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# Integration of renal sensory afferents at the level of the paraventricular nucleus dictating sympathetic outflow

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## Abstract

The sympathetic nervous system has been identified as a major contributor to the pathophysiology of chronic heart failure (CHF) and other diseases such as hypertension and diabetes, both in experimental animal models and patients. The kidneys have a dense afferent sensory innervation positioning it to be the origin of multimodal input to the central nervous system. Afferent renal nerve (ARN) signals are centrally integrated, and their activation results in a general increase in sympathetic tone, which is directed toward the kidneys as well as other peripheral organs innervated by the sympathetic nerves. In the central nervous system, stimulation of ARN increases the neuronal discharge frequency and neuronal activity in the paraventricular nucleus (PVN) of the hypothalamus. The activity of the neurons in the PVN is attenuated during iontophoretic application of glutamate receptor blocker, AP5. An enhanced afferent renal input to the PVN may be critically involved in dictating sympathoexcitation in CHF. Furthermore, renal denervation abrogates the enhanced neuronal activity within the PVN in rats with CHF, thereby possibly contributing to the reduction in sympathetic tone. Renal denervation also restores the decreased endogenous levels of neuronal nitric oxide synthase (nNOS) in the PVN of rats with CHF. Overall, these data demonstrate that sensory information originating in the kidney excites pre-autonomic sympathetic neurons within the PVN and this “renal-PVN afferent pathway” may contribute to elevated sympathetic nerve activity in hyper-sympathetic disease conditions such as CHF and hypertension.

### Keywords

sympathetic activity; cardiovascular; paraventricular nucleus; afferent renal nerves

## Introduction

The paraventricular nucleus (PVN) of the hypothalamus is an important site that integrates and responds to a variety of neural and humoral signals regulating sympathetic drive and

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extracellular fluid volume status (Coote, 2005; Patel, 2000). The kidneys have a dense afferent sensory and efferent sympathetic innervation and are positioned to be the origin as well as target of sympathetic nervous system activation (Booth et al., 2015; Johns et al., 2011; Kopp, 2015). It has been demonstrated that the discharge frequency of putative vasopressinergic magnocellular neurosecretory neurons (MNCs) in the PVN are increased during stimulation of afferent renal nerve (ARN) as well as during the activation of specific renal receptors (Ciriello, 1998). ARN stimulation has been shown to increase neurons containing Fos-like immunoreactivity positive neurons in the PVN, indicating that the PVN neurons are activated by ARN stimulation (Solano-Flores et al., 1997).

The PVN includes neuroendocrine-related functional neurons that project to the median eminence, posterior pituitary and pre-autonomic neurons that send long descending projections to the brain stem and spinal cord regions that are important in dictating autonomic outflow (Armstrong et al., 1980; Swanson et al., 1980a). There are a number of PVN neurons that project to the rostral ventrolateral medulla (RVLM), which have been shown to correlate with activation of renal sympathetic nerve activity (RSNA) (Chen et al., 2010). Recently, we have shown that ARN stimulation activates RVLM projecting PVN neurons (Xu et al., 2015). Stimulation of ARN also increases sympathetic activity and arterial pressure (Patel et al., 1986; Patel et al., 2016; Xu et al., 2015). Afferent information from the kidney may play an important role in the coordination of neural and humeral activation, concerned with body fluid balance and the regulation of arterial blood pressure in normal and disease conditions such as chronic heart failure (CHF) and hypertension (Caverson et al., 1988; Ciriello et al., 1987; Day et al., 1987; Kopp, 2015; Patel et al., 2016; Solano-Flores et al., 1997).

This review highlights and describes the studies that examine activation of renal sensory afferent contribution to the sympathetic outflow, particularly the activation of the PVN by ARN stimulation, ultimately leading to the activation of sympathetic nervous system. Furthermore, an enhanced afferent renal input to the PVN is shown to be intimately involved in processes leading to sympathoexcitation in the CHF condition (Patel et al., 2016; Xu et al., 2012 ).

## PVN and Sympathetic Outflow

Of the five major central nervous system sites that directly control sympathetic outflow (Strack et al., 1989), PVN is the most rostral and only site located in the hypothalamus. This fact, combined with the known role for PVN in fluid balance and vasopressin release, makes the PVN a prime candidate site within the forebrain, responsible for mediating sympathetic outflow. The role of PVN in cardiovascular reflexes is twofold: 1) the MNCs are responsible for the humoral component of the regulation of fluid balance (Swanson et al., 1980b); while 2) the parvocellular neurons of PVN (pPVN) are involved in the mediation of the neural component of cardiovascular reflexes by influencing RSNA (Haselton et al., 1994; Lovick et al., 1993; Patel et al., 1988). Specifically, we have demonstrated that lesion the pPVN with kainic acid altered the renal sympathoinhibition produced in response to acute volume expansion (Haselton et al., 1994). These observations suggest that the PVN plays an essential role in the mediation of RSNA under both resting and reflex conditions (Haselton

et al., 1994; Lovick et al., 1993; Patel et al., 1988). Stimulation of PVN has been shown to elicit an increased discharge from several sympathetic nerves, including: renal (Kannan et al., 1989), adrenal (Katafuchi et al., 1988), and splanchnic (Lu et al., 1991). Stimulation of PVN elevates serum norepinephrine via a neural mechanism (Martin et al., 1992). Activation of the PVN is thought to produce an increase in overall sympathetic outflow. On the contrary, a few studies have also shown sympathoinhibition originating from the PVN (Coote, 2005; Zhang et al., 1997).

