

Journal of Clinical and Basic Cardiology

An Independent International Scientific Journal



Journal of Clinical and Basic Cardiology 2001; 4 (3), 179-182

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The Role of Sympathetic Nervous Activity in Chronic Renal Failure

L. C. Rump

Cardiovascular morbidity and mortality are extremely high in patients with chronic renal failure. Preventing progression of chronic renal failure and reducing the cardiovascular risk of uraemic patients are major challenges for nephrologists. In the past the renin-angiotensin system has been the main focus of research and therapy efforts. Today we know that sympathetic overactivity plays an important role for progression and prognosis in chronic renal disease. Afferent signals arising from the damaged kidneys due to the activation of mechanoreceptors and chemoreceptors lead to efferent sympathetic nervous activation. This results in an enhanced release of the sympathetic neurotransmitters noradrenaline, ATP and NPY at important neuro-effector junctions in heart, kidney and blood vessels. All three sympathetic cotransmitter are able to induce vasoconstriction and to stimulate proliferative processes. Recently it was shown in an animal model of chronic renal failure that inhibition of sympathetic nervous activity by moxonidine ameliorates disease progression. This effect was independent from blood pressure reductions and likely due to reduced cotransmitter release. Thus, interference with sympathetic overactivity may provide a new therapeutic avenue to follow in clinical medicine to prolong the interval between chronic and end-stage renal failure. *J Clin Basic Cardiol* 2001; 4: 179–182.

Key words: chronic renal failure, sympathetic, cotransmitters, proliferation, renin-angiotensin system

There is a dramatic increase in patients with end-stage renal failure due to diabetic nephropathy, chronic glomerulonephritis and uncontrolled hypertension all over the world [1]. Unfortunately, chronic renal failure is a progressive disease. It develops to end-stage renal failure within years. It is therefore a major task for nephrologists to prolong this time period or even to prevent the requirement for renal replacement therapy. In this respect most of the research and therapeutic strategies have focused on interventions in the renin-angiotensin system. However, there is now ample evidence to suggest that sympathetic overactivity plays an important role in the setting of hypertensive chronic renal failure [2]. This article summarizes evidence that increased sympathetic overactivity plays a permissive role in renal disease in a dual way. Enhanced release of sympathetic neurotransmitters induces proliferation through receptor-mediated processes and leads to hypertension (Fig. 1). Both effects have strong impact on progression to end-stage renal disease. Moreover, elevated sympathetic tone contributes to the high cardiovascular mortality seen in patients with chronic and terminal renal failure.

Activation of the Sympathetic Nervous System in Chronic Renal Failure

The issue of sympathetic overactivity in renal failure has not attracted much attention because conventional measurements of sympathetic activity particularly plasma noradrenaline levels were not easily interpretable in renal disease, since neuronal uptake of noradrenaline is reduced. It was only with the introduction of microneurographic techniques that Converse et al. [3] were able to document intense sympathetic overactivity in dialysed patients. The striking observation was that in dialysed patients after bilateral nephrectomy the sympathetic nervous system activity was normalized and comparable to control patients. Moreover, after bilateral nephrectomy patients showed a lower blood pressure than patients without nephrectomy. It was obvious that the diseased kidneys were the origin of stimulatory signals, which provoked sympathetic activity and hypertension. Now there is also evidence that sympathetic overactivity is not restricted to patients with end-stage renal disease. Ligtenberg and colleagues [4] showed that patients with impaired renal function have increased sympathetic nervous activity as well. Even after renal transplantation sympathetic nervous activity remains enhanced [5]. What are the mechanisms for sympathetic overactivity in chronic renal failure? Numerous reports suggest that the type of renal damage is not of great importance. Increased sympathetic nervous activity was documented in patients with the nephrotic syndrome [6], with adult polycystic kidney disease (APKD) [7] and even in ischaemic nephropathy [86]. Interestingly, the increase of sympathetic nervous activity in APKD is independent from renal function. Cerasola et al. [7] measured plasma noradrenaline levels as an index of sympathetic activity in patients with essential hypertension and in APKD patients with and without renal failure. APKD patients with or without renal impairment had higher plasma noradrenaline levels than patients with essential hypertension. This clearly supports the notion that the presence of renal damage is more important than renal function in provoking sympathetic overactivity.

