New mechanism leading to alleviation of salt-sensitive hypertension by a powerful angiotensin receptor blocker, azilsartan

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Hypertension is one of the most life-threatening health problems in the modern world. Particularly, salt-sensitive hypertension is often associated with cardiovascular disease and defects in the circadian rhythm of the blood pressure. To date, the effects of angiotensin receptor blocker (ARB) against salt sensitivity and the blood pressure’s circadian rhythm have been obscure. A strong ARB, azilsartan, was previously reported to improve the circadian rhythm of blood pressure in hypertensive patients. In a recently published study, we investigated the mechanism by which azilsartan brought about this reaction. We speculated that azilsartan modulated sodium transporters located in the renal tubules because the circadian rhythm of blood pressure is linked to salt handling in the kidney. We discovered that one sodium transporter, NHE3 protein, in the proximal tubules was greatly attenuated in the kidneys of 5/6 nephrectomized mice that had been treated with azilsartan, although the expression of other sodium transporter proteins remained unchanged. The genetic expression of NHE3, however, was not changed by azilsartan. In a subsequent in vitro study using OKP cells, we found that NHE3 protein reduction was induced by enhanced protein degradation by proteasomes, not lysosomes, leading to enhanced sodium excretion. It is suggested that diminished salt sensitivity in the 5/6 nephrectomized mice treated with azilsartan was due to a change in sodium handling induced by the reduction of NHE3 protein in the proximal tubules. These mechanisms underlying the decreased salt sensitivity by azilsartan treatment may lead to totally new drug discoveries.

Keywords: angiotensin receptor blocker; salt-sensitive hypertension; circadian rhythm of blood pressure; sodium transporter; NHE3; proteasome

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Salt-sensitive hypertension and circadian rhythm defect in the blood pressure

Hypertension is one of the most important risks for the development of cardiovascular and kidney diseases. About 25% of the adult populations in westernized countries are affected by hypertension [1]. Sodium ingestion has been demonstrated to be closely related to its development [2]. Sodium sensitivity in normotensive patients is defined as a decrease in the mean arterial pressure of at least 3 mmHg following reduced salt intake [3]. Salt-sensitive hypertension patients have a greater tendency to experience cardiovascular and renal events than non-salt-sensitive patients [4]. Disturbed circadian rhythm of the blood pressure is reported to be an independent predictor of cardiovascular events [5-10] and to be highly associated with salt sensitivity [11, 12]. Patients whose blood pressure does not decrease during the night (non-dipper patients) are often found to be salt sensitive.

Causes of salt sensitivity

There are mainly two causes of salt sensitivity related to the kidney: reduced glomerular sodium filtration and increased tubular reabsorption of sodium. In the former case, salt sensitivity derives from impaired sodium excretion due to reduced nephron mass in individuals with chronic kidney disease [13] or those with normally fewer nephrons (African Americans [14] or patients born with low birth weight [15]). In the latter, salt sensitivity is implicated in increased renin-angiotensin-aldosterone system activity [16], hyperinsulinemia [17], insulin resistance [18], and sympathetic hyperactivity [19]. From a molecular viewpoint, sodium channels or sodium transporters are shown to be related to salt sensitivity. To date, four sodium transporters have been identified in nephron segments: NHE3 in the proximal tubules, Na⁺-K⁺-Cl⁻ cotransporter-2 (NKCC2) in the thick ascending loop of Henle, Na⁺-Cl⁻ cotransporter (NCC) in the ductal convoluted tubules, and Enacs in the collecting ducts. It has been reported that NKCC2 causes salt sensitivity in the Milan hypertensive strain of rats [20]. The development of salt-sensitive hypertension in C57B6 mice and Dahl rats was associated with α₂-adrenergic receptor, WNK lysine-deficient protein kinase-4, and NCC [19]. The major sodium transporter in the proximal tubules, NHE3, has been only modestly evaluated as a regulator of salt sensitivity, although transgenic mice overexpressing NHE3 in all body parts were reported to have salt-sensitive hypertension [21].

