Hypertension Research (2023) 46:518–520
https://doi.org/10.1038/s41440-022-01104-x

COMMENT

Intrarenal neurohormonal modulation by renal denervation: benefits for chronic kidney disease and heart failure

Kenichi Katsurada[1,2] · Kazuomi Kario[1]

Received: 4 October 2022 / Revised: 31 October 2022 / Accepted: 1 November 2022 / Published online: 18 November 2022

Excessive activation of the sympathetic nervous system is one of the pathophysiological hallmarks of hypertension. Renal denervation (RDN), a neuromodulation therapy that modifies the circulatory regulatory system, has attracted attention for its potential to reduce the incidence and severity of cardiovascular diseases. The kidneys are the major regulators of circulating fluid volume, and their dysfunction is directly linked to the pathogenesis of hypertension. This treatment involves partial blockade of the renal sympathetic nervous system, which is an organ-connected pathway between the brain and the kidneys. Recently, published randomized controlled trials (i.e., the SPYRAL HTN-OFF MED/ON MED trial and the RADIANCE-HTN SOLO/TRIO trial) have shown that catheter-based RDN has a clear antihypertensive effect [1–4] and is expected to expand the therapeutic targets for chronic kidney disease and heart failure in addition to hypertension. However, before RDN can be introduced into the clinic, an accurate and efficient procedure must be established. Furthermore, the detailed mechanism of the antihypertensive effect of RDN has not been fully elucidated.

In a study published in this issue of *Hypertension Research* [5], Lai et al. examined the effect of selective RDN on the intrarenal renin-angiotensin system (RAS) and transporters involved in sodium and water reabsorption. The study was an extension of previous work from the same laboratory focusing on the method of RDN for the identification of optimal ablation targets [6]. Selective RDN, which involves ablation of sites associated with strong blood pressure (BP) elevations in response to renal nerve stimulation (RNS), showed a greater BP-lowering effect than RDN at weak BP-elevation response sites; it also resulted in a lower level of tyrosine hydroxylase and a lower content of norepinephrine in the kidneys.

A measurement of kidney norepinephrine content was performed for verification of experimental RDN. Surgical cutting of renal nerves performed in rodents has been shown to reduce the renal norepinephrine content to under 5–10% of that seen in innervated kidneys [7]. It is unknown how much catheter-based RDN reduces renal norepinephrine content in humans. The current study and previous reports demonstrate that catheter-based RDN reduces renal norepinephrine content to under 30–50% and under 25% of control levels as well as producing significant BP-lowering effects in canines and swine, respectively [5, 8]. It is important to note that selective RDN, which involves ablation at sites associated with strong BP-elevations in response to RNS, resulted in a lower renal norepinephrine level than ablation at weak BP-elevation response sites in canines in the current study.

The current study was the first to demonstrate that selective RDN significantly attenuated release of renin; synthesis of angiotensinogen; and the expression of angiotensin-converting enzyme (ACE), angiotensin II (Ang II), and angiotensin II type 1 receptor (AT1R) in canines as a large animal model. These effects were accompanied by enhanced expression of ACE2, Ang (1–7), and Mas-receptor (Mas-R). Previously, Lu et al. reported that plasma levels of renin and Ang II are decreased 3 months after RDN in canines [9]. Sharp III et al. reported that serum and renal Ang I and Ang II levels are decreased 3 months after RDN in swine [8]. Mahfoud et al. reported that plasma renin activity levels for RDN patients are significantly lower at 3 months after RDN than at baseline [10]. The findings in the current study, together with these findings in previous reports, suggest that RDN inhibits the intrarenal RAS as well as the systemic RAS, possibly acting in a renoprotective manner. Additionally, the current study shows

✉ Kazuomi Kario
kkario@jichi.ac.jp

[1] Division of Cardiovascular Medicine, Department of Internal Medicine, Jichi Medical University School of Medicine, Shimotsuke, Tochigi, Japan

[2] Division of Clinical Pharmacology, Department of Pharmacology, Jichi Medical University School of Medicine, Shimotsuke, Tochigi, Japan