In the rat CHF model, induced by coronary ligation, norepinephrine is increased in several forebrain and brain stem cell groups, including the PVN (Sole et al., 1982). In the same model of CHF, we have observed a significantly increased hexokinase activity [an index of neuronal activity (Krukoff, 1993)] in the pPVN and MNCs portions of the PVN of rats with CHF compared to sham operated controls (Patel et al., 1993). We also have shown that there is increased FosB [fos family gene, indicating chronic neuronal activation (Dampney et al., 2003)] staining in the PVN of rats with CHF (Zheng et al., 2012), consistent with increased Fra-like (fos family gene, indicating chronic neuronal activation also) staining reported by the others (Kang et al., 2006; Vahid-Ansari et al., 1998). Further, by direct electrophysiological recording, we have demonstrated an increased firing of RVLM projecting PVN neurons in rats with CHF (Xu et al., 2012 ; Zhang et al., 2002b). RVLM projecting PVN neurons are more active under basal conditions and are endogenously driven by an enhanced glutamatergic mechanism in the CHF condition (Li et al., 2003). The responses of RVLM projecting PVN neurons to baroreflex challenge are attenuated, whereas the responses to hypertonic osmotic stimulation are enhanced in rats with CHF (Xu et al., 2012 ). So far, there is mounting evidence to support the idea that the increase in activation of the PVN neurons that drives the sympathoexcitation in CHF is a result of the imbalance between the inhibitory, nitric oxide (NO) and GABA mechanisms, and the excitatory glutamatergic and angiotensinergic mechanisms (Li et al., 2003; Patel et al., 2012; Zhang et al., 2001; Zhang et al., 2002a; Zheng et al., 2009). In addition, it has been reported that increased circulating cytokines cause the induction of cyclooxygenase-2 expression in the microvasculature of the PVN, resulting in enhanced proinflammatory cytokines in the PVN, resulting in sympathoexcitation in CHF (Kang et al., 2011; Kang et al., 2009; Kang et al., 2006; Yu et al., 2013; Yu et al., 2016).

## Renal Sensory Receptor Afferents

The kidneys are distinctly innervated with sensory afferents (Kopp, 2015). The majority of the sensory nerves are located in the renal pelvic area with the greatest density in the pelvic wall (Marfurt et al., 1991). Afferent signals from the kidneys are transmitted by 2 modalities of receptors, mechanoreceptors and chemoreceptors (Recordati et al., 1978). These receptors transmit information to the central nervous system via the ARN.

Mechanoreceptors are found within the renal parenchyma and in the wall of the renal pelvis (Niijima, 1975). These receptors respond to increases in intra-renal pressure and are stimulated by renal vein occlusion/compression and physical compression of the hilus of the kidney (Kostreva et al., 1981; Ueda et al., 1967). Stimulation of renal mechanoreceptors leads to an increase in ipsilateral renal afferent activity and a decrease in ipsilateral and

contralateral efferent RSNA (Kopp et al., 1985; Ueda et al., 1967). The main responses to renal mechanoreceptor activation are abolished by spinal cord transection at the level of T6, indicating that the mechanoreceptor reno-renal reflex is dependent on central integration (Kopp et al., 1985).

The second class of renal sensory receptors is the chemoreceptors: R1 and R2 receptors, which are activated by the chemical environment of intra-renal tissue and renal pelvis (Recordati et al., 1978). R1 receptors are activated by renal ischemia, arterial and venous occlusion and systemic asphyxia (Recordati et al., 1978). R1 receptor activation is associated with an increase in efferent RSNA, which persists after spinal cord transection at the level of T6 (Recordati et al., 1982). R2 receptors are activated by backflow of concentrated urine, hypertonic NaCl and KCl (Recordati et al., 1978). Activation of R2 receptors results in an increase in efferent RSNA and is invariably accompanied by small increases in blood pressure and heart rate (Recordati et al., 1982). The R2 receptor response remains after spinal cord transection at the level of T6 and is enhanced by transection at the level of C3, indicating that the chemoreceptor reflex integrated at a spinal level (Recordati et al., 1982).

There are numerous studies suggesting a supra-spinal integration of the afferent renal signals (Ciriello et al., 1983; Solano-Flores et al., 1997). Within the spinal cord, the ARN project to the ipsilateral dorsal horn in laminae I, III-V (Ciriello et al., 1983), where they synapse with interneurons projecting to various sites within the central nervous system including the PVN, associated with cardiovascular regulation and sympathetic outflow. There is also evidence for a monosynaptic projection of the ARN to areas within the brain stem directly (Wyss et al., 1984).

