Renal Dopamine System
Paracrine Regulator of Sodium Homeostasis and Blood Pressure

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Abstract—All of the components of a complete dopamine system are present within the kidney, where dopamine acts as a paracrine substance in the control of sodium excretion. Dopamine receptors can be divided into D₁-like (D₁ and D₅) receptors that stimulate adenyl cyclase and D₂-like (D₂, D₃, and D₄) receptors that inhibit adenyl cyclase. All 5 receptor subtypes are expressed in the kidney, albeit in low copy. Dopamine is synthesized extraneuronally in proximal tubule cells, exported from these cells largely into the tubule lumen, and interacts with D₁-like receptors to inhibit the Na⁺-H⁺ exchanger and Na⁺,K⁺-ATPase, decreasing tubule sodium reabsorption. During moderate sodium surfeit, dopamine tone at D₁-like receptors accounts for ≈50% of sodium excretion. In experimental and human hypertension, 2 renal dopaminergic defects have been described: (1) decreased renal generation of dopamine and (2) a D₁ receptor–G protein coupling defect. Both defects lead to renal sodium retention, and each may play an important role in the pathophysiology of essential hypertension. (Hypertension. 2001;38:297-302.)

Key Words: receptors, dopamine ■ sodium excretion ■ blood pressure ■ cell signaling

Dopamine is a catecholamine serving 2 important roles in neurobiology: (1) as an intermediate in the biochemical pathway from the amino acid tyrosine to norepinephrine and epinephrine and (2) as a direct neurotransmitter in its own right. In neurons, dopamine is synthesized by the initial hydroxylation of tyrosine (tyrosine hydroxylase) to L-dihydroxyphenylalanine (L-DOPA) followed by decarboxylation to dopamine (aromatic amino acid decarboxylase). The central neurotransmitter role of dopamine in the regulation of motor function and behavior is well established. More recently, dopamine has been recognized as an important peripheral hormone modulating renal sodium excretion and blood pressure by its cell-to-cell actions within the kidney.1 The present article reviews evidence for autocrine and paracrine actions of dopamine formed within the kidney, their cellular signaling pathways, and the potential role of dopamine in the pathophysiology of hypertension.

Renal Dopamine Formation and Secretion
Although the classical pathway for dopamine biosynthesis occurs in neurons, in the kidney dopamine is synthesized independently of nerve activity. Dopamine excreted in urine is almost exclusively derived from intrarenally formed dopamine.2 Dopamine is formed in large quantities in proximal tubule cells as a result of uptake of filtered L-DOPA via a sodium transporter in the apical membrane.3 Inside the proximal tubule cell, L-DOPA is rapidly decarboxylated to dopamine by aromatic amino acid decarboxylase, the activity of which is upregulated by high-sodium diet and downregulated by low-salt diet.4 Essentially nothing is known about the mechanisms by which dopamine is stored in the proximal tubule cell. Dopamine is catabolized in the kidney mainly by catechol-O-methyl-transferase and monoamine oxidase A.5,6 Dopamine can exit the cell at either the apical or the basolateral surface. The basolateral outward transporter is dependent on sodium and pH and is developmentally regulated, but little is known about apical dopamine secretion.7

The supply of L-DOPA to the proximal tubule is an important determinant of the amount of dopamine formed and secreted. L-DOPA or γ-L-glutamyl-L-DOPA (gludopa), a dopamine prodrug, markedly increases urinary dopamine excretion.2 However, the outward transport of dopamine from the proximal tubule cell in vivo is preferentially directed to the tubule lumen rather than across the basolateral surface into the peritubular space, as the increase in urinary dopamine far exceeds the increment of dopamine in the renal interstitial space.8 These observations suggest that dopamine is highly compartmentalized within the kidney. Certainly, dopamine accessibility to its receptors determines functional changes in the control of sodium excretion and blood pressure.

The intrarenal production of dopamine is not significantly modulated by renal sympathetic nerve activity, as chronic renal denervation does not affect basal or gludopa-stimulated renal dopamine.5–10 A schematic representation of proximal tubule cell biosynthesis, release, and action of dopamine is presented in Figure 1.

Renal Dopamine Receptors
Dopamine receptors are members of the G protein–coupled superfamily of hepta-helical cell membrane receptors. At
least 5 distinct dopamine receptors have been identified, which have been divided pharmacologically into D₁-like and D₂-like subfamilies. Both the cloned members of the D₁-like receptor group (D₁ and D₅, also known as D₁A and D₁B in rodents) are coupled to the stimulating G protein, Gₛ, and stimulate adenylyl cyclase. All 3 of the cloned D₂-like receptors (D₂, D₃, D₄) are associated with the inhibitory G protein, Gᵢ/Gₒ, and inhibit adenylyl cyclase. The central dopamine receptors are expressed in peripheral tissues. Figure 2 indicates the members of the D₁-like and D₂-like dopamine receptors and their selective agonists/antagonists.

