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Review

Renal denervation and hypertension - The need to investigate unintended effects and neural control of the human kidney

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ABSTRACT

Increased renal sympathetic nerve activity (RSNA) is present in human and experimental forms of arterial hypertension. Experimental denervation studies showed that renal nerves contribute to the development of hypertension. Clinical trials provided equivocal results on the antihypertensive efficacy of renal denervation in patients spurring discussions on technical aspects of renal denervation and further research on the role of renal nerves for the regulation of kidney function as well as the pathophysiology of hypertension. This review summarizes recent findings on adrenoceptor expression and function in the human kidney, adrenoceptor-dependent regulation of sodium chloride transport in the distal nephron, experimental data on chronic RSNA and the development of high arterial pressure and consequences of renal denervation that may limit its antihypertensive efficacy. Future research needs to reduce the gap between our knowledge on neural control of renal function in animals vs. humans to facilitate translation of experimental animal data to humans. More experimental studies on the temporal relationship between RSNA and arterial pressure in the chronic setting are needed to better define the pathogenetic role of heightened RSNA in different forms of arterial hypertension in order to improve the rational basis for renal denervation in antihypertensive therapy. Finally, research on unintended consequences of renal denervation including but not limited to reinnervation and denervation supersensitivity needs to be intensified to further assess the potential of renal denervation to slow the progression of renal disease and hypertension.
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Contents

1. Introduction

The kidneys are innervated by efferent sympathetic and afferent sensory nerve fibers. Renal efferent innervation regulates renin release, epithelial solute transport and renal blood flow (Johns et al., 2011). Elevations in renal sympathetic nerve activity (RSNA) increase renin release, tubular sodium reabsorption, and renal vascular resistance (RVR) thereby promoting water and sodium retention as well as arterial pressure rises depending on the physiological conditions (Johns et al., 2011). Renal efferent nerve fibers also interact with renal afferents which elicit reflex inhibition of RSNA (Johns et al., 2011; Kopp, 2015).

Abbreviations: ang II, angiotensin II; ATP, adenosine triphosphate; CD, collecting duct; CNT, connecting tubule; DCT, distal convoluted tubule; ECM, extracellular matrix; ENaC, epithelial sodium channel; IMCD, inner medullary collecting duct; ^{123}I-mIBG, ^{123}I-metaiodobenzylguanidine; mRNA, messenger ribonucleic acid; NaCl, sodium chloride; NCC, sodium chloride cotransporter; NOS, nitric oxide synthase; P2X, purinoceptors of the P2X family; RSNA, renal sympathetic nerve activity; RVR, renal vascular resistance; SHR, spontaneously hypertensive rats; SNA, sympathetic nerve activity; VSMC, vascular smooth muscle cell; 2K1C, two-kidney, one clip.

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Increased RSNA has been shown in humans as well as in animals with arterial hypertension and renal denervation lowers arterial pressure in several forms of experimental hypertension (Grassi et al., 2015; Iliescu et al., 2015; Johns et al., 2011). Elevated RSNA can contribute to hypertension by increasing sodium and water retention as well as RVR (DiBona and Kopp, 1997; Tomoda et al., 1997). Under pathological conditions, activation of renal afferents and efferents triggers or maintains renal inflammation (Ditting et al., 2009). In diseased kidneys, reflex inhibition of sympathetic nerve activity (SNA) including RSNA via renal afferents may be blunted or reversed to excitation (de Beus et al., 2014; Kopp, 2015) and the renal nerves may be part of a vicious cycle that promotes hypertension because of deteriorating kidney function and sympathetic activation.

Based on available knowledge on the physiology and pathophysiology of renal innervation (Johns et al., 2011), transcutaneous catheter-based renal denervation has been introduced to treat patients with arterial hypertension who are resistant to pharmacotherapy (Krum et al., 2009). Since its introduction, catheter-based renal denervation has been performed in many centers world-wide and clinical studies provided equivocal results on its efficacy to lower arterial pressure. While several studies reported arterial pressure reductions in patients after renal denervation (Esler et al., 2010; Rosa et al., 2015; Vink et al., 2014) others did not (Bakris et al., 2014; Kario et al., 2015; Mathiassen et al., 2016). The reasons for these conflicting and to some extent disappointing results have been recently discussed with respect to denervation technique, placebo effects, concomitant pharmacotherapy and eligibility of individual patients for renal denervation based on the underlying pathophysiology of hypertension (Gulati et al., 2016; Iliescu et al., 2015; Mahfoud et al., 2015). Currently, most clinicians working in this field agree on the need to further investigate the potential of renal denervation for antihypertensive therapy (Gulati et al., 2016; Iliescu et al., 2015; Mahfoud et al., 2015). This also requires further experimental studies that 1) facilitate the translation of findings obtained in animal models to humans, 2) provide more detailed insight into the role of renal nerves for the pathogenesis of hypertension than currently available and 3) analyze potentially unintended consequences of renal denervation that may limit its use for the treatment of hypertension. This review will summarize recent findings on adrenoceptor expression and function in the human kidney, adrenoceptor-dependent regulation of NaCl transport in the distal nephron, experimental data on RSNA during the development of hypertension, and the consequences of renal denervation that potentially limit its antihypertensive efficacy, thereby identifying areas for future research in this field.

