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UPDATE ON ANGIOTENSIN AT_2 RECEPTORS

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Abstract

Purpose of the review—To update major new findings and concepts introduced during the past year on the role of angiotensin II (Ang II) subtype 2 receptors (AT_2Rs) in the control of blood pressure (BP) and renal function.

Recent findings—AT_2R activation prevents sodium (Na^+) retention and lowers BP in the Ang II infusion model of experimental hypertension and prevents salt-sensitive hypertension in the obese Zucker rat model of obesity and the metabolic syndrome. Ang II metabolite, des-aspartyl^1-Ang II (Ang III) is the predominant AT_2R agonist in the kidney and possibly also in the vasculature; a novel synthetic Ang III peptide, β-Pro-Ang III, is vasodepressor and lowers BP in conscious spontaneously hypertensive rats (SHR) in the presence of low-level Ang II type 1 receptor (AT_1R) blockade. Because nitric oxide (NO) is a product of AT_2R activation, a potential feed forward loop, wherein NO increases AT_2R transcription, may reinforce AT_2R beneficial actions long term. AT_2R activation also reduces proteinuria and oxidative stress in glomerulosclerotic kidneys of high salt obese Zucker rats.

Summary—Studies during the past year have helped clarify the physiological and pathophysiological roles of AT_2Rs and have enhanced the promise of AT_2R agonists in cardiovascular and renal disease.

Keywords

Angiotensin; angiotensin receptors; blood pressure; hypertension; kidney function; sodium excretion; natriuresis; kidney protection

INTRODUCTION

The renin-angiotensin system (RAS) is a complex hormonal cascade governing cardiovascular and renal function (1,2). The RAS is composed of a major effector peptide, angiotensin II (Ang II), formed from renin-induced catalytic cleavage of angiotensinogen (renin substrate) to produce the decapeptide Ang I and subsequent cleavage by angiotensin converting enzyme (ACE) to synthesize the octapeptide Ang II. Ang II acts mainly via AT_1 receptors (AT_1Rs) to initiate and maintain actions that can be detrimental to health, such as vasoconstriction, antinatriuresis, aldosterone secretion, sympathetic nervous system

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activation, cellular dedifferentiation and growth, inflammation and target organ damage. The RAS is also composed of several other peptide metabolites and receptors, many of which oppose these actions. Most important and best studied are the ACE-2-Ang (1–7)-*Mas* receptor pathway and the Ang II/Ang III-AT_2 receptor (AT_2R) pathway, both of which work to offset the actions of Ang II via AT_1Rs. This review will focus on major new findings and concepts introduced during the past year on the role of AT_2Rs in the control of BP and renal function.

AT_2R AGONIST - INDUCED NATRIURESIS AND BP REDUCTION

AT_2Rs are expressed throughout the adult kidney at vascular and tubule sites, albeit in smaller quantities than AT_1Rs (3,4). In particular, AT_2Rs are highly expressed in the renal proximal tubule (4). AT_2R-induced natriuresis was first suggested 17 years ago when AT_2R-null mice were shown to have pressor and antinatriuretic hypersensitivity to exogenous Ang II, indicating that pressure-natriuresis is reduced in the absence of AT_2Rs (5). The antinatriuresis in these animals was attributed to the marked reduction in renal bradykinin (BK), nitric oxide (NO) and guanosine cyclic 3′,5′-monophosphate (cGMP) in AT_2R-null compared to wild type animals at baseline and in response to Ang II (5). Subsequently, studies found that the formal pressure-natriuresis relationship is indeed shifted to the right (less sensitive) in AT_2R-null mice with and without L-NAME-induced hypertension (6,7).

Unequivocal evidence now exists that renal AT_2Rs mediate natriuresis (8–16). AT_2Rs thereby oppose the actions of Ang II via AT_1Rs, which increase renal tubule sodium (Na^+) reabsorption and induce antinatriuresis (17–19). Studies have demonstrated that the predominant, and possibly exclusive, endogenous AT_2R agonist for the natriuretic response is not Ang II, but the Ang II metabolite [des-aspartyl[1]]-Ang II (Ang III) (Figure 1) (9,10,16). In normal animals, the demonstration of Ang III mediated natriuresis via AT_2Rs requires the presence of concurrent low level systemic AT_1R blockade or inhibition of aminopeptidase N, which catabolizes Ang III to inactive metabolites (8–10,16). However, in obese Zucker rats or streptozotocin-induced diabetic rats, concomitant AT_1R blockade is not required because AT_2Rs exhibit increased renal proximal tubule AT_2R expression in this model (11–15). Interestingly, selective intrarenal AT_1R blockade induces natriuresis by an AT_2R-dependent mechanism that is blocked with AT_2R antagonist PD-123319 (PD) (8). Although not formally examined, the mechanism of this acute response is likely related to increased endogenous intrarenal Ang III levels with consequent activation of unblocked AT_2Rs (8–10,16).