Both the D₁-like and D₂-like receptor families are expressed in the kidney at postjunctional sites. The D₁ receptor (and probably also the D₃ receptor) is localized in the smooth muscle layer of renal arterioles, juxtaglomerular cells, proximal tubules, and the cortical collecting duct both by immunohistochemistry and by in situ amplification of mRNA. The D₃ receptor is present in arterioles, glomeruli, proximal tubules, mTAL cells, and the cortical collecting duct by immunohistochemistry. The D₄ receptor is localized to the cortical collecting duct.

**Dopamine Regulation of Renal Sodium Excretion**

The D₁-like receptor family plays a major role in the regulation of tubule sodium reabsorption. Numerous studies have demonstrated that dopamine induces a large increase in urinary sodium excretion that is dependent on inhibition of tubule sodium reabsorption. The natriuretic action of dopamine, which is due to inhibition of both proximal and distal tubule sodium absorption, was first demonstrated in studies in which the selective D₁-like receptor agonist fenoldopam was administered. This effect was distinct from the renal vasodilator action of exogenous dopamine that depended on increased concentrations of circulating dopamine. Since 1988, many additional studies have confirmed that the administration of dopamine engenders natriuresis by inhibiting tubule sodium reabsorption. The natriuretic effect of intrarenal dopamine was first observed after administration of the dopamine prodrug gludopa. Gludopa is devoid of pharmacological activity per se but is converted to L-DOPA and then to dopamine by sequential actions of the brush border enzyme γ-glutamyl transpeptidase and cytosolic L-aromatic amino acid decarboxylase (LAAD) in proximal tubule cells, where both enzymes exist in abundance. Earlier studies had shown significant natriuresis and renal vasodilation with pharmacological quantities of gludopa. However, administration of physiological quantities of gludopa was accompanied by a significant natriuresis with no detectable change in intrarenal blood flow, indicating a predominantly tubule effect.

During conditions of normal sodium balance, endogenous intrarenal dopamine is a major physiological regulator of urine sodium excretion. Studies employing a specific D₁-like receptor antagonist (SCH-23390) in both anesthetized and conscious animals have demonstrated that ≈50% of basal sodium excretion is controlled by dopamine. Administration of SCH-23390 at low infusion rates directly into the renal artery (confined to the kidney during the experimental period) engendered a dose-dependent antinatriuresis that was reversible on cessation of infusion. No changes in renal blood flow (RBF) or glomerular filtration rate (GFR) were observed. These studies were the first to show that dopamine acts as a paracrine substance, locally modulating renal sodium excretion. The ability of renal dopamine to control sodium excretion may be lost during hydropenia, sodium restriction, or marked sodium loading.

A recent study provided direct evidence for a natriuretic effect of endogenous renal dopamine. By infusing rats with antisense oligodeoxynucleotides directly into the renal interstitial space, the expression of D₁A receptor protein was reduced by 35% to 46% without influencing D₁B (D₃) receptors. This procedure decreased urinary sodium excretion during both normal and high sodium intake. The antinatriuresis was transient in spite of continued inhibition of D₁A receptor protein expression. Because the D₁ receptor has been shown to stimulate renin secretion, the D₁A receptor knockdown may have inhibited renin secretion sufficiently to overcome the antinatriuretic action of decreased D₁ receptor expression. However, this action on renin secretion may have been counterbalanced by an upregulation of angiotensin...
type 1 (AT₁) receptors, because dopamine also reduces AT₁ receptor mRNA.31

Recently, some evidence also has been presented indicating that the D₁ receptor may play a role in the control of renal function. The selective D₁ receptor agonist, (±)-7-hydroxy-2-(di-n-propyl-amino)tetralin increased GFR and decreased RBF, an effect abolished by selective D₁ receptor antagonist U-99194A but not by the D₂ receptor antagonist sulpiride.32 These data indicated that D₁ receptor activation may increase GFR by postglomerular (afferent) arteriolar constriction. Furthermore, a D₃-like receptor, possibly D₃, in the basolateral membrane appears to be responsible for the natriuretic action of dopamine in the cortical collecting duct.33 However, very little is known about the role of the D₂-like receptor family in the control of renal function and blood pressure compared with the large amount of information available for the D₁-like receptors. The D₁ and D₄ receptors are particularly fruitful areas for future study.

