Intrarenal Dopamine D₁-Like Receptor Stimulation Induces Natriuresis via an Angiotensin Type-2 Receptor Mechanism


Abstract—We explored the effects of direct renal interstitial stimulation of dopamine D₁-like receptors with fenoldopam, a selective D₁-like receptor agonist, on renal sodium excretion and angiotensin type-2 (AT₂) receptor expression and cellular distribution in rats on a high-sodium intake. In contrast to vehicle-infused rats, sodium excretion increased in fenoldopam-infused rats during each of three 1-hour experimental periods (<0.001). Blood pressure was unaffected by vehicle or fenoldopam. In plasma membranes of renal cortical cells, fenoldopam increased D₁ receptor expression by 38% (P<0.05) and AT₂ receptor expression by 69% (P<0.01). In plasma membranes of renal proximal tubule cells, fenoldopam increased AT₂ receptor expression by 108% (P<0.01). In outer apical membranes of proximal tubule cells, fenoldopam increased AT₂ receptor expression by 59% (P<0.01). No significant change in total AT₂ receptor protein expression was detectable in response to fenoldopam. Fenoldopam-induced natriuresis was abolished when either PD-123319, a specific AT₂ receptor antagonist, or SCH-23390, a potent D₁-like receptor antagonist, was confused with F (P<0.001). In summary, direct renal D₁-like receptor activation increased urinary sodium excretion and the plasma membrane expression of AT₂ receptors in renal cortical and proximal tubule cells. D₁-like receptor–induced natriuresis was abolished by intrarenal AT₂ receptor inhibition. These findings suggest that dopaminergic regulation of sodium excretion involves recruitment of AT₂ receptors to the outer plasma membranes of renal proximal tubule cells and that dopamine-induced natriuresis requires AT₂ receptor activation. (Hypertension. 2007;49:155-161.)

Key Words: angiotensin ■ dopamine ■ receptors ■ sodium excretion ■ natriuresis ■ receptor trafficking ■ kidney

The kidney is endowed with 2 local hormonal systems that play a major role in the regulation of sodium (Na⁺) transport across the renal proximal tubule (RPT): the renin–angiotensin system and the dopaminergic system. In vitro studies show that angiotensin II (Ang II), the major effector peptide of the renin–angiotensin system, acts at angiotensin type-1 (AT₁) receptors on RPT cell membranes to increase Na⁺ transport across the cell from the lumen into the interstitial space and peritubular capillaries by stimulating Na⁺-hydrogen (H⁺) exchanger-3 (NHE-3) and Na⁺,K⁺-ATPase activities, respectively. On the other hand, dopamine (DA), synthesized in and secreted from RPT cells, activates D₁-like receptors (D₁ and D₅ receptor subtypes) on RPT cells to inhibit Na⁺ reabsorption by inhibiting NHE-3 and Na⁺,K⁺-ATPase activities. Although these 2 hormonal systems act in opposite directions on RPT Na⁺ transport in vitro, little is known regarding the physiological interactions of intrarenal Ang II and DA in the control of Na⁺ excretion in vivo.

Approximately 50% of basal Na⁺ excretion is mediated by the paracrine action of renal DA on RPT D₁-like receptors. However, the mechanisms of receptor interaction that govern DA-induced natriuresis are incompletely understood. DA down-regulates AT₁ receptors (AT₁Rs) in the RPT. However, Ang II binds to angiotensin type-2 (AT₂) receptors (AT₂Rs), as well as AT₁Rs, and the effects of DA on AT₂Rs are unknown. AT₂Rs are expressed in the RPT but have a low degree of renal expression compared with that of AT₁Rs. The present study explores the direct renal interstitial (RI) stimulation of D₁ receptors with fenoldopam, a selective D₁-like receptor agonist, and its effects on renal Na⁺ excretion and AT₂R expression in the rat. We demonstrate that natriuresis induced by stimulation of renal D₁-like receptors requires AT₂R expression and recruitment to the RPT plasma membrane. In the presence of AT₂R inhibition, D₁-like receptor stimulation is not able to induce renal Na⁺ excretion.

