Dopamine Receptors
Important Antihypertensive Counterbalance Against Hypertensive Factors
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Essential hypertension, which affects 25% of the middle-aged adult population, constitutes a major risk factor for stroke, myocardial infarction, and heart and kidney failure.1 The kidney, vasculature, and nervous system govern the long-term control of blood pressure by regulating sodium homeostasis and peripheral resistance; they, in turn, are influenced by numerous hormones and neural and humoral factors. These hormones and neural and humoral factors can be divided into 2 groups based on their effects on sodium excretion and vascular smooth muscle contractility. One group leads to natriuresis and vasodilatation whereas the other causes sodium retention and vasoconstriction. The balance between those 2 groups keeps the blood pressure within the normal range. Hypertension may be caused not only by increased activity of prohypertensive systems (for example, the renin-angiotensin system [RAS] and sympathetic nervous system) but also by defects in antihypertensive systems that serve as counterregulatory mechanisms. Aberrations in these counterregulatory pathways, which include the dopaminergic pathway, may be involved in the pathogenesis of essential hypertension.

Dopamine has been shown to be an important regulator of renal and hormonal function and, ultimately, blood pressure, through an independent, nonneural dopaminergic system.2 There is a difference in the synthesis and metabolism of dopamine in neural and nonneural cells (see following paragraphs). For example, dopamine synthesized in renal proximal tubule (RPT) cells is not converted into norepinephrine and epinephrine; it is transported across the basolateral and apical membranes and into the peritubular space and tubular lumen, respectively, where it acts on its receptors locally and in more distal nephron segments. Dopamine, by occupation of its specific receptors as well by direct or indirect interaction with other G protein–coupled receptors (for example, adenosine, angiotensin, endothelin, insulin, oxytocin, and vasopressin) and interaction with other hormones/humoral agents (for example, aldosterone, angiotensins, atrial natriuretic peptide, eicosanoids, insulin, nitric oxide, prolactin, and urodilatin) regulates water and NaCl excretion.3,4 During normal or moderately increased NaCl intake, inhibition of D{sub}1-like receptors decreases NaCl excretion by ≈60%. In hypertensive states, the dopamine-mediated inhibition of sodium transport is often impaired. Although dopamine production is diminished in a few specific hypertensive states, this is not usually the case. Indeed, renal dopamine production is increased in young hypertensive patients. This review updates the role of dopamine and its receptors in the control of normal blood pressure and in the pathogenesis of hypertension. We will provide evidence that dopamine and its receptors act as an important antihypertensive counterbalance against the prohypertensive effects of the α-adrenergic system and RAS.

Dopamine and Its Receptors in Hypertension
Dopamine Synthesis and Blood Pressure Regulation
Dopamine, produced locally and independently of innervation, is important in the control of systemic blood pressure. This blood pressure regulation is achieved by actions on systemic arterial and venous vessels, renal hemodynamics, and water and electrolyte balance, by direct and indirect effects on renal and gastrointestinal epithelial ion transport.2 The affinity of dopamine for its receptors is in the nanomolar to low micromolar range. Normal circulating concentrations of dopamine (picomolar range) are not sufficiently high to activate dopamine receptors, but concentrations in the high nanomolar to low micromolar range can be attained in dopamine-producing tissues (both neural and nonneural, such as the RPT and jejunum).

The synthesis of dopamine differs between neural and epithelial cells (Figure 1). Neural cells, unlike RPT cells, express tyrosine hydroxylase, which converts tyrosine into L-3,4-dihydroxyphenylalanine (L-DOPA), the immediate precursor of dopamine. RPT cells do not express tyrosine hydroxylase and therefore, cannot produce L-DOPA; filtered or peritubular L-DOPA has to be transported into the RPT cells via the Na{sup}+-independent and pH-sensitive types 1 and 2 L-type amino acid transporter, related to the b{sup}(b) amino acid transporter, and as-yet-unidentified transporters.5,6 Unlike neural cells, RPT cells do not express dopamine β-hydroxylase, so synthesized dopamine is not converted to norepinephrine.2

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Dopamine produced in RPT cells is not stored. It enters the peritubular space and the tubular lumen (predominantly the latter), where it acts on its receptors locally and in more distal nephron segments.