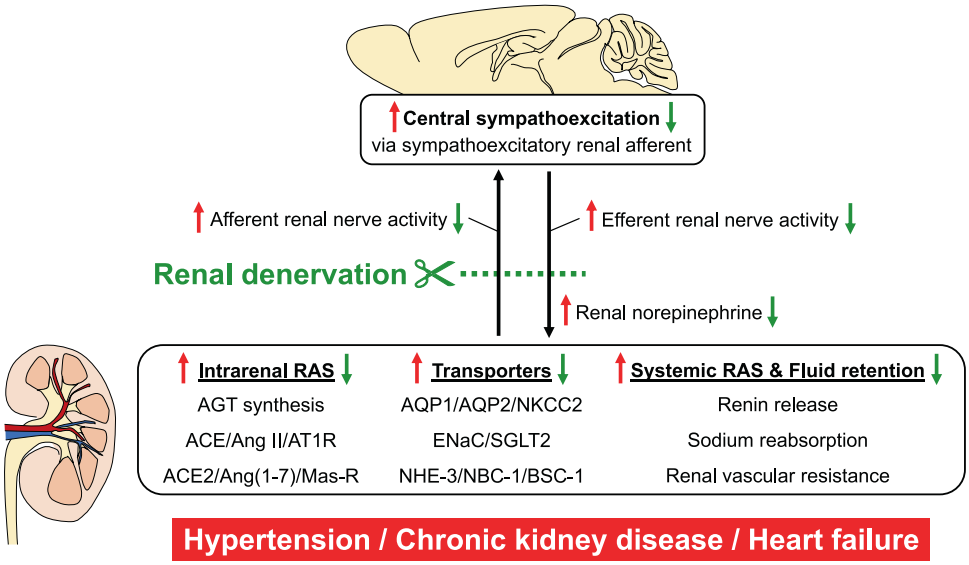

Fig. 1 Potential therapeutic effects of renal denervation on chronic kidney disease and heart failure in addition to hypertension. Red arrows indicate the changes in parameters associated with hypertension, chronic kidney disease, and heart failure. Green arrows indicate the effects of renal denervation on these parameters in hypertension, chronic kidney disease, and heart failure. RAS renin-angiotensin system, AGT angiotensinogen, ACE angiotensin-converting enzyme, Ang II angiotensin II, AT1R angiotensin II type 1 receptor, Mas-R Mas receptor, AQP aquaporin, NKCC2 sodium-potassium-chloride cotransporter 2, ENaC epithelial sodium channel, SGLT2 sodium-glucose cotransporter 2, NHE-3 sodium-hydrogen exchanger 3, NBC-1 sodium-bicarbonate cotransporter 1, BSC-1 bumetanide-sensitive sodium-potassium-chloride cotransporter

that selective RDN significantly reduces the expression of renal aquaporin (AQP)1 and AQP2 and decreases the phosphorylation of sodium-potassium-chloride cotransporter 2 (NKCC2) levels and the trafficking of NKCC2 to the apical membrane, alleviating water and sodium reabsorption. These RDN-mediated modulations of the major transporters associated with water and sodium reabsorption appear to be favorable therapeutic effects for heart failure (Fig. 1).

Renal nerves contain sympathetic efferent fibers and sensory afferent fibers. It is plausible that the antihypertensive effect of RDN is mediated mainly by sympathetic efferent denervation-induced suppression of renin secretion, sodium reabsorption, and renal vascular resistance [11, 12]. Additionally, it has been proposed that specific afferent denervation modulates sensory signals from the kidneys to the central nervous system to suppress sympathetic outflow [11, 12]. However, the role of afferent renal nerves in the regulation of the cardiovascular system has not been fully elucidated. There are different types of afferent fibers that have sympathoexcitatory effects and sympathoinhibitory effects in response to RNS. The optimal RDN target for treating hypertension, which is a site that responds to RNS with strong BP elevation, seems to include abundant sympathoexcitatory afferent fibers. However, it is unclear whether RDN-mediated intrarenal neurohormonal changes are induced by afferent denervation or efferent denervation. It has been reported that selective afferent renal denervation via capsaicin application suppresses the intrarenal RAS in a 2-kidney 1-clip model of renovascular hypertensive rats [13] and a 5/6 nephrectomy model of chronic kidney disease rats [14]. Interactions between some transporters associated with sodium reabsorption and the RAS or sympathetic nervous system have been reported. AT1 receptor blockade with candesartan prevents the upregulation of AQP2 expression, indicating that Ang II-mediated AT1R activation plays an important role in AQP2 expression [15]. Ang II-stimulated NKCC2 activation is related to phosphorylation and trafficking to the apical membrane [16]. On the other hand, norepinephrine reportedly increases renal expression of sodium-hydrogen exchanger 3 (NHE-3), sodium-bicarbonate cotransporter 1 (NBC-1), bumetanide-sensitive sodium-potassium-chloride cotransporter (BSC-1/NKCC2) and AQP2 in rats [17]. Recent studies have suggested that the expression of renal ENaC and AQP2 is enhanced in rats with heart failure but that this elevation is mitigated by RDN [18]. Another study has shown that the expression and functional activity of renal sodium-glucose cotransporter 2 (SGLT2) are enhanced in heart failure rats and reduced by RDN. That study also demonstrates that norepinephrine promotes the translocation of SGLT2 to the cell membrane in vitro [19]. These findings suggest that both afferent and efferent renal nerves contribute to the regulation of components of the intrarenal RAS and transporters involved in sodium and water reabsorption (Fig. 1).

In conclusion, the current paper by Lai et al. [5] confirms that selective RDN by RNS effectively exerts an antihypertensive effect in a hypertensive canine model and newly demonstrates possible underlying mechanisms in which selective RDN downregulates the expression of renal ACE, Ang II, and AT1R and upregulates the expression of renal ACE2, Ang (1–7) and Mas-R while restoring the expression of renal AQP1, AQP2, and NKCC2. These intrarenal neurohormonal modulations are potentially favorable for treating patients with chronic kidney disease and heart failure in addition to hypertension.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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