Recent studies of AT_2R-induced natriuresis have employed the highly selective nonpeptide AT_2R agonist Compound 21 (C-21) (20,21). C-21 administered acutely to normal rats (systemically or intrarenally) induced natriuresis by an action at the renal proximal tubule (RPT) (22). The C-21-induced natriuresis was mediated by AT_2R activation, which was dependent upon a BK-NO-cGMP signaling pathway, as previously described (23,24). Acute C-21 administration recruited AT_2Rs from intracellular sites to the apical plasma membranes of renal proximal tubule (RPT) cells, a possible mechanism for reinforcing and sustaining the AT_2R natriuretic response (22). C-21 also internalized and inactivated major RPT Na^+ transporters Na^+-hydrogen exchanger-3 (NHE-3) and Na^+/K^+ATPase (NKA), indicating that

reduced RPT Na^+ transport is the mechanism for the natriuresis (22). Since no effective diuretic/natriuretic agents are available that act at the RPT, these observations suggested that AT_2R activation might be additive to diuretics acting in the distal portions of the nephron (distal and connecting tubules and/or cortical collecting duct).

Recent studies have confirmed the natriuretic response of acute AT_2R activation with intrarenal administration of highly selective AT_2R synthetic peptide agonist CGP42112A (CGP) (*25). In this study, AT_2R-induced natriuresis was associated with AT_2R receptor recruitment to the apical plasma membranes and inactivation of NKA in RPT cells (*25). Interestingly, co-stimulation of the renal dopamine D_3 receptor (D_3R), a member of the D_2-like receptor family, enhanced the CGP-induced natriuretic response, indicating the possibility that receptor heterodimerization on the plasma membrane is at least partially responsible for the enhancement. This finding reflects on earlier observations that stimulation of the RPT dopamine D_1-like receptor (D_1 and D_5 receptors) family, appears to be absolutely dependent on renal AT_2R activation (26,27). The interactions among angiotensin and dopamine receptors on natriuresis may be key considerations in the regulation of the natriuretic response and require further study.

Building on the findings that acute AT_2R activation induces natriuresis, Kemp *et al.* (**28) demonstrated in the Ang II infusion model of experimental hypertension that chronic AT_2R activation with C-21 prevented the initial (24h) Ang II-induced reduction in Na^+ excretion, induced sustained negative Na^+ balance and lowered BP to near-control levels during a 7-day infusion period. As with acute C-21 administration, concurrent AT_1R blockade was not required to unmask the natriuretic and hypotensive actions of chronic C-21. Again, similar to the acute studies, chronic administration of C-21 was equally effective administered intrarenally or systemically, translocated AT_2Rs to the apical plasma membranes and internalized/inactivated NHE-3 and NKA in RPT cells. C-21-induced natriuresis derived from RPT inhibition of Na^+ reabsorption because it was additive to that of chlorothiazide and amiloride (**28). In addition to preventing Na+ retention and hypertension, the results demonstrated that C-21 was equally effective in lowering BP once the Ang II-dependent hypertension had been established. This study strongly suggests that AT_2R agonists can be effective natriuretic and diuretic agents that improve the pressure-natriuresis relationship and may be effective antihypertensive agents in settings in which the RAS is activated.

Whether AT_2R agonists are antihypertensive by directly reducing peripheral vascular resistance, independently at least in part of their effects on renal Na^+ excretion, has been controversial (29,30). Clear results have been hindered by lack of highly selective AT_2R agonists for study. In order to circumvent this problem, Jones *et al.* (31) applied a novel β-amino acid substitution to Ang II that resulted in >1,000-fold selectivity of AT_2R over AT_1R binding. This compound, β-Ile^5-Ang II, exhibited AT_2R-dependent vasodepressor actions *in vitro* and was antihypertensive in spontaneously hypertensive rats (SHR) *in vivo* in the presence of background low-level AT_1R blockade (31). Interestingly, previous studies showed that the heptapeptide Ang II metabolite, Ang III, elicited a biphasic BP response with an initial pressor response followed by a depressor response that was blocked by AT_2R antagonist PD (32). Building on these findings, Del Borgo and colleagues (**33) recently synthesized a new AT_2R ligand, β-Pro-Ang III, with >20,000-fold AT_2R to AT_1R selectivity.