Methods

Animal Preparation
The experimental protocols, approved by the University of Virginia Animal Care and Use Committee, were conducted on 250-g Sprague–Dawley rats obtained from Harlan Teklad and were housed in the University of Virginia School of Medicine vivarium (temperature: 21±1°C; humidity: 60±10%; and light: 8:00 AM to 8:00 PM). For 1 week before and during the experiments the rats were maintained on a standard high Na⁺ rat chow containing 4% NaCl. On day 7, the
rats were placed in metabolic cages, and 24-hour urine samples were collected and assayed for Na⁺ excretion (U_{NaV}). Representative U_{NaV} was 7.12 μmol/min (normal: 1 μmol/min).

The rats were anesthetized with Nembutal (0.3 mL IP), and a tracheotomy was performed. Arterial access for BP monitoring was achieved by direct cannulation of the right carotid artery. For hydration with 5% dextrose in water at 20 μL/min, cannulation of the left jugular vein was performed. The right kidney was excised, and a microcatheter (PE-10) was inserted into the ureter of the remaining (left) kidney for urine collection.

Renal Cortical Interstitial Infusion
One or 2 microcatheters (PE-10), depending on the study, were inserted into the cortical interstitial space of the left kidney for direct RI infusion of pharmacological agents (see protocols) or vehicle at an infusion rate of 2.5 μL/min. The infusion catheters were connected to a Harvard pump 5522. On completion of the study, the left kidney was carefully excised and the rat euthanized.

RI Microdialysis
Renal cortical interstitial microdialysis for RI fluid Ang II was conducted according to methods used in past studies.⁸⁻⁹

Ang II Assay
RI Ang II was measured by enzyme immunoassay kit (Cayman Chemical). The assay sensitivity is 1 pg/mL. The assay has 4% cross-reactivity with Ang I and 36% cross-reactivity with desaspartyl-Ang II (Ang III). Relative recovery is 90% for Ang II in our microdialysis system.¹⁰

Blood Pressure Measurements
Mean arterial blood pressure was monitored by a carotid artery catheter via a digital blood pressure analyzer (Micromed Inc). Mean arterial blood pressure values were recorded every 5 minutes and averaged for each of the control and experimental periods.

Urine Collection and Analysis
Urine was collected from each rat hourly for 4 hours after a 1-hour equilibrium period and urinary flow rate (V) was calculated as microliters per minute. All of the collected urine was stored at 4°C. U_{NaV} (microliters per minute) was quantified by a flame photometer (IL-943, Instrumentation Laboratory).

Membrane Preparation and Western Blot Analysis
Plasma membranes of both renal cortical and RPT cells were isolated by the method of Nagamatsu et al¹¹ with slight modifications. RPT cells were isolated by the method of Hawksworth.¹² The rat kidneys were minced and homogenized and membranes isolated by methods described above. The membranes were solubilized, and the protein concentration was determined by the bicinchoninic acid kit (Pierce). Sodium dodecylsulfate samples were prepared, separated by SDS-PAGE, and transferred onto a nitrocellulose membrane by electroblotting as reported previously.¹³¹⁴ Ten micrograms of protein were loaded for each lane. Protein loading and equal transfer of proteins to the membrane were verified by Ponceau S staining. The membrane was incubated with a rabbit AT,R polyclonal affinity-purified antibody at a concentration of 0.15 mg/mL (1:100 dilution) raised against a synthetic peptide sequence (MKDNFSFAAATSRNITSS) derived from the amino-terminal extracellular tail of the rat AT,R amino acid sequence. This sequence was selected because of its uniqueness to the AT,R, with absence of significant homology to any other known protein.¹⁵ Blots were washed and incubated with peroxidase-conjugated donkey anti-rabbit secondary antibody for 2 hours. Immunoreactivity was visualized with enhanced chemiluminescence plus Western blotting detection kit (Amersham). Quantitative assessment of band densities was performed by scanning densitometry (ImageQuant, Molecular Dynamics). D1,Rs were detected with D, 408 antibody (a kind gift from Dr Pedro Joes) using a 1:1000 dilution. Western blotting was performed as described previously.¹⁵ Blots were probed with donkey anti-rabbit secondary antibody.

RPT Apical Membrane Isolation
Apical membranes of RPT cells were isolated by first lysing the cells in detergent-free lysing buffer and performing a biotinylated lectin pull-down assay as follows. After the tissue was homogenized, 1 mg of total protein was incubated with 20 μg of biotinylated Lotus tetragonolobus agglutinin (LTA) lectin (Vector Laboratories) in 10-μL volume for 2 hours at room temperature. A 50% vol/vol slurry (40 μL) of Ultralink Neutravidin beads (Pierce Laboratory) was then added and incubated for 30 minutes. The beads were then pelleted and thoroughly washed 5 times using a microcentrifuge spin cup filter. The LTA affinity attached membranes were eluted by incubating the beads in the spin cup filter with 40 μL of 50°C loading buffer and 20 μL loaded per lane on a gel for Western blotting.

