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48	Abstract		Dopamine and urodilatin promote natriuresis and diuresis through a common pathway that involves reversible deactivation of renal Na^+, K^+-ATPase. We have reported that urodilatin enhances dopamine uptake in outer renal cortex through the natriuretic peptide type A receptor. Moreover, urodilatin enhances dopamine-induced inhibition of Na^+, K^+-ATPase activity. The objective of the present work was to investigate the intracellular signals involved in urodilatin effects on dopamine uptake in renal cortex of kidney rats. We show that urodilatin-elicited increase in ^{3}H-dopamine was blunted by methylene blue (10 μM), a non-specific guanylate cyclase inhibitor, and by phorbol-12-myristate-13-acetate (1 μM), a particulate guanylate cyclase inhibitor, but not by 1H-[1,2,4]-Oxadiazolo-[4,3-a]-quinoxalin-1-one (10 μM), a specific soluble guanylate cyclase inhibitor; therefore the involvement of particulate guanylate cyclase on urodilatin mediated dopamine uptake was confirmed. Cyclic guanosine monophosphate and proteinkinase G were also implicated in the signaling pathway, since urodilatin effects were mimicked by the analogous 125 μM 8-Br-cGMP and blocked by the proteinkinase G-specific inhibitor, KT-5823 (1 μM). In conclusion, urodilatin increases dopamine uptake in renal cortex stimulating natriuretic peptide type A receptor, which signals through particulate guanylate cyclase activation, cyclic guanosine monophosphate generation, and proteinkinase G activation. Dopamine and urodilatin may achieve their effects through a common pathway that involves deactivation of renal Na^+, K^+-ATPase, reinforcing their natriuretic and diuretic properties.
49	Keywords separated by ' - '		Urodilatin - Dopamine - Guanylate cyclase - PKG - Kidney
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ORIGINAL PAPER

Urodilatin increases renal dopamine uptake: intracellular network involved

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Abstract Dopamine and urodilatin promote natriuresis and diuresis through a common pathway that involves reversible deactivation of renal Na^+, K^+-ATPase. We have reported that urodilatin enhances dopamine uptake in outer renal cortex through the natriuretic peptide type A receptor. Moreover, urodilatin enhances dopamine-induced inhibition of Na^+, K^+-ATPase activity. The objective of the present work was to investigate the intracellular signals involved in urodilatin effects on dopamine uptake in renal cortex of kidney rats. We show that urodilatin-elicited increase in ^{3}H-dopamine was blunted by methylene blue (10 μM), a non-specific guanylate cyclase inhibitor, and by phorbol-12-myristate-13-acetate (1 μM), a particulate guanylate cyclase inhibitor, but not by 1H-[1,2,4]-Oxadiazolo-[4,3-a]-quinoxalin-1-one (10 μM), a specific soluble guanylate cyclase inhibitor; therefore the involvement of particulate guanylate cyclase on urodilatin mediated dopamine uptake was confirmed. Cyclic guanosine monophosphate and proteinkinase G were also implicated in the signaling pathway, since urodilatin effects were mimicked by the analogous 125 μM 8-Br-cGMP and blocked by the proteinkinase G-specific inhibitor, KT-5823 (1 μM). In conclusion, urodilatin increases dopamine uptake in renal cortex stimulating natriuretic peptide type A receptor, which signals through particulate guanylate cyclase activation, cyclic guanosine monophosphate generation, and proteinkinase G activation. Dopamine and urodilatin may achieve their effects through a common pathway that involves deactivation of renal Na^+, K^+-ATPase, reinforcing their natriuretic and diuretic properties.

Keywords Urodilatin · Dopamine · Guanylate cyclase · PKG · Kidney

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Introduction

Urodilatin is a 32-amino acid peptide, discovered in 1988 from human urine, identical to the circulating form of atrial natriuretic peptide (ANP), except for four extended amino acids at the N terminus [15].

Dopamine, endogenously produced by renal proximal tubules, plays an important autocrine/paracrine role in the regulation of renal function [12]. Dopamine effects on renal sodium handling consist of a large increase in urinary sodium excretion, which is dependent on Na^+, K^+-ATPase activity inhibition, and of diverse sodium influx pathways, in both proximal and distal tubular cells [7]. These effects are mainly

mediated via the dopamine-1 receptor subtype, coupled to adenylate cyclase activation and cyclic adenosine phosphate generation, as well as phospholipase C and proteinkinase C (PKC) signaling in renal tubular cells [10, 13].

