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Research report

Naringin alleviates early brain injury after experimental subarachnoid hemorrhage by reducing oxidative stress and inhibiting apoptosis

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ABSTRACT

This study aims to clarify the neuroprotective effect of naringin on early brain injury (EBI) following subarachnoid hemorrhage (SAH) and the possible mechanisms of naringin in the treatment of SAH. The endovascular puncture model was performed to induce SAH model in rats and the efficacy of 40 mg/kg and 80 mg/kg naringin were tested by intraperitoneally administration. SAH grade, neurological score, brain edema, blood-brain barrier permeability, the changes of oxidative stress related factors, apoptosis-related proteins, mitogen-activated protein kinase (MAPK) signaling pathway and neuronal morphology were detected to analyze the potential effect of naringin against SAH. The results demonstrated that naringin significantly ameliorated EBI, including SAH severity, neurologic deficits, brain edema and blood-brain barrier integrity by attenuating SAH-induced oxidative stress and apoptosis, and reduced the oxidant damage and apoptosis by inhibiting the activation of MAPK signaling pathway, which suggested a therapeutic potential of naringin in providing neuroprotection after SAH.

1. Introduction

Aneurysmal subarachnoid hemorrhage (SAH) is a complex and devastating disease with high mortality and morbidity (Cahill et al., 2006; Hop et al., 1997). Early brain injury (EBI) which was caused by the initial aneurismal hemorrhage and occurred during the first 72 h following SAH, is the major factor which is closely related to prognosis (Hasegawa et al., 2011). There is compelling evidence to suggest that oxidative stress, as a major trigger for the induction of neuronal apoptosis, play a pivotal role in the development of EBI after SAH. It has been demonstrated that, intrinsic antioxidant systems such as superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) are inhibited following SAH, so there is an imbalance between the productions of reactive oxygen species (ROS) induced by oxidative stress and the intrinsic antioxidant systems in both experimental models and the patients (Ayer and Zhang, 2008; Endo et al., 2007; Zhuang et al., 2012).

It was reported that the early brain injury (EBI) after subarachnoid hemorrhage (SAH) can activate mitogen-activated protein kinase (MAPK), and oxidative stress is a strong inducer of the MAPK activation and the activation of MAPK signaling pathway is another prominent change in EBI after SAH (Huang et al., 2013; Ravindran et al., 2011). The activation of MAPK signaling pathway could exacerbate EBI following SAH by provoking proapoptotic cellular signaling pathway (Kusaka et al., 2004; Zhang et al., 2015). And Mitochondria-targeted antioxidant attenuates MAPK pathway activation (Cao et al., 2012). It has been reported that antioxidant therapy could provide neuroprotection effects in experimental SAH. Therefore, compounds with antioxidant properties can show a potential therapeutic efficacy in SAH treatment and is worth investigating.

Naringin (4′,5,7-trihydroxyflavanone-7-rhamnoglucoside, Fig. 1A), a major flavonone glycoside from grapefruits and citrus fruits, has been studied sufficiently in vitro and in vivo, and been demonstrated the pharmacological effects in various disease such as atherosclerosis, cardiovascular disorders, diabetes mellitus, neurodegenerative disorders and osteoporosis (Bharti et al., 2014). In addition, it also been reported that naringin could exert its anticancer attributes in various cancer models such as oral, breast, colon, liver, lung, and ovarian, etc. Naringin exerts numerous biological and pharmacological benefits by its antioxidant, anti-

Abbreviations: SAH, subarachnoid hemorrhage; EBI, early brain injury; ICA, internal carotid artery; ECA, external carotid artery stump; CA, carotid artery; MCA, middle cerebral artery; DMSO, dimethyl sulfoxide; EB, Evans blue; BBB, blood-brain barrier; MDA, malondialdehyde; SOD, superoxide dismutase; CAT, catalase; GSH-Px, glutathione peroxidase; GSH, glutathione; GSSG, oxidized glutathione; MAPK, mitogen-activated protein kinase.

