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Dysregulation of dopamine-dependent mechanisms as a determinant of hypertension: studies in dopamine receptor knockout mice

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Abstract

Dopamine plays an important role in the pathogenesis of hypertension by regulating epithelial sodium transport and by interacting with vasoactive hormones/humoral factors, such as aldosterone, angiotensin, catecholamines, endothelin, oxytocin, prolactin pro-opiomelancortin, reactive oxygen species, renin, and vasopressin. Dopamine receptors are classified into D_1-like (D_1 and D_5) and D_2-like (D_2, D_3, and D_4) subtypes based on their structure and pharmacology. In recent years, mice deficient in one or more of the five dopamine receptor subtypes have been generated, leading to a better understanding of the physiological role of each of the dopamine receptor subtypes. This review summarizes the results from studies of various dopamine receptor mutant mice on the role of individual dopamine receptor subtypes and their interactions with other G protein-coupled receptors in the regulation of blood pressure.

Keywords

knockout mice; dopamine receptor

Essential hypertension is one of the most common risk factors in developed and developing countries, affecting ~25% of the middle-aged adult population. Essential hypertension is heterogeneous and is probably caused by an interaction of genetic and environmental

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factors. The long-term regulation of blood pressure rests on renal and nonrenal mechanisms (53, 84, 87, 104, 161, 189, 234, 268), and abnormalities in the renal regulation of ion transport, intrinsic and extrinsic to the Kidney, have been proposed to cause essential hypertension. Hormones and humoral factors, such as those involved in the renin-angiotensin and sympathetic nervous systems, are preemininent in promoting elevated blood pressure (53, 54, 55, 76, 84, 87, 104, 161, 177, 189, 234, 268). However, hypertension may be caused not only by increased activity of prohypertensive systems but also by defects in antihypertensive systems that serve as counterregulatory mechanisms. Aberrations in these counterregulatory pathways, including the dopaminergic pathway, may be involved in the pathogenesis of essential hypertension (104, 268).

Dopamine receptors expressed in mammals belong to the α-group of the rhodopsin family of G protein-coupled receptors (GPCRs; class A, family A, or family 1) (55, 177, 186, 215). The five mammalian dopamine receptor subtypes, identified by molecular cloning, differ in their primary structures and have distinct affinities for dopamine receptor agonists and antagonists. The D_1-like receptors, comprising the D_1 and D_5 receptor subtypes, couple to the stimulatory G proteins G_s and G_{olf} and activate adenylyl cyclases. The D_2-like receptors, comprising the D_2, D_3, and D_4 receptor subtypes, couple to the inhibitory G proteins G_i and G_o and inhibit adenylyl cyclases and modulate ion channels (104, 268).

In general, D_1-like receptors are expressed postsynaptically/postjunctionally, whereas D_2-like receptors can be expressed presynaptically/prejunctionally as well as postsynaptically/postjunctionally (19, 81, 95, 115, 217, 223, 261, 265, 268). Although the dopamine receptor subtypes are expressed in patterns unique to the subtype, they may be coexpressed within individual cells or in distinct cells in the same organ, including those of the Kidney, intestines, and blood Vessels. This situation often precludes the assignment of one individual receptor subtype to a particular system. Moreover, studies on the distinct functional properties of dopamine receptor subtypes expressed in vivo are limited by the lack of agonists and antagonists with selectivity for the individual receptor subtypes. In recent years, a number of laboratories have used gene targeting, via homologous recombination, to generate mice deficient in one or more of the dopamine receptor subtypes (2, 5, 17, 19, 22, 32, 56, 58, 81, 93, 95, 115, 138, 201, 217, 223, 235, 261).

Several recent studies have shown that in addition to specific intramolecular interactions that could define the activation states of GPCRs, intermolecular interactions may also be important (37). Specifically, GPCRs can regulate the function of other receptors by altering expression and/or via direct protein-protein interactions (187).

A number of direct interactions between dopamine receptors and other GPCRs, as well as between dopamine receptor subtypes, have been described in the central nervous system. In neostriatal slices, D_1 receptor activation affects the trafficking of *N*-methyl-D-aspartate (NMDA) receptors between subcellular compartments (59). Conversely, NMDA receptor activation alters D_1 receptor subcellular distribution (218). The D_1 receptor and subunits NR_1 and NR_2 of the NMDA receptor physically interact in cell lines and hippocampal neurons, resulting in D_1 receptor regulation of NMDA-elicited currents (77, 131, 181). There is a mutually inhibitory modulation between D_5 and $GABA_A$ receptors that results

from a protein-protein interaction between the D_5 receptor and the α_2-subunit of the $GABA_A$ receptor (140). The A_1 adenosine receptor heterodimerizes with D_1 receptors (80), whereas the closely related A_{2A} adenosine receptor heterodimerizes with D_2 receptors (40, 75, 92). These interactions result in cointernalization, cross-desensitization of signaling activities, and functional antagonism between the receptors. D_2 receptors interact physically through heterooligomerization with somatostatin receptor 5 and create a novel receptor with enhanced functional activity and pharmacological properties different than those of the individual receptors (200) that may explain the synergistic interactions between somatostatin and dopamine in the central nervous system (106).

D_1 and D_2 receptors physically interact forming a heteromeric protein complex and coexpress and colocalize within neurons in the human and rat brain. D_1 and D_2 receptor coactivation generates a novel PLC-mediated calcium signal, indicating that D_1 and D_2 receptors acquire a new cellular function when coactivated in the same cell (132). Recombinant human dopamine D_2 and D_3 receptors form functional heterodimers upon coexpression in COS-7 cells, and D_2 and D_3 receptor coexpression enhances the potency of D_2 receptor agonists in transfected cells (149, 214). Because the ultimate effect of dopamine is the sum of the interactions of the different dopamine receptor subtypes and other GPCRs (which may be dependent on the state of sodium balance), impairment of these interactions may result in defective regulation of sodium transport and hypertension.

This review summarizes the role of the different dopamine receptor subtypes in epithelial ion transport, renal physiology, and blood pressure regulation, taking into account clues obtained from mutant mice. Moreover, we also review the role of each dopamine receptor subtype in the pathogenesis of hypertension.

D_1 Receptors

Localization of the D_1 Receptor Subtype

The Kidney—Earlier autoradiographic, radioligand binding, and functional studies using D_1-like receptor agonists and antagonists have shown the presence of D_1-like receptors in the renal cortex (proximal tubules) but not in glomeruli or the medulla in the rat Kidney (71, 72, 73, 90, 98, 230). However, glomerular mesangial cells (222) and podocytes (31), in culture, express D_1-like receptors. As aforementioned, these studies are limited because the ligands cannot distinguish D_1 from D_5 receptors.

D_1 receptor mRNA is expressed in the rat renal cortex (proximal and distal tubule, arteriole, and juxtaglomerular apparatus) but not in the glomerulus or medulla (169, 248, 250). Immortalized renal proximal tubule cells from the rat (171), mouse (unpublished observations), opossum (160), human (241), and pig (123) also express D_1 receptors.

Immunohistochemical and electron microscopic studies have revealed D_1 receptors in the cortex and medulla in the rat (9, 170), mouse (5), and human Kidney (178), specifically in apical and basolateral membranes of the proximal and distal convoluted tubule, medullary thick ascending limb of Henle, macula densa, and cortical collecting duct. There are more D_1 receptors in the S3 segment than in S1 and S2 segments of the proximal tubule of the rat

Kidney (unpublished observations). The expression of D_1 receptors in the collecting duct has not been detailed, but dopamine does not stimulate cAMP production in the inner medullary collecting duct (148). The inhibition of vasopressin action by dopamine in this nephron segment has also been attributed to stimulation of α_2-adrenergic receptors (62).

D_1 receptors are observed throughout the renal vasculature, including juxtaglomerular cells in rats (9,170, 250), but only in large intrarenal arteries in humans (178) (Table 1). In agreement with the latter finding, selective D_1-like receptor stimulation increases plasma renin activity in rats but not in humans (188); the effect in mice is not known. D_1 receptor immunostaining in renal veins has not been described. Consistent with mRNA studies and adenylyl cyclase activation in response to D_1-like receptor agonist (70), D_1 receptors are not expressed in glomeruli in either the rat or human Kidney. Immunoblot studies have revealed the presence of several forms of D_1 receptors in the rat and human renal proximal tubule from 50 to 210 kDa (260), consistent with data obtained in brain tissue (109).

Blood Vessels (Other than in the Kidney)—In addition to the inhibition of ion transport, dopamine, via D_1-like receptors, also causes vasorelaxation. In the pulmonary artery, D_1 receptor immunostaining has been reported in the tunica intima and media of extrapulmonary branches and tunica media of large-sized (but not medium or small sized) intrapulmonary branches. In situ hybridization studies have also shown the expression of the D_1 receptor in the rat pulmonary artery as well as the aorta, common carotid, and vertebral arteries. The superior vena cava (119) but not the portal vein expresses D_1-like receptors (194). In the rat aorta, common carotid artery, and vertebral artery, D_1 receptor mRNA is found only in vascular smooth muscle cells (VSMCs). In contrast, in the pulmonary artery, D_1 receptor mRNA is found within the tunica intima, media, and adventitia (110, 119). D_1 receptor mRNA is not found in the rat caudal artery (110), and, therefore, the apparent vasoconstrictor effect of D_1-like agonists in this blood vessel segment may not be due to a direct vasoconstrictor effect of D_1 receptors. Immunohistochemical studies have shown that the D_1 receptor is localized on the tunica media of rat pial and mesenteric arteries (8, 192, 270).

