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Review Article

Neural Control of Renal Function in Hypertension and Health

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ABSTRACT

The body fluid volume and composition regulation are vital for homeostasis. The renal system is destined to perform the feat of ECF volume and composition regulation along with excretory function. The prime intersystem communication between the kidneys, the CNS and cardiovascular system is for ensuring the optimal blood flow and supply of the essential nutrients to each and every cell and tissues of the body. The renal system is under the control of sympathetic division of autonomic nervous system which through its afferent and efferent nerves ensure the body fluid volume regulation. The long-term hormonal mechanisms are also essential part of this regulation as does the short-term neural mechanism. The interaction between renal afferent and efferent sympathetic innervation is deciding the optimum levels of renal function effected through the nervous control The aim of this review article is to appraise, use and apply the information available through published reports to elaborate, delineate, explore on major knowledge building and to address the definite role of renal sympathetic nerves in the function of kidneys in health and disease. With obvious limitations in studying the role of renal nerve activity in hypertensive humans, the underlying mechanism studied in experimental animal model could shed more light on the disease pathogenesis and the evidences obtained so far can be applied in understanding the underlying mechanism in humans as well.

Keywords: Renal efferent sympathetic nerve, Arterial blood pressure, Hypertension, Afferent renal nerves.

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INTRODUCTION

The fluid and ionic homeostasis regulation function is determined by the high renal blood flow, tubular re-absorptive property and the intra-renal renin system. The control of these renal functions is due to optimal operation of sympathetic efferents coming from the spinal cord. The Sympathetic efferent are appropriately regulated by the medullary sympathetic centres. The afferents converging from cardiac, pulmonary receptors and other areas are crucial as does the renal afferents coming from kidney itself. The selective hyper-activity of efferent renal sympathetic nerves is observed in established hypertension. The significant role played by efferent renal sympathetic nerves in various kidney diseases and hypertension contributing in the pathogenesis of these entities. The peculiar features of neural control of renal functions are elaborated to understand its importance in the hypertension in particular.

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SYMPATHETIC RENAL NERVES

Apart from being the major excretory organ, kidneys are also important in regulation of ECF volume and consequently the blood volume. The pronounced effect on regulation of fluid homeostasis exerted by kidney makes it a prime organ in regulation of blood pressure as well. The regulation of these renal functions is dependent on commands from centres located in brain stem, which in turn are receiving inputs from various parts of circulatory tree and kidneys itself (Afferent innervation).

Renal innervation was of utmost interest for earlier physiologist like Claude Bernard who for the first time demonstrated in anaesthetised dog preparation that unilateral sectioning of splanchnic nerve was associated with increased urine flow.[1]

Many experimental evidences culminated in the wealth of information about reflex regulation of renal sympathetic nerve activity, renal afferent nerve input, the integration of these input at the level of CNS (Central Nervous System) and the influence of the autonomic centres over the overall renal function.

Celiac plexus, lumbar splanchnic nerves, and inter-mesenteric plexus are the main neural structures supplying the kidney and its functional unit-nephron. Efferent renal innervation is densely

distributed to cortex and outer medulla and is also evident to afferent and efferent arteriolar smooth muscles and inner medulla. Stimulation of the renal nerve principally produces reduction in blood flow to outer cortex and with more pronounced stimulation resulting in reduction of medullary blood flow as well.

Animal experimental evidences suggest that the sympathetic fibres supplying kidneys are of varying diameters and are myelinated as well as unmyelinated subserving the different functions like vascular regulation, renin release and sodium-water reabsorption. Experimental studies have put forward the concept of varying degree of specific neural control of a particular renal function like renal blood flow and GFR (Glomerular Filtration rate), renin release and sodium and water reabsorption. Luff and co-workers demonstrated existence of separate kind of sympathetic axon innervating the juxtaglomerular arterioles of the rabbit and rat kidney that differ structurally from those supplying other arteries.[2] DiBona and Sawin have proven the existence of population of nerve fibres governing peculiar renal function.[3] Further it would be of particular interest in studying these areas which are yet to be explored. Barajas and co-workers confirmed the presence of identifiable neuro-effector junctions on afferent and efferent arteriole, proximal and distal tubule, collecting duct, thick ascending limb of Loop of Henle (LOH), Juxta glomerular apparatus.[4,5] The greatest degree of innervation was found on Proximal Convoluted Tubule (PCT) followed by thick ascending limb of LOH (TAL) (6.5%), Distal Convoluted Tubule (DCT) (4.5%), Proximal Convoluted Tubule (PCT) (2.4%) and Collecting Duct (CD) (2.5%). The prominent role played by kidney in Extra Cellular Fluid (ECF) volume regulation through controlled activity of Efferent Renal Sympathetic Nerve (ERSN) activity. The heart and its receptors in particular high pressure baro-receptors and low-pressure volume receptors and associated vagal and glossopharyngeal nerve afferents act as sensors, while the kidneys act as effector organ in regulation of blood volume and ECF volume (Figure 1).

