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The angiotensin II type 2 receptor and the kidney

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Abstract

Recent knowledge demonstrated that the renin-angiotensin system (RAS) functions as a local renal paracrine system. All components of the RAS are present within the kidney and include angiotensinogen, renin, angiotensin I, angiotensin-converting enzymes, angiotensin II, the angiotensin II type 1 (AT_1) receptor and the angiotensin II type 2 (AT_2) receptor. Angiotensin II is the major effector hormone of the RAS and contributes to a variety of renal and cardiovascular physiologic and pathologic mechanisms through stimulation of AT_1 and AT_2 receptors. Angiotensin receptor blockers were developed based on the advanced knowledge of the AT_1 receptor contribution to development of a variety of kidney, vascular and cardiac diseases including but not limited to hypertension, diabetic nephropathy, heart failure, myocardial infarction and atherosclerosis. In contrast, knowledge concerning the role of the AT_2 receptor in health and disease is still emerging. The AT_2 receptor is believed to counterbalance the effects of the AT_1 receptor through influencing cellular differentiation, vasodilation, inhibition of cellular proliferation and hypertrophy, nitric oxide production and natriuresis. Thus, the pursuit of a specific AT_2 receptor agonist is a potentially fruitful area for combating renal and cardiovascular diseases. This review focuses on the role of the AT_2 receptor in the kidney.

Keywords

AT_2 receptors; cGMP; kidney; nitric oxide

Angiotensin II type 2 (AT_2) receptor localisation and expression regulation in the kidney

The AT_2 receptor gene resides as a single copy on the X-chromosome.[1] This receptor is a member of the seven-transmembrane-type G-protein-coupled receptors containing 363 amino acids. It has a low amino acid sequence homology (~34%) with the angiotensin II type 1 (AT_1) receptor.[2]

The intracellular signalling mechanisms that are induced by AT_2 receptor stimulation are not fully understood and appear to be mediated by G-protein-dependent and -independent pathways. [3,4] This receptor stimulation leads to an increase in phosphotyrosine phosphatase activity and an inhibition of MAP kinase enzymes composing the extracellular signal-related kinase (ERK1/2).[5] This signalling activity is opposite to that induced by AT_1 receptor stimulation and leads to ERK1/2 phosphorylation.[3,6–8] In addition, the AT_2 receptor intracellular signals are thought to be mediated by opening the delayed rectifier K^+ channel,

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activation of phospholipase A_2 and prostaglandin generation, and stimulation of ceramide production.[3,6]

Expression of the AT_2 receptor is high during foetal development where it contributes to cellular differentiation and then declines with aging. However, re-expression of this receptor occurs during certain pathologic conditions, suggesting its role in healing.[9,10] In the kidney, expression of the AT_2 receptor is mainly localised in interlobular arteries,[11] the proximal tubules, collecting ducts, renal interstitial cells, arcuate arteries, afferent arterioles and outer medullary descending vasa recta.[12,13] These strategic renal locations suggest involvement of the AT_2 receptor in the regulation of renal haemodynamic and tubular functions.[7] Regulation of the expression of the AT_2 receptor is poorly understood. The AT_2 receptor is upregulated by sodium depletion, insulin and insulin-like growth factor 1,[13,14] and is downregulated by angiotensin II and growth factors such as platelet-derived growth factor and epidermal growth factor,[15] and in diabetes.[16,17] Enhanced AT_1 receptor activity has been reported to downregulate AT_2 receptor expression,[18] and this phenomenon could exaggerate development of a variety of cardiovascular diseases such as in diabetes.

The AT_2 receptor mediates nitric oxide production and vasodilation

Initial studies looking at the influence of sodium diet on the kidney demonstrated increased renal cGMP production during low sodium intake, an effect that was blocked by AT_2 receptor blockade but not by AT_1 receptor blockade.[19] This observation was the first to suggest involvement of the AT_2 receptor in inducing vasodilation. A subsequent study linked the AT_2 receptor to nitric oxide production.[20] In this study, inhibition of nitric oxide synthase led to a reduction in the low sodium intake-induced increase in cGMP and this response was comparable to that induced by AT_2 receptor blockade.[20] The increase in renal cGMP production was also observed during the administration of angiotensin II during normal sodium intake. Combined blockade of the AT_2 receptor and nitric oxide synthase inhibition did not produce any further reduction in cGMP production beyond its reduction with either treatment alone. A follow-up to these studies demonstrated that angiotensin II mediates release of bradykinin;[21] this effect was found to be completely blocked by AT_2 receptor blockade but not by AT_1 receptor blockade.[22] These studies suggest direct involvement of the AT_2 receptor in stimulation of renal bradykinin, nitric oxide and cGMP production.

