scored by an investigator blinded to the study protocol according to the 5-point scoring system of Longa et al. (1989). The scoring system was used as follows: (1) normal walk or no neurologic deficit=0; (2) failure to extend opposite forepaw fully or a mild focal neurologic deficit=1; (3) circling to the contralateral side or a moderate focal neurologic deficit=2; (4) falling to contralateral side or a severe focal neurologic deficit=3; and (5) no spontaneous walking with depressed consciousness level=4.

2.5. Measurements of infarct volume

Brain infarction size was evaluated by the 2,3,5-triphenyltetrazolium chloride (TTC) staining method (Rupadevi et al., 2011). Rats were killed after neurological examination, and brains were carefully removed from the skull and maintained at −20 °C for 10 min. Then, the frozen brains were sliced into consecutive 2 mm coronal sections and immersed in a 2% TTC solution for 30 min at 37 °C. The infarct areas were photographed using a high-resolution digital camera. Image analysis software (NIH Image, National Institutes of Health, Bethesda, MD, USA, version 1.63) was applied to measure the infarcted area.

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