NEUROTRANSMITTERS INVOLVED IN RENAL FUNCTIONS

The principal neurotransmitter in ERSN is NE (Nor-Epinephrine) and this has been evidenced in experimental animals with its decreased renal content after denervation and increased renal concentration after electrical stimulation.[6,7]

Apart from nor-epinephrine, other colocalised co-transmitters were also reported to influence renal function up to some degree. Experimental evidences in pig has demonstrated presence of Neuropeptide Y (NPY) and its increased concentration in renal venous blood following high intensity stimulation of ERSN which was found to reduce the renal blood flow as well.[8,9]

The functional contribution of NPY in vasoconstrictor response is evident only at high intensity of stimulation.

Similarly, apart from NPY other co-transmitters are also released which include purine and pyridine nucleotides like ATP.[10,11] The ATP seem to play its role in sodium reabsorption through its Purinergic Receptors (P2) located on principal and Intercalated cells.

ADRENOCEPTORS INVOLVED IN RENAL FUNCTION

The α1-adrenoceptors present on nephrons, renal vasculature, and proximal tubules contribute to sodium reabsorption, vasoconstriction, glycogenesis and production of prostaglandins.[12] The adrenoceptors in particular, α_{1A}-receptors are mainly responsible for regulating renal blood flow and sodium and water reabsorption by the proximal tubules. The α_2 receptors have same distribution as that of α1, and have synergistic effect on Sodium reabsorption in PCT, the α2-receptors are responsible for diuresis from the collecting duct through the inhibition of secretion and antidiuretic hormone action.[13] While the β_1-adrenoreceptors which are present at the level of juxtaglomerular cells, nephrons, distal tubules, and collecting ducts and are responsible for renin secretion and suppress potassium secretion. However, the renal vasculature, PCT, DCT and collecting ducts has Dopamine D_1-receptors which are accountable for vasodilatation and inhibition of sodium reabsorption.[14]

Various studies have confirmed sympathetic innervation of renal vasculature principally to the arterioles, juxta glomerular apparatus and tubular epithelial cells.[15] The sympathetic nervous system being the prime mediator of renal haemodynamic effects.

RENAL SYMPATHETIC STIMULATION INDUCED RENIN RELEASE

Renal efferent sympathetic nerve activity also mediates renin release from JGA Juxta Glomerular Apparatus (JGA).[16] Also, reflex increase in renal sympathetic nerve activity due to various mechanisms was also shown to be associated with increase renin release.[17,18] Like the neural reflex mechanism for renin release, there are non-neural mechanisms as well for renin release from JGA.[19]

Kopp *et al.* provide confirmatory evidence of renal sympathetic stimulation on renin release at level of electrical stimulation that was subthreshold in frequency and current to alter renal hemodynamics under renal sympathetic nerve stimulation. The renal sympathetic activation was associated with prompt renin secretion which could be effectively blocked by β1-adrenoceptor antagonists.[20] Similar findings were evidenced in humans.[21]

The β-adrenoceptor driven cyclic Adenosine Monophosphate (cAMP) production acts as both short term and long-term mechanism to cause renin granules exocytosis and further increases the rate of renin gene expression. The sympathetic

