Neurogenic Factors in Renal Hypertension

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Introduction

Hypertension is very common in patients with chronic renal failure and contributes to cardiovascular morbidity and mortality. Several mechanisms may contribute to hypertension in these patients, but recently a large body of evidence supports the notion that activation of the sympathetic nervous system (SNS) may play a very important role. In patients with renal disease, the turnover rate of norepinephrine was increased in brain nuclei involved in the noradrenergic control of blood pressure, and dorsal rhizotomy prevented hypertension. Studies in human subjects with chronic renal failure and hypertension have also shown increased peripheral SNS activity measured by micro-eurography in the peroneal nerve and normalization with nephrectomy. In all, these studies indicate that renal injuries may activate renal afferent pathways that connect with integrative brain structures in SNS activity and blood pressure. We have also shown that central SNS activity is modulated by local expression of nitric oxide, which, in turn, is regulated by interleukin-1β.

The Role of Increased Sympathetic Nervous System Activity

Sympathetic nervous stimulation augments cardiac output and increases peripheral resistance. β-Adrenergic stimulation promotes renin release, whereas angiotensin II stimulates the sympathetic nervous system (SNS). A significant body of evidence indicates that hypertension in chronic renal failure may be due to increased activity of the SNS [7–13,14]. Plasma norepinephrine (NE) levels are usually increased in hemodialysis patients [11,12]. Ishii et al. [13] showed that plasma NE levels are also elevated in hypertensive patients with early renal failure compared with healthy subjects and with normotensive patients with the same degree of renal insufficiency. Direct recording of neuronal activity from postganglionic sympathetic fibers in the peroneal nerves of patients on chronic dialysis treatment has shown a greater rate of sympathetic nerve discharge than in control subjects [14]. Moreover, nerve discharge rates in skeletal muscle of hypertensive hemodialysis patients with native kidneys were 2.5 times more frequent than those in hemodialysis patients after bilateral nephrectomy or in healthy subjects [14]. Our studies on 5/6 nephrectomized (CRF) rats have provided the most convincing evidence yet for a role of the SNS in the pathogenesis of hypertension associated with chronic renal failure. The turnover rate of NE, which is a marker ofhypertension undoubtedly contributes to the progression of renal disease [3]. Hypertension is the single most important predictor of coronary artery disease in uremic patients, even more than cigarette smoking or hypertriglyceridemia [4], and treatment of hypertension in these patients is difficult and often inadequate. Understanding the mechanisms of hypertension may help to more adequately treat hypertension in these patients.

The pathogenesis of hypertension in patients with renal disease and in those on maintenance dialysis is multifactorial and may vary depending on the underlying renal disease (Table 2). Activation of the renin-angiotensin-aldosterone system in conjunction with sodium retention and volume expansion have long been recognized as the most important factors [5,6]. However, clinical experience indicates that volume depletion and inhibition of the renin-angiotensin-aldosterone system do not necessarily result in normalization of blood pressure. This suggests that other factors may play a role.

Hypertension is very common in patients with renal disease (Table 1) [1,2]. Although hypertension associated with renal parenchymal disease constitutes approximately 5% of all hypertension cases, it becomes more frequent as patients progress toward end-stage renal disease. Hypertension can occur before an elevation of serum creatinine level or even before a reduction in glomerular filtration rate (GFR) in patients with chronic glomerulonephritis and with polycystic kidney disease. In tubulointerstitial diseases, when salt wasting occurs, hypertension may not appear before end-stage renal disease. Blood pressure increases as renal function deteriorates, until nearly all patients are hypertensive before requiring renal replacement therapy. Approximately 85% of patients with end-stage renal disease have hypertension, which is in part responsible for the high incidence of cardiovascular events and death in these patients. Hypertension undoubtedly contributes to the progression of renal disease [3]. Hypertension is the single most important predictor of coronary artery disease in uremic patients, even more than cigarette smoking or hypertriglyceridemia [4], and treatment of hypertension in these patients is difficult and often inadequate. Understanding the mechanisms of hypertension may help to more adequately treat hypertension in these patients.

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SNS activity, was greater in two areas of the brain involved in the neuroadrenergenic control of blood pressure—posterior hypothalamic (PH) nuclei and the locus coeruleus—of CRF rats compared with control animals. The secretion of NE from the PH was also greater in CRF rats than in control animals [15]. Moreover, microinjection of a neurotoxin, 6-hydroxy-dopamine, in the PH significantly reduced blood pressure in CRF rats [16]. We postulated that the activation of these nuclei in the central nervous system results from impulses generating in the affected kidney and then transmitted to the central nervous system. This possibility is supported by multiple rationales. The kidney is richly innervated with baroreceptors and chemoreceptors [17–19]. Renal afferent nerves are connected directly or indirectly to a number of areas in the central nervous system that contribute to blood pressure regulation [20,21]. Stimulation of renal receptors by adenosine, urea, or electrical impulses evokes reflex increases in SNS activity and blood pressure [22–24].

Renal afferent impulses play an important role in the genesis of hypertension in one-kidney one-clip and two-kidney one-clip Goldblatt hypertension in rats [25], but not in the deoxycorticosterone acetate-salt (DOCA-salt) hypertension in rats, the one-kidney one-wrap Grollman hypertension in rats, or in the spontaneously hypertensive rat (SHR) [26–28].

Renal afferent impulses may also play a role in the pathogenesis of hypertension in rats with experimentally induced CRF. In these animals, bilateral dorsal rhizotomy, at the level T-10 to L-3, prevented the increase in blood pressure and the progression of renal disease [29]. This suggests that increased renal sensory inputs from the injured kidney to the central nervous system may contribute to the development of hypertension and to the progression of renal disease in CRF rats. There is also convincing evidence that the SNS plays an important role in the pathogenesis of hypertension observed in patients with CRF and patients with polycystic kidney disease. Converse et al. [14] found that the rate of SNS discharge directly recorded from postganglionic sympathetic fibers in the peroneal nerves was greater in dialysis patients with their native kidneys than in those after bilateral nephrectomy. Klein et al. [30] have observed increased muscle sympathetic nerve activity in hypertensive patients with polycystic kidney disease regardless of kidney function.

These findings support the notion that increased afferent nervous inputs from kidneys with renal disease may send signals to integrative sympathetic nuclei in the central nervous system and contribute to the pathogenesis of hypertension [18,19,21,23,31–35]. The normalization of blood pressure that follows bilateral nephrectomy may be largely due to elimination of these afferent impulses. Due to extensive amount of scarring, one cannot rule out the possibility of a contribution of renal insufficiency to the genesis of hypertension in the 5/6 nephrectomized rat model. To this end, we have developed a new model of neurogenic hypertension in the rat in which renal injury is not associated with alterations of GFR. Hypertension in this model is caused by injecting 50 µL of 10% phenol in the lower pole of one kidney. This leads to an immediate elevation of NE secretion from the PH and a rise in blood pressure [16]. Renal denervation prevents the rise in NE secretion from the PH and the rise in blood pressure caused by phenol injection. Serum creatinine did not change after the intrarenal administration of phenol, indicating that this model of hypertension does not cause any