Role of nitric oxide in the regulation of nephron transport

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Ortiz, Pablo A., and Jeffrey L. Garvin. Role of nitric oxide in the regulation of nephron transport. Am J Physiol Renal Physiol 282: F777–F784, 2002; 10.1152/ajprenal.00334.2001.—Nitric oxide (NO) plays an important role in various physiological processes in the kidney. In vivo experiments first suggested that the natriuretic and diuretic effects caused by NO may be due to decreased NaCl and fluid absorption by the nephron. In the last 10 years, several reports have directly demonstrated a role for NO in modulating transport in different tubule segments. The effects of NO on proximal tubule transport are still controversial. Both stimulation and inhibition of net fluid and bicarbonate have been reported in this segment, whereas only inhibitory effects of NO have been found in Na/H exchanger and Na/K-ATPase activity. The effects of NO in the thick ascending limb are more homogeneous than in the proximal tubule. In this segment, NO decreases net Cl and bicarbonate absorption. A direct inhibitory effect of NO on the Na-K-2Cl cotransporter and the Na/H exchanger has been reported, while NO was found to stimulate apical K channels in this segment. In the collecting duct, NO inhibits Na absorption and vasopressin-stimulated osmotic water permeability. An inhibitory effect of NO on H-ATPase has also been reported in intercalated cells of the collecting duct. Overall, the reported effects of NO in the different nephron segments mostly agree with the natriuretic and diuretic effects observed in vivo. However, the net effect of NO on transport is still controversial in some segments, and in cases like the distal tubule, it has not been studied.

sodium/hydrogen exchange; sodium-potassium-2 chloride cotransport; epithelial sodium channel; sodium/potassium-adenosine triphosphatase; proximal tubule; thick ascending limb; collecting duct

THE FREE RADICAL NITRIC OXIDE (NO) has been shown to play an important role in various physiological processes in the kidney, including salt and fluid reabsorption (31, 77), renal hemodynamics (32), renin secretion (33) and tubuloglomerular feedback (67, 83). Endogenous NO is enzymatically produced from conversion of the amino acid L-arginine to L-citrulline, a reaction that is catalyzed by the enzyme NO synthase (NOS). Three different NOS isoforms have been identified: a neuronal (nNOS), an endothelial (eNOS), and an inducible (iNOS) isoform. The three isoforms are differentially expressed throughout the kidney. Because of its high diffusibility, NO produced in one nephron segment or the renal vessels could affect the function of surrounding structures. Therefore, NO does not have to be produced in a nephron segment to have an effect. Consequently, one must take into account the regulation of nephron transport by both endogenous NO and NO produced by surrounding tissues.

In vivo experiments performed in animals first suggested the importance of NO in the regulation of NaCl and fluid reabsorption by the kidney. Those studies showed that infusion of substances like acetylcholine, which causes NO release, into the renal artery results in increased urinary volume and sodium excretion (3, 35, 49, 50, 72, 86). In agreement with those results, decreased water and sodium excretion was observed when inhibitors of endogenous NO production were infused into the kidney (34–36, 51). The natriuretic
and diuretic effects of NO were not accompanied by proportional changes in glomerular filtration rate (GFR) or renal blood flow (RBF), indicating that NO regulates nephron transport. In the last 10 years, several reports have directly demonstrated the importance of NO in modulating nephron transport. This review focuses on recent developments concerning the regulation of solute and water transport by NO in the different nephron segments (Fig. 1).

**EFFECTS OF NO IN THE PROXIMAL TUBULE**

The proximal tubule reabsorbs 50–60% of the total filtered load of inorganic solutes and water, whereas organic solutes such as sugars, amino acids, and other metabolites are essentially completely reabsorbed by this segment. Solutes are transported into the cell via apical Na-coupled cotransporters, including the Na-glucose, Na-Po₄, and Na-amino acid cotransporters or exchangers like the Na/H exchanger, which is responsible for HCO₃ reabsorption (4). The energy required for Na-coupled transport is provided by the electrochemical gradient generated by basolateral Na/K-ATPase. Water is reabsorbed by diffusion due to the osmotic gradient generated by active solute absorption via both transcellular and paracellular routes (5).

