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Current Antihypertensive mechanisms of intra-renal dopamine

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Abstract

Purpose of review—This review will highlight recent findings concerning the regulation and signalling of the intrarenal dopaminergic system and the emerging evidence for its importance in blood pressure regulation.

Recent findings—There is an increasing evidence that the intrarenal dopaminergic system plays an important role in the regulation of blood pressure, and defects in dopamine signalling appear to be involved in the development of hypertension. Recent experimental models have definitively demonstrated that abnormalities in intrarenal dopamine production or receptor signalling can predispose to salt-sensitive hypertension and a dysregulated renin–angiotensin system. There are also new results indicating the importance of dopamine receptor mediated regulation of salt and water homeostasis along the nephron, and new studies indicating the role that the intrarenal dopaminergic system plays to mitigate the production of reactive oxygen species and progression of chronic renal disease.

Summary—New studies underscore the importance of the intrarenal dopaminergic system in the regulation of renal function and indicate how alterations in dopamine production or signalling may underlie the development of hypertension and kidney injury.

Keywords

D1-like receptor; D2-like receptor; dopamine; hypertension; reactive oxygen species

INTRODUCTION

In addition to its essential role as a neurotransmitter, dopamine also has an important physiologic role in the kidney to regulate net salt and water excretion. Dopamine's actions are mediated by activation of one or more of the five members of the family of seven transmembrane G protein coupled dopamine receptors in mammals. The dopamine receptors are classified into 'D1-like' (D1R and D5R) and 'D2-like' (D2R, D3R and D4R) on the basis of G protein subtype coupling, with D1-like receptors coupled to G_s, which stimulates adenylate cyclases, and D2-like receptors coupled to G_i, which serves to inhibit adenylate

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Conflicts of interest

None.

cyclase. Both D1-like and D2-like dopamine receptors are expressed in the mammalian kidney [1].

The kidney has an intrarenal dopaminergic system that is distinct from any neural dopaminergic input. Circulating concentrations of dopamine are normally in the picomolar range, although dopamine levels in the kidney can reach high nanomolar concentrations [2]. The dopamine precursor L-DOPA (L-dihydroxyphenylalanine) is taken up by the proximal tubule from the circulation or following filtration at the glomerulus by multiple amino acid transporters, including rBat, L-type amino acid transporter 2 (LAT2) and glutamine/amino acid transporter 2 (ASCT2) [3,4] and is then converted to dopamine by aromatic amino acid decarboxylase (AADC), which is also localized to the proximal tubule [5]. Intrarenal dopamine production increases when dietary salt intake increases [6,7].

Dopamine receptor activation leads to decreases in salt and water reabsorption in the mammalian kidney, mediated at least in part by inhibition of specific tubule transporter activity along the nephron, including sodium-hydrogen exchanger 3 (NHE3), type II sodium-phosphate co-transporter (NaPi-II), sodium bicarbonate co-transporter (NBC) and Na/K-ATPase in the proximal tubule, $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ co-transporter (NKCC2) in the thick ascending limb of the loop of Henle and epithelial Na^+ channel (ENaC) and aquaporin 2 (AQP2) in the collecting duct [2,8–11]. A general characteristic of essential hypertension is a relative defect in renal sodium and water handling. As it is estimated that the intrarenal dopaminergic system is responsible for regulating over 50% of net renal salt and water excretion when salt intake is increased [12], dysfunction of this system could have profound consequences for the regulation of intravascular volume and systemic blood pressure. This review highlights some of the most exciting new findings about the intrarenal dopaminergic system and its regulation of renal salt and water homeostasis and blood pressure.

THE ROLE OF THE INTRARENAL DOPAMINERGIC SYSTEM IN BLOOD PRESSURE CONTROL

Mice with selective intrarenal dopamine deficiency due to AADC deletion develop salt-sensitive hypertension [13]. Conversely, mice deficient in catechol-*O*-methyltransferase (COMT), one of the major dopamine-metabolizing enzymes in the kidney, have increased intrarenal dopamine levels and blunted elevations in blood pressure in response to DOCA/high salt [14], as well as blunted increases in nocturnal blood pressure in response to a high-salt diet [15]. There is also recent evidence that renalase, a kidney-specific catecholamine-metabolizing enzyme [16], is importantly involved in renal dopamine metabolism. Renalase deficiency is associated with increased renal dopamine biosynthesis, stimulation of phosphate excretion and hypophosphatemia, which is not overcome by the compensatory increase in COMT activity [17]. On the contrary, a recent study shows that activation of D5R but not D1R increases renalase mRNA and protein levels in proximal tubule cells through phospholipase C mediated signalling, and this stimulation is impaired in proximal tubule cells from spontaneously hypertensive rats, suggesting that aberrant D5R regulation of renalase expression in proximal tubule may contribute to the pathogenesis of hypertension [18].

