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Sympathetic Activation in Chronic Renal Failure

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ABSTRACT

The potential involvement of sympathetic overactivity has been neglected in this population despite accumulating experimental and clinical evidence suggesting a crucial role of sympathetic activation for both progression of renal failure and the high rate of cardiovascular events in patients with chronic kidney disease. The contribution of sympathetic neural mechanisms to the occurrence of cardiac arrhythmias, the development of hypertension, and the progression of heart failure are well established; however, the exact mechanisms contributing to heightened sympathetic tone in patients with chronic kidney disease are unclear. This review analyses potential mechanisms underlying sympathetic activation in chronic kidney disease, the range of adverse consequences associated with this activation, and potential therapeutic implications resulting from this relationship.

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There has been a dramatic increase in patients with chronic and end-stage renal failure worldwide.[1,2] Hypertension is present in the vast majority of these patients[3] and plays a key role in progressive deterioration of renal function and in the exceedingly high rate of cardiovascular events, which represent the primary cause of morbidity and mortality in this patient group.[4,5] Although such a role of hypertension is widely accepted, control of BP in this population group is often poor,[6,7] probably owing to its multifactorial etiology. Hypervolemia and activation of the renin-angiotensin-aldosterone system (RAAS) are important factors contributing to the increase in BP.[8] Thus, in the past, research into therapeutic strategies focused mainly on interventions targeting volume control and the RAAS. Indeed, RAAS inhibition slows progression of renal disease and proteinuria[9]; however, recent investigations identified several additional factors implicated in the pathogenesis of hypertension in renal disease, which are summarized in Figure 1.

Despite striking evidence of increased sympathetic activity in various forms of hypertension, including essential hypertension,[10] obesity-related hypertension,[11] hypertension associated with obstructive sleep apnea,[12] and preeclampsia,[13] involvement of the sympathetic nervous system in the development of hypertension, progression of renal failure, and cardiovascular prognosis in patients with renal disease has been somewhat neglected in the past; however, recent investigations clearly supported the notion that activation of the sympathetic nervous system is commonly associated with chronic renal failure (CRF) and substantially contributes to the poor prognosis in this patient group, as highlighted by the finding that plasma norepinephrine levels are predictive of both survival and incidents of cardiovascular events in patients with ESRD.[14]

SYMPATHETIC ACTIVITY IN PATIENTS WITH CRF

Clinical studies demonstrating increased concentrations of plasma catecholamines and enhanced sensitivity to norepinephrine were the first indicators of sympathetic hyperactivity in patients with CRF.[15,16] These early observations were substantiated by a pronounced hypotensive effect in response to adrenergic inhibition with clonidine[17] or debrisoquine.[18] In 1992, Converse *et al.*[19] first reported that muscle sympathetic nerve activity, as assessed by clinical microneurography, is increased in patients who have ESRD and undergo hemodialysis. Most interesting, bilaterally nephrectomized patients had a sympathetic drive comparable to control subjects without renal failure and also had lower BP.[19] This was the first clinical finding pointing to a role for the diseased kidneys in sympathetic activation. Initially, uremia-related toxins were suggested to be responsible for afferent renal sympathetic nerve traffic[20]; however, increased sympathetic nerve activity is already evident in compensated CRF,[9] and correction of uremia by renal transplantation does not result in normalization of sympathetic

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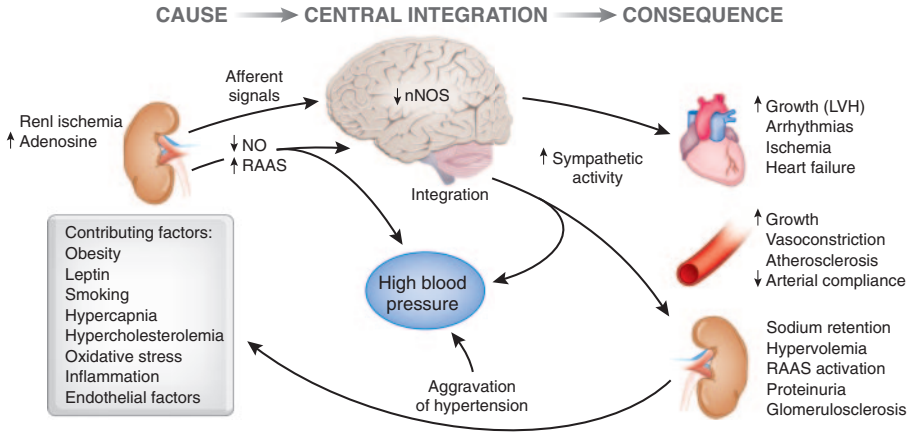

