

Regulatory roles of nitric oxide and angiotensin II on renal tubular transport

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Abstract

Renal tubules regulate blood pressure and humoral homeostasis. Mediators that play a significant role in regulating the transport of solutes and water include angiotensin II (Ang II) and nitric oxide (NO). Ang II can significantly raise blood pressure via effects on the heart, vasculature, and renal tubules. Ang II generally stimulates sodium reabsorption by triggering sodium and fluid retention in almost all segments of renal tubules. Stimulation of renal proximal tubule (PT) transport is thought to be essential for Ang II-mediated hypertension. However, Ang II has a biphasic effect on in vitro PT transport in mice, rats, and rabbits: stimulation at low concentrations and inhibition at high concentrations. On the other hand, NO is generally thought to inhibit renal tubular transport. In PTs, NO seems to be involved in the inhibitory effect of Ang II. A recent study reports a surprising finding: Ang II has a monophasic stimulatory effect on human PT transport. Detailed analysis of signalling mechanisms indicates that in contrast to other species, the human NO/guanosine 3',5'-cyclic monophosphate/extracellular signal-regulated kinase pathway seems to mediate this effect of Ang II on PT transport. In this review we will discuss recent progress in understanding the effects of Ang II and NO

on renal tubular transport.

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Key words: Angiotensin II; Nitric oxide; Proximal tubules; Thick ascending limb; Distal tubules; Na⁺ transport

Core tip: Angiotensin II (Ang II) and nitric oxide (NO) play important roles in the regulation of renal tubular transport. Ang II has a biphasic effect on renal proximal tubule (PTs) transport, and NO seems to inhibit the effect of Ang II. In human PTs, however, Ang II seems to have an NO-dependent monophasic stimulatory effect. We will discuss the recent findings in this field.

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INTRODUCTION

Angiotensin II (Ang II) is a strong pressor, acting on various organs and systems, including the kidney. It binds to angiotensin receptors, of which the main subtypes are angiotensin receptor type 1 (AT1R) and type 2 (AT2R)^[1]. Although other classes of angiotensin and their receptors, such as AT7R^[2], occur, the receptor with the dominant effect in the kidney seems to be AT1R. Recently, Coffman *et al*^[3] demonstrated that renal AT1R is the essential target of Ang II-induced hypertension^[3]. By showing the importance of renal AT1R in the emergence of hypertension, their study suggests that renal AT1R will be the target for therapy and the prevention

of hypertension.

Nitric oxide (NO) is a gaseous vasoactive substance produced by nitric oxide synthase (NOS). NO has been shown to play important roles in the regulation of renal tubular transport. However, its role seems to be pleiotropic and varies according to circumstances.

NOS has three isoforms, NOS1, NOS2 and NOS3, previously referred to as neuronal NOS (nNOS), inducible NOS (iNOS), and epithelial NOS (eNOS), respectively. Renal tubules have each of these NOS isoforms^[4,5]; however, the details of their actions in the tubules are still unclear.

NO seems to inhibit NaCl reabsorption in the renal tubules and induces natriuresis. Inhibiting NOS decreased urine volume and NaCl excretion, without changing renal blood flow and the glomerular filtration rate^[6-10]. Overall, NO is thought to inhibit the reabsorption of NaCl and fluid by tubules.

ANG II AND TUBULES

Ang II in proximal tubules

Ang II has been widely known as a strong pressor and regulator of cardiovascular and renal function^[11]. In the classical pathway, AT1R mediates the effects of Ang II^[11]. Proximal tubules (PTs) reabsorb approximately 60% to 70% of the sodium filtered in the glomeruli. Therefore, the regulation of sodium reabsorption in this segment is important for the maintenance of blood pressure and humoral homeostasis^[12,13]. In the PTs, Ang II is known to stimulate sodium and water transport. Although Ang II affects transport processes in several nephron segments, as discussed below, its effect on PT transport may be its most important effect. In particular, the stimulatory effect of Ang II in the PTs has significant importance for the emergence and progression of hypertension^[14].

Ang II acts mainly *via* type 1 and type 2 angiotensin receptors. The type 1 receptor has 1A and 1B subtypes and is thought to raise blood pressure^[1]. AT2R is also thought to be located in the PTs^[15-17]. Some investigators argue that AT2R may mediate the inhibitory effect of Ang II^[18]. However, most data, including our own obtained from AT1R knockout mice^[13,19-21], indicate that AT1R is the dominant receptor mediating the biphasic effects of Ang II in the PTs.

In PTs, the basolateral electrogenic sodium-bicarbonate cotransporter type 1 (NBCe1) and the apical sodium-proton exchanger type 3 (NHE3) mainly regulate sodium reabsorption^[22]. In addition, sodium is reabsorbed and coupled with amino acids^[23], glucose^[24], phosphate^[25], and other solutes from the apical side^[14]. Sodium is also reabsorbed *via* Na⁺-K⁺-ATPase (NKA) from the basolateral side^[26], which offers the driving forces for NBCe1 and NHE3.

