ScienceDirect

Neuropharmacology

Volume 113, Part A, February 2017, Pages 556-566

Oleuropein improves mitochondrial function to attenuate oxidative stress by activating the Nrf2 pathway in the hypothalamic paraventricular nucleus of spontaneously hypertensive rats

Wenyan Sun [a c], Xin Wang [b], Chen Hou [d], Liang Yang [d], Hongbao Li [c], Jing Guo [c], Chanjuan Huo [c], Molin Wang [c], Yuwang Miao [c], Jiankang Liu [d], Yuming Kang [c]

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https://doi.org/10.1016/j.neuropharm.2016.11.010

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Abstract

Hypertension is associated with increased reactive oxygen species (ROS) production in the paraventricular nucleus (PVN) of the hypothalamus. Oleuropein (OL) has a variety of biochemical roles, including antihypertensive and antioxidative functions. However, there have been few reports on the effects of OL on oxidative stress in the PVN on hypertension. In spontaneously hypertensive rats (SHR), eight-week administration of 60 mg/kg/day of OL significantly reduced blood pressure, pro-inflammatory cytokines and the expression of components of the renin-angiotensin system (RAS) compared with SHR rats treated with saline. Concomitantly, OL inhibited superoxide, and increased the antioxidant defense system in the PVN of SHR. We also found that OL increased mitochondrial biogenesis through mtDNA, PGC-1α, Complex II and Complex IV expression and regulated mitochondrial dynamics through the fusion-related protein Mfn2 and fision-related protein DRP1 to attenuate mitochondrial impairment. Furthermore, the phase II enzyme levels of Nrf2 and its downstream proteins NQO-1 and HO-1 were all markedly increased in the PVN of the OL-treated SHR group compared with the saline-treated SHR rats. Our findings demonstrate that OL administration can protect the PVN of the hypothalamus from oxidative stress by improving mitochondrial function through the activation of the Nrf2-mediated signaling pathway.

Introduction

Hypertension is associated with increased reactive oxygen species (ROS) production in portions of the central nervous system (CNS) that control blood pressure (Sinha and Dabla, 2015). The physiological levels of ROS are important to maintain normal cellular functions, while an overload of ROS could exceed the capacity of the antioxidant system and induce oxidative stress. Mitochondrial dysfunction and the subsequent production of mitochondrial-localized ROS in the CNS play a critical role in the development of hypertension (Chan etal., 2009). The paraventricular nucleus (PVN) of the hypothalamus, one of the most important endocrine-autonomic control areas for regulating sympathetic output and salt appetite, plays an important role in regulating blood pressure and renal sympathetic nerve activity (RSNA) (Busnardo etal., 2013).

Oleuropein ($C_{25}H_{32}O_{13}$, OL), a natural polyphenolic compound, belongs to the secoiridoids and is abundantly found in various olive products from Mediterranean diet (Jemai etal., 2009). Oleuropein has a variety of biochemical roles, including antihypertensive, antioxidative, anticancer, and antimicrobial activities. The antioxidant capacity of oleuropein is much higher than that of vitamin C, green tea or grape seed extract (Andreadou etal., 2006, Andreadou etal., 2007). A recent study reported that oleuropein has the ability to scavenge nitric oxide and increase nitric oxide synthesis *invitro* (de la Puerta etal., 2001). Treatment of the senescent rats with oleuropein reduces the oxidative damage in substantia nigra pars compacta (SNc) by increasing antioxidant enzyme activities (Sarbishegi etal., 2014). Oral administration of olive leaf extract reduces brain edema and improves blood-brain barrier permeability after transient middle cerebral artery occlusion (Mohagheghi etal., 2011).