Figure 1. Causes and consequences of sympathetic activation in CRF: Several forms of "renal injury" seem to have the ability to stimulate afferent signaling *via* sensory renal nerves. These afferent signals are centrally integrated and result in sympathetic outflow being directed toward the affected organ in an attempt to restore appropriate perfusion. Sympathetic outflow is also directed toward other organs such as the heart and the vasculature to improve perfusion of the injured kidney(s). Chronically elevated sympathetic outflow not only contributes to high BP in this scenario but also has adverse effects on other organs, particularly the heart, where sympathetic activation has been demonstrated to contribute to left ventricular hypertrophy and arrhythmias. In concert with stimulation of the RAAS and alterations in the L-arginine/NO pathway, aggravation of hypertension is a common feature in patients with CRF. A large number of additional factors may come into play and further aggravate both the increase in BP and target organ damage, thereby contributing to the increased risk for cardiovascular morbidity and mortality in this patient group.

nerve activity.[21] Furthermore, sympathetic activation is present in models of acute renal damage[22] and renal ischemia[23,24] in the absence of uremia, and increased noradrenaline secretion rates are found in patients with nephrotic syndrome[25] and in individuals with hypertension and autosomal dominant polycystic kidney disease despite normal renal function.[26]

These observations suggest that sympathetic activation, rather than being a consequence of uremia, is an early event in the pathophysiology of CRF and that various forms of renal damage activate the sympathetic nervous system *via* afferent signals of sensory renal nerves. A study by Hausberg *et al.*[21] substantiated this notion. By means of microneurography, this group demonstrated that renal transplant recipients with excellent graft function and no signs of uremia still displayed increased sympathetic activity similar to patients on hemodialysis, whereas renal transplant recipients who had undergone bilateral nephrectomy had normalized muscle sympathetic nerve activity not different from that of healthy control subjects.[21] Although these clinical studies provide good evidence for a role of renal afferent nerves in mediating sympathetic activation related to CRF, they do not provide insights into the underlying pathophysiologic mechanisms.

MECHANISMS OF INCREASED SYMPATHETIC ACTIVITY

Renal Injury and Ischemia

The kidneys have a dense afferent sensory and efferent sympathetic innervation and are thereby strategically positioned to be origin as well as target of sympathetic activation.[27] Postganglionic sympathetic fibers innervate all essential renal structures, including the renal vasculature, the tubules, and the juxtaglomerular apparatus. Renal sympathetic activation leads to volume retention through sodium reabsorption and activates the RAAS by stimulation of renin release from the juxtaglomerular apparatus. Conversely, angiotensin II can stimulate sympathetic nerve activity through central mechanisms and by facilitation of adrenergic neurotransmission at the sympathetic nerve terminal. Recent studies suggested that, among others, renal ischemia, nitric oxide (NO), and oxidative stress are also involved in sympathetic activation associated with hypertension and CRF.

In a series of elegant experiments, Campese and Kogosov[28] intensively studied the role of the sympathetic nervous system in the pathogenesis of hypertension related to CRF and contributed immensely to our current knowledge in this area. In a rat model of CRF, the increase in BP associated with five-sixths nephrectomy is prevented by abrogation of afferent sensory signals. The increased turnover rate[29] and secretion of norepinephrine[30] from the posterior hypothalamic nuclei in this rat model is preventable by dorsal rhizotomy, an operation that severs the afferent renal nerve fibers at the entrance to the ganglionic dorsal root.[31] Progression of renal disease in experimentally induced CRF is also obviated by dorsal rhizotomy.[32] These observations suggest that afferent signals from diseased kidneys to central integrative structures in the brain cause increased sympathetic nerve discharge and contribute to hypertension and deterioration of renal function after renal impairment.

