

## Dopamine Receptors in Hypertension

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### Abstract

There is increased awareness of the role of dopamine in cardiovascular function, renal function and systemic blood pressure regulation. Growing evidence indicates that each of the five dopamine receptor subtypes participates in the regulation of blood pressure by mechanisms distinct for that particular subtype. Some dopamine receptors regulate blood pressure by influencing the central and peripheral nervous system, while others influence renal function and release of renin, aldosterone and vasopressin. This review summarizes the physiology and pathophysiology of the peripheral dopaminergic system and our current understanding of the role of individual dopamine receptors in the pathophysiology of human essential hypertension.

**Key Words:** Hypertension, dopamine, dopamine receptor, sodium transport, transgenic mice.

DOPAMINE IS NOW RECOGNIZED as an important regulator of systemic blood pressure (1). In the periphery, this blood pressure regulation is achieved by direct action on the heart, arterial and venous vessels, to alter renal hemodynamics, and on fluid and electrolyte balance via effects on renal epithelial transport, and gastrointestinal sodium uptake (2–6). Dopamine can indirectly regulate blood pressure via release of hormones and humoral agents such as aldosterone, catecholamines, endothelin, prolactin, pro-opiomelanocortin, renin, and vasopressin (2–5). Centrally, dopamine modulates systemic blood pressure through the regulation of fluid and sodium intake via “appetite” centers in the brain (7). In addition, it controls blood pressure by direct action on neuronal cardiovascular centers.

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### Dopamine Receptors

Dopamine exerts its actions via the D<sub>1</sub>-like and D<sub>2</sub>-like family of cell-surface G protein-coupled receptors (GPCR) (Tables 1 and 2). The D<sub>1</sub>-like receptors cloned in mammals (D<sub>1</sub> and D<sub>5</sub>) are linked to the stimulatory G-protein, G<sub>s</sub>, and stimulate adenylyl cyclases. The cloned D<sub>2</sub>-like receptors (D<sub>2</sub>, D<sub>3</sub>, and D<sub>4</sub>) are linked to inhibitory G-proteins, G<sub>i</sub>/G<sub>o</sub>, and inhibit adenylyl cyclases. The affinity of dopamine to its receptors ranges from low nanomolar to low micromolar range. At higher concentrations, - and -adrenergic and serotonin receptors are occupied. Circulating concentrations of dopamine (picomolar range) are not sufficiently high to activate dopamine receptors, while in dopamine-producing tissues concentrations in the high nanomolar to micromolar range can be attained (1). Dopamine is synthesized not only in noradrenergic and dopaminergic nerves, but also in non-neural tissues (e.g., kidney, gastrointestinal tract) (8).

### Autocrine/Paracrine Regulation of Fluid and Electrolyte Balance by Dopamine

#### Renal Sodium Transporters

Dopamine regulates water and electrolyte excretion indirectly by actions on renal hemodynamics and by modulation of the action of other vasoactive and renoactive hormones (1).

**TABLE 1***Summary of the Physiologic and Pathophysiologic Effects of D<sub>1</sub>-like Receptors in Blood Pressure Regulation.*

Dopamine Receptors	Signal Transduction	Characteristics of Transgenic Animals	Physiologic Responses	Implications in Human Essential Hypertension
D <sub>1</sub> -like receptor family	G <sub>as</sub> stimulation of Adenylyl cyclase (1,75,76) Phospholipase A <sub>2</sub> and eicosanoid formation (22, 24) Phosphatidyl-inositol 3 kinase (77)		Vasorelaxation (1, 2, 45) Decrease sodium and phosphate transport (kidney and intestine) (1, 2, 6, 9–15, 20–25, 27–33, 43, 48, 77).	Uncoupling of renal D <sub>1</sub> receptors from effector enzyme complex (52)
D <sub>1</sub> receptor	Stimulation of Phospholipase C* (78, 79)	D <sub>1</sub> knockout mice (48) Hypertension Sodium retention?	Stimulation of renin secretion (67) Natriuresis (49)	D <sub>1</sub> receptor non-coding region associated with hypertension (53)
D <sub>5</sub> receptor	Inhibition of Phospholipase C (80)	D <sub>5</sub> knockout mice (58, 59) Hypertension Increased central oxytocin/V <sub>1</sub> /non-NMDA/ -adrenergic receptor activity	?	D <sub>5</sub> receptor locus linked to hypertension (60)

\*Needs the adaptor protein calcyon (81).

**TABLE 2***Summary of the Physiologic and Pathophysiologic Effects of D<sub>2</sub>-like Receptors in Blood Pressure Regulation.*

Dopamine Receptors	Signal Transduction	Characteristics of Transgenic Animals	Physiologic Responses	Implications in Human Essential Hypertension
D <sub>2</sub> -like receptor family	G <sub>i</sub> /O inhibition of Adenylyl cyclase (1, 75, 76)		Vasorelaxation (when basal tone is high) (2, 82, 83) Vasoconstriction (when basal tone is low) (2, 84, 85) Inhibition of neural catechol and renin release (2) Increase sodium transport* (kidney and intestine) (34, 35, 84)	Central D <sub>2</sub> -like function decreased in hypertension (61)
D <sub>2</sub> receptor		D <sub>2</sub> knockout mice (66) Increased activity of -adrenergic and ETB receptors		D <sub>2</sub> receptor polymorphism associated with hypertension (64)
D <sub>3</sub> receptor	Phosphatidyl inositol 3 kinase (86)	D <sub>3</sub> knockout mice (70) Hypertension Renin-dependence Sodium retention?	Inhibition of renin secretion (70, 73) Increase in GFR (87)	?
D <sub>4</sub> receptor		D <sub>4</sub> knockout mice Unknown	Inhibition of V <sub>2</sub> receptor action in cortical collecting duct (18)	?

