Published in final edited form as:

Curr Hypertens Rev. 2015 ; 11(1): 38–48.

Salt-Sensitive Hypertension: Perspectives on Intrarenal Mechanisms

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Abstract

Salt sensitive hypertension is characterized by increases in blood pressure in response to increases in dietary salt intake and is associated with an enhanced risk of cardiovascular and renal morbidity. Although researchers have sought for decades to understand how salt sensitivity develops in humans, the mechanisms responsible for the increases in blood pressure in response to high salt intake are complex and only partially understood. Until now, scientists have been unable to explain why some individuals are salt sensitive and others are salt resistant. Although a central role for the kidneys in the development of salt sensitivity and hypertension has been generally accepted, it is also recognized that hypertension is of multifactorial origin and a variety of factors can induce, or prevent, blood pressure responsiveness to the manipulation of salt intake. Excess salt intake in susceptible persons may also induce inappropriate central and sympathetic nervous system responses and increase the production of intrarenal angiotensin II, catecholamines and other factors such as oxidative stress and inflammatory cytokines. One key factor is the concomitant inappropriate or paradoxical activation of the intrarenal renin-angiotensin system, by high salt intake. This is reflected by the increases in urinary angiotensinogen during high salt intake in salt sensitive models. A complex interaction between neuroendocrine factors and the kidney may underlie the propensity for some individuals to retain salt and develop salt-dependent hypertension. In this review, we focus mainly on the renal contributions that provide the mechanistic link between chronic salt intake and the development of hypertension.

Keywords

angiotensin II; angiotensinogen; inflammatory cytokines; intrarenal renin-angiotensin system; oxidative stress; peroxynitrite; tumor necrosis factor-alpha

Introduction

The relationship between dietary salt intake and the development of hypertension has been the subject of continuing debate for decades [1–5]. Despite abundant epidemiological, experimental, and interventional observations demonstrating an association between salt

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Conflict of Interest

None

intake and blood pressure, skepticism still remains regarding how a high salt intake can be mechanistically linked to an increase in blood pressure [6, 7]. This skepticism is partly due to the heterogeneity in the blood pressure responses to increases in salt intake in humans. Our inability to explain why salt raises blood pressure in some individuals described as ‘salt sensitive’, but not in others, termed as ‘salt resistant’, has hampered the development of a comprehensive theory as to how a high salt intake causes high blood pressure in salt sensitive subjects. Extensive studies have been conducted to identify the pathophysiological mechanisms responsible for the heterogeneity of responses to increased salt intake [1, 8–10].

Alterations in kidney function, due either to a primary renal disease or to inappropriate hormonal/neural influences on the kidney, are a cardinal characteristic in all forms of hypertension, and are associated with a reduced ability of the kidneys to excrete sodium leading to the development of hypertension [11–13]. Proof of renal mechanisms and abnormalities in sodium (Na^+) balance causing hypertension comes from numerous experimental findings in genetically hypertensive rat strains [14–18]. In addition, the discovery of monogenic forms of human hypertension specifically due to a single mutation in a specific tubular transport system leading to increased Na^+ reabsorption lends further evidence to the critical role of the kidneys in the development of hypertension [15, 19–21]. When the capacity of the kidneys to maintain Na^+ balance and extracellular fluid volume within the appropriate range is compromised, increases in arterial pressure become necessary to re-establish normal balance [13, 15, 22, 23]. Varying degrees of reduced renal function have been found in hypertensive patients, and subtle disturbances in tubular transport function or microcirculatory dynamics due to either intrarenal defects or inappropriate humoral or neural stimuli are critical factors in the development of hypertension [12, 22, 24, 25]. Multiple renal derangements have been identified including impaired renal hemodynamics, renal autoregulatory capability, and pressure natriuresis, altered microvascular responses to vasoactive stimuli and enhanced Na^+ reabsorptive activity [26–29]. However, many extrarenal factors such as systemic productions of various pro- and anti-inflammatory cytokines as well as oxidant molecules are also important contributors to altered kidney function and hypertension [30–32].

