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Review Article

Sympathetic Renal Innervation and Resistant Hypertension

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Hypertension in chronic renal disease and renovascular disease is often resistant to therapy. Understanding the pathogenic mechanisms responsible for hypertension in these conditions may lead to improved and more targeted therapeutic interventions. Several factors have been implicated in the pathogenesis of hypertension associated with renal disease and/or renal failure. Although the role of sodium retention, total body volume expansion, and hyperactivity of the renin-angiotensin-aldosterone system (RAAS) are well recognized, increasing evidence suggests that afferent impulses from the injured kidney may increase sympathetic nervous system activity in areas of the brain involved in noradrenergic regulation of blood pressure and contribute to the development and maintenance of hypertension associated with kidney disease. Recognition of this important pathogenic factor suggests that antiadrenergic drugs should be an essential component to the management of hypertension in patients with kidney disease, particularly those who are resistant to other modalities of therapy.

1. Hypertension Resistant to Therapy in Patients with Renovascular Disease and with Chronic Kidney Disease

Although the majority of patients with resistant hypertension have essential hypertension, secondary forms of hypertension are more commonly seen in patients with resistant hypertension. Among the most common causes of secondary hypertension are renovascular hypertension and hypertension secondary to chronic kidney disease (CKD). Renovascular hypertension accounts for 2-3% of patients with hypertension and is often difficult to control. Renovascular disease is present in 30% of patients with grade 3 or 4 hypertensive retinopathy [1]. In one study, 16.7% of clinically selected patients had renovascular hypertension, as documented by blood pressure response to correction of renal artery stenosis or removal of the involved kidney [2].

Hypertension is very prevalent among patients with CKD and it contributes to the high prevalence of cardiovascular disease and progression of kidney disease in these patients (Table 1) [3–6]. Hypertension associated with renal parenchymal disease constitutes approximately 5% of all forms of hypertension, and it becomes more frequent as patient progress toward end-stage renal disease (ESRD). Nearly 85% of ESRD patients have hypertension. Hypertension is the single most important predictor of coronary artery disease in ESRD patients, even more so than other known cardiovascular risk factors [7]. Often, treatment of hypertension in ESRD patients is difficult and inadequate. Understanding the mechanisms of hypertension may help improve therapy in such patient populations.

2. Evidence for Activation of the Sympathetic Nervous System (SNS) in Renovascular Hypertension and Kidney Disease

The renin-angiotensin-aldosterone system (RAAS) plays a key role in blood pressure (BP) elevation in the early phase of renovascular hypertension. Later on, other mechanisms such as sodium retention and activation of the sympathetic nervous system (SNS) may contribute to hypertension [8, 9]. In one study, sixty-five patients with hypertension and renovascular disease demonstrated by angiography underwent measurements of plasma renin activity and

Table 1: Factors implicated in the pathogenesis of hypertension in end-stage renal disease.

Sodium and volume excess
The renin-angiotensin-aldosterone system
The sympathetic nervous system
Endothelium-derived vasodepressor substances
Endothelium-derived vasoconstrictor substances
Erythropoietin use
Divalent ions and parathyroid hormone
Atrial natriuretic peptide
Structural changes in the arteries
Pre-existent essential hypertension
Miscellaneous
Anemia/ Hypoxia
A-V fistula
Vasopressin
Serotonin
Thyroid function
Calcitonin gene-related peptide

angiotensin II in conjunction with estimation of SNS activity by means of radiotracer dilution and intraneural recordings of muscle sympathetic nerve activity (MSNA) [8]. Total body norepinephrine (NE) spillover, an index of overall SNS activity, was increased by 100% and MSNA by 60% in the hypertensive patients compared with healthy subjects, which supports the role of SNS activity in the maintenance of hypertension in these patients [8].

The pathogenesis of hypertension in patients with CKD is multifactorial and may vary depending on the underlying disease (Table 1). Activation of the RAAS, sodium retention, and volume expansion have long been recognized as the most important factors [10, 11]. However, clinical experience indicates that volume depletion and inhibition of the RAAS do not necessarily result in normalization of BP. This suggests that other factors may play a role. Among those, activation of the SNS appears to have a prominent role.

