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Short communication

Dopamine D1 receptor-dependent inhibition of NaCl transport in the rat thick ascending limb: mechanism of action

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Abstract

Our previous in vitro microperfusion studies established that dopamine inhibits sodium chloride transport in the rat medullary thick ascending limb. The present study was designed to determine the intracellular signaling pathway mediating this response. The dopamine D1 receptor agonist fenoldopam (1 μM) inhibited sodium chloride transport in the thick ascending limb by 42 ± 5%. The dopamine D1 receptor antagonist R-(+)-7-Chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine-HCl (SCH-23390) completely blocked this effect of fenoldopam. Suppression of protein kinase A activity using either myristoylated protein kinase inhibitor (PKI) or *N*-[2-(*p*-Bromocinnamylamino)ethyl]-5-isoquinolinesulfonamide.2HCl (H-89), as well as suppression of phospholipase C activity using 1-(6-((17β-3-methoxyestra-1,3,5(10)-trien-17-yl)amino)hexyl)-1H-pyrrole-2,5-dione (U-73122), had no effect on fenoldopam-dependent inhibition of transport. In contrast, inhibition of phospholipase A_2 activity using E-6-(Bromomethylene)tetrahydro-3-(1-naphthalenyl)-2H-pyran-2-one (HELSS) significantly attenuated the effect of fenoldopam by 74%. The cytochrome P-450 monooxygenase inhibitor 17-octadecynoic acid (17-ODYA) and the protein kinase C inhibitor staurosporine both significantly attenuated the effects of fenoldopam by 67%. Exposure to 20-Hydroxy-(5Z, 8Z, 11Z, 14Z)-eicosatetraenoic acid (20-HETE) inhibited transport by 31 ± 5%, and this effect was significantly attenuated by 66% in the presence of staurosporine. We propose a signaling pathway in which dopamine activates a calcium-independent phospholipase A_2 in the medullary thick ascending limb. Released arachidonic acid is then metabolized to 20-HETE which subsequently increases protein kinase C activity that acts as a final transport effector.

Keywords: Loop of Henle; Microperfusion, in vitro; Fenoldopam; Arachidonic acid; Protein kinase C

1. Introduction

It is now well established that renal dopamine, primarily synthesized by proximal tubule cells, is an important natriuretic factor. It has been estimated for example that over 50% of the sodium excreted in response to a moderate saline load is under the control of dopamine (Jose et al., 1998). Mechanistically, dopamine inhibits sodium chloride reabsorption in several tubule segments. The earliest in vitro microperfusion studies established that the proximal tubule was one such site of dopamine action (Bello-Reuss et al., 1982), and later studies reported that dopamine can also inhibit arginine vasopressin-dependent sodium reabsorption as well as osmotic water permeability in the collecting tubule system (Muto et al., 1985; Sun and Schafer, 1996; Edwards and Brooks, 2001).

Previous work from this laboratory demonstrated that dopamine can also inhibit sodium chloride reabsorption in the in vitro microperfused medullary thick ascending limb of the rat (Grider et al., 1998). As part of that study, we proposed that the intracellular mechanism of dopamine action probably involved the synthesis of cytochrome P-450 ω-hydroxylase-derived arachidonic acid metabolites such as 20-Hydroxy-(5Z, 8Z, 11Z, 14Z)-eicosatetraenoic acid (20-HETE), based on the fact that dopamine-dependent inhibition of transport could be, at least in part, attenuated by treatment with the suicide-substrate inhibitor, 17-octadecynoic acid (17-ODYA). Using inhibition of Na^+-K^+-ATPase activity as an end-point, these arachidonic acid metabolites have also been implicated in the mechanism of dopamine action in other nephron segments (Ominato et al., 1996; Satoh et al., 1995).

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In the proximal tubule, some studies suggest that 20-HETE is the terminal effector leading to suppressed Na^+-K^+-ATPase activity (Ominato et al., 1996), while others suggest that 20-HETE increases protein kinase C activity, which in turn phosphorylates and thus decreases Na^+-K^+-ATPase activity and/or enhances internalization of the enzyme (Nowicki et al., 1997; Chibalin et al., 1999; Asghar et al., 2001).