We have previously reported that urodilatin stimulates ^{3}H-dopamine uptake by tubular cells in the kidney, effect mediated by the natriuretic peptide type A receptor (NPR-A). Moreover, we have demonstrated that urodilatin, through stimulation of ^{3}H-dopamine uptake, favors dopamine intracellular accumulation, which in turn results in an over inhibition of renal Na^{+}, K^{+}-ATPase activity [4]. These previous findings lead us to hypothesize that urodilatin and the renal dopaminergic system could interact and enhance the natriuretic and diuretic effects of the peptide.

The aim of the present work was to study the signaling pathways that mediate urodilatin stimulatory effects on renal uptake of dopamine, identifying the second messenger and protein kinase involved.

Material and methods

Male Sprague–Dawley rats weighing 250–350 g (from the animal room of the School of Pharmacy and Biochemistry, University of Buenos Aires) were used. The animals were housed in cages, with a 12-h light/dark cycle and controlled temperature and humidity. They were given access to water and food ad libitum (Rodents Purina chow, Cooperacion SRL, Argentina). The experiments were conducted in accordance with the University of Buenos Aires institutional guidelines for the care and use of research animals (resolution no. 4081/2004) which is based on the International Ethical Guiding Principles for Biomedical Research on Animals established by the CIOMS (http://www.fmed.uba.ar/investigadores/cicual/Reglamento%20UBA.doc). The protocols were approved by the University of Buenos Aires (no. B113/08) and the Argentinean National Scientific and Technical Research Council, CONICET (no. 112-2000801-011337/09).

The following drugs were used in the experiments: ^{3}H-dopamine, 28.0 Ci/mmol of specific activity (New England Nuclear, Boston, Mass, USA); urodilatin (95–126), methylene blue, 8-bromo-guanosine 3′,5′-cyclic monophosphate (8-br-cGMP), phorbol 12-myristate 13-acetate (PMA), KT 5823, nomifensine (all from Sigma-Aldrich Inc., Saint Louis, Missouri, USA); ODQ (1H-[1,2,4]-Oxadiazolo-[4,3-a]-quinoxalin-1-one]) (Calbiochem, San Diego, CA, USA) and EcoLite, for liquid scintillation (ICN Pharmaceutical Inc., CA, USA).

The standard Krebs bicarbonate (SKB) solution composition (mM) was: 118 NaCl, 4.7 KCl, 1.2 $MgSO_4.7H_2O$, 1.0 NaH_2PO_4, 2.4 $CaCl_2$, 0.004 EDTA, 11.1 glucose, 0.11 ascorbic acid, and 26.0 $NaHCO_3$.

Rats were anesthetized with 10% *w*/*v* ethyl urethane (1.3 mg/kg ip). Both kidneys were excised and washed with fresh SKB to remove residual blood. Outer renal cortex was isolated by using a small scalpel. The slices were cut, minced and weighed. In order to determine ^{3}H-dopamine uptake, experiments were carried out according to the techniques previously described [8]. Briefly, tissue samples of approximately 50 mg were placed in 2.0 ml SKB incubation medium in a Dubnoff incubator and preincubated at 37°C, pH 7.40, bubbled with a gaseous mixture of 95% O_2 and 5% CO_2 for 15 min. Nomifensine (50 μM) was added to avoid neuronal dopamine uptake. After preincubation, the tissues were transferred to 2.0 ml of fresh SKB medium and incubated for 30 min, in similar conditions, with 22.5 nM (0.625 μ Ci/ml)of ^{3}H-dopamine, 17 μM of nomifensine, without (control) or with the different tested drugs (experimental groups). We employed a concentration of 10 nM urodilatin according to the concentration-response curve obtained in previous experiments [4].

The following experimental groups were studied (number of rats (*n*)):

- Effect of urodilatin on ^{3}H-dopamine uptake in the presence of methylene blue (guanylate cyclase unspecific inhibitor): (a) control, n=7; (b) 10 nM urodilatin, n=8; (c) 10 μM methylene blue, n=8; and (d) 10 nM urodilatin plus 10 μM methylene blue, n=9.