Central to many hypertensinogenic processes is the inappropriate activation of the intrarenal renin-angiotensin system (RAS) by various pathophysiologic mechanisms [11, 15, 33, 34]. The important role of the RAS is supported by many studies involving various experimental models having overactivity of the intrarenal RAS [35–39]. Specific examples include the TGR(mRen2)27 rat model that has an extra renin gene inserted into its genome and also some mouse models that have either an extra renin or angiotensinogen (AGT) gene inserted into its genome [39–43]. Importantly, when the extra AGT gene was restricted to the kidney, the same degree of hypertension developed as in the systemic addition of AGT gene [44, 45].

Physiological Responses to a High Salt Intake

The classic renin-angiotensin-aldosterone system (RAAS) is heavily influenced by dietary salt intake. Multiple mechanisms including changes in renal sympathetic activity, pre-glomerular vascular baroreceptors and the macula densa cells, which respond to decreased

tubular flow or lower concentrations of sodium chloride, will stimulate renin release by the juxtaglomerular cells of the afferent arterioles [46, 47]. Long-term changes in the RAAS are regulated by the increases or decreases in renin secretion mediated via NO, prostaglandins and adenosine [48, 49]. Several studies have evaluated the changes in the components of the intrarenal RAS in response to alterations in salt intake [50–53]. These and other studies have clearly demonstrated that under normal physiological conditions, the RAAS functions exquisitely to maintain body fluid and Na⁺ homeostasis by responding in a coordinated manner. Nevertheless, even in normotensive individuals increased salt intake is associated with sustained increases in plasma and blood volume [54]. A low salt diet markedly stimulates the systemic and intrarenal components of the RAAS causing increased plasma and kidney renin and angiotensin II (Ang II) levels coupled with increased aldosterone concentrations and sympathetic activity to stimulate Na⁺ reabsorption and maintain body fluid volume [53, 55]. Likewise, in the renal medulla, renin production from the principal cells of the collecting duct is also increased in low salt showing the same pattern found in the cortex [53]. In response to a high salt diet, there is a coordinated suppression of the components of the RAAS. The levels of Ang II in the kidneys are higher than in the plasma under both conditions of low and high salt diets [51]. AGT mRNA levels in the renal cortex was shown to increase with low salt (0.03% NaCl) and decrease with high salt (4% NaCl) diet for 7 days in Sprague-Dawley rats [56]. A more recent study failed to show an increase in intrarenal AGT or urinary AGT (uAGT), even though the intrarenal renin and Ang II levels were markedly elevated [53]. Nevertheless, the RAAS system responds to both a high salt diet and a low salt diet but the responses to salt deficiency are robust and rapid occurring by the first day, while the responses to a high salt diet are slower and sluggish thus demonstrating Walter Cannon's concept that our physiological systems have developed primarily to provide a margin of safety protecting us against deficits that could prove disastrous [57]. Unfortunately, we are less efficient in protecting against excesses and there are more pathological conditions associated with insufficient suppression of the RAAS rather than with inadequate stimulation. An excess of salt intake in the presence of inappropriate activation of the RAAS is an example of homeostasis gone awry. Such is the case when a high salt diet is associated with a stimulation of the intrarenal RAAS leading to excess Na⁺ retention and increased vascular resistance and blood pressure. This type of response is exemplified in Dahl salt sensitive rats and spontaneously hypertensive rats which exhibit increases in intrarenal Ang II levels in response to a high salt diet [58, 59].

Salt Sensitivity and Inappropriate Responses of the RAAS

Salt sensitive hypertension is defined as an increase in blood pressure associated with increased salt intake. Approximately 50% of humans with hypertension have salt sensitivity with this number varying between sexes and influenced by race. Among normotensive individuals, approximately 26% are salt sensitive which has led to increased mortality [60]. Some studies suggest that increased salt intake has effects apart from blood pressure and volume expansion that may contribute to tissue injury [5, 61]. Indeed, the end organ structure and function damaged by salt may be the basis for the increased mortality among normotensive individuals with salt sensitivity. In response to a high salt diet, cardiac output increases but salt resistant subjects respond with reciprocal decreases in systemic vascular

resistance, while salt sensitive subjects have a paradoxical increase in vascular resistance associated with increased arterial pressure [62]. Many signaling mechanisms are altered and contribute to salt sensitivity. In addition to suppression of the RAAS, excess salt intake regulates nitric oxide synthase (NOS) through the ERK-MAPK pathway [63]. This study using Sprague-Dawley rats on 4 different diets including 3% and 8% NaCl, showed significantly increased phosphorylated 42–44 ERK in response to high salt diets especially in the renal medulla. An increase in TGF- β 1, an apoptotic factor stimulated by high salt via increased NOS or shear stress, may also increase cellular damage caused by high salt. This means that in addition to its well-known role in hypertension, a high salt diet salt also activates many signaling mechanisms that can contribute to tissue injury.