Plasma NE levels are frequently increased in hemodialysis patients [12, 13] and in patients with early CKD and hypertension compared with healthy subjects and with normotensive CKD patients [14]. Direct recording of neuronal activity from postganglionic MSNA in the peroneal nerves of patients on chronic dialysis treatment has shown a greater rate of SNS discharge than in control subjects [15]. Moreover, MSNA in hypertensive hemodialysis patients with native kidneys were 2.5 times more frequent than those in hemodialysis patients after bilateral nephrectomy or in healthy subjects. Our studies on 5/6 nephrectomized rats have provided the most convincing evidence yet for a role of the sympathetic nervous system in the pathogenesis of hypertension associated with CKD [16]. The turnover rate of NE, which is a marker of SNS activity, was greater in two areas of the brain involved in the noradrenergenic control of BP (posterior hypothalamic (PH) nuclei and the locus coeruleus) of CKD rats compared to that of control rats. Moreover, microinjection of a neurotoxin, 6-hydroxydopamine, in the PH significantly reduced BP in CKD rats [17]. The secretion of NE from the PH was also greater in CKD rats than in control animals [16]. We postulated that the activation of these nuclei in the central nervous system results from impulses generated in the affected kidney which are transmitted to the central nervous system.

The kidney is richly innervated with baroreceptors and chemoreceptors [18–20]. Renal afferent nerves are connected directly or indirectly to a number of areas in the central nervous system that contribute to BP regulation [21]. Stimulation of renal receptors by adenosine, urea, or electrical impulses evoke reflex increases in SNS activity and BP [22, 23]. Renal afferent impulses play an important role in the genesis of hypertension in several other experimental models, including the one-kidney one-clip and two-kidney one-clip Goldblatt hypertension in rats, the one-kidney one-wrap Grollman hypertension in the rat, or in the spontaneously hypertensive rat (SHR) [24–27]. Furthermore, bilateral dorsal rhizotomy at the level T-10 to L-3 resulted in almost complete normalization of BP in 5/6 nephrectomized rats [28]. This suggests that increased renal sensory inputs from the injured kidney to the central nervous system may contribute to the development of hypertension in CKD rats.

Kidney damage can raise BP even in the absence of renal insufficiency. The injection of phenol in the lower pole of one kidney leads to an immediate elevation of BP and activation of the central SNS activity, which can be prevented by renal denervation [16, 29]. There is also convincing evidence that the SNS plays an important role in the pathogenesis of hypertension observed in patients with CKD caused by polycystic kidney disease [30].

However, not all types of injury to the kidney lead to an increase in blood pressure. For example, burning, administration of alkali, acids, or methanol caused no effects [29]. This is of relevance, since clinical experience indicates that not all renal injuries in humans are associated with hypertension. For example, in the absence of renal insufficiency, IgA nephropathy is more likely to be associated with hypertension than membranous glomerulonephritis or minimal change disease (Table 2) [31]. These findings support the notion that increased afferent nervous inputs from kidneys with renal diseases may send signals to integrative sympathetic nuclei in the central nervous system and contribute to the pathogenesis of hypertension. The normalization of BP that follows bilateral nephrectomy may be largely due to elimination of these afferent impulses.

Identification of the factor(s) responsible for the intrarenal activation of these afferent pathways, or for the stimulation of sympathetic output from the brain, may lead to a new understanding of the pathophysiology of sympathetic overactivity and hypertension in renal disease and, hopefully, to novel therapies based on specific inhibitors of these activating factors.

Table 2: Prevalence of hypertension secondary to underlying renal parenchymal disease.