The upstream signaling pathways that lead to 20-HETE synthesis may also differ between segments. In the proximal tubule for example, there is reasonable evidence to suggest that dopamine D1 receptors are initially coupled to phospholipase C, activation of which results in increased phospholipase A_2 activity and the subsequent generation of P-450 ω-hydroxylase metabolites (Ominato et al., 1996). In contrast, Satoh et al. (1995) have proposed that phospholipase A_2 activation is dependent on dopamine D1 receptor coupling to adenylyl cyclase and the generation of cyclic adenosine 3′,5′ monophosphate (cAMP) in both the collecting tubule and the thick ascending limb. At the level of transport however, increases in intracellular cAMP are typically associated with enhanced rather than suppressed sodium chloride reabsorption in the thick ascending limb (Bailly, 1998). Therefore, the goal of the present study was to utilize the in vitro microperfusion approach to determine the intracellular signaling pathway(s) underlying dopamine D1 receptor-dependent inhibition of sodium chloride transport in the rat medullary thick ascending limb. The results suggest that this pathway contains some elements that are unique to the thick ascending limb, and others that have already been established for dopamine action on both the proximal and collecting tubule.

2. Materials and methods

2.1. Tubular microdissection

Male Sprague–Dawley rats (28–30 days old; 35–50 g) were anesthetized with sodium pentobarbital (60 mg/kg i.p.). The kidneys were exposed via a mid-ventral incision, and rapidly cooled with 20 ml of ice-cold bicarbonate-buffered Hanks balanced salt solution containing (in mM): 140 NaCl; 1.4 $CaCl_2$; 0.8 $MgSO_4$; 5.4 KCl; 0.44 KH_2PO_4; 0.33 Na_2HPO_4; 4 $NaHCO_3$; and 100 mg% D-glucose (pH 7.4). They were transferred to a Petri dish containing ice-cold Hanks supplemented with 0.1% bovine serum albumin (fraction V) and cut into transverse sections. Medullary thick ascending limb segments (0.5–0.8 mm in length) were microdissected from the inner stripe of the outer medulla under stereomicroscopic observation. This animal protocol was approved by the University of Kentucky Animal Care and Use Committee.

2.2. In vitro microperfusion

Individual thick ascending limb segments were transferred to a temperature-controlled Lucite bathing chamber attached to the stage of a Nikon Diaphot inverted microscope, and microperfused at 8–15 nl/min with albumin-free Hanks utilizing techniques described previously (Grider et al., 1996, 1997, 1998). The bathing medium (Hanks + albumin) was continuously bubbled with 95% O_2/5% CO_2, maintained at 37 °C and exchanged at a rate of 0.5 ml/min throughout the experiment. Tubules were initially allowed to equilibrate for 10–20 min and the perfusate that was collected during this time was discarded. The standard experimental paradigm consisted of three 10-min control collections and three 10-min post-treatment collections. Chloride transport was calculated as the difference in chloride concentration between the perfusion fluid and the collected fluid multiplied by the volume flow rate. Chloride concentration was determined by electrometric titration as previously described (Grider et al., 1996, 1997, 1998). Tubule length was determined with a calibrated micrometer to allow all transport data to be expressed per mm tubule length.

2.3. Calcium imaging

Intracellular calcium was measured in microdissected thick ascending limb segments using a fura-2-based fluorescence imaging system as described previously (Grider et al., 1997). Briefly, nephron segments were transferred to a Lucite bathing chamber in which the glass coverslip floor had been pretreated with poly-L-lysine (1 μg/ml) to ensure immobilization of the tubules. Segments were incubated for 20–30 min at room temperature in Hanks containing fura-2 acetoxymethyl ester (fura-2/AM; 2.5 μM) and subsequently washed extensively with probe-free Hanks. For each experiment, the 340/380 nm fluorescent images were collected at 5-s intervals for 30 s prior to and for 300 s after initiating treatment. For calibration, following each procedure, an R_{max} and R_{min} were obtained using bromo-A23187 (1 μM) and EGTA (10 μM), respectively (Grider et al., 1997).

2.4. Statistical analysis

Data were analyzed statistically by analysis of variance. Specific differences were obtained using post-hoc analysis by Newman–Keuls multiple range test. Significance was considered to be $P < 0.05$.

