Sympathetic overactivity in renal disease: a window to understand progression and cardiovascular complications of uraemia?

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Introduction

Currently a dramatic increase in patients with end-stage renal failure is seen world-wide [1,2]. Furthermore, cardiovascular morbidity and mortality is exceedingly high in patients with chronic renal failure. Preventing progression of chronic renal failure and reducing cardiovascular complications in uraemia are major challenges to nephrologists. In the following we marshal evidence that sympathetic overactivity, so far a neglected aspect of renal failure, is an important pathomechanism contributing to progression and cardiovascular complications. It is possible that interventions to interfere with sympathetic overactivity will provide new therapeutic approaches.

The sympathetic nervous system in cardiovascular disease and chronic renal failure

In chronic renal disease, the two most important progression factors which are susceptible to intervention are hypertension and proteinuria. In this respect research and therapy in the past focused mainly on interventions concerning the renin-angiotensin-system. Many controlled studies have demonstrated that ACE-inhibitors, compared to placebo, attenuate the rate of progression of chronic renal failure. There is still debate whether the beneficial effect of ACE-inhibition is fully explained by better control of blood pressure [3]. The sympathetic nervous system is known to be important for pathophysiology and prognosis of a variety of cardiovascular diseases including essential hypertension and chronic heart failure. For instance, the degree of sympathetic overactivity is a major predictor of survival in patients with a history of myocardial infarction and determines the risk of arrhythmia and sudden cardiac death [4].

It is therefore surprising that so far nephrologists have neglected the therapeutic potential of modulating sympathetic nervous activity in chronic renal failure. This is even more strange, since there is convincing evidence to show that in chronic renal failure sympathetic overactivity is substantially involved in the development of hypertension, progression of renal failure and cardiovascular prognosis. The available experimental and clinical evidence to suggest such a pathophysiological role of sympathetic overactivity is briefly summarized below.

Renal disease activates the sympathetic system

In 1992 Converse et al. [5] documented that in end-stage renal failure sympathetic tone is increased. They measured sympathetic nerve activity using microneurography of the N. peronaeus and demonstrated an increased sympathetic firing rate even in the intradialytic interval suggesting that this finding was largely volume independent. The most surprising observation was that bilaterally nephrectomized patients had normal sympathetic drive—comparable to that of controls without renal failure. These patients also had lower blood pressure. The authors concluded that the diseased kidneys activate the sympathetic system. This could imply that the sympathetic nervous system plays an important role in renal disease—but what are the underlying mechanisms?

The kidneys have a dense afferent sensory and efferent sympathetic innervation. Therefore, they can be a origin as well as target of overactivity of the sympathetic nervous system (Figure 1). This has been shown convincingly in an animal model of chronic renal failure [6]. Subtotally nephrectomized rats develop a rapid increase of blood pressure within 1 week after renal ablation. In contrast, subtotally nephrectomised rats in which afferent sensory signals have been abrogated by section of the dorsal roots do not develop hypertension. This observation suggests, that afferent signals from the diseased kidneys are transmitted to the vasomotor control center in the brain and thereby increase blood pressure (Figure 1) at least in this model of chronic renal failure.

Is this mechanism of any relevance for patients suffering from chronic renal failure? The answer seems
Fig. 1. Synopsis of pathophysiological events leading to sympathetic overactivity in chronic renal failure. For detailed explanation see text.

to be yes! Ligtenberg and colleagues [7] used the same microneurographic technique and demonstrated that even patients who are not yet on dialysis had increased sympathetic nerve activity as well. What are the mechanisms in the kidney provoking afferent renal nerve traffic? It is conceivable that uraemic toxins act as irritants, but this possibility seems unlikely for various reasons. First, even after correction of uraemia by renal transplantation increased sympathetic nerve activity persists [8]. Second, even acute renal damage [9] and renal ischaemic disease [10,11], not associated with uraemia, lead to sympathetic activation and hypertension. Furthermore, increased noradrenaline secretion rates have been observed in patients with nephrotic syndrome [12] and in hypertensive autosomal dominant polycystic kidney disease [13] despite normal renal function. These results suggest that sympathetic overactivity is an early event in the pathophysiology of chronic renal failure and that renal damage of various aetiologies activates the sympathetic nervous system via afferent signal of sensory renal nerves (Figure 1).