Acute renal failure	40%
caused by glomerular-vascular disease	73%–90%
caused by tubulointerstitial disease	10%–15%
Acute poststreptococcal glomerulonephritis	60%–80%
Primary focal and segmental glomerulosclerosis	45% nephrotic 65% non-nephrotic
Minimal-change disease	Rare
Membranous glomerulonephritis	10%
Membranoproliferative glomerulonephritis	30%
Mesangial proliferative glomerulonephritis	33%
IgA nephropathy	25%–36%
Autosomal dominant polycystic kidney disease	50%–80%
Chronic pyelonephritis	33%
Wilms tumor	50%
Adenocarcinoma of the kidney	38%
Reflux nephropathy	20%
Renal tuberculosis	4%
End-stage renal disease	80%–90%
caused by chronic glomerulonephritis	78%
caused by hypertensive nephrosclerosis	100%
caused by diabetic nephropathy	80%

3. Mechanisms of SNS Activation in Kidney Disease

3.1. Angiotensin II. The activation of the SNS in CKD may be related to the effects of circulating angiotensin II (Ang II) released from the kidneys. We have previously shown that intracerebroventricular (ICV) infusion of Ang II raises BP, renal sympathetic nervous system activity (RSNA), and NE secretion from the PH compared to control rats. Pretreatment with losartan, an AT1 receptor blocker, given as an ICV infusion 20 min prior to the infusion of Ang II completely abolished the effects of Ang II on BP, RSNA, and NE secretion from the PH [32].

Antagonists of the renin-angiotensin system, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II AT1 receptor antagonists, inhibit the production of Ang II or its ability to bind to its receptor, resulting in partial inhibition of the sympathetic nervous system in 5/6 nephrectomized rats [33], in the phenol-renal injury model [34], as well as in humans with CKD [14, 30].

3.2. Oxidative Stress. Reactive oxygen species (ROS) are involved in the regulation of SNS activity [35]. Increased oxidative stress in key brain nuclei mediates the activation of the SNS in the phenol-renal injury model of hypertension [36] and in stroke-prone spontaneously hypertensive rats [37]. Increased oxidative stress within the rostral ventral lateral medulla (RVLM) and paraventricular nucleus (PVN) was associated with hypertension and sympathetic overactivity in the 2K 1C Goldblatt model of renovascular hypertension [38], and superoxide signaling in the RVLM was found to play a major role in sustained hypertension and sympathetic nervous system activation in this model.

ROS are also involved in the intracellular signaling mechanisms of Ang II in the brain. [39, 40], in central SNS activation and BP elevation in experimental models of obesity-induced hypertension [41], renovascular hypertension [38], and salt-sensitive hypertension [42]. Moreover, chronic antioxidant therapy improved oxidative stress and BP in a rat model of renovascular hypertension [38]. Despite these experimental data, antioxidants currently have no definitive role in the management of hypertension in CKD patients.

3.3. Hypoxia. Substantial evidence suggests that kidney ischemia may be responsible for sympathetic nervous system activation in renal hypertension. This is supported by studies in conscious rats with acute renal artery stenosis [21]. Restoration of renal perfusion in humans with renovascular hypertension reduces MSNA to control levels and leads to normalization of BP [43]. Regional hypoxia has also been demonstrated in polycystic kidney disease by immunostaining [44].

3.4. Nitric Oxide. Recent studies have provided convincing evidence that nitric oxide synthase (NOS) is present in specific area of the brain involved in the neurogenic control of blood pressure [45, 46]. Studies on experimental animals have also provided evidence that the neuronal isoform of NOS is an important component of the transduction pathways that tonically inhibit sympathetic outflow from the brain stem [47–50]. In normal rats, the basal activity of the central sympathetic nervous system is regulated by local NO production. Evidence from our laboratory also indicates that local production of NO may modulate sympathetic activity in brain nuclei involved in the neurogenic regulation of BP [51]. Reduced availability of NO in these brain nuclei, may result in increased SNS activity and hypertension.

