Dopamine Receptors

Important Antihypertensive Counterbalance Against Hypertensive Factors

Chunyu Zeng, Pedro A. Jose

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_{1}-like receptors decreases NaCl excretion by \( \approx 60\% \). 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 \( \alpha \)-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 graphs). 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_{1}-like receptors decreases NaCl excretion by \( \approx 60\% \). 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 \( \alpha \)-adrenergic system and RAS.

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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. However, urinary dopamine and dopamine metabolites are actually increased in young subjects with essential hypertension and in white Europeans with borderline hypertension. Renal dopamine synthesis is also increased in the Dahl salt-sensitive (Dahl-SS) rat and the spontaneously hypertensive rat (SHR). Inhibition of renal dopamine synthesis accelerates the development of hypertension in SHRs. However, increasing renal dopamine production in SHRs does not lower their blood pressures or inhibit renal cortical sodium hydrogen exchanger type 3 (NHE3) activity, as is observed in Wistar-Kyoto (WKY) rats, and does not increase sodium excretion to the same degree as that observed in WKY rats. Therefore, decreased renal production of dopamine does not explain the impaired function of endogenous renal dopamine in many cases of hypertension. The increase in urinary dopamine levels in early hypertension may represent an attempt to compensate for the renal dopamine receptor defect.

Dopamine Receptors in Health and Hypertension

Dopamine receptors are classified into the D1- and D2-like receptor subtypes, based on their molecular structure and pharmacology. D1-like receptors, composed of D1 and D5 receptors, stimulate adenyl cyclase activity, whereas D2-like receptors, composed of D2a, D2b, and D3 receptors, inhibit adenyl cyclase activity and regulate/modulate the activity 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 D2 receptor, and the term “D2-like receptor” is used when the effect is not specifically attributable to the D2a, D2b, or D3 receptor. This is particularly apt for D2-like receptors, because no commercially available drugs can distinguish the D1 from the D2 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%. Long-term administration of the long-acting D1-like receptor antagonist, ecopipam, in humans increases blood pressure. The differential contribution of D1 and D2 receptors in this process remains to be determined. Preliminary data suggest that the D2 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 D2 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. Therefore, the D1 receptor function is exerted preferentially over the D2 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. 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. The D2 receptor also plays a role in the regulation of blood pressure, because deletion of the D2 receptor gene (D2−/−) in mice produces hypertension that is aggravated by a high NaCl intake (Yang et al and L.D. Asico and P.A. Jose, unpublished data, 2010). Cross-
Renal D1-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. 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–/HCO3– exchanger, sodium bicarbonate cotransporter, and Na+/K+ ATPase activities.2,12,19,22

The ability of D1-like receptor agonists to decrease RPT sodium transport is also impaired in humans with essential hypertension. 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 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 D3 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+/−) 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 D4 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 NHE3 and Na+/K+ 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–/HCO3– exchanger.20

We have reported that the D3 receptor, as with D1-like receptors, is also important in the regulation of blood pressure. D3−/− and D3+/+ mice have higher systolic and diastolic blood pressures than do their wild-type littermates, either on a mixed C57BL6 and B129 background or in a congenic C57BL/6 background.10 However, Staudacher et al11 reported that D3−/− 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 D3−/− mice have a decreased ability to excrete an acute or a chronic NaCl
D_3_ Receptors and Hypertension

Renal D_3_ receptor–mediated natriuresis and diuresis are impaired in rodent models of essential hypertension. Dahl salt-resistant rats, treated with a D_1_ receptor antagonist, remain normotensive when sodium intake is normal but become hypertensive when sodium intake is increased. Activation of D_3_ 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 D_3_ receptor density is decreased in Dahl-SS relative to Dahl salt-resistant rats. A high-salt diet decreases renal D_3_ 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 D_3_ receptor stimulation in Dahl-SS rats. We have studied the renal effects of another selective D_3_ 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 D_3_ 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 D_3_ receptors in SHRs. As indicated earlier, the hypertension in the SHR is, in part, due to increased renal expression of GRK4; the D_3_ receptor, like the D_1_ 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. D_2_–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 D_2_–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 α_2_–adrenergic receptors, in the rat inner medullary collecting duct.

Adrenergic Receptors Can Regulate Dopamine Production and Receptor Function

Blockade of α_2_–adrenergic receptors enhances brain cortical dopamine output. Activation of the β-adrenergic receptor with isoproterenol increases D_1_ receptor translocation from the cytosol to the plasma membrane and augments D_1_–like dopamine effects of the α-adrenergic nervous system and RAS. Stimulation of dopamine receptors inhibits catecholamine and renin release, AT_1_ 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. D_3_ receptors inhibit renin release but can stimulate it in the absence of cyclooxygenase-2.

