Renal deafferentation: target for treatment of cardiovascular diseases involving sympathetic overactivity

John Ciriello
Department of Physiology and Pharmacology, Schulich School of Medicine and Dentistry, University of Western Ontario, London, Ontario, Canada

HIGH BLOOD PRESSURE associated with sympathetic overactivity is often associated with cardiovascular related mortality and/or morbidity. A therapeutic approach now considered for the treatment of resistant forms of the disease involves the selective denervation of the kidney (16, 51, 52, 57). Kidney function is known to be of primary importance in the long-term regulation and maintenance of arterial pressure (24). However, it is well documented that the autonomic nervous system also plays a critical role in the control of arterial pressure and in the pathogenesis of hypertension (1, 2, 36, 41), especially as it is able to modify renal function (19, 29). The autonomic nervous system and kidney are linked through renal nerves that are composed of both efferent sympathetic and afferent sensory fibers (19, 29). Although considerable evidence exists suggesting an overexcitation of the sympathetic nervous system in conjunction with neurohormonal factors in the pathogenesis of resistant forms of hypertension, these data do not unequivocally demonstrate whether the effects on arterial pressure following renal denervation are mediated by efferent renal sympathetic nerves or afferent sensory nerves originating in the kidney. This is especially true as afferent signals from the kidney alter the activity of preautonomic neurons in central sites involved in controlling arterial pressure and sympathetic nervous system activity (15), as clearly demonstrated in the article by Xu et al. (50), published in this issue of the American Journal of Physiology-Heart and Circulatory Physiology.

Activation of efferent renal sympathetic nerves has been shown to increase renal vascular resistance, renin release, and water reabsorption and decrease sodium ion excretion (19, 29). Thus, as expected, denervation of efferent renal sympathetic nerves to the kidney results in reduced renin release and an increase in sodium excretion, but with little change in renal blood flow, perfusion pressure, and glomerular filtration rate (29). On the other hand, sensory nerves originating within the kidney carry information from renal chemoreceptors that detect changes in the composition of the interstitial fluid environment and renal mechanoreceptors which monitor hydrostatic pressure changes within the kidney (35, 39, 40, 47).

Renal chemoreceptors have been classified as R1 and R2 by Recordati et al. (39, 40). R1 respond to renal ischemia, whereas R2 chemoreceptors are activated by both renal ischemia and changes in the ionic composition of the renal interstitium. R2 chemoreceptors do not respond to changes in arterial pressure but respond in an inverse relationship with a decrease in renal perfusion pressure. This latter group of chemoreceptors has also been suggested to function as renal osmoreceptors (39, 40). Furthermore, these renal chemoreceptors have been shown to be activated following intrarenal infusions of substance-P, bradykinin, and adenosine (27, 29-34). In addition, capsaicin, through activation of the nonselective cation channel transient receptor potential vanilloid 1 (32, 49), has been shown to activate renal chemoreceptors. Prostaglandin production has also been reported to activate these renal chemoreceptors, and inhibition of prostaglandin synthesis prevents the selective activation of R2 chemoreceptors (30). Finally, there are data suggesting that renal chemoreceptors also respond to cycloporine A through a calcineurin-dependent process (56). Calcineurin inhibitors have been shown to enhance sympathetic neurotransmission by stimulating renal sensory nerve endings that contain synapsin-positive microvesicles (55). Renal mechanoreceptors monitor hydrostatic pressure changes in the kidney (35, 47) and at least two types of renal mechanoreceptors appear to exist: those with no spontaneous activity and those with tonic activity. However, both types of mechanoreceptors respond to increases in renal artery, venous, and/or pelvic pressure (35, 47).

These renal receptors through their central connections are able to influence cardiovascular function not only by altering the release of vasopressin from the neurohypophysis (6, 11, 17, 18, 44) but also by increasing sympathetic nerve discharge to different vascular beds (7, 48) and the adrenal medulla (36) and through renorenal reflexes to alter kidney function (37, 38). Thus it is now accepted that afferent renal nerves and the central structures that integrate afferent renal nerve information may play an important role in the development and maintenance of hypertension (14, 15, 20, 22, 25, 28). Ciriello and colleagues were the first to identify central sites of integration of afferent renal nerve information (4, 7, 8, 10–14, 17, 18, 43, 45, 46). Specifically related to the recent article by Xu et al. (50) are the earlier findings that activation of afferent renal nerves in both the rat (11, 17, 18, 43, 45, 46) and cat (7, 8) evoked neuronal responses in the hypothalamic paraventricular nucleus (PVN). In earlier studies the output of vasopressin and oxytocin neurons to the posterior pituitary was primarily investigated (7, 11, 17, 18), as it had been reported that activation of afferent renal nerves resulted in the release of vasopressin into the circulation (6, 44). A study was also completed showing that direct PVN-spinal pathways that terminated within the intermediolateral cell column received afferent renal nerve inputs, suggesting a possible pathway by which afferent renal nerves could activate preganglionic neurons and arterial pressure (8). The study by Xu et al. (50) extends this line of investigation into central structures and pathways involved in integrating afferent renal nerve information and in the control of arterial pressure by examining the responses of PVN neurons that project directly to sympathoexcitatory sites within the rostral ventrolateral medulla (RVLM) to activation of afferent...
renal nerves. The RVLM is well known for its critical role in the function of the reflex regulation and maintenance of vaso- 
motor tone (23). This well-designed and performed study by 
the authors has shown that spontaneously active neurons within 
the PVN antidromically activated by stimulation of RVLM 
pressor sites increased their discharge rate through the activation 
of N-methyl-D-aspartate receptors during afferent renal 
nerve stimulation. The authors interpreted their data to suggest 
that renal mechanoreceptor and/or chemoreceptor afferent 
information is relayed to PVN preautonomic neurons for inte-
gration before activating sympathetic premotor neurons in the 
RVLM. Additionally, these PVN preautonomic neurons were 
found to be inhibited during the reflex activation of arterial 
baroreceptors. This observation further supports the conclusion 
that the PVN preautonomic neurons likely functioned as com-
ponents of descending sympathoexcitatory pathways. Further-
more, the authors demonstrated that these PVN neurons re-
sponding to afferent renal nerves were also activated by cardiac 
receptors. The PVN has been shown to be an integral part of 
central pathways relaying cardiac receptor afferent information 
and activating sympathoexcitatory reflexes (42, 53, 54). Thus it 
is not unreasonable to suggest that afferent renal nerve inputs 
to PVN preautonomic sympathoexcitatory neurons projecting 
to RVLM may in fact exacerbate sympathetic cardiac reflexes 
elicted during chronic heart failure (9, 21, 53). The interaction 
of these functionally similar inputs within PVN with regard to 
driving sympathetic output may also contribute to a sustained 
hypertension.