3. Results

Addition of the dopamine D1-receptor agonist fenoldopam to the bathing medium (1 μM) caused a rapid onset and sustained inhibition of chloride reabsorption in the in vitro microperfused medullary thick ascending limb. In the three 10-min post-treatment collection periods, chloride reabsorption was significantly reduced by 40%, 43% and 40%, respectively when compared to the average control (pretreatment) transport (Fig. 1; top panel). The inhibitory effect of fenoldopam was completely blocked by pretreatment with

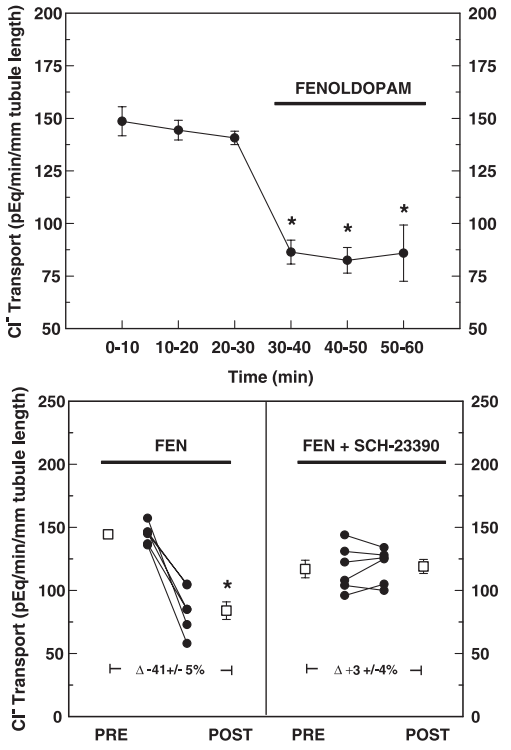

Fig. 1. (Upper panel) Effect of fenoldopam (1 μM) on chloride reabsorption in the in vitro microperfused medullary thick ascending limb of the rat. Each experiment consisted of six 10-min fluid collections. After three control collections, fenoldopam was added to the bath. Chloride reabsorption is expressed as pEq/min/mm tubule length. Data points represent the mean ± S.E.M. of six separate experiments. (Lower panels) Effect of fenoldopam (FEN) on chloride reabsorption in the absence (left panel) and presence (right panel) of the dopamine D1 receptor antagonist SCH-23390 (10 μM). Data points connected by lines represent the mean of the three control (PRE) and the three post-fenoldopam (POST) fluid collections (see upper panel). Open squares represent the mean ± S.E.M. for all PRE and POST values (the same data were used to generate the upper panel and lower left panel figures). *$P < 0.05$ compared to PRE values.

the dopamine D1 receptor antagonist R-(+)-7-Chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine-HCl (SCH-23390) (10 μM; Fig. 1; right lower panel).

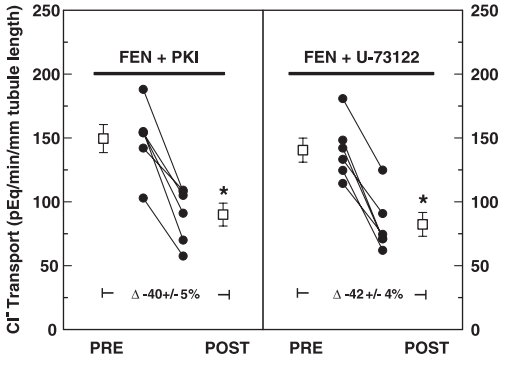

Fig. 2. Effect of fenoldopam (FEN; 1 μM) on chloride reabsorption in the presence of the protein kinase A inhibitor myristoylated protein kinase inhibitor (PKI; 400 nM; left panel) and in the presence of the phospholipase C inhibitor U-73122 (10 μM; right panel). *$P < 0.05$ compared to PRE values.

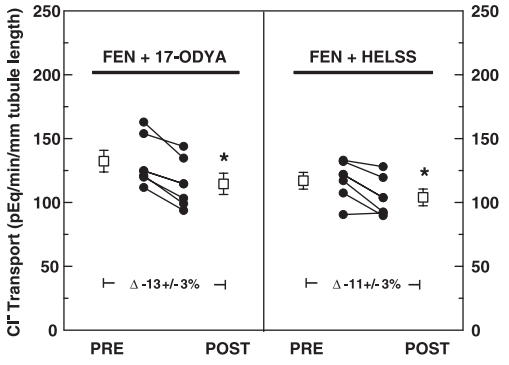

Fig. 3. Effect of fenoldopam (FEN; 1 μM) on chloride reabsorption in the presence of the cytochrome P-450 monooxygenase inhibitor 17-ODYA (100 nM; left panel) and the phospholipase A_2 inhibitor, haloenol lactone suicide substrate (HELSS; 3 μM; right panel). *$P < 0.05$ compared to PRE values.