Renin-angiotensin system blockers and salt sensitivity

Renin-angiotensin system (RAS) blockers

Salt-sensitive hypertension derives from impaired sodium excretion due to reduced nephron mass in individuals with chronic kidney disease or those with normally fewer nephrons (African Americans or patients born with low birth weight). In the latter, salt sensitivity is implicated in increased renin-angiotensin-aldosterone system activity, hyperinsulinemia, insulin resistance, and sympathetic hyperactivity. From a molecular viewpoint, sodium channels or sodium transporters are shown to be related to salt sensitivity. To date, four sodium transporters have been identified in nephron segments: NHE3 in the proximal tubules, Na⁺-K⁺-Cl⁻ cotransporter-2 (NKCC2) in the thick ascending loop of Henle, Na⁺-Cl⁻ cotransporter (NCC) in the ductal convoluted tubules, and Enacs in the collecting ducts. It has been reported that NKCC2 causes salt sensitivity in the Milan hypertensive strain of rats. The development of salt-sensitive hypertension in C57B6 mice and Dahl rats was associated with α₂-adrenergic receptor, WNK lysine-deficient protein kinase-4, and NCC. The major sodium transporter in the proximal tubules, NHE3, has been only modestly evaluated as a regulator of salt sensitivity, although transgenic mice overexpressing NHE3 in all body parts were reported to have salt-sensitive hypertension.

Renin-angiotensin system blockers and salt sensitivity

Renin-angiotensin system (RAS) blockers
Factors affecting NHE3 protein quantity

NHE3 protein reduction due to factors other than mRNA reduction has been reported in several cases. Chronic administration of dopamine in mice decreased NHE3 protein caused by degradation via a ubiquitin–proteasomal pathway [36]. Acute kidney ischemia–reperfusion injury induces NHE3 protein and transcript reduction, which is also mediated by degradation via a ubiquitin–proteasomal pathway. The key factors mediating these phenomena could be proteins or

Figure 1. Proposed mechanism of NHE3 protein degradation through AT1R blockade. NHE3 ubiquitination is in equilibrium with the NHE3 de-ubiquitination by USP48 in the basal state, which is inhibited by the D3 receptor. The D3 receptor is also antagonized by angiotensin II-stimulated AT1R (the upper figure). When azilsartan blocks the AT1R signal, the D3 receptor goes toward inhibition of USP48 expression. NHE3 de-ubiquitination by USP48 is inhibited, so NHE3 subjects to proteasomal degradation (the lower figure).
proteolipid complexes [37]. Our in vitro study confirmed that azilsartan treatment with angiotensin II induced NHE3 degradation via a ubiquitin–proteasomal pathway as well [35]. These data are consistent with those of a previous report on experiments using proximal tubule-specific AT1 receptor (AT1R) knockout mice [38].

Proposed mechanism of NHE3 protein degradation through AT1R blockade

In a previous study, AT1R formed a protein complex with dopamine D3 receptor [39]. Recently, it was reported that ubiquitin-specific peptidase (USP) 48 was implicated in NHE3 degradation via dopamine. The dopamine-stimulated dopamine D3 receptor inhibits USP48 function, which leads to the promotion of NHE3 degradation via a ubiquitin–proteasomal pathway [40]. Thus, we hypothesized that NHE3 ubiquitination is in equilibrium with the NHE3 de-ubiquitination by USP48 in the basal state, which is inhibited by the D3 receptor. The D3 receptor is also antagonized by angiotensin II-stimulated AT1R. When azilsartan blocks the AT1R signal, the D3 receptor starts the course toward inhibition of USP48 expression. NHE3 de-ubiquitination by USP48 is blocked, so NHE3 proceeds to proteasomal degradation (Figure 1). Thus, NHE3 function decreases, which results in increased sodium excretion and alleviated salt sensitivity. In the future, it may be possible for the new drug for salt-sensitive hypertension to be developed using these mechanisms as targets.

Conflicting interests

The authors have declared that no conflict of interests exist.

Author contributions

S.T., Y.I. and H.R. conceived the paper. J.Y.K wrote the paper. M.H., S.Y. and N.I. edited the paper.

Abbreviations

ARB: angiotensin receptor blocker; AT1R: angiotensin type 1 receptor; AT2R: angiotensin type 2 receptor; NCC: Na⁺-Cl⁻ cotransporter; NHE3: Na⁺/H⁺ exchanger; NKCC2: Na⁺-K⁺-Cl⁻ cotransporter-2; OKP: opossum kidney, clone P; RAS: Renin-angiotensin system; USP: ubiquitin-specific peptidase; WNK: with no lysine.

References


