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Angiotensin II Regulation of Renal Dopamine Uptake and Na^+,K^+-ATPase Activity

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Key Words
Dopamine · Angiotensin II · Protein kinase C · Adenylate cyclase · Phospholipase C · CaM kinase II · Na^+,K^+-ATPase

Abstract
Background/Aims: Angiotensin II (ANG II) decreases dopamine (DA) uptake in renal cortex activating AT_1 receptors. We investigated the signaling pathways that mediate this action and the incidence of DA-ANG II interaction on renal Na^+,K^+-ATPase activity. ***Methods:*** ANG II effects on [^{3}H]-DA uptake and Na^+,K^+-ATPase were measured in samples from the outer renal cortex of Sprague-Dawley rats. ***Results:*** Inhibition of the phospholipase C (PLC) pathway blunted ANG II inhibitory effects on [^{3}H]-DA uptake, since U-73122, 2-APB, TMB-8, chelerythrine and KN-93 (PLC, IP_3-dependent Ca^{2+} release channels, IP_3 receptors, protein kinase C and CaM kinase II inhibitors, respectively) each one blocked ANG II effects. Inhibition of adenylate cyclase pathway did not modify ANG II inhibitory effects on DA uptake. ANG II effects on [^{3}H]-DA uptake were able to modify Na^+,K^+-ATPase activity in carbidopa-treated rats. Exogenous DA decreased while ANG II increased the enzyme activity. Neither the addition of DA together with ANG II, nor the extraneuronal DA uptake blocker hydrocortisone altered ANG II stimulatory effects on Na^+,K^+-ATPase activity, but hydrocortisone blocked the inhibitory effects of exogenous DA. ***Conclusion:*** Stimulation of renal AT_1 receptors by ANG II signals through the PLC pathway to inhibit extraneuronal DA uptake. DA and ANG II act through a common pathway involving reversible renal tubular Na^+,K^+-ATPase deactivation and activation, respectively. In addition, ANG II by itself is able to stimulate renal Na^+,K^+-ATPase activity.

Introduction

Blood pressure and sodium handling are regulated by several endocrine, paracrine, autocrine, intracrine and neural factors. Tubular sodium reabsorption in all renal tubular segments is one of the main long-term mechanisms to regulate blood pressure. Natriuretic as well as antinatriuretic agents may achieve their effects through common pathways that involve reversible activation or deactivation of renal tubular Na^+,K^+-ATPase [1].

Angiotensin II (ANG II) is the main active peptide of the renin-angiotensin system and plays a prominent role in maintaining blood pressure and body fluid and electrolyte balance homeostasis [2]. Dopamine (DA) and ANG II exhibit opposed physiological effects. While ANG II, acting through AT_1 receptors, increases blood pressure, elicits renal arterial vasoconstriction, decreases medullary blood flow and renal interstitial pressure,

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stimulates aldosterone release and sodium and water reabsorption and diminishes diuresis and natriuresis [3–5], DA exerts just the opposite effects on these mechanisms [6, 7].

Renal DA is synthesized from neuronal and extraneuronal sources. The neuronal sources are noradrenergic and dopaminergic. Extraneuronal sources involve both L-DOPA decarboxylation after the amino acid has been taken up from tubular fluid or after that DA uptake by tubular cells from the blood occurs. Endogenously produced DA plays an important role in renal function control. DA effects on renal sodium handling are mediated through both D1-like and D2-like receptors and activation of these receptors induces a large increase in urinary sodium excretion that is dependent on inhibition of Na^+,K^+-ATPase activity as well as from diverse sodium influx pathways in both proximal and distal tubular cells [8–12].

We have previously reported that atrial natriuretic factor, a physiological antagonist of ANG II, increases renal DA uptake through natriuretic peptide type A receptors in fragments of renal outer cortex [13], involving cGMP and PKG in the cascade of intracellular events [14]. Moreover, atrial natriuretic factor potentiates the inhibitory effects of DA on renal Na^+,K^+-ATPase activity [14]. On the other hand, we have demonstrated that ANG II also acts as a modulator of DA effects at the renal level, decreasing its uptake through AT_1 receptors in outer and juxtamedullar cortex [15]. Taking into account these findings, we have hypothesized that ANG II modifies renal DA uptake, affecting renal Na^+,K^+-ATPase activity and increasing sodium reabsorption. The aim of this study was to elucidate the intracellular pathways involved in ANG II effects on extraneuronal DA uptake in the kidney and to determine the incidence of DA-ANG II interaction on renal Na^+,K^+-ATPase activity.