2. Adrenoceptors in the human kidney

The renal localization of adrenoceptors and their role for the regulation of renal function have been reviewed in great detail, largely based on data obtained in experimental animals (DiBona and Kopp, 1997; Saunders and Limbird, 1999). At that time, it was known that all α-adrenoceptor subtypes are present in the human kidney, while their localization within the kidney was still uncertain to some extent (Michel and Rump, 1996). The available data indicated that α_2-adrenoceptors mediate reductions in renal blood flow and renin release while they did not provide sufficient evidence to define the role of α-adrenoceptors for the regulation of tubular transport in the human kidney (Michel and Rump, 1996). The stimulatory effect of β_1-adrenoceptor activation on renin release from juxtaglomerular cells was well established (DiBona and Kopp, 1997; Weber et al., 1983). Electric field stimulation experiments combined with pharmacological adrenoceptor blockade in isolated tissue samples provided evidence that presynaptic α_{2a}-adrenoceptors inhibit and presynaptic β_2-adrenoceptors facilitate norepinephrine release from postganglionic sympathetic axons in the human renal cortex (Rump et al., 1995; Trendelenburg et al., 1997).

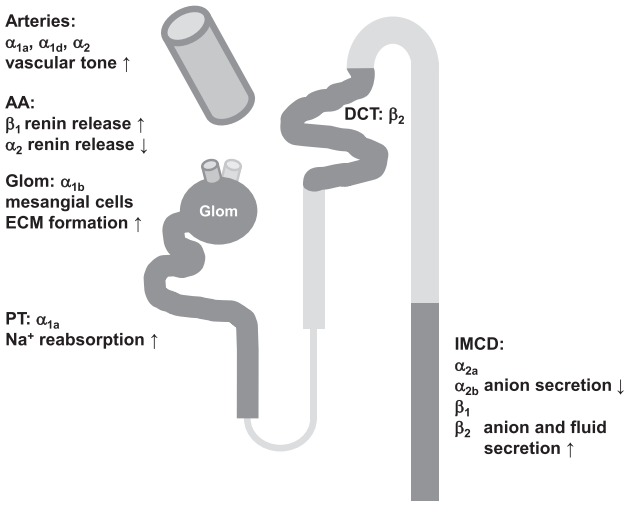

Fig. 1. Overview on the localization and function of postsynaptic adrenoceptors in the human kidney based on currently available morphological and functional data (dark gray). AA: afferent arteriole, Glom: Glomerulus, PT: proximal tubule, DCT: distal convoluted tubule, IMCD: inner medullary collecting duct, ECM: extracellular matrix.

Since then, several studies provided additional information on adrenoceptor localization and function in the human kidney (Fig. 1). The presence of all three α_1-adrenoceptor subtypes in the human renal cortex has been confirmed on the mRNA level (Kurooka et al., 1999). In situ hybridization revealed the presence of α_{1a} and α_{1d}-adrenoceptor mRNA in the media of arcuate and interlobular arteries (Kurooka et al., 1999). Phenylephrine potently constricts isolated human distal arcuate and interlobular arteries (Grisk et al., 2012; Schluter et al., 2010) suggesting that the neurogenic rise in RVR is at least in part mediated by α_1-adrenoceptor activation in humans. Primary human mesangium cells express α_{1b}-receptor mRNA and mesangial extracellular matrix protein production has been shown to be α_1-adrenoceptor-dependent suggesting that α_1-adrenoceptors mediate pro-inflammatory and pro-fibrotic effects in human glomeruli (Pawluczyk et al., 2006). Recently, α_{1a}-adrenoceptor protein expression has been demonstrated in the human proximal tubule (Ennis et al., 2014). Phenylephrine increased plasma membrane Na^+-K^+-ATPase abundance in human renal proximal tubular cells (Ennis et al., 2014) suggesting that α_1-adrenoceptor activation increases proximal tubular sodium reabsorption in humans. Activation of RSNA causes α_2-adrenoceptor-dependend ATP release in the human renal cortex with the majority of ATP being released from postsynaptic sites (Vonend et al., 2002). The RSNA-dependent ATP release has been suggested to contribute to the progression of chronic kidney disease (Vonend et al., 2002). Western blot analyses revealed the presence of α_{2a} and α_{2b}-adrenoceptors in human primary inner medullary collecting duct (IMCD) cells (Wallace et al., 2004).

The expression of β_1-adrenoceptors in human kidneys has been demonstrated on the protein level (Hellgren et al., 2000) and their role for the stimulation of renin release has been confirmed (Molstrom et al., 2009). However, there is currently no evidence that the reflex-mediated withdrawal of β_1-adrenoceptor activity in response to an acute intravascular volume load in humans may contribute to the ensuing increase in diuresis and natriuresis or the reduction in plasma angiotensin II concentrations (Molstrom et al., 2009). Immunohistochemistry in pediatric biopsies showed β_2-adrenoceptors in distal tubuli and provided suggestive evidence that glucocorticoid treatment increases renal β_2-adrenoceptor expression in pediatric patients (Nakamura et al., 2007). Human IMCD cells express β_1- and β_2-adrenoceptors where β_2-adrenoceptor activation increases anion and fluid secretion (Wallace et al., 2004). This effect is blunted by concomitant α_2-adrenoceptor activation (Wallace et al., 2004).

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