Published in final edited form as:
Hypertension. 2013 March ; 61(3): 673–680. doi:10.1161/HYPERTENSIONAHA.111.00241.

CHBPR - Excellence Award for Hypertension Research - THE INTRARENAL RENIN-ANGIOTENSIN AND DOPAMINERGIC SYSTEMS: CONTROL OF RENAL SODIUM EXCRETION AND BLOOD PRESSURE

Robert M. Carey
Division of Endocrinology and Metabolism, Department of Medicine, University of Virginia Health System, Charlottesville, VA 22908

The renin-angiotensin system (RAS) is a coordinated hormonal cascade critical to the control of renal sodium (Na^+) excretion and blood pressure (BP) (1). Angiotensin II (Ang II), the principal RAS effector peptide, binds to two distinct receptors, the Ang type-1 receptor (AT_1R) and the Ang type-2 receptor (AT_2R) with high affinity (1,2). The vast majority of actions of Ang II are transmitted via AT_1Rs, including cellular dedifferentiation and proliferation; vasoconstriction, reduction of vascular compliance, cardiac contractility, increased renal tubule sodium (Na^+) reabsorption; aldosterone, vasopressin and endothelin secretion; salt appetite; thirst and activation of the sympathetic nervous system (1,2). In contrast, AT_2Rs generally oppose the actions of Ang II via AT_1Rs under most circumstances (1–4).

Another major regulatory system in cardiovascular and renal physiology is the peripheral dopaminergic system. Dopamine is mainly synthesized in renal proximal tubule cells (RPTCs) via the decarboxylation of L-dihydroxyphenylalanine (L-DOPA) that has been filtered at the glomerulus and transported into the RPTC across the apical brush border (5). Synthesized DA exits the cell mainly across the apical plasma membrane into the lumen where it can bind to and activate specific DA D_1-like receptors ($D_{1\text{-like}}R$: D_1 and D_5) (5,6). D_1-like receptor activation induces vasodilation and inhibits renal Na^+ reabsorption, actions which also oppose those of Ang II via AT_1Rs.

The purpose of this brief review is to summarize some of the key findings leading to our present concepts of AT_2Rs and D_1-like receptors that oppose the actions of Ang II via AT_1Rs within the kidney.

Evidence for an independent functional intrarenal RAS

Although renin was identified in the brain and the adrenal cortex in the late 1960s and early 1970s, the intrarenal RAS was the first independent functional tissue RAS to be described (7–9). The initial observations were from *in vivo* studies which demonstrated that intrarenal inhibition of the RAS with angiotensin converting enzyme (ACE) inhibitors or Ang receptor blockers, at infusion rates that did not alter systemic BP during the experimental period, increased renal plasma flow, glomerular filtration rate and Na^+ and water excretion (7) (Figure 1). These results were later confirmed by more rigorous approaches showing that

Correspondence: Dr. Robert M. Carey, P.O. Box 801414, University of Virginia Health System, Charlottesville, VA 22908-1414; phone: 434-924-5510; fax: 434-982-3626; rmc4c@virginia.edu.

DISCLOSURES: None

small intrarenal doses of Ang receptor blocker, while not altering pressor responses to systemically administered Ang II, induced marked increases in renal hemodynamic and tubular function (8,9) (Figure 2). Later, it was demonstrated that the mRNAs and proteins for all of the system components (renin, angiotensinogen (Agt), ACE and AT_1Rs) are localized in a site-specific manner within the kidney and that intrarenal formation of Ang II occurs independently of renal uptake of the peptide (1).

Additional evidence for a separate renal tissue RAS came from studies showing that intrarenal Ang II levels were elevated in the nanomolar range in renal interstitial fluid compared to picomolar concentrations in plasma, that intrarenal Ang II concentrations were markedly increased compared to plasma levels in response to Na^+ restriction and that this response was blocked with intrarenal renin inhibition (10). Cellular studies demonstrated that Agt, Ang I and Ang II could be co-localized with renin in proximal tubule and juxtaglomerular cells, that Ang peptides were released from these cells and that the release was regulated (11). Further functional studies demonstrated that combined intrarenal RAS blockade with low doses of ACE inhibitor, AT_1R blocker and renin inhibitor, while confined to the kidney, augmented major increases in renal function that were blocked with concurrent intrarenal Ang II administration (12). Altogether, these studies provided strong support for the existence of an independent functional intrarenal RAS.

Definitive molecular evidence for an independent intrarenal RAS and its importance in the control of BP was obtained using a transgenic mouse model over-expressing Agt either in the kidney or the systemic circulation (13). Expression of Agt selectively within the kidney induced chronic hypertension independently of the endocrine RAS (13). Within the kidney, there is now substantial evidence for a separate intratubular RAS in which Ang II formation is auto-amplified by Ang II-induced up-regulation of Agt, creating a positive feedback loop that may play a role in renal tissue damage and hypertension (14). Current studies are also providing evidence for intracellular RASs that are independently functioning in a specific subcellular compartment. Such subcellular RASs have recently been described both within nuclei and mitochondria (15, 16).

AT_2R Expression and Cell Signaling Pathways

The AT_2R is a 7-transmembrane G-protein-coupled receptor, encoded on the X - chromosome, with only 34% amino acid sequence homology with the AT_1R (2). AT_2Rs are expressed ubiquitously at very high levels in the fetus, but decline precipitously in the neonatal period in most, but not all tissues. Although the expression of AT_2Rs is substantially lower than that of AT_1Rs in the adult, AT_2R mRNA and protein can be easily detected in the adult kidney, adrenal cortex, heart and vasculature and predominates over AT_1Rs in the uterus, ovary, adrenal medulla and in discrete areas of the brain (17–20). Within the kidney, AT_2Rs are expressed predominantly in RPTCs and glomeruli (18, 19).

