Thermoreceptor TRPV1 regulates body weight and blood pressure in the absence of thermogenin

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Although obesity is one of the frequent causes of high blood pressure, the molecular basis is not entirely clear owing to the heterogeneity of the two traits. Genetic, environmental, and behavioral factors all contribute to one being overweight, and increased salt sensitivity constitutes a key feature of obesity-related hypertension. In a subgroup of these patients, blood pressure and waist circumference correlate with plasma aldosterone, the overproduction of which could be attributable to humoral factors released from adipocytes [1, 2]. There are also aldosterone-independent pathways that result in vascular dysfunction and renal salt retention, highlighting the complexity of the underlying mechanisms [3, 4].

Uncoupling protein 1 (UCP1), also known as thermogenin, regulates nonshivering thermogenesis, and modulates total body energy expenditure [5]. UCP1 is predominantly present in the inner mitochondrial membrane of brown adipose tissue (BAT) and allows the reentry of protons from the intermembrane space to the mitochondrial matrix. UCP1 diminishes the proton gradient formed by the electron transfer chain, bypassing ATP synthase and ultimately resulting in the generation of heat [5]. Physiologically, cold signals and sympathetic activation result in β -adrenergic stimulation of UCP1 in BAT, thereby triggering thermogenesis. This process is abrogated by the genetic ablation of *Ucp1*, which is sufficient to increase body weight in mice [6]. Conversely, mice overexpressing *Ucp1* are resistant to obesity induced by a high-fat diet [7]. In addition, several clinical studies have reported the association of UCP1 with obesity and with hypertension in humans [8, 9], thus providing a possible mechanistic link between obesity and hypertension.

Transient receptor potential vanilloid-1 (TRPV1) was identified in 1997 as a cation channel activated by capsaicin (the active substance in chili peppers) and thermal stimuli ($>43^\circ\text{C}$) [10], an achievement recognized by the Nobel Prize in Physiology or Medicine 2021. TRPV1 is now known to be activated by many other noxious stimuli, such as acid and toxins. In addition to nociception in sensory nervous systems, it regulates a number of physiological processes, including thermoregulation, sympathetic activity, and cardiovascular responses [11]. Sensory neurons expressing TRPV1 innervate adipose tissues, and TRPV1 is also present in adipocytes; indeed, clinical studies have indicated that TRPV1 can alter energy expenditure in BAT [12]. Nonetheless, the roles of TRPV1 in obesity and cardiovascular disorders remain controversial.

In this issue of *Hypertens Res*, Li et al. generated TRPV1 and UCP1 double knockout mice (*Trpv1*^{-/-}/*Ucp1*^{-/-}) and analyzed the phenotype in detail (Fig. 1) [13]. In wild-type mice, neither body weight nor blood pressure were altered by the deletion of *Trpv1*. In *Ucp1*^{-/-} mice, however, the authors demonstrated that the knockout of *Trpv1* aggravated obesity and high blood pressure. *Trpv1*^{-/-}/*Ucp1*^{-/-} mice showed reduced oxygen consumption and heat production, which was accompanied by increased lipid content in the adipose tissues and an increase in abdominal circumference. In the BAT of *Trpv1*^{-/-}/*Ucp1*^{-/-} mice, impaired mitochondrial function was suggested by the reduction in key proteins involved in BAT differentiation and lipolysis, altered oxidative phosphorylation, and impaired Ca^{2+} signaling in isolated BAT mitochondria. The authors further demonstrated that leucine-zipper-EF-hand containing transmembrane protein 1 (LETM1), a $\text{Ca}^{2+}/\text{H}^+$ antiporter that is critical for mitochondrial homeostasis [14], is involved in these processes; they found that LETM1 and UCP1 levels were higher in *Trpv1*^{-/-} mice than in wild-type mice, whereas *Trpv1*^{-/-}/*Ucp1*^{-/-} mice had lower levels of LETM1 than *Ucp1*^{-/-} mice. The knockdown experiments indicated that the upregulation of LETM1 plays a compensatory role in the BAT of *Trpv1*^{-/-} mice,

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Graphical Opinion

Fig. 1 Adipose tissue dysfunction in *Trpv1*^{-/-}/*Ucp1*^{-/-} mice results in hypertension through increased aldosterone and decreased nitric oxide (NO). TRPV1 transient receptor potential vanilloid-1, UCP1 uncoupling protein 1, BAT brown adipose tissue, WAT white adipose tissue, RAAS renin-angiotensin aldosterone system

and the process was impaired in the double knockout mice. Mitochondrial dysfunction in *Trpv1*^{-/-}/*Ucp1*^{-/-} resulted in an increase in oxidative stress and mineralocorticoid receptor (MR) locally in the BAT, and it caused an increase

in aldosterone and a decrease in NO bioavailability in the systemic circulation (Fig. 1). These changes likely explain the elevated blood pressure levels in *Trpv1*^{-/-}/*Ucp1*^{-/-} mice.

The study by Li et al. provides additional clues to the pathogenesis of obesity-related hypertension and raises several provocative questions [13]. From the current study, it is unclear whether the blood pressure effects observed in *Trpv1*^{-/-}/*Ucp1*^{-/-} mice are solely attributable to the changes in adipose tissues or to signaling in other tissues, such as the vasculature, adrenal gland, nerve systems, and kidney; indeed, previous studies have shown that the modulation of TRPV1 signaling alters sympathetic nerve activity, vasoconstriction, and urinary sodium excretion [15–17]. It will be of interest to pursue the individual contributions in future studies. Additionally, the study showed that MR abundance in adipose tissues, as well as systemic aldosterone, was significantly increased in *Trpv1*^{-/-}/*Ucp1*^{-/-} mice. In relation to this finding, recent studies have shown that finerenone, a nonsteroidal MR antagonist, improved metabolic parameters in high-fat diet-fed mice, which was mediated by the induction of UCP1 and peroxisome proliferator-activated preceptor gamma coactivator 1 alpha (PGC-1α) in the BAT [18]. Of note, it has been suggested that steroidal MR antagonists and nonsteroidal MR antagonists can differ in their tissue distribution patterns and in the binding modes to the receptor [19], which may result in differences in clinical effects. In support of this possibility, experimental studies have shown that the response of thermogenic markers in BAT was significantly different between finerenone and spironolactone in mice receiving a high-fat diet [20]. Given these data, how available MR antagonists alter the pathologies observed in *Trpv1*^{-/-}/*Ucp1*^{-/-} mice deserves further analysis.

In patients with diabetes mellitus and hypertension, sodium glucose cotransporter 2 (SGLT2) inhibitors, such as empagliflozin, have been shown to produce clinically significant blood pressure reduction, especially in those with salt-sensitive hypertension [21, 22]. In addition, experimental studies have shown that SGLT2 inhibitors can reduce the salt sensitivity of blood pressure [23]. Given the

previous data suggesting that SGLT2 inhibitors promote browning and lipolysis in adipose tissues [24], it is also of interest to address whether SGLT2 inhibition can attenuate adipocyte changes and local renin–angiotensin aldosterone system (RAAS) activation in this model.

In summary, the study by Li et al. showed that the deletion of the cation channel TRPV1 in mice lacking UCP1 compromises mitochondrial function in BAT, resulting in body weight gain. This effect is accompanied by local RAAS activation, aldosterone excess, and hypertension. These data provide novel information regarding the link among obesity, aldosterone, and high blood pressure, which can be further characterized in future studies.

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Compliance with ethical standards

Conflict of interest SS has received honoraria from Daiichi Sankyo outside the submitted work.

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