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Dopamine and Renal Function and Blood Pressure Regulation

Ines Armando¹, Van Anthony M. Villar¹, and Pedro A. Jose^{*,1}

¹Children's National Medical Center—Center for Molecular Physiology Research, Washington, District of Columbia

Abstract

Dopamine is an important regulator of systemic blood pressure via multiple mechanisms. It affects fluid and electrolyte balance by its actions on renal hemodynamics and epithelial ion and water transport and by regulation of hormones and humoral agents. The kidney synthesizes dopamine from circulating or filtered L-DOPA independently from innervation. The major determinants of the renal tubular synthesis/release of dopamine are probably sodium intake and intracellular sodium. Dopamine exerts its actions via two families of cell surface receptors, D₁-like receptors comprising D₁R and D₅R, and D₂-like receptors comprising D₂R, D₃R, and D₄R, and by interactions with other G protein-coupled receptors. D₁-like receptors are linked to vasodilation, while the effect of D₂-like receptors on the vasculature is variable and probably dependent upon the state of nerve activity. Dopamine secreted into the tubular lumen acts mainly via D₁-like receptors in an autocrine/paracrine manner to regulate ion transport in the proximal and distal nephron. These effects are mediated mainly by tubular mechanisms and augmented by hemodynamic mechanisms. The natriuretic effect of D₁-like receptors is caused by inhibition of ion transport in the apical and basolateral membranes. D₂-like receptors participate in the inhibition of ion transport during conditions of euolemia and moderate volume expansion. Dopamine also controls ion transport and blood pressure by regulating the production of reactive oxygen species and the inflammatory response. Essential hypertension is associated with abnormalities in dopamine production, receptor number, and/or posttranslational modification.

Introduction

Dopamine is important in the regulation of water and electrolyte balance and blood pressure. This is achieved, in part, by regulation of the secretion/release of hormones and humoral agents that affect water and electrolyte balance. Dopamine can also regulate or modulate water and electrolyte intake via the “appetite” centers in the brain and ion and water transport in the kidney and gastrointestinal tract. Physiological concentrations of locally produced dopamine, acting in an autocrine or paracrine manner, inhibit ion transporter/channel/pump activity directly and indirectly by regulating their protein expression. The physiological effects of dopamine occur by occupation of its specific receptors, as well via direct physical or indirect interaction with other G protein-coupled receptors (GPCRs) (e.g., adenosine, angiotensin, endothelin, NMDA, and vasopressin receptors) and hormones/humoral agents (e.g., aldosterone, angiotensins, ANP, insulin, nitric oxide, prolactin, and

*Correspondence to pjose@cnmc.org.

urodilatin). In general, under normal conditions and when extracellular fluid volume is moderately expanded, dopamine impairs ion and water transport and facilitates their excretion. More than 60% of the increase in sodium excretion under normal conditions and especially with moderate but not with marked (173,247,341,569) sodium excess is due to dopamine produced in the kidney. However, under conditions of extracellular fluid volume deficit, dopamine may actually increase ion and water transport to maintain a normal extracellular fluid volume and blood pressure (7). Pharmacological concentrations of dopamine, such as those given intravenously to increase blood pressure, stimulate GPCRs (e.g., α and β adrenergic receptors) other than dopamine receptors.

Structure and Function of the Renal Dopaminergic System

Renal dopamine receptors

Renal dopamine receptor subtypes—In mammals, dopamine exerts its actions via two receptor families, the D₁-like and D₂-like receptors, which belong to the α group of the rhodopsin-like family of GPCRs (545). The D₁-like receptors, which include two subtypes in eutherian mammals [D₁ (D₁R) and D₅ (D₅R) in humans, also called D_{1A}R and D_{1B}R in rodents], a third D₁-like receptor in jawed mammals (D_{1A}, D_{1B}, D_{1C}) (314) and invertebrates (425) and a fourth subtype (D_{1D}) in archosaurs (314), stimulate adenylyl cyclases (266,564) D₁R, but not D₅R, couples to G_O (325). In contrast, D₅R, but not D₁R, couples to G_z and G $\alpha_{12/13}$ (565, 717). The D₁-like receptors are also linked to G α_q (169, 302, 368, 640). The linkage of G protein subunits to the specific D₁-like receptor may be tissue-specific (302). In fibroblasts, the D₁R can couple to G α_q and phospholipase C (699). The D₅R is also linked to phospholipase C activation in neural tissue (hippocampus, cortex, and striatum) (521) and phospholipase D inhibition in renal proximal tubule cells (684). In neural (striatal) cells, D₁R mediated stimulation of phospholipase C requires the presence of D₂R, while D₅R, by itself, can increase calcium mobilization that is inhibited by D₂R (572). However, in a pituitary adenoma rat cell line (GH4C1) transfected with the D₅R, the D₅R actually decreases inositol phosphate production (664).

The D₂-like receptors couple to G proteins G α_i and G_o, inhibit adenylyl cyclase and calcium channel activities, and modulate potassium channel activity (369, 403, 545, 662). There are two isoforms of D₂R; postsynaptic D₂R effects are mediated by the long isoform, D_{2L}R, while the presynaptic D₂R effects are mediated by the short isoform, D_{2S}R (95, 266, 627). D₂R can couple to the same extent to G_i and G_z (444) but not to G_{q11} or G $\alpha_{12/13}$ (390). The D_{2S}R, via Rho A, can couple to phospholipase D (553).

The linkage of the D₃R to G α_i is not robust, in contrast to that observed for D₂R and D₄R (511). The D₃R selectively inhibits adenylyl cyclase isoform V (511) but because this adenylyl cyclase isoform is not expressed in the renal proximal tubule (59), D₃R function in this nephron segment is not due to G α_i -mediated signaling. The D₃R also couples to G_z and, in the presence of pertussis toxin, the D₃R can also couple to G_s (444). The D₃R can also couple to G_{q11} (434) and G α_q in renal proximal tubule cells (471). The D₃R, via Rho, can also couple to phospholipase D (165). Robinson and Caron have suggested that the linkage of the D₃R to other effectors, such as inhibition of K⁺ and Ca²⁺ channels, may be more sensitive than its weak linkage to G proteins (511). There could be seven distinct

alternatively spliced D₃R variants. The full-length D₃R and a shorter receptor isoform, the D₃S, bind to dopamine. The five other alternatively spliced D₃R variants do not bind dopamine, but one of them, D₃Rnf, regulates receptor dimerization.

D₄Rs can also couple to G α_{i2} (678) and phospholipase C in neural cells (233, 464). Different numbers of 16-amino acid repeats in the third cytoplasmic loop cause several human D₄R isoforms (e.g., D4-2, D4-4, and D4-7) (110). The role of these D₄R isoforms remains to be determined. However, the D₄R long (at least one 7–10 repeat) has been reported to be associated with higher diastolic and systolic blood pressure (552).

As stated above, the D₂R and D₅R heterodimer stimulates phospholipase C. Also as stated above, the D₂S₅R can stimulate phospholipase D (553), but the latter enzyme is inhibited by D₅R (684). These effects need not be counter-regulatory because as aforementioned, the D₂S₅R is presynaptic, while the D₅R inhibition of phospholipase D is postsynaptic in renal proximal tubule cells, in particular. In addition, presynaptic inhibition of adrenergic neurotransmitters by D₂S₅R facilitates the inhibitory effects of dopamine on ion transport.

D₁-like and D₂-like receptors can also activate MAP kinase (112, 126, 234, 235, 382, 383, 428, 441, 681); the linkage of D₂ receptors (D₂S₅R and D₂L₁R) is via G $\beta\gamma$ (112). The D₄R is linked to SH3 (454) and AKT/Src/SHC/Ras/ERK pathway. The D₂R-mediated NF κ B activation requires G $\beta\gamma$ and c-Src, and possibly involves β -arrestin 1 (683). The D₂L₁R may be linked also to Ras, ERK, and SAP/JNK pathways in rat C6-D2L glioma cells (382). These studies need to be reconciled with reports that D₁R is also linked to MAP kinase via G α_s , although this involves p38 rather than the p44/42 pathway that is linked to D₂R (428,429). D₃R promotes mitogenesis or cell proliferation through the activation of MAP kinases (126) that is mediated by G α_i /G α_o , phosphatidylinositol-3-kinase (PI3 kinase), atypical PKC, and other signaling components like MEK, Ras and Raf-1, but not by PLC, β -arrestin, or receptor sequestration (112). G $\beta\gamma$ was reported to be involved in D₃R-mediated MAP kinase activation in HEK293 cells (64). However, the activation of this receptor does not result in a surfeit of G $\beta\gamma$ subunits in these cells (658), suggesting that this may not be the major pathway by which D₃R promotes cell proliferation. Stimulation with the highly selective D₃R agonist PD128907 increased the phosphorylation of p44/42 MAP kinases and their downstream target p90RSK in human renal proximal tubule cells (634). Dopamine, which targets all of the dopamine receptor subtypes, increases the phosphorylation of the p44/42 MAP kinases in renal proximal tubule cells (244). Aberrant D₁R activation of ERK1/2/MAP kinase has been reported in D₁R supersensitivity (194).

Renal distribution of dopamine receptors—All of the dopamine receptor subtypes are expressed in renal tubules and vasculature (Fig. 1). However, dopamine receptors are not evenly distributed along the mammalian nephron; the dopamine receptor subtype expressed in the thin limb of Henle is not known, although dopamine stimulates prostaglandin E₂ production in rat thin ascending limb cells (231). In human and rodent kidney, D₁R immunostaining is found in the apical and basolateral membrane of the proximal and distal convoluted tubules, medullary thick ascending limb of Henle (mTAL), macula densa, and cortical collecting duct, but not in the glomerulus (15, 315, 452, 465, 609, 646). D₁ receptor immunostaining is greater in the S3 than the S1 or S2 segment of the rat proximal tubules

(unpublished observations, 2007). The expression of D₁R in the juxtaglomerular cell has been reported in the rat but not in the human or mouse kidney (15,465,646,680). D₁R protein is also present in the large intrarenal arteries in humans (465), but not in renal veins. D₁R is probably not expressed in the medullary collecting duct.

In the rat, D_{2L}R mRNA is expressed in the cortex, outer medulla, inner medulla, glomeruli, and intrarenal vascular tissues (190). D₂R receptor immunostaining is found in rat cortical proximal and distal convoluted tubules, collecting duct and glomerular mesangial cells (563); a similar pattern is seen in the mouse kidney. However, the rat D₂R is expressed in the intercalated cells of the medullary collecting duct (563). D₂R protein is also expressed in OK cell, an opossum proximal tubule cell line that also exhibits distal tubular cell characteristics (429). D₂R expression in the human kidney has not been reported.

In the rat, D₃R mRNA, as with D_{2L}R, is expressed in the cortex, outer medulla, inner medulla, glomeruli, and intrarenal vascular tissues (190). In rat renal proximal tubules, D₃R protein is located in the apical and subapical areas but not in the basolateral membrane (440). One of three reports found D₃R immunostaining in the cortical collecting and medullary collecting ducts of the rat (440,447,563). In the mouse, D₃R in the proximal convoluted tubule is mainly observed in the S1 segment. The staining is also found in thick ascending limb of Henle, macula densa, distal convoluted tubule, and the glomerulus, but not in the medullary collecting duct (643).