In the study, the authors chose specifically to systematically 
study spontaneously active neurons within the PVN before 
determining whether they were RVLM projecting neurons. A 
population of tonically active neurons was also found within 
PVN that responded to afferent renal nerve activation but were 
not antidromically activated, suggesting that these were neu-
rons likely projecting to other central sites, including the posterior 
pituitary (11). However, the authors could have also 
entertained the possibility that not all neurons projecting to the 
RVLM were spontaneously active and that these neurons may 
have formed a larger population of PVN-RVLM projecting 
neurons. Several earlier studies investigating renal afferent 
inputs to the hypothalamus showed a number of silent neurons 
were activated by stimulation of afferent renal nerves (4, 12). 
Interestingly, not all renal receptors are tonically active (35, 39, 
40, 47), suggesting the possibility that a relationship may exist 
between the activity of PVN neurons and the activity of renal 
receptors. The authors may wish to do future studies to explore 
the possibility that the afferent renal input contributed to the 
tonic activity of PVN neurons and that this input was renal 
receptor specific. Also of interest is the finding that all PVN-
RVLM neurons studied were excited by afferent renal nerve 
inputs, which could be interpreted to suggest that information 
from renal chemoreceptors, rather than mechanoreceptors, was 
the primary input to these neurons. Additionally, examining the 
interaction between the inputs of a specific renal receptor type 
and with a specific cardiac receptor type on the output of the 
PVN-RVLM neurons would be of considerable interest as both 
renal and cardiac afferents relay through PVN, and their 
combined effects may be to exacerbate the sympathetic drive 
during conditions of renal or cardiac stress as observed in heart 
failure conditions or hypertension.

A number of studies have examined the role of renal nerves 
on arterial pressure and on the maintenance of hypertension in 
experimental models (15) and more recently in humans (3, 15, 
16, 26, 51, 52, 57). In recent clinical studies, either surgical 
sympathectomy involving renal nerves or endovascular radio-
frequency ablation of renal nerves has been shown to cause 
significant long-lasting reductions in arterial pressure and heart 
rate (16, 51, 52, 57). Thus it is likely that renal nerve transec-
tion could become a commonly used procedure to treat resis-
tant forms of hypertension and other chronic diseases associ-
ated with enhanced sympathetic activation (3, 51, 52, 57).

However, data supporting the long-term safety and efficacy of 
renal denervation are limited, and thus a considerable effort 
should be placed in following patients who have had this 
procedure. Additionally, an emphasis should be placed on 
research to identify the patient population that would benefit 
most from this procedure. Furthermore, one of the primary 
unanswered questions that remain is whether the effects on 
sympathetic nerve activity and arterial pressure are due to 
the removal of efferent renal sympathetic fibers or to afferent 
fibers. Although the reduction in arterial pressure following 
renal denervation could be accounted for by the elimination of 
efferent sympathetic nerves to the kidney, it may be in fact that 
both afferent and efferent renal nerves are contributing to the 
overall effect. This possibility is supported by the observation 
that an increase in sympathetic activity alters afferent renal 
nerve activity by the release of norepinephrine, which acts at 
\(\alpha_1\) - and \(\alpha_2\) -adrenergic receptors on afferent renal fibers (30).

These findings suggest that efferent sympathetic nerves can 
alter the sensitivity of renal chemoreceptors and that activation 
of these afferent renal receptors elicits increases in sympathetic 
activity (29). Thus the reflex changes in efferent sympathetic 
activity evoke similar changes in afferent renal nerve activity 
(30), which in turn activates efferent sympathetic activity. 
Thus, in a pathophysiologic condition where there is an 
initial increase in sympathetic activity to the kidney, the 
elevated sympathetic activity activates a positive feedback 
system through afferent renal nerves that may be the sustaining 
factor in resistant forms of hypertension. This reciprocal rela-
tionship between kidney receptors and central structures that 
drive sympathetic activity such as the PVN and RVLM shown 
in the study by Xu et al. (50) may play a critical role in 
cardiovascular disease associated with increased sympathetic 
activity such as hypertension, although the mechanisms still 
remain to be elucidated. Therefore, a greater understanding of 
the neuronal circuitry and the neurotransmitters involved me-
diating afferent renal information, and its putative interaction 
with other cardiovascular reflexes may be of considerable 
significance in developing therapeutic strategies for alleviating 
the long-term cardiovascular consequences associated with 
hypertension and other cardiovascular disease such as heart 
failure.

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