Protocols

Effects of Direct RI D₁-Like Receptor Stimulation on U_{NaV} and Renal D₁R and AT,R
In this study, we evaluated the effects of direct RI infusion of fenoldopam on renal Na⁺ and water excretion in vivo and D₁R and AT,R protein expression in both whole cells and plasma membranes of renal cortical and RPT cells in vitro. We hypothesized that intrarenal D₁-like receptor stimulation would increase V, U_{NaV}, whole cell AT,R expression, and AT,R recruitment to the plasma membranes of RPT cells of Na⁺-loaded rats. Uninephrectomized control rats received a RI infusion of 5% dextrose in water vehicle at 2.5 μL/min for the entire 4-hour study. The experimental rats were infused with vehicle for 1 hour and then received fenoldopam, a highly selective D₁-like receptor agonist, at 1 μg/kg per minute for the remaining 3 hours.

Effects of Intrarenal AT,R Blockade on D₁-Like Receptor–Induced Natriuresis
In this study, we explored the ability of intrarenal AT,R antagonism to influence D₁-like receptor–induced natriuresis. Our hypothesis was that pharmacological AT,R blockade would inhibit D₁-like receptor-induced natriuresis. The RI space of control rats was infused with vehicle. The experimental rat kidneys were infused either with fenoldopam 1 μg/kg per minute alone or fenoldopam plus PD-123319 (PD), a specific AT,R antagonist, at 2 μg/kg per minute. The PD infusion was initiated at the beginning of the control period and continued for the entire 4-hour experiment, and fenoldopam was infused from hour 2 through hour 4 of the experiment.

Effects of D₁-Like Receptor Blockade on Intrarenal D₁-Like Receptor–Induced Natriuresis
This study was designed to demonstrate that fenoldopam-induced natriuresis is because of specific renal D₁-like receptor activation. The control rats were similarly infused with vehicle. However, the experimental rats received an RI infusion of SCH-23390, a selective D₁-like receptor antagonist, at 10 μg/kg per minute, for the entire 4 hours. After a 1-hour control period, rat kidneys simultaneously received an RI infusion of fenoldopam at 1 μg/kg per minute.

Effects of High Na⁺ Diet on Intrarenal Ang II Levels and AT,R Expression
In this study, we determined whether high Na⁺ intake would suppress intrarenal Ang II levels in either RI fluid or cortical tissue and/or influence AT,R expression. Rats (N=6 per group) were studied after 1 week on a normal (0.28%) or high (4%) NaCl diet. An interstitial microdialysis catheter was inserted into 1 kidney (subcapsular renal cortex) with animals under anesthesia, and RI fluid was collected for 60 minutes. The animals were euthanized thereafter, and the kidneys were immediately excised, homogenized, and assayed for Ang II and AT,R expression.
Effects of Intrarenal D1-Like Receptor Activation on Na+ and Water Excretion

As demonstrated in Figure 1A, for RI fenoldopam-infused rats, UNaV increased from 0.31±0.05 μmol/min in the control period to 0.59±0.10 μmol/min at 1 hour (P<0.01) and continued to be elevated at 0.76±0.11 μmol/min at 2 hours and 0.80±0.12 μmol/min at 3 hours (both P<0.001). In contrast, UNaV values for the control vehicle-infused rats did not change significantly at any time. The ANOVA value comparing UNaV values for fenoldopam- versus vehicle-infused rats for the entire study was F=12.1 (P<0.001). As shown in Figure 1B, urinary flow rate (V) for fenoldopam-infused rats increased from 0.003±0.0002 to 0.005±0.0003 μL/min (P<0.01) at 1 hour. Thereafter, V continued to be increased significantly throughout the fenoldopam infusion. V also increased significantly in vehicle control rats, but the increase in V in fenoldopam-infused rats was significantly greater than with vehicle (P<0.01). The overall ANOVA value comparing V in fenoldopam- versus vehicle-infused animals was F=4.0 (P<0.01). As shown in Figure 1C, Mean arterial blood pressure decreased slightly but significantly in both RI fenoldopam- and vehicle-infused groups during the 4 hours of the experiment. However, there was no significant difference in mean arterial blood pressure between vehicle and fenoldopam-infused rats (F=1.9; P value not significant).