The effects of NO on the proximal tubule are controversial. Using the in vivo split-droplet technique, Eitle et al. (12) reported that luminal or basolateral addition of the NO donor nitroprusside (10⁻⁴ M) decreased proximal tubule fluid absorption (Jᵥ) by 20–35% in rats. No effects on Jᵥ were observed when lower concentrations of nitroprusside were tested, suggesting an inhibitory effect of NO on proximal tubule transport. In a more recent study, Wu et al. (85) reported that luminal addition of the NOS inhibitor NG-nitro-L-arginine methyl ester (L-NAME) increased rat proximal tubule Jᵥ, suggesting that endogenous NO tonically inhibits transport in this segment. Consistent with an inhibitory effect of endogenous NO on proximal tubule transport, Vallon et al. (79) observed that in vivo microperfused proximal tubules of nNOS knockout mice exhibited higher fluid and chloride absorption rates compared with proximal tubules of normal mice. Taken together, these data indicate that endogenously produced NO inhibits proximal tubule transport.

In contrast, a stimulatory effect of NO on proximal tubule transport has been reported. In an in vivo microperfused rat proximal tubule preparation, low concentrations of the NO donor nitroprusside (10⁻⁶ M) stimulated Jᵥ and bicarbonate absorption (JHCO₃) by 30–50%, whereas higher concentrations of nitroprusside (10⁻⁴ M) inhibited Jᵥ and JHCO₃ by 50–70% (80). It has also been reported that after intravenous infusion of L-NAME to block systemic NO production, perfusion of proximal tubules with L-NAME decreased Jᵥ and JHCO₃ (80). More recently, Wang et al. (81) reported that nNOS knockout mice exhibited lower fluid and HCO₃ absorption rates than proximal tubules from wild-type mice. Taken together, these data suggest that NO produced by nNOS in the proximal tubule stimulates transport.

The explanation for the disparate results regarding the effect of NO on proximal tubule transport is unclear. However, in nNOS knockout mice nNOS is genetically deleted from all tissues, not just the proximal tubule. Thus the difference between wild-type and nNOS knockout mice may be due to the effect of deleting nNOS from other organs. For instance, nNOS knockout mice have gastrointestinal tract malformations that could lead to acid-base disturbances (28). Such disturbances could alter the transport characteristics of the proximal nephron. The explanation as to why some investigators find that L-NAME inhibits whereas others find that it stimulates may rest with the renal nerves. It has been shown that the stimulatory effect of L-NAME on proximal tubule transport is prevented by denervating the kidney, suggesting that different degrees of neural activity could modulate the effect of NO on proximal tubule transport (85). Therefore, the distinct effects of NO donors observed in normal animals may also be explained by differences in renal nerve activity. In addition, it has recently been reported that intravenous infusion of L-NAME causes a paradoxical increase in NO production in the renal cortex (37). Thus the effects of L-NAME on proximal tubule transport obtained from in vivo preparations are difficult to interpret and may not only reflect the effects of decreasing endogenous NO.

Although the data on net flux are controversial, effects on individual transporters are consistent. The inhibitory effect of NO on proximal tubule JHCO₃ may be caused by a decrease in apical Na/H exchange ac-
tivity. Rocznia and Burns (68) studied the effect of NO on Na/H exchanger activity in primary cultures of proximal tubule cells. They found that the NO donors nitroprusside (10⁻³ M) and S-nitroso-N-acetylpenicillamine (1 mM) decreased amiloride-sensitive, ouabain-insensitive Na uptake, indicative of decreased Na/H exchanger activity. These effects on Na/H exchanger activity were mimicked by the cGMP analog 8-bromo-adenosine 3',5'-cGMP and were partially prevented by pretreatment with a guanylate cyclase inhibitor, suggesting that cGMP mediates the effects of NO.