In the rat, D₄R immunostaining is present in the S1 segment of the proximal tubule, the distal convoluted tubule (506), and especially in the cortical and medullary collecting ducts, where it is more abundant in at the luminal side than at the basolateral area. D₄R staining is weak in the glomerulus (563). D₄R mRNA is expressed in the human kidney (398). The D₄R is expressed in both intercalated and principal cells of cortical and medullary collecting ducts (600).

In the rat, D₅R immunostaining is present in the proximal and distal convoluted tubules, and arteriole, but not in the juxtaglomerular cell, glomerulus, or macula densa (15, 684, 687, 688, 717). D₅R immunostaining is also present in the outer medullary collecting duct in the mouse (645). D₅R protein is also expressed in human renal proximal tubule cells in culture (363) and D₅R may be expressed preferentially over the D₁R in the thick ascending limb of Henle and the cortical collecting duct, while the D₁R is preferentially expressed in the proximal tubule (15, 688). Nevertheless, the D₅R, as with the D₁R, is also expressed in the brush border membrane of the proximal tubules (711).

Renal dopamine production

Independent of innervation, the kidney synthesizes dopamine that is not metabolized to norepinephrine. Sodium intake and intracellular sodium are probably the major determinants of the renal tubular synthesis/release of dopamine (11, 86, 103, 399, 486, 566). The stimulatory effect of increased dietary sodium on renal dopamine production is impaired in some hypertensive humans (128,129,586).

Dopamine in the urine has several potential sources. Although plasma dopamine is freely filtered through the glomerulus, the concentration of free dopamine in the plasma is usually too low (below 1 nmol/liter) (127, 495) to account for any significant contribution to urinary dopamine, which is in the micromolar range (40,212,352,654). Levels of conjugated dopamine in the plasma are several-fold higher than those of free dopamine (333, 495). However, there has been no experimental proof that conjugated dopamine is deconjugated in the kidney and can account for the free dopamine in the urine (626). Dopaminergic nerves in the kidney (60, 139) contribute less than 30% of renal dopamine production (3, 8, 40, 67, 258, 414, 594, 654). Renal denervation does not prevent the dopaminergic-mediated increase in sodium excretion associated with saline volume expansion (31,307).

The major source of renal dopamine is derived from the decarboxylation of L-3, 4-dihydroxyphenylalanine (L-DOPA) from the plasma (41,77,228,603,672,721). L-DOPA is taken up by renal tubules from either the circulation or the glomerular filtrate and is converted to dopamine by aromatic amino acid decarboxylase (AADC) (37, 38, 556, 603, 641). This occurs mainly in the proximal tubules since AADC activity is highest in this nephron segment, although AADC is also present in distal nephron segments (217, 252). AADC activity decreases progressively along the nephron; 75% of renal AADC is present in the cortex and 25% in the medulla (252,580). Dopamine production from L-DOPA could not be detected in highly purified glomeruli isolated without tubular or arteriolar contamination (38). However, patients with AADC deficiency have normal or increased levels of urinary dopamine that may be explained in part by tyramine hydroxylation by renal CYP2D6 (655).

A number of factors affect renal dopamine production, including L-DOPA availability, L-DOPA uptake into renal tubule cells, AADC activity, dopamine metabolism, and sodium intake.

L-DOPA availability—Although it was a concept that was contentious for a while (159, 355), it is now accepted that the major fraction of L-DOPA in the plasma derives from sympathetically innervated tissues and reflects catecholamine turnover (155, 162, 213, 216, 228). In humans, arterio-venous increments of plasma L-DOPA concentrations occur in the arm, leg, head, heart, adrenal gland, and gut indicating regional release of DOPA into the bloodstream (211). Sympathetic nervous system stimulation by short-term exercise (137) or handling and immobilization of rats (339, 340) increases plasma L-DOPA levels very rapidly. Conversely, chemical destruction of sympathetic nerve terminals eliminates regional arterio-venous increments in plasma L-DOPA levels in the hindlimb, gut, and kidneys in laboratory animals (228). Inhibition of tyrosine hydroxylase with α -methylparatyrosine decreases arterial levels of L-DOPA within 1 h and blunts the increase in L-DOPA elicited by immobilization (340), indicating that tyrosine hydroxylation contributes largely to plasma L-DOPA. Treatment with a ganglionic blocker also decreases both the baseline plasma L-DOPA levels and the immobilization-induced increase in plasma L-DOPA, indicating dependence of L-DOPA responses on increased ganglionic transmission (340). Patients with sympathectomized limbs have reduced regional arterio-venous increments in L-DOPA levels (211) and those with diseases associated with loss of sympathetic terminals in the heart also have an absence of the increment in plasma L-DOPA levels between the arterial inflow and coronary sinus outflow (213). Studies of L-DOPA spillover into arterial plasma show that a

prominent source of L-DOPA is the skeletal muscle (228) where it may be stored in muscle cells rather than in sympathetic nerve terminals (159, 161, 462, 512). In pithed rats, stimulation of the spinal cord rapidly increases arterial plasma L-DOPA. In these rats, pre-treatment with a skeletal muscle relaxant attenuates by 50% the increase in plasma L-DOPA caused by spinal cord stimulation, while a ganglionic blocker almost completely abolishes it. These studies provide strong evidence that L-DOPA formed in sympathetic neurons can be stored in a non-neuronal pool and released during skeletal muscle contraction (605). Acute or repeated immobilization in rats decreases muscle content of L-DOPA suggesting that muscle cell uptake and release play a role in regulating plasma levels of L-DOPA (23).

Because rats subjected to chemical sympathectomy (228) and humans with pure autonomic failure continue to have circulating arterial plasma L-DOPA (213), albeit in low levels, the existence of non-neuronal sources of plasma L-DOPA has been suggested. There are dopamine-containing enterochromaffin cells in the mucosa/submucosa of several regions of the stomach and small intestine (164). Significant and detectable quantities of L-DOPA produced by non-neuronal cells that express tyrosine hydroxylase in mesenteric organs (gastrointestinal tract, spleen, and pancreas) are released into the circulation (154). L-DOPA is produced during melanogenesis by the conversion of tyrosine to L-DOPA, catalyzed by tyrosinase. High plasma L-DOPA levels occur in malignant melanoma (357), therefore, the possibility of L-DOPA synthesis in non-neuronal cells via tyrosinase has been suggested (508).

Dietary factors may also influence plasma L-DOPA concentrations. In animals and normal humans, meal ingestion increases plasma L-DOPA levels (215, 668) although this is not a universal finding (51,160). In contrast, fasting decreases L-DOPA levels in the gastrointestinal tract (161).

Renal demethylation of 3-O-methyl DOPA may also be a source of dopamine in the urine (281). Although further evidence is needed to show the importance of this source of L-DOPA, the fact that catechol-O-methyltransferase (COMT) deficiency in mice increases the availability of L-DOPA and dopamine excretion and is associated with resistance to salt-induced hypertension (260) could support a role of 3-O-methyl DOPA in the renal production of dopamine.

L-DOPA uptake into renal tubular cells—The synthesis of dopamine in intact renal tubule cells is dependent on cell uptake of the precursor, L-DOPA, and this process may be the rate-limiting step in the formation of renal dopamine (583). l-amino acids filtered by the glomerulus are almost completely reabsorbed in the proximal tubule by carrier-mediated, stereospecific, energy-dependent and lphenylalanine-mediated transporters (97). Experiments using isolated brush border membranes also demonstrated saturable, stereospecific transport sites for L-aromatic amino acids (242). The formation of dopamine in human, dog, and rat kidney is partially dependent on the concentration of sodium and partially sensitive to inhibition of Na^+/K^+ ATPase (576,580). Initial studies suggested that renal tubular L-DOPA uptake involves an organic cation transporter (218, 487) at both apical and basolateral membranes (582). The renal tubular uptake of L-DOPA uses at least two major transporters, systems LAT-2 and $\text{b}^{0,+}$. Both are sodium-independent amino acid

transporters. Whereas system rBAT/b^{0,+} has a predominant distribution in apical membranes, LAT-2 is present at both apical and basolateral membranes (219). Overexpression of LAT-2 in the kidney of the spontaneously hypertensive rat (SHR) is associated with enhanced L-DOPA uptake that is organ-specific and precedes the onset of hypertension (484). Other studies demonstrated that rBAT/b^{0,+} and LAT-2 may account for more than 50% of the L-DOPA uptake in renal proximal tubules. LAT-2 has low affinity and may be related to basolateral L-DOPA uptake, while rBAT/b^{0,+} is expressed in the apical membrane of the proximal tubule and may account for the high affinity apical L-DOPA transport (496). In SHRs, 50% of L-DOPA uptake occurs via LAT-1, 25% via LAT-2, and 25% via sodium-dependent transport systems (486). Two sodium-dependent amino acid transporters (ASCT2 and B0AT1) are potentially involved in the tubular transport of L-DOPA (486). The renal expression of B0AT1 is decreased in SHR; this precedes the onset of hypertension and correlates negatively with the renal tubular transport of sodium (486). The expression of L-DOPA transporters is age dependent, sensitive to high salt intake, and differently regulated in normotensive and hypertensive animals (486). In young (4 weeks old) Wistar-Kyoto (WKY) rats an acute (24 h) increase in salt intake that results in increased dopamine production is associated with increased expression of LAT-1 and decreased expression of LAT-2, ASCT2 and B0AT1. In contrast, in the adult SHR, the increase in renal dopamine production associated with an acute increase in salt intake may be due to increased expression of sodium-dependent transport systems (ASCT2 and B0AT1) for L-DOPA (486).

Alterations in the uptake of L-DOPA and production of dopamine with aging and in disease states have been described. In aged rats, decreased tubular uptake of L-DOPA results in a decrease in urinary dopamine production (21). Stimulation of β_2 -adrenergic receptors reduces the uptake of L-DOPA and the production of dopamine (91). In patients with left ventricular systolic dysfunction with decreased renal blood flow, urinary dopamine is normal probably because of an increased renal uptake of L-DOPA (180). Deficient renal dopamine production in insulin-dependent diabetes is associated with decreased tubular L-DOPA transport (89). In contrast, insulin stimulates L-DOPA uptake into proximal cells by activation of protein kinase C (PKC)- ζ and Akt/PKB pathways (89,90).

Aromatic amino acid decarboxylase activity—Changes in AADC activity are unlikely to be a major factor in the regulation of renal dopamine production (3, 247, 352, 486) but may contribute under certain circumstances. Thus, the increase in urinary dopamine in sodium-replete states is caused, in part, by increased AADC activity (253, 556, 574, 576). The increase in urinary excretion of dopamine after high salt diet is associated with increased AADC activity in some but not all experimental models (247, 486). However, in sodium-replete states, the increased activity of AADC in rat renal tissues is counterbalanced by enhanced inhibition of dopamine formation by PKC activation (584).

Adenosine, through the activation AADC, increases renal dopamine production (611). In nephrotic syndrome, decreased AADC activity may contribute to the blunted renal dopaminergic activity (530). D₂R may modulate AADC activity; AADC activity and urinary dopamine are suppressed in D₂^{-/-} mice (466). This finding, however, may be dependent on

the genetic background of the mice studied since the $D_2^{-/-}$ mice studied in our laboratory have normal dopamine excretion (unpublished data).