Physiology of the D_1 receptor

Renal Function—Endogenous renal dopamine is a major physiological regulator of renal ion transport (104, 268). During conditions of moderate sodium balance, >50% of renal sodium excretion is regulated by D_1-like receptors (104, 268). Stimulation of the D_1-like receptor by exogenous ligands results in an increase in sodium excretion that is in part due to an increase in renal blood flow and a direct inhibition of renal tubular sodium transport (104, 265,268); the glomerular filtration rate is variably affected (73, 164, 171, 231). In contrast, inhibition of renal D_1-like receptors decreases sodium excretion without affecting renal blood flow or the glomerular filtration rate in sodium-replete states (42, 73, 114).

As indicated above, the D_1-like receptor family is composed of two receptor subtypes: D_1 and D_5. The D_1-like receptor subtype mediating the natriuretic effect of D_1-like receptor is not known because of the lack of specific agonists for each D_1-like receptor subtype. Because cAMP is involved in the inhibition of renal ion transport by D_1-like receptors and

the D_1 receptor increases cAMP production to a greater extent than the D_5 receptor in renal proximal tubule cells (206), it is likely that the natriuretic effect of dopamine is due mainly to the D_1 receptor in this nephron segment. This remains to be tested, however. Direct evidence of the involvement of the D_1 receptor in the inhibition of renal sodium transport comes from studies with a chronic selective intrarenal cortical infusion of D_1 receptor antisense oligodeoxynucleotides, which selectively decrease D_1 receptor protein without affecting D_5 receptors (239). In this study, sodium excretion during a normal or high salt intake is decreased by the selective renal cortical inhibition of D_1 receptor expression (239).

D_1-like receptors decrease ion transport in many segments of the nephron (proximal tubule, medullary thick ascending limb of Henle, and cortical collecting duct) by inhibiting the activities of sodium/hydrogen exchanger 3 (NHE3; SLC9A3), sodium-phosphate cotransporter (NaPi-IIa/SLC34A1 and NaPi-IIc/SLC34A3), and Cl^-/HCO_3^- exchanger (SLC26A6) at the apical membrane and electrogenic Na^+/HCO_3^- cotransporter (NBCe1A; SLC4A4) and Na^+-K^+-ATPase at the basolateral membrane (5, 11, 16, 21, 24, 86, 97, 164, 180, 247). In the medullary thick ascending limb of Henle, D_1-like receptors decrease sodium transport (78) by inhibiting Na^+-K^+-ATPase activity, but dopamine actually increases sodium-potassium-chloride cotransporter (NKCC2; SLC12A1) activity in this nephron segment (10). We have suggested that D_1-like stimulation of NKCC2 may be important in K^+ recycling. However, eicosanoids [20-hydroxyeicosatetraenoic acid (20-HETE)] may synergize with D_1-like receptors to inhibit NKCC2 activity. G proteindependent, cAMP/PKA-dependent, and PKC-independent mechanisms are involved in the D_1-like receptor inhibition of Na^+/Pi_2, NHE3, Na/HCO_3^- cotransporter, and Cl^-/HCO_3^- exchanger activity, including their translocation out of brush-border membranes (20, 23, 24, 68, 125, 180, 245). In contrast, D_1-like receptors inhibit Na^+-K^+-ATPase activity via cAMP/PKA, certain PKC isoforms, and 20-HETE, which internalize its subunits (15, 57, 65, 86, 101, 121, 135, 167, 176, 211). The inhibitory effect of D_1-like receptors on Na^+-K^+-ATPase is nephron segment specific: PKA is involved in D_1-like receptor-mediated inhibition in the cortical collecting duct, whereas PKC is involved in the proximal convoluted tubule; eicosanoids are involved in all nephron segments studied (15, 57, 65, 101, 118, 135, 167, 211, 212).

In addition to the direct inhibition of D_1-like receptors on sodium excretion, D_1-like and D_2-like receptors interact to enhance this effect. We have reported that the increase in sodium excretion induced by Z-1046, a dopamine receptor agonist with a rank order potency of $D_4 > D_3 > D_2 > D_5 > D_1$, is blocked by either D_1-like or D_2-like receptor antagonists (127). D_2-like receptors may potentiate the inhibitory effect of D_1-like receptors on Na^+-Pi cotransport, NHE3, and Na^+-K^+-ATPase activities in renal proximal tubules (see below).

Cardiovascular Function—Circulating concentrations of dopamine are too low to stimulate its own receptors (104, 268). Dopamine administered systemically to increase blood pressure exerts its effect via nondopaminergic receptors; β-adrenergic receptors increase cardiac output, whereas α-adrenergic receptors increase vascular resistance. D_1 receptors are expressed in the human and rat heart (152, 178, 277). However, D_1-like receptor agonists do not directly affect myocardial contractility (184).

Dopamine, at low concentrations, dilates resistance arteries via D_1-like receptors (87,104, 268). The vasorelaxant effect of dopamine in the rabbit pulmonary artery has been reported to be both endothelium dependent and independent (251). However, in the mesenteric artery, the vasodilatory effect of the D_1 receptor agonist is endothelium independent (269, 270). The vasorelaxant effect of the D_1 receptor is enhanced by calcium channel blockade with nifedipine, indicating that calcium channels are involved in the vasodilatory effect of D_1 receptors (269, 270). The vasodilatation induced by D_1-like receptors is probably mediated by cAMP; inhibition of Na^+-K^+-ATPase activity would cause vasoconstriction. In coronary arteries, cAMP cross activation of cGMP-dependent protein kinase stimulates large-conductance calcium-activated potassium channel activity (244).

Interactions with the Renin-Angiotensin system—The D_1 receptor may also regulate renal and cardiovascular function by interacting with other systems, including the renin-angiotensin-aldosterone and sympathetic nervous systems. Angiotensin type 1 (AT_1) receptors stimulate all renal proximal tubular ion-transporting proteins that are inhibited by D_1-like receptors (46, 64, 220). The natriuretic effect of D_1-like receptors is enhanced when angiotensin II production is decreased or when AT_1 receptors are blocked (46). The renal vasoconstrictor effect of angiotensin II can also be antagonized by D_1-like receptor agonists. D_1-like and AT_1 receptors have opposing effects on the generation of second messengers: D_1-like receptors stimulate adenylyl cyclases, whereas AT_1 receptors inhibit them. While both D_1-like and AT_1 receptors stimulate PLC activity, they stimulate different PKC isoforms (18, 63, 88, 256). Dopamine, via the D_1-like receptor, also decreases AT_1 receptor expression and angiotensin II binding sites in renal proximal tubule cells from normotensive Wistar-Kyoto (WKY) rats (49, 267, 274). However, the D_1 receptor can also inhibit AT_1 receptor function by direct physical interactions (267), whereas the D_5 receptor may be responsible for the D_1-like receptor inhibition of AT_1 receptor expression (274) (see below). In contrast, angiotensin type 2 (AT_2) receptors participate in the natriuresis induced by D_1-like receptors (203). There is a negative interaction between D_1-like and adrenergic receptors, similar to the negative interaction between AT_1 and D_1-like receptors in the regulation of renal sodium transport and VSMC contractility. In opossum Kidney cells, the dopaminergic inhibition of Na^+/Pi_2 is potentiated by treatment with a-adrenergic receptor antagonists (129). We have preliminary data showing that the increase in proliferation of VMSCs produced by stimulation of α_1-adrenergic receptors is inhibited by stimulation of D_1-like receptors (Li Z, Zeng C, and Jose PA; unpublished observations).

D_1 Receptors and Hypertension

Impaired Renal D_1 Receptor Function—In rodents with genetic hypertension [spontaneously hypertensive rats (SHRs) and Dahl salt-sensitive rats], D_1-like receptor agonist-mediated diuretic and natriuretic responses are impaired (47, 73, 104, 113, 164, 268). The impaired natriuretic response to exogenous D_1-like agonists is accompanied by an impaired natriuretic effect of endogenous renal dopamine (47, 73, 127). The impaired natriuretic effect of D_1-like receptor agonists has specificity, because the natriuretic effect of cholecystokinin is not impaired in SHRs (127). In hypertensive humans, the ability of D_1-like receptor agonists to inhibit proximal tubular reabsorption is impaired (171); however, the overall natriuretic effect of exogenously administered D_1 receptor agonists may be

greater in hypertensive subjects than in normotensive subjects (163, 171). This is due to the fact that the actions of D_1-like receptors on renal hemodynamics and distal renal tubule function (see below) are preserved in hypertension (163, 171).