LOCALIZATION AND REGULATION OF RENAL DOPAMINE RECEPTORS

There is distinct intrarenal distribution of the different dopamine receptors (Table 1). Of the D1-like receptors, D1R is found most predominantly in the proximal tubule, with greatest distribution in the S3 segments and in the large intrarenal arteries, as well as the distal convoluted tubule, thick ascending limb of Henle, macula densa and cortical collecting duct. D5R is expressed in a similar distribution, in both proximal and distal convoluted tubules, thick ascending limb of Henle and cortical collecting duct, as well as renal arterioles. Of the D2-like receptors, D2R is found in both proximal and distal collecting ducts, as well as mesangial cells and intercalated cells, D3R is found in the proximal tubule, especially the S1 segment, as well as the thick ascending limb of Henle, macula densa, distal convoluted tubule and glomerulus, and D4R is found in the proximal and distal convoluted tubules and in both cortical and medullary collecting ducts (reviewed in [19]).

In addition to the regulation of intrarenal dopamine production and metabolism, previous studies have indicated that dopamine receptor expression can be regulated by transcriptional [20] and posttranslational modulation of dopamine receptors, including receptor endocytosis [21]. Sorting nexin 5 (SNX5), a component of the mammalian retromer, a complex of proteins relating the recycle of transmembrane receptors from endosomes to the *trans*-Golgi network, regulates the internalization of agonist-activated D1R as well as its recycling/reinsertion to the plasma membrane through interacting with the C-terminus of D1R [22]. In addition, SNX1 regulates D5R trafficking and function [23]. There is also recent evidence that dopamine receptors can be regulated by post-transcriptional mechanisms. In this regard, mir-142-3p was found to interact with a single consensus binding site in the 1277 bp 3' untranslated region of D1 receptor mRNA. Inhibition of endogenous miR-142-3p increased endogenous D1R expression and activity. There is an inverse correlation between miR-142-3p levels and D1 receptor protein expression in the mouse brain during postnatal development [24].

There has been a recent advance in the ability to image dopamine receptors *in vivo*. PET facilitates in-vivo imaging of biochemical processes non-invasively. [¹¹C]NNC 112, a PET radioligand for D1-like receptors, has previously been used to probe D1-like receptors in the human central nervous system. Granda *et al.* [25] described in-vivo measurement of D1-like receptors in the renal cortex of Sprague-Dawley rat and the *Papio anubis* baboon by using [¹¹C]NNC 112. They demonstrated that the [¹¹C]NNC 112 binding in the kidney was self-saturable, specific and responsive to drug treatment. The use of PET imaging provides a new tool to investigate intrarenal dopamine function in animal models and in humans [25].

NEW INSIGHTS INTO RENAL DOPAMINE SIGNALLING AND FUNCTION

There have also been new insights into the mechanisms of signalling of dopamine receptors. The D1-like receptor agonist, fenoldopam, is known to stimulate both adenylyl cyclase and phospholipase C activation (PLC) in the proximal tubule. However, the respective roles of the D1-like receptors, D1R and D5R in this signalling have not been previously elucidated. Using a novel, selective D5R antagonist, LE-PM436, and siRNA against D1R and D5R in association with fluorescent resonance energy transfer microscopy, Gildea *et al.* [26]

reported that D1R activation primarily stimulates adenylyl cyclase, while D1R/D5R heterodimers modulate the D1R function through the PLC signalling pathway, thereby inhibiting transporters on both the apical (NHE3) and basolateral (NaKATPase) membranes.

Raising luminal flow is known to increase volume reabsorption $J(v)$ and reabsorption of sodium $J(Na)$, and bicarbonate $J(HCO_3)$ in proximal tubules. Administration of luminal dopamine did not change $J(v)$, $J(Na)$ and $J(HCO_3)$ at low flow rates but completely abolished the increments of sodium absorption induced by increasing flow rates and partially inhibited the flow-stimulated bicarbonate absorption. The D1-like receptor blocker SCH23390 and the PKA inhibitor H89 blocked the effect of exogenous dopamine and increased the sensitivity of proximal $J(Na)$ to luminal flow rate. Therefore, dopamine inhibits flow-stimulated NHE3 activity by activation of the D1R receptor via a PKA-mediated mechanism, modulating proximal tubule transporters [27]. A potentially novel mechanism of activation of dopamine receptors in response to luminal flow was recently reported by Upadhyay *et al.* [28^{*}]. They localized D5R to primary cilia in pig kidney epithelial cells. Activation of D5R with either dopamine or fenoldopam increased primary cilia length in association with an increased sensitivity of the cells in response to fluid-shear stress. This finding suggests a potential role for intrarenal dopamine signal transduction in response to volume expansion and also raises the possibility that dopaminergic agonists might be used as potential agents to treat diseases associated with abnormal cilia structure and/or function [28^{*}].