\*In concert with D<sub>1</sub>-like receptors, sodium transport is decreased when extracellular fluid volume is moderately expanded (33, 88).

Direct actions of dopamine on renal tubules are mediated by multiple mechanisms. In proximal tubules, D<sub>1</sub>-like receptors inhibit Na<sup>+</sup>/H<sup>+</sup>-ex-

changer 3 activity (NHE3) and Na/phosphate (Pi)-co-transporter activity in the luminal membrane, and Na<sup>+</sup>/HCO<sub>3</sub><sup>-</sup>-cotransporter activity in

the basolateral membrane (1, 9–13). In addition,  $D_1$ -like receptors inhibit  $Na^+/K^+$ -ATPase activity in the proximal tubule, medullary thick ascending limb of Henle (mTAL), and cortical collecting duct (CCD) (14–16).  $D_1$ -like receptors can also regulate sodium channels, although this action has not been shown in the kidney so far. The ability of dopamine to inhibit tubular transport in multiple nephron segments may explain the marked natriuretic effect of dopamine in spite of its limited inhibitory effect on individual sodium transporters.

In renal proximal tubules,  $D_2$ -like receptors stimulate sodium transport through an increase in NHE3- and  $Na^+/K^+$ -ATPase activity, an effect which is mediated mainly by a decrease in cAMP production (1, 9, 17). In the CCD and the medullary collecting duct (MCD),  $D_2$ -like receptors antagonize the actions of aldosterone and vasopressin (18, 19).

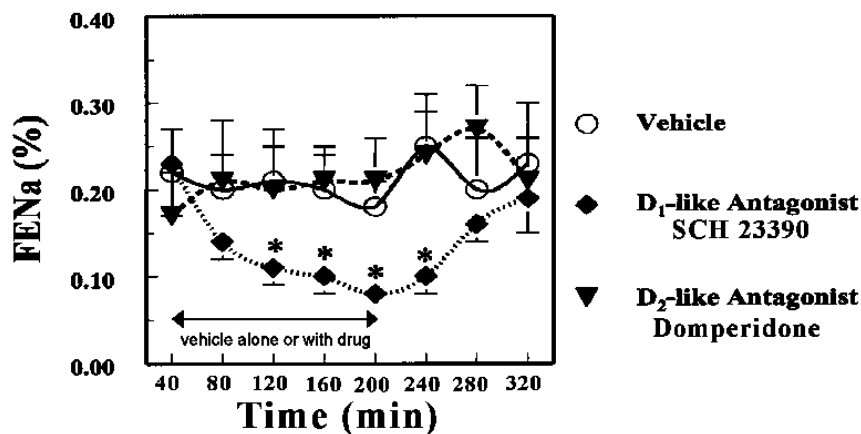
### Signal Transduction Pathways

The inhibitory action of  $D_1$ -like receptors on NHE3- and  $Na^+/HCO_3^-$ -cotransporter activities in renal proximal tubules is mainly due to activation of the cAMP/protein kinase A (PKA) and eicosanoid pathways (1, 9, 20). The contribution of  $D_1$  and/or  $D_5$  receptors in these actions remains to be determined. Dopamine can also inhibit NHE3- and  $Na^+/Pi$ -cotransporter activity by activating a G protein-linked pathway

independent of PKA, protein kinase C (PKC), eicosanoids, and protein tyrosine kinase (11, 12, 21). The signal transduction pathways of dopamine-mediated inhibition of  $Na^+/K^+$ -ATPase activity are complex. It is nephron segment specific, time dependent, and intracellularly calcium modulated (1). Thus, only PKA may be needed to transduce the  $D_1$ -like signal in the mTAL and CCD while PKA, PKC, and eicosanoids [20-HETE] are involved in the proximal tubule (22–25). Furthermore, phosphatidylinositol 3 kinase may be involved in the dopamine-mediated inhibition of  $Na^+/K^+$ -ATPase and NHE3 (26, 27) (Table 1).

### $D_1$ - and $D_2$ -like Effects on Fluid and Electrolyte Balance

Some actions of dopamine appear to be counterregulatory (e.g.,  $D_1$ -like inhibition of sodium transport and  $D_2$ -like stimulation of sodium transport,  $D_1$ -like receptor stimulation of renin and vasopressin secretion,  $D_2$ -like receptor inhibition of renin and aldosterone secretion). Increasing evidence suggests that the state of overall sodium balance determines which dopamine receptor subtype function predominates. The natriuretic effect of dopamine can be seen under conditions of “normal” sodium intake; it is magnified under conditions of “moderate” sodium excess (1). In sodium-replete states, endogenous renal dopamine is responsible for more than 50% of sodium excretion



**Figure.** Effect of the  $D_1$ -like antagonist, SCH 23390, the  $D_2$ -like antagonist (domperidone), or vehicle on urinary fractional sodium excretion (FENa) in pentobarbital-anesthetized normotensive Wistar Kyoto (WKY) rats. WKY rats were given a saline load (5% of body weight). After a baseline period, the vehicle alone, or with the indicated antagonist, was given intravenously (SCH 23390, 400 ng/kg/min; domperidone, 1 g/kg/min) for four periods followed by three periods of recovery. Each period lasted 40 minutes.