While high salt suppresses the RAS in normotensive subjects excessive salt intake leads to renal injury in hypertensive individuals through pressure-independent mechanisms [64–67]. A sustained RAS activity is involved in these adverse effects of salt since RAS blockade ameliorates salt-induced renal injury [59, 68, 69]. The RAS activity in spontaneously hypertensive rats is not suppressed or may actually be augmented after 4 weeks of salt loading indicating that maintained intrarenal RAS combined with high salt diet contributes to greater renal damage in this experimental model of hypertension [59]. Chronic Ang II-infused hypertensive rats fed a high salt diet exhibit infiltration of CD68 positive cells to the kidney interstitium, sustained O_2^- production, tissue injury and exacerbation of urinary excretion of AGT. As shown in Figure 1, the combination of high salt and Ang II infusion caused a greater increase in blood pressure than obtained with Ang II infusion alone [70]. In this rat model, these responses are mediated by AT₁ receptor activation since treatment with AT₁ receptor blockers ameliorates the development of these alterations (Figure 1).

Although a high salt diet alone does not alter systolic blood pressure, it is able to cause mesangial expansion and kidney fibrosis, without eliciting cell proliferation [70]. However, a high dietary salt given in chronic Ang II-infused rats leads to greater levels of systolic blood pressure along with marked exacerbation of mesangial expansion, kidney fibrosis, and tubular epithelial cell proliferation (Figure 2). In these rats, treatment with AT₁ receptor blockers prevented fibrosis in the glomeruli but not in the interstitium suggesting that despite a potential protection on glomeruli by AT₁ receptor blockade, interstitial injury may be sustained with infiltration of inflammatory CD68 positive cells facilitating progression to chronic kidney disease [70]. In addition, the immune system contributes to the exacerbation of hypertension in Ang II infused rats subjected to a high salt diet by increasing infiltration of inflammatory cells in the tubulointerstitial areas [71, 72]. Importantly, the combination of high salt intake and Ang II infusion leads to the infiltration of inflammatory cells, although no infiltration was observed when high salt diet or Ang II infusion was administered alone [70]. The detection of macrophages in the renal interstitium of Ang II-salt hypertensive rats most likely contributes to greater activation of intrarenal RAS during high salt intake leading to further accumulation of superoxide level and greater oxidative stress.

Mechanisms Mediating Renal Injury during Chronic Ang II Infusion

During chronic Ang II-infusion, sustained and moderate elevations in circulating Ang II lead to augmentation of intrarenal Ang II and AGT levels, impairment in renal function, and

progressive hypertension in the Ang II-infused rat model [73–75]. In this model of experimental hypertension, there are structural and functional derangements other than those directly induced by the elevation of arterial blood pressure, which contribute to the development of hypertensive nephropathy [76] and that persist beyond cessation of chronic Ang II infusion [77]. After discontinuing the Ang II infusion, the levels of intrarenal Ang II content and AGT expression returned to control levels within 3 days of cessation, but the changes in interstitial fibrosis, preglomerular hypertrophy and augmentation of MCP-1 and TGF- β , persisted even while systolic blood pressure and proteinuria returned to normal levels [77]. Because proteinuria was reduced, these results suggest that the primary mechanism mediating proteinuria during the early days of chronic Ang II infusion is hemodynamic. In chronic Ang II-infused rats, Ang II also stimulates MCP-1 levels, which is responsible for aggregation of inflammatory cells into the renal interstitium and increases the TGF- β 1 levels. The maintained elevations of MCP-1 and TGF- β levels in the kidneys of chronic Ang II-infused rats even after Ang II infusion discontinuation suggest these inflammatory molecules have a mechanistic link to the development of salt sensitivity [78–81].