This AT_2R agonist evoked vasorelaxation *in vitro* and lowered BP acutely by ~ 35 mmHg during low-level AT_1R blockade in conscious SHR. These vascular actions of β-Pro-Ang III were abolished by AT_2R blockade with PD and also by BK B_2R antagonist icatibant or NOS inhibitor L-NAME, indicating that they were caused by AT_2R activation via the well-recognized BK-NO AT_2R signaling pathway in the vasculature (**33). Of primary importance, the vasodepressor actions of Ang III and β-Pro-Ang III were much more impressive than those of Ang II under the same experimental conditions (in the presence of low-level AT_1R blockade) (**33). Similar to reports on natriuresis, these results demonstrate the differential effects of Ang III over Ang II on AT_2R activation in the vasculature (8–10,15, **33).

POSITIVE NO FEEDBACK SIGNALING LOOP MAY REGULATE AT_2R EXPRESSION

Among the cell signaling mechanisms that have been implicated in AT_2R-induced biological responses in multiple organs and tissues, the BK-NO-cGMP pathway is of paramount importance (34,35). AT_2Rs can either activate NOS directly or indirectly via increased BK production and subsequent activation of its B_2Rs (36). Indeed, mice lacking the B_2R have normal BP and renal function, so direct NOS activation may serve as the default signaling pathway (37).

Surprisingly, as reported recently, NO has been shown to upregulate the expression of AT_2Rs in endothelial cells primarily by increasing AT_2R gene expression (transcription) (*38). Pharmacological inhibition of NOS with L-NAME reversed the upregulation of aortic AT_2R expression in eNOS transgenic animals (*38). As reported earlier, AT_2R upregulation was associated with reduced activity of angiotensin converting enzyme (ACE) (39). Mice with increased AT_2R expression had reduced ACE activity whereas AT2R-null mice manifested increased ACE activity (*38). Thus, AT_2Rs appear to be ACE inhibitors. When NO increased the AT_2R message, the signaling pathway involved was increased soluble guanylyl cyclase activity increasing cGMP production, activation of protein kinase G (PKG) and p38 MAP kinase (*38). Because AT_2R activation increases synthesis and release of NO and cGMP, this finding raises the interesting possibility that a selective AT_2R agonist, via a feed-forward mechanism involving NO generation, may in turn increase AT_2R transcription, thus reinforcing vascular responses to the agonist chronically. This putative positive feedback mechanism might engender a favorable AT_2R:AT_1R ratio that could contribute to a sustained reduction of BP in response to chronic agonist administration. This exciting concept deserves further validation with experiments testing BP responses to chronic AT_2R agonist administration. Whether this feed-forward concept also applies to cells and tissues other than endothelium awaits further study.

BENEFICIAL EFFECTS OF AT_2R ACTIVATION IN OBESITY/METABOLIC SYNDROME

The obese Zucker rat is an established model of obesity with insulin resistance and mild hyperglycemia that approximates the metabolic syndrome in humans. This model has

elevated BP and renal dysfunction (40). Previous studies have shown that AT_2R activation in the obese Zucker rat induces natriuresis by inactivating RPT NKA and exerts a protective role in lowering BP (11,13–15,41). As indicated above, in the obese Zucker rat, activation of AT_2Rs alone appears sufficient to lower BP without the addition of concurrent AT_1R blockade (42). This may be due to upregulation of AT_2R expression by hyperglycemia. Furthermore, chronic AT_2R blockade with PD increased BP in obese rats, suggesting a tonic protective role for AT_2Rs on BP in this experimental model (41).

Evidence for a role of AT_2Rs in BP control in the obese Zucker model has now been reported (**43). Chronic administration of C-21 over a 2-week period prevented a high salt diet (HSD)-induced increase in BP in these animals (**43). Ang II levels in the renal cortex were approximately 4-fold higher in the HSD-fed rats than in their normal salt diet (NSD) controls. C-21 partially blocked the HSD-induced increase in renal Ang II levels and reduced renal AT_1R protein expression by Western blot analysis (**43). However, antibodies employed for AT_1R detection have been criticized as being non-specific (44). Interestingly, C-21 significantly increased 24h urine Na^+ excretion in both control and HSD-fed animals chronically (on days 11–14 of the study) (**43). This observation is similar to earlier findings of an enhanced natriuresis in response to C-21 at 2 weeks in this model (42) and is reminiscent of the chronic negative Na^+ balance induced by C-21 in the Ang II infusion model of experimental hypertension (**28), with obese Zucker rats and Ang II-infused rats having increased Ang II levels in common. Thus, pathophysiologic states characterized as having an activated RAS may respond best to the chronic natriuretic and BP lowering power of AT_2R activation. Since AT_2Rs are translocated to the apical plasma membranes of RPT cells (22,**28) and do not internalize in renal epithelial cells (45), these receptors likely remain active in promoting natriuresis without desensitization and, thereby, reducing BP over a prolonged period of time (46).