\* $P < 0.05$  vs baseline period, repeated measures analysis of variance, Scheffe's test.

\* $P < 0.05$  vs others, analysis of variance, Scheffe's test (adapted from 33).

tion (28–32) (Figure). D<sub>1</sub>-like receptors, independent of D<sub>2</sub>-like receptors, can inhibit NHE3- and Na<sup>+</sup>/HCO<sub>3</sub><sup>-</sup>-cotransporter activities. However, in sodium-replete states, D<sub>1</sub>- and D<sub>2</sub>-like receptors, rather than acting in opposing directions, synergistically inhibit Na<sup>+</sup>/K<sup>+</sup>-ATPase activity and increase sodium excretion (23, 33). The mechanism by which this occurs is unknown. An increased renal production of dopamine as well as an increased inhibitory effect of dopamine on sodium transporters might be involved (1). Alterations in dopamine receptor expression and effector protein functions (adenylyl cyclase, phospholipase C, sodium transporter/pump) do not explain the synergism between D<sub>1</sub>- and D<sub>2</sub>-like receptors in sodium-replete states (1). However, sodium-induced decreases in the concentrations of humoral factors that oppose D<sub>1</sub>-like receptor action (e.g., angiotensin II, adenosine, serotonin) may play a role in sodium reabsorption and in renal hemodynamics (1). Sodium loading, for instance, attenuates the stimulatory effect of D<sub>1</sub>-like receptors on renin release and enhances the D<sub>2</sub>-like inhibitory effect on aldosterone secretion (and possibly renin). Moreover, during volume expansion, D<sub>4</sub> receptors may facilitate diuresis and natriuresis by antagonizing the hydro-osmotic and sodium retaining effect of vasopressin and aldosterone in the CCD (18, 19). Under conditions of positive sodium balance, dopamine not only increases renal water and electrolyte excretion but also decreases gastrointestinal water and electrolyte absorption.

When sodium loading is excessive, the natriuretic effect of dopamine is no longer evident, presumably because other natriuretic factors predominate (1, 29, 32). In addition, the inhibitory effect of endogenous dopamine on renal and gastrointestinal sodium transport is lost during hydropenia and sodium-deplete states (1, 28). Under conditions of negative sodium balance, D<sub>2</sub>-like receptors may actually increase sodium reabsorption in the renal tubule and gastrointestinal tract and stimulate sodium appetite (7, 34, 35). When endogenous renal tubular dopamine subserves a paracrine/autocrine function, its natriuretic effect is mainly due to tubular rather than glomerular or renal hemodynamic action (1). However, dopamine produced by renal nerves may participate, via D<sub>3</sub> receptors, in the regulation of glomerular filtration rate, especially with the hyperfiltration that occurs during amino acid infusion (36).

## Regulation of Blood Pressure by Dopamine

Dopamine regulates blood pressure by several mechanisms (2). In addition to dopaminergic regulation of fluid and electrolyte balance, dopamine regulates central cardiovascular centers and catecholamine release by sympathetic nerves and adrenal medulla (1). Direct and indirect actions of dopamine receptors can cause vasorelaxation (D<sub>1</sub> and D<sub>5</sub>) or vasoconstriction (D<sub>3</sub>) (2). At higher concentrations (high micromolar range), dopamine produces vasoconstriction by occupation of  $\alpha_1$ -adrenergic receptors. These apparently counterregulatory actions are influenced by the basal tone of the vascular smooth muscles. When basal arterial tone is high, D<sub>2</sub>-like receptors promote relaxation; the opposite action occurs when basal tone is low. Dopamine increases cardiac output by stimulating myocardial  $\beta$ -adrenergic receptors. The heart also expresses D<sub>1</sub> and D<sub>4</sub> receptors, but their role, if any, on heart rate or myocardial contraction remains to be determined (37, 38).

## Dopamine and Hypertension

Abnormalities in dopamine production and receptor function have been described in genetic hypertension, and there is abundant evidence that, in the absence of a normally functioning dopaminergic system, hypertension develops (1–3, 13–15, 24, 25, 31, 39). Inhibition of dopamine synthesis outside the central nervous system accelerates the development of hypertension in the spontaneously hypertensive rat (SHR) (40). Moreover, dopamine receptor blockade is associated with the development of hypertension in saline-loaded Wistar rats and potentiates the renal effects of nitric oxide inhibition in humans (41, 42). Finally, disruption of dopamine receptor genes in mice produces hypertension (see below) (Tables 1 and 2).