Dopamine transporters—Vesicular monoamine transporters 1 and 2 (VMAT1, VMAT2) are responsible for the accumulation of monoamines from the cytoplasm to storage organelles, as well their secretion. VMAT-2 is expressed in neurons and certain neuroendocrine cells, while VMAT-1 is expressed in endocrine cells and rat renal proximal tubules (399). $D_{2S}R$ and D_3R can also regulate extracellular dopamine concentrations by increasing its up-take via the dopamine transporter (702). VMAT-1 may participate in the dopaminergic regulation of renal tubular function because renal tubular VMAT-1 mRNA and protein expression are increased by high sodium diet (399).

Dopamine metabolism—Dopamine produced by renal tubules is not converted to norepinephrine because renal cells do not express dopamine β hydroxylase (360). This enzyme is however expressed in adrenergic nerves supplying the kidney. Inhibition of dopamine β hydroxylase increases renal dopamine concentration three-fold (327). The concentration of dopamine can be increased by inhibiting the enzymes involved in its breakdown. Dopamine is degraded in renal tissues both by deamination, via monoamine oxidase (MAO) to 3, 4-dihydroxyphenylacetic acid (DOPAC) and by methylation, via COMT to 3-methoxytyramine. Studies in rat renal slices, rat renal tubules, and isolated renal cells demonstrated that newly formed dopamine is metabolized predominantly by MAO A (175, 236, 479). Increased renal MAO activity that is dependent on stimulation of angiotensin type 1 receptors (AT_1Rs) may contribute to the decrease in urinary dopamine during low sodium intake (133). Urinary excretion of dopamine in MAOAB-deficient subjects is greatly increased (356). COMT inhibition also increases sodium excretion that is inhibited by D_1 -like receptor antagonists (157). $COMT^{-/-}$ mice have increased basal renal dopamine levels and increased urinary dopamine excretion along with decreased renal levels of 3-methoxytyramine (260, 714), but are unable to increase urinary dopamine excretion and induce the expected natriuresis in response to sodium loading (450). Renal cortical COMT activity is reduced during isotonic sodium loading that increases dopamine excretion (449). In the rat renal cortex, atrial natriuretic peptide (ANP) modifies dopamine metabolism by enhancing dopamine uptake and decreasing COMT activity (118). These studies suggest that both pathways, MAO and COMT, are important in the regulation of dopamine degradation. The relative contribution of each pathway may depend on where along the nephron dopamine is metabolized and the model used. Studies in microdissected tubules have shown that dopamine is metabolized predominantly by MAO in proximal segments and by COMT in the more distal ones (282). Another variable in the relative contribution of MAO and COMT in the degradation of dopamine is the duration of enzyme inhibition. In microdialysis and clearance studies, acute inhibition of COMT increases urine dopamine, while acute MAO inhibition does not have a significant effect (647). In the anesthetized rat, acute COMT inhibition increases urinary dopamine about 42%, while acute MAO inhibition increases it about 55% (448). However, chronic MAO but not COMT inhibition increases urinary dopamine in the conscious rat (282).

A novel flavin adenine dinucleotide-dependent amine oxidase named renalase has been identified in the kidney.

Renalase is secreted into the blood by the kidney and metabolizes dopamine most efficiently than other catecholamines *in vitro*. In humans, renalase gene expression is highest in the kidney but is also detectable in the heart, skeletal muscle, and the small intestine. The role of renalase in the intrarenal metabolism of renal dopamine is unknown (676)

Dietary influence including salt intake—A protein load (115) or feeding (420) increases urinary dopamine that may be secondary to an increase in L-DOPA synthesis. Most studies have shown that a low sodium diet is associated with low urinary dopamine, while a high sodium diet is associated with increased urinary dopamine (9, 11, 40, 42, 43, 86, 214, 253, 352, 420, 443, 504, 577, 654). This may be related to increased spillover of L-DOPA into the arterial blood (214,229), although plasma L-DOPA levels are not increased with high sodium diet. Chloride seems to be an important ion in regulating renal dopamine production since an increase in the intake of chloride, with or without sodium, increases urinary dopamine, while sodium bicarbonate does not (9,43). Phosphate (67,289) and calcium (9,602) also increase renal dopamine production. However, calcium channel blockade variably affects dopamine excretion. The L-type calcium channel blocker nifedipine does not impair the increase in sodium excretion associated with sodium loading (129) but clonidine, an α_1 - and L-type calcium channel blocker, decreases urinary dopamine in hypertensive subjects (607).

Acute expansion of the extracellular fluid volume increases renal dopamine production, but the type of ion and its concentration are important determining factors. Thus, volume expansion with isotonic saline but not hypo-tonic saline or albumin increases urinary dopamine excretion (8, 11, 124, 166, 400, 550). The increase in dopamine excretion is greater with moderate than with modest volume expansion (saline load of 2.5–5% body weight) but is not increased further by marked (saline load of 10% body weight) sodium loading (102). The increase in urinary dopamine with salt loading is not due to decrease in its breakdown (40, 214, 352). Although salt loading does not increase the plasma levels of the precursor of dopamine L-DOPA (214,253), the increase in urinary dopamine is associated with an increase in urinary excretion of L-DOPA (202,230). Therefore, the increase in urinary excretion of dopamine appears to be secondary to an increase in the uptake of L-DOPA by renal proximal tubules, presumably from the circulation (37,41,54,77,97,577).

Another important factor in the increase in urinary dopamine in chronic sodium loading is the preferential egress of dopamine into the lumen rather than into the interstitium (68, 654). Chronic sodium loading increases the expression of the VMAT-1 in the renal proximal tubule which may contribute to the modification of the polarity of dopamine secretion during sodium loading (399). Inhibition of sodium hydrogen exchanger (NHE) activity decreases efflux of dopamine into the peritubular space, which presumably favors luminal outflow (573). Thus, dopamine, by inhibiting proximal tubular luminal NHE activity, may facilitate its own egress into the tubular lumen (37,135,167,168,195,196,296); dopamine egresses at the apical surface by a nonsaturable process (582). The preferential luminal efflux results in

high nanomolar concentrations (238,654) of dopamine in the tubular lumen, concentrations that approach the EC₅₀ of dopamine and D₁-like receptor agonists to stimulate adenylyl cyclase and phospholipase C activity (49,95,167–170,172,186,196,296,439,640, 657,699,703). The facilitation of sodium excretion by the increase in renal dopamine production associated with chronic saline loading may be minimized by the decrease in dopamine receptor density after 2 weeks of chronic sodium loading (559).

Other investigators have failed to find a relationship between urinary dopamine and sodium excretion (52, 376, 418–421, 633). The reason for these negative reports is not clear. Mühlbauer and colleagues have claimed that the difference between their studies and those of others is due to food in-take (418, 420, 421). However, all the acute saline loading studies performed in several laboratories were performed in rats in which food, but not water, was withheld for 24 h (102,173,306,473). Differences in the amount (247,473) and duration (443) of the sodium load are possible explanations, as well as differences in the strains of rats studied (*vide infra*). In humans, an increase in sodium intake from 20 to >200 mmol/day results in an increase in renal dopamine production peaking at the second day, followed by a gradual decline by the 5th day to 50% of the value on the peak day (443). In rats, sodium chloride loading maximally increased dopamine excretion on the first few days, with the excretion decreasing close to control levels at 1 week, only to gradually increase again from 2 to 4 weeks (230, 297, 692, 694). However, after 6 weeks of long-term sodium chloride loading in rats, renal dopamine concentrations are not higher than in non-loaded rats (480).

There is strain dependence in the production of dopamine in mice and rats. Urine dopamine is lower in Sprague Dawley rats than in Dahl salt-sensitive or -resistant rats (230) or in WKY and SHR (130). A strain of WKY rats increases urinary dopamine after 24 h of salt loading (486) and at 4 weeks but not at 12 weeks of age. Wistar-Han rats from two different suppliers have differences in the urinary dopamine response to uninephrectomy; uninephrectomy increased urinary dopamine in Wistar-Han from Harlan but not from Charles-Rivers and WKY rats from Harlan (485, 531). The increase in urinary dopamine with chronic sodium chloride loading is less in the salt-sensitive C57BL/6 than the salt-resistant SJL mice from Jackson Laboratory (163). Sex may also play a role, as sodium loading increases dopamine excretion in Chinese females but not Chinese males (96). There are other modifiers of dopamine excretion, such as urban versus rural settings in humans (513).

Renal dopamine production in aging and disease states, including

hypertension—Dopamine production has been reported to be decreased with aging (337). The formation of dopamine and dopamine metabolites in kidney slices from old rats is decreased (578) and an inverse correlation between urinary dopamine and age has been reported in humans (212). Urinary excretion of dopamine (21) and urinary dopamine response to high salt are also decreased in aged rats (632). Urinary excretion of dopamine is decreased in patients with renovascular hypertension, chronic renal insufficiency and failure (300,478,693) in whom the reduced activity of their renal dopaminergic system correlates well with the degree of deterioration of renal function. Patients with primary aldosteronism (333) and women with pre-eclampsia (475) have increased urinary dopamine.

Abnormalities in renal dopamine production have been reported in hypertension. The defects are heterogeneous and specific to a particular subgroup of hypertensive patients. Essential hypertensive patients have lower urinary dopamine levels than normotensive subjects (334,561). Protein intake or high dietary sodium intake may not increase urinary dopamine in essential hypertensive patients or even normotensive subjects with a family history of hypertension (250, 517, 561). However, subjects with borderline hypertension, including those with autosomal dominant polycystic kidney disease(52), and young hypertensives (522) have higher renal release of dopamine than control subjects or stable hypertensive patients (93, 299, 334), suggesting that the renal dopaminergic system may act as an early defense against hypertension that fails during its progression (336). Other studies, however, have suggested that renal dopaminergic activity could be suppressed already at the prehypertensive stage (285,286). Normotensive subjects with a family history of hypertension have decreased urinary dopamine (523, 562), an impaired dopamine response to sodium loading (96,517), and a reduction in the conversion of L-DOPA to dopamine. Interestingly, mild exercise has been reported to increase renal dopamine production in Stage 1 hypertensive subjects (525).

Essential hypertensive patients with nonmodulating hypertension (667) and those with low renin but not normal renin have decreased urinary dopamine excretion that may be associated with a decreased rate of conversion of L-DOPA to dopamine and an enhanced natriuretic response to infused dopamine (284, 287). In salt-sensitive normal-renin essential hypertensives, urinary dopamine is normal but have a blunted response to increased sodium intake (201,202) despite higher rates of L-DOPA excretion (202). Salt-sensitive hypertensive type 1 diabetic patients have a lower urinary excretion of dopamine at baseline (193), while in normotensive patients with type 1 diabetes and those with a family history of hypertension, the increase in urine dopamine in response to salt loading is impaired (517). Even if blood pressure and family history of hypertension are not taken into consideration, type 1 and type 2 diabetes are associated with decreased basal urinary dopamine (551), as well as a deficient response to high sodium chloride diet (517) or infusion (593). Rats with type 1 diabetes have also decreased renal dopamine production (88). Decreased dopamine production in human adults (550, 560) and children (385) with type 2 diabetes may be related to a progression of diabetic nephropathy (423).

The ability of the kidney to produce dopamine may depend on race and ethnicity (122, 351, 513). Hypertensive blacks who are salt-sensitive have decreased urinary dopamine (586). The blunted increase in urinary dopamine in response to acute volume expansion in blacks may be caused by reduced decarboxylation of L-DOPA (128). Parous women excrete less dopamine than non-parous women, while African-American women excrete more dopamine than European-American women (75). However, the absence of differences in urinary dopamine between normotensive American whites and American blacks has also been reported (660).