Figure 3. Dopamine counterbalances the prohypertensive effects of the α-adrenergic nervous system and RAS. Stimulation of dopamine receptors inhibits catecholamine and renin release, AT_1_ 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. D_3_ 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

D_2_–/– mice, which are hypertensive, have an elevated urinary epinephrine to norepinephrine ratio, indicating increased adrenal catecholamine production. Adrenalectomy or α-adrenergic blockade decreases blood pressure to a greater extent in D_2_–/– mice than in D_2_+/+ littermates. Similarly, D_2_–/– mice, which are also hypertensive, have higher epinephrine excretion than do their D_2_+/+ littermates. α-Adrenergic blockade also decreases the blood pressure to a greater extent in D_2_–/– than in D_2_+/+ mice. These results suggest that the hypertension in D_2_–/– mice is caused, in part, by increased sympathetic activity. The salt sensitivity of D_2_–/– mice may be related to renal nerve activity.

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 AT_1_ 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 AT_1_
Dopamine Interacts With Other Components of the RAS

D1-like receptors negatively interact with angiotensin II, including a negative regulation of AT1 receptor action/expression and a positive regulation of AT2 receptor action/expression. The natriuretic effect of D1-like receptors is enhanced when angiotensin II production is decreased or when AT1 receptors are blocked.37 These short-term effects probably occur via protein-protein interaction40 that includes D1-like receptor-mediated internalization of the AT1 receptor.4 Not only do D1-like receptors interfere with the antinatriuretic effect of AT1 receptors, but they also interact with AT2 receptors to increase sodium excretion; Salomone et al49 reported that D1-like receptors increase AT2 receptor expression in RPT cells. The intermediate-term effects of dopamine on AT1 receptor actions are probably exerted at the posttranslational level (for example, increased degradation);50 whereas the long-term antagonistic effect of dopamine receptors on AT1 receptor actions is probably exerted at the transcriptional level.48 Harris and coworkers51 reported that in rabbit RPT cells, dopamine, via D1-like receptors, decreases AT1 receptor mRNA and protein levels.

D2-Like Receptors

D2-like receptors also negatively interact with angiotensin II, including a D3 and D4 receptor-mediated decrease in AT1 receptor action/expression.45,52 AT1 receptor expression is increased in mice lacking the D3 or D4 receptor.45 A D3 receptor agonist was found to decreases AT1 receptor expression in RPT cells from WKY rats.52 Bromocriptine, which has a greater affinity for the D2 and D3 receptors than the D4 receptor, prevents angiotensin II-mediated stimulation of Na+/K+-ATPase activity and decreases AT1 receptor protein expression in rat RPTs.53 The negative regulatory effect of bromocriptine on AT1 receptor expression is probably exerted at the D3 receptor because AT1 receptor expression is not increased in mice in which the D2 receptor gene is disrupted (P.A. Jose, unpublished observations, 2008).

Dopamine Receptors in Hypertension

The D1 receptor is expressed in juxtaglomerular cells in rodents but not in humans.54,55 In contrast, the D3 receptor, the other D1-like receptor, is not expressed in juxtaglomerular cells in all species studied. In vivo, the D3 receptor inhibits renin release in rodents via inhibition of macula densa cyclooxygenase 2.56 When cyclooxygenase 2 activity in the macula densa is suppressed56 or when the macula densa is not present, as in juxtaglomerular cells in culture, the D3 receptor stimulates renin secretion.55 The D3 but not the D4 receptor also inhibits renin secretion.57 Preliminary data show that stimulation of D3 receptors increases angiotensin-converting 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-converting enzyme 2 converts angiotensin II into angiotensin 1-7, which has natriuretic and vasodilatory properties. D1-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.58 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 AT1 Receptors Occurs in RPT Cells in Hypertensive States

In RPT cells from WKY rats, D1 and AT1 receptors heterodimerize and inhibit each other’s function; the ability of the D1 receptor to heterodimerize and inhibit AT1 receptor function is impaired in SHRs.48 The D3 receptor decreases AT1 receptor expression in RPT cells from WKY rats, whereas D3 receptor stimulation increases AT1 receptor expression in SHRs.53 The impaired natriuretic effect of the D3 receptor in SHR53,54 may, in part, be related to aberrant D3 receptor inhibitory regulation of the AT1 receptor.53 AT1 receptor expression is increased in D3−/− mice.59

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 (D1 through D5), 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, D1 and D3 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 AT1 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.
References


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