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Tert-butylhydroquinone attenuates oxidative stress and inflammation in hypothalamic paraventricular nucleus in high salt-induced hypertension

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ABSTRACT

Excessive oxidative stress and inflammation in hypothalamic paraventricular nucleus (PVN) are implicated in the pathogenesis of hypertension. It is reported that *tert*-butylhydroquinone (tBHQ), a nuclear factor erythroid 2-related factor 2(Nrf2)–inducer, has a variety of pharmacological activities such as anti-oxidation and anti-inflammatory effect. The objective of this study was to investigate the effects of tBHQ in high salt induced hypertension and to identify whether the beneficial effects were induced by inhibiting PVN oxidative stress and inflammation. Male Sprague-Dawley rats were fed with high salt diet (HS, 8% NaCl) or normal salt diet (NS, 0.3% NaCl). These rats were administration of tBHQ (150 mg/kg/d) by oral gavage for 16 weeks. Our results showed that high salt intake resulted in higher mean arterial pressure, cardiac hypertrophy as well as increased plasma level of norepinephrine and interleukin (IL)-1β, IL-6 compared with NS rats. It increased PVN level of reactive oxygen species, $gp91^{phox}$, IL-1β, IL-6, p-IKKβ and nuclear factor-kappa B (NF-κB) activity, decreased PVN level of Nrf2 and Cu/Zn-SOD. Chronic administration of tBHQ significantly attenuated these changes in HS rats. These data suggest that the protective effects of tBHQ in salt induced hypertension are partly due to inhibiting oxidative stress and inflammation in PVN.

1. Introduction

High salt diet is one of the major causes of hypertension (Imaizumi et al., 2016; Rust and Ekmekcioglu, 2016). Accumulating evidence has demonstrated that high salt intake is associated with increased risks of cardiovascular diseases (Ma et al., 2015; Polonia et al., 2016). The hypothalamic paraventricular nucleus (PVN) is an essential central site to modulate body fluid homeostasis and sympathetic activity, and accordingly plays a key role in high salt induced hypertension (Dos Santos Moreira et al., 2017; Zheng and Patel, 2017). It is also reported that reactive oxygen species (ROS) and proinflammation cytokines (PICs) in the PVN are the major players in the genesis and development of high salt induced hypertension (Gabor and Leenen, 2011; Kang et al., 2010). In our previous study, we found that inhibition of PVN oxidative stress and inflammation has beneficial influences on reducing sympathetic outflow and blood pressure (Qi et al., 2016b).

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a crucial regulator of the antioxidant defense system by directly binding to an antioxidant response element and modulating antioxidant genes (Buendia et al., 2016). It can also moderate ROS production by regulating mitochondria and NADPH oxidase (Kovac et al., 2015). In addition, recent studies have established Nrf2 as a major modulator in NF-κB-inflammatory response (Sun et al., 2015a, 2016a; Wardyn et al., 2015). In our earlier study, we found that Nrf2 expression was decreased in the PVN of spontaneously hypertensive rats, and administration of oleuropein improved mitochondrial function and attenuated oxidative stress and inflammatory cytokines by activating the Nrf2 pathway in the PVN of hypertensive rats (Sun et al., 2017). These studies demonstrate that

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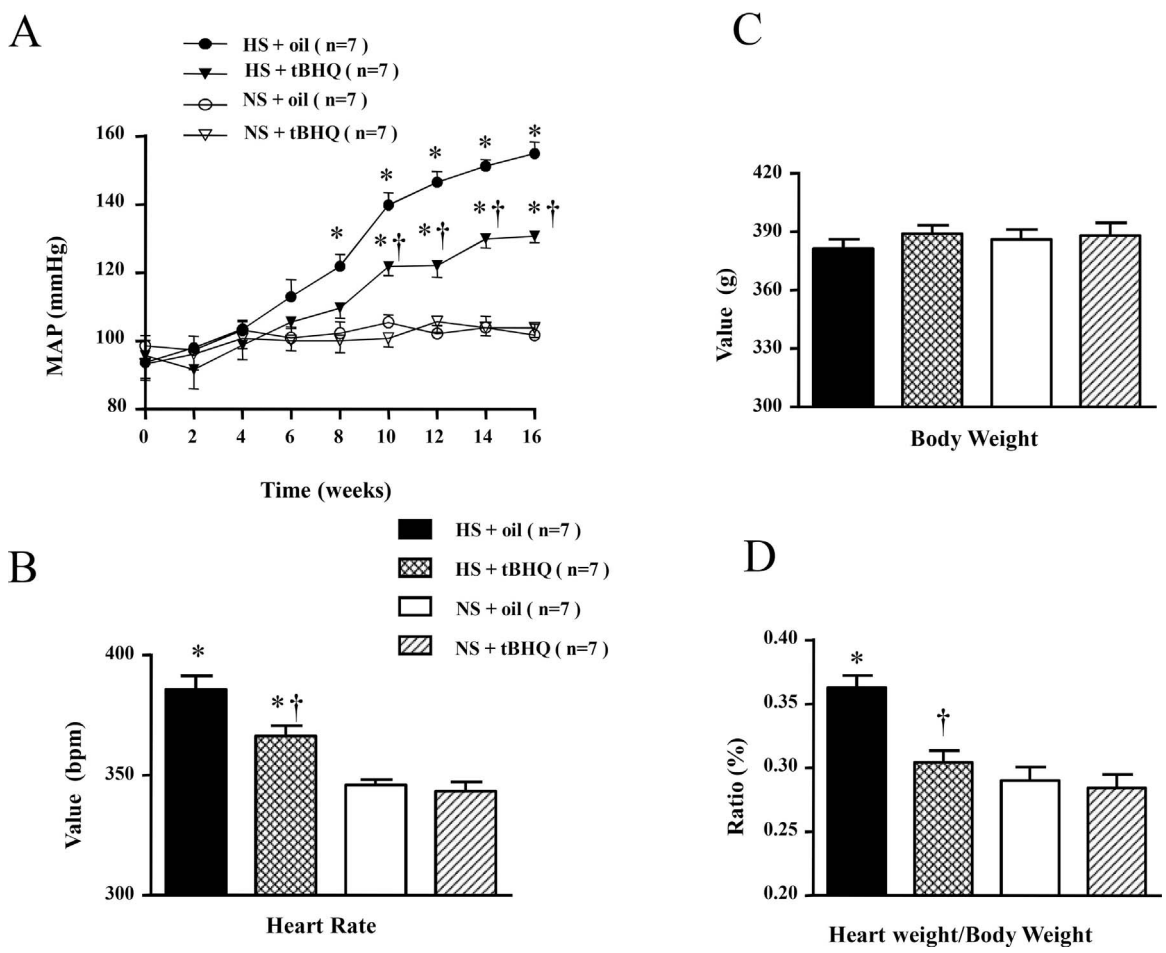