In addition to a progressive Na^+-dependent increase in BP, obese Zucker rats also manifest salt-sensitive renal morphological changes of focal glomerulosclerosis (47). AT_2Rs have anti-inflammatory, anti-proliferative and anti-fibrotic effects and may protect against oxidative stress (48–50). A recent report sheds light on the pathophysiology of the renal dysfunction in obese Zucker rats fed HSD and demonstrates the attenuation of the renal target organ damage with AT_2R activation via C-21 (**51). HSD rats exhibited an increase in cortical nicotinamide adenine dinucleotide phosphate osidase activity, urinary hydrogen peroxide, and 8-isoprostanes and severe glomerulosclerosis, interstitial fibrosis reduction in glomerular filtration rate, urinary protein leak, and activity of N-acetyl-β-D-glucosaminidase, a lysosomal marker of tubular damage (**51). C-21 significantly attenuated these changes. Although further work needs to be done, particularly as to whether these C-21 effects are independent of reductions in BP, the results clearly show that AT_2R activation protects against HSD-induced renal target organ damage in obesity.

CONCLUSION

AT_2Rs constitute an important component of the “protective arm” of the RAS, counter-balancing the untoward actions the main RAS effector peptide, Ang II, via AT_1Rs. The functions of AT_2Rs have been more difficult to elicit than those of AT_1Rs, at least in part due

to the relatively low expression level of AT_2Rs compared to AT_1Rs in adult cardiovascular and renal cells. With the recent development of highly selective AT_2R agonists, however, the physiological and pathophysiological roles of these receptors are beginning to be clarified. Several concepts governing the role of AT_2Rs in biological actions have emerged (Figure 2). First, AT_2R activation seems to exert a beneficial role, such as natriuresis and/or hypotension, when the RAS is activated, as in Ang II-dependent hypertension or obesity with the metabolic syndrome. Second, AT_2R beneficial effects are also observed when AT_1Rs are blocked, so that AT_2R responses are not swamped by AT_1Rs and concurrently by facilitating stimulation of the unblocked AT_2Rs. Third, the endogenous AT_2R agonist (predominant or exclusive) appears to be the Ang II metabolite, Ang III. Fourth, because AT_2Rs are recruited to plasma membranes and do not internalize, at least in renal epithelial cells, AT_2R activation can sustain long-term beneficial effects, such as natriuresis, without desensitization. Fifth, AT_2R activation has the capacity to improve or abolish target organ damage in certain cardiovascular and renal disease states. Many of these principles have been derived from work during the past year, which when coupled with past studies, have improved our understanding of the role of AT_2Rs in pathophysiology and highlighted the promise of AT_2R agonist therapy in the near future.

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KEY POINTS

- Angiotensin AT_2 receptor (AT_2R) activation induces natriuresis, maintains negative Na^+ balance and lowers blood pressure chronically in angiotensin-dependent hypertension due to reduced Na^+ reabsorption at the renal proximal tubule.
- AT_2R activation prevents salt-sensitive hypertension in the obese Zucker rat model of obesity and the metabolic syndrome.
- Nitric oxide is both a product and a stimulator of AT_2Rs, potentially reinforcing the AT_2R biological response.
- β-Pro-angiotensin III, a novel synthetic AT_2R peptide agonist, reduces blood pressure in spontaneous hypertension.
- AT_2R activation improves renal structural and functional damage high salt diet-fed obese Zucker rats.