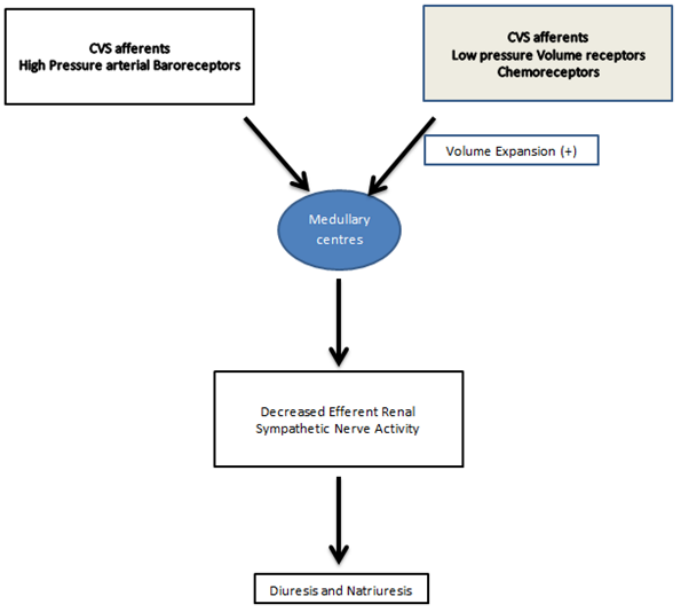

Figure 1: Peripheral afferents modifying renal sympathetic nerve activity.

renal denervation attenuates renin release induced by reduction in systemic blood pressure. Underlying basal levels of renal sympathetic nerve activity have crucial role in deciding the sensitivity of renal baroreceptor and macula densa mechanism for renin secretion.

RENAL SYMPATHETIC STIMULATION MEDIATED TUBULAR SODIUM REABSORPTION

Efferent renal sympathetic nerve activity primarily serves to regulate renal tubular sodium excretion by two effects.[22]

By altering the renal arteriolar vasoconstrictor tone resulting in changes in renal haemodynamics and By direct effect on renal tubular sodium reabsorption.

Historical studies in experimental animals have shown that denervation of one or other kidney resulted in natriuresis and diuresis. Thus, the renal sympathetic nerve activity is one of the important regulators of cardiovascular haemostasis as it affects the urinary sodium excretion and consequently affect the changes in ECF volume and effective circulating blood volume and blood pressure. Similarly excessive activity in these nerves promotes hypertension.[6]

The prejunctional nor epinephrine released play a significant role in regulation of Sodium balance. The efferent renal sympathetic nerves have innervation on renal tubule with α1receptors located on glomerulus, PCT, late DCT, CT, while α2 receptors in addition to above on medullary and cortical collecting duct. While β adrenoceptors located on glomerulus, thick ascending limb of LOH, distal convoluted tubule and connecting tubule. With increased RSNA and NE release, there is increased Epithelial Sodium Channels (ENaCs) expression and activation,[23,24] while denervation in experimental animal have shown decreased expression of ENaCs this seems to highlight the role of NE amount release on ENaCs expression.

In distal nephron Nor-Epinephrine (NE) influences activation and expression of Na-Cl Co-transporter (NCC) and consequently the sodium excretion in this part of nephron. While in PCT, these sympathetic nerves stimulate Sodium reabsorption by activation of Na-H Exchanger (NHE1 and 3) through α2-adrenoceptors[25,26] and by intra-renal Renin-Angiotensin II mechanism.[27] Graded responses to sympathetic nerve stimulation have been evidenced in anesthetized experimental animal like dog. The graded increase in renin secretion rate, grade decrease in urinary sodium excretion and further increase in renal stimulation results in decreased renal blood flow. The renal renin secretion rate increased at low intensity of sympathetic stimulation that didn't appear to influence the sodium reabsorption and renal blood flow. While at slightly higher levels of sympathetic stimulation tend to causes both increases in renin secretion and tubular sodium reabsorption, while the maximum renal sympathetic nerve stimulation tends to cause increase in the renin secretion maximally and sodium reabsorption to greater extent with beginning of fall in the renal blood flow. Thus, at rest within physiological limit the renal blood flow remains unaltered with sympathetic stimulation.

ROLE OF EFFERENT RENAL SYMPATHETIC NERVE IN HYPERTENSION

The very first evidence of involvement of renal efferent sympathetic nerves in hypertension was proposed by Kottke *et al.* where-in they demonstrated that chronic renal nerve stimulation in experimental animal like dog resulted in Hypertension.[28]

These findings were supplemented by Katholi RE, where it was found that chronic intrarenal arterial infusion of epinephrine in conscious dogs produced sustained hypertension. This infusion resulted in both a positive sodium balance and an increase in plasma renin activity. However, the hypertension observed was not due to increase Plasma Renin Activity, as the use of Angiotensin II antagonist Saralasin in these animals was not found to cause significant decrease in Blood pressure.[29] For the evident Hypertension associated with intrarenal nor-epinephrine infusion it was proposed by Winternitz SR that selective increases in renal sympathetic activity are required to maintain the hypertension.[30] The proposed mechanism is in agreement with the findings put forward by Guyton wherein it was proposed that there is resultant pressure natriuresis and fall in arterial blood pressure whenever there is increase in blood pressure due to generalized increase in peripheral resistance.