Methods

Male Sprague-Dawley rats weighing between 250 and 350 g (from the Department of Pathophysiology, Faculty of Pharmacy and Biochemistry) were used. The animals were housed in cages, with a 12-hour light/dark cycle, controlled temperature and humidity. All animals were given water and food ad libitum (commercial rodents Purina chow, Cooperacion SRL, Argentina). Experiments were conducted in accordance with institutional guidelines for the care and use of research animals.

The following drugs were used in the experiments: [^{3}H]-DA, 28.0 Ci/mmol specific activity (from New England Nuclear, Boston, Mass., USA); ANG II (from American Peptide Company, Calif., USA); nomifensine (inhibitor of neuronal DA uptake), DA, hydrocortisone (HC, inhibitor of extraneuronal DA uptake), SQ 22536 [adenylate cyclase (AC) specific inhibitor], H89 [protein kinase A (PKA) specific inhibitor], 2-APB [1,4,5-inositol triphosphate (IP_3)-dependent Ca^{2+} release channel selective inhibitor], TMB-8 (IP_3 receptor antagonist), KN-93 [calcium/calmodulin-dependent protein kinase II (CaM kinase II) specific inhibitor], KN-92 (inactive analogue of KN-93), imidazole, adenosine 5′-triphosphate and bovine seroalbumin fraction V of Cohn (all from Sigma Chemical Co., St. Louis, Mo., USA); Folin reactive (from Merck Co., USA); carbidopa (DA synthesis inhibitor, gently provided by Dr. Victor Nahmod, Buenos Aires, Argentina); 8-Br-cAMP [adenosine 3′,5′-cyclic monophosphate (cAMP) analogue] and U-73122 (phospholipase C specific inhibitor; both from MP Biomedicals, LLC, Ohio, USA); chelerythrine [protein kinase C (PKC) specific inhibitor, from Alomone Labs Ltd., Jerusalem, Israel]; EcoLite, a liquid scintillation solution (from ICN Pharmaceutical Inc., Calif., USA).

Standard Krebs bicarbonate solution (SKBS) of the following composition (mM) was used as incubation medium: 118 NaCl; 4.7 KCl; 1.2 $MgSO_4 \cdot 7H_2O$; 1.0 NaH_2PO_4; 2.4 $CaCl_2$; 0.004 EDTA; 11.1 glucose; 0.11 ascorbic acid; 26.0 $NaHCO_3$.

Experimental Protocols

Rats were anesthetized with 10% w/v ethyl urethane (1.3 mg/kg body weight, i.p.). Both kidneys were removed and slices of the outer cortex were cut and weighed. [^{3}H]-DA uptake was measured according to previously described techniques [13]. Briefly, tissues were minced, placed in 2.0 ml SKBS incubation medium in a Dubnoff incubator and preincubated at 37°C, pH 7.40, bubbled with carbogen (95% O_2 and 5% CO_2) for 15 min. Nomifensine (50 μM) was added in the medium to avoid neuronal DA uptake. After preincubation, the tissues were transferred to a fresh SKBS medium and incubated for 30 min, in similar conditions, with 22.5 nM (0.625 μCi/ml) of [^{3}H]-DA, 17 μM nomifensine and the different tested drugs.

The following experimental groups were studied:

- Effect of ANG II on [^{3}H]-DA uptake in the presence of U-73122: (a) control group; (b) 100 nM ANG II; (c) 25 μM U-73122; (d) 25 μM U-73122 plus 100 nM ANG II.
- Effect of ANG II on [^{3}H]-DA uptake in the presence of 2-APB: (a) control group; (b) 100 nM ANG II; (c) 100 μM 2-APB; (d) 100 μM 2-APB plus 100 nM ANG II.
- Effect of ANG II on [^{3}H]-DA uptake in the presence of TMB-8: (a) control group; (b) 100 nM ANG II; (c) 10 μM TMB-8; (d) 10 μM TMB-8 plus 100 nM ANG II.
- Effect of ANG II on [^{3}H]-DA uptake in the presence of chelerythrine: (a) control group; (b) 100 nM ANG II; (c) 10 μM chelerythrine; (d) 10 μM chelerythrine plus 100 nM ANG II.
- Effect of ANG II on [^{3}H]-DA uptake in the presence of KN-93: (a) control group; (b) 100 nM ANG II; (c) 25 μM KN-92; (d) 25 μM KN-93 plus 100 nM ANG II.
- Effect of ANG II on [^{3}H]-DA uptake in the presence of 8-Br-cAMP: (a) control group; (b) 100 nM ANG II; (c) 125 μM 8-Br-cAMP; (d) 125 μM 8-Br-cAMP plus 100 nM ANG II.
- Effect of ANG II on [^{3}H]-DA uptake in the presence of SQ 22536: (a) control group; (b) 100 nM ANG II; (c) 100 μM SQ 22536; (d) 100 μM SQ 22536 plus 100 nM ANG II.
- Effect of ANG II on [^{3}H]-DA uptake in the presence of H89: (a) control group; (b) 100 nM ANG II; (c) 2 μM H89; (d) 2 μM H89 plus 100 nM ANG II.