Cell Signaling Pathways

The major cell signaling pathways of renal dopamine are depicted in Figure 1. A major signaling mechanism whereby renal dopamine induces natriuresis is by its inhibition of Na⁺,K⁺-ATPase.34–36 Dopamine inhibits Na⁺,K⁺-ATPase in the entire nephron, including the proximal duct, the thick ascending limb of Henle, the distal tubule, and the cortical collecting duct.37–41 The dopamine receptor(s) responsible for the regulation of Na⁺,K⁺-ATPase activity are currently unresolved. In general, D₁-like receptors inhibit, whereas D₂-like receptors stimulate, Na⁺,K⁺-ATPase activity. However, D₂-like receptors can act synergistically with D₁-like receptors to increase sodium excretion by inhibition of Na⁺,K⁺-ATPase.42–45 The cell signaling pathways whereby dopamine mediates inhibition of Na⁺,K⁺-ATPase activity appear to be nephron specific. In the proximal duct, both protein kinase A (PKA) and protein kinase C (PKC) are involved, whereas in mTAL and the cortical collecting duct only PKA is required.42,43,46 PKC may inhibit Na⁺,K⁺-ATPase activity also by stimulation of Pₐ₂ activity and the generation of 20-HETE by cytochrome P-450.46,47 PKA and PKC mediate the phosphorylation of the catalytic subunit of Na⁺,K⁺-ATPase, which directly inhibits its enzymatic activity.48 Phosphorylation may also lead to internalization and inactivation of the enzyme.49 A major component of the regulatory control of Na⁺,K⁺-ATPase by dopamine may be the primary action of dopamine to inhibit the Na⁺/H⁺ exchanger and the Na⁺/P⁺ cotransporter in the apical membrane of the tubule cell. As a result of this action of dopamine, intracellular Na⁺ is too low to stimulate Na⁺,K⁺-ATPase activity.

Dopamine inhibits sodium entry into tubule cells via its action at the D₁-like receptor to inhibit sodium-hydrogen exchange (NHE) and Na⁺/P⁺ cotransport activation.50,51 On the other hand, D₁-like receptors stimulate sodium entry by these mechanisms. The inhibitory action of dopamine on NHE is predominantly due to activation of cAMP and PKA.50 Renal proximal tubule apical NHE activity also can be inhibited by D₁-like receptors via G proteins directly, independently of cAMP and phosphorylation mechanisms.52 Dopamine also can reduce NHE activity by stimulation of P-450 eicosanoids, such as 20-HETE.46

Dopamine D₁ Receptor Sensitization and Desensitization

Studies of the cell membrane and cytosolic expression of the D₁ receptor have been greatly facilitated by the development of a highly specific antibody that recognizes the third extracellular loop of the receptor.62 Under basal conditions, it was found that most of the D₁ receptors are located in the cytosol, not on the membrane, in both proximal tubule and cardiac myocytes.12 In keeping with the concept that G protein-coupled receptors undergo a cycle of internalization and desensitization, the D₁ receptor has been shown to uncouple from its effector complex by a ligand-independent process of desensitization.53 This process is thought to be related to phosphorylation of the receptor by one of the G protein-coupled receptor-related kinases (GRKs) resulting in their desensitization. The internalized receptors are packaged in vesicles and endosomes that have an acidic environment. It was assumed that the recycling of vesicles and endosomes and the insertion of the receptor into the cell membrane is an unregulated (constitutive) process. However, recent studies have demonstrated in proximal tubule cells that are exposed to dopamine or the D₁-like receptor agonist fenoldopam that the agonist initiated recruitment of the D₁A receptor to the cell membrane.54 This effect was abolished by an inhibitor of the vesicular H⁺ pump, requires agonist binding to the D₁ receptor, and is mediated by cAMP or cGMP. Thus, agonist-specific ligand binding to the receptor creates a positive feedback mechanism for sustaining a physiological response, such as stimulation of sodium excretion. The known mechanisms of dopamine receptor sensitization and desensitization are shown in Figure 3.

Renal Dopamine and Hypertension

Over the years, it has become apparent that the common factor in the generation of hypertension in man and experimental animals is disruption of normal sodium excretion. Therefore, there has been much interest in the possible role of renal dopamine and of dopamine receptors in hypertension.

Two fundamental defects in the renal dopamine system have been described in hypertension: (1) deficient renin
dopamine production due to reduced renal uptake and/or decarboxylation of DOPA and (2) defective D1-like receptor–G protein coupling such that renal dopamine is ineffective in transmitting a signal to inhibit sodium excretion. Both defects may result in sodium retention and hypertension.