The complementary role of the renal nerves in hypertension was confirmed by the evident increased renal noradrenaline spill over in young adult hypertensive patients and in obesity-related hypertension.[31,32] In hypertensive individuals, the increased activity of sympathetic nervous system plays role in initiating and

sustaining hypertension. Tachycardia, increased Cardiac output and venoconstriction with normal systemic vascular resistance points towards sympathetic hyperactivity. Increased renovascular resistance with 20% decrease in renal blood flow have been documented in benign essential hypertension as compared to normotensives.[33] This renal vasoconstriction has basis of sympathetic mediation. In essential hypertension, increased renal norepinephrine secretion was evident as compared to normotensive subjects thus supporting the abnormal sympathetic neural activity in these subjects.[34] Role of renin angiotensin system was studied in renovascular hypertension due to renal artery stenosis. However, many studies have proven the role of increased sympathetic nerve activity in maintenance of such type of hypertension. There is no fall in plasma renin activity in patients with renal hypertension after administration of propranolol (Beta blocker) suggestive of maintenance of basal renin activity by factors other than renal sympathetic nerve activity.

Concrete evidences of sympathetic nervous system overactivity in development of hypertension have been depicted through following mechanisms:[35]

- Predominantly Increased Muscle Sympathetic Nervous Activity in early hypertension.
- Substantially increased renal norepinephrine spill over in essential and reno-vascular hypertension.
- Significantly increased renal sympathetic nerve firing.
- Likewise, possibly increased activity of renal sensory nerves has been proposed as an aetiology for treatment resistant hypertension even more relevant than renin angiotensin system and volume overload.

CONCEPT OF AUTO INHIBITORY FEEDBACK

The evidence for auto inhibitory feedback operating through α2-adrenoceptors present on ERSN endings aid in control of its own activity (Figure 2). These set of auto-inhibitory receptors are important as far as renal sympathetic function is concerned. The NE released from the sympathetic fibres acts on the presynaptically located α2-adrenoceptors which determines the release of NE from the same nerve endings. Thus, the rate of release of NE is regulated by its own receptors in a negative feedback fashion.

In experimental set up in animals (dog), administration of α2-antagonist followed by electrical stimulation of ERSN resulted in increased nor epinephrine release and enhanced renal vasoconstrictor response. Similarly in rabbits with α2 antagonist, the renal anti-natriuretic and antidiuretic response was accentuated although no change in renal vasoconstrictor response was observed.

However, in contrary to above in SHR (Spontaneous Hypertensive Rat), neither the renal vasoconstrictor nor the anti-natriuretic and antidiuretic response to renal sympathetic nerve stimulation was blunted after α2 antagonist drug administration.

The increased ERSNA tend to cause elevated release of sympathetic neurotransmitter. The normal auto regulatory prejunctional α2-adrenoceptors present of ERSN fibres are for control of its own activity. However, in pathological states inhibition of these α2-adrenoceptors accelerates hypertension and kidney injury through various mechanisms. Increased nor-epinephrine release through inhibition of these receptors leads to increase renin release, renal vascular tone, sodium and water retention. Similarly, it has been proposed that increased norepinephrine release has a role in mediating renal injury as well.

Secondarily α2-adrenoceptor activation from renal epithelial cells, VSMCs, or immune cells can alter vascular tone, sodium balance, and immune cell response in the renal parenchyma. Robust evidences from animal experiments have proven interaction between sympathetic nervous system and immune system and hence the Sympathetic Nervous System (SNS) may be having inflammation modulating response which can lead to fibrosis and progression of the underlying pathology.[36,37]