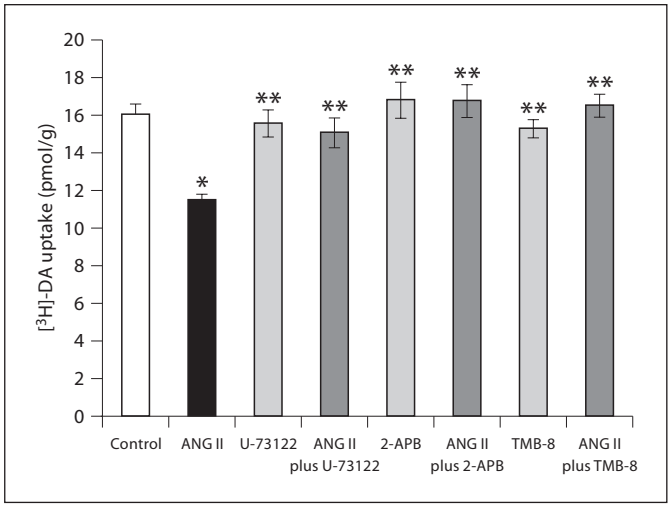

Fig. 1. Effects of U-73122 (25 μM), 2-APB (100 μM) and TMB-8 (10 μM) on 100 nM ANG II-inhibited [^{3}H]-DA uptake (pmol/g of fresh tissue ± SEM) in the outer renal cortex; * $p < 0.01$ compared with control, ** $p < 0.05$ compared with ANG II. Number of cases: n = 6–10.

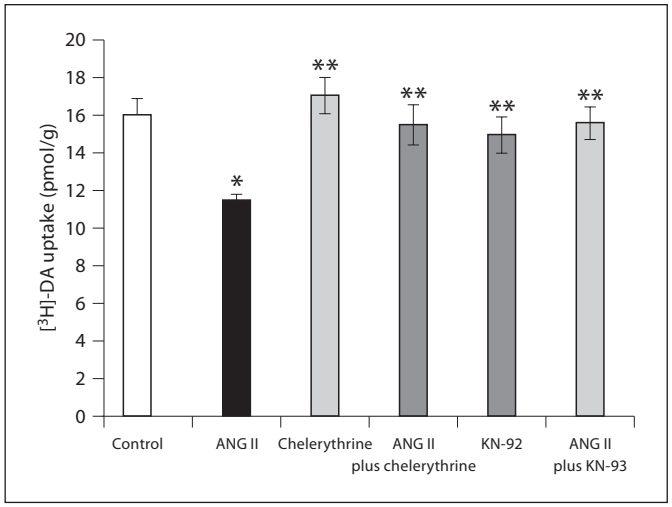

Fig. 2. Effects of chelerythrine (10 μM) and KN-93 (25 μM) on 100 nM ANG II-inhibited [^{3}H]-DA uptake (pmol/g of fresh tissue ± SEM) in the outer renal cortex; * $p < 0.01$ compared with control, ** $p < 0.05$ compared with ANG II. Number of cases: n = 6–8.

After incubation, three washing periods of 5 min, each one with cold SKBS, were carried out, and then the samples were homogenized with 2.0 ml of 10% trichloroacetic acid. The homogenates were centrifuged at 1,700 *g* at 4°C for 30 min and tritium activity in the supernatants was determined by scintillation counting method. [^{3}H]-DA uptake was expressed as picomoles per gram of fresh tissue.

