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Differential Role of Renal Alpha 1 Adreno Receptors Subtypes in Renal Vasculature in Normotensive and Hypertensive Conditions Subjected to High Dietary Salt Load

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Chronic high salt intake is well known to be linked to cause an increase in the blood pressure and one of the pathogenic effects of high salt on blood pressure is vascular functional impairment. The effect of sodium on vasculature involves an increase in the vascular resistance that could triggers a rise in the blood pressure. Sodium-induced increase in vascular resistance is primarily independent of any change in blood pressure; however, it could be an initiating factor for increase in the blood pressure. Salt induced increase in the vascular resistance involves alterations in several vaso regulatory mechanisms as evidenced in various vascular beds. A mechanism exhibiting a substantial effect on vascular function is the alpha (α_1)-adrenergic system that significantly influences vascular resistance, thereby affecting peripheral vascular resistance and blood pressure. This review focused on the effects of increase dietary sodium intake on the α_1-adrenergic system in renal vascular beds under normotensive and hypertensive conditions. Because the α_1-adrenergic regulations of renal vascular function and renal hemodynamics affect blood pressure to a great extent, renal vascular assessment was performed. Study reports enhanced renal vascular sensitivity to α_1-adrenergic agonist in high sodium normotensive and hypertensive condition, this could be due to functional alterations in the renal α_1-adrenoreceptor density. This provide additional evidence on the underlying vascular pathology in salt-induced hypertension.

Keywords: Salt, Vascular function, Blood pressure, Adrenergic system.

High blood pressure is a key risk factor for mortality from cardiovascular and renal diseases. Chronic dietary sodium intake is one of the dietary influences that cause an increase in blood pressure. However, the risk of high dietary sodium is not limited only to its effect on blood pressure but also its blood pressure-independent effect.[1] High sodium is reported to cause an increase invascular resistance. Inability to decrease systemic vascular resistance in response to the increase in sodium intake is the primary pathological abnormality in salt-sensitive individuals.[2] An abnormal vascular response to high salt intake,generally mediates the commencement of salt-induced hypertension.[3] The mechanisms mediating abnormalities in vascular responses during the beginning of salt-induced hypertension may contribute to an abnormal increase in the systemic vaso constriction that

characterized by sustained hypertension. Studies have revealed that chronic high dietary sodium intake is associated with aortic hypertrophy and decreased diameters of brachial and carotid arteries, suggesting vascular stiffness and distending pressure alteration. The high-salt-induced increase in vascular resistance was attenuated by a low salt period.[1,4,5] studies also reported that salt-induced hypertension occurs due to an increase in blood volume and cardiacoutput.[6]However, several studies have suggested that irregularities in the systemic vascular resistance initiates salt induced high blood pressure.[3]

Vascular resistance is a significant factor regulating blood pressure and tissue perfusion. High salt intake enhances vascular resistance that may increase peripheral vascular resistance and compromised tissue perfusion. This high-salt provoked vascular effect may be an initiating factor for salt-induced hypertension.[7]Additionally, high-salt-induced enhanced vaso constriction is considered a pathogenic event in salt sensitivity.[8]Several studies have reported the deleterious effect of high salt on various vascular beds, stating that high salt impairs the dilation of mesenteric and skeletal muscle resistance arteries in normotensive and hypertensive experimental rat models.[5,9]Moreover, high salt reduces cutaneous vasodilation, a measure of microvascular function.[1]