- Effect of urodilatin on ^{3}H-dopamine uptake in the presence of ODQ (soluble guanylate cyclase specific inhibitor) and in the presence of PMA (which inhibits the particulate guanylate cyclase - mediated signaling cascades of NPR-A): (a) control, n=7; (b) 10 nM urodilatin, n=8; (c) 10 μM ODQ, n=7; (d) 10 nM urodilatin plus 10 μM ODQ, n=9; (e) 1 μM PMA, n=7; and (f) 10 nM urodilatin plus 1 μM PMA, n=11.

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- Effect of urodilatin on ^{3}H-dopamine uptake in the presence of the cGMP analog, 8-Br-cGMP: (a) control, n=7; (b) 10 nM urodilatin, n=8; (c) 125 μM 8-Br-cGMP, n=7; and (d) 10 nM urodilatin plus 125 μM 8-Br-cGMP, n=10.
- Effect of urodilatin on ^{3}H-dopamine uptake in the presence of KT 5823, a PKG-specific inhibitor: (a) control, n=7; (b) 10 nM urodilatin, n=8; (c) 1 μM KT 5823, n=7; (d) 10 nM urodilatin plus 1 μM KT 5823, n=9.

At the end of the incubation period, the tissue samples were washed with 2.0 ml of cold KBS solution for three periods of 5 min each one and then 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. Results of ^{3}H-dopamine uptake are expressed as picomoles per gram of fresh tissue. The concentrations of all mentioned compounds were chosen from previous reports [4, 5, 8, 11].

Statistical analysis

All values are expressed as mean ± SEM. The Student's t test and one-way ANOVA followed by the Tukey's test were performed. P values of 0.05 or less were considered statistically significant.

Results

Guanylate cyclase unspecific inhibitor, 10 μM methylene blue, blocked the urodilatin-enhanced ^{3}H-dopamine uptake (see Fig. 1), suggesting that guanylate cyclase activation is involved in the stimulatory effect of urodilatin. The inhibitor agent itself did not modify ^{3}H-dopamine uptake.

As Fig. 2 shows, urodilatin effects on ^{3}H-dopamine uptake were not affected by the presence of soluble guanylate cyclase specific inhibitor 10 μM ODQ, demonstrating that soluble guanylate cyclase is not the enzyme coupled to its effect. On the other hand, ODQ per se did not alter ^{3}H-dopamine uptake. To confirm that urodilatin effects on ^{3}H-dopamine uptake are coupled to particulate guanylate cyclase, we employed 1 μM PMA, which inhibits particulate guanylate cyclase-mediated signalling cascades of NPR-A (see Fig. 2). PMA itself showed no effects, but blunted urodilatin enhancing effects on ^{3}H-dopamine uptake.

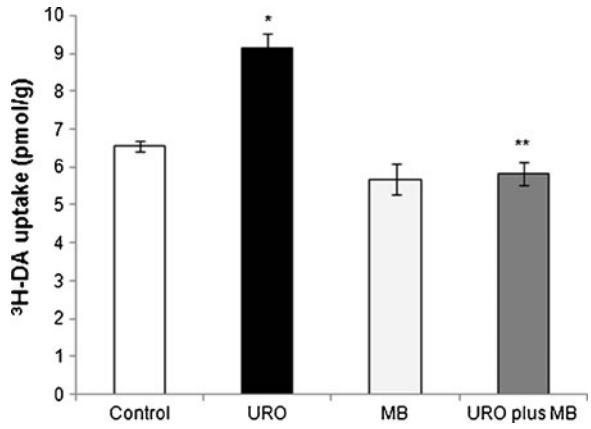

Fig. 1 Effects of 10 μM methylene blue (*MB*) on ^{3}H-dopamine (^{3}*H-DA*) uptake (pmol/g±SEM) in renal outer cortex. *p<0.01 compared with control; **p<0.01 compared with 10 nM urodilatin (*URO*). Number of samples, seven to nine

Figure 3 shows the effects of the analog 125 μM 8-Br-cGMP on ^{3}H-dopamine uptake. The cGMP analog increased ^{3}H-dopamine uptake and reproduced 10 nM urodilatin actions on the amine uptake. When urodilatin and the analog were used together, neither potentation nor synergic effects were observed.

Increase in cGMP cytosolic concentration leads to activation of cGMP-dependent PKG. As shown in Fig. 4, urodilatin-stimulated ^{3}H-dopamine uptake was blocked by 1 μM KT 5823, a PKG-specific inhibitor. Moreover, KT 5823 alone did not alter ^{3}H-dopamine uptake.