D2-like receptors also inhibit renal ion transport. NHE3 is the principal renal Na^+ transporter in the proximal tubule, mediating 67 and 100% of the transcellular reabsorption in this segment of sodium and bicarbonate, respectively. In this regard, it has previously been shown that D3R activation suppresses renal ion transport via inhibiting proximal tubule NHE3 activity. Mice with D3R deletion develop hypertension and have a decreased ability to excrete an acute sodium load and dietary salt load. However, the underlying mechanisms by which D3R regulates NHE3 have not been previously described. Ubiquitin-specific proteases (USPs) are a group of structurally diverse proteases that function to remove ubiquitin moieties from proteins and thereby inhibit internalization and degradation of targeted proteins. One such protein, USP48, binds to the third intracellular loop of the human D₃R. Dopamine treatment has been reported to increase cell surface NHE3 ubiquitinylation in opossum kidney cells. USP48 is expressed in proximal and distal tubules, mTAL, and collecting duct of human kidney. Activation of D3R inhibits USP48 activity, preventing the removal of ubiquitin from NHE3 and leading to NHE3 degradation, with subsequent inhibition of proximal tubule sodium transport activity [29]. Other recent studies have indicated that in addition to increasing NHE3 internalization and degradation, dopamine also decreases NHE3 synthesis, although the receptor subtype(s) involved were not determined [30].

In addition to the proximal tubule, recent studies have indicated a role for dopamine to modulate distal nephron function. Basolateral K^+ channels in the distal renal tubule are critical for recycling and control of basolateral membrane potential to establish the driving force for Na^+ reabsorption. Inward rectifying Kir4.1 and Kir5.1 channels (encoded by *Kcnj10* and *Kcnj16* genes, respectively) are highly expressed on the basolateral membrane

of mouse cortical collecting ducts. These channels function as heterodimers and work in tandem with $\text{Na}^+\text{-K}^+\text{-ATPase}$ to regulate K^+ recycling across the basolateral membrane. In addition, Kir4.1 and Kir4.1/5.1 contribute to the establishment of the resting basolateral membrane potential, providing the net driving force for Na^+ and Cl^- reabsorption. Dopamine inhibits basolateral Kir4.1/5.1 and Kir4.1 K^+ channels in cortical collecting duct cells via stimulation of D2-like receptors and subsequently protein kinase C. This leads to depolarization of the basolateral membrane and a decreased driving force for Na^+ reabsorption in the distal renal tubule [31].

INTERACTIONS OF CYP450 AND DOPAMINERGIC SYSTEMS

Recent studies have indicated a potentially important role for cyp450 arachidonic metabolites in the mediation of the physiologic effects of dopamine receptor activation. Global catechol-*O*-methyl-transferase deletion (COMT $^{-/-}$) mice with increased intrarenal dopamine levels and proximal tubule deletion of aromatic amino acid decarboxylase (ptAADC $^{-/-}$) mice with renal dopamine deficiency were treated with low-salt diet or high-salt diet for 2 weeks. Wild-type or mice deficient in the major renal P450 involved in the production of epoxyeicosatrienoic acids (EET) from arachidonic acid (*Cyp2c44*) were treated with gludopa, which selectively increased renal dopamine levels. In low-salt treated mice, urinary EET levels were related to renal dopamine levels, being highest in COMT $^{-/-}$ mice and lowest in ptAADC $^{-/-}$ mice. In high-salt treated mice, total EET and individual EET levels in both kidney and urine were also highest in COMT $^{-/-}$ mice and lowest in ptAADC $^{-/-}$ mice. Selective increases in renal dopamine in response to gludopa administration led to marked increases in both total and all individual EET levels in the kidney without any changes in blood levels. Gludopa increased renal *Cyp2c44* mRNA and protein levels and induced marked increases in urine volume and urinary sodium excretion in wild-type mice. In contrast, gludopa did not induce significant increases in urine volume or urinary sodium excretion in *Cyp2c44* $^{-/-}$ mice. These studies indicate that renal EET levels are maintained by intra-renal dopamine, and *Cyp2c44*-derived EETs play an important role in intrarenal dopamine-induced natriuresis and diuresis [32]. There is also evidence that a different cyp450 arachidonic acid metabolite (20-HETE) may also be a mediator of intrarenal dopamine actions. In rats, dopamine-mediated increases in urine flow, sodium excretion, fractional sodium excretion and proximal and distal delivery of sodium were partially inhibited by 20-HETE inhibition [33].