Several experimental studies have also confirmed the adverse effect of salt on the renal vasculature. High-salt-induced impaired renal vasodilatory mechanism involves a series of complex events that are independent of their effect on blood pressure. However, the exact mechanism by which salt increases renal arterial constriction remains unclear. Some of these events that were extensively studied to explain the salt-induced increase in vascular resistance include endothelial dysfunction and molecular signaling events that promote TGF-beta (α)1 production.[10]Studies have also reported that impaired renal vasodilatory mechanisms after salt loading in salt-sensitive Dahl rats include abnormal activation of the ET-1 system, prostanoid-mediated contractions, and failure to increase nitric oxide synthase activity.[11] Additionally, the role of the renin-angiotensin system (RAS) as a major determinant of salt-induced vascular dysfunction in the renal vasculature is strongly supported by studies. The RAS is a major blood pressure regulatory mechanism; however, high-salt-induced abnormal activation of the RAS leads to enhanced renal vascular resistance, insufficient renal vasodilation, sodium retention, and hypertension development. The use of RAS blockers provides evidence of the impaired renal vascular effect of RAS in response to high sodium intake.[12]Thus, multiple mechanisms underlying blood pressure-independent salt-induced renal vascular dysfunction are important pathogenic events in salt sensitivity. Salt-induced changes in renal vascular resistance can substantially affect renal hemodynamics, and alterations inrenal hemodynamics play a crucial role in blood pressure regulation through its effect on sodium hemostasis and blood volume regulation. These altered mechanisms can precede the initiation of salt-induced increase in blood pressure response. The relative significance of different mechanisms leading to failure in normal vasodilation in response to salt intake increase remains unclear despite extensive research on the subject. However, hypersensitivity of the renal blood vessels to vasoconstrictor stimuli in salt-induced hypertensive conditions is supported by several studies. The á-adrenergic vasoconstrictor stimulation is proposed as a major cause for the increase and regulation of blood pressure in spontaneously hypertensive rat and deoxycorticosterone (DOCA) acetate salt-hypertensive rat models.[13-15]The vasoconstrictor effects of á-adrenergic stimulation on the renal vasculature under normotensive and hypertensive conditions remain unexplained.

This study reviewed the effect of high salt on the renal α-adrenergic mechanism (vasoconstrictor stimuli), a central regulator of renal vascular function and blood pressure. Off the various subtypes of the renal adrenoreceptors, special emphasis is being given to renal α_1-adrenoreceptorsubtypes(α_1-ARs), due to the keyrole of these receptors in renal vascular constriction and renal hemodynamic.[16,17] Recent experiments performed on AR-knockout models suggest an important role of this ARsin the overall regulation of blood pressure.

Renal alpha Adrenoreceptors

The renal sympathetic nervoussystem, through activation of various adrenoreceptor subtypes present on the renal vasculature, mediates adrenergic regulation of the kidneys. Adrenoceptors

are seven-transmembrane receptors that mediate the central and peripheral actions of noradrenaline and adrenaline. These receptors are found in nearly all the central and peripheral tissues.[18] In the kidneys,they are located on the renal vasculature, nephrons, and proximal tubules and contribute to renal hemodynamic and tubular functions. On the basis of pharmacological and molecular evidences, adrenergic receptors are classified as α and β receptors which are further sub divided as α_1, α_2 and β_1, β_2, and β_3 receptors, respectively. Both α_1 and α_2 receptors have three subtypes, all of which are G-protein-coupled receptors. The α_1 receptors are Gq-couple dreceptors, whereas α_2 receptors are Gi-coupledreceptors. The β receptors are also Gs-coupledreceptors.[19] β_2 and β_3 are Gi-coupled receptors. Amongst the various ARs, α-ARs are the most vital determinants of renal vascular tone.[20]

Signal transduction mechanism of α_1-AR

During an adrenergic response,the adrenalin and noradrenalin released into the bloodstream bind to the α_1 receptors (Gq protein) of the smooth muscle cells, causing activation of phospholipase C, producing inositol triphosphate (IP3). IP3 diffuses into the cytosol and interacts with its receptors on the sarcoplasmic reticulum membrane, thereby causing the release of Ca2+into the cytosol. This results in activation of the calcium-dependent protein kinase, leading to smooth muscle contraction.[21]Other signaling pathways that get activated by α_1 receptors include Ca^{2+} influx through voltage-dependent and -independent calcium channels, release of arachidonic acid, and activation of phospholipase A2 and phospholipase D, and mitogen-activated protein kinase.[21]

Vasoconstrictor effect of renal α_1-ARs in various physiological and pathological conditions