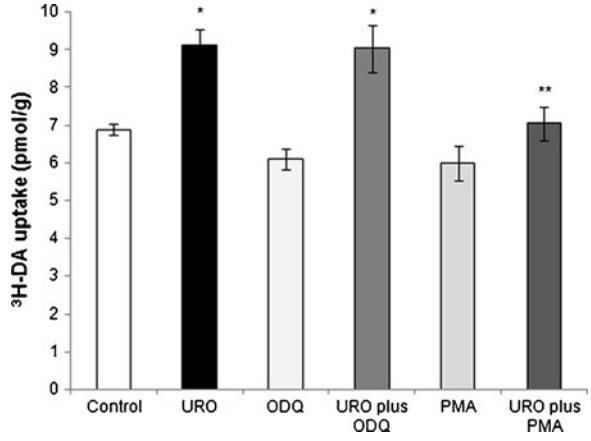

Fig. 2 Effects of 10 μM ODQ and 1 μM PMA on ^{3}H-dopamine (^{3}*H-DA*) uptake (pmol/g ± SEM) in renal outer cortex. *p<0.05 compared with control; **p<0.05 compared with 10 nM urodilatin (*URO*). Number of samples, seven to 11

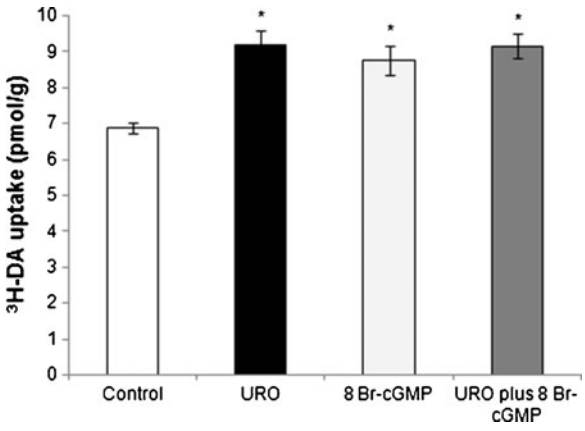

Fig 3 Effects of 125 μM 8-Br-cGMP on ^{3}H-dopamine (*^{3}H-DA*) uptake (pmol/g ± SEM) in renal outer cortex. *$p<0.05$ compared with control. Number of samples, eight to ten

Discussion

We have previously reported that urodilatin increases dopamine uptake in a concentration-dependent fashion in renal cortex and medulla, being this effect coupled to NPR-A, but not NPR-C receptors [4]. Renal dopamine uptake was characterized as an extraneuronal hydrocortisone-sensitive and temperature dependent process [4, 8]. Moreover, we examined the influence of urodilatin on Na^{+}, K^{+}-ATPase activity in outer renal cortex and observed that the natriuretic peptide increased the dopamine-dependent inhibition of the enzyme [4].

It was hypothesized that dopamine generation is essential for the exertion of ANP effects [1]. Given the fact that urodilatin natriuretic and diuretic effects are more potent than those of ANP, urodilatin could be the main natriuretic peptide needed by dopamine to exert part of its effects [9].

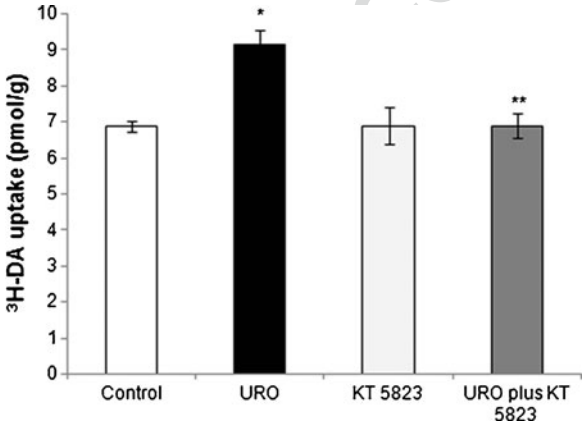

Fig 4 Effects of 1 μM KT 5823 on ^{3}H-dopamine (*^{3}H-DA*) uptake (pmol/g ± SEM) in renal outer cortex. *$p<0.01$ compared with control; **$p<0.05$ compared with 10 nM urodilatin (*URO*). Number of samples, seven to nine