The cell signaling mechanisms of AT_2Rs differ substantially from those of AT_1Rs. AT_2R activation initiated by binding of Ang II to the receptor in the plasma membrane triggers G protein coupling of Giα2 and Giα3 via the third intracellular loop of the receptor. G protein coupling initiates the activation of phosphotyrosine phosphatases, which dephosphorylate and inactivate mitogen-activated protein (MAP) kinases including extracellular-regulated kinase (ERK)-1 and ERK-2. Phosphotyrosine phosphatase activation can also occur through a non-G protein-coupled mechanism. MAP kinase inhibition via AT_2Rs opposes MAP kinase activation as a result of AT_1R activation. The opposing action of AT_1Rs and AT_2Rs on MAP kinases is considered a fundamental signaling mechanism for receptor-receptor interactions (1–4).

AT_2Rs can also activate the phospholipase A_2 pathway leading to arachidonic acid release and long-term AT_2R activation can also increase the biosynthesis of ceremides, which can stimulate stress kinases and caspases to induce apoptosis (4).

Vascular AT_2R Actions and Mechanisms

Overwhelming evidence currently exists that AT_2Rs mediate vasodilation and oppose the AT_1R-mediated vasoconstrictor actions of Ang II (21–35). AT_2R-mediated vasodilation has been demonstrated in small resistance arteries of the mesenteric, uterine, adrenal, coronary and peripheral circulations in many animal models and in humans. AT_2R-induced vasodilation has also been demonstrated in large capacitance vessels such as the aorta and in the fetus (29–31). AT_2R-stimulated vasodilation is mediated by a signaling cascade composed of bradykinin (BK), nitric oxide (NO) and 3′,5′-cyclic guanosine monophosphate (cGMP) (Figures 3 and 4)(21;36–38). AT_2Rs increase NO and cGMP production either by increasing BK production with activation of BK B2 receptors or by direct activation of NO production independently of BK (39–41).

AT_2R-mediated vasodilation is most readily demonstrated when AT_1Rs are blocked with an AT_1R antagonist (22,23,25,26). This is almost certainly because AT_1R expression predominates over that of AT_2Rs in the vasculature (42,43). AT_2R-stimulated vasodilation is also augmented when the RAS is activated, such as during Na^+ restriction, Ang II infusion or in renal vascular hypertension (21, 22, 44). Under all three circumstances, AT_2Rs are upregulated, enhancing the vasodilator response to Ang II (18,21,44). Another condition which upregulates AT_2R expression (by 300%) and unmasks its vasodilator action is increased pressure load from aortic banding (29,30). AT_2R blockade with specific antagonist PD-123319 (PD) or BK B_2 receptor inhibition with icatibant restores the diminished Ang II contractile responses and abolishes the 9-fold increase in aortic cGMP stimulated by Ang II under these circumstances (29,30). Taken altogether, the results of these studies emphasize the likely importance of counter-regulatory AT_2R upregulation and activation in circulatory disorders associated with chronic vasoconstriction via AT_1Rs.

The vasodilator and depressor actions of AT_2Rs are both acute and chronic and are not accompanied by desensitization, rendering these receptors a potential therapeutic target in hypertension (23,25). Indeed, the BP lowering effects of AT_1R blockade may be mediated, at least in part, by AT_2R activation as a result of increased renin biosynthesis and release and increased Ang II that can act via unblocked AT_2Rs (21,22). An example of this principle was demonstrated in diabetic, hypertensive humans in whom chronic AT_1R inhibition upregulated vascular AT_2Rs and facilitated a vasodilator response to Ang II *in vitro* (34). In addition, in spontaneously hypertensive rats during AT_1R blockade, pharmacological activation of AT_2Rs by Compound 21 (a non-peptide AT_2R agonist with >25,000-fold selectivity for AT_2Rs over AT_1Rs) resulted in decreased BP (35). These observations indicate the potential importance of a non-peptide AT_2R agonist combined with an AT_1R blocker in the treatment of hypertension.

AT_2R-mediated vasodilation and hypotension were confirmed in AT_2R-null mice. (45). Although baseline BP was similar between AT_2R-null and wild-type (WT) mice, AT_2R-null mice demonstrated marked and sustained hypersensitivity to the pressor actions of infused Ang II over the course of 7 days, emphasizing the importance of AT_2Rs in counter-regulating Ang II actions via AT_1Rs. Ang II pressor hypersensitivity was accompanied by a highly significant reduction in baseline and Ang-II stimulated renal interstitial levels of BK, NO and cGMP in AT_2R-null mice.

Intrarenal AT_2R Actions and Mechanisms

AT_2R-null mice also had marked antinatriuresis (and inhibition of pressure- natriuresis) during the chronic Ang II infusion that was not present in WT mice (45). These results suggested the possibility that intrarenal AT_2Rs might increase renal Na^+ excretion via BK, NO and cGMP (45).

We subsequently explored and presented definitive evidence that intrarenal AT_2R activation mediates natriuresis (46–48). These studies were enabled by the technique of renal interstitial microinfusion of pharmacological agents, which affords direct evaluation of the intrarenal mechanisms governing renal function without systemic hormonal or hemodynamic influences. Selective intrarenal AT_1R blockade in rats induced a highly significant natriruesis that was abolished by intrarenal co-administration of AT_2R-specific antagonist PD indicating that the natriuretic effect of AT_1R blockade is mediated by AT_2R activation (46).