3.5. Cytokines. Complex relationships exist between SNS, nitric oxide, and cytokines [52–55]. One possible mediator for the increase in NO expression is interleukin 1β (IL-1β). Our study has demonstrated for the first time that administration of IL-1β in the lateral ventricle of control and CKD rats lowers BP and NE secretion from the PH [56]. Moreover, we have shown that the modulatory action of IL-1β on SNS activity is mediated by increased expression of neuronal NOS mRNA in the brain. Several lines of evidence strongly support this conclusion. First, the administration of IL-1β in the lateral ventricle of control and CKD rats caused a dose-dependent decrease in BP and NE secretion from the PH and an increase in neuronal NOS mRNA abundance in the brain nuclei. Second, infusion of a specific anti-rat IL-1β antibody in the lateral ventricle led to an elevation in BP and secretion of NE from the PH of control rats, and to a

further rise in BP and NE secretion from the PH of CKD rats. Third, the administration of an anti-rat IL-1β antibody decreases NOS mRNA expression in the several brain nuclei (PH, locus coeruleus, and paraventricular nuclei) of both control and CKD rats. Finally, in CKD rats we observed an increase in the abundance of IL-1β mRNA in all brain nuclei tested. In all, these findings suggest that IL-1β modulates the activity of the SNS via activation of neuronal NOS and partially mitigates the rise in BP and SNS activity in CKD as well as in control rats.

3.6. Treatment of Resistant Hypertension with Antiadrenergic Agents. Given the evidence for the role of the sympathetic nervous system in hypertension, antiadrenergic agents may be considered in the treatment of hypertension, especially in the setting of difficult to control BP. The numerous antihypertensive agents that have become available over the last few decades have overshadowed the potential of centrally acting agents such as clonidine and guanfacine in conventional antihypertensive therapy. However, experimental evidence has demonstrated the ability for these agents to decrease peripheral SNS activity and BP. For example, in salt-sensitive SHR, intrahypothalamic infusion of clonidine abolished the hypertensive effect of dietary salt supplementation and decreased the salt-related increase in plasma NE seen in control rats supplemented with dietary salt [57]. In operative candidates, clonidine administration has been shown to decrease plasma NE levels typically associated with the stress of surgery in comparison to placebo [58]. We were the first to demonstrate that clonidine administration reduced SNS activity and caused natriuresis in salt-sensitive patients with essential hyperitension [59] and in patients with chronic kidney disease [60, 61]. Further studies are needed in the setting of resistant hypertension to determine the efficacy of antiadrenergic agents.

3.7. Catheter-Based Renal Denervation for the Treatment of Resistant Hypertension. New advances in technology recently have brought about the translation of basic science animal models of therapy for resistant hypertension into the forefront of current therapy for resistant hypertension. A recent case report by Schlaich et al. describes a 59-year-old patient on seven antihypertensive medications who underwent renal sympathetic ablation of the afferent renal nerves, which resulted in a BP reduction to 127/81 mg Hg from a baseline blood pressure of 161/107 mm Hg over a twelve-month period [62]. A concomitant reduction of total body norepinephrine spillover and plasma renin was noted.

A multicenter study involving 40 patients with resistant hypertension on an average of four or more antihypertensive medications who underwent ablation of the renal sympathetic afferent and efferent nerves was recently published [63]. An average BP reduction of 27 mm Hg systolic and 17 mm Hg diastolic was achieved, although the authors do clarify that BP medications were adjusted and in some patients, uptitrated after renal nerve ablation. Data on noradrenaline spillover in this study correlated closely with the reduction in BP, and the authors suggest that renal sympathetic nerve ablation is a safe and effective approach to the treatment of resistant hypertension. Long-term followup on patients undergoing renal sympathetic nerve denervation will be needed to determine the duration of benefit and long-term safety of such an approach.

4. Conclusions and Future Directions

SNS activation plays a major role in the pathogenesis of resistant hypertension, particularly when it is due to renal parenchymal or renovascular disease. Mechanisms responsible for increased SNS activity include intrarenal stimulation of renal afferent nerves, direct central effects of angiotensin II, oxidative stress, cytokines, and NO inhibition.

References

[1] B. A. Davis, J. E. Crook, R. E. Vestal, and J. A. Oates, "Prevalence of renovascular hypertension in patients with grade III or IV hypertensive retinopathy," *New England Journal of Medicine*, vol. 301, no. 23, pp. 1273–1276, 1979.