## Activation of the PVN by Afferent Renal Nerve Stimulation

A number of studies utilizing anterograde tract tracing of fluorescent dyes (Wyss et al., 1984), horseradish peroxidase transport (Ciriello et al., 1983; Kuo et al., 1983), or pseudorabies virus injected into the kidneys (Weiss et al., 2001) as well as electrophysiological evidence (Calaresu et al., 1981b; Ciriello et al., 1980; Xu et al., 2015) indicate that the renal afferent information is transmitted to various sites within the spinal cord and brain stem. ARN relay information to the central nervous system associated with cardiovascular regulation, including nucleus tractus solitaries (NTS), RVLM, preoptic area, subfornical organ (SFO), lateral hypothalamus and the PVN. In the hypothalamus, stimulation of ARN affected the activity of 197 of the 407 units, the majority of the units were excited but 8% were found to be inhibited (Calaresu et al., 1981b). Renal afferent nerve signals can elicit both inhibitory reno-renal reflexes as well as long looped supra-medullary reno-excitatory responses (Ciriello et al., 1987; Saeki et al., 1988).

Renal afferent nerve fibers are mainly unmyelinated (primarily C-fibers) with a small population of faster conducting, A-delta, myelinated fibers (Knuepfer et al., 1987; Simon et al., 1984). We have found that the mean onset latency of response in RVLM projecting PVN neurons to ARN stimulation was comparable to those reported in cats (Caverson et al., 1983) and rats (Day et al., 1985) with a fairly wide range of values (Xu et al., 2015). The onset latency of RVLM projecting PVN neurons to low frequency ARN stimulation was longer compared with high frequency ARN stimulation. One possible explanation for these

observations is the differences in conduction velocities of the different afferent fibers. The renal afferent A fibers are elicited by stimulation with trains of pulses at low voltage and high frequency, and the renal afferent C fibers are stimulated by trains of pulses at high voltage and low frequency (Calaresu et al., 1980; Felder, 1986). It is thought that mechanoreceptor information is carried by the myelinated large fibers and the chemoreceptor information is transmitted by the unmyelinated small fibers (Calaresu et al., 1980; Ciriello, 1998; Simon et al., 1984).

The precise pathway by which ARN information is relayed to the PVN neurons is not fully clear. A possible pathway may involve the NTS and the RVLM, since neurons in these areas alter firing rates in response to ARN stimulation (Calaresu et al., 1981a; Felder, 1986). By stimulating myelinated renal afferent fibers, investigators have shown that there are direct projections from the kidney to the most medial segment of the fasciculatus gracilis and the caudal half of the NTS (Simon et al., 1984). The fluorescent tracer studies examining the connection between the kidneys and posterior medulla show that some of the renal afferents directly project to the medulla but not to higher regions of the brain. Approximately 8% of the total amount of renal afferents are typically shown to have direct projections to the medulla (Wyss et al., 1984).

In cats, electrical stimulation of ARN affects activity of medullary neurons in the lateral tegmental field, paramedical reticular nucleus and dorsal vagal complex, and hypothalamic neurons in the lateral preoptic area, lateral hypothalamic area, and the PVN (Calaresu et al., 1981b). These data provide the electrophysiological evidence for a neural pathway originating in the kidney and projecting to hypothalamic structures implicated in central cardiovascular regulation. Our recent studies have shown that there is a neural connection from the PVN to the RVLM that is activated by stimulation of ARN (Xu et al., 2015). Increased Fos-labelled neurons were found in the PVN and the brain stem after ARN stimulation, suggesting ARN information originating in kidneys is conveyed to a number of central areas known to be involved in the regulation of body fluid balance and arterial pressure (Solano-Flores et al., 1997).

Calaresu and Ciriello confirmed projections to the hypothalamus in the rat by determining the effect of RDN on hypothalamic catecholamine concentrations (Calaresu et al., 1981a). Four days after RDN, a decreased epinephrine concentration has been reported in the PVN. The finding of catecholamine changes in the PVN after RDN is interesting because brain stem catecholaminergic pathways are thought to provide direct inputs to MNCs in the PVN. This suggests that ARN may alter the activity of MNCs in the PVN via ascending brain stem catecholamine pathways. Caverson et al have demonstrated that neurons in the PVN that project directly to the neurohypophysis increase their rate of discharge during stimulation of ARN (Caverson et al., 1987). Administration of the vasopressin antagonist abolished the rise in arterial pressure that had a long onset latency and outlasted the duration of ARN stimulation (Caverson et al., 1987). These findings demonstrate that afferent information from renal receptors contributes to a reflex pathway by which the kidney may alter the release of vasopressin from the neurohypophysis to influence circulatory and body fluid homeostasis.