However, we were surprised to find that intrarenal Ang II infusion did not alter Na^+ excretion even at high infusion rates. This finding provoked a question as to whether a downstream metabolite of Ang II might be required for renal AT_2R activation. Indeed, intrarenal infusion of des-aspartyl[1] Ang II (Ang III) into systemically AT_1R blocked rats induced a significant natriuretic response, which was abolished with intrarenal co-infusion of PD (46) (Figure 5). Intrarenal Ang III infusion in the absence of systemic AT_1R blockade did not change Na^+ excretion, similar to AT_2R-mediated vascular responses (46). In follow up of this observation, we hypothesized that Ang II needs to be converted to Ang III to interact with AT_2Rs within the kidney. Ang II is converted to the heptapeptide Ang III by aminopeptidase A (APA), and Ang III is converted to the hexapeptide Ang IV by aminopeptidase N (APN). In the presence of systemic AT_1R blockade, intrarenal infusion of Ang III induced a natriuretic response that was markedly augmented by intrarenal co-administration of APN inhibitor 2-amino-methylsulfonyl-butane-thiol, methane-thiol (PC-18) (47). The PC-18-augmented natriuresis was abolished by intrarenal AT_2R inhibition with PD, indicating an AT_2R-mediated effect (47). The necessity for conversion of Ang II to Ang III for AT_2R-mediated natriuresis was confirmed by demonstrating that intrarenal administration of Ang II is only effective in inducing natriuresis when APN is blocked and that this response is abolished by intrarenal co-administration of APA inhibitor 3-amino-4-thio-butyl-sulfonic acid (EC-33) (48). Taken altogether, these studies demonstrate that Ang III is the preferred agonist for AT_2R-mediated natriuresis. In systematic receptor binding studies, Ang III has been found to have about 30-fold selectivity over Ang II for AT_2Rs (49). Confirming these results, Ang III has been shown to be the preferred AT_2R agonist in other tissues such as the coronary microcirculation and adrenal cortex (50, 51).

Recent *in vivo* studies have demonstrated that Ang III induces natriuresis via AT_2R activation in the renal proximal tubule by a NO/cGMP signaling mechanism (52). *In vitro* studies also have recently shown that AT_2Rs reduce AT_1R function in the proximal tubule by the common NO/cGMP pathway and also reduce AT_1R mRNA via the ubiquitous transcription factor Sp1 (53). Ligand-activated AT_2Rs also heterodimerize with AT_1Rs reducing their expression via protein-protein action in the plasma membrane (53). Thus, AT_2Rs may oppose AT_1Rs by several pathways in the kidney.

The recent *in vivo* investigations cited above have confirmed that Ang III is the preferred endogenous ligand for the activation of renal AT_2Rs (52). Unexpectedly, these studies were unable to elicit a natriuretic effect of Ang (1-7), which has counter-regulatory effects offsetting AT_1R actions in other tissues (55). No natriuretic response to Ang (1-7) was observed at equimolar doses as Ang III even in the presence of AT_1R blockade, ACE

inhibition to reduce Ang (1-7) metabolism or APA blockade to augment Ang (1-7) formation from Ang II via ACE-2 (52). However, these studies did demonstrate that intrarenal administration of APN inhibitor PC-18 induces natriuresis even in the absence of systemic AT_1R blockade. Furthermore, renal interstitial Ang peptide levels during Ang III administration with and without PC-18 demonstrated a marked augmentation of renal interstitial and tissue Ang III concentrations and AngIII/Ang II ratios during PC-18 administration, consistent with the role of Ang III in the augmented natriuretic effect (52). These studies also demonstrated that systemic administration of the highly selective non-peptide AT_2R agonist Compound 21 induces natriruesis that is abolished with intrarenal AT_2R antagonist PD in both male and female rats even in the absence of AT_1R blockade, suggesting the potential for this compound as a natriuretic/diuretic agent in the treatment of disorders associated with extracellular fluid volume expansion and hypertension.

Recent studies also have suggested that AT_2Rs in the thick ascending limb of Henle (TAL) may contribute to the natriuretic response (54,55). Ang II increases NO production in TALs via activation of AT_2Rs and NO inhibits the $Na^+/K^+/2Cl^-$ co-transporter and reduces Na^+ reabsorption in this nephron segment (55). Whether this response requires Ang II conversion to Ang III awaits further study.

The Intrarenal Dopaminergic System

The renal dopaminergic system is a major hormonal system controlling renal Na^+ excretion and BP (5). $D_{1\text{-like}}R$ activation inhibits renal Na^+ reabsorption through an adenylyl cyclase-cyclic AMP (cAMP) mechanism. In both humans and experimental animals highly selective $D_{1\text{-like}}R$ agonist fenoldopam elicits a substantial natriuretic response that is based almost exclusively on inhibition of renal proximal tubule Na^+ reabsorption (5, 56–60). Thus, the renal dopaminergic system is an important counter-regulatory system offsetting the antinatriuretic actions of AT_1Rs. Indeed, fenoldopam was demonstrated to be close to ideal as an antihypertensive agent in that it normalized BP without reflex tachycardia and induced natriuresis in patients with primary hypertension (61) (Figure 6). In spite of its low bioavailability, these and other favorable observations led to FDA approval for emergency treatment of hypertension in intensive care settings.