The resulting overactivity at the neuroeffector junction of peripheral organs has important cardiovascular consequences. Enhanced sympathetic neurotransmitter release aggravates hypertension and leads to cardiac hypertrophy. Both events may explain at least in part the high cardiovascular mortality of patients with chronic renal failure, analogous to the deleterious effect of high sympathetic tone after myocardial infarction.
Moreover, in uraemic patients survival after myocardial infarction is extremely poor. Only 20% of diabetic patients with nephropathy will survive the first year after myocardial infarction as compared to 80% of diabetic patients without nephropathy [4]. It is possible that an imbalance between the sympathetic and parasympathetic nervous system aggravates the effect of sympathetic overactivity [14,15]. A lack of vagal influence in patients with diabetic nephropathy has been shown by analysis of heart rate variability [14,15] and by acetylcholine release studies of human cardiac tissue in vitro [16].

Can one slow progression of renal failure by inhibiting sympathetic tone?

As discussed above, sympathetic overactivity is present in chronic renal failure. It could be shown that renal noradrenaline release is enhanced by more than 30% in kidney cortex of subtotally nephrectomized rats [17]. Growth factors (TGFB-β, PDGF, angiotensin II) as well as sympathetic neurotransmitters are able to directly stimulate DNA-synthesis and proliferation of tubular, glomerular epithelial and smooth muscle cells [18–20]. In progression of renal failure renal growth plays an important permissive role. Together with its cotransmitters neuropeptide Y and ATP [21,22] noradrenaline may induce growth by activation of receptor mediated signalling cascades in chronic renal failure. If enhanced renal neurotransmitter release is involved in the development of glomerulosclerosis, then inhibition of sympathetic nerve activity would be expected to reduce structural renal damage and possibly prevent the decline of renal function. This concept was proven by treating subtotal nephrectomized rats with a sympatholytic drug, moxonidine [17,23]. Moxonidine is an imidazoline, which activates presynaptic α2-receptors [24] in the kidney and possibly imidazoline I1-receptors in the rostral ventrolateral medulla [25] to inhibit release of noradrenaline and its cotransmitters at the autoreceptor junction. When subtotally nephrectomized rats were treated with this peripherally and centrally active sympatholytic drug, the development of glomerulosclerosis was significantly attenuated. Moreover, there was less proteinuria than in untreated rats [17]. The antimitogenic and antiproteinuric effect was demonstrated at a dose of moxonidine, which did not reduce blood pressure in these rats [17]. This indicates, that inhibition of sympathetic nerve activity by itself is of structural and functional benefit in chronic failure. There may be other explanations. Moxonidine may interact with imidazoline binding sites present on renal cells [26]. Furthermore, diminished β1-receptor mediated renin release and hence reduced local angiotensin II formation may have contributed. However, the latter possibility seems less likely since renal angiotensin II levels were already lower in subtotally nephrectomized rats than in controls and treatment with moxonidine did not reduce these levels any further [17]. Nevertheless, changes of the angiotensin II concentration in critical compartments are not excluded. The available data are compatible with the notion that enhanced release of noradrenaline and other neurotransmitters is an important pathomechanism of progressive glomerulosclerosis (Figure 1) at least in the ablation model of chronic renal failure. It is interesting to note, that in chronic renal failure patients the ACE inhibitor enalapril was able to reduce central sympathetic overactivity measured by microneurography when given chronically [7]. Since enalapril does not readily penetrate into the central nervous system it is possible, that the release of neurotransmitters within the kidney is modulated by ACE-inhibitors leading to reduce afferent signalling to the vasomotor center in the brain.

Taken together, it appears too early to generally recommend sympatholytic drugs for patients with chronic renal failure. Nevertheless mitigation of sympathetic overactivity does not only slow progression of renal disease; previous studies also documented that sympatholytic drugs are extremely effective in lowering blood pressure in patients with chronic renal failure [7,27]. 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 [14–16]. Thus, one would expect that patients with chronic renal failure will benefit from inhibition of sympathetic overactivity.

References