Renal afferent nerve signals are centrally integrated and their activation results in an increase in sympathetic tone, which is not only directed toward the kidneys, but also toward other organs (Grisk et al., 2004; Malpas et al., 2006; Schlaich et al., 2009a). The ARN pressor response, which was locked in time with stimulus duration, was shown to be due to the activation of the sympathetic nervous system (Caverson et al., 1987). Renal afferent signals are also involved in spinal feedback loops, termed reno-renal reflexes, whereby afferent activity from one kidney can modulate ipsilateral and contralateral efferent renal nerve activity to regulate diuresis and natriuresis to balance overall renal function between the two kidneys (Kopp, 2015). Kopp et al. showed that the inhibitory mechanoreceptor reno-renal reflex was blunted in CHF, due to desensitization of renal mechanoreceptors by high circulating angiotensin II (Kopp et al., 2003) and activation of endothelin A receptors (Kopp et al., 2010). Blunting of the inhibitory reno-renal reflex may be a mechanism by which sodium is retained and efferent sympathetic drive to non-renal vascular beds is stimulated in CHF.

## PVN and Vasopressin

Anatomically the PVN includes vasopressin-producing MNCs which project to neurohypophysis. Day and Ciriello have demonstrated that putative vasopressin MNCs in the hypothalamus increase their rate of discharge during electrical stimulation of ARN (Day et al., 1987). In contrast, ARN stimulation has no effect on the rate of discharge of putative oxytocin neurons. Putative vasopressin neurosecretory neurons have also been shown to increase their rate of discharge during intra-renal infusion of bradykinin and capsaicin, whereas renal vein occlusion and increased systemic arterial pressure after transection of sinoaortic and cardiopulmonary afferent fibers did not alter the discharge rates of these cells. Vasopressin neurosecretory neurons selectively receive an excitatory input from chemoreceptors within the kidney, but are unresponsive to activation of renal vascular mechanoreceptors. These findings also suggest that afferent information originating from renal receptors and baroreceptors converge on hypothalamic neurons and contribute to neural mechanisms controlling the release of vasopressin from the neurohypophysis.

In the hypothalamus, vasopressin neurosecretory neurons selectively receive an excitatory input from chemoreceptors within the kidney, but are unresponsive to activation of renal vascular mechanoreceptors (Ciriello et al., 2002). These findings suggest that afferent information originating from renal receptors and baroreceptors converge on hypothalamic neurons and contribute to neural mechanisms controlling the release of vasopressin from the neurohypophysis. We have previous found that ARN stimulation activates RVLM projecting PVN neurons (Xu et al., 2015). In the same study, we also observed that part of the non-antidromically identified neurons responded to the stimulation of the ARN. It is possible that this population of PVN neurons represents the projection to the neurohypophysis to influence vasopressin release observed previously (Caverson et al., 1987).

Chronically elevated plasma vasopressin levels have been reported both in animal models and human patients with CHF, being an important factor contributing to altered fluid/electrolyte balance, as well as detrimental myocardial effects (Goldsmith et al., 1983; Riegger et al., 1985). Studies in animal models of CHF support elevated vasopressin

neuronal activity in the PVN (Potapenko et al., 2011). Postsynaptic properties of GABAergic and glutamatergic synaptic function contribute to enhanced MNCs activity in the CHF rats (Potapenko et al., 2011; Stern et al., 2013). In the PVN, vasopressin can also act in a diffusible manner to stimulate the activity of neighboring pre-autonomic neurons, leading to an increased RSNA (Son et al., 2013).

## Activation of the Afferent Renal Nerve Produces Exaggerated Sympathetic Outflow during Chronic Heart Failure

The sympathetic nervous system has been identified as a major contributor to the complex pathophysiology of CHF both in experimental models and patients (Grassi, 2009; Parati et al., 2012). There are very few studies that have examined the role of the ARN in CHF. CHF is associated with a number of symptoms that would be expected to stimulate renal afferent activity, such as increased venous congestion and decreased renal blood flow (Ciriello, 1998; Recordati et al., 1978). Direct electrical stimulation of the ARN in animals has been shown to produce sympathoexcitation in various vascular beds and an increase in arterial pressure (Caverson et al., 1988; Chinushi et al., 2013; Spelman et al., 1991). It is possible that a pathological positive feedback signal/s, which remains to be identified, from the level of the kidney may exist, whereby causing an increase in overall sympathetic tone. Ablation of the renal sympathetic nerves remains an attractive therapeutic approach in hypertension and CHF (Krum et al., 2009; Lambert et al., 2012; Laurent et al., 2012; Sobotka et al., 2012).

It is unknown whether the excitatory renal-chemoreflex is enhanced in CHF, potentially in parallel with the enhanced arterial chemoreflex response already observed in CHF. In this regard, it is of interest to note that such inhibitory reno-renal reflexes are reported to be blunted in rats with CHF (Kopp, 2015; Kopp et al., 2003). These data are consistent with the concept that this reduced inhibitory input may be overwhelmed by excitatory input generated within the kidneys of rats during the CHF condition, since RDN is able to abrogate the increase in global sympathetic activation. Therefore, the kidney is not only a target of sympathetic outflow, but also a source of signals that have the potential to directly modulate overall sympathetic outflow in disease conditions such as CHF (Kopp, 2015).