Decreased renal synthesis of dopamine may be involved in the pathogenesis of essential hypertension in some human subjects. Some black and Japanese salt-sensitive subjects, with or without hypertension, do not increase renal dopamine production in response to an NaCl or protein load.7 However, urinary dopamine and dopamine metabolites are actually increased in young subjects with essential hypertension8 and in white Europeans with borderline hypertension.9 Renal dopamine synthesis is also increased in the Dahl salt-sensitive (Dahl-SS) rat and the spontaneously hypertensive rat (SHR).10 Inhibition of renal dopamine synthesis accelerates hypertension in SHR.11 Long-term administration of the long-acting D1-like receptor antagonist SCH-23390 decreases sodium excretion by ≈60%.12,13 Long-term administration of several ion channels. In this review, the term “D2-like receptor” is used when the effect is not specifically attributable to the D1 or D5 receptor, and the term “D1-like receptor” is used when the effect is not specifically attributable to the D5 receptor. This is particularly apt for D2-like receptors, because no commercially available drugs can distinguish the D1 from the D5 receptor.

The normal circulating levels of dopamine are too low to stimulate vascular dopamine receptors, and vascular smooth muscle cells do not synthesize dopamine. Because the direct vascular effect of dopamine is not important in the normal regulation of blood pressure, the contribution of arterial dopamine receptors to hypertension is not discussed.

**Renal D1-Like Receptors**

**Physiologic Role of D1-Like Receptors**

As stated earlier, during normal or moderately increased NaCl intake, dopamine, by direct or indirect interaction with other hormones/humoral agents, regulates NaCl excretion. In salt-loaded dogs and rats, the systemic or renal arterial infusion of the D1-like receptor antagonist SCH-23390 decreases sodium excretion by ≈60%.12,13 Long-term administration of the D1-like receptor antagonist ecopipam, in humans increases blood pressure.14 The differential contribution of D1 and D5 receptors in this process remains to be determined. Preliminary data suggest that the D5 receptor is expressed preferentially over the D1 receptor in the thick ascending limb of Henle and the cortical collecting duct, whereas the D1 receptor is expressed preferentially over the D5 receptor in the proximal tubule. Indeed, in RPT cells, 70% of the cAMP generated after D1-like receptor stimulation is due to the D1 receptor.15 Therefore, the D1 receptor function is exerted preferentially over the D5 receptor in the proximal nephron, whereas the converse is true in the distal nephron.

The infusion of D1 receptor antisense oligodeoxynucleotides directly into the renal interstitial space in uninephrectomized Sprague-Dawley rats causes a transient decrease in sodium excretion and does not affect blood pressure.16 The failure of the selective renal “silencing” of the D1 receptor to increase blood pressure may suggest that nonrenal D1 receptors, whose location(s) are yet to be determined, are also important in the overall regulation of blood pressure. Indeed, general disruption of the D1 receptor gene in mice leads to the development of hypertension.17 The D1 receptor also plays a role in the regulation of blood pressure, because deletion of the D1 receptor gene (D1−/−) in mice produces hypertension that is aggravated by a high NaCl intake (Yang et al18 and L.D. Asico and P.A. Jose, unpublished data, 2010). Cross-
hypertension is caused by diminished D1-like receptors to inhibit renal sodium transport in rodent genetic hypertension. 

bicarbonate (Cl$^-$/HCO$_3^-$/H11001) exchanger, probably the NaCl cotransporter, and the epithelial sodium channel at the luminal membrane.2,4,12,19,20

The natriuretic and diuretic effects of D₁-like receptors are dependent on sodium balance. In sodium-depleted states, a D₁-like receptor-mediated natriuresis may not be evident, whereas during sodium-replete states, the natriuretic effect of D₁-like receptors appears.2,12,13 D₁-like receptors can inhibit the NHE3, sodium phosphate cotransporter type IIa, chloride bicarbonate (Cl$^-$/HCO$_3^-$/H11001) exchanger, probably the NaCl cotransporter, and the epithelial sodium channel at the luminal membrane, as well as Na$^+$/K$^+$/H11001 ATPase and the sodium bicarbonate cotransporter at the basolateral membrane.2,4,12,19,20