The physiological importance of the renal dopaminergic system in the control of Na^+ excretion was demonstrated initially during the 1980s. Studies employing intrarenal arterial administration of highly selective $D_{1\text{-like}}R$ antagonist SCH-23390 revealed that, similar to the intrarenal RAS, DA synthesized within the kidney acts in a local cell-to-cell (paracrine) manner exclusively at the renal proximal tubule to control Na^+ excretion (62,63) (Figure 7). These studies demonstrated that approximately 60% of basal Na^+ excretion in the Na^+-replete state is controlled by intrarenal dopaminergic mechanisms acting at the proximal tubule. These observations were later confirmed using renal interstitial infusion of D_1R antisense oligodeoxynucleotides to inhibit receptor expression directly (64). The importance of the renal dopaminergic system in the control of Na^+ excretion was further underscored by the demonstration that the natriuretic and diuretic effects of $D_{1\text{-like}}Rs$ are dependent on the state of Na^+ balance. In Na^+ - deplete states, $D_{1\text{-like}}R$ - mediated natriuresis does not occur, whereas in normal or high Na^+ states $D_{1\text{-like}}Rs$ induce a robust natriuretic response (60). Additional evidence for the physiological importance of renal dopaminergic control of Na^+ excretion included the observation that renal DA production is increased during Na^+ surfeit but reduced during Na^+ depletion (65). Elegant studies in mice with selective proximal tubule knockout of aromatic amino acid decarboxylase, the enzyme generating DA from L-DOPA, inducing intrarenal DA depletion have recently confirmed the importance of intrarenal DA in the control of Na^+ excretion and BP (66). Taken altogether, these studies

strongly support the physiologic importance of renal DA and $D_{1\text{-like}}$Rs as counter-regulatory systems limiting at least in part the Na^+-retaining actions of intrarenal Ang II via AT_1Rs.

In the mid-1990s, with antibodies directed towards the extracellular domain of D_1Rs, receptor protein was localized in the renal proximal tubule and in several other cells and tissues (67–69). Similar to the AT_2R, D_1R mRNA is expressed only in low copy and was difficult to demonstrate using standard molecular techniques. However, D_1R protein cellular distribution was later confirmed using more sensitive *in situ* amplification of D_1R mRNA (70).

D_1R/AT_2R Interactions

Renal interstitial administration of fenoldopam in Na^+-loaded rats elicits a robust natriuretic response that is abolished with intrarenal co-administration of $D_{1\text{-like}}$R antagonist SCH-23390 (71). However, we were surprised to find that fenoldopam-induced natriuresis is also completely inhibited with intrarenal co-infusion of AT_2R antagonist PD (71) (Figure 8). To explore the possible mechanism of AT_2R involvement in $D_{1\text{-like}}$R-induced natriuresis, studies were performed to determine the intracellular trafficking of AT_2Rs in RPTCs (71,72). *In vivo* administration of fenoldopam was associated with translocation of AT_2Rs from intracellular sites to the apical plasma membranes of RPTCs. Fenoldopam-induced AT_2R translocation to the apical plasma membrane and natriuresis were abolished in the presence of microtubulin inhibitor nocodazole but were unaffected by actin microfilamint inhibitor cytochalasin D, suggesting that microtubules are required for the translocation process (72). Because $D_{1\text{-like}}$Rs signal via an adenylyl cyclase, cAMP and protein kinase A pathway, we explored the role of these signaling processes in $D_{1\text{-like}}$R – induced AT_2R recruitment to the apical plasma membrane and its necessity for the natriuretic response. *In vivo* experiments demonstrated that intrarenal administration of direct adenylyl cyclase activator forskolin together with 3-isobutyl-1-methyl xanthine (IBMX) to inhibit its metabolism increased renal interstitial fluid levels of cAMP, stimulated AT_2R recruitment to the RPTC apical plasma membrane and induced natriruesis that was abolished with AT_2R antagonist PD (72). Direct agonist stimulation of $D_{1\text{-like}}$Rs was not necessary for AT_2R-mediated natriuresis since forskolin/IBMX-induced AT_2R translocation and natriuresis persisted in the presence of $D_{1\text{-like}}$R blockade with SCH-23390 (72). Therefore, the mechanism by which AT_2Rs and $D_{1\text{-like}}$Rs interact during high Na^+ conditions to induce natriuresis is $D_{1\text{-like}}$R-cAMP signaling, which provides the necessary stimulus for AT_2R translocation and natriuresis. We also demonstrated that similar to agonist-stimulated D_1R recruitment to the plasma membrane, AT_2Rs are translocated via microtubules to the apical plasma membrane, where they are required to induce the natriuretic response (72, 73).

Recently, AT_1R-null animals were demonstrated to have increased longevity (74). In current studies, the aging process is beginning to be linked to reduction in AT_2R and D_1R expression and/or activation in different tissues and at the mitochondrial level (16, 75,76). It is possible that D_1R and/or AT_2R pharmacological activation may provide a new target for the reversal of certain aspects of the aging process and/or for the extension of lifespan in the future.

Conclusions and Perspectives

In conclusion, the intrarenal renin-angiotensin and dopaminergic systems play a major critical role in cardiovascular and renal function, the subject of this brief review. AT_2Rs and D_1Rs cooperatively oppose the vasoconstrictor and antinatriuretic functions mediated by Ang II at AT_1Rs. Reduced AT_2R expression and/or activity may contribute to the initiation and/or acceleration of disease processes including hypertension, edema-forming states and inflammation/fibrosis leading to cardiovascular and renal damage. Conversely,

pharmacological activation of AT_2Rs and/or D_1Rs may provide therapeutic advantages or even preventive strategies in the presence or absence of AT_1R blockade. Increased understanding of angiotensin and dopamine receptor functions and interactions currently provides hope for improved treatment and prevention of hypertension and other Na^+/fluid retaining states and for the extension of healthier lives in the future.