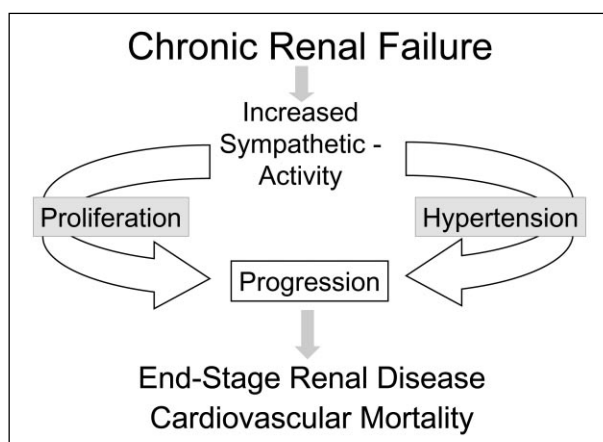


Figure 1. Sympathetic overactivity and disease progression in chronic renal failure

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Thus, a hypothesis is formulated to explain the activation of the sympathetic nervous system in renal disease (Fig. 2). This hypothesis finds strong support in a series of experiments by Campese and colleagues [8–12] using an experimental model of chronic renal failure. Within one week after subtotal nephrectomy rats develop a sustained increase of blood pressure. This progressive rise of blood pressure was abrogated to a considerable extent, when afferent renal nerve signalling was prevented in these animals by cutting the dorsal roots (rhizotomy). This leads to the following conclusion: In diseased kidneys mechanoreceptors and chemoreceptors are activated and stimulate afferent sensory nerves. The afferent signals then travel via the dorsal roots into blood pressure regulating centres of the central nervous system (CNS) to increase efferent sympathetic activity (Fig. 2). Accordingly an increased catecholamine turnover as an index of enhanced central sympathetic activity has been documented in animals with renal damage [12]. However, with respect to disease progression it is also important to assess sympathetic nervous activity within the kidney itself. When renal cortex slices of subtotally nephrectomised rats were electrically stimulated, noradrenaline release was enhanced by about 30 % compared to controls (Fig. 3A). This enhancement is comparable to the increase of renal noradrenaline release observed in an animal model of genetic hypertension [13]. Since an increased central and peripheral sympathetic nerve activity is of such importance in chronic renal failure it is obvious that one should test the effect of sympathetic inhibition in this setting.

Involvement in Renal Progression

While very good experimental and clinical evidence has been provided for a deleterious role of the activation of the renin-angiotensin-system and progression of renal disease, until recently, no such information had been available with respect to the sympathetic nervous system. Again, this is surprising in the light of the evidence reviewed above. Only recently Amann et al. [14] had reasoned that sympathetic overactivity either directly or indirectly (eg via activating the renin-angiotensin system) might have a deleterious effect on progression of renal disease. This hypothesis was subjected to an experimental test in the already mentioned established model of progressive renal damage, ie the subtotally nephrectomised rat. Sympathetic overactivity was reduced by administering

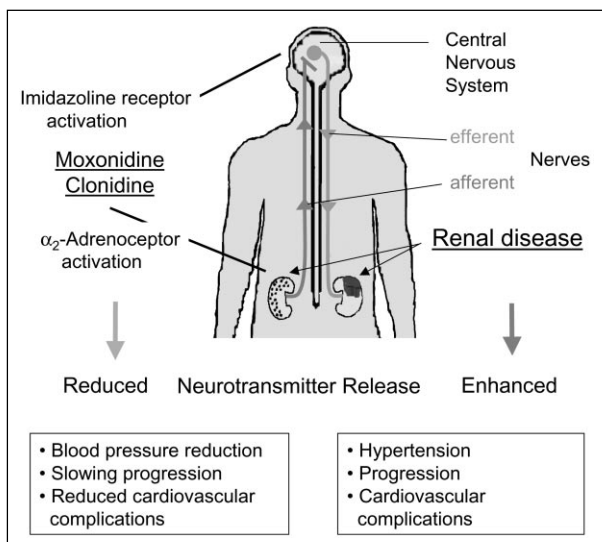


Figure 2. Synopsis of sympathetic activation in chronic renal disease and its inhibition by sympatholytic drugs

moxonidine, a sympatholytic agent [15], which is known to inhibit noradrenaline release within the kidney [16]. It was used at a dose which failed to affect blood pressure as measured by telemetric monitoring. After subtotal nephrectomy nephrosclerosis and albuminuria (Fig. 3B) were seen. Both indices of renal damage were significantly reduced by administration of non-hypertensive doses of moxonidine [16]. This seems not to be a pharmacological effect of moxonidine on the kidney, since comparable results were obtained in a subsequent study using low non-hypertensive doses of beta-blockers [17]. Moreover, another piece of evidence has been provided by the observation that surgical denervation is similarly effective as moxonidine in ameliorating progression in animal models of chronic renal failure [18].