Renal D₃-Like Receptors and Hypertension

Impaired D₁-like receptor function plays a role in the pathogenesis of hypertension. In rodents with genetic hypertension (Dahl-SS rats and SHRs), D₁-like receptor agonist–mediated diuretic and natriuretic responses are consistently impaired.2,12,21 The decreased ability of D₁-like receptor agonists to inhibit renal sodium transport in rodent genetic hypertension is consistently caused by diminished D₁-like receptor inhibition of the NHE3, Cl$^-$/HCO$_3^-$/H11001 exchanger, sodium bicarbonate cotransporter, and Na$^+$/K$^+$/H11001 ATPase activities.2,12,19,20

The ability of D₁-like receptor agonists to decrease RPT sodium transport is also impaired in humans with essential hypertension.23 The impaired inhibitory effect of D₁-like receptors on renal epithelial sodium transport in the proximal tubule and thick ascending limb in human essential hypertension, SHRs, and Dahl-SS rats is due to an uncoupling of the D₁ receptor (but not the D₅) receptor from its G protein/effector complex2,12,24 (Figure 2); decreased expressions of D₁ and D₅ receptors also play a role.2 The uncoupling of the D₁ receptor in hypertension is receptor-specific, organ-selective, and nephron-segment–specific; precedes the onset of hypertension; and cosegregates with the hypertensive phenotype.12

In the human kidney, the D₁ receptor uncoupling in hypertension is due to increased constitutive activity of G protein–coupled receptor kinase type 4 (GRK4), which is caused by the presence of GRK4 variants (especially R65L, A142V, and A486V)24 (Figure 2). Whether or not the D₅ receptor is regulated by these GRK4 gene variants remains to be determined. There are polymorphisms in the promoter region of human GRK4, but their role in essential hypertension remains to be determined.²⁵ However, increased expression of renal GRK4 has been shown to be responsible for the renal D₁ receptor uncoupling in the SHR12,24 and the salt sensitivity of C57BL/6j mice from The Jackson Laboratory (Bar Harbor, Me).26 Deletion of the GRK4 gene in C57BL/6j mice (GRK4$^-$/H11002$^-$) decreases basal blood pressure and prevents salt sensitivity.²⁶ It should be noted, however, that normal expression of wild-type GRK4 is needed for normal D₁ and D₃ receptor function.

In summary, D₁-like receptor function outside the central nervous system is impaired in essential hypertension. Whereas D₁-like receptor function is fully functional in some tissues (for example, the artery) in hypertension, the predominant organ involved in humans is probably the kidney.

D₂-Like Receptors

As indicated earlier, the D₂-like receptor family includes D₂, D₃, and D₅ receptors. The D₂ receptors in the rat kidney are located prejunctionally in dopaminergic nerves and postjunctionally in the proximal (S2 segment) and distal convoluted tubules and cortical collecting duct, whereas the D₃ receptor is expressed in the proximal (S1 segment) and distal convoluted tubules and especially in the cortical and medullary collecting ducts. In the rat kidney, the major D₂-like receptor in RPTs is the D₃ receptor; therefore, this review deals only with role of the D₃ receptor and not the other D₂-like receptors in hypertension.

