Ablation of uncoupling protein 2 exacerbates salt-induced cardiovascular and renal remodeling associated with enhanced oxidative stress

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It has also been demonstrated that high-salt intake may lead to cardiovascular and renal fibrosis independent of the blood pressure raising. However, the mechanisms by which salt induces fibrosis are not fully understood. Oxidative stress has been implicated in cardiovascular and renal damages. The uncoupling protein 2 (UCP2) is a mitochondrial transporter and is ubiquitously expressed in the heart, vessels and kidneys. The basic function of UCP2 is involved in superoxide generation. Our previous studies demonstrated that ablation of UCP2 exacerbates salt-induced vascular dysfunction [1], while in UCP2 transgenic mice, the opposite occurs [2]. However, the role of UCP2 in salt-induced cardiovascular and renal remodeling was unclear.

In the present study, UCP2 knockout (KO) mice (Jackson Laboratory, Bar Harbor, Maine, USA) and wild-type (WT) littermates were fed a normal salt (NS, 0.5% NaCl) or a high salt (HS, 8% NaCl) diet for 16 weeks. All experimental procedures were approved by the Institutional Animal Care and Use Committee.

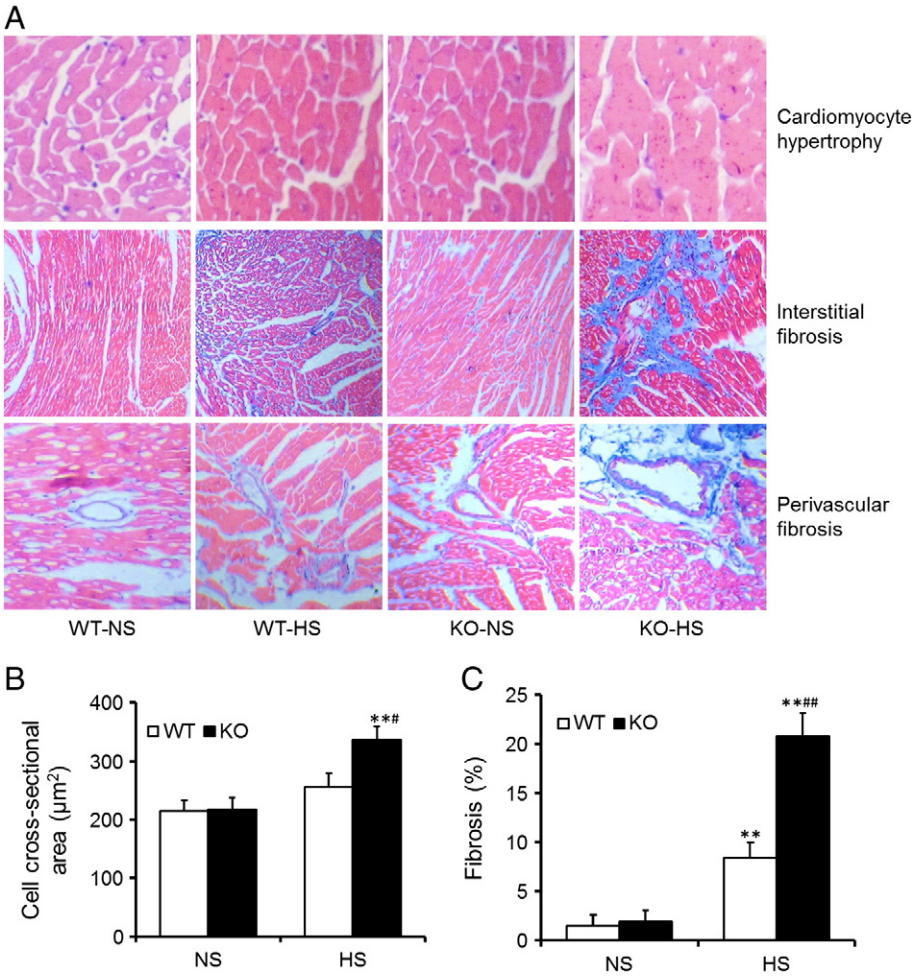

Fig. 1. The representative images of HE and Masson staining of the myocardial tissue (A). Original magnification = ×40. The quantification of cardiomyocyte size (B) and fibrosis (C). $^{**}P < 0.01$ vs. isogenic NS group. $_{\#}P < 0.05$, $_{\#\#}P < 0.01$ vs. salt-treated WT mice.