Ang II is known to have biphasic effect on the PTs of rats, mice and rabbits. Low concentrations (picomolar to nanomolar) of Ang II stimulate PT transport, while high concentrations (nanomolar to micromolar) inhibit

PT transport^[27,28]. In PTs, Ang II regulates major sodium transporters, such as NHE3, NBCe1, and NKA, in a biphasic manner^[19,29-32]. The activation of protein kinase C and/or a decrease in cAMP concentration, followed by the activation of the extracellular signal-regulated kinase (ERK) pathway, may be responsible for the stimulatory effect of Ang II^[33-35]. On the other hand, the activation of the phospholipase A2/arachidonic acid/5,6-epoxyeicosatrienoic acid (EET) and/or the NO/guanosine 3',5'-cyclic monophosphate (cGMP) pathways^[29,36,37] may be responsible for the inhibitory effect of Ang II. The concentration of Ang II is known to be much higher in kidney than plasma^[38,39], suggesting that the inhibitory effect of Ang II may also have some physiological significance in the regulation of renal tubular function and blood pressure.

Ang II in the thick ascending limb

There are some reports that Ang II stimulates net NaCl absorption in the thick ascending limb (TAL). Wang and colleagues showed that Ang II stimulates basolateral Cl⁻ channels by activating the protein kinase C-dependent NADPH oxidase pathway, inducing net NaCl absorption^[40]. Garvin *et al.*^[41] investigated the regulation of NKA activity in Ang II-induced hypertension^[41]. They showed that Ang II-induced hypertension is accompanied by increased NKA activity in rat TAL, which may be at least partially due to Ang II-stimulated superoxide production^[42] *via* NADPH oxidase^[43]. Moreover, Ang II binding to AT1R was shown to inhibit ADH-stimulated transport in the rat TAL suspension cells^[44]. Overall, Ang II seems to stimulate Na⁺ reabsorption in the TAL *via* AT1R.

Ang II in the distal tubules

In the distal tubules, approximately 10% to 20% of the filtered Na⁺ is reabsorbed. Na⁺ enters the tubule cells *via* the sodium-chloride cotransporter (NCC) and exits from the basolateral side *via* NKA, while Cl⁻ exits *via* chloride channels (ClC-Kb)^[14].

Recent studies indicate that With-No-Lysine Kinase (WNK), Oxidative stress-responsive kinase (OSR) 1, and STE20/SPS1-related proline alanine-rich kinase (SPAK) importantly regulate transport in distal tubules.

WNKs are atypical protein kinases, as their name "With No Lysine (K)" implies^[45]. They are expressed in various organs and tissues, including renal distal tubules, and modulate several biological processes, such as solute transport, cell growth, and neurotransmission^[46]. WNKs have subtypes, such as WNK1, WNK2, WNK3, WNK4 and kidney-specific (ks-) WNK1. The kidney expresses WNK1, WNK3, WNK4 and ks-WNK1, where they modulate the function of NCC in the distal tubules.

In distal tubules, Ang II seems to activate NCC *via* phosphorylation. Hoorn *et al.*^[47] showed that Ang II induces the phosphorylation of NCC, enhancing sodium retention in rat kidneys, independent of aldosterone^[47]. On the other hand, Uchida and colleagues showed that,

although Ang II increases NCC phosphorylation *via* the WNK-OSR1/SPAK pathway, the effect of aldosterone in this pathway is predominant^[48]. Using WNK4 knockout mice, Gamba *et al.*^[49] showed that Ang II stimulates NCC *via* a WNK4-SPAK dependent pathway and that WNK4 is involved in Ang II-stimulated aldosterone secretion^[49]. The detailed mechanisms by which Ang II, WNK-SPAK/OSR1 and aldosterone regulate transport in the distal tubules transport remain to be clarified.

Ang II in the connecting tubules and collecting tubules

In the last portion of the tubules, the connecting tubules (CNT) and the collecting tubules (CD), Na⁺ is mainly reabsorbed *via* an epithelial Na⁺ channel (ENaC) on the luminal side and NKA on the basolateral side. The amount of Na⁺ reabsorbed from these segments represents only a small fraction of the total Na⁺ absorption by the kidney, but its regulation contributes to the fine-tuning of sodium and fluid homeostasis.

ENaC is a heteromultimeric channel, with three homologous subunits (α , β , γ)^[50,51]. Loss-of-function mutations of ENaC cause pseudohypoaldosteronism type I (PHA-I), while gain-of-function mutations cause Liddle's syndrome^[52,53]. PHA-I features renal salt wasting associated with hyperkalaemia, while Liddle's syndrome shows arterial hypertension with hypokalaemia. Pharmacologically, amiloride directly and reversibly blocks the ENaC.