Further important data come from an acute renal injury model with normal renal function, thereby ruling out potential influences of renal insufficiency on BP rise and sympathetic activation. In this model of neurogenic hypertension, the increase in BP is caused by injecting 50 μl of 10% phenol into the lower pole of one kidney.[33] Injection of phenol leads to an immediate rise in BP, norepinephrine secretion from the posterior hypothalamus, and renal sympathetic nerve activation, which again can be prevented by renal denervation.[33] Of note, these effects are long lasting and do not occur with infusion of vehicle.[34]

In conjunction with the demonstration of elevated sympathetic activity in experimental renal artery stenosis[35] and

restoration of BP to normal levels after de-afferentation of the clipped kidney in the 2K-1C model of hypertension, it seems that renal ischemia is an important primary event in sympathetic nerve activation. Normalization of BP and muscle sympathetic nerve activity after restoration of renal perfusion in humans with renal artery stenosis supports this notion.[36] The increased muscle sympathetic nerve activity seen in hypertensive patients with autosomal dominant polycystic kidney disease[37] may also be explained by local renal ischemia caused by growing cysts with subsequent stimulation of renal sympathetic afferences.[38] The link between renal ischemia and sympathetic activation is complex and is likely to be initiated by mechano- and chemoreceptor-mediated secretion of adenosine in response to ischemia-induced hypoxia.[39] In both animal and human studies, adenosine infusion stimulated sympathetic outflow.[40,41] Renal ischemia also activates the RAAS, which further contributes to sympathetic stimulation *via* central and peripheral pathways.[42]

Chemoreflex Activation

Recent findings indicated that tonic arterial chemoreceptor activation is involved in sympathetic activation associated with renal impairment. Deactivation of arterial chemoreceptors by inhalation of 100% oxygen substantially decreased muscle sympathetic nerve activity in patients with chronic renal disease, whereas muscle sympathetic nerve activity was unchanged during 100% oxygen inhalation in healthy control subjects.[43] Interestingly, peripheral chemoreceptor hypersensitivity determined cardiovascular prognosis in yet another condition characterized by heightened sympathetic drive, namely congestive heart failure.[44] Parallels may exist with regard to the poor cardiovascular prognosis in patients with renal failure; however, unlike patients with heart failure, patients with chronic renal disease typically have hemoglobin levels in the anemic range, which *per se* can act as a stimulus for chemoreceptor activation.[45] Despite that correction of anemia with recombinant erythropoietin improves cardiovascular prognosis in patients with renal failure,[46] sustained elevation of hemoglobin levels for more than 5 mo by erythropoietin treatment did not reduce muscle sympathetic nerve activity in a small cohort of patients who had ESRD and were on renal replacement therapy.[47] Whether structural alterations of arterial chemoreceptors[48] and/or uremia-related toxins rather than anemia contribute significantly to the tonic arterial chemoreceptor activation observed in renal failure remains unclear.

NO-Related Mechanisms

Another moiety involved in sympathetic activation related to renal disease is NO. Accumulating evidence suggests CRF is a state of reduced NO availability. Several factors may account for impairment of the NO pathway, including decreased availability of the NO precursor L-arginine, decreased renal NO synthase (NOS), accumulation of natural inhibitors of NOS such as ADMA, and the presence of cardiovascular risk factors interfering with NOS such as hypercholesterolemia.[49,50] Indeed, NOS activity within the kidney progressively decreased in a rat model of CRF induced by ablation.[51] A similar decrease in NOS activity was found in hypercholesterolemia-induced renal injury.[52] As a consequence, oxidative stress may occur with subsequent production of superoxide, which is capable of stimulating sympathetic nerve activity.[53] Probably more important is a central effect of NO deficiency in the hypothalamus. Various studies in normotensive and hypertensive rat models demonstrated that infusion of NO into the rostral ventrolateral medulla inhibited sympathetic outflow, whereas infusion of NOS inhibitors stimulated sympathetic outflow.[54] Interestingly, Campese *et al.*[55] demonstrated downregulation of neuronal NOS also mediates sympathetic stimulation induced by intracerebral administration of angiotensin II. Thus, brain NOS is critically involved in transduction pathways that tonically inhibit sympathetic outflow from the brain stem.[56] In rats with CRF, NO also modulates neurogenic control of BP.[33] Importantly, central sympathetic activation in the five-sixths nephrectomy model of CRF is dampened by central synthesis of NO from neuronal NOS.[33]