### D<sub>1</sub>-like Receptors

The renal autocrine/paracrine natriuretic function of dopamine via D<sub>1</sub>-like receptors is impaired in genetic hypertension of rodents (SHR and Dahl salt-sensitive rat) (1, 2). This impairment is not caused by a decreased renal dopamine production but by a diminished D<sub>1</sub>-like inhibition of NHE3, Na<sup>+</sup>/HCO<sub>3</sub><sup>-</sup>, and Na<sup>+</sup>/K<sup>+</sup>-ATPase activity in proximal tubules and the mTAL (1, 2, 13–15, 24, 25, 43). Recent data indicate that the failure of D<sub>1</sub>-like receptors to inhibit sodium transport in genetic

hypertension is not caused by abnormalities in G-proteins or effector proteins (adenylyl cyclases, NHE3, Na<sup>+</sup>/K<sup>+</sup>ATPase), or the expression of D<sub>1</sub>-like receptors. Rather, the D<sub>1</sub>-like receptor is uncoupled from its G protein/effector protein complex (1, 2, 13–15, 24, 25, 43–45). The reason for the uncoupling of the D<sub>1</sub>-like receptor from its G protein/effector protein complex is currently unknown, but abnormalities in the desensitization process of D<sub>1</sub>-like receptors might be involved (see below). There is evidence that the uncoupling of D<sub>1</sub>-like receptors in hypertension is genetically determined, and receptor-, organ-, and nephron-segment specific (1, 2). This explains why the vasodilatory and “distal” renal tubular responses to D<sub>1</sub>-like agonists are preserved even in hypertensive subjects (46, 47).

**D<sub>1</sub> receptor.** Because the major receptor involved in the dopamine-mediated natriuresis is the D<sub>1</sub> receptor (1, 26, 48, 49), we have suggested that the renal dopaminergic defect in genetic hypertension probably involves the D<sub>1</sub> rather than the D<sub>5</sub> receptor. The D<sub>1</sub> receptor locus is linked to variations in systolic blood pressure levels in Caucasians (50) and cardiac hypertrophy in rats (51). Disruption of the D<sub>1</sub> receptor in mice leads to the development of hypertension (48). However, no mutations have been found in the coding region of the D<sub>1</sub> receptor in patients with essential hypertension or in genetically hypertensive rats (1, 52). A polymorphism in the noncoding region of the D<sub>1</sub> receptor has been reported to be associated with human essential hypertension; however, the mechanism by which this polymorphism induces hypertension remains to be determined (53).

We have suggested that the uncoupling of D<sub>1</sub> receptor from its effector complex in renal proximal tubules is due to a ligand-independent serine phosphorylation and subsequent desensitization of the D<sub>1</sub> receptor (52). Because G protein-coupled receptor kinases (GRKs) phosphorylate GPCRs, resulting in their desensitization, it is of interest that total GRK activity and GRK2 expression are increased in lymphocytes of patients with essential hypertension and in lymphocytes and aortic smooth muscle cells of rats with genetic hypertension (54, 55). However, it is unlikely that GRK2 is the proximate cause of the D<sub>1</sub> receptor desensitization, because the parathyroid hormone receptor, a substrate of GRK2, functions normally in hypertension (1, 2, 52). Thus, the desensitization of the D<sub>1</sub> receptor in hypertension may be due to a kinase other than GRK2. A kinase related to

GRK that interacts with genes controlling the renin-angiotensin system may be involved in the hypertensive process (56). The uncoupling of the D<sub>1</sub>-like receptor in renal proximal tubules in hypertension may also be a consequence of a defective resensitization process (57).

**D<sub>5</sub> receptor.** The other D<sub>1</sub>-like receptor, the D<sub>5</sub> receptor, may also play a role in the pathogenesis of genetic hypertension. Disruption of the D<sub>5</sub> receptor gene in mice results in the development of hypertension without an impairment in the ability to excrete an acute saline load (58). We have suggested that the hypertension in D<sub>5</sub> receptor mutant mice is caused, in part, by interactions of the D<sub>5</sub> receptor with other GPCRs utilizing a common pathway in the central nervous system. The high blood pressure in the D<sub>5</sub> receptor knockout mouse was normalized by blockade of V<sub>1</sub>-vasopressin, and -adrenergic receptors (59). Furthermore, the hypertension in D<sub>5</sub>-receptor mutant mice was antagonized by a non-NMDA receptor antagonist that crosses the blood-brain barrier, while a non-NMDA receptor antagonist that does not cross the blood-brain barrier had no effect on blood pressure (59). This indicates that non-NMDA receptors are involved in the signal transduction pathway of D<sub>5</sub> dopamine receptors in the brain. Although mutations of the D<sub>5</sub> receptor are not found in the SHR (unpublished data), a locus in human chromosome 4 containing the D<sub>5</sub> receptor gene has been linked to hypertension in some populations with essential hypertension (60).

### D<sub>2</sub>-like Receptors

**D<sub>2</sub> receptor.** Abnormalities of D<sub>2</sub>-like receptor function have been reported in hypertension (3, 61–63). Several D<sub>2</sub> receptor polymorphisms have been reported, one of which is associated with hypertension (64). Transfer of a segment of chromosome 8, containing the D<sub>2</sub> receptor gene, from the normotensive Brown-Norway rat onto SHR background decreases blood pressure (65). Disruption of the D<sub>2</sub> receptor gene in mice produces hypertension that is not associated with a decreased ability to excrete a sodium load. Rather, the hypertension in D<sub>2</sub> receptor knockout mice is caused by increased activity of the adrenergic nervous system (66). An unexpected finding in D<sub>2</sub> knockout mice was the ability of an endothelin B (ETB) antagonist (BQ788) to normalize the blood pressure in the D<sub>2</sub> mutant mice without affecting blood pressure in D<sub>2</sub> wild type mice.