The decreased ability of D_1-like receptor agonists to inhibit ion transport in rodent genetic hypertension is due to diminished D_1-like receptor inhibition of NHE3 (5), Cl^-/HCO_3^- exchanger (180), Na^+/HCO_3^- cotransporter (125), and Na^+-K^+-ATPase activities (101, 164). The impaired inhibition of ion transport by D_1-like receptors in rodent models of genetic hypertension is due, in part, to impaired production of second messengers (e.g., cAMP, diacylglycerol, eicosanoids) in renal proximal tubules (45, 69, 72, 101, 103, 120, 180) and the thick ascending limb of Henle (164) but not in the cortical collecting duct (174). The impaired ability of D_1-like receptors to stimulate cAMP production in renal proximal tubules in genetic hypertension need not be due to decreased total cellular expression of D_1 receptor (259) but rather to increased serine phosphorylation and decreased expression of D_1 receptors at the plasma membrane (205, 259). The impaired ability of D_1-like receptors to stimulate cAMP production in renal proximal tubules is specific because the ability of parathyroid hormone to stimulate cAMP production or stimulate G proteins is intact (103, 120, 205); β-adrenergic function is also intact, at least in young SHRs (153). There is organ specificity because D_1 receptor action in the brain striatum is also intact (72). The impaired D_1-like receptor function is probably of genetic origin, because it precedes the onset of hypertension and cosegregates with high blood pressure (5, 72, 128, 175).

Impaired Arterial D_1 Receptor Function—In general, the renal and nonrenal vasodilatory effects of D_1-like receptors in hypertension are not impaired (156, 171). There are, however, reports of an impaired renal vasodilatory effect of D_1-like receptor agonist in humans with essential hypertension (39) and in SHRs (43). Indeed, there is an impaired ability of D_1-like receptors to stimulate adenylyl cyclase in renal arteries of SHRs (43). We have also reported an impaired ability of D_1-like receptor agonists to vasodilate mesenteric arteries of SHRs (269).

D_1 Receptor Mutant Mice

D_1 receptor-null ($D_1^{-/-}$) mice were generated by targeted mutagenesis. The targeting construct contained 7.0 kb of 129/Sv-derived D_1 receptor genomic sequence in the pPNT vector (5, 58). Both homozygous and heterozygous mice had greater systolic, diastolic, and mean arterial pressures than wild-type mice. Renal tubules from homozygous D_1 receptor knockout mice have no binding sites for ^{125}I-labeled SCH-23982, a D_1-like receptor antagonist, and do not increase cAMP accumulation in response to D_1-like receptor agonist stimulation. The response to parathyroid hormone, however, is intact. These data provide reasonable correlation between defective D_1 receptor/signal transduction and the development of hypertension in mice (5).

Deficiency of the D_1 receptor could be involved in human essential hypertension. The human D_1 gene locus at chromosome 5 at q35.1 is linked to human essential hypertension (124). A polymorphism, A-48G, identified at 248 bp of the 5′-untranslated region, is associated with essential hypertension in Japanese subjects (210) but not in Caucasian

subjects (30) and has also been reported to be associated with albuminuria (191). There are no reports of the association of polymorphisms of the coding region of the D_1 receptor and essential hypertension.

D_1 Receptors and Blood Pressure Regulation Summary

D_1 receptors regulate blood pressure in the long term by decreasing renal sodium transport and may interact directly and negatively to regulate AT_1 receptor function and increase AT_2 receptor expression. While D_1 receptors can also increase renin secretion, this may only be manifest in rats on a low-sodium diet or during hypovolemia (250); a role of D_1 receptors on renin secretion in humans has not been proved. D_1 receptors may also exert antihypertensive effects by preventing oxidative stress (see below). It remains to be proved, however, if $D_1^{-/-}$ mice are salt sensitive and whether D_1 receptor-mediated ion transport is impaired in the renal proximal tubule of $D_1^{-/-}$ mice.

D_2 Receptors

Localization of the D_2 Receptor Subtype

The Kidney—The D_2 receptor is expressed as D_{2short} and D_{2long} (154). It has been suggested that the D_{2short} receptor functions as the presynaptic receptor, whereas the D_{2long} receptor functions as the postsynaptic receptor; the D_{2short} receptor is expressed to a greater extent in presynaptic receptors than in postsynaptic receptors (111, 139). D_{2long} mRNA is expressed in renal tubules and glomeruli (79). Most of D_2-like receptors in the rat Kidney are prejunctional (25). However, D_2 receptor protein has been described in the opossum Kidney cell, a proximal tubule cell line that has some distal tubular cell characteristics (159). The expression of D_2 receptors in the intact Kidney is not well documented (Table 1).

Blood Vessels—D_2 receptor protein has been described in the heart and coronary artery (44). Dopamine at low and high concentrations constricts isolated porcine pial veins via postsynaptic α_2-adrenoceptors and dopamine D_1 and D_2 receptors (228). However, in the cat and other species, D_1 receptors are vasodilatory; the D_2 receptor agonist LY-141865 is vasodilatory only at high concentrations (61). The reason for this apparent species difference is not readily apparent. As stated above, D_1 receptor-mediated inhibition of Na^+-K^+-ATPase, per se, should lead to vasoconstriction because of an increase in intracellular sodium and, subsequently, intracellular calcium by the activation of the sodium/calcium exchanger. The D_2 receptor could cause vasoconstriction by inhibition of cAMP production but could also cause vasodilation by inhibition of norepinephrine release.

Physiological Role of the D_2 Receptor

Renal Function—D_2 receptors have variable effects on sodium transport that could not be entirely related to the lack of selectivity of D_2 receptor ligands (213). D_2 receptors can affect renal function by regulating dopamine transporter activity (130) and renal dopamine production (179). There are studies showing vasodilatory and natriuretic effects of D_2-like receptors (104, 179, 268). However, in rat renal proximal tubules, bromocriptine, a D2-like receptor agonist with a 10-fold affinity for D_2 over D_3 receptors, stimulates Na^+-K^+-ATPase activity by increasing its α-subunit in the plasma membrane (100, 158). Bromocriptine also

increases chloride transport in the medullary thick ascending limb of the rat (85). LY-171555, a D_2-like receptor agonist with some selectivity to the D_2 receptor, stimulates Na^+-K^+-ATPase activity in murine fibroblasts heterologously expressing D_{2Long} receptors (249). Interestingly, in sodium-depleted women, dopamine produces an antinatriuretic effect (3). Sulpiride, a D_2-like receptor antagonist with an equal affinity for all D_2-like receptors, impairs the natriuretic effect of dopamine in volume-expanded women (4). Thus, it is possible that the antinatriuretic effect of the D_2 receptor may become manifest during volume depletion, whereas the natriuretic effect becomes manifest during volume-expanded states. Whether this is a direct effect or whether it is due to an interaction with other dopamine receptors (e.g., the D_1 receptor) remains to be determined.

As stated above, D_1 and D_2 receptors can heterodimerize (60) and interact with each other (183, 185). In LTK2 cells transfected with either rat D_1 or D_{2Long} cDNA, D_1-like receptor stimulation decreases Na^+-K^+-ATPase activity, whereas D_2-like receptor stimulation produces the opposite effect; these effects are transduced by increases or decreases in cAMP production, respectively (85, 96). Bromocriptine and LY-171555 inhibit adenylyl cyclase activities; this has been thought to be the mechanism of the D_2 receptor-mediated stimulation of Na^+-K^+-ATPase activity (100, 249). Unlike the D_3 receptor, the D_2 receptor can inhibit adenylyl cyclase activity even in the absence of adenylyl cyclase V (199), which is not expressed in the Kidney (33). However, in Chinese hamster ovary (CHO) cells heterologously expressing 10 times more D_2 than D_1 receptors, stimulation of either receptor results in a potentiation of arachidonic acid release compared with those cells expressing only one receptor (117, 183). Arachidonic acid cytochrome *P*-450 products have been shown to inhibit renal sodium transport (12, 101, 209). Thus, D_1-D_2 synergism in the production of cAMP, PLC, and arachidonic acid products might account for the D_2 receptor-mediated natriuretic effect. The D_1 receptor-mediated activation of PKC could lead to a D_{2long} receptor-mediated sensitization of adenylyl cyclase VI (29). D_1 and D_2 receptors also synergistically interact to increase *c-fos* (50) and inhibit Na^+-K^+-ATPase activity (35). We have speculated that the D_2-like receptor stimulates sodium transport under conditions of "low" sodium intake; in contrast, under conditions of "moderate" sodium excess, D_2-like receptors, in concert with D_1-like receptors, inhibit Na^+-K^+-ATPase activity in renal proximal tubules cells and synergistically increase sodium excretion (3, 4, 34, 66, 112).

D_2 Receptors and Ros—D_2 receptors, like D_1 and D_5 receptors, may also have an antioxidant function. D_2 receptor-null ($D_2^{-/-}$) mice, which are hypertensive, have increased urinary excretion of 8-isoprostane, increased NADPH oxidase activity, and increased renal expression of NADPH oxidase subunits Nox1, Nox2, and Nox4 as well as decreased expression of the antioxidant enzyme heme oxygenase-2 in the Kidneys. Apocynin, which impairs NADPH oxidase subunit assembly and activity, or hemin, an inducer of heme oxygenase, normalizes blood pressure in $D_2^{-/-}$ mice (14).

D_2 Receptors and Hypertension

Abnormalities of D_2-like receptor function have been reported in hypertension. One of the polymorphisms of the D_2 receptor is associated with hypertension (232, 233). This polymorphism is also associated with decreased D_2 receptor expression (165). Transfer of a

segment of chromosome 8 containing the D_2 receptor gene from the normotensive Brown-Norway rat onto an SHR background decreases blood pressure (122).