The antihypertensive effects of oleuropein might be partly mediated by improving the release of nitric oxide and antioxidant and sympathoplegic activities in a rat model of diabetic hypertension (Nekooeian etal., 2014a). Olive leaf extract administered to hypertensive rats at dosages ranging from 100 to 1000mg/kg for 2–6 weeks significantly lowered mean arterial pressure (MAP) and heart rate (HR) (Khayyal etal., 2002). In a human clinical trial, ethanolic olive leaf extract reduced MAP and decreased cholesterol (Perrinjaquet-Moccetti etal., 2008). Nuclear factor (erythroid-derived-2)-like 2 (Nrf2), a master regulator of the antioxidant response element, is a crucial transcription factor that mediates protection against oxidants (Li and Kong, 2009). Nrf2 activity correlates strongly with mitochondrial function by promoting the mitochondrial biogenesis pathway. Spontaneously hypertension exhibits significantly oxidative damage and inflammation within the paraventricular nucleus (Nishihara etal., 2012, Song etal., 2014). Reducing oxidative stress and inflammation in the hypothalamus by antioxidant treatment can lower blood pressure in rat model of hypertension (Su etal., 2014), suggesting that antioxidant-based reduction of oxidative stress in the paraventricular nucleus may be an effective strategy for lowering blood pressure. Therefore, despite the fact that OL has promising roles as an antioxidant, and antihypertensive, there have been few reports on the effects of OL on oxidative stress in the PVN or the effects of OL on the Nrf2-mediated phase II enzyme pathway in PVN during hypertension.

Section snippets

Animals and experimental design

Eight-week-old male normotensive Wistar-Kyoto (WKY) rats and spontaneously hypertensive rats (SHR) were purchased from the Charles River Laboratory Animal, Ltd. The rats were housed in individual standard cages on a 12-h light/12-h dark cycle in a temperature-controlled (21±2.0°C) environment during a week of acclimatization, with ad libitum access to water and a commercial standard chow (10% calories from fat, 20% calories from protein, 70% calories from carbohydrate; Research Diets,…

OL reduced blood pressure and cardiac hypertrophy in SHR

SBP and MAP were significantly higher in SHR than WKY at the beginning of the experiment (at age 8 weeks) and remained increased for the duration of the study (main effect of genotype: SBP, $F_{(1, 32)}$=9.5, p=0.0047; MAP, $F_{(1, 32)}$=12.3, p=0.0016. Table1). At the end of the 8-week feeding study, chronic OL administration significantly reduced SBP and MAP in the SHR+OL group compared with the SHR+Saline group (main effect of treatment: SBP, $F_{(1, 32)}$=7.5, p=0.0101; MAP, $F_{(1, 32)}$…

Discussion

Levels of PVN PICs, such as TNF-α, IL-1β and IL-6, are increased in several animal models of hypertension (Kang et al., 2009b). Hypertension is closely related to overactivity of the pressor axis of the RAS and the RAS activation plays a central role in the brain to regulate blood pressure (Cuadra et al., 2010). Our results indicated that OL supplementation significantly reduced PICs, including TNF-α, IL-1β and IL-6, and RAS components, such as ACE and AT_1R levels within the PVN of hypertensive …

Conflict of interest

The authors declare no conflict of interest.…

Acknowledgments

This work was supported by the Major State Basic Research Development Program (2015CB856302), China Postdoctoral Science Foundation (No. 2015M582639), the Fundamental Research Funds for the Central Universities No. 83, National Basic Research Program of China (No. 2012CB517805) and National Natural Science Foundation of China (Nos. 91439120, 81370356, 81573104).…

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> …Under the action of drugs or oxidative stress, Nrf2 uncouples from Keap1 and enters the nucleus, where it interacts with the antioxidant response element (ARE) to induce the expression of antioxidant genes or proteins (such as haem oxygenase-1 [HO-1]) and enhance their antioxidant effects (Fig. 7) (Lee and Johnson, 2004). Oleuropein (3) and isoacteoside (7) inhibit the formation of reactive oxygen species (ROS) in cells by activating the transcription of Nrf2 (Braca et al., 2001; Oliveras-López et al., 2013; Perez-Herrera et al., 2013; Sun et al., 2017) and by increasing the expression of HO-1 and the levels of enzymatic antioxidants (SOD, GSH-Px and CAT) (Alirezaei et al., 2012; Chae et al., 2005; Dekanski et al., 2009; Jemai et al., 2008; Kotyzová et al., 2011). Additionally, verbascoside (6), echinacoside (8) and forsythoside B (9) extracted from plants can exert antioxidant effects by regulating Nrf2 to induce phase II cytoprotective enzymes (such as HO-1) (Li et al., 2018b; Sgarbossa et al., 2012)….

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