Urinary AGT (uAGT) is a marker for the intrarenal RAS activity, but not a primary consequence of the elevated arterial pressure or of hypertension-induced proteinuria [82, 83]. In the Ang II-salt induced hypertensive rats, the excretion of uAGT is markedly elevated to much greater levels than that seen in Ang II infused rats (Figure 1) [70]. These uAGT levels contrast with those in normal rats fed high salt which remain at basal levels similar to those observed in rats fed a normal salt diet [70]. High salt alone suppresses the systemic RAS and renal AGT mRNA expression [52, 56]. However, during Ang II infusion, a salt-sensitive hypertension develops and high salt paradoxically stimulates the intrarenal RAS activity as reflected by exacerbation of the uAGT despite inhibition of plasma renin activity. During augmented renal oxidative stress, the high salt synergizes with Ang II to stimulate much greater increases in uAGT and injury [70]. Also, the blood pressure is positively correlated with renal Ang II concentrations but not plasma Ang II [71]. Thus, the combined effects of high salt intake and the exacerbated intrarenal RAS activity are associated with increased systolic blood pressure and proteinuria [71, 84].

Various studies have demonstrated that chronic Ang II infusion stimulates AGT expression in proximal tubule and increases uAGT excretion rate. The uAGT excretion rate is highly correlated with kidney Ang II content but not with plasma Ang II concentration [82, 85]. These data suggest that uAGT provides a specific index of intrarenal AGT production in Ang II-dependent hypertension and elevated uAGT excretion rates have been observed in patients with hypertension, diabetes and several types of kidney diseases [83, 86–90]. Initial clinical studies in hypertensive subjects indicate that treatment with blockers of the RAS reduce uAGT levels back to those in non-hypertensive subjects [91]. In addition, renin is present in the principal cells of connecting tubules and collecting ducts and is also augmented in Ang II dependent hypertension [35, 92–94]. Thus, in addition to forming more Ang II in proximal tubules, the increased AGT secreted into the tubules spills over into the distal nephron segments and forms more Ang I and II under the influence of renin and ACE of distal nephron origin [95–97]. Many of the effects of Ang II in angiotensin dependent hypertension are mediated indirectly via activation of other systems that amplify its

hypertensinogenic actions including aldosterone, thromboxane, endothelin and reactive oxygen species [98–101]. The systems activated by Ang II also include several growth factors [102–106], reactive oxygen species [99, 107–112] and inflammatory factors [113–115] which, in turn, contribute to the development of renal and vascular injury. Ang II can enhance vascular endothelial superoxide (O_2^-) production leading to increased oxidative stress, and increased proliferation and inflammation [70, 113, 116]. Several studies have indicated that interleukin-6 (IL-6) is a key cytokine involved in the augmentation of intrarenal AGT [117–119]. There is an augmentation of AGT formation by proximal tubule cells and sometimes spreading to glomerular, mesangial and vascular smooth muscle cells in hypertension and diabetes [120, 121]. While it is clear that AT_1 receptor activation is a key factor in the stimulation of AGT, it is also apparent that full manifestation of the effect requires the presence of other growth factors and cytokines, in particular, IL-6 and tumor necrosis factor- α (TNF- α) [32, 118, 122–124]. These conditions often involve inappropriately elevated intrarenal Ang II levels, and oxidative stress levels induced by an imbalance between nitric oxide (NO) and O_2^- generation in the kidney. Blockade of NOS with L-NAME causes an increase in blood pressure, which is exacerbated by combining the L-NAME treatment with high salt diet (Figure 3). The salt sensitivity developed in this model is linked to impaired pressure natriuresis and tubulointerstitial immune cell infiltration [29].