D_2 Receptor Mutant Mice

The D_2 receptor gene was mutated by homologous recombination in embryonic stem cells with a targeting vector to delete all of exon 7 and the 5′-half of exon 8, the region encoding the majority of the putative third intracellular loop, the last two transmembrane domains, and the carboxy terminus. Blastocyst injection was used to generate chimeric mice on a mixed 129/Sv × C57BL/6J background. The original F2 hybrid strain (129/Sv × C57BL/6J) that contained the mutated D_2 receptor allele was backcrossed to wild-type C57BL/6J for five generations and genotyped (138). These mice have normal basic motor skills without tremor, ataxia, or abnormal stance or posture but had decreased initiation of movement. We have reported that systolic and diastolic blood pressures are higher in D_2 homozygous and heterozygous mutant mice than in control ($D_2^{+/+}$) mice. $D_2^{-/-}$ and $D_2^{+/+}$ mice have a similar ability to excrete an acute saline load. α-Adrenergic blockade decreases blood pressure to a greater extent in $D_2^{-/-}$ mice than in $D_2^{+/+}$ mice. Epinephrine excretion is greater in $D_2^{-/-}$ mice than in $D_2^{+/+}$ mice, and acute adrenalectomy decreases blood pressure to a similar level in $D_2^{-/-}$ and $D_2^{+/+}$ mice. An endothelin type B (ET_B) receptor blocker for both ET_{B1} and ET_{B2} receptors decreases, whereas a selective ET_{B1} blocker increases, blood pressure in $D_2^{-/-}$ mice but not $D_2^{+/+}$ mice. ET_B receptor expression is greater in $D_2^{-/-}$ mice than in $D_2^{+/+}$ mice. We have concluded that the enhanced vascular reactivity in $D_2^{-/-}$ mice may be caused by increased sympathetic and ET_B receptor activities (138) and increased ROS production (14). We have also found that $D_2^{-/-}$ mice have increased production of aldosterone and that treatment with a mineralocorticoid receptor blocker ameliorates hypertension in these mice (14).

In another strain of $D_2^{-/-}$ mice, blood pressure is normal on a normal salt diet but is increased on a high-salt diet with a decrease in renal dopamine production (235). Sympathetic activity is not different between these $D_2^{-/-}$ mice and their wild-type littermates. However, renal aromatic amino acid decarboxylase activity and dopamine synthesis are reduced in these $D_2^{-/-}$ mice. Basal urine flow and sodium excretion are lower in $D_2^{-/-}$ mice than in $D_{2+/+}$ mice, but dopamine increases urine volume and sodium excretion in $D_2^{-/-}$ mice to levels similar to those in $D_2^{+/+}$ mice (179). As with the differences in two different strains of $D_3^{-/-}$ mice, the differences between the two strains of $D_2^{-/-}$ mice could be related to genetic background.

D_2 Receptors and Blood Pressure Regulation Summary

D_2 receptors affect renal function by regulating dopamine production, dopamine transporter activity, and sympathetic nerve activity. D_2 receptors, by themselves, increase renal sodium transport, but coactivation of D_1 receptors produces the opposite effect. D_2 receptors regulate blood pressure by influencing sodium transport and by inhibiting ROS production. D_2 receptors may also have anti-inflammatory actions (13).

D_3 Receptors

Localization of D_3 Receptors

The Kidney—Specific radioligand binding of (±)-7-hydroxy-*N*,*N*-di-*n*-propyl-2-aminotetralin (7-OH-DPAT), which has a high affinity for both D_2 and D_3 receptors, is reported in cortical tubules and mesangial cells of the rat Kidney (26). D_3 receptor mRNA is expressed in glomerular, tubular, and vascular fractions of the rat Kidney (79). D_3 receptor protein is expressed in the apical/subapical area but not in the basolateral areas of the rat renal proximal tubule (168) (Table 1). The expression of the D_3 receptor in other nephron segments has not been consistent. Nurnberger et al. (194) could not detect any D_3 receptor protein in the distal tubule, cortical collecting duct, glomeruli, and renal Vessels. This is in contrast to the report of O'Connell et al. (172), in which D_3 receptor protein was found not only in the renal proximal tubule but also in the apical membrane of the distal convoluted tubule and cortical collecting duct (intercalated cells); D_3 receptor protein was also observed in glomeruli and renal blood Vessels. In mice, D_3 receptor protein, detected by immunocytochemistry, is mainly found in apical vesicles, subjacent to the microvillous brush borders of the S1 segment of the proximal convoluted tubule, the macula densa, cytoplasm of the thick ascending limb of loop of Henle, distal convoluted tubule, and glomeruli, but not in the collecting duct (238). All three studies are in agreement in the absence of specific staining in the medulla. O'Connell et al. (172) could not find D_3 receptors in juxtaglomerular cells but found them expressed in the macula densa of the rat Kidney. However, D_3 receptor mRNA and functional D_3 receptors have been described in rat juxtaglomerular cells in primary culture (207). The discrepancy between the findings in the Kidney in situ and juxtaglomerular cells in culture suggests that the expression of D_3 receptors is conditional (e.g., culture dependent). Two species of D_3 receptor (45 and 90 kDa) are expressed in renal brush-border membranes (127) and proximal tubule cells (264), as detected by immunoblot studies.

Blood Vessels—D_2-like receptors are located mainly in the intima and adventitia of blood Vessels. In the rat renal artery, the D_3 receptor is located at both prejunctional (adventitia) and post-/extrajunctional sites (tunica media) (27). In contrast, in the rat mesenteric artery, we found that the D_3 receptor is expressed in both the tunicae intima and media (270). Rat pulmonary arteries do not express D_3 receptors (196), and, therefore, it is possible that the localization of the D_3 receptor is blood vessel specific.

Physiology of the D_3 Receptor

Renal Function—The D_3 receptor agonists 7-OH-DPAT and PD-128907 (134), which have preferential selectivity for D_3 receptors over D_2 and D_4 receptors, decrease renal sodium transport (144). Acute intravenous administration of 7-OH-DPAT in salt-resistant Dahl rats increases the glomerular filtration rate and sodium and water excretion without affecting blood pressure (144). Quinerolane, a D_2-like receptor agonist with 21-fold selectivity for the D_3 receptor over the D_2 receptor, opens K^+ channels, resulting in hyperpolarization and inhibition of Na^+-K^+-ATPase activity (82). PD-128907, a selective D_3 receptor agonist with a 120-fold selectivity over the D_2 receptor, infused directly into the renal artery, dose dependently increases fractional sodium excretion in WKY rats (but not in

SHRs) fed a normal salt diet or high-salt diet (263). That D_3 receptors can mediate natriuresis is supported by the decreased ability of D_3 receptor-deficient mice to excrete an acute saline load (17). The renal effects of D_3 receptor activation are mediated by actions on postjunctional glomerular and tubular receptors and presynaptic modulation of norepinephrine release because renal denervation attenuates the effects of 7-OH-DPAT (155).

Arteries—Systemic administration of D_3 receptor agonists decreases systemic blood pressure (144, 146). The postjunctional D_3 receptor-mediated vasodilation is more manifest when renal vascular resistance is increased. Our studies in the isolated relaxed mesenteric artery have shown that two different D_3 receptor agonists, PD-128907 and 7-OH-DPAT, have no effects on basal vascular contractility (269, 270). However, when mesenteric artery rings are preconstricted by high-potassium or norepinephrine, both PD-128907 and 7-OH-DPAT induce vasorelaxation. In norepinephrine-preconstricted mesenteric artery rings, a calcium channel blocker increases the vasorelaxant effect of PD-128907, indicating that the vasorelaxant effect of the D_3 receptor is, in part, caused by a decrease in intracellular calcium. The vasodilatory effect of D_3 receptors may also involve small- and/or large-conductance calcium-activated potassium channels (50, 269), a mechanism that also occurs in renal tubules (82). The hyperpolarization caused by a decrease in intracellular potassium probably prevents the vasoconstriction that occurs with inhibition of Na^+-K^+-ATPase (82). As with the inhibitory effect of the D_3 receptor on sodium transport, the vasodilatory effect of the D_3 receptor is probably not related to its ability to inhibit adenylyl cyclase activity. Indeed, the D_3 receptor may not inhibit renal cAMP production because this action necessitates the presence of adenylyl cyclase V (199), which is not expressed in the Kidney (33). Thus, the D_3 receptor induces a natriuresis and vasodilation via mechanisms that are different from but complement the D_1 receptor, which induces a natriuresis and vasodilation by activation of $G\alpha_s$ and/or adenylyl cyclase activity.