Abnormalities in renal dopamine production have also been reported in animal models of genetic hypertension. Renal dopamine production may or may not be decreased in the SHR and Dahl salt-sensitive rat relative to their normotensive controls, the WKY and Dahl salt-resistant rat, respectively, depending on age (230,534,656). Urinary free dopamine and renal

tissue dopamine are increased in young SHR in comparison with WKY rats (335, 497, 534), but the difference disappears at age 16 weeks (534). Urinary dopamine is normal in the young Dahl salt-sensitive rat and increases with salt intake as in Dahl salt-resistant rats (136, 230), although kidney levels of dopamine are lower in Dahl salt-sensitive than in salt-resistant rats on high salt diet (136). Young Dahl salt-resistant rats increase dopamine in response to volume expansion (526), but prehypertensive Dahl salt-sensitive and salt-resistant rats show the same urinary dopamine response to marked (10%) isotonic sodium load (411). However, in adult Dahl salt-sensitive rats, the renal concentration and urinary excretion of dopamine are actually decreased by salt loading (335). The hypertensive response resulting from the long-term administration of L-NAME is accompanied by an increase in urinary excretion of dopamine, presumably a compensatory response (581).

The effect of dopamine in the regulation of blood pressure differs in the kidney from that in the central nervous system. An overactivity of the dopaminergic system in the brain, for example, amygdala is associated with hypertension (132). Rats made hypertensive by decreasing blood flow to one kidney have increased levels of dopamine and dopamine catabolites in the brain striatum (542). However, monkeys made hypertensive by constricting the aorta have decreased D₁-like receptor binding in the pre-frontal cortex (413), and SHRs have decreased postsynaptic dopaminergic and cholinergic functions in the ventrolateral striatum (187), reinforcing the similarities and differences on the regulation of blood pressure between the dopaminergic system inside and outside the central nervous system.

Dopamine and renal hemodynamics

D₁-like receptors—Dopamine, given systemically or into the renal artery at low doses, increases renal blood flow and decreases renal vascular resistance (210,459,571). The renal vasodilatory effect of dopamine is exerted at D₁-like receptors since it is blocked by the D₁-like antagonist SCH 23390 (184) and mimicked by D₁-like receptor agonists (240, 306, 345, 597, 690, 691). In the normal state, dopamine and D₁-like receptors agonists dilate afferent and efferent arterioles to the same extent (150, 610, 612). However, dopamine may preferentially dilate afferent arterioles (592, 613) when renal blood flow is decreased. The vasodilatory effect of dopamine is greater in the renal artery than in the mesenteric or coronary artery (345,555), in agreement with the receptor density data (303).

The renal vasodilator effect of dopamine via D₁-like receptors is mediated mainly by cAMP/protein kinase A (PKA) (12, 99, 191, 257, 409, 424, 612). In cultured renal vascular smooth muscles, a dopamine-mediated stimulation of PKC is associated with upregulation of D₁-like receptors that results in an enhancement of cAMP production (689). The vasorelaxant effect of D₁-like receptors has also been attributed to KATP channel opening in response to increased cAMP-dependent PKA activity (318). In porcine coronary arteries, dopamine, via D₁-like receptors, induces a vasodilation that is mediated by protein kinase G-dependent activation of calcium- and voltage-activated K⁺ channels (243, 665). The dopamine-mediated relaxation of human coronary artery smooth muscle cells is exerted at the D₅R by activation of big K calcium activation calcium channel, and also by a cAMP-cross talk with protein kinase G (430).

Prostacyclins may also contribute to dopamine- and D₁-like receptor-mediated renal vasodilation (389, 408). Nitric oxide plays a role on the vasodilatory effect of dopamine in the renal artery (631) but not in the aorta (121). Indeed, a complicated effect of D₁-like receptors has been described in the rat aorta and tail artery. Borin (78) reported that dopamine decreases both sodium influx and efflux by inhibition of Na⁺/H⁺ exchanger (NHE) and Na⁺/K⁺ATPase activity, respectively, in part via PKA, in rat aorta smooth muscle cells. This dual inhibition of sodium influx and efflux may or may not result in a change in intracellular sodium. A predominant inhibitory effect on NHE activity would result in a decrease in intracellular sodium and a decrease in vessel tone, while a predominant inhibitory effect on Na⁺/K⁺ATPase activity would result in an increase in intracellular sodium and an increase in vascular tone (78). The latter situation may explain the apparent vasoconstrictor action of a D₁-like receptor agonist in the rat tail artery (502,503). In these studies, dopamine and SKF 38393, a D₁-like receptor agonist, inhibited Na⁺/K⁺ATPase and increased vascular tone, an effect that was associated with activation of phospholipase C (502, 503). Since the effects were abolished by pertussis toxin, the receptor involved in the rat tail artery is different from the phospholipase C that is stimulated by D₁-like agonists in renal proximal tubules in which phospholipase C is pertussis-toxin resistant and linked to Gq (169, 277). When phospholipase Cβ1 is not expressed, D₁-like agonists can be indirectly linked to phospholipase Cγ1 via PKA (699). It is possible that the effect of dopamine in resistance vessels may not be the same as that in conduit vessels (e.g., aorta) and in the rat tail artery, which may subserve a thermoregulatory function.

D₂-like receptors—In renal, mesenteric, pial, and coronary arteries, D₁-like receptors are postjunctional and located in the tunica media (15). In contrast, D₂-like receptors are expressed in pre- and postjunctional regions, and located in the adventitia and the junction between the adventitia and media in pial, renal, coronary, and mesenteric vessels (15,94). The D₃R and D₄R may be preferentially expressed over the D₂R in renal arterioles (15,535).

In the central nervous system, the short D₂R isoform, D_{2S}R (95, 627), and D₃R (104, 207) can function as autoreceptors (presumably located in prejunctional areas). In the kidney, prejunctional D₂-like receptors have been shown to inhibit norepinephrine release (373,519,520). Dopamine can vasodilate the renal vasculature via prejunctional D₂-like receptors (144, 209, 515, 519, 555, 604). This effect is mainly evident when renal nerve activity is increased, a situation that is seen during anesthesia and sodium-depleted states. Action at prejunctional D₂-like receptors to inhibit norepinephrine release may explain the ability of bromocriptine, a D₂-like receptor agonist with some selectivity for the D₂R and D₃R over the D₄R but also with D₁-like antagonistic properties (203, 549), to increase renal blood flow in the anesthetized rat (554, 555, 595) and the renal vasodilatory effect of endogenous dopamine in humans on a low sodium diet (82).

The effect of postjunctional D₂-like receptors on the renal vasculature is still controversial. In the dog kidney, when both α- and β-adrenergic receptors are blocked, the renal vasodilatory effect of dopamine is antagonized by a D₁-like antagonist (SCH 23390), but not by a D₂-like antagonist (domperidone) (184). However, in a similar preparation, (269) bromocriptine has been reported to decrease renal blood flow. In the conscious, chronically instrumented dog on a moderate sodium intake (40 mmol/day), low (picomolar)

concentrations of quinpirole, a D₂-like receptor agonist with some selectivity for the D₃R and D₄R over the D₂R (203, 548), also produce vasoconstriction (570). The effect is exerted at a D₂-like receptor since it is blocked by low concentrations (picomolar) of the D₂-like antagonist YM-09151 (570). The D₃R has been shown to induce a post glomerular vasoconstriction in anesthetized rats (378) and constrict renal vessels in volume-loaded rats (381). D₄R, located on the postjunctional site of guinea pig vas deferens, enhances contractile responses to agonists without affecting muscle tone (416). D₂-like receptor agonists may also constrict renal vessels in volume-loaded rats (305) that is dependent on intact renal nerves and the renin angiotensin system (1).

In the precontracted isolated perfused rat kidney, bromocriptine has been shown to induce vasodilation via postjunctional D₂-like receptors (673). In precontracted rat mesenteric arterial rings, D₃R stimulation induces vasorelaxation (707, 708). The renal vasodilatory effect of D₂-like receptors in humans is reduced during sodium loading and increased during sodium restriction (82). This is in contrast to the lack of effect of sodium loading on the renal vasodilatory effect of D₁-like receptors (498). These studies suggest that when renal vascular resistance is high (e.g., sodium restriction), a D₂-like receptor blockade of calcium influx and stimulation of potassium efflux could result in renal vasodilation. Dopamine receptors can regulate K⁺ channels in vascular smooth muscles but may be related to the D₅R rather than to D₂-like receptors (430,431,665).

In summary, D₁-like receptors are linked to vasodilation. The effect of D₂-like receptors on the renal vasculature is probably dependent upon the state of renal nerve activity. Stimulation of postjunctional D₂-like receptors (D₃R and/or D₄R) can result in either vasodilation or vasoconstriction. With chronic sodium chloride loading, basal reactivity of renal vessels may be enhanced by increased levels of endogenous Na⁺/K⁺ATPase inhibitor and increased intracellular sodium (700). Under these conditions, dopamine can further increase intracellular sodium by stimulating NHE activity via D₂-like receptors (433). The increase in intracellular sodium increases vascular reactivity and thus, dopamine via D₂-like receptors can then elicit vasoconstriction. When renal nerve activity is increased, as seen in renal nerve stimulation, low sodium diet, hypovolemia, or during anesthesia, the vasodilator effect of dopamine occurs via prejunctional D₂-like receptors, presumably of the D₃R subtype (108,707,708). In addition, when the renal vascular resistance is increased, the D₂-like receptor effect at postjunctional sites would be that of vasodilation, since D₂-like receptors inhibit Ca²⁺ channels and stimulate K⁺ channels, both of which can lead to vasorelaxation. Under these conditions, a synergistic effect between D₁- and D₂-like receptors may become evident (158, 240, 305, 554, 555, 707, 708). The effect of dopamine on vascular tone may differ between conduit (e.g., aorta) and resistance (e.g., mesenteric and renal arterioles) vessels. The increase in vascular tone produced by D₁-like receptor agonists in conduit vessels may serve to increase perfusion in downstream vessels dilated by D₁-like receptors.

Glomerular filtration—The dopamine-induced increase in renal blood flow is not consistently associated with an increase in glomerular filtration rate (397,446,490). This may be due in part to failure of transglomerular pressure to increase as a consequence of equal vasodilation of afferent and efferent arterioles (150). However, dopamine can ameliorate the

reduction in glomerular filtration rate caused by amphotericin B (505), radiocontrast material, and hypovolemic states (613). This could be a direct effect on glomerular cells, since dopamine has been shown to attenuate the contractile response to angiotensin II in isolated glomeruli (53). The mechanism by which glomerular filtration rate is increased by dopamine is not clear. An increase in glomerular cAMP is unlikely, since D₂-like, but not D₁-like, receptors are expressed in glomeruli (15,170,447,465). In isolated dog glomeruli, dopamine increases cGMP formation (305). It is only after culture that glomeruli express D₁-like receptors (53, 57, 564) and increase cAMP production. Dopamine can induce a cAMP-dependent depolarization via a D₁-like receptor in differentiated mouse podocytes (57). In isolated rat glomeruli, dopamine decreases adenylyl activity, in keeping with the presence of D₂-like receptors (170). Dopamine also induces ecto-5'-nucleotidase and inhibits DNA synthesis of cultured human mesangial cells (638). Assuming that the isolated glomeruli are not contaminated with arterioles, the ability of dopamine to attenuate the vasoconstrictor effect of angiotensin II *in vitro* may be due to the ability of D₂-like receptors to inhibit Ca²⁺ channels; angiotensin II produces mesangial contraction, in part, by increasing intracellular calcium (301). *In vivo*, D₂-like receptors can decrease or increase glomerular filtration rate, depending upon the state of renal vascular D₂-like receptor activation. When the interaction of D₁- and D₂-like receptors results in a greater vasodilatory effect on afferent than efferent arterioles, glomerular filtration rate can increase (554). D₂-like receptors, especially D₃Rs, are thought to be involved in the increase in glomerular filtration rate associated with amino acid infusion (376,377,380,418,419). This action apparently is mediated by renal nerves since it is abolished by renal denervation (421). Baines and Drangova (39) have reported that neural dopamine regulates glomerular filtration rate. When D₂-like receptors decrease renal blood flow, there is greater afferent than efferent constriction, resulting in a greater decrease in glomerular filtration rate than renal blood flow and a fall in filtration fraction (568,570).