Effects of Pharmacological Renal AT2R Inhibition on D1R Protein Expression

Simultaneous RI infusion of PD abolished the fenoldopam-induced increase in UNaV and V for all time periods (Figure 5A). UNaV values for fenoldopam and fenoldopam plus PD infusions, respectively, were 0.95±0.24 and 0.25±0.08 μmol/min (P<0.01) at 1 hour, 1.07±0.21 and 0.32±0.06 μmol/min (P<0.001) at 2 hours, and 0.82±0.14 and 0.31±0.07 μmol/min (P<0.01) at 3 hours. ANOVA comparing UNaV values of fenoldopam-infused rats demonstrated F=3.9 (P<0.01).

Effect of Intrarenal D1-Like Receptor Activation on Renal AT2R Protein Expression

As shown in Figure 2A, fenoldopam increased the expression of a 44-kDa band specific for the AT2R in enriched plasma membranes from renal cortical cells. As delineated in Figure 2B, fenoldopam infusion increased AT2R density by 69% (P<0.01) in enriched plasma membranes from renal cortical cells. In contrast, fenoldopam infusion did not increase total AT2R protein expression in renal cortical cells (Figure 2C). In enriched plasma membranes from RPT cells (Figure 2D), fenoldopam increased AT2R protein expression by 108% (P<0.01). In contrast, in Figure 2E, fenoldopam infusion did not increase total AT2R protein expression in RPT cells. Because the preparation of Nagamatsu et al11 yields outer plasma membranes that may be contaminated with some internal cellular membranes, we isolated RPT outer apical membranes (AMs) and determined the effects of D1-like receptor activation on total cell and AM AT2R expression. Figure 3A shows a significant enrichment of RPT-specific marker villin in AMs isolated by the lectin pull-down assay compared with total RPT cell expression. Figure 3B demonstrates that fenoldopam did not significantly increase total RPT cell AT2R expression but increased RPT outer apical plasma membrane expression by 59% (P<0.01).

Results

Effects of Intrarenal D1-Like Receptor Activation on Na+ and Water Excretion

Effects of Anesthesia on Intrarenal Ang II Levels

Rats (N=6) on normal Na+ intake were implanted with renal cortical microdialysis catheters 48 hours before study. On the study day, a 60-minute collection of RI fluid was made, after which the animals were anesthetized for 4 hours, and RI fluid was again collected for 60 minutes during hour 4 of anesthesia. RI fluid was analyzed for Ang II.

Statistical Analysis

Data are presented as mean±SE. ANOVA with a repeated-measures term was used to analyze for variation between the groups. A 2-tailed Student’s t test was used to compare individual means between groups. A P value of <0.05 was considered statistically significant.
ANOVA for the fenoldopam plus PD infused animals was not significant ($F_{11,050.5; P_{11,050.7}}$). The transient fenoldopam-induced diuresis also was abolished by RI PD infusion ($P_{11,021.01}$; Figure 5B). ANOVA of $V$ for fenoldopam demonstrated $F_{4,4; P_{11,021.01}}$ for the RI fenoldopam plus PD infusions. ANOVA for $V$ was not statistically significant ($F_{1.0; P_{11,005.4}}$).

To determine whether the effects of fenoldopam were attributable to D$_1$-like receptor activation, we also coinfused fenoldopam with and without SCH-23390 (SCH), a potent, highly selective D$_1$-like receptor antagonist. Both fenoldopam-induced natriuresis and diuresis were abolished by intrarenal SCH. UNaV values for fenoldopam alone and fenoldopam plus SCH infusions, respectively, were $0.95 \pm 0.24$ and $0.13 \pm 0.00 \mu$mol/min ($P<0.01$) at 1 hour, $1.07 \pm 0.21$ and $0.20 \pm 0.01 \mu$mol/min ($P<0.001$) at 2 hours, and $0.82 \pm 0.14$ and $0.20 \pm 0.01 \mu$mol/min ($P<0.001$) at 3 hours. Although the SCH-infused rats tended to have an antinatriuretic response during the control period before fenoldopam infusion, this difference did not reach statistical significance. Figure 5C, shows that none of the RI infusions of pharmacological agents caused any significant change in systemic arterial blood pressure at any time.