Effects of ANG II and DA on Na^+,K^+-ATPase Activity

To test whether the decrease in renal DA related to the ANG II-inhibited DA uptake is associated with changes in Na^+,K^+-ATPase activity, the following experiments were performed in the presence of 17 μM nomifensine (to avoid neuronal DA uptake) and carbidopa (to avoid the incidence of synthesized endogenous DA). Then, the effects of ANG II and DA, added separately or together, on renal Na^+,K^+-ATPase activity were studied in rats treated with carbidopa in vivo (200 μg/kg, i.p., 24 and 2 h before the sacrifice) and in vitro (100 μM of carbidopa) during the preincubation and incubation periods.

The following groups were studied: (a) control group; (b) 100 μM carbidopa; (c) 1 μM DA plus 100 μM carbidopa; (d) 100 nM ANG II plus 100 μM carbidopa; (e) 100 μM HC plus 100 μM carbidopa; (f) 100 nM ANG II plus 1 μM DA plus 100 μM carbidopa; (g) 100 μM HC plus 100 nM ANG II plus 1 μM DA plus 100 μM carbidopa.

Tissues were incubated for 30 min as described above and then homogenized (1:10 weight/volume) in 25 mM imidazole (pH 7.40), 1 mM EDTA, 0.25 M sucrose solution and centrifuged at 3,000 rpm at 4°C for 15 min. Supernatant was used to assay Na^+,K^+-ATPase activity as previously described [16, 17].

Results are expressed as percentage of Na^+,K^+-ATPase activity taken as 100% values obtained in control conditions.

Statistical Analysis

All values are expressed as mean ± SEM. Student's t test or one-way analysis of variance followed by Tukey test were used for statistical analysis; p values of 0.05 or less were considered statistically significant.

Results

Figure 1 shows the effect of ANG II on renal [^{3}H]-DA uptake. ANG II (100 nM) caused a 28 ± 2% decrease in DA uptake in rat renal cortex and this inhibitory effect was blocked by either the specific inhibitor of phospholipase C U-73122 (25 μM), the selective blocker of IP_3-dependent Ca^{2+} release channels 2-APB (100 μM) or the IP_3 receptor antagonist TMB-8 (10 μM), suggesting that the ANG II-induced decrease in DA uptake was mediated by phospholipase C activation. Neither U-73122 nor 2-APB or TMB-8 altered [^{3}H]-DA uptake by themselves.

In addition, the specific PKC inhibitor chelerythrine (10 μM) or the CaM kinase II inhibitor KN-93 (25 μM) reversed ANG II inhibitory action on [^{3}H]-DA uptake. Chelerythrine and the KN-92 (inactive analogue of KN-93) did not affect renal [^{3}H]-DA uptake by themselves (fig. 2).

In order to investigate whether the AC pathway is involved in the ANG II-induced decrease of [^{3}H]-DA uptake, we tested the effect of the peptide in the presence of

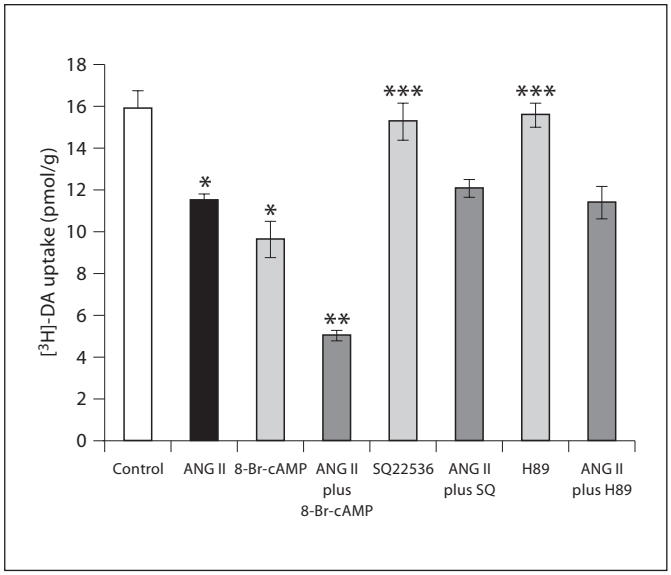

Fig. 3. Effects of 8-Br-cAMP (125 μM), SQ 22536 (100 μM) and H89 (2 μM) on 100 nM ANG II-inhibited [^{3}H]-DA uptake (pmol/g of fresh tissue ± SEM) in the outer renal cortex; * $p < 0.01$ compared with control, ** $p < 0.001$ compared with 8-Br-cAMP, *** $p < 0.01$ compared with ANG II. Number of cases: n = 6–12.