In order to determine the signaling mechanisms involved in urodilatin- enhanced dopamine uptake, we analyzed the intracellular transduction pathways. NPR-A receptors are coupled to guanylate cyclase. Two types of guanylate cyclase were described: particulate guanylate cyclase (which mediates signaling cascades of NPR-A stimulation) and soluble guanylate cyclase (which mediate signaling cascades of nitric oxide). According to our results, whereas both methylene blue and PMA suppressed urodilatin stimulatory effects on dopamine uptake, ODQ failed to inhibit urodilatin enhancing effects. Considering these results, we propose that nitric oxide participation may not be involved, since soluble guanylate cyclase inhibition does not prevent urodilatin effects on DA uptake. Further and complementary studies must be performed to unquestionably rule out nitric oxide role. Guanylate cyclase enzyme is responsible for intracellular cGMP generation, which in turn leads to the activation of PKG. To prove that cGMP and PKG are the second messenger and the protein kinase effector involved in urodilatin-dependent dopamine uptake, respectively, we tested the effects of the analogous 8-Br-cGMP and PKG inhibitor, KT 5823. The analogous also increased dopamine uptake, confirming that cGMP mediates urodilatin effects on renal fragments. KT 5823 (a PKG-specific antagonist) blocked urodilatin enhancing effects on renal dopamine uptake. Then, PKG would be involved in urodilatin effects mediating NPR-A responses.

Renal dopamine derives from neuronal to extraneuronal sources. The neuronal sources of dopamine are noradrenergic and dopaminergic neurons [6]. Extraneuronal sources are L-DOPA decarboxylation, which produces dopamine in proximal tubular cells and dopamine uptake by tubular cells [2]. Little is known about the mechanisms by which the proximal tubular cells take up dopamine. Extraneuronal uptake of catecholamines is mediated by organic cation transporters (OCTs), which are regulated by PKG, PKC, and PKA [3, 14]. Moreover, OCT1 and OCT2 mediate dopamine translocation in rat proximal convoluted and straight tubules [6, 16]. Since our study shows that PKG is involved in urodilatin stimulatory effect on dopamine uptake, OCTs could

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be involved in renal urodilatin–dopamine interaction. Further experiments have to be carried out to test this hypothesis.

Although there is no evidence to update that a dopamine receptor blocker prevents urodilatin effects, it must be consider that urodilatin exerts direct as well as indirect dopamine-mediated effects. Then, dopamine receptor blockade can only diminish urodilatin effects mediated through dopamine, but not urodilatin direct effects. In this order, we have previously demonstrated that inhibition of renal dopamine synthesis (by carbidopa) and uptake (by hydrocortisone), diminished urodilatin inhibitory effects on renal Na^+, K^+-ATPase activity [4]. Taking together this context and present results, the intracellular signal triggered by the effects of urodilatin on dopamine uptake should be considered as the signaling pathway that mediates urodilatin effect on Na^+, K^+-ATPase activity.

Despite acting on the same receptor, urodilatin is a longer half-life peptide and more potent that the ANP (in agreement with its greater stability to neutral endopeptidase) [9]. Our results show that although endogenous urodilatin is synthesized in distal tubules, exogenous urodilatin is able to stimulate NPR-A receptors located at the proximal tubules. Therefore the design of future drugs that closely resemble the structure of urodilatin would give greater stability and potency as NPR-A agonist, extending its effects not only at distal level but also at the proximal level.

In conclusion, urodilatin increases dopamine uptake in renal cortex. Considering that urodilatin binds to NPR-A receptors, our results demonstrate that particulate guanylate cyclase activation is necessary to mediate urodilatin effects on renal dopamine uptake. Moreover, urodilatin renal dopamine uptake stimulation involves generation of cGMP as second messenger and activation of PKG. This way, urodilatin may favor dopamine intracellular accumulation and therefore it release to tubular lumen, where dopamine receptors are mainly located, which in turn may contribute to a greater inhibitory effect on Na^+, K^+-ATPase activity.

Thus, dopamine and urodilatin may achieve their effects through a common pathway that involves reversible deactivation of renal tubular Na^+, K^+-ATPase, reinforcing their natriuretic and diuretic properties and contributing to blood pressure control and electrolyte homeostasis.

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