ERSNA regulation is affected by complex interaction between renal afferent nerve activity and central mechanism. Reno-renal reflex is controlled by afferent renal chemo and mechanosensitive nerve fibres through a negative feedback mechanism. Reno-renal reflex normally tend to regulate ERSNA. Similarly, the Afferent Renal nerve activity in turn is regulated by α1- or α2-adrenoceptors located on its ending in the renal pelvis. With hypertension or kidney damage, there are disturbances in this normal inhibitory reno-renal reflex mechanism, the proinflammatory cytokines, hypoxic injury, uremic toxins rather increase the renal sympathetic nerve activity and thus attendant excessive sodium and water retention causes development of resistant hypertension. The effects of increased ERSNA are reduction in renal blood flow and Glomerular Filtration Rate (GFR), increased renal vascular resistance, increased tubular sodium and water reabsorption, increased renin secretion and all these changes leads development and maintenance of sustained elevated blood pressure.

Experimental studies where renal denervation was shown to reduce Blood pressure emphasizes the crucial relationship between sympathetic nervous system and kidney function in chronic diseases like hypertension.[38,39] Animal experimental findings revealed increased renal sympathetic nerve activity, renal sympathetic driven Sodium and water reabsorption, renin release upon reduction in carotid sinus pressure caused by occlusion of carotid artery without altering renal blood flow and GFR.[40,41] Thus the high-pressure baroreceptors are implicated in playing role in hypertension owing to their influence on ERSNA

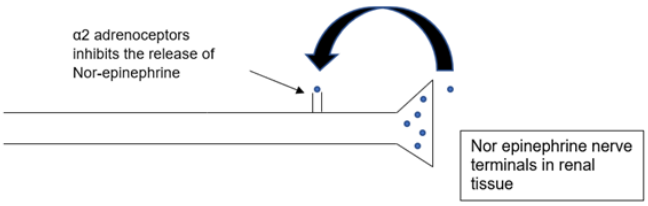

Figure 2: Auto inhibitory feedback of α2-adrenoceptors.

and having the property of resetting its activity at higher arterial blood pressure levels owing to maintenance of renal blood flow and renal function.

PARACRINE REGULATORS OF RENAL SYMPATHETIC ACTIVITY AND THEIR ROLE IN HYPERTENSION

The Nitric Oxide (NO) plays essential role in regulation and modulation of sympathetic noradrenergic actions at the levels of renal vasculature, JG cells and tubular sodium re-absorptive functions. Experimental finding points out towards the facilitatory role of NO in release of NE from prejunctional sympathetic nerve fibres. Similarly, NO also acts post junctionally to exert diuretic and natriuretic effects which are exactly opposite too sympathetic nor-adrenergic actions. Hence the net effect is due to delicate balance between the actions of NO at these various sites.

In systemic hypertension there is evidence of oxidative stress at the level of tissues and organs. The reactive oxidative species exert their actions by two mechanisms: by directly scavenging the local intra-renal NO which leads to its decreased bioavailability and additionally by their actions on sympathetic nerve endings. Thus, the oxidative stress seen in hypertension could contribute in increased generation of superoxide anions that could elevate the level of renal sympathetic neural outflow. Thus, the fact that oxidative stress and consequent superoxide anion generation in the internal environment of the body has a magnitude altering effect on ERSNA, however the functional significance of this on neural control of renal functions can't be ascertained.

The NO could act possibly in two ways: directly at postjunctional membrane of the various effectors where it may depress the neurally mediated effects and secondarily at the prejunctional membrane to facilitate norepinephrine release. Further the various forms of NOS (Nitric oxide synthase) systems are operational in for local regulation of the sympathetic nervous activity (Figure 3).

Local renal tissue AT II (Angiotensin II) concentration is high and it has a facilitatory role in sympathetic innervation and its effects on tubules, vasculature and sodium re-absorptive function. Likewise other paracrine mediators, the ATII is having a sympathetic prejunctional action. A postjunctional action on PCT cells is allowing sodium and water reabsorption in the presence of intact renal innervation.[42,43] The renal sympathetic nerve activity is influenced by environmental, social, and psychological challenges as does the overall sympathetic nervous system activity. Evidences from experimental studies have proven that central commands in responses to environmental factors/ stressor can modulate the renal sympathetic nerve activity during day-to-day routine challenges. Clinical studies have shown that in 2/3rd of young essential hypertensive subjects there is slight reduction in Renal Blood Flow (RBF) or defective ability to excrete a saline volume load. Similarly intrarenal arterial administration of α-adrenoceptor antagonist was found to cause a greater renal vasodilatation in hypertensive patients compared with normotensive controls.[44,45] Likewise, renal NE spill over-an index of renal sympathetic nerve activity is found to be increased in hypertensive subjects.[46,47]