D_3 Receptor-Mediated Antioxidative Effects—The effect of D_3 receptors on ROS is controversial. One report (67) has shown that the D_3 receptor stimulates PLD activity in human embryonic Kidney (HEK)-293 cells heterologously expressing the human D_3 receptor. However, the D_3 receptor has been reported to increase a dopamine autotrophic factor that has an antioxidant action, and, thus, the D_3 receptor may have an antioxidant effect, albeit indirectly (41). The D_3 receptor is expressed in the tunica intima (269, 270), and activation of the D_3 receptor inhibits superoxide production in human brain endothelium cells as measured by a cytochrome *c* reduction assay (Yang Z, Zeng C, and Jose PA; unpublished observations). The hypertension in D_3 receptor-null ($D_3^{-/-}$) mice is not associated with increased production of ROS, but this may be due to increased expression of D_5 receptors in these mice (unpublished data). As discussed above, the D_5 receptor exhibits significant antioxidant activity.

Interactions with the Renin-Rngiotensin System—$D_3^{-/-}$ mice have renin-dependent hypertension (17), and renal AT_1 receptor expression (266, 276) is higher in $D_3^{-/-}$ mice than in their wild-type ($D_3^{+/+}$) littermates, supporting the notion discussed earlier that the dopaminergic and renin-angiotensin systems interact to regulate renal function (46, 64, 99,

220, 266). Activation of the D_3 receptor decreases AT1 receptor expression in renal proximal tubule cells from normotensive rats (266). The D_3 receptor probably also inhibits renin release; plasma renin levels are elevated in $D_3^{-/-}$ mice (17). Because renal proximal tubule cells can generate angiotensin II (48), a D_3 receptor-mediated decrease in angiotensin II formation could also be responsible for the decrease in AT_1 receptor expression since angiotensin II has been reported to increase AT_1 receptor mRNA in rats (48). However, long-term infusion of angiotensin II in vivo in rats has no effect on AT_1 receptor expression in renal proximal tubules (89). Angiotensin II does not increase AT_1 receptor expression in immortalized renal proximal tubule cells from normotensive rats (264). Therefore, the D_3 receptor, independent of angiotensin II, can regulate AT_1 receptor expression.

D_3 Receptors and Hypertension

D_3 receptor deficiency may be important in the development of salt-sensitive hypertension. As discussed above, $D_3^{-/-}$ mice are hypertensive (17, 266, 276). Salt-resistant Dahl rats on a high-sodium diet and chronically treated with a highly selective D_3 receptor antagonist (BSF-135170) have increased blood pressure (146). D_3 Ser9Gly, heterologously expressed in CHO cells, has been reported to impair D_3 receptor-mediated inhibition of cAMP production but acquires the ability to decrease PGE2 production (91). However, there is no association of D_3 Ser9Gly, or other D_3 receptor gene variants, with hypertension (224), although the chromosome locus of the D_3 receptor gene (3q13.3) has been linked to human essential hypertension (108, 197).

Impaired Renal D_3 Receptor Function—Activation of D_3 receptors induces a natriuresis in salt-sensitive Dahl rats on a normal sodium diet but not in hypertensive salt-sensitive Dahl rats on a high-sodium diet. The diminished functional response in the hypertensive salt-sensitive Dahl rats rat is associated with a decreased [^{3}H]7-OH-DPAT binding to renal membrane protein (146). However, the same group (145) did not find a strain-dependent natriuretic effect of 7-OH-DAT in WKY rats and SHRs. The interpretation of this study is confounded by the systemic administration of 7-OH-DPAT; the activation of D3 receptors outside of the Kidney may have obfuscated any differential effect on sodium excretion between WKY rats and SHRs. To overcome any confounding systemic effects of administered ligands, we studied the renal effects of another selective D_3 receptor agonist, PD-128907, infused directly into the renal artery in WKY rats and SHRs fed a high-salt diet. PD-128907 dose dependently increases fractional sodium excretion in WKY rats. No such effect is noted in SHRs (263). The mechanisms causing the impaired D_3 receptor in the Kidney in hypertension are not completely known. The stimulatory effect of the D_3 receptor agonist PD-128907 on D_3 receptor expression is no longer evident in renal proximal tubule cells from SHRs (266). It is possible that mechanisms that impair D_1 receptor function in SHRs also impair D_3 receptor, e.g., increased GPCR-related kinase-4 (GRK4) activity (208) or the impaired synergistic interaction between D_1 and D_3 receptors occurs because of an impaired D_1 receptor function, per se. The impaired natriuretic function of D_3 receptors in SHRs may, in part, be related to the aberrant D_3 and AT_1 receptor interaction in renal proximal tubule cells (266). The D_3 receptor decreases AT_1 receptor expression in renal proximal tubule cells from WKY rats, whereas D_3 receptor stimulation increases AT_1 receptor expression in SHRs (266).

Impaired Arterial D_3 Receptor Function—In isolated mesenteric arterial rings, D_3 agonist-induced vasorelaxation is similar in WKY rats and SHRs except at very high concentrations; this effect is via the D_3 receptor, because it can be blocked by the D_3 receptor antagonist U99194A. There is an additive vasodilatory effect between D_1 and D_3 receptors in WKY rats, which is lost in SHRs (269, 270).

D_1/D_3 Receptor Interactions—D_1 and D_3 receptors have been shown to colocalize inside and outside the central nervous system (198, 272, 279). In the central nervous system, these receptors are coexpressed in the same neurons, particularly in the nucleus accumbens and caudate-putamen, and elicit opposite effects on target gene expression by regulating ERK activation and *c-fos* induction (279). $D_3^{-/-}$ mice have blunted dorsal striatal and extrastriatal *c-fos* responses to D_1 receptor stimulation, indicating cooperativity between these receptors in the modulation of *c-fos* responses (116). Moreover, in neocortical neurons, constitutive inactivation of D_3 receptors leads to a decrease in agonist-promoted D_1 receptor activity (216). In neurons of the island of Calleja, basal *c-fos* expression is maintained by endogenous dopamine acting tonically on D_1 and D_3 receptors, subserving opposite effects on the same cell while having a synergistic effect in the nucleus accumbens (198). These indicate that the two receptor subtypes may affect cells in synergy or in opposition depending on the cell type or signal generated.

In denuded preconstricted mesenteric rings, D_1 receptor stimulation augments the vasodilatory effects of D_3 agonists (270). In the same way, D_3 receptor stimulation augments the vasodilatory effects of the D_1-like agonist fenoldopam (269), supporting a role of cooperative D_1/D_3 interaction in the regulation of blood pressure.

Stimulation of D_1 receptors increases D_3 receptor expression in the medulloblastoma TE671 cell line (133), embryonic thoracic aortic smooth muscle cells (A10) (270), human coronary artery VSMCs, and immortalized renal proximal tubular cells from normotensive WKY rats (269). Conversely, in renal proximal tubular cells from WKY rats, stimulation of D_3 receptors increases D_1 receptor protein expression (269, 275).

D_1 and D_3 receptors coimmunoprecipitate in VSMCs (270) and renal proximal tubular cells from WKY rats (269). The coimmunoprecipitation is increased in renal proximal tubular cells from WKY rats after long-term treatment with the D_1-like agonist fenoldopam (269) as well as after treatment with the D_3 agonist PD-128907. These effects are probably mediated by increased receptor protein expression (272) and indicate a physical interaction between D_1 and D_3 receptors. Furthermore, in renal proximal tubular cells from WKY rats, treatment with a D_3 agonist rapidly and transiently increases the amount of D_1 receptors at the cell surface membrane (272). D_1 receptors can be recruited to the cell surface membrane from the cytosol within minutes after D_1 receptor stimulation (38). The mechanisms for the synergism between D_3 and D_1 receptors may be time related. The D_3 receptor-mediated increase in cell surface membrane expression of D_1 receptors occurs in the short term, whereas the D_3 receptor-mediated increase in total D_1 receptor expression is a long-term effect (272).

The D_1/D_3 receptor interaction is impaired in SHRs. Preconstricted mesenteric artery rings are less sensitive to the vasorelaxant effects of fenoldopam in SHRs than in WKY rats. Pretreatment with the D_3 agonist PD-128907 does not produce any additional vasorelaxant effect in SHR rings as it does in WKY rings (269). There is a lack of responsiveness of SHRs to infusion of the preferential D_2-like agonist Z-1046. SHRs, unlike WKY rats, do not react to the infusion of Z-1046 by increasing glomerular filtration and water and sodium excretion (127). In renal proximal tubular cells from SHRs, the D_1-like agonist fenoldopam decreases rather than increases the expression of D_3 receptor protein, and the D_1-like agonist does not increase the coimmunoprecipitation of D_3 and D_1 receptors (269). Similarly, treatment with a D_3 agonist does not increase the expression of D_1 receptors in renal proximal tubular cells from SHRs and does not affect the coimmunoprecipitation of the two receptors (272). Furthermore, the basal level of cell surface membrane expression of D_1 receptors in renal proximal tubular cells is lower in SHRs than in WKY rats and is decreased further after treatment with a D_3 agonist (272). Taken together, these data indicate that the interaction between D_1 and D_3 receptors is absent or lessened in hypertension, and results in defective inhibition of sodium transport and relaxation of vascular smooth muscles and ultimately in the development and/or maintenance of high blood pressure.