In the CNT and CD segments, aldosterone has been thought to play a principal role in regulating basal and long-term ENaC activity^[54]. Recently, however, Korbmayer *et al.*^[55] demonstrated that, in the distal convoluted tubules (DCT2) and CNT, ENaC function is largely independent of aldosterone^[55]. They suggested that glucocorticoids and/or Ang II may be responsible for the aldosterone-independent ENaC activity. Ang II itself may directly stimulate amiloride-sensitive Na⁺ reabsorption in CNT and CD, independent of aldosterone^[56,57]. Indeed, several studies have reported that the Ang II/AT1R pathway can regulate ENaC expression^[58-61]. This effect of Ang II is thought to be mediated *via* AT1R^[62,63]. In obese Zucker rats, moreover, enhanced AT1R activity may result in the ENaC activation, suggesting a role for Ang II in Na retention in diabetes and obesity^[60].

THE EFFECT OF NO IN THE TUBULES

NO in the PTs

As described above, NO has been thought to inhibit net NaCl and fluid absorption through renal tubules. However, Wang and colleagues argued that NO has a biphasic effect on the PTs. Low concentrations of an NO donor, sodium nitroprusside (SNP; 10⁻⁶ mol), stimulated PT fluid (J_v) and bicarbonate absorption (J_{HCO₃}) by 30%-50%, while high concentration of SNP (10⁻³ mol) inhibited J_v and J_{HCO₃} by 50%-70%^[64]. However, most other studies report that NO inhibits PT transport^[65-67]. In particular, NO has been shown to decrease NHE3 and NKA ac-

tivities^[67,68]. Overall, NO is generally thought to inhibit NaCl, HCO₃⁻, and volume reabsorption in the PTs.

NO in the TAL

In the TAL, approximately 30% of filtered Na⁺ is reabsorbed^[14]. The major Na⁺ transporters here are the Na⁺/K⁺/2Cl⁻ cotransporter (NKCC2) and NHE3 on the apical side as well as NKA on the basolateral side.

Garvin and colleagues found that NO donors inhibit Cl⁻ and HCO₃⁻ reabsorption^[69,70]. They found that NO inhibits NKCC2 and NHE3 activity, but not NKA activity^[71,72]. Using NOS3^{-/-} mice, they also showed that NOS3 is responsible for NO production in the TAL^[73,74]. HCO₃⁻ reabsorption in the TAL is accomplished by H⁺ secretion *via* apical NHE3^[75]. In the rat TAL, NO increases cGMP levels^[76,77], and cGMP analogues inhibit J_{HCO₃}^[70] and J_{Cl}^[78,79]. The inhibition of cGMP-dependent kinase (cGK) blocked the inhibitory effect of NO on J_{HCO₃}, but not on J_{Cl}^[70,80]. On the other hand, the inhibition of cGMP-stimulated phosphodiesterase (PDEII) blocked the inhibitory effect of NO on J_{Cl}^[80]. Thus, the NO/cGK pathway seems to mediate the inhibitory effect on J_{HCO₃}, while the NO/PDEII pathway seems to mediate the inhibitory effect on J_{Cl}^[80].

NO in the CNT and CD

Recently, Wall and colleagues have showed that NO reduces Cl⁻ absorption through ENaC in mouse CD^[81]. In the cultured *Xenopus laevis* distal nephron cell line 2F3, Bao and colleagues showed that the activity of ENaC was reduced by a cyclic GMP analogue or by an atrial natriuretic peptide^[82]. Moreover, in cGKII knockout mice, ENaC inhibition induced a much greater increase in UNa⁺V (2.6-fold) than in wild-type mice (1.9-fold), suggesting that ENaC activity is upregulated in the knockouts^[83]. Integrating these results, NO and its signal transduction system appear to inhibit ENaC in CD and to induce natriuresis, therefore preventing sodium retention and hypertension.

The interaction between Ang II and NO in PT

As previously described, the Ang II effect on Na⁺ reabsorption in the proximal tubule is biphasic in rodents and rabbits^[27,28]. The inhibitory effect of Ang II is mediated by the PLA2/arachidonic acid/EET and/or NOS/NO/cGMP pathways. In rat PTs, for example, the regulation of NKA by Ang II seems to be dependent on the NO/cGMP pathway^[35,36].

On the other hand, the effects of Ang II on PT sodium transport in humans have not yet been clarified. To this end, we analysed the effects of Ang II on human PTs isolated from the cortex of kidneys removed for renal carcinoma. Surprisingly, Ang II, in contrast to other species, was found to induce a monophasic stimulation of human PT transport^[84]. Specifically, Ang II induced a dose-dependent stimulation of NBCe1, NHE3, and J_{HCO₃} that was apparently mediated by both luminal and basolateral AT1Rs.