RENAL AFFERENT NERVES

Similar to efferent innervation, the renal afferent nerves also have wide spread innervation. However, the majority of afferent nerve fibres are located in renal pelvic area and carry sensory information from renal mechanoreceptors and chemoreceptors. The neurotransmitters mediating afferent sensations are substance P and Calcitonin Gene Related Peptide (CGRP). The sensory nerve fibres enter the spinal cord through dorsal root ganglion at the level of T6-L4 with predominance at the level of T12-L3.[48]

The functional studies using renal pelvic administration of capsaicin at lower concentration increased the ARNA when given in renal pelvis than into the renal interstitium.[49] The capsaicin is a stimulant for renal sensory nerves through activation of nonselective cation channel Transient Receptor Protein (TRP V1).[49]

The circumferential arrangement of renal sensory fibres serves the function of mechanical sensing of stretching of renal pelvic wall.[50] Similarly, Recordati *et al.* have described the existence of R2 chemo-sensitive nerve fibres which are activated by changes in urinary chemical composition.[51] Renal ischemia is the potent stimulus for their activation.

There are widespread projections from these afferent renal fibres to brainstem cardiovascular areas concerned like Nucleus Tractus Solitarius (NTS), Rostral Ventro Lateral Medulla (RVLM), Sub Fornicial Organ (SFO) and Para Ventricular Nucleus (PVN) in regulation of renal efferent sympathetic nerve activity. The renal mechanoreceptors are present and located in renal cortex and renal pelvis,[52] while the renal chemoreceptors are located primarily in the sub-mucosal layers of the renal pelvis.[53]

The reno-renal reflex is the evidence of interaction between sympathetic efferent nerves and renal afferent nerves (Figure 4). The afferent renal nerves hold a tonic inhibitory effect on

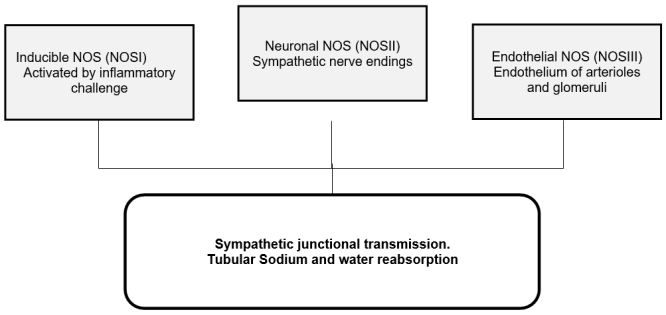

Figure 3: Renal NOS (Nitric Oxide Synthase) system

efferent renal sympathetic nerves so as to maintain a goal of low basal ERSNA during conditions of increased water/sodium load. Similarly, the intake of dietary sodium would also be a deciding factor which affects Afferent Renal Sympathetic Nerve (ARSN) activity. As high sodium diet tends to cause greater afferent renal nerve activity as compared to low sodium diet.

In experimental animals, the threshold for reno-renal reflex activation was found to be 3 mm of Hg renal pelvic pressure. While the threshold in high dietary sodium fed rats was as low as 2.5 mm of Hg and those with low dietary sodium it was 7.5 mm of Hg.[54]

The importance of renal afferent nerve is demonstrated in animal studies in rats with NaCl sensitive hypertension where lack of intact afferent renal innervation may contribute to the increased arterial blood pressure when fed with high sodium diet.[55] As ARNA influences the ERSNA so is the vice-a-versa. Reflex mediated increases and decreases in ERSNA tend to increase and decrease ARNA, respectively (Figure 5).[56,57] Altogether, there is sufficient evidence for operation of a negative feedback loop system in which increase in ERSNA increases ARNA that in turn would decrease ERSNA via activation of the reno-renal reflex.

Variations in ERSNA cause changes in ARNA by the release of NE which can activate α1-adrenoceptors and α2-adrenoceptors on afferent renal sensory nerves leading to increases and decreases in ARNA.[58] The coupling link between the ERSNA and ARNA is dietary sodium, the high sodium diet enhances and low sodium diet reduces the ERSNA induced ARNA increase.[57,59] The inhibitory reno-renal reflex will be increased with high dietary sodium intake owing to high activity of ERSNA and consequent ARNA activity with resulting decrease in ERSNA.