Dopamine, dopamine receptors, endothelin, and ETB receptors have been found in brain and spinal regions known to control cardiovascular function (3).

**D<sub>3</sub> receptor.** Renin secretion in rats is stimulated by D<sub>1</sub>-like receptors and inhibited by D<sub>2</sub>-like receptors (1, 67). Both D<sub>1</sub>- and D<sub>2</sub>-like receptors downregulate AT<sub>1</sub> receptor expression and function (68, 69). Disruption of the D<sub>3</sub> receptor gene in mice is associated with renin-dependent hypertension and a decreased ability to excrete an acute saline load (70). Aberrant dopaminergic regulation of aldosterone secretion (via D<sub>3</sub> receptors) may be involved in some forms of hyperaldosteronism and hypertension (71, 72).

**D<sub>4</sub> receptor.** D<sub>4</sub> receptors are expressed in rat juxtaglomerular cells and cortical and medullary collecting ducts (73). However, the consequence of disruption of the D<sub>4</sub> receptor gene on blood pressure has not been reported.

### Conclusions

Dopamine regulates fluid and electrolyte balance by direct and indirect actions in the kidney, blood vessels, gastrointestinal tract, adrenal glands, sympathetic nervous system, hypothalamus and other "brain centers." Dopaminergic regulation of the secretion of angiotensin and aldosterone, catecholamines, and vasopressin contributes to this process. Furthermore, dopamine can also regulate the expression of receptors other than its own (e.g., ETB, AT<sub>1</sub>). Abnormalities of dopamine receptors (or their regulation) may be important in the pathogenesis of essential hypertension. The pathogenetic pathway of hypertension is specific for each type of dopamine receptor abnormality (Tables 1 and 2). The dopaminergic system is, phylogenetically, an old system (74), which may serve to regulate blood pressure.

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### References

1. Jose PA, Eisner GM, Felder RA. The renal dopamine receptors in health and hypertension. *Pharmacol Ther* 1998; 80:149–182.
2. Jose PA, Eisner GM, Felder RA. Dopaminergic mechanisms in the development of hypertension. In: Development of the hypertensive phenotype: Basic and clinical studies. In: McCarty R, Blizard DA, Chevalier RI, editors. *Handbook of hypertension*, 19. Amsterdam: Elsevier Science; 1999. pp. 1–44.
3. van den Buuse M. Role of the mesolimbic dopamine system in cardiovascular homeostasis. Stimulation of the ventral tegmental area modulates the effect of vasopressin on blood pressure in conscious rats. *Clin Exp Pharmacol Physiol* 1998; 25:661–668.
4. Sowers JR, Viosca SP, Windsor C, Korenman SG. Influence of dopaminergic mechanisms on 24-hour secretory patterns of prolactin, luteinizing hormone and testosterone in recumbent men. *J Endocrinol Invest* 1983; 6:9–15.
5. Carey RM, Sen S. Recent progress in the control of aldosterone secretion. *Recent Prog Horm Res* 1986; 42:251–296.
6. Vieira-Coelho MA, Teixeira VA, Finkel Y, et al. Dopamine-dependent inhibition of jejunal Na<sup>+</sup>-K<sup>+</sup>-ATPase during high-salt diet in young but not in adult rats. *Am J Physiol* 1998; 275:G1317–G1323.
7. Roitman MF, Schafe GE, Thiele TE, Bernstein IL. Dopamine and sodium appetite: Antagonists suppress sham drinking of NaCl solutions in the rat. *Behav Neurosci* 1997; 111:606–611.
8. Bell C, Ferguson M, Petrovic T. Neurochemistry of dopaminergic nerves. In: Bell C, McGrath B, editor. *Peripheral actions of dopamine*. London: The MacMillan Press Ltd; 1988. pp. 41–55.
9. Felder CC, Campbell T, Albrecht F, Jose PA. Dopamine inhibits Na<sup>+</sup>-H<sup>+</sup> exchanger activity in renal BBMV by stimulation of adenylate cyclase. *Am J Physiol* 1990; 259:F297–F303.
10. LeClaire MM, Berndt TJ, Knox, FG. Effect of renal interstitial infusion of L-DOPA on sodium and phosphate excretions. *J Lab Clin Med* 1998; 132:308–312.
11. Baines AD, Drangova R. Does dopamine use several signal pathways to inhibit Na-Pi transport in OK cells? *J Am Soc Nephrol* 1998; 9:1604–1612.
12. Lederer ED, Sohi SS, McLeish KR. Dopamine regulates phosphate uptake by opossum kidney cells through multiple counter-regulatory receptors. *J Am Soc Nephrol* 1998; 9:975–985.
13. Kunimi M, Seki G, Hara C, et al. Dopamine inhibits renal Na<sup>+</sup>:HCO<sub>3</sub><sup>-</sup> cotransporter in rabbits and normotensive rats but not in spontaneously hypertensive rats. *Kidney Int* 2000; 57:534–543.
14. Nishi A, Eklöf A-C, Bertorello AM, Aperia A. Dopamine regulation of renal Na<sup>+</sup>, K<sup>+</sup>-ATPase activity is lacking in Dahl salt-sensitive rats. *Hypertension* 1993; 21:767–771.
15. Hussain T, Lokhandwala MF. Renal dopamine DA1 receptor coupling with GS and Gq/11 proteins in spontaneously hypertensive rats. *Am J Physiol* 1997; 272:F339–F346.
16. Aoki Y, Albrecht FE, Bergman KR, Jose PA. Stimulation of Na<sup>+</sup>-K<sup>+</sup>-2Cl cotransport in rat medullary thick ascending limb by dopamine. *Am J Physiol* 1996; 271:R1561–R1567.
17. Hussain T, Abdul-Wahab R, Lokhandwala MF. Bromocriptine stimulates Na<sup>+</sup>,K<sup>+</sup>-ATPase in renal proximal tubules via cAMP pathway. *Eur J Pharmacol* 1997; 321:259–263.
18. Sun D, Wilborn TW, Schafer JA. Dopamine D4 receptor isoform mRNA and protein are expressed in the rat cortical collecting duct. *Am J Physiol* 1998; 275:F742–F751.
19. Muto S, Tabei K, Asano Y, Imai M. Dopaminergic inhibition of the action of vasopressin on the cortical collecting tubule. *Eur J Pharmacol* 1985; 114:393–397.
20. Sheikh-Hamad D, Wang Y-P, Jo OD, Yanagawa N. Dopamine antagonizes the actions of angiotensin II in renal brush-border membrane. *Am J Physiol* 1993; 264:F737–F743.