Redox equilibrium is critical for many aspects of cellular metabolism, signaling, and survival. Interaction between NO and O_2^- play a protective role in maintaining normal function in the kidneys [125–128]. Numerous studies implicate an imbalance in this interaction which alters tubular Na^+ reabsorptive function leading to salt-retention that contributes to salt sensitive hypertension. NO reacts chemically with O_2^- to form peroxynitrite ($ONOO^-$) [8, 125–133]. Although much is known about the actions of NO or O_2^- on the renal tubules, the specific role for $ONOO^-$ to regulate Na^+ reabsorption is not yet clearly defined. Moreover, its regulation in salt sensitive hypertension is not yet clarified. $ONOO^-$ formation is increased by Ang II as well as by high salt intake as these stimulate both NO and O_2^- production. However, a condition such as impairment in NOS activity (uncoupling), its pharmacological inhibition or gene deletion, reduces the formation of $ONOO^-$. Importantly, high salt intake and chronic Ang II infusions in endothelial NOS knockout (eNOSKO) mice which have less formation of $ONOO^-$ compared to WT mice results in an augmented hypertension with greater renal injury [134]. These findings suggest a protective role for $ONOO^-$ in the development of salt sensitive hypertension and associated renal injury [135]. An increase in tissue NO and O_2^- production and thus, $ONOO^-$ generation, may be linked to increases in TNF- α activity that primarily involves activation of TNFR1 [136]. Thus, it is possible that an increase in $ONOO^-$ formation by enhanced Ang II activity mediates the protective role of TNF- α via activation of TNFR1.

High salt intake either alone or in combination with Ang II increases O_2^- formation by increasing NADPH oxidase activity [70]. However, as high salt alone increases NO formation, it also increases $ONOO^-$ formation by reducing the increased level of O_2^- formation [70]. This is critical to prevent increases in blood pressure and renal injury [8, 137, 138]. When high salt is combined with Ang II infusion, the increased O_2^- formation is sustained or even slightly increased but the $ONOO^-$ generation is reduced thus leading to

the increase in O_2^- levels which contributes to the exacerbation of the uAGT and increased renal injury [70]. A biphasic effect of $ONOO^-$ activity has been demonstrated at physiologically relevant lower concentrations which produce vasorelaxation [139]. However, at higher concentrations that are more relevant in pathophysiological conditions, $ONOO^-$ causes renal vasoconstriction and also induces tissue injury [139, 140]. Thus, the formation of $ONOO^-$ during high salt intake alone which remains at more physiologically relevant concentrations, may be a key molecular mechanism preventing increases in systolic blood pressure. However, the sustained formation of $ONOO^-$ in rats fed a high salt diet with Ang II infusion may induce sulfhydryl oxidation, protein nitration and lipid peroxidation, thus leading to kidney injury [141], including glomerular expansion and renal fibrosis even at systolic blood pressures in the normal range [70], suggesting the contribution of pressure-independent factors stimulated with greater deleterious effects in response to Ang II infusions [138]. High salt independently stimulates transforming growth factor $\beta 1$ and other intracellular signaling pathways leading to an enhanced response to Ang II [138]. An enhancement in O_2^- generation may also contribute to the early developmental phase of Ang II-induced salt sensitive hypertension [8]. The exacerbation of kidney injury in the chronic Ang II infused rats subjected to a high salt diet can be explained, at least in part, by the interaction between the RAS and ROS [70]. These rats exhibited marked increases in uAGT excretion which paralleled the increases in O_2^- in the renal tissue, and were dependent on sustained AT_1 receptor activation since treatment with AT_1 receptor blockers prevented the increases in NADPH oxidase activity, reducing the O_2^- levels to a normal range [70].

An overactivated RAS can act synergistically with ROS leading to salt sensitive hypertension [64]. In normal conditions, a low level of oxidative stress is maintained by the balance between the production and the degradation of ROS such as O_2^- . Reactive O_2^- is rapidly reduced by the enzyme superoxide dismutase or reacts with NO; however, when there is enhanced O_2^- activity in the kidney, salt and water retention may occur [125, 131]. In chronic Ang II infused rats and mice the augmented O_2^- is considered a key determinant of the development of salt-sensitive hypertension [112, 142]. Furthermore, ROS-dependent enhancement of AGT and increased Ang II formation may be involved in the development and progression of renal injury [143, 144]. Ang II infused rats on high salt diet (Ang II-salt hypertension) developed impairment in dynamic renal blood flow autoregulation which was attenuated by tempol [145]. However, the unique effect of high salt in the pathogenesis of Ang II-salt hypertension has been difficult to establish.