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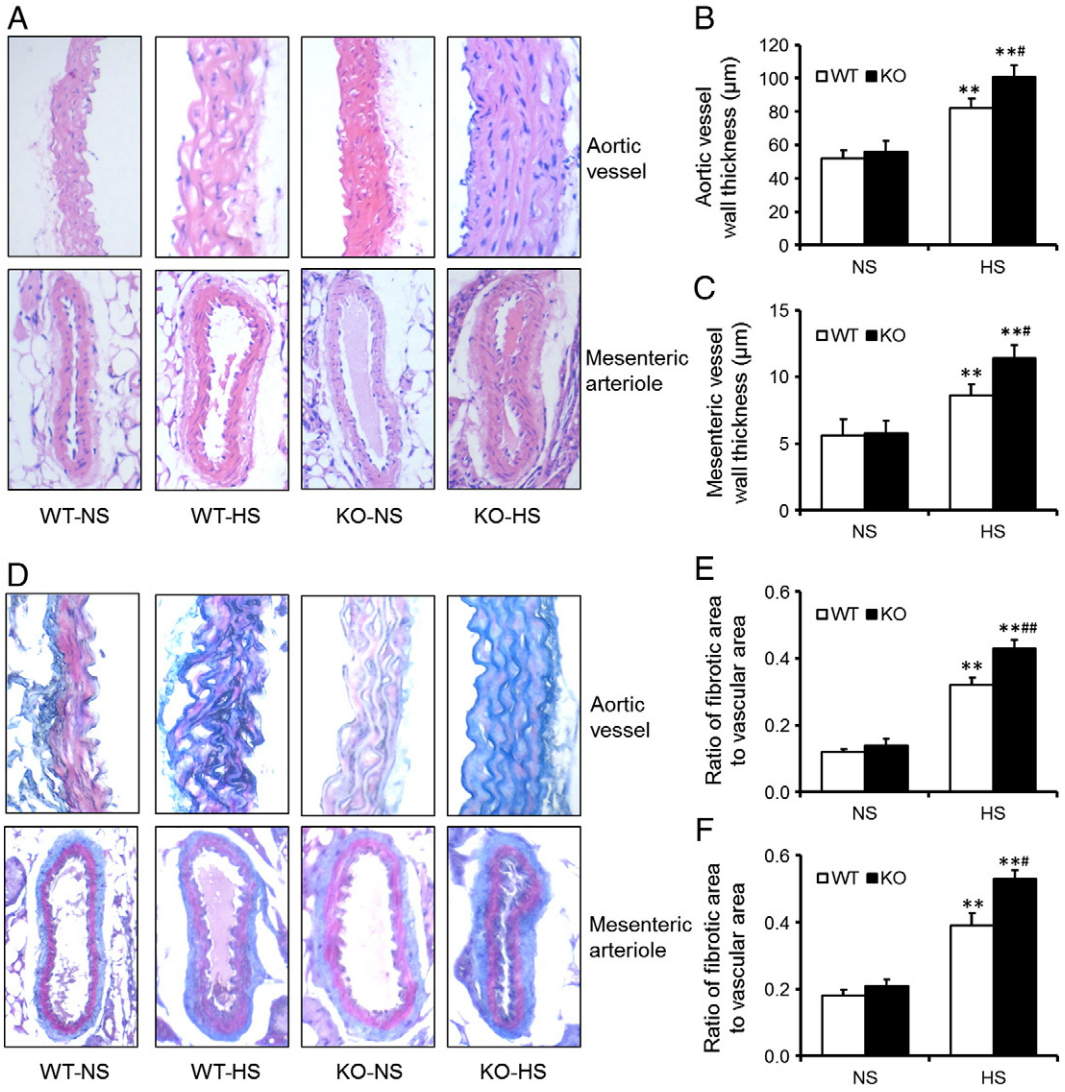

Fig. 2. The representative images of HE (A) and Masson staining (D) of the aortas and mesenteric arterioles. Original magnification = ×40. The quantification of aortic wall (B) and mesenteric arteriolar wall thickness (C) and aortic (E) and mesenteric arteriolar (F) fibrosis. $^{**}P < 0.01$ vs. isogenic NS group. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ vs. salt-treated WT mice.

In WT mice, salt had little effect on cardiomyocyte size (Fig. 1), but, in KO mice, salt caused a significant increase in cardiomyocyte size compared with the NS group (Fig. 1). As expected, salt-fed animals from both genotypes were found to have a significant fibrosis (Fig. 1). Interestingly, KO mice showed greater fibrosis after a high-salt intake compared with WT littermates (Fig. 1). The wall thickness of both the aorta and mesenteric arterioles was increased significantly due to salt-treated WT mice (Fig. 2) but was significantly higher in KO mice (Fig. 2). High-salt intake greatly increased aortic and mesenteric arteriolar fibrosis in both genotypes (Fig. 2), and had a significantly higher effect in KO mice (Fig. 2). The high-salt diet resulted in no significant changes in glomerular and tubular sizes in WT mice, but a significant increase in KO mice (Fig. 3). After 16 weeks of salt feeding, the glomerular tuft area in KO mice was significantly increased compared with WT mice (Fig. 3). The salt administration caused a remarkable renal fibrosis in both genotypic mice (Fig. 3), while the salt-induced renal fibrosis was exacerbated in KO mice compared with WT mice (Fig. 3).

The salt increased superoxide production (detected using dihydroethidium, DHE) in the aorta, mesenteric arterioles and kidneys, but not in the heart tissue (Fig. 4). In KO mice, the salt dramatically increased the superoxide level in both cardiovascular and renal tissues (Fig. 4). Moreover, the superoxide levels in cardiovascular and renal tissues were significantly higher in salt-treated KO mice compared with salt-treated WT animals (Fig. 4). The matrix metalloproteinase (MMP)-2, MMP-3 and MMP-9 expressions in the heart, aorta and kidney tissues of high-salt-administered WT and KO mice were significantly higher than in the paired normal-salt-administered mice (Fig. 5). The tissue inhibitor of MMP (TIMP)-1 expression was significantly lower in the heart, aorta and kidney tissues of salt-administered WT and KO mice than that of the paired NS mice (Fig. 5), but the decrease was greater in the heart and aorta and similar in the kidney in salt-administered KO mice (Fig. 5).

This study demonstrates that UCP2 KO mice receiving high-salt diet develop more severe cardiovascular and renal remodeling associated with increased oxidative stress, upregulations of MMP-2/-3/-9 and downregulation of TIMP-1. These findings provide the evidence of a protective role for the UCP2 against salt-induced cardiovascular and renal injury.

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