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Crocetin, a carotenoid derivative, inhibits retinal ischemic damage in mice

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Abstract

Crocetin, an aglycone of crocin, is found both in the saffron crocus (*Crocus sativus* L.) and in gardenia fruit (*Gardenia jasminoides* Ellis). We evaluated the protective effects of crocetin against the retinal ischemia induced by 5 h unilateral ligation of both the pterygopalatine artery (PPA) and the external carotid artery (ECA) in anesthetized mice. The effects of crocetin (20 mg/kg, p.o.) on ischemia/reperfusion-induced retinal damage were examined by histological, electrophysiological, and antioxidant analyses. Data for anti-apoptotic analysis was obtained by terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining. Using immunohistochemistry and immunoblotting, the protective mechanism mediating the effects of crocetin was evaluated by examining crocetin's effects on the expression of 8-hydroxy-2-deoxyguanosine (8-OHdG; used as a marker of oxidative stress), and on phosphorylations of mitogen-activated protein kinases [MAPK; viz. extracellular signal-regulated protein kinases (ERK), c-Jun N-terminal kinases (JNK) and p38], and the redox-sensitive transcription factors nuclear factor-kappa B (NF-κB) and c-Jun. The histological analysis revealed that ischemia/reperfusion (I/R) decreased the cell number in the ganglion cell layer (GCL) and the thickness of inner nuclear layer (INL), and that crocetin inhibited GCL and INL ERG measurements revealed that crocetin prevented the I/R-induced reductions in a- and b-wave amplitudes seen at 5 days after I/R. In addition, crocetin decreased the numbers of TUNEL-positive cells and 8-OHdG-positive cells, and the phosphorylation levels of p38, JNK, NF-κB, and c-Jun present in the retina after I/R. These findings indicate that crocetin prevented ischemia-induced retinal damage through its inhibition of oxidative stress.

Introduction

Retinal ischemia, which leads to irreversible neuronal cell death, is involved in many ocular diseases, such as ischemic optic neuropathies, diabetic retinopathy, rubeotic glaucoma, and ocular ischemic syndrome (Bucolo et al., 2009, Bucolo et al., 2012, Bucolo and Drago, 2011). Ocular ischemic syndrome is the name given to a variable spectrum of aggregated ocular signs and symptoms that result from chronic ocular hypoperfusion, usually secondary to severe carotid artery occlusion may involve amaurosis fugax, central retinal artery occlusion, or branch retinal artery occlusion. Severe carotid artery stenosis or occlusion related to atherosclerosis is a common cause of this syndrome. As yet, a therapeutic agent has not been developed for ocular ischemic syndrome. Recently, we reported a new murine retinal ischemic model in which both the pterygopalatine artery (PPA) and the external carotid artery (ECA) were ligated (Ogishima et al., 2011). The PPA supplies blood to the ophthalmic artery (Lelong et al. 2007). Although the anastomotic site between PPA and ECA has not been determined accurately, the ECA contributes to the vascular network between the PPA and the ophthalmic artery (Fig. 1A) (Tamaki et al., 2006). This animal model is useful both for the clarification of the pathologic mechanisms underlying ocular ischemic syndrome and for the evaluation of neuroprotective drugs that might be used to target that syndrome. In our previous study, we found that edaravone, a free-radical scavenger, prevented the retinal ischemic damage present in that model (Ogishima et al., 2011). We therefore hypothesized that oxidative stress is likely to be causally involved in ischemia/reperfusion (I/R)-induced retinal damage.

Crocetin is one of the major active compounds both in the saffron crocus (*Crocus sativus* L.) and in gardenia fruit (*Gardenia jasminoides* Ellis) (Ichi et al., 1995, Li et al., 1999). In these plants, crocetin is estimated to be synthesized from zeaxanthin by enzymatic cleavage and then glycosylated to crocins. Crocetin exhibits a yellow color, and is an amphiphilic low-molecular weight carotenoid compound, as shown in Fig. 1. Crocetin has been used as an important spice and natural food colorant in various parts of world (Selim et al., 2000, Watanabe and Terabe, 2000). Crocetin and crocin have been reported to possess a number of biological activities, as exemplified by anti-oxidation (Yamauchi et al., 2011), anti-apoptosis (Ohno et al., 2012), anti-VEGF-induced angiogenesis (Umigai et al., 2012), anti-inflammatory (Hosseinzadeh and Younesi, 2002), anti-cancer (Wang et al., 1995), and hepatoprotective (Wang et al., 1991) effects, and by induced increases in retinal and choroidal blood flow (Xuan et al., 1999). Crocin has been shown to have a protective effect against the neuronal injury induced by occlusion of the middle cerebral artery (MCAO) in mice (Ochiai et al., 2007). However, the nothing is known about effects of crocetin in the model described above, in which retinal ischemia is induced in mice by ligation of the PPA and ECA.

In the present study, we used that model to examine the protective effects of crocetin orally administered against retinal cell death. To that end, we performed histological and electrophysiological analyses, and we also explored the underlying mechanism.

Section snippets

Animals

Male ddY mice (Japan SLC, Hamamatsu, Japan), aged 8 to 9 weeks, were used in this study. They were kept under controlled lighting conditions (12 h: 12 h light/dark). All experiments were performed in accordance with the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research, and they were approved and monitored by the Institutional Animal Care and Use Committee of Gifu Pharmaceutical University....

Retinal ischemia model in mice

Anesthesia was induced by means of...

Crocetin protected against the histological damage in the mouse retina induced by I/R

I/R caused decreases in the cell number in the GCL and in the thickness of the IPL and that of the INL in the mouse retina [versus the control (no I/R) retina] at 5 days after ischemia. Oral administration of crocetin significantly prevented such reductions in the GCL cell number and INL thickness (versus the vehicle group) (Fig. 3A–C). Although crocetin tended to prevent the reduction in IPL thickness, the significance level was not reached (Fig. 3D)....

Crocetin prevented the induction of cell apoptosis in the mouse retina following I/R

Terminal deoxynucleotidyl transferase dUTP...

Discussion

In the present study, oral administration of crocetin protected against I/R-induced retinal cell death and decreased the numbers of TUNEL-positive and 8-OHdG-positive cells in the retina. Crocetin also reduced the phosphorylations of MAPK, JNK, and p38, and those of the redox-sensitive transcriptional factors c-Jun and NF-κB in the mouse retina.

Neuronal cell death in the inner retina is induced by retinal I/R, which can be caused by such maneuvers as PPA and ECA ligation (Ogishima et al., 2011....

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