The renal sympathetic nervous system, greatly influences the renal hemodynamics by mediating catecholamine-induced effects on α_1-ARs present on the renal vasculature. Based on receptor–ligand interaction and receptor-mediated signaling, α_1-AR is further classified into three subtypes: α_{1A}, α_{1B}, and α_{1D}.[22] In the rat all sub types of α_1-AR mediated catecholamine-induced renal vascular constriction, with α_{1A}-AR and α_{1D}-AR playing a significant role.[20] However, an alteration may occur in the functional involvement of α_1-ARs under several physiological and pathological conditions. Studies have reported a role of α_{1A}-AR and α_{1D}-AR and a greater role of α_{1B}-ARin mediating the renal vasoconstrictor responses in streptozotocin-induced diabetes and in a combined state of hypertension and renal failure.[23]In metabolic syndromes, α_{1B}-AR is the functional subtype that mediates renal vasoconstriction inrats on high fructose diet over a long period.[24]In a state of hypertension and diabetes, α_{1A}-ARs plays a vital role in enabling adrenergically induced renal vascular constriction in 2K1C Goldblatt rats. The potential role of presynaptic α_1-AR was reported.[20] The mRNA expression of all the three α_1-ARs

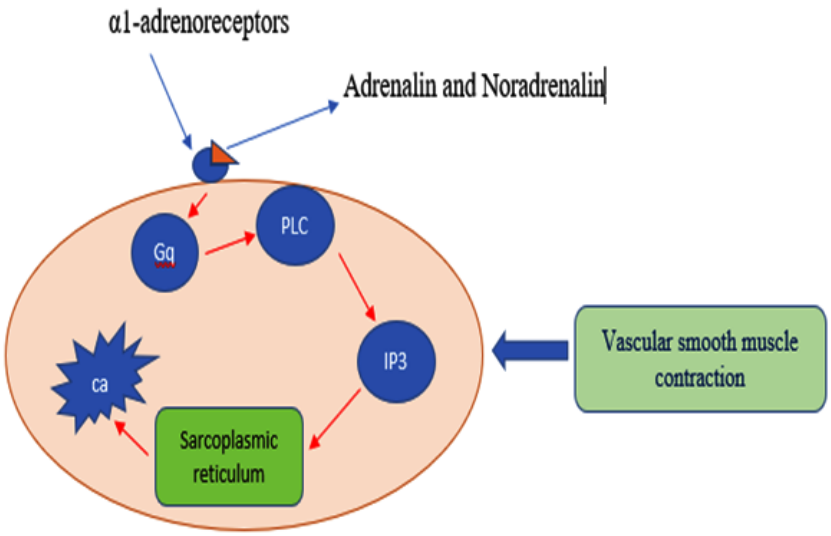

Fig. 1. Alpha-1 adrenoreceptor activation of smooth muscle cells

was detected in the rat kidney cortex, and the α_1-*AR*gene was highly up regulated,as confirmed by immunostaining of the smooth muscle of the arterial walls in diabetic animals.[25]

Renal vascular α-1 adrenergic response to high salt load in normotensive and hypertensive conditions

Renal hemodynamic adaptation plays a significant role in the regulation of blood pressure. Regulation of renal hemodynamic and renal vascular resistance is greatly influenced by α_1-AR. Role of high salt on α_1-ARand its subtype involvement in the regulation of renal hemodynamic in normotensive and hypertensive conditions were studied. Renal hemodynamic parameters were measured to determine renal vasoconstriction following the administration of adrenergic agonists and antagonists.[26-28]