Tubuloglomerular feedback—Tubuloglomerular feedback is a mechanism in which changes in distal tubular sodium chloride delivery induce changes in glomerular arteriolar resistance. Dopamine inhibits tubuloglomerular feedback (546) by occupation of luminal D₁R but not D₂R on macula densa cells that may be more evident during sodium surfeit (239). It has been suggested that this may depend on changes in the filtration coefficient, independent of glomerular pressure and/or a constituent of natural tubular fluid (490). The ability of dopamine to inhibit tubuloglomerular feedback is impaired in the SHR (238) and an increased sensitivity of tubuloglomerular feedback has been suggested as a mechanism for the increased renal vascular resistance in these rats (19).

Autocrine/paracrine regulation of renal function by dopamine—The autocrine/paracrine regulation of renal tubular sodium transport, via D₁-like receptors, is mediated by tubular and not by hemodynamic mechanisms (156, 173, 256, 305, 341, 473, 569). Thus, systemically administered dopaminergic drugs may not mimic the autocrine/paracrine function of dopamine. The quantitative contribution of dopamine receptor subtypes on renal sodium transport and glomerular dynamics is not yet studied. The D₁R is responsible for ~80% of D₁-like receptor activity in renal proximal tubules; D₅R may be more important in the distal nephron (645, 688), while the D₃R may regulate glomerular dynamics (381). Each

of the dopamine receptor subtypes, alone, or via interaction with the other dopamine receptor subtypes or other GPCRs, regulates sodium transport in a unique fashion (171). Indeed, disruption of any of the dopamine receptor genes results in hypertension, the pathogenesis of which is specific for each subtype (171)

Regulation of ion and water transport

Ion transport

Euvoemia and moderate volume expansion: Dopamine and its receptors are important in the regulation of ion transport under conditions of euvoemia and moderate volume expansion but have a minor role under marked volume expansion (102, 247). The increase in ion excretion caused by dopamine cannot be entirely ascribed to its ability to increase renal blood flow or increase in glomerular filtration rate. Reduction in renal blood flow to control values decreases but does not abolish the natriuretic effect of the D₁-like receptor agonist fenoldopam administered into the renal artery (306). Rather, dopamine can directly inhibit renal tubular ion transport by inhibition of ion transporters, sodium channels, and sodium pump activity (305). The short-term inhibition of ion transport by dopamine involves alteration in enzyme kinetics (220, 556, 575) and internalization of ion transporters (14, 34, 35, 106, 114, 125, 152, 198, 221, 322, 332, 338, 344, 544, 661). The long-term inhibition of sodium transport by dopamine may involve regulation of protein expression by decreasing gene transcription and translation, and increasing their degradation (644).

The inhibitory effect of dopamine on ion transport is exerted via its own receptors (10, 83, 123, 173, 204, 210, 220, 352, 396, 401, 402, 457–459, 597, 628, 690) and via the regulation of the release or secretion of other hormones/humoral substances. Such hormones may directly inhibit ion transport, interact with dopamine to increase [e.g., ANP (118,318,392, 393,481), nitric oxide (631), prolactin (280), and eicosanoids (272, 328)] their inhibition of ion and water transport, and/or prevent their stimulatory effect on sodium transport [e.g., angiotensin II (100,101,116,134,274,321,363,558,628), insulin (44,45,682), and vasopressin (16,559)]. Dopamine receptors also inhibit renal nerve activity (520), although the natriuretic effect of D₁-like receptor stimulation persists even after renal denervation (307).

Most of the effects of dopamine on renal ion transport *in vivo* are mediated by D₁-like receptors (*vide infra*). The effect of D₂-like receptor antagonists on ion transport *in vivo* is not well established, ranging from no effect (305), attenuation of sodium excretion (63, 119), and even an increase in sodium excretion (568). The apparent discrepancies in these studies may be related not only to the status of the extracellular fluid volume (82) and other hormonal systems, but also to the specificity of the drugs used. For example, in hypovolemic or euvolemic states where vasopressin levels are elevated, the ability of D₂-like receptor agonists, probably exerted at the D₄R to inhibit the effects of vasopressin (426, 599), may obscure the stimulatory effect of D₂-like receptors on water and ion transport in more proximal parts of the nephron. Bromocriptine, a D₂-like receptor agonist with some selectivity for the D₂R and D₃R over the D₄R, applied to the basolateral membrane of isolated medullary thick ascending limb transiently increases chloride transport (225). Stimulation of D₃R inhibits NHE3 activity via PKC in the rat renal proximal tubule (471). The D₃R probably participates in natriuresis associated with volume expansion (305, 341)

that may involve an interaction with D₁-like receptors (311). The natriuresis in rats with streptozotocin-induced diabetes is decreased by D₃R antagonist (377).

Dopamine inhibits transport in the proximal and distal nephron (361, 437, 456, 457, 498), as estimated from lithium clearance studies. It must be noted that the renal tubular site of action of endogenous dopamine and its agonists on ion transport may not always match that given exogenously. Most of the renal dopamine is produced in the proximal tubule and so its effects in the distal nephron could be limited, while exogenously administered dopamine would reach all nephron segments equally.

As stated earlier, all the dopamine receptor subtypes are expressed in the proximal tubule. In the mouse kidney, the D₃R, D₄R, and D₅R are most abundant in the S1 segment, while the D₁R is most abundant in the S3 segment; the D₂R may be mainly expressed in the S2 segment (unpublished observations). The stimulation of D₁-like receptors decreases the activity of several sodium transporters, including the sodium hydrogen exchanger 3 (NHE3, SLC9A3) (10, 35, 167, 168, 195, 196, 220, 271, 296, 471, 666), sodium phosphate cotransporter (NaPi-IIa/SLC34A1 and NaPi-IIc/SLC34A3) (34, 125, 135, 476, 661) and Cl⁻/HCO₃⁻ exchanger (SLC26A6) (472) at the apical membrane, and electrogenic Na⁺/HCO₃⁻ co-transporter (NBCe1A, SLC4A4) (338) and Na⁺/K⁺ATPase (18, 27, 47, 69–72, 106, 114, 151–153, 156, 157, 186, 198, 221, 255, 322, 328, 370, 438, 470, 540, 541, 556, 608) at the basolateral membrane. G protein-dependent, cAMP/PKA- and PKC/NHERF-1-dependent and -independent mechanisms are involved in the dopamine or D₁-like receptor inhibition of NHE3, Na⁺/Pi2, and Cl⁻/HCO₃⁻ exchanger activity, including their translocation out of the brush border membranes into the cytosol (34, 47, 106, 168, 256, 322, 338, 472, 661, 675). Specific PDZ domains of Pals-associated tight junction protein (PDZ 2, 4, or 5) or NHERF-1 (PDZ 1) may be important in organizing the signaling pathways by which dopamine inhibits sodium transporter/pump activity (106, 322, 661). A type III PDZ binding site may be present in D₁R (106).

The D₃R (471) and D₄R may also regulate NHE3 because its expression is increased in D₃^{-/-} and D₄^{-/-} mice, on normal salt intake (644); NaPi2 expression is not altered in D₂^{-/-}, D₃^{-/-}, and D₄^{-/-} mice and is actually decreased in D₅^{-/-} mice. The expression of NHE3 and NaPi2 has not been determined in D₁^{-/-} mice (Table 1).

The medullary thick ascending limb of Henle expresses the D₁R, D₃R (in the mouse but not in the rat), D₄R, and D₅R. D₁-like and D₂-like receptor agonists administered to the apical membrane do not affect chloride transport. However, their application to the basolateral membrane decreases chloride transport, via D₁-like receptors (225). In contrast, bromocriptine, a D₂-like receptor agonist with some selectivity for the D₂R and D₃R over the D₄R, increases chloride transport (225), reminiscent of the ability of this agonist to increase Na⁺/K⁺ATPase activity in renal proximal tubules (275). In addition, incubation of medullary thick ascending limb suspensions with dopamine increases sodium potassium 2 chloride cotransporter (NKCC2, SLC12A1) but decreases overall transport (17), probably because Na⁺/K⁺ATPase activity is inhibited (see below). The D₁-like receptor-mediated stimulation of NKCC2 may be important in K⁺ recycling in the mTAL (17). The D₄R and D₅R may regulate NKCC2 because its expression is increased in D₄^{-/-} and D₅^{-/-} mice

(646). NKCC2 expression is not altered in $D_2^{-/-}$ and $D_3^{-/-}$ mice and has not been reported in $D_1^{-/-}$ mice (Table 1).

The distal convoluted tubule expresses all the dopamine receptor subtypes but their effect on ion transport in this nephron segment has not been reported. However, the D_2R , D_3R , D_4R , and D_5R may regulate NCC because its expression is increased in $D_2^{-/-}$, $D_4^{-/-}$, and $D_5^{-/-}$ mice (645). NCC expression has not been reported in $D_1^{-/-}$ mice (Table 1).

D_1R , D_2R , D_4R , and D_5R are expressed in the cortical collecting duct (524, 646). The expression of the D_3R in the cortical collecting duct has been reported in the rat in two studies (447, 563) but not in another study (440); it is not expressed in the cortical collecting duct in the mouse (unpublished data). The D_4R may be responsible for the inhibition of the increase in sodium transport mediated by vasopressin (599,600). The D_5R may regulate ENaC because α and γ subunit expressions are increased in $D_5^{-/-}$ mice (645); α ENaC is increased in $D_4^{-/-}$ mice but only following a high salt diet (unpublished observations). ENaC expression is not altered in $D_2^{-/-}$ and $D_3^{-/-}$ mice. ENaC expression has not been reported in $D_1^{-/-}$ mice (Table 1). The D_1R is probably not expressed in the outer or inner medullary collecting duct, while the D_5R is expressed in the outer but not the inner medullary collecting duct in the mouse kidney.

In the rat inner medullary collecting duct, dopamine does not stimulate cAMP production (149, 386). This is in agreement with the finding that of the dopamine receptor subtypes, only the D_2 -like receptors are expressed in this nephron segment; the D_2R is expressed in the intercalated cells (563), while D_3R and D_4R are not differentially expressed (intercalated vs. principal cell) in the medullary collecting duct (563, 646). A D_2 -like receptor has been shown to stimulate PGE2 production in rat medullary collecting duct cells (273). However, this D_2 -like receptor effect on ion transport in this nephron segment has not been determined.