Physiologic Role of the Renal D₃ Receptor

As with D₁-like receptors, stimulation of renal D₃ receptors induces natriuresis and diuresis. D₃ receptor agonists, infused systemically or directly into the renal artery, increase sodium excretion.²⁷ The D₃ receptor, like the D₁-like receptors,²,12,19,20 inhibits NHE3²⁸ and Na$^+$/K$^+$/H11001 ATPase activity²⁹ and may also inhibit the NaCl cotransporter and α-epithelial sodium channel. However, the D₃ receptor, unlike the D₁-like receptor, does not inhibit sodium phosphate cotransporter type IIa or the apical Cl$^-$/HCO$_3^-$/H11001 exchanger.²⁰

We have reported that the D₃ receptor, as with D₁-like receptors, is also important in the regulation of blood pressure. D₃$^-$/H11001 and D₃$^-$/H11002 mice have higher systolic and diastolic blood pressures than do their wild-type littermates, either on a mixed C57/BL6 and B129 background or in a congenic C57BL/6 background.³⁰ However, Staudacher et al. reported that D₁$^-$/H11001 mice, in a congenic C57BL/6 background fed a low, normal, or high salt intake, have normal blood pressure. This report has to be interpreted with caution because C57BL/6 mice from The Jackson Laboratory may develop hypertension when fed a high-NaCl diet, whereas C57BL/6 mice from Taconic Farms (Hudson, NY) do not.²⁶ Nevertheless, these 2 strains of D₁$^-$/H11001 mice have a decreased ability to excrete an acute or a chronic NaCl diet.
load, which would lead to an expansion of the extracellular fluid volume.

**D₃ Receptors and Hypertension**

Renal D₃ receptor–mediated natriuresis and diuresis are impaired in rodent models of essential hypertension. Dahl salt-resistant rats, treated with a D₁ receptor antagonist, remain normotensive when sodium intake is normal but become hypertensive when sodium intake is increased. Activation of D₃ receptors induces natriuresis in normotensive Dahl-SS rats on a normal-sodium diet but not in hypertensive Dahl-SS rats fed a high-sodium diet. With a normal salt intake, renal D₃ receptor density is decreased in Dahl-SS relative to Dahl salt-resistant rats. A high-salt diet decreases renal D₃ receptor agonist binding to a greater extent in Dahl-SS than in Dahl salt-resistant rats, suggesting that this may be the cause of the decreased natriuretic effect of D₃ receptor stimulation in Dahl-SS rats. We have studied the renal effects of another selective D₃ receptor agonist, PD128907, infused directly into the renal artery of WKY rats and SHRs. PD128907 increased sodium excretion in WKY rats but not in SHRs. Renal D₃ receptor expression is lower and its degree of phosphorylation is greater in SHRs than in WKY rats, which may, in part, explain the impaired natriuretic effect of D₃ receptors in SHRs. As indicated earlier, the hypertension in the SHR is, in part, due to increased renal expression of GRK4; the D₃ receptor, like the D₁ receptor, is regulated by GRK4.

**Interaction Between Dopamine and Other Blood Pressure–Regulatory Systems**

**Interaction With Catecholamines and Their Receptors**

Catecholamines have long been recognized to be important in the initiation and maintenance of high blood pressure. Increased sympathetic activity contributes to hypertension not only by increasing vascular tone and inducing cardiac and vascular remodeling but also by altering renal sodium and water homeostasis.

**Dopamine Receptors Regulate Catecholamine Release and Adrenergic Receptor Function**

Stimulation of dopamine receptors inhibits catecholamine release. D₂-like receptors inhibit the release of norepinephrine in gastric and uterine arteries and circulating norepinephrine levels in humans with heart failure. An inhibitory effect of D₂-like receptors on sympathetic tone or endogenous production of catecholamines has also been reported (Figure 3). Dopamine has also been reported to inhibit the ability of arginine vasopressin to increase water permeability and cAMP accumulation, via α₂-adrenergic receptors, in the rat inner medullary collecting duct.

**Adrenergic Receptors Can Regulate Dopamine Production and Receptor Function**

Blockade of α₂-adrenergic receptors enhances brain cortical dopamine output. Activation of the β-adrenergic receptor with isoproterenol increases D₃ receptor translocation from the cytosol to the plasma membrane and augments D₃-like dopamine receptor–mediated inhibition of Na⁺-K⁺ ATPase activity in RPT cells.