D_3 Receptor Mutant Mice

$D_3^{-/-}$ mice were generated by targeted mutagenesis. The targeting construct contained 7 kb of 129/sv-derived D_3 receptor genomic sequence in the GKNeo cassette in the antisense orientation at the *Sal*I site in exon 2 (2). Homologous recombination resulted in a mutant allele in which sequences downstream of Arg^{148} in the second intracellular loop of the D_3 receptor were replaced by sequences derived from the Neo gene. Despite the similarity of the primary peptide sequences of the three members of the D_2-like receptors, the locomotor phenotype of D_3 mutants does not resemble that of D_2 mutants. $D_3^{-/-}$ mice develop normally, are fertile, and, at most, show a transient and rapidly habituating locomotor hyperactivity in a novel environment. Heterozygous and homozygous D_3 mutant mice on a mixed C57/BL6 and B129 background (17) as well as those in a congenic C57BL/6 background (238) have higher systolic and diastolic blood pressures than their wild-type ($D_3^{+/+}$) littermates. In a report by Staudacher et al. (225), $D_3^{-/-}$ mice, also in a congenic C57BL/6 background, have blood pressures similar to their $D_3^{+/+}$ littermate on a low, normal, or high salt intake. This report has to be interpreted with caution because C57BL/6 mice fed a high-salt diet may or may not have increased blood pressure depending on the source of these mice. Thus, C57BL/6 mice from Jackson Laboratories develop hypertension when fed a high-salt diet (226), whereas those from Taconic (253) do not. Nevertheless, these two strains of $D_3^{-/-}$ mice cannot increase sodium excretion after an acute or a chronic salt load (17, 225). In our study (17), renal renin activity and AT_1 receptor expression are greater in homozygous mice than in wild-type mice; values for heterozygous mice are intermediate. Blockade of AT_1 receptors decreases systolic blood pressure for a longer duration in mutant mice than in wild-type mice. Thus, disruption of the D_3 receptor increases renal renin production and produces renal sodium retention and renin-dependent hypertension (17).

D_3 Receptors and Blood Pressure Regulation Summary

D_3 receptors may regulate blood pressure directly by inhibition of renal sodium transport or indirectly by interaction with D_1 receptors or by inhibition of renin secretion and AT_1 receptor expression. These effects are impaired in hypertensive states.

D_4 Receptors

Localization of the D_4 Receptor Subtype

The Kidney—D_4 receptor mRNA is expressed in the Kidney (151), especially in the cortical and medullary collecting ducts (227). D_4 receptor mRNA has also been reported in rat juxtaglomerular cells in culture (207). D_4 receptor protein expression is highest in the cortical and medullary collecting ducts (227) (luminal > basolateral), followed by the proximal tubule (S1 > S2 > S3; unpublished data) and distal convoluted tubule (195). D_4 receptors are not expressed in the glomerulus or loop of Henle (Table 1).

Blood Vessels—The D_4 receptor is expressed in human aortic and umbilical endothelial cells and modulates von Willebrand factor secretion (262). D_4 receptor protein has been reported to be expressed in the adventitia and adventitia-media border of pulmonary (196) as well as pial and mesenteric arteries (8). D_4 receptors may be expressed pre- and postjunctionally (8). In the renal artery, D_4 receptor protein is observed perivascularly in the adventitia and adventitia-media border, especially in the afferent and efferent arterioles. D_4 receptor immunostaining disappears in the blood vessel (but not in the tubule) after renal denervation, indicating that vascular D_4 receptors are prejunctional, whereas tubular D_4 receptors are postjunctional (195). D_4 receptors are expressed in the atria but not ventricles of rats and humans (193). In contrast, the right and left ventricles of the guinea pig express D_4 receptors. The D_4 receptor agonist PD-168077 exerts a negative chronotropic and inotropic effect associated with a decrease in cAMP production in the isolated guinea pig heart preparation (83). However, D_4 receptors normally have minimal effects on the rat cardiovascular system (184).

Physiology of the D_4 Receptor

Renal Function—D_4 receptors antagonize vasopressin- and aldosterone-dependent water and sodium reabsorption in the cortical collecting duct (137, 202). In the rabbit cortical collecting duct, the D_4 receptor-mediated decrease in sodium transport is exerted mainly at the basolateral membrane despite a greater expression of D_4 receptors in luminal membranes (202). However, renal cortical and medullary Na^+-K^+-ATPase activities are similar in D_4 receptor-null ($D_4^{-/-}$) and control ($D_4^{+/+}$) mice. $D_4^{-/-}$ mice also do not have an impaired ability to excrete an acute saline load. It is possible that high blood pressure in $D_4^{-/-}$ mice, which elicits a pressure natriuresis, obfuscates any deficit in the renal handling of sodium in $D_4^{-/-}$ mice (32).

D_4 Receptors and Ros—D_4 receptors may not have inhibitory effects on the production of ROS (28).

D_4 Receptors and Hypertension

A locus near the D_4 receptor gene (11p15.5) has been linked to hypertension. The most intensively studied D_4 receptor polymorphism is a 48-bp repeat located in exon 3 of the D_4 receptor gene. This variant codes for a 16-amino acid sequence located in the third intracellular loop of D_4 receptor protein, a region that is thought to interact with G proteins and influence intracellular levels of cAMP (236). The number of repeats at the D_4 site varies from 2 to 10, but in Caucasian subjects the 4- and 7-repeat lengths are the most common. In this population, the long variant of the D_4 gene is associated with a 3.0-mmHg higher systolic blood pressure and 2.0-mmHg higher diastolic blood pressure (219).

D_4 receptor protein is increased in the renal cortex of SHRs relative to WKY rats, but D_4 protein in the inner medulla is similar in those two rat strains (221). The effects of D_4 agonists and antagonists on cardiovascular and renal function in genetically hypertensive rats have not been reported.

D_4 Receptor Mutant Mice

A 129SvEv mouse genomic library was screened with a human D4.4 receptor probe. Positive phages were mapped and partially sequenced. The CsCl banded targeting vector was linearized (NotI),electroporated into ~2 × 107 129/Ola Hsd E14TG2A embryonic stem cells, and maintained under double selection. The original F2 hybrid strain (129/Sv × C57BL/6) carrying a mutant form of the dopamine D_4 receptor was backcrossed to C57BL/6J mice. We have reported that in conscious or pentobarbital-anesthetized mice, systolic and diastolic blood pressures are elevated in $D_4^{-/-}$ mice compared with $D_4^{+/+}$ littermates. Juxtaglomerular cells in culture also express D_4 receptors (207), but $D_4^{-/-}$ mice do not have altered circulating or renal renin levels (32). The protein expression of the AT1 receptor is increased in homogenates of the Kidney and brain of $D_4^{-/-}$ mice relative to $D_4^{+/+}$ mice, although AT1 receptor expression in the heart is similar in the two strains. Bolus intravenous injection of the AT1 receptor antagonist losartan initially decreases mean arterial pressure to a similar degree in $D_4^{-/-}$ and $D_4^{+/+}$ littermates. However, the hypotensive effect of losartan dissipates after 10 min in $D_4^{+/+}$ mice, whereas the effect persists for >45 min in $D_4^{-/-}$ mice. The absence of the D4 receptor increases blood pressure, possibly via increased AT1 receptor expression (32).

D_4 Receptors and Blood Pressure Regulation Summary

D_4 receptors may serve to antagonize vasopressin and aldosterone effects during conditions of normal salt intake. A role of D_4 receptors in cardiovascular and renal physiology remains to be determined. However, disruption of the D_4 receptor results in increased blood pressure that may be related to the activation of AT_1 receptors in the brain. D_4 receptors may negatively regulate the expression of AT_1 receptors involved in the central regulation of blood pressure. However, areas in the brain where D_4 receptors interact with AT_1 receptors remain to be described. AT1 receptors are also increased in the Kidneys of $D_4^{-/-}$ mice, but these mice do not have an impaired ability to excrete an acute sodium load. It is possible that $D_4^{-/-}$ mice may not be able to excrete a chronic sodium load, but that remains to be determined.

D_5 Receptors

The D_5 receptor has generated significant interest because of its relatively high affinity for dopamine compared with the other dopamine receptors (229). Moreover, the D_5 receptor can be activated in the absence or presence of low concentrations of endogenous agonist. The physiological role of the D_5 receptor in the regulation of renal and cardiovascular function has been difficult to determine with certainty. This is due, in large part, to the fact that the D_1 and D_5 receptors are pharmacologically indistinguishable. As mentioned above, the lack of selective ligands has made it virtually impossible to selectively activate or block D_1 or D_5 receptors in vivo. Genetic approaches to this problem have been employed by investigators who used gene silencing techniques to inhibit D_1 or D_5 receptor expression and generate D_1 or D_5 receptor-deficient mice (5, 58, 93, 95, 223).

Localization of the D_5 Receptor Subtype

The Kidney—In rats and mice, the D_5 receptor is expressed in the proximal (S3 > S1 = S2) (unpublished observations) and distal convoluted tubules, cortical collecting duct, medullary ascending limb of Henle, and arterioles, but not in the glomeruli, juxtaglomerular cells, or macula densa (7, 9, 252, 254, 255, 280) (Table 1). The thick ascending limb of Henle and cortical collecting duct may also preferentially express the D_5 receptor over the D_1 receptor (7, 255). The opossum Kidney also expresses the D_5 receptor, but its expression is lost in an opossum Kidney cell line (160). Immortalized rat and human proximal tubule cells express D_5 receptors; the molecular sizes are similar to those described for the D_1 receptor (259, 274).