In essence, a high salt diet given to chronic Ang II infused Sprague-Dawley rats for 2 weeks exacerbates Ang II dependent hypertension and leads to malignant hypertension as reflected by the reduced body weight gain, severe lethargy, piloerection, and assumption of hunched posture, along with increased Na^+ excretion and proteinuria [70]. Ang II also causes skeletal muscle wasting via an increase in muscle catabolism, associated with an increase of proteasome activity mediated, at least in part, by NADPH oxidase derived ROS [146]. Chronic Ang II infusions leads to decreases in body mass with decreases in retroperitoneal and epididymal fat even though food consumption remains the same [147]. These characteristics are similar to those observed in the Cyp1a1-Ren2 rats, a model of Ang II-dependent malignant hypertension associated with increased PRA and high circulating and

intrarenal Ang II levels [84, 148]. Dietary salt loading in this model exacerbates the hypertension and is paradoxically associated with increased kidney Ang II levels [149].

The emerging consensus is that hypertension is considered to be a low grade inflammatory condition induced by various pro-inflammatory cytokines [32, 72, 123, 150]. Recent studies have implicated an involvement of TNF- α in the development of Ang II induced hypertension and renal injury [32, 122–124]. However, the specific role that TNF- α has in mediating hypertension and renal injury involvement is not yet clearly defined. Hypertension induced by chronic Ang II infusion is attenuated in mice lacking TNF- α gene or the one of its sources, T-lymphocytes [123, 124]. While such attenuation of Ang II induced response could be linked to attenuation of NF- κ B activation by this cytokine [124, 151], increases in TNF- α level in mice also inhibit tubular Na⁺ reabsorption [136, 152, 153] suggesting its participation in a counter-regulatory mechanism opposing salt-retention and the associated hypertension.

TNF- α exerts its biological responses via interaction with two cell surface receptors, TNF receptor type 1 (TNFR1) and type 2 (TNFR2) which are differentially expressed and regulated in the kidney [154]. Although the specific roles of these receptors in various conditions have not been fully delineated, activation of TNFR1 and TNFR2 trigger shared and distinct signaling pathways upon TNF- α binding, which in turn result in cellular outputs that may promote tissue injury, on the one hand, but also elicit protective, beneficial responses. Chronic Ang II infusion in knockout (KO) mice lacking TNFR1 (TNFR1KO) attenuates systolic blood pressure indicating a protective role of TNFR1 in the Ang II induced hypertension [155]. The inhibitory action of TNF- α on tubular Na⁺ reabsorption is also mediated by TNFR1 [136]. On the other hand, renal injury but not the hypertension induced by chronic Ang II and a high salt (4% NaCl) intake is markedly attenuated in knockout (KO) mice lacking TNFR2 (TNFR2KO), indicating a contributory role by TNFR2 in renal injury [151]. While it is known that TNFR2 generally plays a role in chronic Ang II induced renal injury [151], TNFR1 is usually linked to apoptotic activity of TNF- α , and thus exerts a protective role [154]. These findings reveal a differential signal transduction mechanism via activation of these two receptors in the hypertension and associated renal injury induced by Ang II and high salt intake.

Ang II induced increases in tissue NO and O₂⁻ production, and thus in tissue ONOO⁻ formation, depends on intact TNF- α which mainly involves activation of TNFR1 [136]. Thus, it is possible that the protective role of TNFR1 activation is mediated by increases in ONOO⁻ formation. The endogenous formation of ONOO⁻ enhances the anti-inflammatory function of interleukin-10 (IL-10) [31]. IL-10 is produced by almost all cell types within the innate and adaptive immune systems. It is generally known that the anti-inflammatory cytokines effectively down-regulate the generation of the pro-inflammatory cytokines [31]. Recent studies indicate that IL-10 is normally present in plasma and that IL-10 protein is constitutively expressed in the renal tissue mostly in epithelial cells of distal tubular segments in the kidney [156]. Acute systemic NO inhibition in mice reduces IL-10 levels, but increases TNF- α levels in plasma and in renal tissues [156]. These results suggest a mechanistic link between IL-10 activity, NO and ONOO⁻ formation in the kidney in normal conditions as well as in conditions associated with renal inflammatory disorders. As ONOO⁻

enhances the anti-inflammatory function of IL-10 [31], it is important to understand the relationship between renal tissue levels of ONOO^- and the levels of IL-10 and TNF- α and its impact on the development of salt sensitive hypertension and associated renal injury. As shown in Figure 4, chronic Ang II infusion down-regulates TNFR1 mRNA and up-regulates TNFR2 mRNA in the kidney [155], and it is possible that a decrease in ONOO^- formation and thus, IL-10 levels due to reduction in TNFR1 activity could further enhance salt retention as well as the pro-inflammatory response during high salt intake.