In addition to a decrease in Na/H exchanger activity, several studies have shown that NO decreases Na/K-ATPase activity. Guzman et al. (21) first reported that endogenously produced NO inhibits Na/K-ATPase activity in cultured mouse proximal tubule cells stimulated with lipopolysaccharides and interferon-γ. In this study, cytokine treatment was used to induce iNOS expression, which generates large amounts of NO. In agreement with these data, Linas and Repine (43) reported that NO produced by endothelial cells inhibited apical-to-basolateral Na fluxes (JNa) and Na/K-ATPase activity in primary cultures of rat proximal tubule cells. In the presence of the Na/H exchanger inhibitor dimethylamiloride, NO still decreased Na/K-ATPase activity (43), indicating that the effect of NO was not due to changes in intracellular Na. Consistent with an effect of NO on Na/K-ATPase, Liang and Knox (40) found that nitroprusside decreased Na/K-ATPase activity in membrane vesicles isolated from opossum kidney cells. However, the effect of NO on Na/K-ATPase activity was not reproduced in LLC-PK1 cells (40, 41). These data suggest that the regulation of Na pump activity by NO is cell-type specific and/or concentration dependent.

Overall, the published data favor an inhibitory effect of NO on proximal tubule transport, most likely caused by a decrease in apical Na/H exchanger activity and Na/K-ATPase (Table 1). The contribution of NO produced by the proximal tubule to the regulation of transport in relation to that produced by other structures is still unknown.

### THICK ASCENDING LIMB

The thick ascending limb reabsorbs 25–30% of the filtered NaCl load while being water impermeable. The Na-K-2Cl cotransporter accounts for most of the NaCl reabsorbed by this segment (53). As in the proximal tubule, the driving force for NaCl entry is generated by Na/K-ATPase (26). The thick ascending limb also plays a role in acid-base balance by reabsorbing most of the HCO₃⁻ that escapes proximal reabsorption via luminal Na/H exchangers (18, 19). The apical membrane of the thick ascending limb has two types of K channels (82). K recycling across the apical membrane is important for Na-K-2Cl cotransport and generates a positive luminal potential that provides the driving force for paracellular transport of cations such as Ca²⁺ and Mg²⁺ (20).

In isolated, perfused rat thick ascending limbs, the NO donor spermine NONOate decreased net Cl absorption (JC), indicating that NO inhibits transport (65). Adding L-arginine, the substrate for NOS, to the bath stimulated endogenous NO production (57) and also reversibly decreased thick ascending limb JC (65). The effect of L-arginine was prevented by blocking NOS with L-NAME, indicating that endogenously produced NO mediates the effect of L-arginine. Although these data indicate that NO inhibits JC, they do not address which NOS isoform mediates this effect.

The thick ascending limb expresses all three isoforms of NOS. To determine the contribution of NO produced by the different isoforms to thick ascending limb transport, we studied the effect of L-arginine on JC by thick ascending limbs isolated from nNOS, iNOS, and eNOS knockout mice. L-Arginine decreased JC in thick ascending limbs isolated from nNOS and iNOS knockout mice but failed to inhibit JC in eNOS knockout mice (64). These data indicate that NO produced by eNOS is responsible for inhibition of thick ascending limb JC.

The effects of NO on net NaCl transport could be mediated by inhibition of apical transporters or basolateral Na/K-ATPase. Using the initial rate of increase in intracellular Na when NaCl is added to the luminal