A large body of evidence regarding the role of dopamine receptors in hypertension has accumulated from animal models in which the individual dopamine receptors have been disrupted. Disruption of the D1 receptor in mice leads to the development of hypertension, but a mutation in the coding region of the D1 receptor has not been found in human essential hypertension or in genetically hypertensive rats. Disruption of the D2 receptor also leads to hypertension, but the increased blood pressure is related to increased noradrenergic discharge and is not associated with sodium retention. Disruption of the D1 receptor gene induces a renin-dependent form of hypertension, and these mice also cannot excrete a sodium load. These results with whole body knockout of a dopamine receptor for a lifetime are informative, but compensatory mechanisms may alter the resulting phenotype. Additional value would be obtained by conducting renal-specific knockout of the dopamine receptors during adulthood, for example using antisense oligonucleotides for the dopamine receptors administered into 1 kidney via an adenovirus vector.

Recently, a great deal of interest has been focused on the defect in D1 receptor–G protein coupling in spontaneously hypertensive rats and Dahl salt-sensitive hypertensive rats. The first demonstration of such a coupling defect was made in 1989. Subsequently, studies from many laboratories have confirmed and extended these observations. This defect is present in human proximal tubule cells and is confined to the proximal tubule.

Studies now are beginning to point toward a possible defect in D1 receptor–G protein complex recycling and recruitment of receptors to the cell membrane. Felder et al reported that the D1 receptor is hyperphosphorylated at the serine residue in renal proximal tubule cells from humans with essential hypertension and from spontaneously hypertensive rats. It is now thought that possibly one of the GRKs that phosphorylate and desensitize the receptor may be involved. In this regard, it is interesting that GRK activity was increased in the lymphocytes of patients with essential hypertension. On the other hand, there is some preliminary evidence that there may also be a defect in recruitment of the D1 receptor to the cell membrane.

Very few clinical studies have addressed the presence of a renal tubule D1 receptor defect in human hypertension. Salt-sensitive hypertensive subjects were demonstrated to have a proximal tubule D1-like receptor defect similar to that of spontaneously hypertensive rats and Dahl salt-sensitive hypertensive rats. Interestingly, however, there was upregulation of D1-like receptor function in the distal nephron, which offset the proximal tubule defect. The compensatory inhibition of distal sodium reabsorption could be related to upregulation of D1-like receptors due to concomitant reduction in renal dopamine formation or simply to unopposed receptors in that nephron segment.

**Physiological Analysis of a Dopaminergic Defect in Hypertension**

In light of the present evidence (summarized above), it is likely that a substantial number of patients with essential hypertension may have a selective proximal tubule defect wherein there is absent D1 receptor–G protein coupling, leading to increased proximal tubule sodium reabsorption, extracellular fluid volume expansion, and increased blood pressure (Figure 4). This defect may be due to inactivation of D1 receptors secondary to hyperphosphorylation, to defective receptor cycling, or both. The increase in blood pressure should cause a reduction in baseline proximal sodium reabsorption to normal via pressure natriuresis. The initial increase in proximal tubule sodium reabsorption should decrease distal tubule sodium delivery, which should decrease afferent arteriolar resistance, due to tubuloglomerular feedback mechanisms, leading to an increase in RBF and GFR. Decreased distal tubule sodium delivery also should increase renin secretion, which would not be expected to be entirely suppressed by the increase in blood pressure. Increased blood pressure would normalize both proximal and distal tubule sodium reabsorption, but at the expense of increased blood pressure.

The foregoing scenario would be expected to result in hypertension, normal baseline proximal and distal sodium reabsorption, normal (non-suppressed) plasma renin activity, and increased GFR and RBF. In response to D1-like receptor agonist (eg, fenoldopam) administration at a dose that does not alter blood pressure, one would expect no reduction in proximal tubule sodium reabsorption, a major decrease in distal tubule sodium reabsorption due to ”unopposed” or upregulated D1 and D2 receptors, and natriuresis. These are precisely the baseline and D1-like receptor agonist responses that have been demonstrated in patients with salt-sensitive hypertension. Future studies addressing the specific dopamine receptor defect(s) in patients with genetic predisposition for salt-sensitive hypertension and in hypertensives themselves will be important to clarify the role of the renal dopamine system in the pathogenesis of hypertension.

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**Figure 4.** Physiological analysis of the consequences of a selective proximal renal tubule GRK-activating mutation, based on recent literature.
References


46. Carey Renal Dopamine, Sodium, and Blood Pressure

301


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