Reduced Renalase Secretion

Renalase is a novel soluble monoamine oxidase[57] that is involved and may prove to be a key factor in heightened sympathetic tone and increased noradrenaline levels in patients with kidney disease. Renalase is predominantly expressed in glomeruli and proximal tubules but also in cardiomyocytes and skeletal muscle. Detection of renalase in plasma and urine of healthy individuals suggests secretion by renal cells. Interestingly, renalase is readily detectable in venous plasma of healthy individuals but not in the plasma of patients with uremia, a further argument for secretion by the intact kidney. Renalase metabolizes catecholamines such as dopamine and norepinephrine and is specifically inhibited by a renalase antibody. Under basal conditions, blood renalase lacks significant amine oxidase activity[58]; however, physiologic stimuli such as epinephrine infusion to raise mean BP modestly results in a 10-fold increase in renalase activity in rats.[58] Enzyme activation is detectable within 30 s and lasts for at least 60 min. The rapid increase in activity observed with catecholamine infusion does not depend on *de novo* secretion and indicates that renalase circulates in blood in an inactive form (prorenalase). In the renalase pathway, catecholamines acutely activate prorenalase and in a more delayed manner also stimulates its secretion. Because renalase metabolizes circulating catecholamines and has acute and significant hemodynamic effects, it likely participates in the regulation of cardiovascular function.

The Dahl salt-sensitive rat model develops moderately severe hypertension, along with evidence of increased sympathetic activity and elevated circulating catecholamines. When fed an 8% NaCl diet for 3 wk, these animals developed severe renalase deficiency, and plasma and kidney renalase became virtually undetectable.[59] Although GFR was pre-

served, there was evidence of glomerular damage with hypercellularity, mesangial expansion, and focal segmental sclerosis.[59] Whereas renalase circulates in blood in an inactive form as prorenalase, a 2-min surge in circulating catecholamines and/or a transient increase in BP not leads only to a rapid and significant (15- to 25-fold) stimulation in enzymatic activity but also to a delayed three-fold to four-fold increase in blood prorenalase. Abnormalities in the renalase pathway were also operative in rats subjected to surgical removal of five sixths of their kidney mass.[58] Renalase blood levels decreased progressively after five-sixths nephrectomy and were nearly undetectable 4 wk after surgery. In addition, renalase activation induced by epinephrine was markedly reduced in magnitude and duration in five-sixths nephrectomized rats compared with controls.[58] Inasmuch as renalase plays a role in regulating BP, its deficiency in chronic kidney disease would likely weaken these homeostatic mechanisms and contribute to the development and maintenance of hypertension.

Alterations in renalase secretion and/or expression, for example, reduced secretion with progressive impairment of renal function as well as alterations in enzyme activity, may play a causative role in increased plasma catecholamine levels characteristic of CRF. Increasing the endogenous expression of renalase or administering recombinant renalase may offer a new approach to reducing the high morbidity and mortality associated with increased sympathetic drive in patients with renal failure.

ADVERSE CONSEQUENCES OF SYMPATHETIC ACTIVATION

Hyperactivity of the sympathetic nervous system has considerable adverse consequences for the renal and cardiovascular systems. Important progression factors for chronic renal disease include hypertension and proteinuria. Sympathetic activation further aggravates hypertension and proteinuria and contributes to interstitial fibrosis and glomerulosclerosis.[60] Accelerated atherosclerosis, vasoconstriction, and proliferation of smooth muscle cells and adventitial fibroblasts in the vessel wall are further consequences of sympathetic activation related to progression of renal damage.[61,62] Norepinephrine exerts trophic effects on cardiac myocytes, and recent investigations demonstrated that cardiac sympathetic activity is related to left ventricular hypertrophy in patients with essential hypertension.[63] Sympathetic activation and vagal withdrawal are closely linked to cardiac arrhythmias,[64] which, in concert with the aforementioned factors, is partly responsible for the high rate of sudden cardiac death in patients with CRF.[5]

SYMPATHETIC INHIBITION: A VALUABLE THERAPEUTIC STRATEGY IN CRF?