### Table 1. Summary of transporters affected by NO along the nephron

<table>
<thead>
<tr>
<th>Transporter</th>
<th>Nephron Segment</th>
<th>Effect</th>
<th>Reference No(s.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺/K⁺-ATPase</td>
<td>Proximal tubule</td>
<td>Inhibition</td>
<td>40, 41, 43</td>
</tr>
<tr>
<td></td>
<td>Thick ascending limb</td>
<td>Inhibition</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Cortical collecting duct</td>
<td>No effect</td>
<td>75, 76</td>
</tr>
<tr>
<td>NHE3</td>
<td>Proximal tubule</td>
<td>Inhibition</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>Thick ascending limb</td>
<td>Inhibition</td>
<td>16</td>
</tr>
<tr>
<td>NKCC2</td>
<td>Thick ascending limb</td>
<td>Inhibition</td>
<td>60</td>
</tr>
<tr>
<td>ENaC</td>
<td>Cortical collecting duct</td>
<td>Inhibition</td>
<td>75</td>
</tr>
<tr>
<td>H⁺-ATPase</td>
<td>Inner medullary collecting duct</td>
<td>Inhibition</td>
<td>78</td>
</tr>
<tr>
<td>K⁺ channels</td>
<td>Thick ascending limb</td>
<td>Stimulation</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>Cortical collecting duct</td>
<td>Stimulation</td>
<td>45</td>
</tr>
</tbody>
</table>

NO, nitric oxide; NHE3, type 3 Na⁺/H⁺ exchanger; NKCC2, Na⁺-K⁺-2Cl⁻ cotransporter; ENaC, epithelial Na⁺ channel.

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effect of NO on the thick ascending limb, while cGMP analogs mimic the stimulatory effect of L-arginine and NO donors on rat NaCl absorption, consistent with the sodium/proton exchange. However, unlike NaCl absorption, the effect of NO on NaHCO3 absorption is controversial. We found that stimulation of endogenous NO production by L-arginine reversibly decreased thick ascending limb JHCO3. The effect of L-arginine was prevented by blocking NOS with L-NAME and was not mimicked by D-arginine, indicating that an increase in NO production mediates the effect of L-arginine (58).

In contrast to our results, Good et al. (17) found a stimulatory effect of L-arginine and NO donors on rat thick ascending limb JHCO3. We cannot explain these disparate results. However, we have found that in a small number of tubules NO stimulated JHCO3 and Na/H exchanger activity, suggesting that under some conditions NO could stimulate JHCO3. It is possible that differences in resting levels of cyclic nucleotides or diet can modify the hormonal state of the animals and affect the response to NO.

Bicarbonate reabsorption in the thick ascending limb occurs because of the secretion of protons via apical Na/H exchangers (19). By measuring the rate of intracellular pH recovery after an acid load, we found that NO donors inhibit both apical and basolateral Na/H exchanger activity (16). Because NO does not affect Na/K-ATPase activity and decreases steady-state concentrations of intracellular Na, a decrease in Na/H exchange can only be explained by a direct effect of NO on the exchanger.

Na-K-2Cl cotransport and Na/H exchange are differentially regulated by intracellular signaling cascades. NO acts primarily by stimulating soluble guanylate cyclase and increasing cGMP. We (13) and others (47) have shown that NO increases cGMP levels in the rat thick ascending limb, while cGMP analogs mimic the effect of NO on JCl (54, 55) and JHCO3 (58). Interestingly, the inhibitory effect of endogenous NO on thick ascending limb JHCO3 was prevented by inhibition of cGMP-dependent protein kinase, but JCl was not (58, 59). In contrast, inhibition of JCl by NO was prevented by blockade of cGMP-stimulated phosphodiesterase (phosphodiesterase II) (59). Given that cAMP stimulates cotransport activity, the data indicate that under basal conditions there is sufficient cAMP to enhance JCl. Thus an increase in NO production increases cGMP, activates phosphodiesterase II, and consequently decreases the stimulatory effect of cAMP. Whether a decrease in cAMP affects the phosphorylation state and activity or the number of Na-K-2Cl cotransporters in the apical membrane is not known. The molecular mechanism ultimately responsible for the inhibitory effect of NO on cotransporter activity has not been elucidated.