Evidence for excitatory reflexes originating in diseased kidneys is derived from studies in rats with chronic renal failure and patients with renal failure (Kopp, 2015). There is also considerable strong evidence that the diseased kidneys exert an excitatory effect on sympathetic nerve activity in various pathological conditions involving renal injury, including hypertension, CHF, chronic renal failure, diabetes, and obesity (Giamouzis et al., 2011; Henegar et al., 2014; Kopp, 2015; Linz et al., 2015; Ott et al., 2014; Schlaich et al., 2009b). It has been proposed that renal inflammation is prevalent in many of these pathological conditions and may contribute to the increased sympathetic outflow via activation of ARN (Kopp, 2015).

In CHF rats induced by left coronary ligation surgery, there was a two-fold increase in FosB-positive cells in the PVN compared to sham-operated rats. Extracellular recordings in the PVN have also shown that RVLM projecting PVN neurons are more active in rats with CHF at 4 weeks. (Xu et al., 2012 ), suggesting that perhaps there is a potential for tonic ongoing activation by the ARN during CHF condition, which may contribute to the state of activation

of the PVN which would then translate into an increased overall sympathoexcitation under basal conditions. It should be noted that there are multiple triggers in the CHF condition that have the potential for increased activation of the ARN activity, including reduced perfusion pressure, increased venous pressure, increased inflammation, increased oxidative stress to name a few.

Our previous studies have shown that the PVN is activated in rats with CHF in conjunction with enhanced glutamatergic tone and blunted NO mechanism within the PVN (Li et al., 2003; Patel et al., 2012; Zhang et al., 2001; Zheng et al., 2011). $NR_1$ receptor mRNA expression and protein in the PVN are significantly increased in CHF, which may contribute to the elevated sympathoexcitation during CHF (Li et al., 2003). In our recent study, NMDA activated all PVN neurons that were excited by inputs from ARN, and these responses were attenuated during iontophoretic application of the glutamate receptor blocker, AP5 (Figure 1) (Xu et al., 2015). Thus, it is possible that the upregulation of NMDA receptor and the subsequent increase in glutamate activity within the PVN may be contributing to the altered compensatory responses in disease states such as CHF.

## Renal Denervation Abrogates Activation of the PVN during Chronic Heart Failure

The kidneys communicate with integral structures in the central nervous system via the renal sensory afferent nerves (Grisk et al., 2004). Intra-renal stimuli or pathology, such as ischemia or hypoxia, results in an increase in ARN activity (Ye et al., 1998; Ye et al., 2002). Renal sensory afferent nerve activity directly influences sympathetic outflow to the kidneys and other organs such as the heart and peripheral blood vessels, which are also modulated by the PVN (DiBona, 2003). Thus, RDN is likely to be valuable in the treatment of several clinical conditions such as hypertension and CHF characterized by increased sympathetic outflow overall, and particularly RSNA to the kidney (Kline, 1987; Patel et al., 2016; Patel et al., 1996).

Renal denervation in most experimental forms of hypertension as well as drug resistant hypertensive patient has been shown to reduce arterial pressure and sympathetic activity (DiBona et al., 1997; Kline, 1987; Krum et al., 2009). Since exaggerated sympathoexcitation is characteristic of CHF, the efficacy of RDN to reduce sympathoexcitation has been explored in both ischemia-induced and pacing heart models of CHF (Hu et al., 2012; Nozawa et al., 2002; Schiller et al., 2013) and patients with CHF (Bohm et al., 2014; Schiller et al., 2015). Recently, we have shown that bilateral RDN was sufficient to reduce global sympathetic outflow, as evident by a reduction in urinary excretion of norepinephrine as well as basal level of lumbar sympathetic nerve activity in the CHF rats (Figure 2) (Patel et al., 2016). One plausible interpretation of these data is that there may be an enhanced tonic level of ARN activity during the CHF condition (Figure 3), which may contribute to the state of activation of the PVN resulting in an increased overall sympathoexcitation. Reducing norepinephrine is very important, as CHF patients with lower levels of plasma norepinephrine have better prognosis (Cohn et al., 1984). These results suggest that RDN may alter the activity of neurons in central cardiovascular regulatory sites, such as the PVN, thereby contributing to the reduction in sympathetic tone.

Particularly, we have found RDN restored the endogenous neuronal NO synthase (nNOS) in the PVN that had been decreased in rats with CHF (Figure 4) (Patel et al., 2016). Previously, we have shown nNOS mediated sympathoinhibition from the PVN was blunted in CHF (Zhang et al., 2001). RDN normalized the blunted lumbar sympathetic nerve activity response to inhibition of endogenous NOS within the PVN observed in CHF rats (Patel et al., 2016). We proposed that a possible mechanism for the therapeutic effects of RDN during CHF might be through an NO-dependent mechanism within the PVN. This is consistent with previous observations showing NO synthesizing cells in the PVN may affect renal autonomic pathways by interacting with the renal sensory information (Weiss et al., 2001).

