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Review

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.

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Abbreviations: 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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1. 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 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 and Kuypers, 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 and Toney, 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 and Knuepfer, 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 and Ciriello, 1988; Ciriello and Caverson, 1987; Day and Ciriello, 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).

2. 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 and Sawchenko, 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 and Schmid, 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 and Schmid, 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 and Haywood, 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 and Horiuchi, 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 and Leenen, 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 and Zheng, 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).

3. 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 and Echtenkamp, 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