In addition to Na, Cl, HCO3, and K, the thick ascending limb also absorbs Ca2+ and Mg2+. It is not known whether NO modulates Ca2+ and Mg2+ transport in this segment. In cultured opossum kidney cells, NO has been shown to increase paracellular permeability (39). Because Ca2+ and Mg2+ absorption by the thick ascending limb occurs via the paracellular pathway (20), it is possible that NO could also regulate transport of divalent cations. However, because NO would also be expected to decrease the lumen positive potential that drives divalent cation absorption, one cannot predict the net effect.

In summary, most in vitro microperfusion data support an inhibitory effect of NO on thick ascending limb NaCl and NaHCO3 transport, consistent with the natriuretic and diuretic effects of NO observed in vivo. However, the actions on luminal K channels and Na/H exchange do not appear to be uniform. The explanation for these disparate results in some instances may be related to the use of different methodologies, but others cannot be explained. Furthermore, the effect of NO on KCl cotransport and Cl channels in the thick ascending limb has not been studied to our knowledge.

DISTAL TUBULE

The different cell types that comprise the distal tubule play an important role in the regulation of NaCl, NaHCO3 reabsorption and K secretion. Previous reports have suggested the presence of different NOS isoforms in the distal convoluted tubule (52, 84). However, to date, we know of no reports regarding the effects of endogenous or exogenous NO on transport characteristics of the distal tubule.

CORTICAL COLLECTING DUCTS

Principal Cells

The cortical collecting duct plays an important role in the fine control of NaCl and water absorption and K excretion. Principal cells of the cortical collecting duct are involved in Na and water reabsorption and K secretion. Na enters the cell via amiloride-sensitive apical Na channels due to the electrochemical gradient and is pumped from the cell by basolateral Na/K-ATPase (71). Luminal and basolateral membranes contain K channels involved in K secretion and recycling across the basolateral membrane, respectively (70).

It was first reported by our laboratory that NO produced by endothelial cells decreased short-circuit cur-
recent ($I_{sc}$), a measure of net active ion transport, in mouse cortical collecting duct cells cultured on permeable supports (74, 75). The inhibition of $I_{sc}$ could be accounted for by a decrease in net $J_{Na}$ (75). More recently, we have reported that NO derived from endothelial cells and donors also decreased $J_{Na}$ in isolated, perfused rat cortical collecting ducts (76). However, others have reported seeing no effect (27).

Indirect evidence suggests that the inhibition of net Na flux is due to reduced luminal membrane Na channel activity. NO decreased intracellular Na in isolated, perfused rat cortical collecting ducts (76) but did not affect Na/K-ATPase activity in either cultured (75) or freshly isolated cells (76). Because essentially all net $J_{Na}$ was inhibited by amiloride, these data indicate that entry of Na into the cell via amiloride-sensitive Na channels is reduced by NO. However, Lu et al. (44) reported that the NOS inhibitor L-NAME inhibited luminal Na currents in this segment, suggesting a stimulatory effect of NO on amiloride-sensitive Na channels. Although it is difficult to reconcile these data, it is important to note that Lu’s experiments were performed in the absence of L-arginine, so it is unclear how their results can be explained by L-NAME inhibiting NO production.

In addition to the effects of NO on the amiloride-sensitive Na channel, there is a growing body of work concerning K channels in the rat cortical collecting duct. Using the whole-cell-attached, patch-clamp technique, Lu and Wang (45) reported that a NO donor increased K channel activity. However, in a later study a biphasic effect of NO on the basolateral K channel was observed (46). The authors suggested that the biphasic effect of NO was due to the reaction of superoxide with NO and that the product of this reaction, peroxynitrite, was ultimately responsible for the inhibitory effect. The oxygen-derived free radical superoxide may be produced by different oxidases, such as xanthine oxidase, NADPH oxidase, and, under some conditions, by NOS itself (2, 61, 66). However, it is still not known whether the cortical collecting duct can produce sufficient amounts of superoxide under basal conditions to generate a significant amount of peroxynitrite.