### Summary

In summary, sensory information originating in the kidney excites pre-autonomic neurons within the PVN know to be involved in the regulation of sympathetic outflow, suggests that this “renal-PVN afferent pathway” may contribute to overall sympathetic tone (Figure 5). It is thus conceivable that an enhanced/altered afferent renal input to the PVN in disease conditions such as CHF and hypertension may be critically involved in producing elevated sympathetic nerve activity commonly observed in these disease states.

## Non-standard Abbreviations and Acronyms

| | |
|---|---|
| **PVN** | paraventricular nucleus |
| **MNCs** | magnocellular neurosecretory neurons |
| **ARN** | afferent renal nerves |
| **RVLM** | rostral ventrolateral medulla |
| **RSNA** | renal sympathetic nerve activity |
| **CHF** | chronic heart failure |
| **pPVN** | parvocellular neurons of the PVN |
| **NO** | nitric oxide |
| **NTS** | nucleus tractus solitaries |
| **SFO** | subfornical organ |
| **RDN** | Renal denervation |
| **nNOS** | neuronal nitric oxide synthase |

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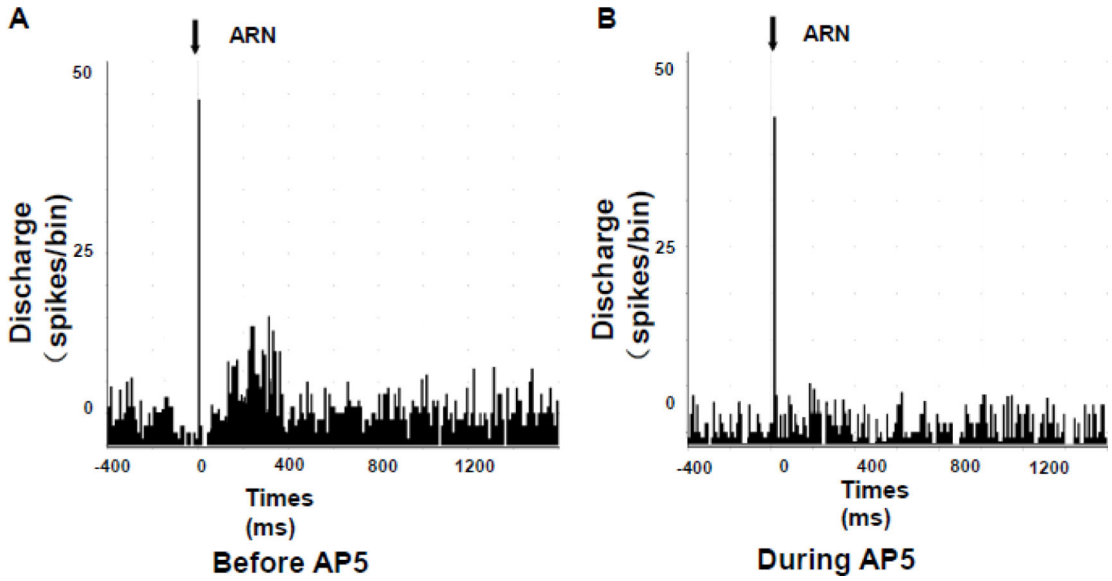


**Figure 1.**

Peristimulus histogram of spike occurrence triggered by electrical stimulation of the ARN with 50 sweeps. A: before iontophoretic application of NMDA receptor antagonist AP5 and B: during iontophoretic application of AP5. [From (Xu et al., 2015)]