Effects of High Na$^+$ Intake and Anesthesia on Intrarenal Ang II Levels and AT$_2$R Expression

To determine the intrarenal levels of endogenous AT$_2$R agonist Ang II in these experiments, we performed studies on the effects of high Na$^+$ intake and anesthesia on RI fluid and/or renal cortical Ang II levels. High Na$^+$ diet did not alter RI Ang II levels from that on normal Na$^+$ intake (high Na$^+$ $0.01 \pm 0.006$ versus low Na$^+$ $0.01 \pm 0.004 \mu$mol/min; $N=4$; $P$ value not significant). High Na$^+$ diet increased renal tissue
levels of Ang II insignificantly compared with values during normal Na⁺ intake (high Na⁺ 295±146 versus normal Na⁺ 220±75 pg per gram of kidney wet weight; N=6; P value not significant). Anesthesia did not alter RI fluid levels of Ang II (anesthetized 0.05±0.01 versus nonanesthetized 0.05±0.01 fmol/min; N=4; P value not significant). High Na⁺ intake induced a nonsignificant reduction in renal AT₁R expression (high Na⁺ 84.2±10.6% versus 100% of normal Na⁺ control; N=6; P value not significant).

Discussion

Intrarenal DA and Ang II are thought to act in paracrine fashion to modulate Na⁺ transport in renal tubules at D₁-like receptors (D₁ and D₂) and AT₁Rs, respectively. DA and Ang II oppose each other in the regulation of Na⁺ transport in the RPT. DA, synthesized in and secreted from RPT cells, binds to D₁-like receptors on the same or adjacent cells stimulating adenylyl cyclase activity and inhibiting NHE-3 activity, reducing Na⁺ reabsorption. When renal D₁-like receptors are inhibited selectively by SCH, sustained antinatriuresis occurs. Also, when D₁R expression in rat kidney is reduced by local tissue administration of specific antisense oligodeoxynucleotides, a significant antinatriuresis occurs during both normal and high Na⁺ intake. On the other hand, activation of AT₁Rs, the major renal Ang II receptors in the kidney, inhibits adenylyl cyclase and increases Na⁺ transport in the RPT via NHE-3 and Na/KATPase, resulting in antinatriuresis. Conversely, inhibition of AT₁Rs increases renal blood flow, glomerular filtration rate, filtration fraction, and Na⁺ and water excretion.

Ang II binds to 2 major receptor subtypes, AT₁ and AT₂. Although the vast majority of actions of Ang II are mediated by AT₁Rs, comparatively little is known regarding the renal actions of AT₂Rs. The AT₂R is expressed in the adult rat kidney at multiple sites, including proximal and distal tubules, glomeruli, renal blood vessels, juxtaglomerular cells, cortical and medullary collecting ducts, and cortical interstitial cells. The role of AT₂Rs in renal hemodynamic function is largely unknown, although AT₂Rs have been demonstrated to oppose AT₁R-mediated vasoconstriction in the renal cortex.
Several studies suggest that AT1R stimulation initiates a vasodilator cascade consisting of bradykinin, NO, and cGMP in direct opposition to Ang II-mediated vasoconstriction via AT1Rs.\textsuperscript{8,25–27} Available data suggest that AT1Rs have a functional role in BP regulation wherein systemic receptor activation induces vasodilation and hypotension in the presence of AT1R blockade in normal rats.\textsuperscript{28,29} In addition, the decrease in arterial pressure observed in normal rats infused with CGP-42112A, a selective AT1 receptor agonist, was abolished in the presence of AT1R antagonist PD.\textsuperscript{29}

In contrast to its vascular actions, information regarding the actions of AT1Rs in the renal tubule Na$^+$ transport is scant. The only available cellular study suggests that RPT Na$^+$ reabsorption is opposed by AT1Rs.\textsuperscript{30} Most of the current knowledge comes from AT1R-null mice, which have exaggerated antinatriuretic responses to systemic Ang II infusion and are unable to generate a normal pressure–natriuretic response.\textsuperscript{31,32} However, because AT1Rs are chronically upregulated in AT1R-null mice, the interpretation of these studies is open to question.\textsuperscript{33} Recently, Padia et al\textsuperscript{34} have demonstrated a natriuretic action of des-aspartyl-Ang II mediated via AT1Rs in the AT1R-blocked rat.

