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COMMENT

The role of afferent renal nerves in regulating sympathetic outflow via central nervous system mechanisms

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Exaggerated activation of the sympathetic nervous system is one of the hallmarks in cardiovascular diseases such as hypertension and heart failure with deleterious consequences. Recent accumulating evidence suggest that the kidneys play a critical role in regulating the sympathetic nervous system in such disease states [1–4]. The renal nerves are mainly composed of both efferent sympathetic and afferent sensory nerves. Previous studies of immunohistochemistry using retrograde tracer and electrophysiological experiments suggest that afferent renal nerves relay information to sites within the central nervous system associated with cardiovascular regulation such as the paraventricular nucleus (PVN), rostral ventrolateral medulla (RVLM), nucleus tractus solitarius (NTS), preoptic area, subfornical organ, and lateral hypothalamus [1, 3–5]. Direct electrical stimulation of afferent renal nerves has been shown to activate RVLM projecting PVN neurons [6]. The interactions between the hypothalamic PVN and the RVLM as well as the NTS in the brainstem have been well established [7]. Hence, renal afferent activation can possibly influence these nuclei resulting in modulation of general sympathetic outflow to the periphery and specifically effect the heart (Fig. 1).

The study by Katsuki et al. in the current issue of the *Hypertension Research*, examined the effects of renal denervation (RDN) on blood pressure, cardiac hypertrophy, and an index of overall sympathetic activity in spontaneously hypertensive rats (SHR) with established hypertension. This study is the first to demonstrate that oxidative stress, as estimated by the levels of thiobarbituric acid reactive substances is significantly reduced in the RVLM by RDN, with concomitant decreases in urinary norepinephrine, blood pressure and cardiac hypertrophy [8]. These observations suggest that RDN inhibits an excitatory renal afferent signal to the central nervous system which results in reduced oxidative stress within the RVLM, thereby attenuating sympathetic outflow and ameliorating hypertension and cardiac hypertrophy in SHR.

Consistent with these observations previous studies have demonstrated that RDN restored the expression of neuronal nitric oxide synthase (nNOS) in the PVN and attenuated increases in urinary norepinephrine excretion and lumber sympathetic nerve activity in rats with heart failure [9]. Selective afferent RDN using capsaicin application exerted comparable effects of surgical RDN on the expression of nNOS and lumber sympathetic nerve activity [10], indicating that inhibition of renal afferent pathway is critical for ameliorating the sympatho-excitation in this model of heart failure. Specifically, selective afferent RDN has been shown to attenuate superoxide production in the PVN and decrease in blood pressure and plasma norepinephrine in SHR [11]. Additionally, in stroke-prone SHR, RDN mitigated the increase in activated microglia that are immunoreactive to ionized calcium binding adaptor molecule-1 (Iba-1) in the PVN and decreased blood pressure [12]. In renovascular hypertensive rats, selective afferent RDN decreased Iba-1 positive cells in the PVN and arterial blood pressure [13]. Furthermore, RDN has been shown to normalize γ-aminobutyric acid (GABA)ergic changes in the NTS and ameliorate hypertension and cardiac hypertrophy in rats with chronic kidney disease induced by 5/6 nephrectomy [14]. In hypertensive canine model induced by high-fat diet,

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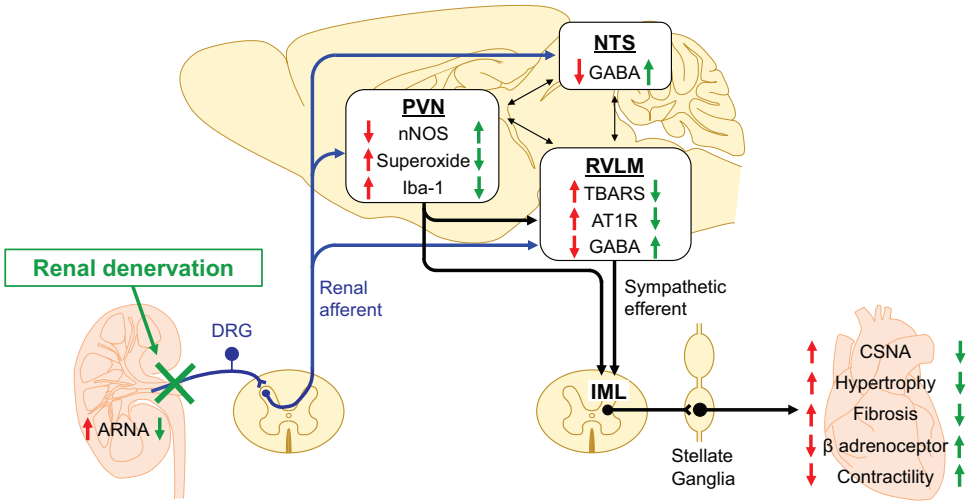