DOPAMINE MODULATION OF RENAL REACTIVE OXYGEN SPECIES

There is recent evidence that both D1-like and D2-like receptors regulate the production of reactive oxygen species (ROS). D5R can inhibit ROS production by inhibiting NADPH oxidase [34]. Conversely oxidative stress mediated nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) activation downregulates D1R function and increases blood pressure. Inhibition of D2R also results in ROS-dependent hypertension. Aged Fischer 344 $\times$ Brown Norway F1 (FBN) rats exhibited increased oxidative stress, diminished D1R number, impaired G protein coupling as well as increased G protein-coupled receptor kinase (GRK) levels, but had exaggerated AT1R activity, and all these abnormal parameters were restored by treatment with the antioxidant, tempol [35,36]. Paraoxonase 2 is a member of

the paraoxonase gene family and protects against oxidative stress. Paraoxynase 2 is colocalized with D2R in the brush border of mouse proximal tubules, and its expression is decreased in D2R^{-/-} mice or increased by a pharmacological agonist of D2R. Furthermore, inhibition of paraoxynase 2 expression increases both ROS production and expression of NADPH oxidase 1 (NOX1). D2R has also been shown to regulate the expression of sestrin2, which regulates ROS levels by regenerating hyperoxidized peroxiredoxins [37]. Inhibition of sestrin2 expression inhibited D2R inhibition of ROS production, and inhibition of paraoxynase 2 decreased sestrin 2 expression [38^{***}]. Therefore, D2R's inhibition of ROS production appears to be mediated by coordinated activity of paraoxynase 2 and sestrin 2.

RENAL DOPAMINE AND CHRONIC KIDNEY INJURY

Recent progress has also been made in the understanding of the role of the intrarenal dopaminergic system in the pathogenesis of chronic kidney injury. Dopamine receptors have been shown to inhibit inflammation in renal proximal tubule cells [19]. D2R null mice exhibit hypertension and increased renal inflammation and injury, and treatment with apocynin, an inhibitor of NADPH oxidase, normalized blood pressure and decreased oxidative stress, but had no effect on the expression of inflammatory factors [39]. In cultured rodent renal proximal tubule cells, D2R inhibits inflammation status. Furthermore, human renal proximal tubule cells carrying D2R SNPs had decreased D2R expression and function, in association with increases in the proinflammatory cytokine, tumour necrosis factor- α (TNF- α) and the profibrotic cytokine, transforming growth factor- β 1 (TGF- β 1) and its signalling targets Smad3 and Snail1, as well as induction of extracellular matrix proteins such as vimentin, fibronectin 1 and collagen I [40]. These results suggest that dopamine may direct regulate the expression of inflammatory cytokines/chemokines in renal proximal tubule cells. *In vivo*, the development of diabetic nephropathy in streptozotocin-induced models of type 1 diabetes was attenuated in COMT^{-/-} mice, which have increased renal dopamine production, but augmented in ptAADC^{-/-} mice, which have decreased renal dopamine production. Protection against diabetic nephropathy was also seen in wild-type diabetic mice with a transplanted kidney from COMT^{-/-} mice. These results indicate that the decreased renal dopamine production may have important consequences in the pathogenesis of diabetic nephropathy [41].

CONCLUSION

Recent studies investigating the intrarenal dopamine system have provided strong evidence that it plays an important role in the overall regulation of renal salt and water homeostasis and blood pressure regulation, and dysregulation of this system can lead to the development of salt-sensitive hypertension, as well as acceleration of progressive kidney injury.

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KEY POINTS

- There is increasing evidence for an important role for the intrarenal dopaminergic system in the regulation of salt and water balance by affecting transport at multiple sites along the nephron.
- New studies indicate interactions between the intrarenal dopaminergic system and cyp450-mediated arachidonic acid metabolites, EETs and 20-HETE.
- In the kidney, dopamine modulates the production of ROS and serves to limit progressive kidney injury.
- Dysregulation of the intrarenal dopaminergic system can lead to the development of salt-sensitive hypertension.

Table 1

Renal distribution of dopamine receptor subtypes

Receptor subtype	Distribution
D1R	Renal arteries, PT, macula densa, JG cells, MTALH, DCT, CCD
D2R	Glomerulus, PT, DCT, CCD, outer MCD, inner MCD
D3R	Glomerulus, PT, MTALH, CTALH, DCT, CCD, outer MCD, inner MCD
D4R	Glomerulus, PT, MTALH, DCT, CCD, outer MCD, inner MCD
D5R	Renal arterioles, PT, MTALH, DCT, CCD

CCD, cortical collecting duct; CTALH, cortical thick ascending limb of Henle; DCT, distal convoluted tubule; JG, juxtaglomerular; MCD, medullary collecting duct; MTALH, medullary thick ascending limb of Henle; PT, proximal tubule.