[2] L. P. Svetkey, S. I. Himmelstein, N. R. Dunnick et al., "Prospective analysis of strategies for diagnosing renovascular hypertension," *Hypertension*, vol. 14, no. 3, pp. 247–257, 1989.

[3] J. L. Izzo and V. M. Campese, "Hypertension and renal disease," in *The Kindy*, B. M. Brenner and F. C. Rector's, Eds., Elsevier, New York, NY, USA, 7th edition, 2004.

[4] V. M. Campese, "Hypertension secondary to renal parenchymal disease," in *Clinical Nephroslogy, Dialysis, and Transplantation*, S. B. Malluche, R. M. Hakim, and M. H. Sayegh, Eds., pp. 7–12, Dusti, 1999.

[5] J. H. Galla, "Hypertension in renal parenchymal disease," in *The Kidney*, B. M. Brenner, Ed., pp. 2035–2058, W. B. Saunders, Philadelphia, Pa, USA, 2000.

[6] M. J. Klag, P. K. Whelton, B. L. Randall et al., "Blood pressure and end-stage renal disease in men," *New England Journal of Medicine*, vol. 334, no. 1, pp. 13–18, 1996.

[7] R. N. Foley, P. S. Parfrey, J. D. Harnett, G. M. Kent, D. C. Murray, and P. E. Barre, "Impact of hypertension on cardiomyopathy, morbidity and mortality in end-stage renal disease," *Kidney International*, vol. 49, no. 5, pp. 1379–1385, 1996.

[8] M. Johansson, M. Elam, B. Rundqvist et al., "Increased sympathetic nerve activity in renovascular hypertension," *Circulation*, vol. 99, no. 19, pp. 2537–2542, 1999.

[9] J. M. Lazarus, C. L. Hampers, and J. P. Merrill, "Hypertension in chronic renal failure: treatment with hemodialysis and nephrectomy," *Archives of Internal Medicine*, vol. 133, no. 6, pp. 1059–1066, 1974.

[10] M. A.D.H. Schalekamp, M. P.A. Schalekamp Kuyken, and M. De Moor Fruytier, "Interrelationships between blood pressure, renin, renin substrate and blood volume in terminal renal failure," *Clinical Science and Molecular Medicine*, vol. 45, no. 4, pp. 417–428, 1973.

[11] J. J. Brown, D. L. Davies, J. J. Morton et al., "Mechanism of renal hypertension," *The Lancet*, vol. 1, pp. 1219–1221, 1976.

[12] J. L. Izzo, M. S. Izzo, R. H. Sterns, and R. B. Freeman, "Sympathetic nervous system hyperactivity in maintenance hemodialysis patients," *Transactions—American Society for Artificial Internal Organs*, vol. 28, pp. 604–607, 1982.

[13] J. L. Cuche, J. Prinseau, and F. Selz, "Plasma free, sulfo- and glucuro-conjugated catecholamines in uremic patients," *Kidney International*, vol. 30, no. 4, pp. 566–572, 1986.

[14] G. Ligtenberg, P. J. Blankestijn, P. L. Oey et al., "Reduction of sympathetic hyperactivity by enalapril in patients with chronic renal failure," *New England Journal of Medicine*, vol. 340, no. 17, pp. 1321–1328, 1999.

[15] R. L. Converse, T. N. Jacobsen, R. D. Toto et al., "Sympathetic overactivity in patients with chronic renal failure," *New England Journal of Medicine*, vol. 327, no. 27 I, pp. 1912–1918, 1992.

[16] S. Ye, B. Ozgur, and V. M. Campese, "Renal afferent impulses, the posterior hypothalamus, and hypertension in rats with chronic renal failure," *Kidney International*, vol. 51, no. 3, pp. 722–727, 1997.

[17] R. Bigazzi, E. Kogosov, and V. M. Campese, "Altered norepinephrine turnover in the brain of rats with chronic renal failure," *Journal of the American Society of Nephrology*, vol. 4, no. 11, pp. 1901–1907, 1994.