A slight elevation in dietary sodium intake

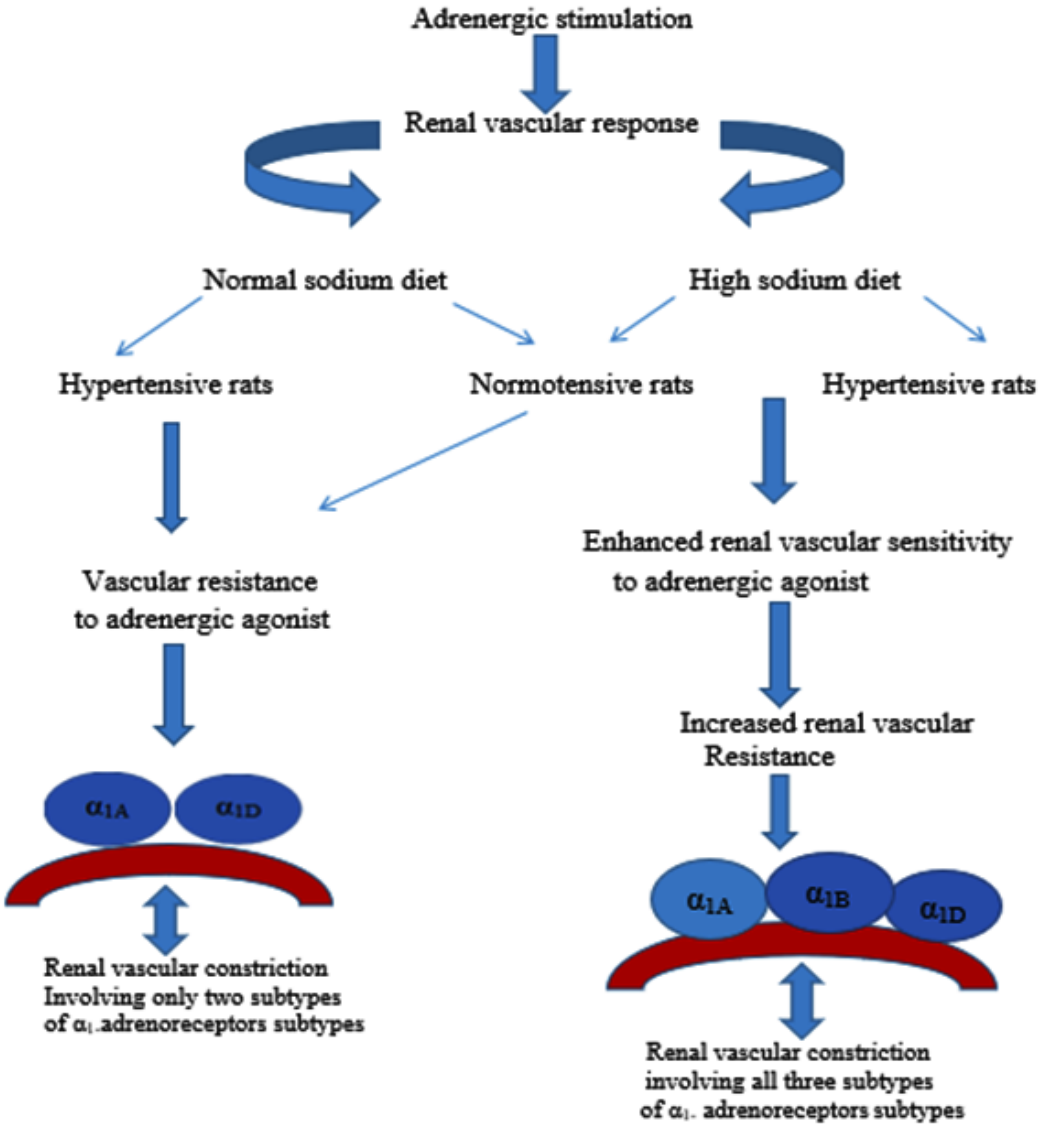

Fig. 2. Alpha-1 adrenoreceptor subtypes involvement in renal vascular constriction in normotensive and hypertensive rats on normal and highsodium diets

increased the sensitivity of the renal vasculature to α_1-ARagonists in high-sodiumfed normotensive and hypertensive rats. Notably, a slight increase in dietary sodium increased the renal vascular response to vasoconstrictor stimuli even in normotensive rats. Moreover, the adrenergically induced renal vasoconstrictions were reduced by specific antagonists of α_{1A}-AR and α_{1D}-AR in both normotensive and hypertensive rats on high and normal sodium diets. However, unexpectedly, a decrease in the renal vasoconstrictor effect for α_{1B}-AR antagonists was observed in rats on high sodium diet. Irrespective of alterations in dietary sodium intake, α_{1A}-AR and α_{1D}-AR are the functional subtypes mediating the adrenergically induced renal vascular constriction in both normotensive and hypertensive rats. Additionally, α_{1B} functionally involved in mediating the renal cortical vaso constriction in rats fed with a high salt diet. The enhanced sensitivity could be explained on the basis of maximum presser response to the α_1-AR agonist and additional involvement of the ARs in rats feda high sodium diet. A moderate salt load caused functional alterations in the renal vascular α_1-AR density that was indicated as enhanced sensitivity of the renal vasculature to α_1-AR agonists. Despite the fact that these changes were independent of any additional rise in arterial blood pressure. This mechanism provides critical insights into how high salt load can enhance the vascular response to vasoconstrictor stimuli that can increase the vascular resistance which could be an initiating factor for the salt-induced increase in the arterial blood pressure.[26-28]