Fig. 1. Effects of tBHQ supplementation on mean arterial pressure (MAP), heart rate(HR), body weight and heart weight in high salt (HS) induced hypertensive rats and normal salt (NS) control rats. MAP, HR and heart weight were increased in HS rats; tBHQ treatment attenuated hypertension and cardiac hypertrophy in HS rats. (A) The MAP in hypertensive and control rats. (B) The heart rate in hypertensive and control rats. (C) The body weight in hypertensive and control rats. (D) The heart weight/body weight ratio in different groups. Values are expressed as means ± SE. n = 7 per group; *$P < 0.05$ vs. NS groups (NS + tBHQ or NS+ oil); †$P < 0.05$, HS + tBHQ vs. HS + oil.

Nrf2 might be an important signaling molecule in modulating PVN oxidative stress and inflammation and may serve as a therapeutic target in the prevention and treatment of hypertension.

Tert-butylhydroquinone (TBHQ) is an Nrf2–inducer and has been reported to possess antioxidant, anti-inflammation and cardiovascular protecting properties *in vitro* and *in vivo* (Jin et al., 2010; Turley et al., 2015; Ye et al., 2016). Previous studies found that tBHQ decreased blood pressure in AngII-induced hypertension in mice (Xu et al., 2016). However, the underlying molecular mechanism remains to be elucidated in detail. Given that tBHQ can pass through the blood-brain barrier (Saykally et al., 2012), we hypothesis that tBHQ might produce beneficial effect by inhibiting oxidative stress and inflammation in PVN. Therefore, the purpose of this study was to observe the effects of tBHQ in high salt induced hypertension and to determine whether the protective effect was through reducing oxidative stress and inflammation in PVN.

2. Material and methods

2.1. Animals

Sprague-Dawley rats weighing 180–220 g were purchased from the Experimental Animal Center of Xi'an Jiaotong University. Rats were caged in a temperature (23°–25 °C) and light-dark cycle (12: 12, lights on at 6 a.m.) controlled room with access to tap water *ad libitum*. The experimental procedures were performed in strict accordance with National Institutes of Health Guide for the Care and Use of Laboratory Animals. All animal works were approved by the Institutional Animal Care and Use Committees of Xi'an Jiaotong University.

2.2. General experimental protocol

Rats were randomly divided into four groups after one week of acclimatization with normal diet: (i) high salt diet (8% NaCl) + oil (HS + oil), (ii) high salt diet (8% NaCl) + tBHQ (HS + tBHQ), (iii) normal salt diet (0.3% NaCl) + oil (NS + oil) and (iv) normal salt diet (0.3% NaCl) + tBHQ (NS + tBHQ). TBHQ was purchased from Sigma-Aldrich and dissolved in corn oil. TBHQ was given at 150 mg/kg daily by oral gavage for 16 weeks (Ye et al., 2016). Control group was given corn oil (0.5 ml) daily by oral gavage. At the end of 16 weeks, rats were sacrificed to collect samples for further analysis.

2.3. Blood pressure measurements

Mean arterial pressure (MAP) and heart rate (HR) was non-invasively recorded by an indirect tail-cuff method in conscious rats as described previously (Li et al., 2015a). We also evaluated MAP and HR in direct way at the end of the 16-week feeding periods. Briefly, rats were anesthetized with mixture of ketamine (80 mg/kg) and xylazine (10 mg/kg) intra-peritoneally. The carotid artery was cannulated for continuous MAP and HR recording. The value was collected for 20 min and averaged.