[18] F. R. Calaresu, P. Kim, H. Nakamura, and A. Sato, "Electrophysiological characteristics of renorenal reflexes in the cat," *Journal of Physiology*, vol. 283, pp. 141–154, 1978.

[19] J. Ciriello and F. R. Calaresu, "Central projections of afferent renal fibers in the rat: an anterograde transport study of horseradish peroxidase," *Journal of the Autonomic Nervous System*, vol. 8, no. 3, pp. 273–285, 1983.

[20] G. DiBona, "The function of the renal nerves," *Reviews of Physiology, Biochemistry & Pharmacology*, vol. 94, pp. 75–181, 1982.

[21] J. E. Faber and M. J. Brody, "Afferent renal nerve-dependent hypertension following acute renal artery stenosis in the conscious rat," *Circulation Research*, vol. 57, no. 5, pp. 676–688, 1985.

[22] M. J. Brody, "Role of the anteroventral third ventricle region in fluid and electrolyte balance, arterial pressure regulation and hypertension," in *Frontiers in Neuroendocrinology*, W. F. Ganong, Ed., pp. 249–292, Raven Press, New York, NY, USA, 1980.

[23] R. E. Katholi, P. L. Whitlow, G. R. Hageman, and W. T. Woods, "Intrarenal adenosine produces hypertension by activating the sympathetic nervous system via the renal nerves in the dog," *Journal of Hypertension*, vol. 2, no. 4, pp. 349–359, 1984.

[24] J. M. Wyss, N. Aboukarsh, and S. Oparil, "Sensory denervation of the kidney attenuates renovascular hypertension in the rat," *American Journal of Physiology*, vol. 250, no. 1, part 2, pp. H82–H86, 1986.

[25] R. E. Katholi, S. R. Winternitz, and S. Oparil, "Decrease in peripheral sympathetic nervous system activity following renal denervation or unclipping in the one-kidney one-clip Goldblatt hypertensive rat," *Journal of Clinical Investigation*, vol. 69, no. 1, pp. 55–62, 1982.

[26] U. C. Kopp, L. A. Olson, and G. F. DiBona, "Renorenal reflex responses to mechano- and chemoreceptor stimulation in the dog and rat," *The American journal of physiology*, vol. 246, no. 1, part 2, pp. F67–F77, 1984.

[27] R. E. Katholi, "Renal nerves and hypertension: an update," *Federation Proceedings*, vol. 44, no. 13, pp. 2846–2850, 1985.

[28] V. M. Campese, E. Kogosov, and M. Koss, "Renal afferent denervation prevents the progression of renal disease in the renal ablation model of chronic renal failure in the rat," *American Journal of Kidney Diseases*, vol. 26, no. 5, pp. 861–865, 1995.

[29] S. Ye, M. Gamburd, P. Mozayeni, M. Koss, and V. M. Campese, "A limited renal injury may cause a permanent form of neurogenic hypertension," *American Journal of Hypertension*, vol. 11, pp. 723–728, 1998.

[30] I. H. H. T. Klein, G. Ligtenberg, P. L. Oey, H. A. Koomans, and P. J. Blankestijn, "Sympathetic activity is increased in polycystic kidney disease and is associated with hypertension," *Journal of the American Society of Nephrology*, vol. 12, no. 11, pp. 2427–2433, 2001.

[31] V. Campese, "Hypertension in dialysis patients," in *Principles and Practice of Dialysis*, W. Henrich, Ed., pp. 209–234, Williams & Wilkins, Baltimore, Md, USA, 1999.

[32] V. M. Campese, S. Ye, and H. Zhong, "Downregulation of neuronal nitric oxide synthase and interleukin-1β mediates angiotensin II-dependent stimulation of sympathetic nerve activity," *Hypertension*, vol. 39, no. 2, part 2, pp. 519–524, 2002.

[33] V. M. Campese, S. Ye, R. H. Truong, and M. Gamburd, "Losartan reduces sympathetic nerve outflow from the brain of rats with chronic renal failure," *Journal of the Renin-Angiotensin-Aldosterone System*, vol. 1, no. 2, pp. 202–208, 2000.