This result strengthen the earlier view that harmful effects of salt loading are not limited to increase in blood pressure.[1] Moreover, the obtained data suggests that even the lowest amount of salt intake (0.9% NaCl), nearly equivalent to the average salt intake currently observed in industrialized and urbanized countries, may promote and increase the adrenergic responsiveness of the renal vasculature to adrenergic vasoconstrictor stimuli, leading to alterations in the vascular resistance. This greater vascular smooth muscle responsiveness may lead increased vascular resistance for perfusion of blood causing an increase in pressure, which then predisposes the individual to increased arterial wall thickness and remodeling mechanisms. In these conditions, hypertension is mediated by enhanced vascular resistance, leading to vasoconstriction and addition alincrease of total peripheral vascular resistance. Studies have revealed that increase in vascular reactivity occurring after sodium loading might be due to the sodium-dependent impairment of noradrenaline uptake. Augmented vascular responsiveness provide greater resistance to blood flow and predisposes an individual to salt-induced blood pressure response.[29] Studies using other salt-related hypertensive rat models, the DOCA-salt-hypertensive rats, have stated that the enhanced responsiveness of the mesenteric vascular bed to α_1-AR agonists could be due to a local alteration in the α_1-AR density. Suzuki et al. found an increase in both density and affinity of α_1-AR in the mesenteric vasculature of DOCA-salt hypertensive rats.[30] An increased affinity of the small mesenteric artery á$_1$-ARwas demonstrated in spontaneously hypertensive rats compared with normotensive Wistar-Kyoto rats.[31] Higher renal densities of α_1-AR and α_2-ARwere demonstrated in both spontaneously hypertensive rats and Dahl salt-sensitive rats.[32] Additional studies in other salt-related hypertensive animal models have revealed that the enhanced responsiveness of the vasculature to catecholamine might be due to a local alteration in the α_1-AR density.[33] These differences in sensitivity of different vascular beds due to high salt load could cause a change in neurovascular transduction processes.[33] Evidences also suggest disturbance in nitric oxide and intrarenal RAS activities causing abnormal vasodilatory response to salt,which usually precede and initiate salt-induced hypertension. Hence,the underlying mechanisms that promote vascular salt sensitivity are complex involving genetic and environmental influences on the vasculature that are independent of blood pressure. The relative significance of different mechanisms leading to failure in normal vasodilation in response to increases in salt intake remainsunclear. Present study reports that enhanced renal vascular response to adrenergic agonist is due to α_1-AR functional alterations and that this may be one of the causes for salt-induced impaired renal vasodilatory response. Abnormal relationship between high salt intake and renal vascular α_1-AR can have an implication on the renal vascular resistance and renal hemodynamics. Altered renal hemodynamic parameters can have greater effect on blood pressure response through altered sodium

tubular handling. Additionally, we suggest that the relation between salt and á-adrenergic system in other vascular beds need to be further considered.

CONCLUSION

High salt intake enhances the renal vascular responsiveness to vasoconstrictor stimuli. The enhanced sensitivity was not only observed in hypertensive conditions but unexpectedly also in normotensive conditions. Increased renal vascular sensitivity is because of functional alterations in the renal α_1-ARdensity. These findings provide additional evidence on the underlying vascular pathology in salt-induced hypertension.

Conflict of interest

We have no financial, consultant, institutional and other relationships that might lead to bias or a conflict of interest.

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