Acknowledgments

SOURCES OF FUNDING: None

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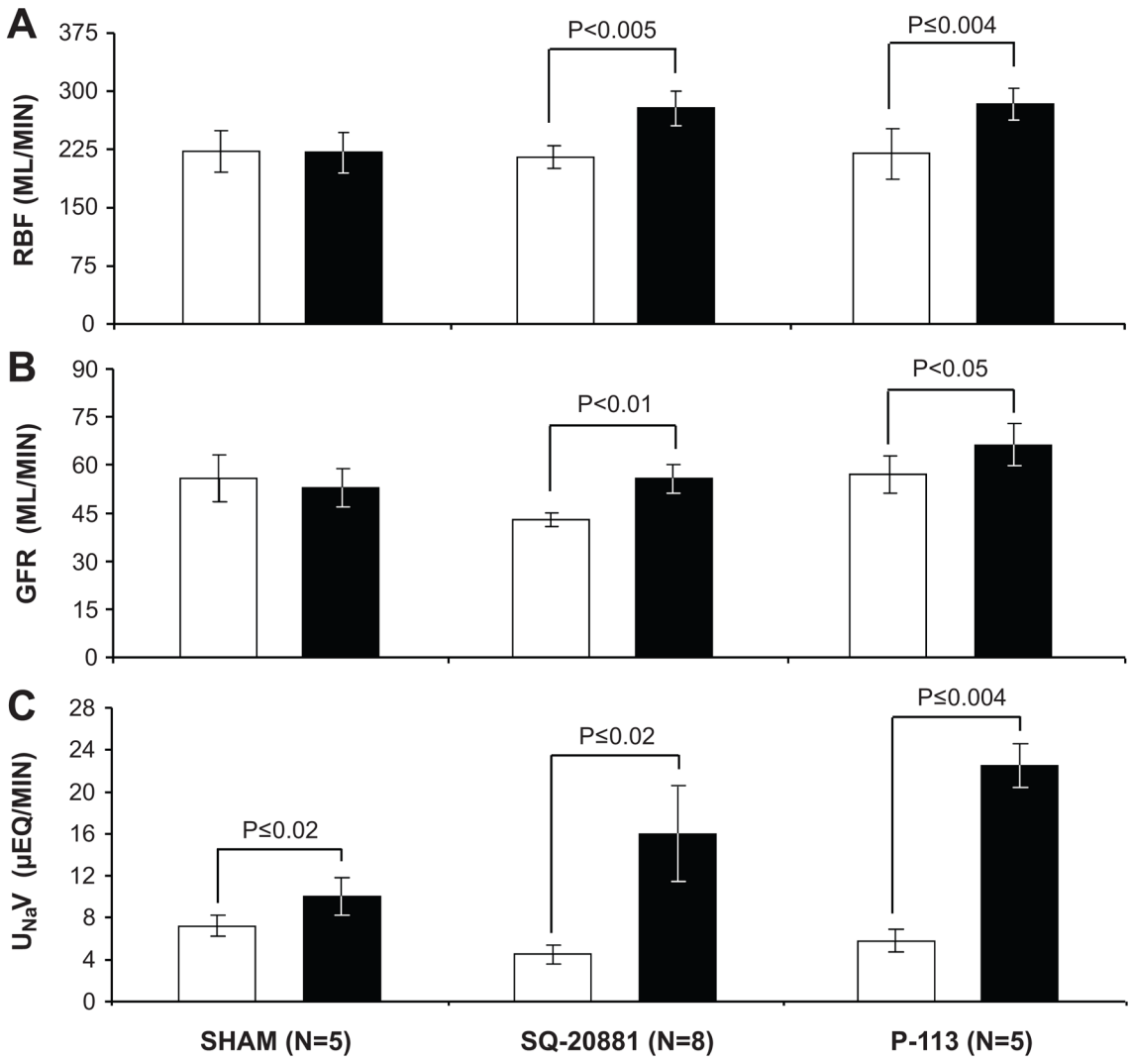

Figure 1.

Evidence for a functional intrarenal renin-angiotensin system in uninephrectomized conscious dogs. **Panel A**: Renal blood flow (RBF); **Panel B**: glomerular filtration rate (GFR); **Panel C**: Urinary Na^+ excretion ($U_{Na}V$) in response to intrarenal arterial administration of ACE inhibitor SQ-20881 (2 μg/kg/min) or Ang receptor blocker P-113 (saralasin; 2 μg/kg/min). Control vehicle infusion, white bars; experimental agent infusion, black bars. Sham data include vehicle infusion only. Data are expressed as mean ± 1 SE. Adapted from Kimbrough HM *et al. Circ Res*. 1977;40:174–178.

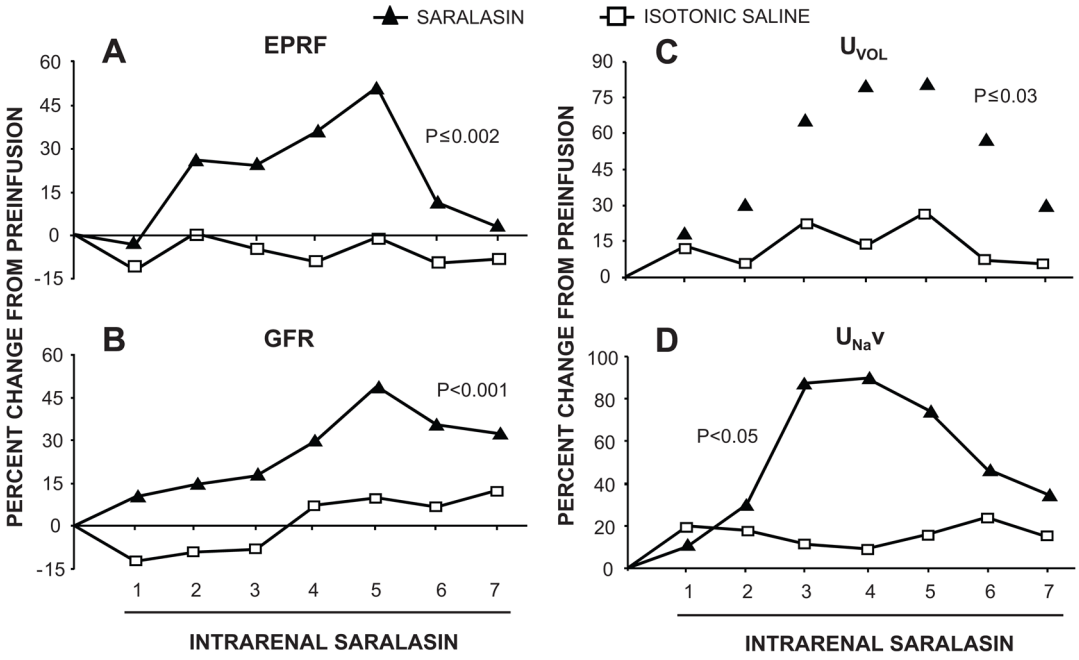

Figure 2.