[34] S. Ye, H. Zhong, VU. N. Duong, and V. M. Campese, "Losartan reduces central and peripheral sympathetic nerve activity in a rat model of neurogenic hypertension," *Hypertension*, vol. 39, no. 6, pp. 1101–1106, 2002.

[35] V. M. Campese, S. Ye, H. Zhong, V. Yanamadala, Z. Ye, and J. Chiu, "Reactive oxygen species stimulate central and peripheral sympathetic nervous system activity," *American Journal of Physiology*, vol. 287, no. 2, pp. H695–H703, 2004.

[36] S. Ye, H. Zhong, and V. M. Campese, "Oxidative stress mediates the stimulation of sympathetic nerve activity in the phenol renal injury model of hypertension," *Hypertension*, vol. 48, no. 2, pp. 309–315, 2006.

[37] T. Kishi, Y. Hirooka, Y. Kimura, K. Ito, H. Shimokawa, and A. Takeshita, "Increased reactive oxygen species in rostral ventrolateral medulla contribute to neural mechanisms of hypertension in stroke-prone spontaneously hypertensive rats," *Circulation*, vol. 109, no. 19, pp. 2357–2362, 2004.

[38] E. B. Oliveira-Sales, E. E. Nishi, B. A. Carillo et al., "Oxidative stress in the sympathetic premotor neurons contributes to sympathetic activation in renovascular hypertension," *American Journal of Hypertension*, vol. 22, no. 5, pp. 484–492, 2009.

[39] V. M. Campese, YE. Shaohua, and Z. Huiquin, "Oxidative stress mediates angiotensin II-dependent stimulation of sympathetic nerve activity," *Hypertension*, vol. 46, no. 3, pp. 533–539, 2005.

[40] M. C. Zimmerman, E. Lazartigues, J. A. Lang et al., "Superoxide mediates the actions of angiotensin II in the central nervous system," *Circulation Research*, vol. 91, no. 11, pp. 1038–1045, 2002.

[41] AI. Nagae, M. Fujita, H. Kawarazaki, H. Matsui, K. Ando, and T. Fujita, "Sympathoexcitation by oxidative stress in the brain mediates arterial pressure elevation in obesity-induced hypertension," *Circulation*, vol. 119, no. 7, pp. 978–986, 2009.

[42] M. Fujjita, K. Ando, A. Nagae, and T. Fujita, "Sympathoexcitation by oxidative stress in the brain mediates arterial pressure elevation in salt-sensitive hypertension," *Hypertension*, vol. 50, no. 2, pp. 354–359, 2007.

[43] E. Miyajima, Y. Yamada, Y. Yoshida et al., "Muscle sympathetic nerve activity in renovascular hypertension and primary aldosteronism," *Hypertension*, vol. 17, no. 6, part 2, pp. 1057–1062, 1991.

[44] W. M. Bernhardt, M. S. Wiesener, A. Weidemann et al., "Involvement of hypoxia-inducible transcription factors in polycystic kidney disease," *American Journal of Pathology*, vol. 170, no. 3, pp. 830–842, 2007.

[45] D. S. Bredt, P. M. Hwang, and S. H. Snyder, "Localization of nitric oxide synthase indicating a neural role for nitric oxide," *Nature*, vol. 347, no. 6295, pp. 768–770, 1990.

[46] S. R. Vincent and H. Kimura, "Histochemical mapping of nitric oxide synthase in the rat brain," *Neuroscience*, vol. 46, no. 4, pp. 755–784, 1992.

[47] C. J. Tseng, H. Y. Liu, H. C. Lin, L. P. Ger, C. S. Tung, and M. H. Yen, "Cardiovascular effects of nitric oxide in the brain stem nuclei of rats," *Hypertension*, vol. 27, no. 1, pp. 36–42, 1996.

[48] M. Barinaga, "Is nitric oxide the 'retrograde messenger'?" *Science*, vol. 254, no. 5036, pp. 1296–1297, 1991.