It is difficult to extrapolate from results obtained by studying channel activity to the net transport effect in the cortical collecting duct, because many levels of regulation may be lost. Therefore, it is impractical to conclude from the patch-clamp studies what the final effect of NO on net Na and K transport in cortical collecting ducts might be. Overall, the present data support an inhibitory effect of NO on net Na transport by the cortical collecting duct. The mechanism by which NO inhibits $J_{Na}$ appears to involve a direct effect on apical Na channels and possibly an inhibitory effect on basolateral K channels. Because peroxynitrite may have different effects from native NO, it is possible that the disparate effects of NO on Na transport are due to different levels of superoxide and thus peroxynitrite.

In addition to absorbing Na, the cortical collecting duct is important to the regulation of water excretion (25). Water transport is regulated by arginine vasopressin (AVP); in the absence of AVP, the osmotic water permeability ($P_{w}$) of the cortical collecting duct is low and water reabsorption ($J_{w}$) is negligible. Addition of AVP causes the insertion of aquaporins in the apical membrane of principal cells, dramatically increasing $P_{w}$ (7). We have reported that NO donors decrease AVP-stimulated $J_{w}$. This effect was due to a decrease in AVP-stimulated $P_{w}$ and $J_{Na}$ (14). The effect of NO on $P_{w}$ was blocked by guanylate cyclase and cGMP-dependent protein kinase inhibitors, indicating that activation of both soluble guanylate cyclase and cGMP-dependent protein kinase is involved in the effects of NO. Activation of cGMP-dependent protein kinase leads to a decrease in cAMP. If this decrease is blocked, the effects of NO are also inhibited (15). Although NO decreases cAMP, it is not known whether it reduces the rate at which water channels are inserted into the luminal membrane, enhances their retrieval, or blocks the channels themselves.

In contrast to the inhibitory effect of NO on AVP-stimulated $P_{w}$, other groups have reported that NO either has no effect (27) or enhances the insertion of aquaporins into the luminal membrane (6). The explanation for the lack of an effect of NO on ADH-stimulated $P_{w}$ may reside in cAMP analogs (10, 15, 56). Thus the lack of an effect of NO on $P_{w}$ may be due to either 1) an inability of NO to enhance phosphodiesterase II because of a lack of the enzyme or 2) an inability of NO to reduce cAMP below the threshold necessary to inhibit $P_{w}$ due to an exaggerated effect of AVP on cAMP levels. The results of the latter study may be explained by the different experimental conditions used. First, in the study by Bouley et al. (6) the effects of NO were examined in the absence of AVP. Because AVP enhances aquaporin insertion via cAMP (7) and we have found that NO inhibits AVP-stimulated $P_{w}$ by decreasing cAMP accumulation (15), the effects of NO on aquaporin insertion may depend on cAMP levels. Additionally, in the study by Bouley et al. (6) the effects of NO were examined in the absence of an osmotic gradient. Water flow as the result of an osmotic gradient is necessary for retrieval of aquaporins from the luminal membrane (22, 23). Thus the latter study may not reflect the net effect of NO under physiological conditions. While NO may enhance insertion, it may stimulate retrieval to a greater extent. Alternatively, NO may inhibit the channels themselves rather than their trafficking.

**Intercalated Cells**

In addition to reabsorbing Na, the cortical collecting duct can secrete either H$^+$ or HCO$_3^-$ depending on whether α- or β-intercalated cells predominate (73). In freshly isolated cortical collecting ducts, NO donors decrease bafilomycin-sensitive H-ATPase activity in a dose-dependent fashion. In cortical collecting duct cells stimulated with lipopolysaccharides to stimulate iNOS...
expression, addition of l-arginine decreased H-ATPase activity. This effect was prevented by l-NAME, indicating that it was NO dependent (78). Inhibition of H-ATPase by NO is likely mediated by cGMP, because cGMP analogs also inhibit H-ATPase activity. Whether NO affects other transporters involved in acid-base flux, or the mechanism by which NO inhibits H-ATPase in intercalated cells, is still unknown.