The dopamine D1 receptor is commonly G-protein coupled to adenylyl cyclase and the subsequent generation of cAMP (Missale et al., 1998). In order to determine whether the inhibitory effects of fenoldopam in the thick ascending limb are mediated by the cAMP signaling pathway, tubules were pretreated with myristoylated protein kinase inhibitor (PKI; 400 nM) in order to block the downstream activation of cAMP-dependent protein kinase. This treatment had no effect on the response to fenoldopam; in the presence of PKI, fenoldopam still inhibited chloride reabsorption by 40 ± 5% (Fig. 2; left panel). Similarly, fenoldopam-dependent inhibition of chloride reabsorption was unaffected by exposure to a second protein kinase A inhibitor, *N*-[2-(*p*-Bromocinnamylamino)ethyl]-5-isoquinolinesulfonamide.2HCl (H-89; 10 μM; Δ -42 ± 4%). The dopamine D1 receptor can also be G-protein coupled to phospholipase C, and the subsequent generation of inositol trisphosphate (Missale et al., 1998). In order to determine whether the inhibitory effects of fenoldopam are mediated via this pathway, tubules were pretreated with the phospholipase C inhibitor, 1-(6-((17β-3-methoxyestra-1,3,5(10)-trien-17-yl)amino)hexyl)-1H-pyrrole-2,5-dione (U-73122; 10 μM). The response to fenoldopam was also unaffected

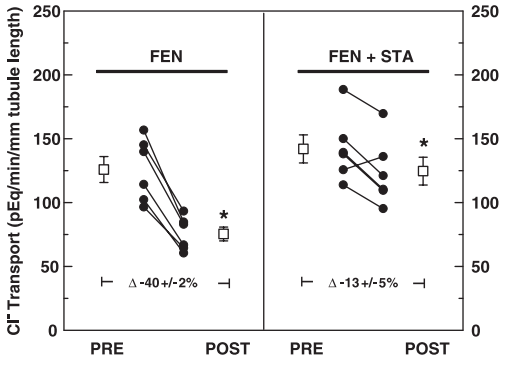

Fig. 4. Effect of fenoldopam (FEN; 1 μM) on chloride reabsorption in the absence (left panel) and the presence (right panel) of the protein kinase C inhibitor staurosporine (STA; 200 nM). *$P < 0.05$ compared to PRE values.

by this pretreatment paradigm (Δ -42 ± 4%; Fig. 2; right panel). The effectiveness of U-73122 was established in a separate series of calcium imaging experiments, in which we confirmed that this same pretreatment paradigm completely eliminated the bradykinin-induced rise in cytosolic calcium, which is caused by activation of phospholipase C and the subsequent generation of inositol trisphosphate (Grider et al., 1997). Additional experiments also confirmed that 1 μM fenoldopam had no effect on cytosolic calcium concentration in the thick ascending limb (data not shown).

Our previous studies had indicated that cytochrome P-450-dependent arachidonic acid metabolism may at least in part be implicated in the response to dopamine D1 agonists in the thick ascending limb based on the observation that the P-450 ω-hydroxylase inhibitor 17-ODYA significantly attenuated the inhibitory effect of dopamine (Grider et al., 1998). Consistent with these earlier data, in the present study, 17-ODYA (100 nM) significantly attenuated the inhibitory effect of fenoldopam on chloride reabsorption by 67% (Fig. 3; left panel). The effect of fenoldopam was also significantly attenuated by 75% after pretreatment with E-6-(Bromomethylene)tetrahydro-3-(1-naphthalenyl)-2H-pyran-2-one (HELSS; 3 μM; Fig. 3; right panel), suggesting that an upstream activation of calcium-independent phospholipase A_2 causes the release of arachidonic acid.

In the proximal tubule, activation of protein kinase C has been implicated in the mechanism of dopamine action (Nowicki et al., 1997; Chibalin et al., 1999; Asghar et al., 2001). In the thick ascending limb, preincubation with the broad-spectrum protein kinase C inhibitor staurosporine (200 nM) significantly suppressed fenoldopam-induced inhibition of chloride reabsorption by 67% (Fig. 4). Addition of the P-450 ω-hydroxylase metabolite 20-HETE (100 nM) to the bathing medium significantly inhibited chloride reabsorption by 31 ± 5% (Fig. 5; left panel). Pretreatment with staurosporine reduced this degree of inhibition by over 70%, suggesting that activation of protein kinase C is downstream of 20-HETE generation in this signaling pathway (Fig. 5; right panel).