While with low sodium intake there is suppression of the ERSNA-induced increases in ARNA that results in decreased activity of inhibitory reno-renal reflex and thus leads to adaptive sodium retention. Similarly, a reduction in the responses of renal afferent nerve is seen due to increased renal ANG II levels in variety of physiological and pathophysiological states like hypertension, congestive heart failure, and ischemia-induced acute renal failure. The normal inhibitory reno-renal reflex is impaired which contributes to Sodium retention and high blood

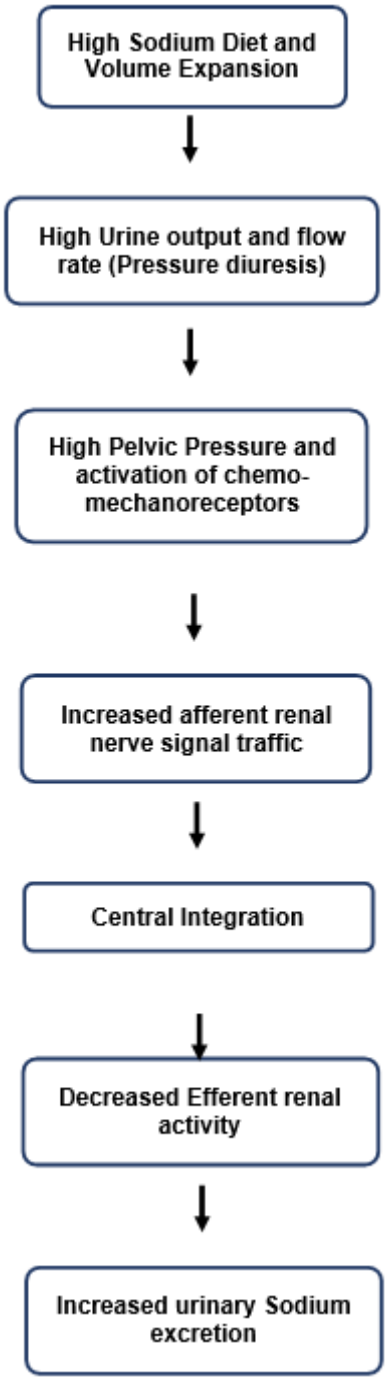

Figure 4: Reno-renal Reflex.

pressure and conversely the pathological excitatory reflex prevail which also contributes in the pathogenesis of these entities.

EFFECT OF RENAL NERVE ABLATION

The ERSNA plays an important role in regulation of blood pressure. In experimental setup it has been observed that the sudden increase in central sympathetic outflow results in disproportionately large vasoconstriction in renal vascular bed as compared to other beds so to conserve the circulating blood

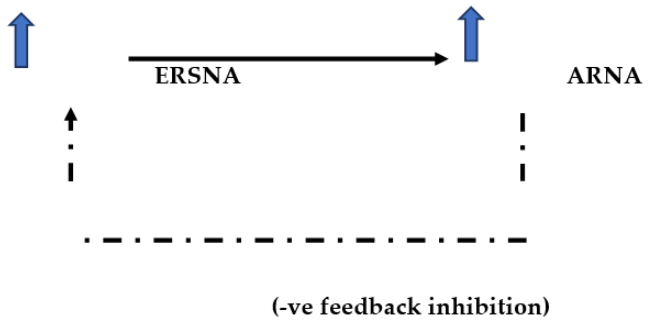

Figure 5: The negative feedback mechanism of operation of renorenal reflex.

volume as kidneys receive ~20% of cardiac output under resting condition. Similarly, the ERSNA is responsible for conservation of Sodium and water through active reabsorption from tubules in an attempt to conserve blood and ECF volume.