The current experiments were designed to clarify the role of AT1 receptors in renal Na$^+$ excretion according to the following hypothesis: dopaminergic regulation of renal Na$^+$ and water handling requires activation of AT1Rs. Although substantial data exist regarding the opposing functions of intrarenal D1-like receptors and AT1Rs on Na$^+$ balance, the interplay between the dopaminergic system and the AT1R has yet to be defined. The present analysis further elucidates this relationship.

Our studies demonstrate the following: (1) selective intrarenal activation of D1-like receptors induces sustained natriuresis and diuresis in Na$^+$-loaded Sprague–Dawley rats; (2) D1-like receptor-mediated natriuresis is accompanied by recruitment of both D1Rs and AT1Rs to the plasma membranes of RPT cells; and (3) intrarenal pharmacological inhibition of AT1Rs abolishes the natriuretic and diuretic responses to D1-like receptor stimulation. These in vivo and in vitro results suggest that D1-like receptor–induced natriuresis and diuresis are modulated by functional AT1Rs that are translocated from intracellular compartments to outer plasma membranes of RPT cells in response to D1-like receptor activation.

The Nagamatsu et al\textsuperscript{11} method used for plasma membrane isolation in these studies yields a 100 000 g pellet that is enriched in outer plasma membranes but may be contaminated with intracellular membranes. Therefore, we specifically isolated apical plasma membranes of RPT cells using an LTA lectin pull-down assay. LTA binds to specific glycoproteins present only in proximal tubule brush border (apical) membranes.\textsuperscript{35,36} We demonstrate that AM fractions isolated with LTA were enriched with villin, validating the isolation of the outer brush border membrane fraction. Our results show that intrarenal administration of fenoldopam increased the quantity of AT1R protein in these AMs.

AT1R translocation is likely the result of intracellular receptor protein trafficking within RPT cells consisting of stimulation of cytoskeletal elements, such as microtubules and microfilaments.\textsuperscript{37} These cellular “motors” cause vesicle/organellae movement within the cell, a relationship necessary to maintain proper distribution of membrane proteins.\textsuperscript{38} Observations from RPT cells have demonstrated that administration of the DA precursor L-3,4-dihydroxyphenylalanine or D1-like receptor agonist fenoldopam induces translocation of D1Rs from the intracellular compartment to the plasma membrane and that subcellular receptor translocation was prevented by nocodazole, a microtubulin network disruptor.\textsuperscript{39,40} We speculate that D1-like receptor stimulation with fenoldopam, similar to its action on D1R recruitment, causes microtubules to move both D1R and AT1R proteins to the plasma membrane. Under this scenario, D1-like receptor recruitment of AT1Rs to the plasma membrane would require an intact microtubulin network. According to our hypothesis, AT1R activation by D1-like receptor stimulation would lead to inhibition of the NHE-3 and Na/K ATPase activities, thereby reducing Na$^+$ reabsorption in RPT cells, as hypothesized in Figure 6.

A possible limitation of the present study is that the changes in Na$^+$ and water excretion observed with fenoldopam infusion may have been attributable, at least in part, to downregulation of AT1Rs. However, AT1R downregulation is unlikely to have occurred within a time span of fenoldopam infusion as short as 3 hours in these experiments. Furthermore, the abolition of fenoldopam-induced natriuresis with PD, a specific AT1R antagonist, indicates the primary role of AT1Rs in the regulation of Na$^+$ excretion.

Whether or not fenoldopam-induced natriuresis requires Ang II binding and activation of AT1Rs in the traditional manner has not yet been tested. However, we were able to demonstrate that intrarenal Ang II levels were not suppressed by either high Na$^+$ intake or anesthesia. Therefore, Ang II would be available for binding to AT1Rs under these experimental conditions.

Perspectives
This study elucidates the interaction between the renal dopaminergic system and renin–angiotensin system, affording a
better understanding of renal Na\(^{+}\) and water handling. Our results demonstrate that D\(_1\)-like receptors not only oppose the actions of Ang II via AT\(_R\)Rs but also require AT\(_R\)Rs to reduce renal Na\(^{+}\) reabsorption. These findings have clinical implications in cardiovascular medicine and hypertension where the focus has been predominantly on AT\(_R\)R blockade and inhibition of the entire renin–angiotensin system. The present study encourages the clinical development of renal AT\(_R\)R and/or D\(_1\)-like receptor agonists to take advantage of their probable beneficial effects on renal Na\(^{+}\) and water excretion.

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**Disclosures**

None.

**References**


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