Blood Vessels—The D_5 receptor is expressed in VSMCs outside the Kidney, e.g., the coronary artery (7, 162). The vascular distribution of the D_1 receptor is similar to the D5 receptor. As with the D_1 receptor, the D_5 receptor is expressed in pulmonary, mesenteric, and pial arteries (8, 192). In the pulmonary artery, D_5 receptor immunostaining has been reported in the tunica intima and media of extrapulmonary branches and tunica media of large-sized (but not medium or small sized) intrapulmonary branches, similar to those described for the D_1 receptor (196).

Physiology of the D_5 Receptor

Renal Function—As indicated above, D_1-like receptors induce a diuresis and natriuresis in WKY rats (104, 268). Due to the lack of selective D_1 and D_5 receptor agonists or antagonists, the relative contribution of D_1 and D_5 receptors to the natriuretic effect caused by D_1-like receptor stimulation is not known. We have presumed that both D_1 and D_5 receptors are involved because both receptors increase cAMP production and cAMP mediates the D_1-like receptor-mediated inhibition of ion transport (206). As indicated earlier, the D_1 receptor increases cAMP production to a greater extent than the D_5 receptor in renal proximal tubule cells (206); therefore, it is possible that the natriuretic effect of dopamine is mainly due to the D_1 receptor. As also indicated above, the effect of a high-salt diet on blood pressure in $D_1^{-/-}$ mice has not been determined. However, in D_5 receptor-null ($D_5^{-/-}$) mice, a high-salt diet further increases blood pressure, suggesting that the renal D_5 receptor plays an important role in the control of blood pressure by regulating renal salt

transport (see below). However, the nephron segments in which the D_5 receptor regulates ion transport remain to be determined. Because D_5 receptor expression may be greater than D_1 receptor expression in distal nephron segments (255), the D_1-like receptor regulating sodium excretion in those nephron segments may be the D_5 receptor.

D_5 Receptor-Mediated Antioxidative Effects—Dopamine has contrasting, concentration-dependent effects on ROS production. High concentrations of dopamine and D1-like receptors agonists (2–300 μM) increase the generation of ROS (36, 147, 173, 237, 242). Excessive stimulation of D_2-like receptors (e.g., D_2 and D_3) can also increase ROS production (246). However, D_1-like and D_2-like receptors act as antioxidants at physiologically relevant concentrations of dopamine and low concentrations of their respective agonists (51, 105, 204). It should also be noted that renal tubules do not normally synthesize dopamine at the high concentrations shown to induce oxidative stress (240).

Low concentrations of dopamine, acting on D_1 and D_5 receptors, decrease ROS in human lymphocytes (51), brain cortical cells (166), and renal VSMCs (258). Increased oxidative stress enhances vascular VSMC contractility and proliferation (190). The activation of both D_1 and D_5 receptors inhibits oxidative stress in VSMCs stimulated by PDGF-BB (258). We have reported that the D_5 receptor inhibits the production of ROS by inhibition of PLD and NADPH oxidase expression and activity in HEK-293 cells heterologously expressing the human D_5 receptor (252, 253). NADPH oxidase protein expression and activity in the Kidney and brain are higher in $D_5^{-/-}$ mice than in control ($D_5^{+/+}$) mice. Apocynin, a drug that impairs the assembly and activity of NADPH oxidase subunits, normalizes blood pressure and NADPH oxidase activity and subunit expression in $D_5^{-/-}$ mice. In addition, the D_5 receptor increases the expression and activity of antioxidant enzymes. For example, in the same HEK-293 cells heterologously expressing the human D_5 receptor, D_5 receptor stimulation increases the activity and expression of heme oxygenase-1. Heme oxygenase-1 protein expression and activity in the Kidney are lower in $D_5^{-/-}$mice than in $D_5^{+/+}$ mice. Furthermore, hemin, a heme oxygenase inducer, normalizes blood pressure and renal heme oxygenase activity in $D_5^{-/-}$ mice (143). Thus, the ability of the D_5 receptor to decrease ROS production may explain, in part, its antihypertensive action.

D_5 Receptors and Proliferation of VSMC—Proliferation of VSMCs is believed to play a key role in hypertension. Vasodilator hormones such as natriuretic peptides and β-adrenergic receptor agonists have been shown to act as antigrowth factors (1, 157). As aforementioned, D_1-like receptors have also been shown to inhibit the proliferative effect of some hormones, such as PDGF-BB (258). This inhibition is reversed by a D_1-like receptor antagonist and by D_1 or D_5 receptor antisense oligonucleotides, indicating that both D_1 and D_5 receptors have an antiproliferative effect in VSMCs. Vascular D_1-like receptor agonists inhibit the proliferation of VSMCs, possibly through PKA activation and suppression of PLD, PKC, and MAPK activity (257). Inhibition of PLD and PKC is probably mediated by the D5 receptor (102, 243, 252). D_1 receptors can stimulate PLC (69) and, therefore, PKC activity (63, 88, 101, 118, 167, 212, 256, 257), which can in turn increase D_1 receptor function. In contrast, D_5 receptors inhibit PKC activation (243); PKC can also inhibit D_5 function (107).

D_5 Receptors and Hypertension

D_5 receptor gene locus (chromosome 4p15.1–16.1) is linked to essential hypertension (6); the human D_5 receptor gene has polymorphisms that code for receptors with abnormal coupling to adenylyl cyclase (52).

D_5 Receptor Mutant Mice

$D_5^{-/-}$ mice were generated by injecting into C57BL/6 mouse blastocysts 129/SV embryonic stem cells containing the targeting construct generated by ligating the neomycin resistance gene in reverse orientation at the unique *Sfi*I site in the second intracellular loop of the D_5 receptor. $D_5^{-/-}$ mice are viable and develop normally (93, 94). Disruption of the D_5 receptor gene is not associated with an altered expression of the other dopamine receptors, including the D_1 receptor (93, 94).

Hollon et al. (93) reported that $D_5^{-/-}$ mice (>F6) are hypertensive, with an elevated epinephrine-to-norepinephrine ratio and a greater reduction in mean arterial pressure after adrenalectomy or treatment with an α-adrenergic blocker compared with $D_5^{+/+}$ mice. This study indicates that the hypertension is caused by increased sympathetic activity. However, because the percentage decrease in systolic blood pressure after adrenalectomy is similar in both $D_5^{-/-}$ and $D5^{+/+}$ mice, the hypertension in $D5^{-/-}$ mice is ascribed to central nervous system mechanisms (93, 273).

D_5 receptors, present in the prefrontal cortex, project to several brain areas involved with cardiovascular regulation. Sympathetic responses from the prefrontal cortex, transmitted to the lateral hypothalamic area, stimulate non-NMDA glutamate receptors in the ventrolateral medulla (41, 150, 278). A centrally, but not peripherally, acting non-NMDA glutamatergic antagonist decreases blood pressure in $D_5^{-/-}$ mice, suggesting that the increased blood pressure in $D_5^{-/-}$ mice may be caused by the activation of a sympathetic/non-NMDA glutamatergic axis (93). V_1 vasopressin and oxytocin antagonists that cross the blood-brain barrier also decrease blood pressure in $D_5^{-/-}$ mice but not in $D_5^{+/+}$ mice. Interestingly, the hypotensive effect of the oxytocin antagonist occurs only 24 h after its administration and negates any further reduction in blood pressure by vasopressin or glutamatergic blockade. These results are consistent with the observation that oxytocin sensitizes V_1 vasopressin receptors and further suggest that the decrease in blood pressure in $D_5^{-/-}$ mice engendered by these various antagonists occurs via a central nervous system pathway involving glutaminergic, oxytocin, vasopressin, and adrenergic receptors (Fig. 1) (93, 273).

The acute responses to GPCR-blocking agents are contrasted to the chronic regulation of blood pressure by the D_5 receptor. Long-term (5–7 days) blockade of AT_1 receptors decreases blood pressure in $D_5^{-/-}$ mice but not in $D_5^{+/+}$ mice (136). This finding is in agreement with our observations of a counterregulatory interaction between D_5 and AT_1 receptors (274). The activation of D_1-like receptors inhibits AT_1 receptor expression (274); indirect evidence suggests that the D_5 receptor may be involved in the inhibitory effects of a D_1-like receptor agonist on the AT_1 receptor (267). This is consistent with our finding in human renal proximal tubule cells showing that the D_5 receptor but not the D_1 receptor decreases AT_1 receptor expression (74). The ability of the D_5 receptor to negatively regulate

AT_1 receptor expression may have a significant impact on the regulation of blood pressure. Indeed, renal D_5 receptor protein is increased in AT_{1A}-deficient mice relative to their wild-type littermates (274). This effect is reciprocal: the activation of the AT_1 receptor in renal proximal tubule cells also inhibits D_5 receptor protein expression; in $D_5^{-/-}$ mice, AT_1 receptor expression in the renal cortical membrane is increased relative to wild-type littermates (274). Additional preliminary studies have shown that D_5 receptors increase the degradation of AT_1 receptors (74, 136). Because the D_1 receptor may also regulate the function of the AT_1 receptor by direct D_1 and AT_1 receptor interaction (267), an impaired regulation of AT_1 receptors by both D_1 and D_5 receptors may be one of the mechanisms involved in the increased AT_1 receptor function in SHRs.