21. Albrecht FE, Xu J, Moe OW, et al. Regulation of NHE-3 activity by G-protein subunits in renal brush border membranes. *Am J Physiol* 2000; 278:R1064–R1073.
22. Ominato M, Satoh T, Katz AI. Regulation of Na-K-ATPase activity in the proximal tubule: role of the protein kinase C pathway and of eicosanoids. *J Membr Biol* 1996; 152:235–243.
23. Bertorello A, Aperia A. Inhibition of proximal tubule Na<sup>+</sup>-K<sup>+</sup>-ATPase activity requires simultaneous activation of DA<sub>1</sub> and DA<sub>2</sub> receptors. *Am J Physiol* 1990; 259:F924–F928.
24. Hussain T, Lokhandwala MF. Altered arachidonic acid metabolism contributes to the failure of dopamine to inhibit Na<sup>+</sup>,K<sup>+</sup>-ATPase in kidney of spontaneously hypertensive rats. *Clin Exp Hypertens* 1996; 18:963–974.
25. Debska-Slizien A, Ho P, Drangova R, Baines AD. Endogenous dopamine regulates phosphate reabsorption but not Na K-ATPase in spontaneously hypertensive rat kidneys. *J Am Soc Nephrol* 1994; 5:1125–1132.
26. Kurashima K, Szabo EZ, Lukacs G, et al. Endosomal recycling of the Na<sup>+</sup>/H<sup>+</sup> exchanger NHE3 isoform is regulated by the phosphatidylinositol 3-kinase pathway. *J Biol Chem* 1998; 273:20828–20836.
27. Chibalin AV, Ogimoto G, Pedemonte CH, et al. Dopamine-induced endocytosis of Na<sup>+</sup>,K<sup>+</sup>-ATPase is initiated by phosphorylation of Ser-18 in the rat alpha subunit and is responsible for the decreased activity in epithelial cells. *J Biol Chem* 1999; 274:1920–1927.
28. Pelayo JC, Fildes RD, Eisner GM, Jose PA. Effects of dopamine blockade on renal sodium excretion. *Am J Physiol* 1983; 245:F247–F253.
29. Siragy HM, Felder RA, Howell NL, et al. Evidence that intrarenal dopamine acts as a paracrine substance at the renal tubule. *Am J Physiol* 1989; 257:F469–F477.
30. Hegde SS, Jadhav AL, Lokhandwala MF. Role of kidney dopamine in the natriuretic response to volume expansion in rats. *Hypertension* 1989; 13:828–834.
31. Felder RA, Seikaly MG, Cody P, et al. Attenuated renal response to dopaminergic drugs in spontaneously hypertensive rats. *Hypertension* 1990; 15:560–569.
32. Hansell P, Fasching A. The effect of dopamine receptor blockade on natriuresis is dependent on the degree of hypervolemia. *Kidney Int* 1991; 39:253–258.
33. Jose PA, Asico L, Eisner GM, et al. Effects of costimulation of dopamine D<sub>1</sub>- and D<sub>2</sub>-like receptors on renal function. *Am J Physiol* 1998; 275:R986–R994.
34. Agnoli GC, Cacciari M, Garutti C, et al. Effects of extracellular fluid volume changes on renal response to low-dose dopamine infusion in normal women. *Clin Physiol* 1987; 7:465–479.
35. Donowitz M, Elta G, Battisti L, et al. Effect of dopamine and bromocriptine on rat ileal and colonic transport. Stimulation of absorption and reversal of cholera toxin-induced secretion. *Gastroenterology* 1983; 84:516–523.
36. Mühlbauer B, Spöhr F, Schmidt R, Osswald H. Role of renal nerves and endogenous dopamine in amino acid-induced glomerular hyperfiltration. *Am J Physiol* 1997; 273:F144–F149.
37. Ozono R, O'Connell DP, Vaughan C, et al. Expression of the subtype 1A dopamine receptor in the rat heart. *Hypertension* 1996; 27:693–703.
38. Habuchi Y, Tanaka H, Nishio M, et al. Dopamine stimulation of cardiac beta-adrenoceptors: The involvement of sympathetic amine transporters and the effect of SKF38393. *Br J Pharmacol* 1997; 122:1669–1678.
