Editorial Note
Volume 11:12, 2021

Journal of Nephrology & Therapeutics

ISSN: 2161-0959 Open Access

Angiotensin Type-2 Receptors in Renal Proximal Tubule

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Description

Angiotensin is a peptide hormone that causes vasoconstriction and an increase in blood pressure. It is part of the renin–angiotensin system, which regulates blood pressure. Angiotensin also stimulates the release of aldosterone from the adrenal cortex to promote sodium retention by the kidneys.

Angiotensin II (Ang II) type-2 receptors (AT2R) are expressed in the adult kidney, prominently in renal proximal tubule cells (RPTCs), and play an important role in opposing renal sodium (Na^+) retention induced by Ang II stimulation of Ang II type-1 receptor (AT1R). Natriuresis induced by AT1R blockade is due at least in part to AT2R activation and whole body deletion of AT2Rs reduces the natriuretic response to increased blood pressure (BP). The major endogenous AT2R agonist mediating the natriuretic response is Ang III, the Ang II heptapeptide metabolite generated by aminopeptidase A, and the principal nephron site mediating inhibition of Na^+ reabsorption by the AT2R is the renal proximal tubule (RPT). AT2Rs induce natriuresis *via* a bradykinin, nitric oxide and cyclic GMP (cGMP) signaling cascade. Recent studies demonstrated a key role for protein phosphatase 2A (PP2A) in the AT2R-mediated natriuretic response upstream of cGMP. By inducing natriuresis, AT2Rs lower BP in the Ang II-infusion model of hypertension. PP2A activation and the natriuretic response to AT2R stimulation are defective in spontaneously hypertensive rats, a model of primary hypertension in humans. AT2R agonists are candidates for proximal tubule natriuretic agents in Na+ and fluid retention disorders.

Primary (essential) hypertension (HT) affects about half of the adult population in the United States and is a leading cause of stroke, myocardial infarction, heart failure, and end-stage renal disease. Despite this grave threat to public health, scientists have yet to identify the processes that cause and perpetuate HT. A fundamental impairment in the kidneys' capacity to excrete sodium (Na^+), followed by a compensatory increase in renal perfusion pressure to ensure appropriate Na^+ excretion, is the current leading theory underlying the onset of HT in both humans and experimental animal models. The renin-angiotensin system (RAS) is a complicated hormonal system that regulates renal Na^+ excretion (UNaV) and blood pressure (BP).

The principal RAS effector peptide angiotensin II (Ang II) acts on two major receptors: the Ang II type-1 receptor (AT1R), which increases BP by promoting renal Na^+ reabsorption, and the Ang II type-2 receptor (AT2R), which works in the opposite direction. The activities and molecular signalling pathways of AT2Rs in the induction of natriuresis and decrease of blood pressure in experimental animal models, as well as AT2R signalling abnormalities in primary hypertension. Although both AT1Rs and AT2Rs are expressed in the adult kidney, AT1R mRNA is more abundant than AT2R mRNA throughout the nephron and renal microvasculature. However, the AT2R typifies several seven-transmembrane G protein-coupled receptors such as dopamine receptors that, despite low levels of mRNA, have significantly higher levels of receptor protein expression in the adult kidney. Reverse transcription PCR and/or immunohistochemistry have demonstrated widespread tubular and vascular distribution of AT2R mRNA and protein in the adult kidney, including proximal and distal tubules, collecting ducts, arcuate arteries, afferent arterioles, and outer medullary vasa recta, with dense expression in the vasculature of the renal cortex and the proximal tubules of the outer medulla. Subsequent studies have unequivocally confirmed AT2R protein in rat renal proximal tubule cells (cytoplasm, mitochondria, and apical plasma membranes) by confocal and electron microscopy immunocytochemistry. It is important to note that all systematic studies documenting renal tubule expression of AT2Rs along the nephron have been conducted in rodent models.

The major effector peptide of the RAS, Ang II, was thought to be the endogenous agonist for renal Ang receptors. However, at any physiological infusion rate, the octapeptide was shown to be devoid of natriuretic activity. Intrarenal infusion of the APN inhibitor PC-18 alone generated natriuresis and significantly increased the natriuretic response to exogenous intrarenal Ang III, which was eliminated by PD (Peritonial Dialysias). The natriuretic response to Ang II was abolished in the presence of APN inhibition when the conversion of Ang II to Ang III was lowered by the APA inhibitor EC-33. Renal AT2Rs acting in tandem with dopamine receptors counter balance Na^+ retention elicited by Ang II *via* AT1Rs. The primary cellular mechanisms by which AT2Rs induce natriuresis are protein phosphatase PP2A. AT2R agonist C-21 can restore Na+ balance and reduce BP to baseline in the chronic Ang II infusion model of hypertension. However, AT2R-induced natriuresis is defective in SHR. Since AT2Rs inhibit Na^+ transport in the RPT

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Received: December 02, 2021; **Accepted**: December 16, 2021; **Published**: December 23, 2021

where the majority of Na^+ is reabsorbed and no effective RPT natriuretic/diuretic agent.

How to cite this article: Patrick, John. "Angiotensin Type-2 Receptors in Renal Proximal Tubule" *J Nephrol Ther* 12 (2021): 375.