**Figure 3.** Dopamine counterbalances the prohypertensive effects of the α-adrenergic nervous system and RAS. Stimulation of dopamine receptors inhibits catecholamine and renin release, AT₁ receptor (and probably α-adrenergic)-mediated sodium reabsorption. The actions of dopamine receptors, by themselves, and by counterbalancing the prohypertensive effects of the α-adrenergic nervous system and RAS, keep the blood pressure in the normal range. D₃ receptors inhibit renin release but can stimulate it in the absence of cyclooxygenase-2.

**Interaction Between Dopamine and Adrenergic Receptors Is Supported by Studies in Dopamine Receptor–Deficient Mice**

D₂−/− mice, which are hypertensive, have an elevated urinary epinephrine to norepinephrine ratio, indicating increased adrenal catecholamine production (L.D. Asico and P.A. Jose, unpublished data, 2010). Adrenalectomy or α-adrenergic blockade decreases blood pressure to a greater extent in D₂−/− mice than in D₂+/+ littermates. Similarly, D₂−/− mice, which are also hypertensive, have higher epinephrine excretion than do their D₂+/+ littermates. α-Adrenergic blockade also decreases the blood pressure to a greater extent in D₂−/− than in D₂+/+ mice. These results suggest that the hypertension in D₂−/− and D₂−/− mice is caused, in part, by increased sympathetic activity. The salt sensitivity of D₂−/− mice may be related to renal nerve activity (L.D. Asico and P.A. Jose, unpublished data, 2010).

**Interaction With the RAS**

The RAS, especially in the kidney, is pre-eminent in the regulation of arterial pressure and sodium homeostasis, especially during conditions of sodium depletion. As noted next, different dopamine receptor subtypes interact with different components of the RAS, with the ultimate effect of increasing renal sodium excretion and maintaining a normal blood pressure (Figure 3).

**The RAS Regulates Dopamine Release**

In rats fed a low-salt diet, angiotensin II decreases urinary dopamine by increasing renal monoamine oxidase activity. In contrast, angiotensin 1-7 increases the release of extracellular dopamine in the rat striatum and hypothalamus, which becomes more evident with blockade of AT₁ receptors. Inhibition of angiotensin-converting enzyme also increases dopamine content in the mouse striatum. Whether or not these effects also occur in the kidney remains to be determined.

**Interactions Between Dopamine and the RAS Also Occur at the Receptor Level**

The interaction between dopamine and the RAS becomes very evident in receptor-deficient mice. Blockade of AT₁...
receptors results in a decrease in blood pressure that is greater and longer in $D_1^{-/-}$, $D_2^{-/-}$, and $D_3^{-/-}$ mice than in their wild-type littermates. In contrast, the hypertension of $D_2^{-/-}$ mice is unrelated to activation of the RAS but rather to increased aldosterone secretion.

**D$_1$-Like Receptors**

D$_1$-like receptors negatively interact with angiotensin II, including a negative regulation of AT$_1$ receptor action/expression and a positive regulation of AT$_2$ receptor action/expression. The natriuretic effect of D$_1$-like receptors is enhanced when angiotensin II production is decreased or when AT$_1$ receptors are blocked. These short-term effects probably occur via protein-protein interaction that includes D$_1$-like receptor–mediated internalization of the AT$_1$ receptor.

Not only do D$_1$-like receptors interfere with the antinatriuretic effect of AT$_1$ receptors, but they also interact with AT$_3$ receptors to increase sodium excretion; Salomone et al reported that D$_1$-like receptors increase AT$_2$ receptor expression in RPT cells. The intermediate-term effects of dopamine on AT$_1$ receptor actions are probably exerted at the posttranslational level (for example, increased degradation), whereas the long-term antagonistic effect of dopamine receptors on AT$_1$ receptor actions is probably exerted at the transcriptional level. Harris and coworkers reported that in rabbit RPT cells, dopamine, via D$_1$-like receptors, decreases AT$_1$ receptor mRNA and protein levels.