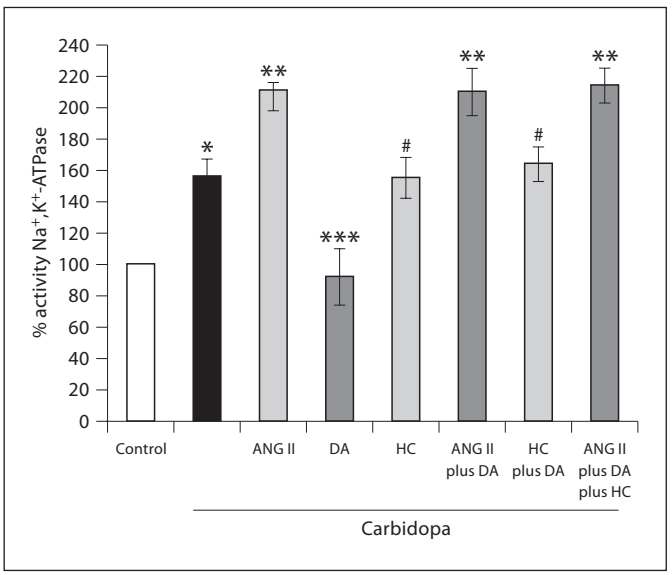

Fig. 4. Effects of DA (1 μM), ANG II (100 nM) and HC (100 μM) on Na^+,K^+-ATPase activity calculated as a percentage of Na^+,K^+-ATPase activity of control in the outer renal cortex. The experiments were carried out in the absence (control) or in the presence of carbidopa; * $p < 0.05$ compared with control; ** $p < 0.001$ compared with carbidopa, HC or HC plus DA; *** $p < 0.05$ compared with carbidopa; # $p < 0.05$ compared with DA. Number of cases: n = 6–11.

AC and PKA inhibitors. Figure 3 shows that the cAMP analogue 8-Br-cAMP (125 μM) potentiated the inhibitory effect of ANG II on renal [^{3}H]-DA uptake and decreased it by itself. On the other hand, ANG II inhibitory action on [^{3}H]-DA uptake was not modified by the addition of either the AC inhibitor SQ 22536 (100 μM) or the PKA-specific inhibitor H89 (2 μM), demonstrating that ANG II acts through an AC- or PKA-independent pathway. The inhibitors alone did not modify [^{3}H]-DA uptake.

To test if the inhibition of renal DA uptake caused by ANG II may affect Na^+,K^+-ATPase activity, we assayed the effect of ANG II and DA, alone or together, on the enzyme activity. As shown in figure 4, Na^+,K^+-ATPase activity increased when renal DA synthesis was inhibited by carbidopa, but it was reversed to control values when exogenous DA was added. Under DA synthesis blockade, we observed that exogenous DA caused a 41 ± 11% decrease in enzyme activity while ANG II increased it (35 ± 3%). When ANG II was added simultaneously with DA, there was no change in the enzyme activity compared with ANG II alone. HC did not modify Na^+,K^+-ATPase activity when DA synthesis was blocked with carbidopa, but inhibited exogenous DA effects on the enzyme. In addition, HC did not affect the stimulatory action of ANG II on the Na^+,K^+-ATPase activity in the presence of exogenous DA. Taken together, these results suggest that ANG II diminishes renal DA uptake and affects Na^+,K^+-ATPase activity. In addition, ANG II stimulates the enzyme activity by itself.

Discussion

We have previously reported that ANG II decreases DA uptake in a concentration-dependent fashion in the outer renal cortex, this effect being coupled to AT_1 receptor, but not to AT_2 receptor stimulation [15]. Renal DA uptake was characterized as an extraneuronal hydrocortisone-sensitive and temperature-dependent process [13, 15].

In order to determine the signaling mechanisms involved in ANG II-DA uptake process after AT_1 receptor stimulation, we analyzed the involvement of different ANG II signal transduction pathways. Our results demonstrated that phospholipase C activation is necessary to

mediate ANG II effects on renal DA uptake. Moreover, ANG II stimulation on renal DA uptake implied IP_3-dependent Ca^{2+} release and activation of PKC and CaM kinase II.