Interaction of the Renin-Angiotensin System and the Sympathetic Nervous System

Since the effect of sympathetic inhibition by moxonidine was independent from blood pressure effects, it is likely that the amount of noradrenaline released at the neuroeffector junctions within the kidney is of paramount importance for progression. Thus, the self-evident question is: Which mechanisms regulate exocytosis of neurotransmitters at the release site within the kidney? The most important control is exerted by the renin-angiotensin system. Angiotensin (Ang) II can be formed locally within the tissue, which then activates presynaptic Ang II receptors of the AT₁ subtype to enhance noradrenaline release (Fig. 4). This presynaptic facilitation of noradrenaline release by locally formed Ang II is relevant for humans as it was discovered in superfused human renal cortex tissue [19]. Ang I, the inactive precursor of Ang II, dose dependently enhanced noradrenaline and this effect of Ang I was totally blocked by the Ang II receptor antagonist losartan, while the angiotensin-converting-enzyme (ACE) inhibitor captopril shifted the dose response curve of Ang I to the right. This clearly suggests that an activated renin-angiotensin system as present in chronic renal failure is able to locally enhance noradrenaline release and may thereby contribute to progression of renal disease (Fig. 4).

As another case in point for interactions between the renin-angiotensin and the sympathetic nervous system Ligtenberg and colleagues [4] showed that the ACE inhibitor enalapril reduced sympathetic overactivity in chronic renal failure. Enalapril (10 mg) given in a short-term study reduced blood pressure and slightly increased sympathetic activity. However, in the long-term study enalapril reduced blood pressure and at the same time decreased sympathetic activity as measured by microneurography. As enalapril does not readily penetrate into the central nervous system one could

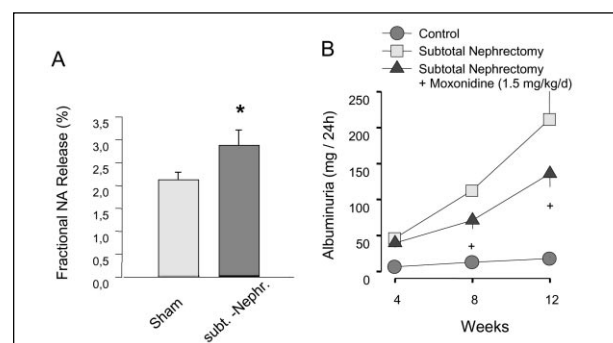


Figure 3. A: Fractional noradrenaline (NA) release from superfused kidney slices of subtotally nephrectomised and control (sham) rats B: Albuminuria in controls, subtotally nephrectomised with and without moxonidine treatment [13]

speculate that a peripheral interaction of the renin-angiotensin system with afferent sensory nerves might be involved. Interestingly, long-term administration of a subpressor dose of Ang II to rats lead to pressor hyperresponsiveness and slow development of hypertension with an upregulation of mRNA expression for calcitonin-gene related peptide in dorsal root ganglia [20]. In this context it is of interest that the renin system is variably activated in different renal diseases. In adult polycystic kidney disease (APKD), overexpression of renin was shown not only in the juxtaglomerular apparatus, but also in arterioles [21] and in tubular epithelial cells [22]. Thus, one can summarize that inhibition of the renin-angiotensin system has various positive influences on sympathetic overactivity in chronic renal failure.

Cotransmitters of the Sympathetic Nervous System

So far, noradrenaline was the only sympathetic neurotransmitter addressed. This gives, however, an incomplete picture. In many sympathetically innervated tissues [23], including the kidney, adenosine triphosphate (ATP) [24, 25] and neuropeptide Y [26] (NPY) are cotransmitters of noradrenaline. All three neurotransmitters released from one sympathetic nerve ending upon stimulation are able to induce vasoconstriction by activating specific membrane bound receptor systems on vascular smooth muscle cells (Fig. 5). One may wonder why nature has invented various neurotransmitters of one sympathetic nerve ending. The answer lies probably in the different time spans of neurotransmitter action. While ATP is a very fast neurotransmitter, acting in milliseconds by opening ion channels via P2-receptors, noradrenaline has an intermediate action time of seconds to minutes. In contrast, NPY is a large peptide with long lasting effects up to hours. Thus, it is of special importance in chronic renal disease characterised by increased sympathetic activity. Accordingly, increased plasma levels of NPY have been reported in diabetic nephropathy [27], after renal transplantation [28] and in chronic and endstage renal disease [29]. While NPY is a renal vasoconstrictor by itself, its major role seems to be to enhance vasoconstrictory signals elicited by α_1 -adrenoceptor and ATP (P2X-receptor) activation [29]. This has been demonstrated in isolated kidney of rats. When the renal nerves were stimulated to mimick sympathetic overactivity there was a progressive rise in pressor responses. This progressively increasing renovascular resistance was entirely due to NPY since it was blocked by a selective NPY (Y1) receptor antagonist [29]. It is well known that neuropeptide Y and ATP release is regulated by central and peripheral presynaptic receptor mechanisms [25].