D_5 Receptors and Blood Pressure Regulation Summary

D_5 receptors, being constitutively active, may play a greater role than D_1 receptors in the basal regulation of blood pressure. The D_5 receptor may acutely regulate blood pressure by inhibition of the central adrenergic nervous system, via the NMDAoxytocin-V_1 receptor-adrenergic axis (Fig. 1). Long-term regulation of blood pressure may involve sodium transport and AT_1 receptors and ROS; $D_5^{-/-}$ mice are salt sensitive. Because D_5 receptors are more numerous than D_1 receptors in more distal nephron segments, the D_5 receptor-mediated regulation of sodium transport may be exerted in the distal nephron.

Overall Summary

Dopamine regulates blood pressure by renal and nonrenal mechanisms, some of which are specific to the five dopamine receptor subtypes (104, 268). All dopamine receptor subtypes participate in the regulation of sodium balance, individually and by interacting with each other to increase sodium excretion under conditions of moderate sodium balance. All dopamine receptors, except the D_4 receptor, have antioxidant functions. A deficiency in dopamine production and/or a dysfunction in dopamine receptors contribute to various forms of hypertension in both humans and animal models.

$D_1^{-/-}$ mice have greater systolic, diastolic, and mean arterial pressure and do not increase cAMP production in response to D_1-like receptor agonist stimulation (5). $D_5^{-/-}$ mice develop hypertension via increased central sympathetic activity through activation of glutaminergic, oxytocin, vasopressin, and adrenergic receptors (93). Besides these central nervous system mechanisms, renal AT_1 receptors and ROS are also involved (252, 253, 265, 274).

$D_4^{-/-}$ mice have increased blood pressure, in part by increased AT_1 receptor activity in the brain and Kidney (32). The increased blood pressure of $D_2^{-/-}$ mice seems to be related to impaired renal dopamine production, impaired ability to excrete a chronic salt load, increased sympathetic activity, and increased ET_B receptor expression in VSMCs (138, 179, 235). The increased blood pressure in $D_3^{-/-}$ mice may be related to the activation of the renin-angiotensin-aldosterone system and a decreased ability to excrete a chronic sodium load (5, 225). Some discrepancies in the characteristics of different strains of $D_2^{-/-}$ and $D_3^{-/-}$ mice could be related to differences in genetic background. C57BL/6 mice may or

may not increase their blood pressures in response to sodium intake depending on their genetic background (226, 253).

Finally, it seems that under conditions of salt depletion, dopamine, via D_2 receptors, induces sodium retention, probably by stimulating sodium transport. In addition, the stimulatory effect of D_1 receptors on the renin-angiotensin system may become manifest. During states of moderate sodium excess, dopamine receptors, individually or by interacting with each other, increase sodium excretion (Fig. 2). The inhibitory effect of D_3 receptors also becomes manifest. Therefore, dopamine receptors may increase or decrease sodium transport to maintain sodium balance and blood pressure. Abnormalities in dopamine receptor subtypes, per se or caused by constitutively active variants of GRK4, result in hypertension. A major limitation of the studies in dopamine receptor subtype-null mice is the fact that the mutations are neither tissue specific nor inducible knockout mice. Studies in mice with inducible and tissue-specific deletion of dopamine receptor subtype genes are needed to decipher the exact role and mechanism(s) by which dopamine receptor subtypes regulate renal function and blood pressure.

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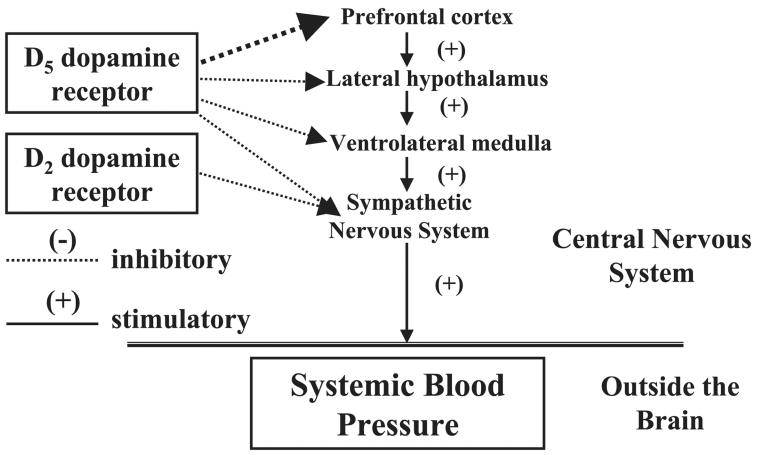

Fig. 1.

D_2 and D_5 receptors affect blood pressure by inhibition of the central sympathetic nervous system. D_5 receptors are present in the prefrontal cortex, which projects to several brain areas involved with cardiovascular regulation, including the lateral hypothalamic area and ventrolateral medulla. D_5 and D_2 receptors affect blood pressure by decreasing the central sympathetic nervous system, although the detailed mechanisms remain to be determined. The dotted lines indicate inhibitory effects, whereas the solid lines indicate stimulatory effects.

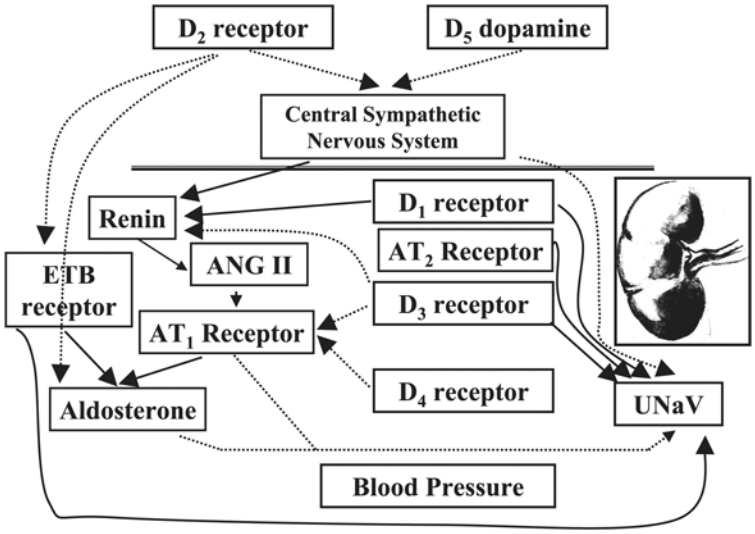

Fig. 2.

Dopamine receptors and cardiovascular function. Each of the dopamine receptor subtypes participates in the regulation of blood pressure by mechanisms specific for the subtype. The major dopamine receptor that regulates blood pressure may be the D_1 receptor, which synergies with the D_3 receptor to regulate sodium transport in the Kidney and intestines directly or indirectly by the inhibitory effect of D_1 and D_3 receptors on angiotensin II (ANG II) type 1 (AT_1) receptor expression and/or interactions during conditions of modest sodium excess. D_4 receptors help in this process. Furthermore, D_3 receptors can inhibit renin secretion; D_2 receptors aid in the excretion of sodium by decreasing aldosterone secretion and by inhibiting the vasconstrictor effect of endothelin type B (ET_B) receptors. D_2 and D_5 receptors negatively regulate the sympathetic nervous system. UNaV, urinary excretion of sodium.

Table 1

Expression of dopamine receptor subtypes

	PT	PCT	TAL	mTAL	DT	DCT	CCD	MCD	Glom	JGA	JGC	MD	RV	Species	References
								D_1 receptors							
mRNA Protein	+				+					+			$_{+}d$	Several	169, 248, 250
		+		+		+	+					+		Rat	9, 170
		+		+		+	+					+		Mouse	5
		+		+		+	+					+		Human	178
		$_{+}a$												Rat	Unpublished data
											+		+	Rat	9, 170, 250
													$_{+}e$	Human	178
								D_5 receptors							
mRNA Protein		$_{+}a$		+		+	+							Rat, mouse	Unpublished data
		+		+		+	+							Rat, mouse	7, 9, 252, 254, 255, 280
								D_3 receptors							
mRNA Protein	TF	TF	TF	TF	TF	TF	TF	TF	+				+	Rat	79
	+													Rat	168
	+					+	+		+			+	+	Rat	172
		$_{+}b$	+			+			+			+		Mouse	238
								D_4 receptors							
mRNA Protein							+	+						Rat	227
	+				+		+	+						Rat	195, 227
		$_{+}c$												Rat	Unpublished data
								D_2 receptors							
mRNA Protein	T	T	T	T	T	T	T	T						Rat	79
		+												Opossum	159

PT, proximal tubule; PCT, proximal convoluted tubule; TAL, thick ascending limb of loop of Henle; mTAL, medulla TAL; DT, distal tubule; DCT, distal convoluted tubule; CCD, cortical collecting duct; Glom, glomerulus; MCD, medullary collecting duct; JGA, juxtaglomerular apparatus; JGC, juxtaglomerular cell; MD, macula densa; RV, renal vasculature; TF, tubular fraction; T, tubules. Proximal tubular segments:

^{a}S3 > S1 = S2,

[b] S1 only, and

[c] S1 > S2 > S3;

[d] arterioles;

[e] large intrarenal arteries only.