In the basolateral membrane, D_1 -like receptors inhibit Na^+/K^+ ATPase activity in all the nephron segments studied and electrogenic Na^+/HCO_3^- co-transporter (NBCe1A, SLC4A4) in the proximal tubule (18, 27, 47, 69–72, 106, 114, 151–153, 156, 157, 186, 198, 221, 255, 322, 328, 338, 370, 438, 470, 540, 541, 556, 608). Although stimulation of D_2 -like receptors may increase Na^+/K^+ ATPase activity (275,428,679), the interaction of D_1 -like and D_2 -like receptors results in a potentially greater inhibition of the sodium pump. In the rat proximal tubule, but not in the mTAL or cortical collecting duct, D_2 -like receptors act in conjunction with D_1 -like receptors to inhibit Na^+/K^+ ATPase activity and decrease sodium transport (69, 70, 341, 540, 541, 554, 608). The expression of α subunit of Na^+/K^+ ATPase is not altered in $D_2^{-/-}$, $D_3^{-/-}$, $D_4^{-/-}$, and $D_5^{-/-}$ mice on a normal salt intake.

The inhibitory effect of D_1 -like receptors on Na^+/K^+ ATPase is mediated by cAMP/PKA, certain PKC isoforms, and 20-HETE. The overall consequence of D_1 -like receptor stimulation is internalization of Na^+/K^+ ATPase subunits (30, 53, 141, 153, 225, 328, 362, 439, 460). The inhibitory effect of D_1 -like receptors on Na^+/K^+ ATPase involves PKC in the proximal convoluted tubule and PKA in the distal convoluted tubule and cortical collecting duct, while the eicosanoids are involved in all nephron segments, including the mTAL

(30,141,153,362,439,540,541). It should be noted that D₁R, D₃R, D₄R, D₅R can increase phospholipase C activity and presumably PKC activity (169,353,368,521,572,699).

The effect of dopamine on Na⁺/K⁺ATPase is tissue-specific. Dopamine inhibits Na⁺/K⁺ATPase activity in renal tubules. However, in human ciliary non-pigmented epithelial cells, D₁-like receptors do not affect Na⁺/K⁺ATPase activity (507) and stimulates it in pulmonary alveolar cells (72). D_{2L}R also stimulates Na⁺/K⁺ATPase in murine fibroblasts (679). D₁R and D₂R, on the one hand, and Na⁺/K⁺ATPase, on the other, can also negatively regulate each other in the strain T of human embryonic kidney cells (HEK293T) by direct protein-protein interaction (254). While the inhibition of Na⁺/K⁺ATPase in the kidney by dopamine under conditions of sodium chloride excess is beneficial, inhibition of Na⁺/K⁺ATPase activity in neuronal cells by high concentrations of dopamine can lead to cell death (36). Inhibition of Na⁺/K⁺ATPase activity in vascular smooth muscle cells would increase vascular resistance, as has been reported in the rat tail (503). Low concentrations of dopamine, however, decrease systemic vascular resistance probably by mechanisms other than via regulation of sodium transporter or pump activity (453, 489, 708), for example, opening of potassium channels (243, 244, 318, 430, 665) (vide supra, in *Dopamine and renal hemodynamics*).

Water transport—Dopamine may also regulate water transport. Dopamine inhibits arginine vasopressin-mediated increase in water transport, via the D₄R in the rat cortical collecting duct (599). Dopamine has been reported also to inhibit vasopressin-stimulated increase in water permeability in inner medullary collect duct cells (149). The effect was inhibited by clozapine, which is not just a D₄R antagonist but also an α_2 adrenergic receptor antagonist. The dopamine-mediated reversal of vasopressin-mediated increase in water transport has been related to a decrease in expression and increase in phosphorylation of aquaporin 2 at the apical plasma membrane (432, 701). D₁-like receptors probably do not play a role in the vasopressin-mediated transport, at least in the rat inner medullary collecting duct because dopamine does not increase cAMP levels in this nephron segment (386). Aquaporin 4-mediated increase in basolateral permeability is also impaired by dopamine, via an as yet to be determined receptor subtype that is linked to PKC (703). The D₂R can regulate aquaporin 4 in glial cells (467) but is probably not the dopamine receptor involved in medullary collecting duct because the D₂R is not expressed in principal cells of this nephron segment (646).

Hypovolemia: In contrast to the natriuretic effect of endogenous renal dopamine in euvolemic and in moderately volume-expanded states, dopamine actually decreases sodium excretion in sodium-depleted states (7,498). A limited number of studies have assessed the mechanism by which dopamine decreases sodium excretion in sodium-depleted states. In conscious, chronically instrumented dogs on a sodium intake of 40 mmol/day, quinpirole, a D₂-like receptor agonist with selectivity to the D₃R and D₄R over the D₂R (203, 548, 549), decreased sodium excretion as a consequence of both a decrease in renal blood flow and an increase in tubular sodium reabsorption (570). Dopamine has also been reported to stimulate NHE3 and Na⁺/K⁺ATPase activity in rabbit renal proximal tubule cells (346); bromocriptine, a D₂-like receptor agonist with some selectivity for the D₂R over the D₄R

stimulate Na^+/K^+ ATPase activity in rat renal proximal tubule cells (275) and increase chloride transport in the mTAL (225). The D_2 -like receptor may be the post-synaptic D_2R because the stimulation of heterologously expressed D_2R increased Na^+/K^+ ATPase (679) and NHE1 activity in murine LTK cells (433).

Dopamine receptor mutant mice: The generation of mutant mice deficient for each dopamine receptor helped to determine the role of each dopamine receptor in the regulation of blood pressure (10,31,58,265,365,645,646,684,685). Each of the dopamine receptor subtypes participates in the regulation of blood pressure by mechanisms specific for the subtype. As described above some receptors influence epithelial transport. Others, as described below, regulate blood pressure by influencing the central and/or peripheral nervous system and regulating the secretion and receptors of several humoral agents (see Table 1).

D_1 receptor mutant mice: Systolic, diastolic, and mean arterial pressures are higher in both homozygous and heterozygous mice than in wild-type mice (10). The homozygous $\text{D}_1^{-/-}$ mice do not increase cAMP accumulation in response to D_1 -like receptor agonist stimulation but their response to parathyroid hormone is intact. These data indicate that defective D_1 receptor/signal transduction results in increased blood pressure in mice (10). However, there is no report available on the renal function or activity of the renin-angiotensinaldosterone system in $\text{D}_1^{-/-}$ mice. It is also unknown whether or not the hypertension of $\text{D}_1^{-/-}$ mice is salt-dependent.

D_2 receptor mutant mice: $\text{D}_2^{-/-}$ mice in C57BL6J genetic background have decreased initiation of movement but otherwise normal basic motor skills without tremor, ataxia, or abnormal stance or posture. $\text{D}_2^{-/-}$ and $\text{D}_2^{-/+}$ mice have higher systolic and diastolic blood pressures than D_2 wild-type ($\text{D}_2^{+/+}$) mice. α -Adrenergic blockade decreases blood pressure to a greater extent in $\text{D}_2^{-/-}$ mice than in $\text{D}_2^{+/+}$ mice but acute adrenalectomy decreases blood pressure to a similar level in $\text{D}_2^{-/-}$ and $\text{D}_2^{+/+}$ mice. ETB receptor expression is greater in $\text{D}_2^{-/-}$ mice than in $\text{D}_2^{+/+}$ mice and ETB receptor blocker decreases blood pressure in $\text{D}_2^{-/-}$ mice but not $\text{D}_2^{+/+}$ mice. These data indicate that $\text{D}_2^{-/-}$ mice may have enhanced vascular reactivity caused by increased sympathetic and ETB receptor activities (365), as well as increased reactive oxygen species (ROS) production (22). The $\text{D}_2^{-/-}$ mice also have increased production of aldosterone and treatment with a mineralocorticoid receptor blocker normalizes blood pressure in these mice (22). In another strain of $\text{D}_2^{-/-}$ mice, blood pressure is increased only when the mice are fed a high salt diet; this is associated with a decrease in renal AADC activity and in renal dopamine production. Sympathetic activity is not increased in these $\text{D}_2^{-/-}$ mice (623). Basal urine flow and sodium excretion are lower in $\text{D}_2^{-/-}$ mice than in $\text{D}_2^{+/+}$ mice. The differences between the two strains of $\text{D}_2^{-/-}$ mice could be related to differences in the genetic background.

D_3 receptor mutant mice: The locomotor phenotype of $\text{D}_3^{-/-}$ mice does not resemble that of $\text{D}_2^{-/-}$ mice. $\text{D}_3^{-/-}$ mice develop normally, are fertile, and may show a transient locomotor hyperactivity in a novel environment (2). $\text{D}_3^{-/-}$ and $\text{D}_3^{-/+}$ mice have higher both systolic and diastolic blood pressures than their wild-type littermates (32, 643). Another strain of $\text{D}_3^{-/-}$

mice have normal blood pressure regardless of salt in-take in these mice (591). Nevertheless, these two strains of $D_3^{-/-}$ mice have decreased sodium excretion after an acute or a chronic sodium chloride load, which may lead to an expansion of the extracellular fluid volume. Differences in phenotypes can occur depending on the genetic background and even with the same mouse strain from different commercial sources. For example, C57BL/6 from Jackson Laboratories are salt-sensitive, while C57BL/6 mice from Taconic are salt-resistant (685, 686). The salt-sensitive hypertensive phenotype of human G protein-coupled receptor kinase type 4 (GRK4) 486V transgenic mice is dependent on the percentage of genetic background from salt-resistant SJL mice (652). Disruption of the D_3 receptor, in C57BL/6J background, increases renal renin production, renal sodium retention, and renin-dependent hypertension. Renal renin activity and AT_1R protein are greater in $D_3^{-/-}$ than in wild-type mice; values for $D_3^{+/+}$ mice are intermediate of those of $D_3^{-/-}$ and $D_3^{+/+}$ mice, while blockade of AT_1R decreases systolic blood pressure for a longer extent in $D_3^{-/-}$ mice than in wild-type littermates (32).

D₄ receptor mutant mice: D_4R -deficient ($D_4^{-/-}$) mice, back-crossed to C57BL/6J mice for more than six generations, have increased systolic and diastolic blood pressures that are increased further with increased sodium intake (58). $D_4^{-/-}$ mice do not have altered circulating or renal renin levels (58). The expression of AT_1R is increased in homogenates of kidney and brain of $D_4^{-/-}$ mice relative to $D_4^{+/+}$ mice, but AT_1 receptor expression in the heart is similar in the two strains. However, the hypotensive effect of a bolus intravenous injection of the ARB, losartan, dissipates after 10 min in $D_4^{+/+}$ mice, whereas the effect persists for more than 45 min in $D_4^{-/-}$ mice. Thus, the hypertension brought about by the absence of the D_4 receptor is mediated, in part, by increased AT_1 receptor expression (58).

D₅ receptor-deficient mice: $D_5^{-/-}$ mice are viable, develop normally, and have normal expression of the other dopamine receptors, including the D_1 receptor (265, 266). $D_5^{-/-}$ mice are hypertensive and salt-sensitive. Epinephrine/norepinephrine ratio and the hypotensive response to the acute administration of an α -adrenergic blocker are greater in $D_5^{-/-}$ mice than their $D_5^{+/+}$ littermates, indicating that increased sympathetic activity plays a role in the elevated blood pressure observed with deletion of the *Drd5* gene. Central nervous systems pathways involving glutaminergic, oxytocin, vasopressin, and adrenergic receptors may have a role in the high blood pressure of $D_5^{-/-}$ mice (265). Besides these central nervous system mechanisms, renal AT_1 receptors (363, 711) and increased production of ROS are also involved (684,685) in the hypertension of $D_5^{-/-}$ mice.