OUTER MEDULLARY COLLECTING DUCT

There have been few studies of the regulation of transport by NO in the outer medullary collecting duct. Zeidel et al. (88) reported that nitroprusside, a NO donor, increased cGMP levels in the outer medullary collecting duct. However, nitroprusside did not affect oxygen consumption rates, suggesting that NO does not influence outer medullary collecting duct transport (88).

INNER MEDULLARY COLLECTING DUCT

The inner medullary collecting duct is the last site for regulation of NaCl and water excretion in urine. Na reabsorption by this segment occurs primarily via apical amiloride-sensitive Na channels and basolateral Na/K-ATPase. A basolateral Na/H exchanger and Na-K-2Cl cotransporter have been reported in this segment, but their role in net transport is unclear.

Zeidel et al. (88) first reported that nitroprusside increased cGMP levels and caused dose-dependent inhibition of ouabain-sensitive oxygen consumption in the rat inner medullary collecting duct, a measure of active transport. We have reported similar results (13). It was later reported that nitroprusside inhibited Na uptake in suspensions of inner medullary collecting duct cells (87). The effect of NO on oxygen consumption is likely secondary to inhibition of Na entry. Light et al. (42) reported finding a cGMP-inhibitable Na channel in this segment, and the effects of cGMP on oxygen consumption can be reversed by Na ionophores (88).

To our knowledge, there have been no studies on the effect of endogenously produced NO on transport, even though this segment expresses all three NOS isoforms. Interestingly, Cai et al. (8) reported that inner medullary collecting duct cells exposed to different levels of shear stress showed increased production of NO. The possibility that flow regulates inner medullary collecting duct transport via NO production has not been explored.

NO, TUBULAR TRANSPORT, AND BLOOD PRESSURE REGULATION

The present data concerning the effects of NO on different tubule segments suggest that endogenously produced NO may tonically regulate transport. Defects in NO regulation of Na absorption may increase salt and fluid retention, leading to hypertension. In agreement with this hypothesis, we and other investigators have reported observing abnormalities in the regulation of transport by NO (13, 30). In addition, several vasoactive hormones involved in blood pressure control (e.g., endothelin 1, α2-receptor agonists) regulate tubule transport via the NO pathway (62, 63).

Although the results obtained with whole-animal models support a role for defective regulation of transport as a possible cause of hypertension, the issue has only been addressed directly by a few investigators (1, 11, 13, 24, 29, 30, 48, 69, 85, 89). Similarly, most investigators studying cellular and molecular regulation of the different transporters in the nephron have not extrapolated their findings to whole-animal physiology. Essential questions regarding tubular ionic transport and its role in the long-term regulation of arterial pressure remain unanswered, and intensive research in these areas is required.

CONCLUDING REMARKS

In the past few years we have gained some insight into how NO regulates salt and water excretion. However, the effects of NO on many nephron segments remain controversial, and in some cases, such as the distal tubule and the thin limbs, have not been studied. The explanation for the disparate results is unclear but may involve factors such as differences in basol cAMP levels.

The data obtained from in vivo and in vitro microperfusion and cell culture studies predict that NO is a potent natriuretic factor. However, changes in urinary volume and Na excretion caused by NO synthesis inhibition are frequently model dependent. Although this may seem contradictory to the effects of NO on nephron transport, one must keep in mind that urinary volume and sodium excretion do not directly reflect nephron transport alone but rather a host of other physiological parameters including renal blood flow, blood pressure, and hormonal status. The effects of NO on these parameters can mitigate its ability to promote natriuresis and diuresis by inhibiting nephron transport (9).

The questions regarding the effects of NO on solute transport in different nephron segments should be posed not as which data are correct and which are wrong but rather why the data differ. It is only through the resolution of the discrepancies that we will gain a thorough understanding of how NO regulates tubular transport along the nephron.

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INVITED REVIEW