Table 1 Summary of angiotensin II effects on tubular transport

Nephron segment	Potential targets	Effects	Ref.
PT	NHE3, NBCe1 J _{HCO3}	biphasic in rats, mice, rabbits monophasic stimulation in humans	[19,27-32] [84]
TAL	NKA, NKCC2, Cl channel NADPH oxidase	stimulation	[40-43]
DCT	NCC WNK4?	stimulation	[47,49]
CNT/CD	ENaC	stimulation	[55,59-61]

PT: Proximal tubule; TAL: Thick ascending limb; DCT: Distal convoluted tubules; CNT: Connecting tubules; CD: Collecting tubules; NHE3: Apical sodium-proton exchanger type 3; NBCe1: Basolateral electrogenic sodium-bicarbonate cotransporter type 1; NKA: Na⁺-K⁺-ATPase; NKCC2: Na⁺/K⁺/2Cl⁻ cotransporter; NCC: Sodium-chloride cotransporter; ENaC: Epithelial Na⁺ channel.

Table 2 Summary of nitric oxide effects on tubular transport

Nephron segment	Potential targets	Effects	Ref.
PT	NHE3, NBCe1 J _{HCO3}	inhibition in rats, mice, rabbits biphasic in rats? monophasic stimulation in humans	[65-68,84] [64] [84]
TAL	NKA, NKCC2 J _{Cl} , J _{HCO3}	inhibition	[69-72]
CNT/CD	ENaC	inhibition	[81,83]

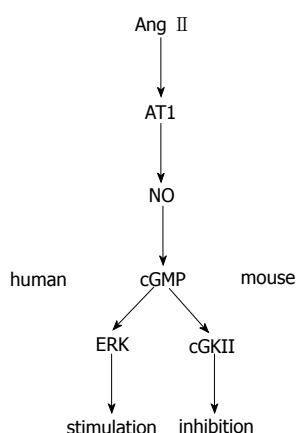


Figure 1 Species difference in angiotensin II/nitric oxide signalling in proximal tubules. In humans, NO/cGMP stimulates PT transport via ERK. In mouse, by contrast, NO/cGMP inhibits PT transport via cGKII. Ang II: Angiotensin II; NO: Nitric oxide; cGMP: Guanosine 3',5'-cyclic monophosphate; ERK: Extracellular signal-regulated kinase.

In contrast to other animals, both arachidonic acid and 5,6-EET failed to inhibit NBCe1 stimulation, which may partly account for the lack of an inhibitory effect of Ang II in human PTs. Notably, however, we found that the contrasting responses to the NO/cGMP pathway could largely explain the different actions of Ang II on PT transport in humans and other species. Thus, inhibition of the NOS/cGMP/cGKII pathway converted the inhibitory effect of 10⁻⁶ mol Ang II on mouse PT transport into a stimulatory effect. SNP dose-dependently inhibited PT transport in wild-type but not in cGKII mice. By contrast, the inhibition of NOS/cGMP/ERK pathway completely suppressed the stimulatory effect

of Ang II on human PT transport. While the inhibition of cGKII did not affect the Ang II effects, SNP dose-dependently stimulated transport in human PT. Western blotting with phosphor-specific antibodies revealed that Ang II induced a dose-dependent cGKII activation in mouse but not in human kidney cortex samples. On the other hand, SNP induced a dose-dependent ERK activation in human but not in mouse samples. Collectively, these results indicate that while the NO/cGMP/cGKII pathway mediates the inhibitory effect of Ang II in mouse PTs, the NO/cGMP/ERK pathway mediates the stimulatory effect in human PTs as shown in Figure 1.

We confirmed that human PTs do express cGKII. On the other hand, NO/cGMP failed to activate ERK in PTs from cGKII KO mice, indicating that the simple removal of cGKII from mouse PTs cannot reproduce the dose-dependent stimulatory effect of Ang II in human PTs. Therefore, the reason why the NO/cGMP pathway, acting as the down-stream mediator of Ang II, has contrasting effects on PT transport in humans and in other species is currently unknown. However, it is interesting to note that while the role of intrarenal NO in the adaptive natriuretic response to sodium loading has been well established in rodents, a similar role for NO has not been established in humans^[85-90]. In any case, the human-specific stimulatory effect of the NO/cGMP pathway on PT transport may offer a novel therapeutic target for human hypertension.

CONCLUSION

The absorption of Na⁺ in renal tubules is regulated by various factors, among which Ang II and NO play

significant roles. In general, Ang II stimulates sodium reabsorption and triggers fluid retention, leading to hypertension, while NO seems to induce natriuresis. However, our in vitro data suggest that NO may have distinct effects on PT transport in human and other species. Tables 1 and 2 summarize the effects of Ang II and NO on renal tubular transport.

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