[49] H. Togashi, I. Sakuma, M. Yoshioka et al., "A central nervous system action of nitric oxide in blood pressure regulation," *Journal of Pharmacology and Experimental Therapeutics*, vol. 262, no. 1, pp. 343–347, 1992.

[50] S. Harada, S. Tokunaga, M. Momohara et al., "Inhibition of nitric oxide formation in the nucleus tractus solitarius increases renal sympathetic nerve activity in rabbits," *Circulation Research*, vol. 72, no. 3, pp. 511–516, 1993.

[51] S. Ye, S. Nosrati, and V. M. Campese, "Nitric oxide (NO) modulates the neurogenic control of blood pressure in rats with chronic renal failure (CRF)," *Journal of Clinical Investigation*, vol. 99, no. 3, pp. 540–548, 1997.

[52] A. Terao, M. Oikawa, and M. Saito, "Tissue-specific increase in norepinephrine turnover by central interleukin-1, but not by interleukin-6, in rats," *American Journal of Physiology*, vol. 266, no. 2, part 2, pp. R400–R404, 1994.

[53] S. Liu, I. M. Adcock, R. W. Old, P. J. Barnes, and T. W. Evans, "Lipopolysaccharide treatment in vivo induces widespread tissue expression of inducible nitric oxide synthase mRNA," *Biochemical and Biophysical Research Communications*, vol. 196, no. 3, pp. 1208–1213, 1993.

[54] A. Niijima, T. Hori, S. Aou, and Y. Oomura, "The effects of interleukin-1β on the activity of adrenal, splenic and renal sympathetic nerves in the rat," *Journal of the Autonomic Nervous System*, vol. 36, no. 3, pp. 183–192, 1991.

[55] M. Shibata, H. Parfenova, S. L. Zuckerman, J. M. Seyer, J. M. Krueger, and C. W. Leffler, "Interleukin-1ß peptides induce cerebral pial arteriolar dilation in anesthetized newborn pigs," *American Journal of Physiology*, vol. 270, no. 5, pp. R1044–R1050, 1996.

[56] S. Ye, P. Mozayeni, M. Gamburd, H. Zhong, and V. M. Campese, "Interleukin-1β and neurogenic control of blood pressure in normal rats and rats with chronic renal failure," *American Journal of Physiology*, vol. 279, no. 6, pp. H2786–H2796, 2000.

[57] H. Jin, R. H. Yang, J. M. Wyss, Y. F. Chen, and S. Oparil, "Intrahypothalamic clonidine infusion prevents NaCl-sensitive hypertension," *Hypertension*, vol. 18, no. 2, pp. 224–229, 1991.

[58] T. Dorman, K. Clarkson, B. A. Rosenfeld, C. Shanholtz, P. A. Lipsett, and M. J. Breslow, "Effects of clonidine on prolonged postoperative sympathetic response," *Critical Care Medicine*, vol. 25, no. 7, pp. 1147–1152, 1997.

[59] V. M. Campese, M. Romoff, and N. Telfer, "Role of sympathetic nerve inhibition and body sodium-volume state in the antihypertensive action of clonidine in essential hypertension," *Kidney International*, vol. 18, no. 3, pp. 351–357, 1980.

[60] V. M. Campes, D. Levitan, M. S. Romoff, Y. Saglikes, I. Sajo, and S. G. Massry, "Effect of sympa thetic nerve inhibition on the state of sodium volume balance in hypertensive pa-tients with normal or impaired renal function," *Clinical Science*, vol. 63, pp. 301s–303s, 1982.

[61] V. M. Campese and S. G. Massry, "Effects of acute and chronic treatment with clonidine," *Chest*, vol. 83, no. 2, pp. 380s–383s, 1983.

[62] M. P. Schlaich, P. A. Sobotka, H. Krum, E. Lambert, and M. D. Esler, "Renal sympathetic-nerve ablation for uncontrolled hypertension," *New England Journal of Medicine*, vol. 361, no. 9, pp. 932–934, 2009.

[63] H. Krum, M. Schlaich, R. Whitbourn et al., "Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study," *The Lancet*, vol. 373, no. 9671, pp. 1275–1281, 2009.