**D$_2$-Like Receptors**

D$_2$-like receptors also negatively interact with angiotensin II, including a D$_3$ and D$_4$ receptor–mediated decrease in AT$_1$ receptor action/expression. AT$_1$ receptor expression is increased in mice lacking the D$_3$ or D$_4$ receptor. A D$_3$ receptor agonist was found to decrease AT$_1$ receptor expression in RPT cells from WKY rats. Bromocriptine, which has a greater affinity for the D$_2$ and D$_3$ receptors than the D$_4$ receptor, prevents angiotensin II–mediated stimulation of Na$^+$-K$^+$ ATPase activity and decreases AT$_1$ receptor protein expression in rat RPTs. The negative regulatory effect of bromocriptine on AT$_1$ receptor expression is probably exerted at the D$_3$ receptor because AT$_1$ receptor expression is not increased in mice in which the D$_3$ receptor gene is disrupted (P.A. Jose, unpublished observations, 2008).

**Dopamine Interacts With Other Components of the RAS**

The D$_1$ receptor is expressed in juxtaglomerular cells in rodents but not in humans. In contrast, the D$_3$ receptor, the other D$_1$-like receptor, is not expressed in juxtaglomerular cells in all species studied. In vivo, the D$_1$ receptor inhibits renin release in rodents via inhibition of macula densa cyclooxygenase 2. When cyclooxygenase 2 activity in the macula densa is suppressed or when the macula densa is not present, as in juxtaglomerular cells in culture, the D$_1$ receptor stimulates renin secretion. The D$_3$ but not the D$_4$ receptor also inhibits renin secretion. Preliminary data show that stimulation of D$_3$ receptors increases angiotensin-convertase enzyme 2 expression and activity in RPT cells from WKY rats (X.J. Chen, C. Zeng, and P.A. Jose, unpublished data, 2010), which may have physiologic significance; angiotensin-convertase enzyme 2 converts angiotensin II into angiotensin 1-7, which has natriuretic and vasodilatory properties. D$_1$-like receptors have been reported to increase rat angiotensinogen gene expression in opossum kidney cells with a gene containing the 5′-flanking regulatory sequence of the rat angiotensinogen gene fused with a human growth hormone gene as a reporter. This effect, which would negate the natriuretic effects of dopamine receptors, remains to be confirmed. It is also not known whether or not any such interaction occurs in vivo.

**An Abnormal Interaction Between Dopamine and AT$_1$ Receptors Occurs in RPT Cells in Hypertensive States**

In RPT cells from WKY rats, D$_1$ and AT$_1$ receptors heterodimerize and inhibit each other’s function; the ability of the D$_1$ receptor to heterodimerize and inhibit AT$_1$ receptor function is impaired in SHRs. The D$_3$ receptor decreases AT$_1$ receptor expression in RPT cells from WKY rats, whereas D$_3$ receptor stimulation increases AT$_1$ receptor expression in SHRs. The impaired natriuretic effect of the D$_3$ receptor in SHR may, in part, be related to aberrant D$_3$ receptor inhibitory regulation of the AT$_1$ receptor. D$_1$ receptor expression is increased in $D_3^{-/-}$ mice.

**Conclusion**

Renal function is regulated by physical factors, numerous hormones, and neural and humoral factors. Among those factors is dopamine; activation of any of the dopamine receptor subtypes (D$_1$ through D$_5$), especially in salt-replete conditions, induces natriuresis. These actions of dopamine are impaired in human essential hypertension and rodent models of essential hypertension. In addition, the numerous other abnormalities in essential hypertension may well prove to be linked to the regulation of dopamine receptor function. For example, GRK4 gene variants, which impair dopamine receptor function (for example, D$_1$ and D$_3$ receptors) or expression, may increase the activity of prohypertensive mechanisms. The natriuretic effects of dopamine are due to synergistic interaction with other natriuretic factors and negative interaction with antinatriuretic factors. The presence of constitutively active variants of GRK4, for example, GRK4 142V, increases AT$_1$ receptor expression and function. Therefore, abnormal interactions between dopamine receptors on the one hand and the α-adrenergic system and RAS on the other may be involved in the pathogenesis of hypertension. Restoration of dopamine receptor function could be a complementary or even an alternative method to lower blood pressure in hypertensive patients.

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**Disclosures**

None.
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