Interestingly, the AT_2 receptor seems to mediate some of the effects associated with AT_1 receptor blockade.[7] Studies conducted in normal rats and a renovascular hypertension rat model demonstrated reversal of the hypotensive effects of AT_1 receptor blockade with inhibition of AT_2 receptor activity.[22,23] In these studies, the AT_2 receptor-mediated release of nitric oxide seems to play an important role in counter-regulating the pressor effects of increased angiotensin II production. In the 2-kidney, 1 clip or 2-kidney, 1-wrap hypertension models, AT_1 receptor expression is downregulated in both kidneys, while the AT_2 receptor is only downregulated in the ischaemic kidney and is preserved in the contralateral kidney.[24] In these angiotensin II-dependent hypertension models, there is significant reduction in bradykinin, nitric oxide and cGMP production in the ischaemic kidney, but substantially increased production in the contralateral kidney.[22] In addition, several reports from different laboratories have demonstrated a role for the AT_2 receptor in mediating vasodilation. Mice lacking the AT_2 receptor have a slight but significant increase in baseline blood pressure.[25,26] These mice have markedly decreased tissue levels of bradykinin, nitric oxide and cGMP associated with pressor and natriuretic hypersensitivity to angiotensin II.[27,28] The pressor hypersensitivity seen in these mice is exaggerated by upregulation of the AT_1 receptor.[29] In contrast, mice with overexpression of the AT_2 receptor in vascular smooth muscle cells demonstrate a decrease in the pressor responses to angiotensin II, a

phenomenon that is reversed by blockade of nitric oxide synthase activity or the bradykinin B_2 receptor.[30] These observations suggest the possibility of enhancing the hypotensive effects of AT_1 receptor blockade by increasing the activity of the AT_2 receptor.[31,32]

Taken together, these observations suggest that both endogenous (during sodium depletion) and exogenous angiotensin II stimulate the AT_2 receptor to enhance the bradykinin-nitric oxide-cGMP vasodilatory cascade.

The AT_2 receptor and regulation of renin release

Renin is mainly produced in the kidney by juxtaglomerular cells and its enzyme activity is the rate-limiting step that regulates angiotensin II formation. AT_1 receptor blockade enhances renin release through what is known as a short negative feedback mechanism. Until recently, it was thought that angiotensin II exerts this negative feedback on renin production through stimulation of the AT_1 receptor only. However, emerging data suggest that the AT_2 receptor also contributes to the regulation of renin release.[33,34] In these studies, AT_2 receptor blockade increased renal renin mRNA and protein, intrarenal renin and angiotensin II content, and plasma renin activity.[33] Administration of a nitric oxide donor or cGMP or decreasing the degradation of cGMP by inhibiting its degrading enzymes caused a significant reduction in renal renin mRNA and protein and its renal levels.[34] In contrast, inhibition of renal nitric oxide and cGMP led to an increase in renin production. Combined AT_2 receptor blockade and nitric oxide/ cGMP inhibition did not produce any further increase in renin production as compared to each individual blockade. These data suggest that, similar to the AT_1 receptor, the AT_2 receptor inhibits renin production through stimulation of the renal nitric oxide-cGMP cascade. This effect on renin release constitutes a rare similarity between the function of the AT_1 and AT_2 receptors since they usually have opposite effects.

The AT_2 receptor and sodium excretion

In the kidney, the AT_2 receptor is expressed in the vasculature and renal tubules, particularly the proximal tubules,[13,14] and its ability to enhance the nitric oxide-cGMP cascade activity suggests its involvement in the regulation of sodium homeostasis. [35,36] Initially, the AT_2 receptor was thought to inhibit pressure natriuresis.[37] However, subsequent studies have demonstrated that the AT_2 receptor enhances natriuresis.[30,38,39] Utilising AT_2 receptor-knockout mice, studies have demonstrated that pressure diuresis and natriuresis curves were shifted rightwards.[40] The AT_2 receptor may modulate sodium reabsorption through inhibition of bicarbonate reabsorption, an effect that opposes AT_1 receptor-mediated facilitation of sodium and bicarbonate reabsorption.[35] Inhibition of Na^+, K^+-ATPase activity in the proximal tubules also offers another mechanism for AT_2 receptor-induced natriuresis.[39,41] Mice lacking the AT_2 receptor demonstrated salt sensitivity when challenged with high sodium intake.[27] It is unclear if this antinatriuretic effect is directly related to the absence of the AT_2 receptor or due to a reduction in renal nitric oxide-cGMP levels. Earlier studies on the contribution of cGMP in the kidney revealed its role as a paracrine factor that has cell-to-cell signalling functions to promote natriuresis.[36] This concept was confirmed by studies demonstrating pressure-natriuresis during renal interstitial administration of cGMP or its second messenger protein kinase G.[42] Similarly, renal interstitial administration of a nitric oxide donor induced natriuresis.[43] Other studies have directly linked the AT_2 receptor to sodium excretion by abolishing the natriuretic effect associated with AT_1 receptor blockade with a specific AT_2 receptor blocker.[44,45] Interestingly, the natriuretic effects of dopamine in the kidney seem to involve the AT_2 receptor.[46]

Conclusion

Over the last decade, our knowledge of AT_2 receptor functions in the kidney has expanded significantly. The finding that the AT_2 receptor mediates release of nitric oxide, inhibits renin release and enhances sodium excretion suggests a role for this receptor in the regulation of blood pressure and sodium homeostasis. In addition, the inhibition of renin release in the kidney by the AT_2 receptor with subsequent reduction in angiotensin II formation has a great potential for improving kidney diseases, particularly diabetic nephropathy. Taken together, stimulation of the AT_2 receptor forms the basis for a new strategy to manage a variety of renal and cardiovascular diseases. The development of a novel, specific AT_2 receptor agonist constitutes a great step towards this goal.

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