39. Kuchel O. Peripheral dopamine in hypertension and associated conditions. *J Hum Hypertens* 1999; 13:605–615.
40. Yoshimura M, Kambara S, Okabayashi H, et al. Effect of decreased dopamine synthesis on the development of hypertension induced by salt loading in spontaneously hypertensive rats. *Clin Exp Hypertens A* 1987; 9:1141–1157.
41. Shigetomi S, Ueno S, Kohno H, et al. Role of renal dopamine receptor in the pathogenesis of hypertension after sodium loading [in Japanese]. *Nippon Naibunpi Gakkai Zasshi* 1986; 62:26–33.
42. Montanari A, Tateo E, Fasoli E, et al. Dopamine-2 receptor blockade potentiates the renal effects of nitric oxide inhibition in humans. *Hypertension* 1998; 31:277–282.
43. Horiuchi A, Albrecht FE, Eisner GM, et al. Renal dopamine receptors and pre- and post-cAMP mediated sodium transport defect in the spontaneously hypertensive rat. *Am J Physiol* 1992; 263:F1105–F1111.
44. Felder RA, Kinoshita S, Ohbu K, et al. Organ specificity of the dopamine 1 receptor/adenylyl cyclase coupling defect in spontaneously hypertensive rats. *Am J Physiol* 1993; 264:R726–R732.
45. Chatziantoniou C, Ruan X, Arendshorst WJ. Defective G protein activation of the cAMP pathway in rat kidney during genetic hypertension. *Proc Natl Acad Sci U S A* 1995; 92:2924–2928.
46. O'Connell DP, Ragsdale NV, Boyd DG, et al. Differential human renal tubular responses to dopamine type 1 receptor stimulation are determined by blood pressure status. *Hypertension* 1997; 29:115–122.
47. Post JB 4th, Frishman WH. Fenoldopam: A new dopamine agonist for the treatment of hypertensive urgencies and emergencies. *J Clin Pharmacol* 1998; 38:2–13.
48. Albrecht FE, Drago J, Felder RA, et al. Role of the D<sub>1A</sub> dopamine receptor in the pathogenesis of genetic hypertension. *J Clin Invest* 1996; 97:2283–2288.
49. Wang Z-Q, Felder RA, Carey RM. Selective inhibition of the renal dopamine subtype D<sub>1A</sub> receptor induces antinatriuresis in conscious rats. *Hypertension* 1999; 33(Part II):504–510.
50. Krushkal J, Ferrell R, Mockrin SC, et al. Genome-wide linkage analyses of systolic blood pressure using highly discordant siblings. *Circulation* 1999; 99:1407–1410.
51. Kren V, Pravenec M, Lu S, et al. Genetic isolation of a region of chromosome 8 that exerts major effects on blood pressure and cardiac mass in the spontaneously hypertensive rat. *J Clin Invest* 1997; 99:577–581.
52. Sanada H, Jose PA, Hazen-Martin D, et al. Dopamine-1 receptor defect in renal proximal tubular cells in essential hypertension. *Hypertension* 1999; 33:1036–1042.
53. Sato M, Soma M, Nakayama T, Kanmatsue K. Dopamine D1 receptor gene polymorphism is associated with essential hypertension. *Hypertension* 2000; 36:183–186.
54. Gros R, Benovic JL, Tan CM, Feldman RD. G-protein-coupled receptor kinase activity is increased in hypertension. *J Clin Invest* 1997; 99:2087–2093.
55. Gros R, Chorazyczewski J, Meek MD, et al. G-protein-coupled receptor kinase activity in hypertension. *Hypertension* 2000; 35:38–42.
56. Williams SM, Addy JA, Phillips JA III, et al. Combinations of variations in multiple genes are associated with hypertension. *Hypertension* 2000; 36:2–6.
57. Yu P-Y, Asico LD, Eisner GM, et al. Renal protein phosphatase 2A activity and spontaneous hypertension in rats. *Hypertension* 2000; 36:1053–1058.
58. Bek M, Asico LD, Li XX, et al. AVP-dependent hypertension in mice with disrupted dopamine D5 receptor [abstract]. *J Am Soc Nephrol* 1999; 10:341A.