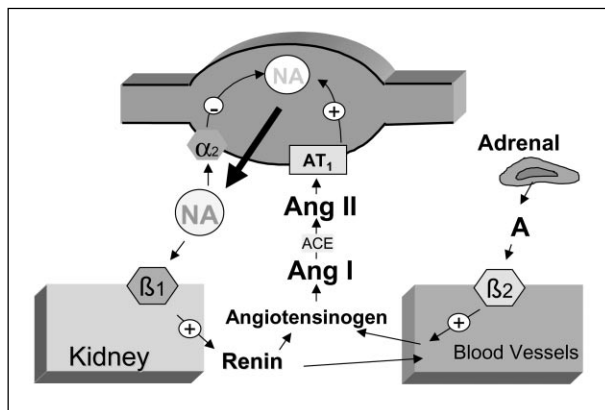


Figure 4. Control of noradrenaline release by local angiotensin II formation

Thus, one can assume that a sympatholytic drug such as moxonidine will not only inhibit noradrenaline but also inhibit NPY and ATP release within the kidney.

For blood pressure regulation and the development of hypertension these short-term vasoconstrictor effects of ATP, NPY and noradrenaline are essential. However, with respect to prevention of organ damage in hypertension and renal failure the long-term effects of sympathetic neurotransmitters are even more important. Stimulation of β -receptor activation induces proliferation of renal cells in culture [31, 32]. Moreover, ATP has been observed to have mitogenic effects in rat renal mesangial cells [33], human smooth muscle [34] and visceral glomerular epithelial cells [35]. It has to be noted that the proliferative effects of ATP, noradrenaline and NPY are concentration dependent and even more than additive [36].

Conclusion and Outlook

In chronic renal failure sympathetic overactivity is an ubiquitous event. It depends on activation of renal sensory receptors sending afferent signals to the central nervous system. The sequence of events is independent from the type of damage or the presence of uraemia. The cotransmitters noradrenaline, NPY and ATP released at neuroeffector junctions of blood vessels and within the kidney are likely to contribute to the development of hypertension and promote progression of renal disease. Experimental and clinical evidence showed that inhibition of sympathetic nervous activity by sympatholytic drugs or ACE-inhibitors lead to inhibition of sensory and efferent sympathetic nerve activity thereby lowering blood pressure and slowing progression. Mitigation of sympathetic overactivity may not only interfere with renal disease progression. Previous studies also documented that sympatholytic drugs are extremely effective in lowering blood pressure in patients with chronic renal failure [4, 37]. Autonomic dysfunction with an imbalance between parasympathetic and sympathetic nervous function is documented in end-stage renal failure and this apparently contributes to the high cardiovascular morbidity and mortality [38, 39]. Thus, one would expect that patients with chronic renal failure would benefit from inhibition of sympathetic overactivity.

Acknowledgement

Work in the author's laboratory was supported by the Deutsche Forschungsgemeinschaft (Ru 401/5-6).

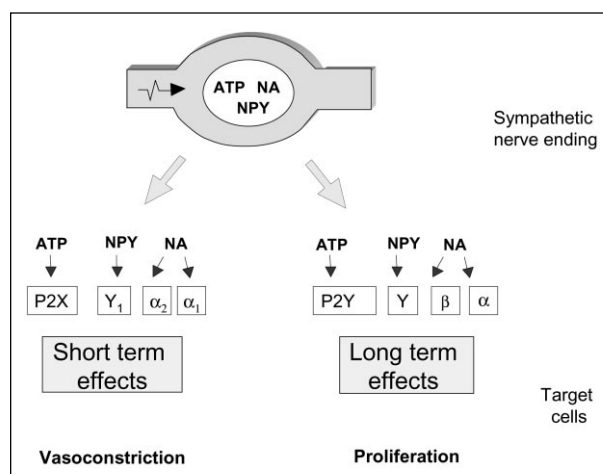


Figure 5. Sympathetic cotransmitter effects in blood vessels and kidney

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