Dopamine Receptor Interactions

Interaction among the dopamine receptors and with other GPCRs

Dopamine receptor subtype interaction— D_1 -like and D_2 -like receptors (158) [specifically, D_3R (311)] interact to enhance the natriuretic effect of dopamine. In sodium-replete states, D_2 -like receptors act synergistically with D_1 -like receptors to increase sodium excretion (341) by inhibiting NHE3 (666) and Na^+/K^+ ATPase (69,328) activity.

D₁R and D₃R: D₁R and D₃R (706) synergistically interact to decrease sodium transport in renal proximal tubule cells (706, 707) and to relax vascular smooth muscle cells (366,707,708). Reciprocal regulation of D₁R and D₃R function and trafficking has also been shown in HEK293 cells heterologously expressing tagged D₁R and D₃R, but not D₅R (181). According to Fiorentini et al., the heterodimerization of D₁R and D₃R causes D₃R desensitization similar to that of the D₁R (see below). Interestingly, G α_s , which by itself decreases NHE3 activity, independently of PKA (167), is linked to both D₁R (171, 305) and D₃R (444). G $\alpha_{q/11}$, involved in the D₁-like receptor inhibition of Na⁺/K⁺ATPase (171, 277, 305), can also be linked to D₃R (434). The natriuretic action (311) and inhibition of phospholipase C (699) by the D₃R agonist pramipexole are partially blocked by a D₁-like receptor antagonist. The D₃R colocalizes with D₁R in renal proximal tubule cells of WKY rats (Fig. 2). In these cells, stimulation of D₃R increases both the coimmunoprecipitation of D₁R with D₃R and the protein expression of D₁R (706). The individual inhibitory effect of either D₁-like receptors or the D₃R on transporters is not 100%, not always on the same transporter, or in the same nephron segment, and thus, additive or even synergistic effects are possible with co-stimulation. In mouse brain, the ALG-2 interacting protein 1 may be important in the interaction between D₁R and D₃R (713). Whether or not this protein is also important in D₁R and D₂R interaction in the kidney remains to be determined. This is a possibility because the D₁R can inhibit the cellular sequestration of D₂R or D₃R (110).

Therefore, the D₃R promotes natriuresis (Fig. 3) in the short term by itself (377, 704) and by interacting with the D₁R (311). In the long term, the D₃R increases the expression of the pro-natriuretic D₁R (707). The interaction between D₁R and D₃R receptors is absent or impaired in hypertension and results in defective inhibition of sodium transport and relaxation of vascular smooth muscles and ultimately in the development or maintenance of high blood pressure (341,706, 707,710).

D₂R and D₃R: In a monkey cell line, heterologously expressed D₂R and D₃R receptors form heteromers with unique functional properties (543). In HEK293 cells, activation of heterologous D₂R inhibits both adenylyl cyclases V and VI, while activation of D₃R inhibits only adenylyl cyclase V and does not affect the activity of adenylyl cyclase VI (511). However, when D₂R and D₃R are coexpressed, lower concentrations of a D₂-like receptor agonist are needed to induce inhibition of adenylyl cyclase VI than those needed in cells expressing only the D₂R (543). These suggest that the D₂R/D₃R heterodimer may enable the G protein coupling of the D₃R to adenylyl cyclase VI. The D₃R, however, cannot inhibit adenylyl cyclase V in renal proximal tubules because this isoform is not expressed in this nephron segment (59).

D₁R, D₅R, and D₂R: D₁R and D₂R heterodimerize in expression systems (146) and neural tissues (353) and the degree of receptor protein-protein interaction is significantly enhanced by concomitant addition of D₁R and D₂R receptor subtype-specific agonists (146). The physical interaction between D₁R and D₂R is increased by the chaperone calnexin (185). The co-activation of D₁R and D₂R increases phospholipase C products (353) and eicosanoids (329) that are inhibitory of sodium transport. In the brain striatum, the D₁R and D₂R complex activates calcium/calmodulin-dependent protein kinase 2 α (436). The D₂R

also hetero-oligomerizes with D₅R that causes a decrease in D₅R-mediated increase in intracellular calcium levels (572). However, there is no evidence of a D₁R and D₂R or D₅R and D₂R heterodimerization in renal tubule cells. It remains to be determined whether or not D₁R and D₅R interact to regulate renal ion.

D₄R and other dopamine receptor subtypes: A direct interaction between D₄R and the other dopamine receptor subtypes has not been reported. However, the dopaminergic regulation of glutamate N-methyl-D-aspartate receptor activity in the amygdala may be due to a functional interaction between D₁R and D₄R (394). Gene-gene interaction between D₂R and D₄R is associated with the development of conduct disorder and adult antisocial behavior in males (55).

Dopamine interaction with other GPCRs—The dopamine receptor subtypes interact with several GPCRs, for example, D₁R and mu opioid receptor (308), and N-methyl-D-aspartic acid glutamate receptor (237, 350, 547). Only those receptors that have been shown to be involved or have the potential to be involved in the regulation of renal function are included in this review.

Adenosine receptors: Stimulation of renal adenosine receptors lowers glomerular filtration rate by constricting afferent arterioles and exerts differential effects on NaCl transport along the nephron, depending upon the adenosine receptor subtype; the adenosine type 2 receptor (A₂R) decreases, while the adenosine type 1 receptor (A₁R) increases sodium transport. Adenosine antagonizes some effects of dopamine. The dopamine-mediated inhibition of tubuloglomerular feedback is antagonized by adenosine via the regulation of adenylyl cyclase activity in the macula densa in a concentration-dependent manner (238). In opossum kidney cells, low concentrations of an adenosine analog, via A₁R, stimulate NHE3 activity and attenuate dopamine-mediated inhibition of NHE3 (138). A₁R modulates D₁R; co-administration of A₁R and D₁R agonists in HEK293 cells stably expressing both receptors potentiated the effect the D₁R-mediated desensitization of D₁R (85). Interestingly, A₁R and D₁R have been shown to physically interact in the central nervous system with the formation of a heteromeric complex that leads to the uncoupling of the D₁R from its Gs-like protein complex (178,188). However, in COS-7 cells and fibroblasts heterologously expressing A₁R, D₁R, and D₅R, activation of A₁R blocks the desensitization of D₁R but not D₅R (348), another instance of cell specific effect or related to gene overexpression.

The A₂R isoform, A_{2A}R, heterodimerizes with D₂R in striatal membranes and reduces the high-affinity state of D₂Rs, especially the high affinity for agonists (177, 179). The heterodimerization of A_{2A}R and D₃R or D₄R also results in an impairment of D₃R and D₄R function (616).

Adrenergic receptors: β -adrenergic receptor agonists interact with dopamine in the regulation Na⁺/K⁺ATPase activity in the rat kidney. Activation of β -receptors with isoproterenol increases D₁R translocation from the cytosol to the membranes and D₁R-mediated inhibition of Na⁺/K⁺ATPase activity renal proximal tubule cells (79). However, as stated above, stimulation of β_2 Rs reduces the uptake of L-DOPA and the production of

dopamine (91). Thus, endogenous renal β -adrenergic receptors may not enhance the dopaminergic inhibition of sodium transport.

Dopamine receptors may counter-regulate the actions of α -adrenergic receptors on vascular proliferation. Stimulation of α_1 Rs increases proliferation of vascular smooth muscle cells. However, in the presence of D_1 -like or D_3 R agonists, the proliferative effect of norepinephrine, via α_1 Rs, is inhibited, although D_1 -like or D_3 R agonists have no effect by themselves. Moreover, co-stimulation of D_1 -like or D_3 R has an additive inhibitory effect on norepinephrine-mediated vascular smooth muscle cell contraction (708) and proliferation (366). The failure of dopamine to induce natriuresis in sodium-depleted states may be a consequence of increased sympathomimetic activity (7).

Angiotensin II and angiotensin receptors

AT₁R and dopamine receptors: Many reports have shown an interaction between the dopamine and the renin-angiotensin system. The D_3 R inhibits renin secretion (32), while the D_4 R or D_5 R decreases AT₁R expression (58, 198, 363). Intravenous infusion of angiotensin II in humans reduces urinary dopamine (147). D_1 R can also stimulate renin secretion (680) but only when COX-2 expression or activity is inhibited (714,715) (*vide infra*).

Angiotensin II via AT₁R causes renal vasoconstriction, while low concentrations of dopamine via D_1 -like receptors cause vasodilation (98, 99, 690). Activation of the reninangiotensin system may cause the development of tolerance to the hypotensive action of D_1 -like receptor agonists (354). In the rat, dopamine attenuates the glomerular mesangial contractile response to angiotensin II, independently of eicosanoids (53). Infusion of D_1 -like receptor agonists, YM-435 or fenoldopam, into the renal artery blocks angiotensin II-induced afferent and efferent arteriolar constriction (98, 610). Blockade of AT₁R normalizes the impaired renal vasodilator effect of D_1 -like receptor stimulation in the SHR (134). The increased vasodilatory effect of a D_3 R/ D_4 R agonist (quinpirole) (203, 548) after renal denervation may also depend on a decreased activity of the renin-angiotensin system (379).

Activation of the renin-angiotensin system has been suggested to cause the attenuation of the natriuretic effect of D_1 -like receptor agonist, fenoldopam in sodium-deplete states (498). When angiotensin II generation is inhibited or AT₁Rs are blocked, the natriuretic effect of dopaminergic drugs is enhanced (100,101,116). In humans, this effect is seen mainly in subjects on low salt diet (Natarajan et al., unpublished studies). D_1 - and D_2 -like receptor agonists also antagonize the stimulatory effect of angiotensin II, acting on AT₁R, on renal proximal tubule sodium transport (113, 274, 321, 558, 690). This counteracting effects of dopamine and angiotensin II on sodium transport occurs by the regulation of sodium transporter/channel/pump activity in the short term and their expression in the long term (106,151,646). The short-term counteracting actions may occur by differential cell membrane trafficking. Thus, angiotensin II, via the AT₁R in renal proximal tubule cells, induces the recruitment of Na^+/K^+ ATPase to the plasma membrane. At an intracellular concentration of sodium of 9 mM, angiotensin II increases Na^+/K^+ ATPase activity; dopamine is without effect. Increasing intracellular sodium to 19 mM is associated with an increasing inhibition of Na^+/K^+ ATPase activity by dopamine and blunting of the stimulatory

effect of angiotensin II. This is associated with the recruitment of D₁R to the plasma membrane and a reduction in plasma membrane AT₁R (151).

The mechanism by which dopamine receptors interact with the angiotensin receptors is receptor subtype specific. The D₁R (321, 709) and the D₃R (706) inhibit angiotensin II effects via physical interaction (heterodimerization) with the AT₁R. In contrast, the D₅R and AT₁R can also heterodimerize and negatively regulate each other's expression. In renal proximal tubule cells, the D₅R (not the D₁R) decreases AT₁R expression and AT₁R-mediated extracellular signal-regulated kinase phosphorylation. The D₁-like receptor-induced decrease in AT₁R expression is reversed by tyrosine-kinase inhibition and proteasome inhibitor, demonstrating that the D₅R mediated decrease in total cell AT₁R expression is a result of a c-Src-dependent and proteasome-dependent process (Fig. 4) (199, 363, 711). Dopamine has also been reported to decrease AT₁R mRNA expression in renal proximal tubules (107). The D₄R also negatively regulates AT₁R expression but the mechanism remains to be determined (58).