Validation of an independent functional intrarenal renin-angiotensin system in uninephrectomized conscious dogs. Estimated renal plasma flow (ERPF; **Panel A**), glomerular filtration rate (GFR; **Panel B**), urine flow rate ($U_{VOL;}$ **Panel C**) and urinary Na^+ excretion ($U_{Na}V$; **Panel D**) in response to low-dose intrarenal arterial infusion of Ang receptor blocker saralasin (0.07 μg/kg/min). Numbers on abscissa represent 20 min clearance periods. Adapted from Levens NR *et al. Endocrinology*. 1983:112:43–49 with permission.

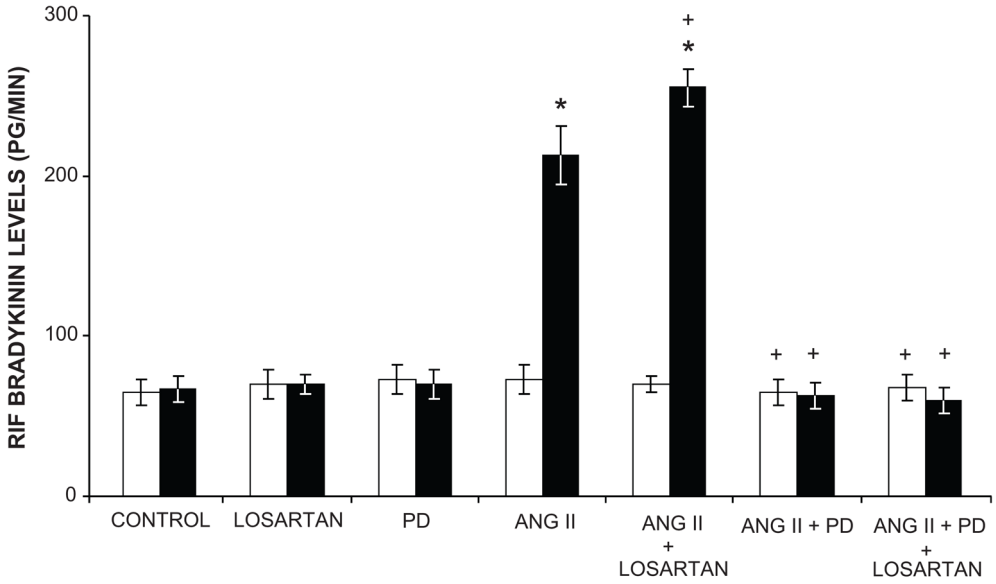

Figure 3.

Ang II releases renal bradykinin (BK) by AT_2R activation. Renal interstitial fluid BK levels in response to intravenous infusion of Ang II, Losartan, an AT_1R antagonist; PD, PD-123319, an AT_2R antagonist, and combinations in Sprague-Dawley rats. Control vehicle infusions, white bars; experimental agent infusions, black bars. Data are expressed as mean ± 1 SE. * $P<0.0001$ from control; + $P<0.05$, ++$P<0.0001$ from Ang II alone. Data from Siragy HM *et al. Am J Physiol Reg Int Comp Physiol.* 1996;271:R1090–R1095 and Siragy HM and Carey RM, *Hypertension* 1999;33:1237–1242.

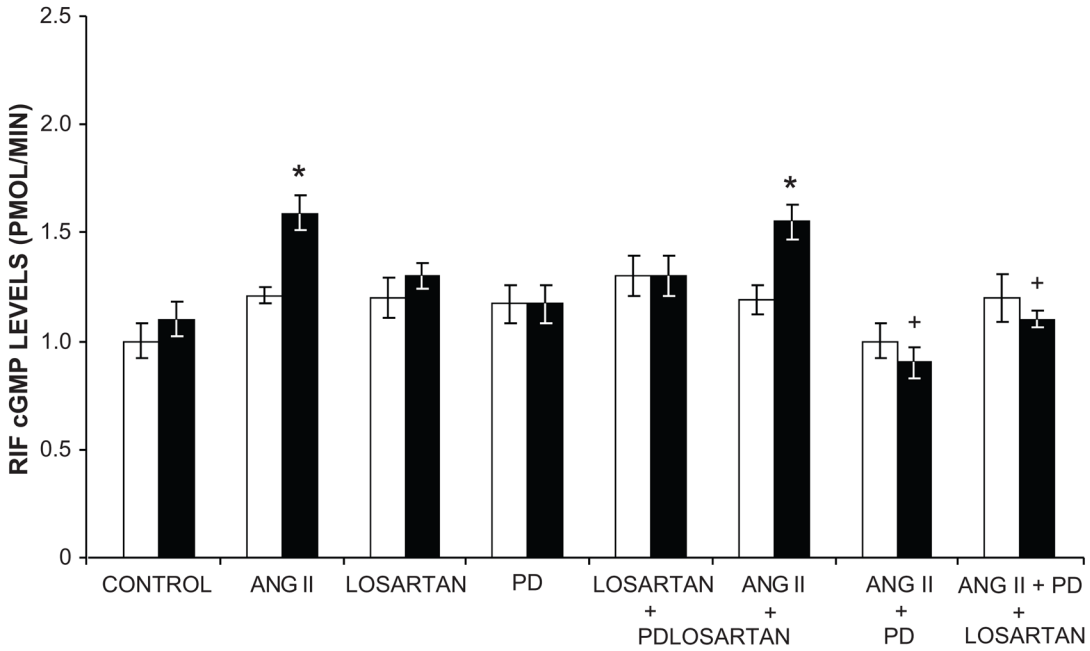

Figure 4.