Conclusion

In summary, it is clearly recognized that there are multiple complex renal and neurohumoral factors mediating salt induced hypertensive response. Particular emphasis is given to the inappropriate renal responses to high salt intake due to dysregulation of intrarenal RAS, oxidative stress and inflammatory cytokines by the kidney, which are key factors that modulate renal hemodynamics and tubular reabsorptive function to enhance Na^+ retention that leads to the development of salt sensitive hypertension.

Acknowledgments

This work was supported by the National Institute of General Medical Sciences IDeA Program (COBRE, P30GM103337). Additional studies in Dr. Majid's laboratory were supported by National Heart, Lung, and Blood Institute (HL-66432) and the Tulane Bridge Fund. Dr. Prieto's studies were supported by NIDDK (1R01DK104375). The authors also acknowledge the excellent technical assistance of Debbie M. Olavarrieta (Tulane University).

List of Abbreviations

Ang II	angiotensin II
AGT	angiotensinogen
eNOSKO	endothelial NOS knockout
IL-6	interleukin-6
IL-10	interleukin-10
NO	nitric oxide
NOS	nitric oxide synthase
ONOO^-	peroxynitrite
RAAS	renin-angiotensin-aldosterone system
RAS	renin-angiotensin system
Na^+	sodium
O_2^-	superoxide
TNF-α	tumor necrosis factor-alpha
TNFR1	TNF receptor type 1
TNFR2	TNF receptor type 2

uAGT

urinary uAGT

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Figure 1.

During 14 days of systemic infusions of angiotensin (Ang) II (80 ng/min) in male Sprague-Dawley rats, mean (SEM) systolic blood pressure (SBP) in mm Hg was measured by tail-cuff method on days -1, 5, 8 and 12 (left panel) and urinary angiotensinogen (uAGT) concentrations in ng AGT/g BW were quantified by ELISA (IBL Ltd, Fujioka, Japan; right panel). Black circle= Normal salt diet (0.3% NaCl, n=9); diamond = high salt diet (8% NaCl, n= 9); dark triangles= Ang II (n=8); light triangles- Ang II + high salt diet (n=9); and squares= Ang II + high salt diet + candesartan (25 mg/L in drinking water, n= 5). * $P < 0.05$ ** $P < 0.001$ compared with normal salt diet; # $P < 0.05$ ## $P < 0.001$ compared with Ang II. Modified from Rands et al, Gender Medicine 9:207–218, 2012.

Figure 2.

Representative (A) and average of glomerular fibrosis (B) and interstitial fibrosis (C) in collagen deposition as visualized by Masson's trichrome stain in male Sprague-Dawley rats maintained on normal salt (NS, 0.3 % NaCl), high salt (HS, 8% NaCl), chronic Ang II infusion (80 ng/min for 14 days) alone, high salt plus Ang II infusion and treatment with an AT1 receptor blocker (ARB, Candesartan 25 mg/L in drinking water) during high salt plus Ang II infusion. * $P < 0.05$ ** $P < 0.001$ compared with normal salt diet. From Lara et al, AJP Renal 302:F85–F94, 2012.

Figure 3.

Blood pressure responses to high salt intake in L-NAME treated in rats. NS - Normal salt diet (0.4% NaCl); HS - High salt diet (4% NaCl); L-NAME - Nitro-L-arginine methyl ester (nitric oxide inhibitor); n=7 in each group; *, $P < 0.05$ vs NS/HS; #, $P < 0.05$ vs LNAME+NS. Kopkan and Majid, Hypertension, 46:1026–1031, 2005.

Figure 4.

Prospective mechanism how chronic Ang II infusion + high salt (HS) intake induces exaggerated hypertension and renal injury via reduced TNFR1 activity. Chronic Ang II infusion down-regulates TNFR1 mRNA and up-regulates TNFR2 mRNA in the kidney. A decrease in ONOO^- formation and thus, IL-10 levels due to reduction in TNFR1 activity minimize the natriuretic effects of TNF- α . This enhanced salt retention leads to a greater hypertensive response. An upregulation of TNFR2 activity enhances the pro-inflammatory response leading to enhanced renal injury during chronic Ang II + HS intake.