On the other hand, our study shows that the decreased DA uptake induced by ANG II is independent of AC, cAMP and PKA cascade. The fact that 8-Br-cAMP, a nonhydrolizable cAMP analogue, reduced renal DA uptake, suggests that this pathway is involved in renal DA uptake regulation and it could be activated by other mechanisms that are independent of ANG II participation.

Little is known about the mechanisms by which the proximal tubular cells incorporate DA. Extraneuronal uptake of catecholamines is mediated by organic cation transporters (OCTs) which are regulated by PKG, PKC and PKA [18, 19]. Moreover, OCT1 and OCT2 mediate translocation of DA in rat proximal convoluted and straight tubules [20, 21]. Since our study shows that PKC is involved in the ANG II inhibitory effect on DA uptake, it could be suggested that OCTs may be involved in renal ANG-DA interaction. Further experiments have to be done to test this hypothesis.

Renal DA, through its second messengers and associated protein kinases or protein phosphatases, initiates a cascade of events ultimately resulting in the phosphorylation and inhibition of Na^+,K^+-ATPase enzymatic activity [1, 22]. This enzyme is present at high concentrations in the basolateral membrane of all tubular cells and is a key enzyme for sodium reabsorption [23]. A balance between natriuretic (as DA, parathyroid hormone, endothelin, prostaglandin E) and antinatriuretic (as noradrenaline, neuropeptide Y, insulin and ANG II) factors that inhibit or stimulate Na^+,K^+-ATPase, respectively, may modulate its activity [22, 24, 25]. To examine whether ANG II inhibiting effect on DA uptake is associated with changes in Na^+,K^+-ATPase activity, the effects of endogenous renal DA and neuronal DA were ruled out by blockade of renal DA synthesis by carbidopa and neuronal DA uptake by nomifensine. Our results show that renal Na^+,K^+-ATPase activity increased when DA synthesis was inhibited by carbidopa, according to the reduction of DA content. In contrast, when exogenous DA was added, the activity of the enzyme decreased, in agreement with the restored DA availability. The addition of ANG II stimulated the sodium pump activity, reaching higher levels than those observed in the group treated with carbidopa alone. This suggests that ANG II is able to enhance Na^+,K^+-ATPase activity, even in the absence of endogenous DA. When exogenous DA and ANG II were added together, Na^+,K^+-ATPase activity increased as much as in the ANG II group, showing that ANG II-induced inhibition of DA uptake did not allow exogenous DA to inhibit Na^+,K^+-ATPase activity. To assess whether the ANG II-induced stimulation of Na^+,K^+-ATPase activity is related to ANG II-inhibited non-neuronal DA uptake, additional experiments were performed in the presence of HC, a known inhibitor of non-neuronal uptake, plus the DA synthesis inhibitor carbidopa in order to avoid any influence from endogenous DA. HC did not modify Na^+,K^+-ATPase activity by itself, but reversed DA inhibition of the enzyme, confirming that this latter effect is closely related to the inhibition of renal DA uptake. However, HC did not affect the ANG II-stimulatory effect on the enzyme in the presence of exogenous DA, suggesting a direct action of the peptide on Na^+,K^+-ATPase activity. The fact that ANG II, even when renal DA synthesis and renal uptake were inhibited, was able to stimulate Na^+,K^+-ATPase activity could explain the controversial reports about the capacity of the peptide to alter pump activity and it also suggests that DA activity must be masked to observe ANG II effects. ANG II regulates sodium reabsorption through modulation of Na^+,K^+-ATPase activity in a biphasic manner [26]. At low concentrations, ANG II stimulates the Na^+,K^+-ATPase pump [23, 27], whereas at high concentrations, ANG II (micromolar) inhibits sodium and water transport [28, 29], but the latter effect was never observed under physiological conditions [30].

In conclusion, our results demonstrated that ANG II inhibits renal DA uptake and stimulates renal Na^+,K^+-ATPase activity, while DA inhibits this enzyme. DA uptake inhibition in renal tubular cells elicited by ANG II is mediated by AT_1 receptors and signal through the phospholipase C pathway, including the generation of second messengers, IP_3 and DAG, intracellular calcium release and activation of PKC and CaM kinase II. By this way, ANG II diminishes intracellular accumulation of renal DA, which in turn might favor sodium reabsorption and reduce natriuresis linked to Na^+,K^+-ATPase activity in renal tubules.

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