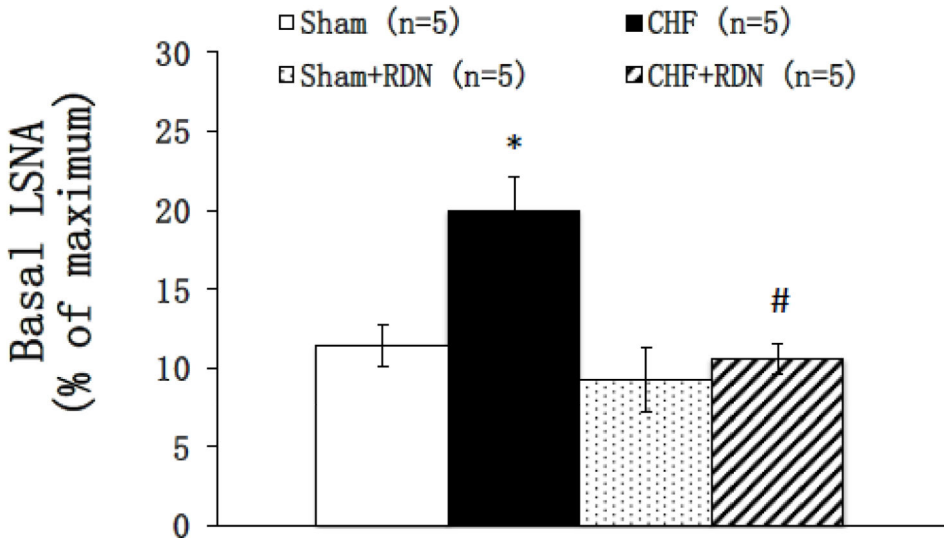


**Figure 2.**

Basal lumbar sympathetic nerve activity (LSNA) in four groups of rats: sham, sham+RDN, CHF and CHF+RDN. Data are presented as mean ± SE. CHF: chronic heart failure; RDN: renal denervation. *P < 0.05 vs. sham; #P < 0.05 vs. without RDN.

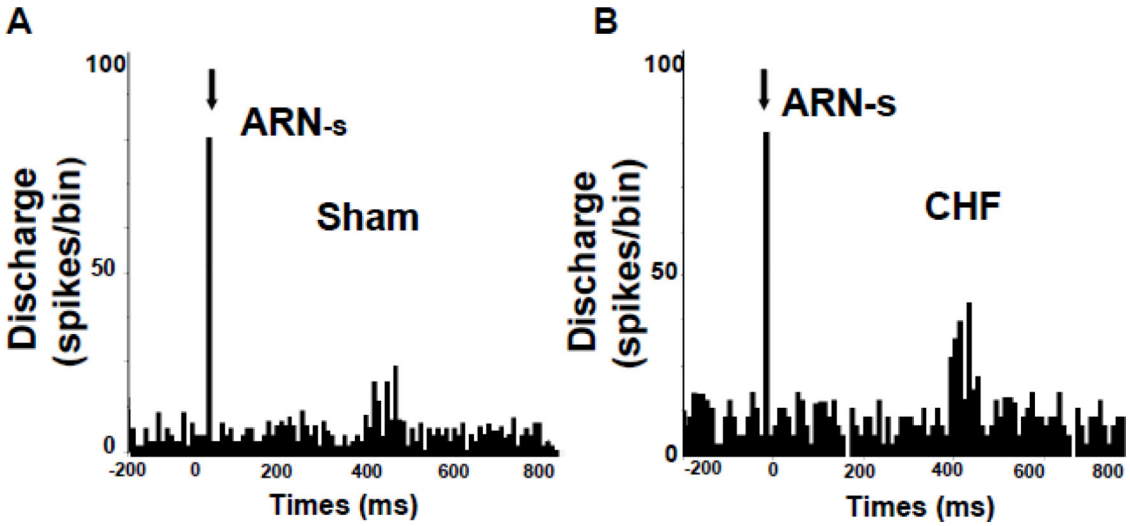


**Figure 3.**

Peristimulus histogram of spike occurrence triggered by electric stimulation of the afferent renal nerve with 100 sweeps, bin = 0.02 s. ARN-s: afferent renal nerve stimulation. Segments of original recordings of changes in discharge after afferent renal nerve (ARN) stimulation in sham (A) and CHF (B) rats. [From (Patel et al., 2016)]