Pharmacotherapy

If sympathetic activation is a fundamental process in CRF, then one would expect inhibition of adrenergic drive to antagonize the progression of renal damage. Indeed, numerous experimental studies revealed β blockade in five-sixths nephrectomy reduced glomerulosclerosis and progression of renal failure.[65] In a study by Brooks *et al.*,[66] carvedilol had similar renoprotective effects when compared with the angiotensin-converting enzyme (ACE) inhibitor captopril. Of note, the well-described renoprotective effects of ACE inhibitors are, at least in part, also mediated by a reduction in sympathetic activity.[9,67] Sympatholytic agents such as imidazoline receptor agonists, which act on I_1-receptors in the brain stem and the kidney,[68,69] reduced glomerulosclerosis and albuminuria in a rat model of subtotal nephrectomy in the absence of any reduction in BP.[70] Studies of humans addressing this issue are scarce. In a small placebo-controlled study by Strojek *et al.*,[71] patients with normotension and type 1 diabetes with microalbuminuria received moxonidine for a period of 3 wk. Although moxonidine treatment did not affect ambulatory BP, there was a significant reduction in the albumin excretion rate at the end of the study period.[71] These findings suggest that sympathetic overactivity is already relevant at the very early stages of CRF. Another study comparing the effects of β blockade with ACE inhibition in 65 patients with CRF found no difference in decline of renal function between the two study arms after 2 yr of treatment,[72] pointing to similar renoprotective effects between these two treatment strategies; however, it needs to be emphasized that each drug was combined with a calcium antagonist, making a direct comparison difficult. Further convincing data for a beneficial effect of sympathetic inhibition in patients with CRF comes from a recent study by Vonend *et al.*[73] In a prospective, randomized, double-blind study, 177 patients with CRF were randomly assigned to receive either the sympatholytic agent moxonidine or the calcium antagonist nitrendipine added to standard therapy with an ACE inhibitor or AT_1 receptor antagonist for a period of 24 wk. The decline in renal function assessed by creatinine clearance and serum creatinine was significantly less pronounced in the moxonidine group, although BP was hardly affected.[73] Further support for a beneficial effect of sympathoinhibition comes from a recent report on patients with ESRD and heart failure, which demonstrated a marked improvement of cardiac function and survival by treatment with carvedilol.[74]

Renal Denervation

On average, patients require medications from three classes to obtain satisfactory management of BP. Unfortunately, this strategy is frequently foiled by adverse effects associated with polypharmacy, patient noncompliance, and the difficulty of attaining adequate therapeutic response to this pharmacologic intervention.

In this setting, the use of direct sympathetic renal nerve interference to modify systemic sympathetic nervous system activity, renal production of renin, and intrarenal hemodynamics could prove to be an invaluable additional therapeutic tool in the treatment of chronic hyper-

tension and the prevention of advanced cardiovascular disorders, such as heart failure and sudden cardiac death, as well as progression of chronic renal disease to ESRD.

In fact, there is a substantial literature that reports on unilateral and/or bilateral renal denervation in various animal models. Surgical renal denervation of the kidney is often used to study the influence of the sympathetic nervous system on renal function. Surgical renal denervation has been shown to result in increased urine output (natriuresis and diuresis) and reduced renin release without adversely affecting other functions of the kidney.[75,76] The maintenance of functionality after renal denervation is also evident in kidney transplantation, where surgical renal denervation is an inherent consequence.

In 1953, Smithwick *et al.*[77] discussed the practice of surgical renal denervation for patients with severe (or malignant) hypertension. He reported on a series of 1266 patients who underwent thoracolumbar splanchnicectomy for "persistent" hypertension and compared them with a concurrent control population of 467 medically treated patients (who although offered surgery did not undergo the procedure). The surgery, which resulted in renal denervation of the kidneys, resulted in significant improvement in survival at 5 yr.[77] With the advent of more effective hypertensive agents, the invasiveness and significant adverse effects associated with this complex surgical procedure rendered it obsolete; however, the clinical benefit of renal denervation demonstrated in this large series of patients was compelling.

Consequently, this relatively old but appealing concept of renal sympathetic denervation has recently regained considerable interest with the availability of a novel catheter-based device designed specifically to target renal sympathetic nerves to functionally denervate the human kidney. Ongoing studies of patients with resistant hypertension and of patients with ESRD will determine the safety, feasibility, efficacy, and durability of such an approach.

CONCLUSIONS

Sympathetic activation plays an important and distinct role in hypertension and target organ damage associated with CRF. The available data suggest that afferent signals from diseased kidneys to integrative structures in the brain result in activation of sympathetic outflow, which has adverse consequences on the cardiovascular and renal system and most likely contributes to the high cardiovascular mortality in patients with CRF. Consequently, inhibition of the sympathetic nervous system is an appealing therapeutic option; however, further clinical trials are warranted to assess adequately the potential benefit of sympathoinhibition in these patients. In view of the available literature, it is plausible that treatment strategies targeting the sympathetic nervous system may become an integral part of the standard therapy in chronic kidney disease to slow progression of renal failure and improve cardiovascular prognosis in this high-risk patient group.

DISCLOSURES

None.

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