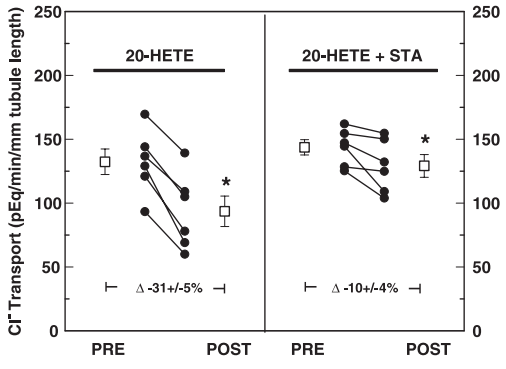

Fig. 5. Effect of the P-450 ω-hydroxylase metabolite of arachidonic acid, 20-HETE (100 nM), on chloride reabsorption in the absence (left panel) and the presence of staurosporine (STA; 200 nM; right panel). *$P < 0.05$ compared to PRE values.

4. Discussion

Previous studies from this laboratory established that dopamine, acting via basolateral membrane dopamine D1 receptors, could inhibit sodium chloride reabsorption in the in vitro microperfused medullary thick ascending limb of the rat (Grider et al., 1998). The present studies used the dopamine D1 selective agonist fenoldopam to determine the intracellular signaling pathway(s) involved in this response. Our data suggest that this pathway contains some elements that are unique to the thick ascending limb, and other elements that have previously been proposed to be involved in the mechanism of dopamine action on the proximal tubule and cortical collecting tubule.

Dopamine D1-like (D1 and D5) receptors are typically G-protein coupled to either adenylyl cyclase or to phospholipase C (Missale et al., 1998). The general consensus in the proximal tubule is that dopamine D1 receptors are coupled to phospholipase C (Ominato et al., 1996; Nowicki et al., 2000). We could find no evidence to support the concept that phospholipase C is involved in the response to fenoldopam in the thick ascending limb. This conclusion is based on the observation that the phospholipase C inhibitor U-73122 had no effect on the fenoldopam-dependent inhibition of sodium chloride reabsorption. We are reasonably sure that the dose of U-73122 used in these experiments was effective since bradykinin-induced intracellular calcium transients in the thick ascending limb, which are dependent on phospholipase C activation (Grider et al., 1997), could be completely blocked at this concentration of inhibitor. In further support of this conclusion, fenoldopam alone had no effect on intracellular calcium levels in this nephron segment (data not shown).

Studies by Satoh et al. (1995) proposed that an elevation in intracellular cyclic AMP was the initial step involved in dopamine-dependent inhibition of Na^+-K^+-ATPase activity in the rat thick ascending limb and in the collecting tubule. However, our data suggest that fenoldopam-dependent suppression of sodium chloride transport in the microperfused rat thick ascending limb is independent of the cAMP signaling pathway. This conclusion is supported by the fact that the response to fenoldopam was not affected by pretreatment with either myristoylated protein kinase inhibitor (PKI) or with H-89, both of which block the downstream activation of cAMP-dependent protein kinase. While we have no direct evidence of the efficacy of these drugs in our tissue preparation, a recent study by Good and George (2002) reported that the identical concentration of PKI completely blocked both neurotrophin-3 and forskolin-induced inhibition of HCO_3^- transport in the in vitro microperfused rat thick ascending limb. We have no explanation for the fact that these data are inconsistent with previous reports suggesting that cAMP plays a central role in dopamine-dependent inhibition of Na^+-K^+-ATPase activity in the thick ascending limb (Satoh et al., 1995; Aoki et al., 1996), other than to point out that agonist-dependent increases in cAMP accumulation

are typically associated with enhanced rather than suppressed sodium chloride reabsorption in the thick ascending limb (Bailly, 1998). Interestingly however, Kiroytcheva et al. (1999) have demonstrated that the specific effects of cAMP on Na^+-K^+-ATPase activity in the thick ascending limb are dependent on oxygen availability. Under hypoxic conditions, cAMP inhibits Na^+-K^+-ATPase activity, while in well-oxygenated cells, Na^+-K^+-ATPase activity is enhanced by this ubiquitous intracellular second messenger.