Fig. 1 Proposed hypothesis for the renal afferent nerve mediated changes of sympathetic outflow to the heart involving specific sites and mechanisms within the central nervous system. Red arrows represent effects of activation of afferent renal nerves and green arrows represent effects of renal denervation (RDN). ARNA afferent renal nerve activity, AT1R angiotensin II type 1 receptor, CSNA cardiac sympathetic nerve activity, DRG dorsal root ganglia, GABA γ-aminobutyric acid, Iba-1 ionized calcium binding adaptor molecule-1, IML intermediolateral cell column, nNOS neuronal nitric oxide synthase, PVN paraventricular nucleus, RVLM rostral ventrolateral medulla, TBARS thiobarbituric acid reactive substances

catheter-based radiofrequency RDN decreased blood pressure accompanied with upregulation of GABA levels and downregulation of angiotensin II type 1 receptor (AT1R) mRNA and protein expressions in the RVLM [15].

There are also several reports showing cardioprotective effects of RDN. The levels of cardiac sympathetic nerve activity were higher in sheep with heart failure induced by rapid ventricular pacing compared to normal sheep and were significantly reduced after catheter-based radiofrequency RDN [16]. Furthermore, the expression of β-1 and β-2 adrenoceptors were decreased in rats with heart failure and were restored after RDN [17]. Consistent with these findings, RDN improved cardiac function expressed as isoproterenol induced increase in positive and negative dP/dt [17]. RDN mitigated cardiac fibrosis and inflammation, and decreased angiotensin converting enzyme (ACE) and AT1R protein expression, and increased ACE2 and mas receptor protein expression and microRNAs, including miR-29b, miR-30c and miR-133a in left ventricular tissue in rats with isoproterenol induced cardiomyopathy [18, 19]. RDN prevents atrial remodeling in spontaneously hypertensive obese rats by reducing atrial sympathetic innervation and by modulating receptor for advanced glycation end products (RAGE)/soluble RAGE balance and reducing pro-inflammatory and pro-fibrotic RAGE ligands, which provides a potential therapeutic mechanism to reduce the development of atrial fibrillation [20]. These findings suggest that interruption of renal afferent pathway by RDN provides cardioprotective effects by reducing sympathetic nerve activity via modulation of central mechanisms (Fig. 1).

Various types of renal damage or dysfunction seem to affect afferent renal nerve activity [4, 21]. It has been reported that resting afferent renal nerve activity is increased in disease model of animals including rats with heart failure induced by coronary artery ligation [10, 22], DOCA-salt hypertensive rats [23], 2-kidney 1-clip renovascular hypertensive mice [24], and rats with polycystic kidney disease [25].

Overall, the study by Katsuki et al. clearly demonstrated that RDN reduced oxidative stress in the RVLM to mitigate hypertension and cardiac hypertrophy in SHR. These results support clinical application of RDN for hypertension and other cardiometabolic diseases with sympatho-excitation. Some of the issues that should be addressed are the changes in afferent renal nerve activity of SHR and stroke-prone SHR, and interactions between oxidative stress in the RVLM and other factors to modulate sympathetic outflow, including the involvement of the renin-angiotensin system, glutamatergic and GABAergic system, the nitric oxide system, inflammation and immune systems in the central nervous system.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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