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Renal Denervation and Salt Induced Hypertension

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A high-salt diet is linked to elevation in blood pressure in salt-sensitive individuals. The relationship between chronic high dietary salt intake and blood pressure variability has been established in many experimental studies, especially in primary hypertensive patients [1]. Nonetheless, the exact mechanism underlying this relationship remains unclear. Functional disturbance in the kidney is considered to be an important factor in mediating the effect of high salt on arterial blood pressure. High salt ingestion over long periods of time alters kidney function through its effect on renal hemodynamic and tubular function that subsequently decreases renal salt and fluid excretory capacity. This could greatly affect the body fluid homeostasis leading to a high blood pressure response [2,3]. On another hand, high sodium induced blood pressure response in the kidney is associated with increased urinary albumin excretion possibly due to salt induced blood pressure effect on glomerular arteriole causing endothelial cell damage. Furthermore, recent reports suggest that high salt induced damage of ultrafiltration barrier and proteinuria is due to a decrease in nephrin, a protein found in glomerular capillary bed and an increase in angiotensin converting enzyme/angiotensin converting enzyme 2 (ACE/ACE2) ratios [4]. However, it is also reported that the resultant state of renal impairment in response to high salt intake can occur independently of any variations in blood pressure [5]. Hence, the adverse effects of high salt intake on renal function involve various underlying mechanisms.

Elevated renal sympathetic nerve activity has been suggested as a key factor in mediating salt related renal impairment. The role of the renal sympathetic nerves in the development of salt-induced hypertension is supported by pharmacological and renal denervation studies [6]. The renal sympathetic nervous system directly innervates all the components of the kidney including the tubules, vessels, and juxtaglomerular apparatus. Through this pattern of innervation, the renal sympathetic nerves regulate renal hemodynamic and tubular functions. Tubular effects of renal nerve stimulation include a decrease in urinary sodium and water excretion while renal hemodynamic responses include a decrease in renal blood flow, and glomerular filtration. Additionally, renal nerve input increases the release of angiotensin II (Ang II) from the juxtaglomerular apparatus. The renal effects of Ang II include renal tubular salt and water reabsorption, arteriolar constriction and decreased renal blood flow [7]. Consequently, elevated renal nerve activity in salt induced hypertensive conditions will influence these abovementioned renal hemodynamic and tubular functions, which will have a greater impact on arterial blood pressure.

The salt-induced alteration of the sympathetic system and its impact on renal function and hemodynamic were found to be mediated through various adrenoreceptors. Studies have reported that the density and sensitivity of adrenoceptors in the renal vasculature are altered in hypertensive and normotensive subjects in conditions of high salt load. This observation is supported by elevated renal vascular responses to administered adrenergic agonist [8-10]. Further, it is reported that high salt intake enhances the sensitivity of specific subtypes of adrenoceptor. Among the various subtypes of renal adrenoreceptors, α_{1A}-subtype was found to play a major role in renal cortical vascular hypersensitivity, antidiuresis, and antinatriuresis in spontaneously hypertensive rats under conditions of high salt diet [9]. Additionally, findings from a study in Wistar rats subjected to a high-salt diet implicated the functional involvement of α_{1B}-adrenoceptors in mediating the effects of high salt on the renal vasculature [10]. On another hand, increased α_{2B}-adrenoreceptor gene expression, density and protein expression were also observed in association with salt-induced elevations in blood pressure in sabra hypertension-prone rats [11]. Therefore, it seems that various subtypes of adrenoceptors are involved in mediating salt-induced effects on renal function.

One of the important regulators of renal sympathetic nerve activity in salt-induced hypertension is brain Ang II [12,13]. Studies

have demonstrated that brain angiotensin II is activated in salt-induced hypertension through a baroreflex mechanism, resetting the baroreceptor reflex regulation of renal sympathetic nerve activity to a higher pressure level. Notably, the baroreceptor reflex regulates renal sympathetic nerve activity to maintain normal arterial blood pressure. However, increased sympathetic regulation by the baroreflex in salt-induced hypertension contributes to reduced renal excretory function. Thus, the effect of dietary sodium intake on brain Ang II is to produce a hypertensinogenic state by impairing baroreflex sympathetic regulation [14]. In addition to brain angiotensin, circulating Ang II under conditions of high salt intake also promotes sympathetic nerve activity through direct receptor effects in the area postrema, subfornical organ, and other circumventricular organs of the brain. Ang II interacts with sodium-sensitive neurons in these brain areas and drives sympathetic premotor neurons in the rostral ventrolateral medulla via the paraventricular nucleus [15]. It is notable that the influence of dietary sodium intake on renal sympathetic nerve activity is more pronounced in individuals with an underlying genetic predisposition for hypertension. Thus, a combination of environmental (dietary) and genetic factors may accelerate pathological alterations in renal sympathetic nerve activity in salt-sensitive individuals leading to a hypertensive state [16]. Consequently, improving sodium and water excretion is a possible therapeutic target in salt-sensitive hypertension by modifying renal hemodynamic and tubular responses to sympathetic innervation.

Current renal denervation methods have been used to target hypertension in humans with an important implication on cardiovascular and kidney functions [17,18]. The impact of renal denervation is a significant reduction in systolic and diastolic blood pressure and improved renal function with reduced micro albuminuria [19,20]. In relation to that, reports are emerging on the use of renal nerve denervation as a therapeutic target for salt-sensitive hypertension [21-23]. These studies emphasize the role of renal sympathetic nerves in the development of salt-sensitive hypertension with a strong influence on the renal function. It can be expected therefore that renal sympathetic innervation could be a forthcoming therapeutic target in the treatment of salt sensitive hypertension in humans.

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