Our data suggest that in the rat thick ascending limb, dopamine D1 receptors are coupled to a calcium-independent phospholipase A_2. This conclusion is based on the observation that the inhibitory effect of fenoldopam on sodium chloride reabsorption could be almost completely blocked by treatment with haloenol lactone suicide substrate (HELSS), an irreversible mechanism-based inhibitor of phospholipase A_2 with 1000-fold selectivity for the calcium-independent over the calcium-dependent forms of the enzyme. To our knowledge, this is the first report of dopamine coupling to this enzyme. Jenkins et al. (2002) have demonstrated that this family of enzymes mediates arginine vasopressin-induced arachidonic acid release in A-10 smooth muscle cells, and we believe that this coupling mechanism may also exist in the thick ascending limb. Previous studies from this laboratory demonstrated that luminal administration of an arginine vasopressin V1 receptor agonist inhibited sodium chloride reabsorption in the microperfused thick ascending limb (Grider et al., 1996). This effect of arginine vasopressin was ultimately proposed to be dependent on cytochrome P-450-monooxygenase-dependent arachidonic acid metabolites, since the response could be blocked by pretreatment with the monooxygenase inhibitor 17-ODYA. Although not tested directly, we have proposed that the release of arachidonic acid is caused by activation of a calcium-independent phospholipase A_2, since vasopressin had no effect on intracellular calcium concentration. Studies are currently ongoing to establish the existence of this enzyme in the thick ascending limb at the molecular level.

In addition to arginine vasopressin, previous studies from this laboratory have established that cytochrome P-450-monooxygenase-dependent arachidonic acid metabolites are also implicated in the bradykinin-dependent inhibition of sodium chloride reabsorption in the thick ascending limb (Grider et al., 1997). Dopamine also appears to utilize this pathway, since treatment with 17-ODYA markedly suppressed fenoldopam-dependent inhibition of transport. This concept is certainly consistent with a number of studies in the proximal tubule. For example, Ominato et al. (1996) reported that dopamine-induced Na^+-K^+-ATPase inhibition could be blocked by the monooxygenase inhibitor ethoxyresorufin, but not by the cyclooxygenase inhibitor indomethacin or the lipoxygenase inhibitor nordihydroguaiaretic acid (NDGA). Indeed, this component of the signaling cascade is not inconsistent with the work of Satoh et al. (1995) in the thick ascending limb. However, while they would propose that an upstream dopamine-dependent increase in cAMP stimulates phospholipase A_2 activity and as a consequence an increase in arachidonic acid metabolism, our data are more consistent with a direct coupling of dopamine D1 receptors to a calcium-independent phospholipase A_2 that leads to metabolite generation.

A final series of experiments established a role for protein kinase C in this signaling pathway, based on the initial observation that the response to fenoldopam could be markedly blunted by treatment with the broad spectrum protein kinase C inhibitor, staurosporine. We have also demonstrated that the 20-HETE-induced inhibition of sodium chloride reabsorption in the thick ascending limb is significantly attenuated by staurosporine treatment, supporting the concept that protein kinase C is downstream of 20-HETE. Consistent with this conclusion, Nowicki et al. (1997) have reported that 20-HETE-dependent inhibition of Na^+-K^+-ATPase is mediated via protein kinase C in the proximal tubule, based on a series of observations including the facts that protein kinase C inhibitors and mutation of the protein kinase C phosphorylation site on the Na^+-K^+-ATPase abolished the inhibitory effects of 20-HETE and that 20-HETE stimulated protein kinase C-dependent phosphorylation of histone. Since staurosporine did not completely block the response to 20-HETE or indeed to fenoldopam, we cannot discount the possibility that this metabolite may elicit additional protein kinase C-independent effects on sodium chloride transport. In this context, there is certainly evidence to suggest that 20-HETE can modulate the activity of other key transport elements in the thick ascending limb including the luminal membrane Na^+-K^+-$2Cl^-$ cotransporter and potassium channel (Roman, 2002). Future studies will be designed to address these possibilities in detail.

In summary, the present studies have established that dopamine D1 receptor occupancy inhibits sodium chloride reabsorption in the rat thick ascending limb of the loop of Henle. Intracellularly, we propose a signaling pathway in which dopamine activates a calcium-independent phospholipase A_2 in the thick ascending limb. Released arachidonic acid is then metabolized to 20-HETE which activates protein kinase C that acts as a final transport effector.

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