The marked renal vasoconstrictor effect seen in experimental animal's points towards the possibility of disproportionately larger sympathetic activity in renal vasculature than in other vascular beds. Such disproportionately high sympathetic activity would facilitate the hypertensive process by shifting the arterial pressure-sodium excretion curve of kidney to right (renal function curve). This right ward shift of renal function curve is supposed to cause hypertension which is also observed in neurogenic hypertension following destruction of nucleus tractus solitarius.[59]

In experimental hypertension in animals, shift of renal function curve towards right was a cause of hypertension as no change in Sodium excretion was evident despite increase in arterial blood pressure. Experimental intervention like Aortic baroreceptor deafferentation in rats was found to initiate neurogenic hypertension with increased renal sympathetic nerve activity. In Spontaneous Hypertensive Rats (SHR) selective activation of sympathetic ganglion supplying splanchnic region as well as increased renal epinephrine turnover was observed than in control animals.[60]

The influence of efferent renal sympathetic activity on vascular walls as measure of renal vascular constrictor activity was assessed in Deoxycorticosterone Acetate (DOCA)-salt treated hypertensive rats. The measurement of renal precapillary vessel wall to lumen ratio in DOCA-salt treated hypertensive rats was found to be significantly higher than other vascular beds (hind limb and cremaster vessels). While in the renal denervated animal's precapillary arteriolar resistance vessels wall to lumen diameter ratio was not different than in other vascular beds. The renal denervation caused the leftward shift of renal function curve in induced hypertension in animals.

Thus, the all findings from the animal model of hypertension points towards the increased activity of sympathetic nervous system. The efferent renal sympathetic nerves appear to make a major contribution in the development of hypertension through its control over renal vasculature and sodium excretion. Further the renal denervation studies emphasize the role of efferent renal sympathetic nerve pathways as an important factor in attenuation of the development of hypertension, the likelihood of involvement of afferent renal nerve contribution in reducing BP and sodium reabsorption can't be excluded. Nevertheless, added factors like vasopression, circulating pressor substances, increased vascular reactivity and structural changes in blood vessels are also contributing in pathogenesis of hypertension. An observation in patients with therapy resistant hypertension have shown a vigorous reduction in blood pressure following renal denervation and thus emphasizes an important crosstalk between the ERSN and the kidney in hypertension.[38,61]

In addition findings on single nephron GFR by Bello-Rous and co-workers revealed no change in SNGFR but significant reduction in absolute and fractional Sodium reabsorption in PCT after renal denervation.[62] Similarly, many studies confirmed reduction in solute and water reabsorption in LOH and DCT after renal denervation.[63,64]

Similarly, it was proven that at low range of voltage stimulation of renal sympathetic nerves which didn't reduce renal blood flower GFR, there was an increased sodium and water reabsorption by renal tubular cells in PCT. Experimental studies have put forward compelling evidences regarding the importance of increased renal sympathetic nerve activity in pathogenesis of hypertension. The intervention of renal denervation in animal models of hypertension has resulted in the prevention, delay of onset or reduction in the magnitude of elevated blood pressure. Hence in treatment resistant hypertension bilateral renal denervation has been found to be associated with marked and sustained decrease in arterial blood pressure.[57,61]

CONCLUSION

The renal efferent sympathetic nervous system plays a prime role in fluid and electrolyte homeostasis and is major effector for arterial blood pressure homeostasis in long run. The renal efferent nerve activity is in turn under the influence of various afferent signals coming from kidney, its pelvi-calycial system, pulmonary receptors and others. The operation of reno-renal reflex is evidence pointing towards the existence of the interaction between the sympathetic efferent and afferent nerves thus maintaining the optimum renal function. The animal experimental evidences have put forward the prime role of this system in genesis of systemic hypertension. Similarly, the effect of renal ablation was conclusive enough in lowering the arterial blood pressure in the animals. The selective renal sympathetic ablation could be of therapeutic benefits in human hypertension as well.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

GFR: Glomerular Filtration Rate; **LOH:** Loop of Henle; **PCT:** Proximal Convoluted Tubule; **TAL:** Thick Ascending Limb of LOH; **DCT:** Distal Convoluted Tubule; **PCT:** Proximal Convoluted Tubule; **CD:** Collecting Duct; **ECF:** Extra Cellular Fluid; **ERSN:** Efferent Renal Sympathetic Nerve; **JGA:** Juxtaglomerular Apparatus; **NPY:** Neuropeptide Y; **NE:** Nor Epinephrine; **cAMP:** cyclic Adenosine Monophosphate; **DOCA:** Deoxycorticosterone Acetate; **NTS:** Nucleus Tractus Solitarius; **RVLM:** Rostral Ventro Lateral Medulla, **SFO:** Sub Fornicial Organ; **PVN:** Para Ventricular Nucleus; **ARSN:** Afferent Renal Sympathetic Nerve.

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