Ang II releases renal cyclic GMP (cGMP) by AT_2R activation. Renal interstitial fluid cGMP levels in response to intravenous infusion of Ang II; Losartan, an AT_1R antagonist; PD, PD-123319, an AT_2R antagonist, and combinations in Sprague-Dawley rats. Control vehicle infusion data, white bars; experimental agent infusion, black bars. Data represent mean ± 1 SE. * $P<0.001$ from vehicle or time control; + $P<0.001$ from Ang II alone. Adapted from Siragy *HM and Carey RM. *J Clin Invest.* 1996;97:1978–1982 and Siragy HM and Carey RM. *J Clin Invest.* 1997:100:264–269 with permission.

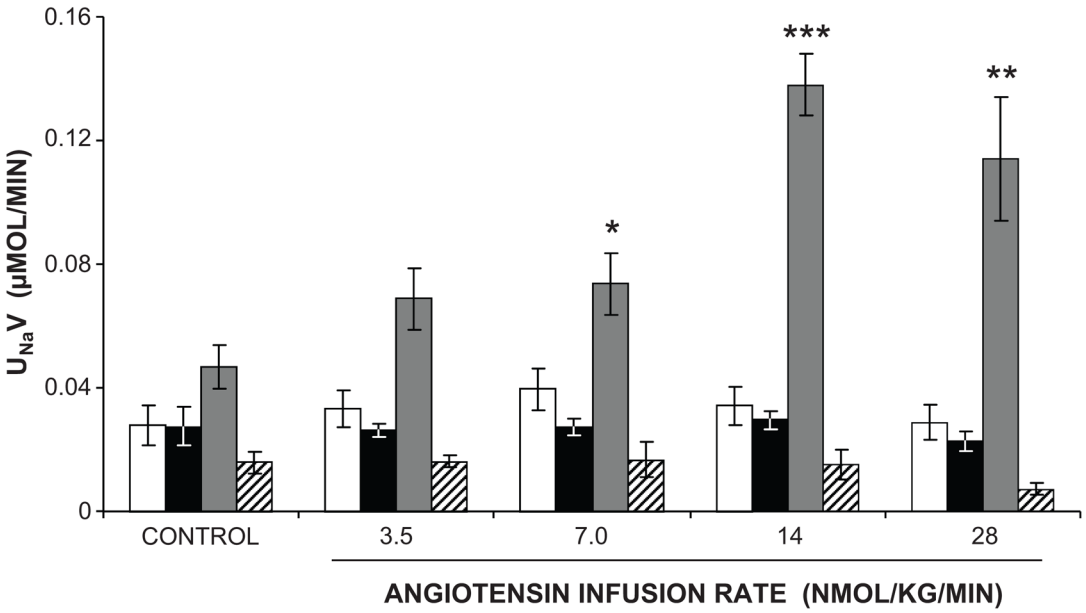

Figure 5.

Ang III is the preferred endogenous AT_2R agonist mediating natriuresis. Urinary Na^+ excretion ($U_{Na}V$) in anesthetized Sprague-Dawley rats in response to direct renal interstitial infusion of vehicle (white bars), Ang II (black bars), Ang III (gray bars) or Ang III +PD (PD-123319, an AT_2R antagonist) (striped bars). Data are expressed as mean ± 1 SE. * P<0.05, ** P<0.01, *** P<0.001 from time control. Adapted from Padia SH *et al. Hypertension.* 2006.

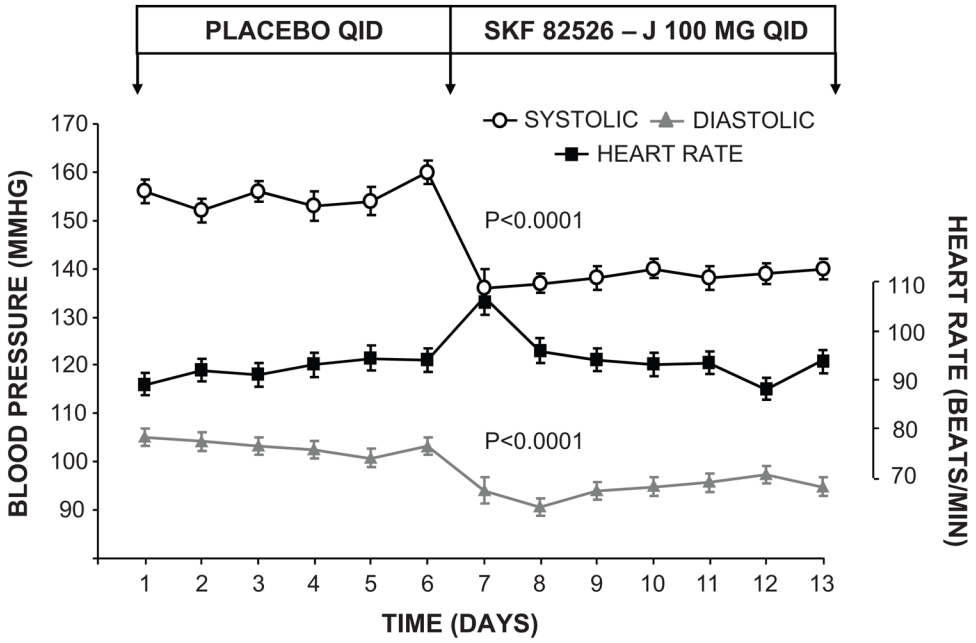

Figure 6.