59. Bek M, Asico LD, Eisner GM, et al. Non-N-methyl D-aspartate receptors are involved in the hypertension of D5 dopamine receptor knockout mice. *Hypertension* 2000; 36:726.
60. Casari G, Barlassina C, Cusi D, et al. Association of the *-adducin* locus with essential hypertension. *Hypertension* 1995; 25:320–326.
61. Sowers JR, Nyby M, Jasberg K. Dopaminergic control of prolactin and blood pressure: Altered control in essential hypertension. *Hypertension* 1982; 4:431–438.
62. Linthorst AC, van Giersbergen PL, Gras M, et al. The nigrostriatal dopamine system: Role in the development of hypertension in spontaneously hypertensive rats. *Brain Res* 1994; 639:261–268.
63. Vaughan CE, van den Buuse M, Roland BL. Brain dopamine D2 receptor mRNA levels are elevated in young spontaneously hypertensive rats. *Neurosci Res* 1999; 34:199–205.
64. Thomas GN, Tomlinson B, Critchley JA. Modulation of blood pressure and obesity with the dopamine D2 receptor gene *Taq1* polymorphism. *Hypertension* 2000; 36:177–182.
65. Kren V, Pravenec M, Lu S, et al. Genetic isolation of a region of chromosome 8 that exerts major effects on blood pressure and cardiac mass in the spontaneously hypertensive rat. *J Clin Invest* 1997; 99:577–581.
66. Li XX, Asico LD, Low M, et al. Disruption of the dopamine D2 receptor produces non-renal dependent hypertension [abstract]. *J Am Soc Nephrol* 1998; 9:311A.
67. Yamaguchi I, Yao L, Sanada H, et al. Dopamine D1A receptors and renin release in rat juxtaglomerular cells. *Hypertension* 1997; 29:962–968.
68. Cheng H-F, Becker BN, Harris RC. Dopamine decreases expression of type-1 angiotensin II receptors in renal proximal tubule. *J Clin Invest* 1996; 97:2745–2752.
69. Hussain T, Abdul-Wahab R, Kotak DK, Lokhandwala MF. Bromocriptine regulates angiotensin II response on sodium pump in renal proximal tubules. *Hypertension* 1998; 32:1054–1059.
70. Asico LD, Ladines C, Fuchs S, et al. Disruption of the dopamine D3 receptor gene produces renin-dependent hypertension. *J Clin Invest* 1998; 102:493–498.
71. Naruse M, Naruse K, Yoshimoto T, et al. Dopaminergic regulation of aldosterone secretion: Its pathophysiologic significance in subsets of primary aldosteronism. *Hypertens Res* 1995; 18 Suppl 1:S59–S64.
72. Williams GH, Gordon MS, Steunkel CA, et al. Dopamine and non-modulating hypertension. *Am J Hypertens* 1990; 3:112S–115S.
73. Sanada H, Yao L, Jose PA, et al. Dopamine D3 receptors in rat juxtaglomerular cells. *Clin Exp Hypertens* 1997; 19:93–105.
74. Cardinaud B, Sugamori KS, Coudouel S, et al. Early emergence of three dopamine D1 receptor subtypes in vertebrates: Molecular phylogenetic, pharmacological, and functional criteria defining D1A, D1B, and D1C receptors in European eel *Anguilla anguilla*. *J Biol Chem* 1997; 272:2778–2787.
75. Sibley DR. New insights into dopaminergic receptor function using antisense and genetically altered animals. *Annu Rev Pharmacol Toxicol* 1999; 39:313–341.
76. Missale C, Nash SR, Robinson SW, et al. Dopamine receptors: From structure to function. *Physiol Rev* 1998; 78:189–225.
77. Chibalin AV, Zierath JR, Katz AI, et al. Phosphatidylinositol 3-kinase-mediated endocytosis of renal Na<sup>+</sup>, K<sup>+</sup>-ATPase alpha subunit in response to dopamine. *Mol Biol Cell* 1998; 9:1209–1220.
78. Felder CC, Jose PA, Axelrod J. The dopamine-1 agonist, SKF 82526, stimulates phospholipase-C activity independent of adenylate cyclase. *J Pharmacol Exp Ther* 1989; 248:171–175.
79. Chen CJ, Vyas SJ, Eichberg J, Lokhandwala MF. Diminished phospholipase C activation by dopamine in spontaneously hypertensive rats. *Hypertension* 1992; 19:102–108.
80. White BH, Kimura K, Sidhu A. Inhibition of hormonally induced inositol trisphosphate production in transfected GH4C1 cells: A novel role for the D5 subtype of the dopamine receptor. *Neuroendocrinology* 1999; 69:209–216.
81. Lezcano N, Mrzljak L, Eubanks S, et al. Dual signaling regulated by calydon, a D1 dopamine receptor interacting protein. *Science* 2000; 287:1660–1664.
82. Lokhandwala MF, Tadepalli AS, Jandhyala BS. Cardiovascular actions of bromocriptine: Evidence for a neurogenic mechanism. *J Pharmacol Exp Ther* 1979; 211:620–625.
83. Bass AS, Robie NW. Stereoselectivity of *S*- and *R*-sulpiride for pre- and postsynaptic dopamine receptors in the canine kidney. *J Pharmacol Exp Ther* 1984; 229:67–71.
84. Siragy HM, Felder RA, Howell NL, et al. Evidence that dopamine-2 mechanisms control renal function. *Am J Physiol* 1990; 259:F793–F800.
85. Bughi S, Jost-Vu E, Antonipillai I, et al. Effect of dopamine 2 blockade on renal function under varied sodium intake. *J Clin Endocrinol Metab* 1994; 78:1079–1084.
86. Cussac D, Newman-Tancredi A, Pasteau V, Millan MJ. Human dopamine D3 receptors mediate mitogen-activated protein kinase activation via a phosphatidylinositol 3-kinase and an atypical protein kinase C-dependent mechanism. *Mol Pharmacol* 1999; 56:1025–1030.
87. Luippold G, Kuster E, Joos TO, Mühlbauer B. Dopamine D3 receptor activation modulates renal function in anesthetized rats. *Naunyn Schmiedeberg Arch Pharmacol* 1998; 358:690–693.
88. Eklöf A-C. The natriuretic response to a dopamine DA1 agonist requires endogenous activation of dopamine DA2 receptors. *Acta Physiol Scand* 1997; 160:311–314.