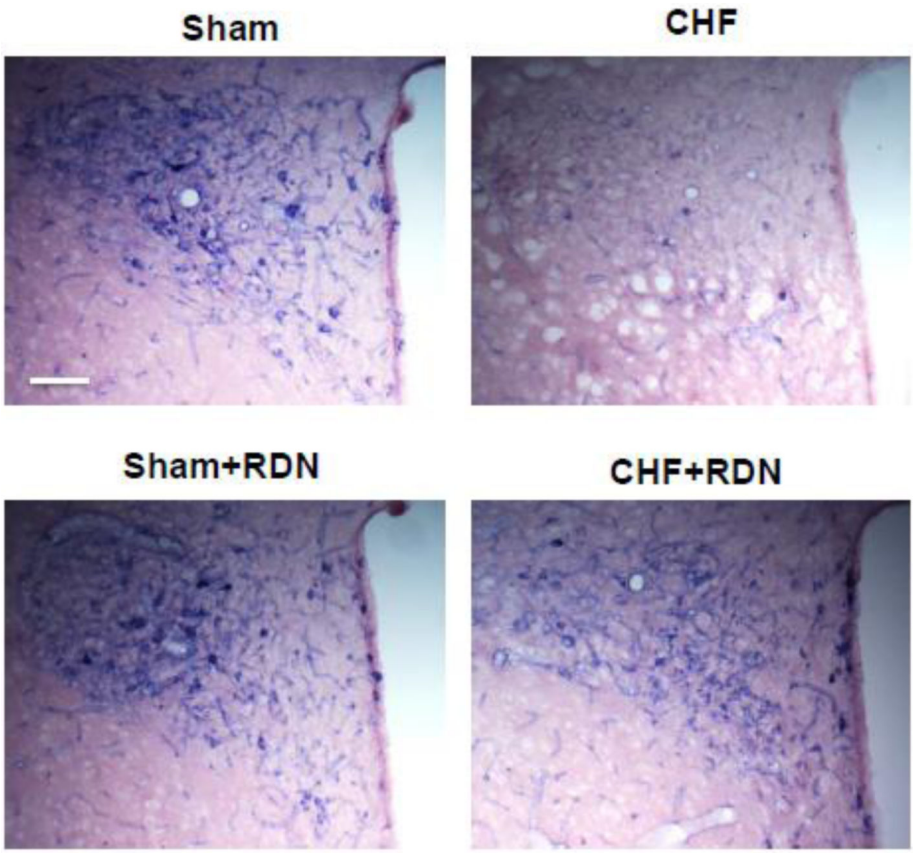


**Figure 4.**

A. The effect of renal denervation (RDN) on NADPH-diaphorase in the paraventricular nucleus (PVN) of rats with CHF. Representative pictures of PVN with NOS positive staining in four groups of rats, sham, CHF, sham+RDN and CHF+RDN. Bar = 100 μm.

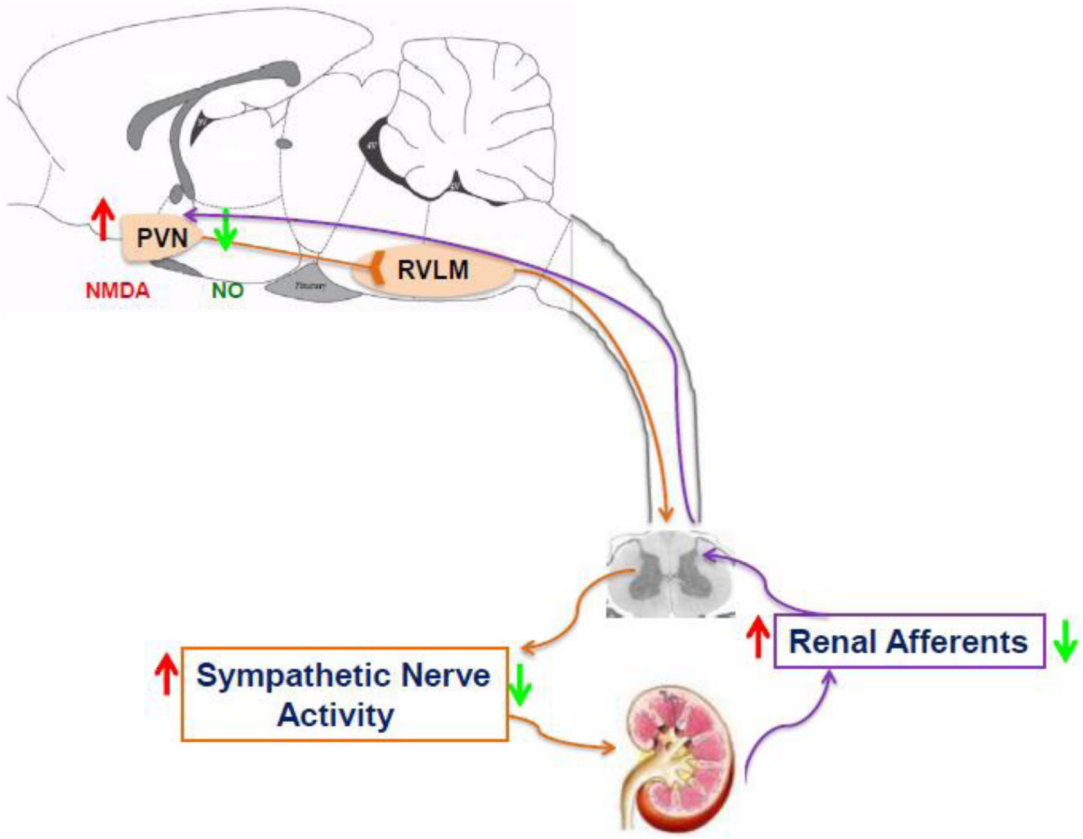


**Figure 5.**

Schematic diagram illustrating that sensory information originating in the kidney is transmitted by renal afferent nerves to the dorsal column of the spinal cord which results in exciting pre-autonomic neurons in the PVN via multiple synaptic pathway. The pre-autonomic neurons in the PVN project to the RVLM as well as the intermediary column of the spinal cord, where pre-sympathetic neurons terminating in the kidney reside. These pre-autonomic neurons are activated by NMDA and inhibited by NO. This long loop pathway involving the PVN suggests that this renal-PVN pathway may contribute to the elevated sympathetic nerve activity in disease conditions such as CHF. Renal denervation reduces afferent renal nerve signaling, neuronal activity in the PVN and sympathetic nerve activity in the CHF. RVLM, rostral ventrolateral medulla; NMDA, N-methyl-d-aspartate; NO, nitric oxide. Orange arrows indicate efferent pathway affecting the kidney. Purple arrows indicate afferent pathway to the PVN. Red arrows: indicate changes during CHF; green arrows: indicate changes after renal denervation.