Oral fenoldopam lowers BP in hypertensive humans. BP responses to oral fenoldopam (SKF-82526-J) in patients with primary hypertension. Data are expressed as mean ± 1 SE. Adapted from Carey RM *et al. J Clin Invest*. 1984;74:2198–2207 with permission.

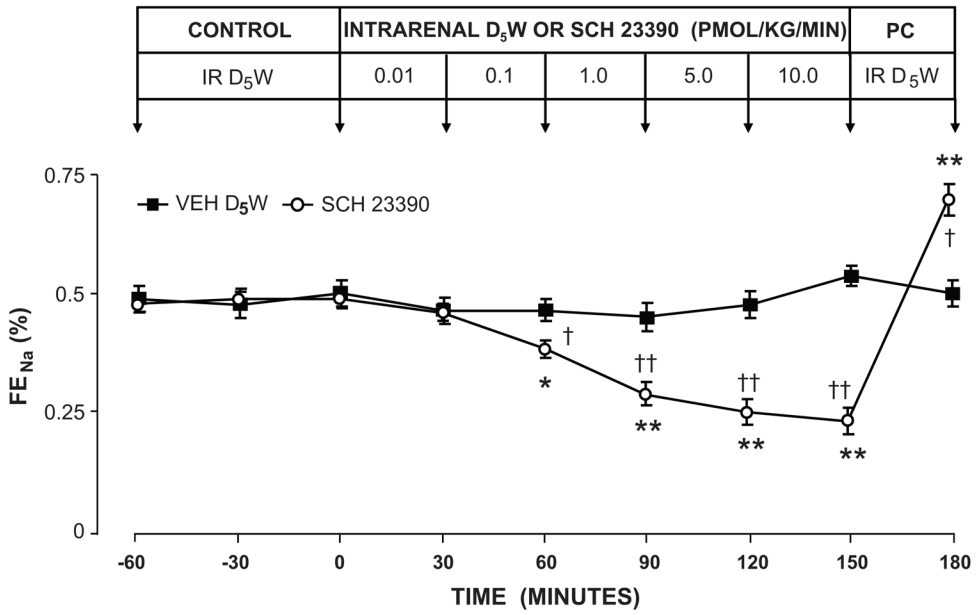

Figure 7.

Evidence that intrarenal dopamine controls renal Na^+ excretion by a paracrine mechanism acting at the level of the renal tubule. Urinary Na^+ excretion ($U_{Na}V$) in uninephrectomized conscious dogs infused intrarenally with $D_{1\text{-LIKE}}$ receptor antagonist SCH-23390. Data are expressed as mean ± 1 SE. * P<0.001, ** P<0.0001 from pre-control; † P<0.05, †† P<0.01 from time control. Adapted from Siragy HM *et al. Am J Physiol Renal Physiol.* 1988;257:F469–F477 with permission.

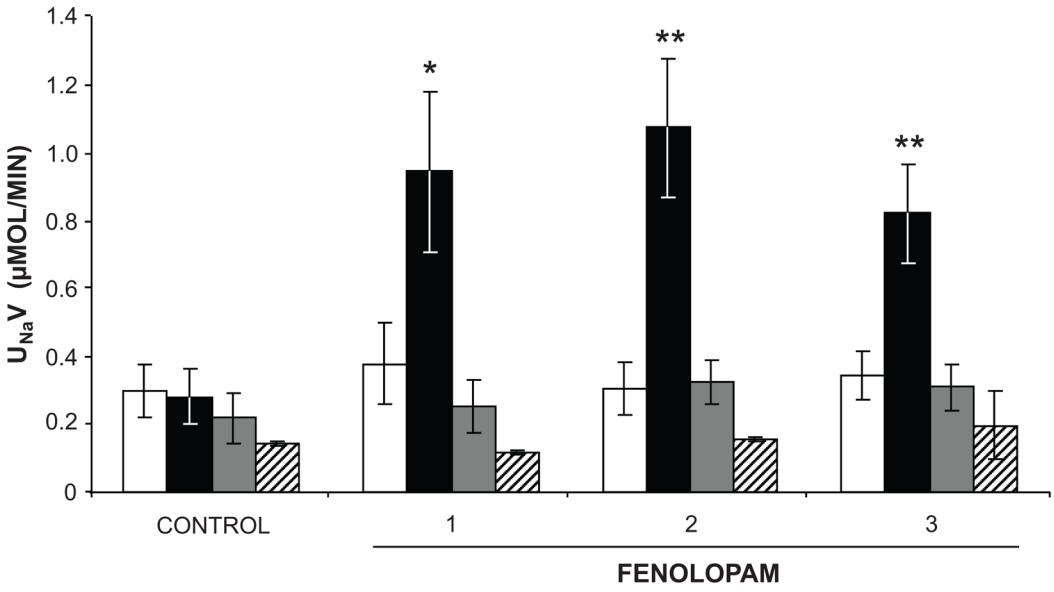

Figure 8.

Intrarenal interstitial fenoldopam-induced natriruesis is abolished by intrarenal $D_{1\text{-LIKE}}$ receptor antagonist SCH-23390 (SCH) or AT_2R antagonist PD-123319 (PD) in anesthetized, uninephrectomized Sprague-Dawley rats. Vehicle infusion, white bars; fenoldopam (1 μg/kg/min) infusion, black bars; fenoldopam + PD infusion, gray bars; fenoldopamn + SCH infusion, striped bars. Data are expressed as mean ± 1 SE. Numbers on the abscissa refer to experimental one-hour periods. * P<0.01, ** P<0.001 from vehicle control. Adapted from Salomone LJ *et al. Hypertension.* 2007;49:155–161 and Padia SH *et al. Hypertension.* 2012;59:437–445.