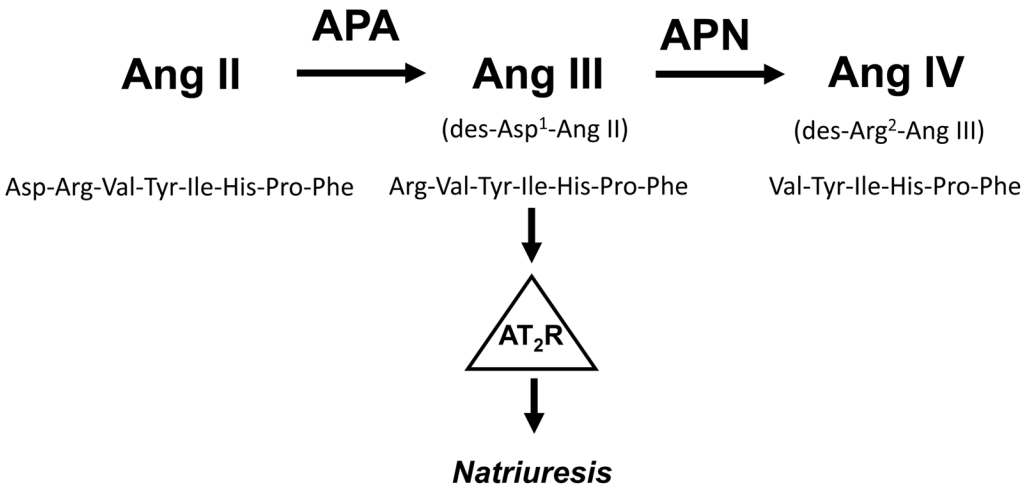

Figure 1.

Schematic representation of the metabolism of Ang II to Ang III by aminopeptidase A (APA) and Ang III to Ang IV by aminopeptidase N (APN) with peptide sequences. Ang III is the major endogenous AT_2R agonist inducing natriuresis in rodents. Ang II: angiotensin II; Ang III: angiotensin III; AT_2R: angiotensin subtype 2 receptor.

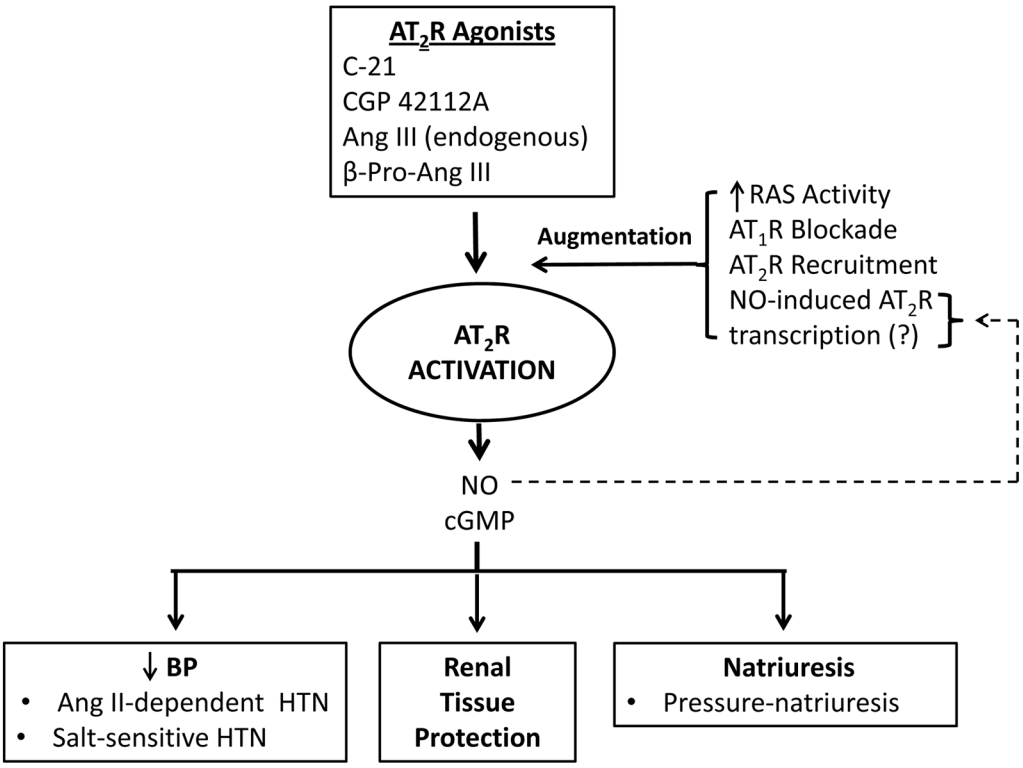

Figure 2.

Schematic representation of the current understanding of the role of AT_2R activation in the control of BP and renal function on the basis of studies published during the past year. The ability of an AT_2R agonist to activate the receptor is dependent on at least four factors shown at the upper right of the diagram. The biological effects are shown at the bottom of the figure. Ang II: angiotensin II; Ang III: angiotensin III; AT_1R: angiotensin subtype 1 receptor; AT_2R: angiotensin subtype 2 receptor; BP: blood pressure; β-Pro-Ang III: beta-proline-angiotensin III; C-21: Compound 21; cGMP: guanosine cyclic 3′,5′-monophosphate; HTN: hypertension; NO: nitric oxide; RAS: renin-angiotensin system; (?): putative.