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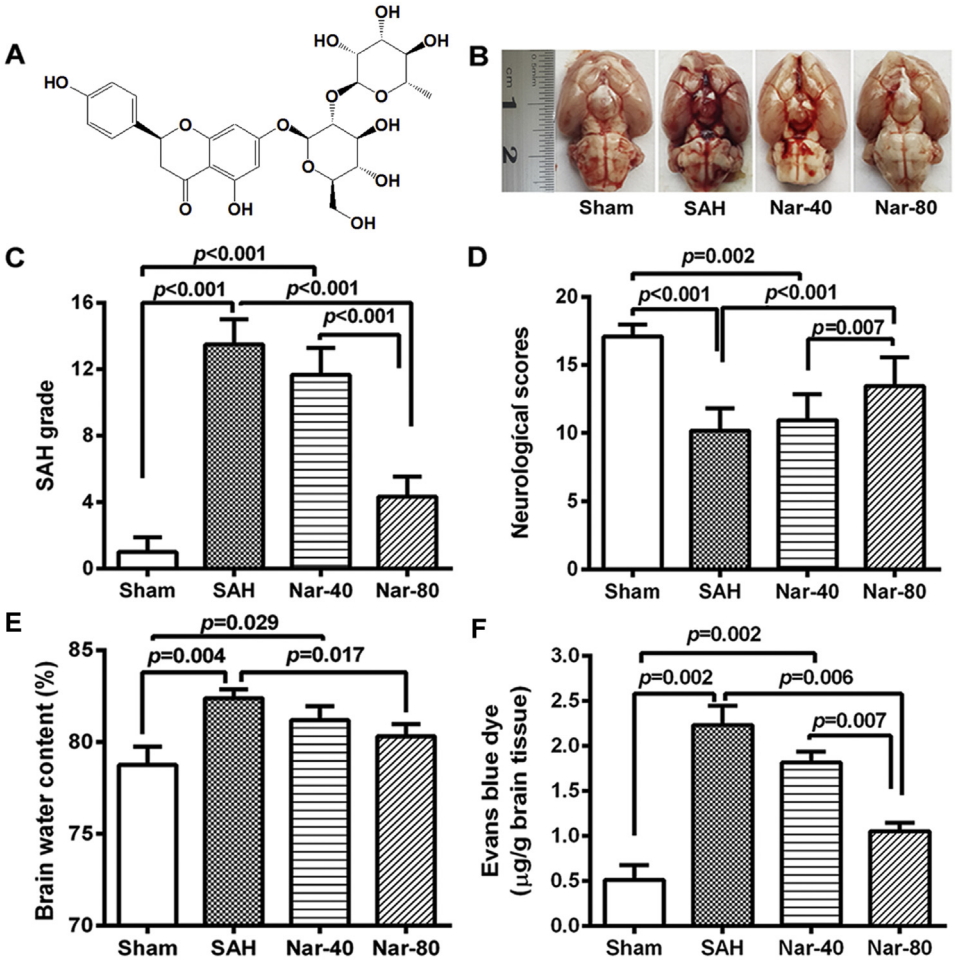

Fig. 1. Effect of naringin on EBI at 24 h after SAH. (A) The chemical structure of naringin (Nar). (B) Representative the severity of hemorrhage in different groups. (C) Quantitative analysis of the SAH grade scores. (D) Neurologic scores for each group. (E) Brain water content as indices of edema. (F) Evans blue content as indices for BBB permeability. Data are expressed as mean ± SD, n = 6/group.

inflammatory, and anti-apoptotic properties (Qin et al., 2016). It also has been considered as a neuroprotective agent not only because it can activate the anti-apoptotic pathways but also due to the induction of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF). Apart from these, the neuroprotective effect of naringin is also due to its free radical scavenging, antioxidant and anti-inflammatory properties (Golechha et al., 2011), which has been studied in ischemic brain injury (Raza et al., 2013). However, there is no report about whether naringin can alleviate EBI following SAH and promote the recovery of neurological function.

Given the above, the aim of this study is to observe the effects of naringin on EBI after SAH, and to clarify the correlation of neuroprotective effect of naringin and its antioxidant and anti-apoptosis activity.

2. Materials and methods

2.1. Animal preparation

All studies were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23) revised 1996. Experimental protocols including animal use and all surgical procedures were approved by the Institutional Animal Care and Use Committee of General Hospital of Shenyang Military Command (Shenyang, China). Male Sprague-Dawley rats weighing 280–320 g were used. The rats were raised on a 12 h dark-light cycle circumstance with free access to food and water.

2.2. Rat SAH model

The endovascular perforation model of SAH in rats was performed as described previously (Bederson et al., 1995). In short, with 10% chloral hydrate (0.35 ml/100 g) anesthesia, a sharpened 3.0 monofilament nylon suture was inserted rostrally into the right internal carotid artery (ICA) from the external carotid artery stump (ECA) while clamping the common carotid artery (CA) in front of the junction toward ICA and ECA. The suture was further advanced into the intracranial ICA until resistance was felt and then pushed 3 mm further penetrating the ICA near the bifurcation with the middle cerebral artery (MCA). The suture was then withdrawn, the ECA was closed entirely and the CA clamp was released which leads to reperfusion in the ICA and producing SAH, and perforated the bifurcation of the anterior and middle cerebral arteries. Sham-operated control rats underwent an identical procedure, however, without puncturing the bifurcation of the ICA and MCA. Body temperature was strictly monitored with a rectal probe. Arterial blood pressure and arterial blood gas were measured using Physiological Pressure Transducer (AD Instruments Pty Ltd, Australia).