AT₂R and dopamine receptors: Stimulation of D₁-like receptors induces an AT₂R-dependent natriuresis (528). Selective intrarenal activation of D₁-like receptors induces sustained natriuresis and diuresis in sodium-loaded Sprague-Dawley rats that is abolished by intrarenal AT₂R inhibition. D₁-like receptor-mediated natriuresis is accompanied by recruitment of both D₁Rs and AT₂Rs to the plasma membrane of renal proximal tubular cells. These suggest that that D₁-like receptor-induced natriuresis and diuresis are modulated by functional AT₂Rs that are translocated from intracellular compartments to the plasma membrane of renal proximal tubule cells in response to D₁-like receptor activation and that dopamine-induced natriuresis requires AT₂R activation (528). Therefore, in the normotensive state, dopaminergic stimulation favors natriuresis not only via specific dopamine receptor subtype mechanisms but also by impairing AT₁R function and increasing AT₂R expression, via D₁R, by decreasing AT₁R expression via D₃R (706) D₄R (58), and D₅R (199, 363), as well as negative interaction with D₁R (709), D₃R, and D₅R (707,708).

Renin secretion, angiotensinogen, and dopamine receptors: The rat juxtaglomerular cell expresses D₁R, D₃R, D₄R but not D₂R or D₅R (535, 680). The D₃R tonically inhibits renin secretion because deletion of the D₃R gene in mice causes renin-dependent hypertension (32). In the rat, the D₁R positively regulates renin release from juxtaglomerular cells in culture (680). However, the stimulatory effect of D₁R on renin release in rats *in vivo* is only present when cyclooxygenase 2 activity is decreased that occurs when sodium intake is high. The suppression of cyclooxygenase activity in this state has been shown to be due to dopaminergic inhibition of salt and fluid transport in the proximal tubule (714, 715). Harris and co-workers have suggested that dopamine indirectly decreases renin secretion in normal or volume-depleted states and directly stimulates a small increase in renin secretion in volume-expanded states (686, 714, 715). Thus, dopamine via D₁-like receptors can regulate renin secretion even when D₁R is not expressed in juxtaglomerular cells (465). In opossum kidney cells with a fusion gene containing the 5'-flanking regulatory sequence of the rat angiotensinogen gene fused with a human growth hormone gene (pOGH) as a reporter, dopamine, via both D₁- and D₂-like receptors increased the expression of the pOGH but

only when phosphodiesterase is inhibited (642). It is possible that the stimulatory effect of dopamine on renin and angiotensinogen becomes apparent during conditions of volume depletion. This remains to be determined, however.

Atrial natriuretic peptide: There is a clear interaction between dopamine receptors and ANP. The natriuretic response to ANP requires an intact renal dopamine system (263, 392, 481, 504, 574, 659). The natriuretic effect of ANP is abolished by D₁R but not D₂R antagonists (246, 316, 375, 393, 463) or carbidopa, an inhibitor of dopamine synthesis (309). ANP and dopamine may have additive effects on sodium excretion (263) and dopamine and ANP synergistically inhibit NHE3 (671) and Na⁺/K⁺ATPase activity that is abolished by a D₁R antagonist (268). This may entail the ability of ANP to recruit D₁Rs from the cytoplasm to the plasma membrane in renal tubule cells (81). The response is mimicked by cGMP, the second messenger for ANP, and requires dopamine binding to the D₁-like receptor (267, 268). ANP may affect dopamine synthesis and metabolism. ANP has been reported to decrease dopamine formation in rat renal slices (574, 579). The inhibitory effect of ANP on the renal synthesis of dopamine is dependent on the activation of a membrane-operated mechanism, coupled to guanylate cyclase, controlling the entry of L-DOPA into the cells (579). This may not be operative *in vivo* because, ANP increases urinary dopamine (309) that may be due to an ANP-mediated decrease in renal dopamine turnover and catabolism by inhibiting COMT activity (118).

Cholecystokinin receptors: There are two cholecystokinin receptors, namely, cholecystokinin type A receptor (CCKAR) and cholecystokinin type B receptor (CCKBR). Cholecystokinin modulates dopamine release in the nucleus accumbens through CCKAR. Cholecystokinin may also modulate D₂R expression in this nucleus accumbens; D₂R expression is higher in CCKAR^{-/-} and lower in CCKBR^{-/-} mice than in wild-type controls (410). The CCKBR is involved in the regulation of Na⁺/K⁺ATPase activity; low levels of cholecystokinin activates Na⁺/K⁺ATPase in the brain of CCKBR-deficient mice (514). Also, activation of CCKBR reduces the affinity of the D₂R in the brain (6) *in vivo*, *ex vivo* (364), and *in vitro* (131). CCKBR is expressed in the kidney and the postprandial increase in sodium excretion may be mediated by an increase in serum gastrin acting at CCKBR in the kidney (488).

Endothelin receptors: There are two endothelin receptors, endothelin A receptor (ETAR) and endothelin B receptor (ETBR) (491, 622). In the brain striatum, stimulation of ETBRs increases dopamine release but dopamine does not increase endothelin-1 levels (630). The ETB and dopamine receptors can interact to regulate renal function and blood pressure. Stimulation of the D₃R increases ETBR protein expression and D₃R/ETB receptor co-immunoprecipitation and colocalization (Fig. 5) in renal proximal tubules. The interaction between D₃R and ETBR has physiological significance because pretreatment with a D₃R agonist increases the ETBR-mediated inhibitory effect on Na⁺/K⁺ATPase activity in renal proximal tubule cells from WKY rats (370,695). Conversely, stimulation of ETBR increases D₃R expression and function in renal proximal tubule cells from WKY rats (255). The natriuretic effect D₃R may be, in part, mediated by ETBR because the natriuretic effect of D₃R is attenuated in WKY rats when the renal ETBR is blocked (76,704). In renal proximal

tubule cells, the ability of D₃R to stimulate ETB expression is blocked by an L-type calcium channel blocker (695)

The D₂R may also regulate ETB receptor expression. D₂R^{-/-} mice have increased ETBR expression and an ETBR blocker normalized blood pressure in these mice but did not affect the blood pressure of D₂R wild-type littermates (365). GPR37, a parkin-associated endothelin-like receptor, can associate with D₂R in HEK-293 cells (143). In rat lactotrophs, D₂-like receptor stimulation antagonizes the ETAR-mediated activation of large-conductance K⁺ channels (313). The functional consequences of D₂R and ETBR interaction on renal ion transport remain to be determined.

Insulin and Insulin receptors: Insulin and dopamine have opposite effects on Na⁺/K⁺ATPase activity in renal proximal tubule cells and may counter-regulate each other. Chronic exposure of cells to insulin causes a reduction in D₁R abundance and uncoupling from G proteins that result in impairment of the inhibitory effect of dopamine on Na⁺/K⁺ATPase and NHE3 activity (276, 372), suggesting a direct role of insulin on D₁R regulation (44, 624). Insulin causes renal D₁R desensitization via GRK2-mediated receptor phosphorylation (*vide infra*) involving PI3 kinase and PKC (45). Hyperinsulinemic animals and patients with type 2 diabetes have a defective renal dopaminergic system (550, 620). In obese Zucker rats, a model of type 2 diabetes, or in insulin-induced hypertension, renal D₁Rs is downregulated and dopamine fails to produce diuresis and natriuresis (276, 372). Treatment with an insulin sensitizer, rosiglitazone, decreases plasma insulin levels and restores D₁R function (618, 624). Insulin has also been shown to increase the expression of the D₅R in renal proximal tubular cells from WKY rats, probably a compensatory response. In HEK293 cells heterologously expressing the D₅R, pre-treatment with insulin increases the D₅R-mediated inhibition of Na⁺/K⁺ATPase (682). Both PKC and PI3 kinase are involved in the signaling pathway leading to increased D₅R expression.

Dopaminergic activity may influence insulin secretion. The D₁-like receptor agonist fenoldopam improves peripheral insulin sensitivity and renal function in streptozotocin-induced type 2 diabetes in rats (625). D₂-like receptors in pancreatic beta cells inhibit (516) or stimulate glucose-stimulated insulin secretion depending on dopamine concentration; an inhibitory effect occurs at higher dopamine concentration (10⁻⁷ to 10⁻⁴M), while the effect is stimulatory at lower dopamine concentrations (<10⁻⁸M) (557). Activation of D₂-like receptors with bromocriptine decreases insulin levels and ameliorates several metabolic features in obese women (330). In D₃R-deficient mice, plasma insulin levels are increased and high-fat diet induces adiposity, supporting an inhibitory effect of D₂-like receptors on insulin secretion (404). The counter-regulatory actions of the insulin and dopamine receptors extend to their effects on vascular proliferation. Bromocriptine, a D₂-like receptor inhibitor, inhibits the insulin-like growth factor-mediated proliferation in rat vascular smooth muscle cells (A7r5) and human aortic smooth muscle cells (716). Stimulation of D₁-like or D₃ receptor inhibits insulin receptor expression and insulin-mediated proliferative effects in vascular smooth muscle cells showing an interaction between dopamine (D₁-like and D₃Rs) and insulin receptors (705). A D₃R antagonist was found to be protective of renal injury in hypertensive type II diabetic SHR/Ncp rats (227). In these rats, a D₃R antagonist ameliorated glomerulosclerosis and prevented mesangial cell proliferation. As indicated

above, D₃R increases glomerular filtration rate that is mediated by renal nerves (376,377,380,407,421).

Dopamine and prostaglandins—Earlier studies have suggested that the renal vasodilatory effect of dopamine is independent of prostaglandins because indomethacin, an inhibitor of prostaglandin synthase, did not affect the renal vasodilatory effect of dopamine or the D₁-like receptor agonist fenoldopam in the dog or rat (474, 510) or human (206). The intrarenal arterial infusion of the D₁-like receptor agonist fenoldopam is also not associated with an increase in urinary prostaglandin E₂ (PGE₂) and F₂ α in the dog (306). Subsequent studies in normotensive humans revealed that the renal vasodilatory effect of dopamine was also not associated with an increase in urinary excretion of PGE₂ but rather with 6-keto-PGF₁ α , a stable metabolite of prostacyclin. The effect of dopamine was blocked by metoclopramide or domperidone, D₂-like receptor antagonists, and two cyclooxygenase inhibitors (270,389). These studies suggest that the dopamine and prostaglandin communication is via the D₂-like rather than D₁-like receptors. D₂-like but not D₁-like receptors may also regulate PGE₂ synthesis in rat inner medullary collecting cells (272, 386). Dopamine stimulates medullary prostaglandin production and may be involved in the attenuation of deoxycorticosterone acetate/high salt-induced increase in blood pressure (686).

As aforementioned, eicosanoids may act synergistically with D₁-like receptors to inhibit NKCC2 activity in the mTAL and Na⁺/K⁺ATPase in all nephron segments (225, 328, 388, 460). As mentioned above, the renal cortical expression of COX-2 is tonically suppressed by the renal D₁-like receptors secondary to inhibition of proximal tubular reabsorption (715).

Regulation of reactive oxygen species

Dopamine has contrasting effects on ROS production. At high concentrations, dopamine, D₁-like receptors agonists (226), and D₂-like receptors can increase ROS production. However, physiological concentrations of dopamine and low concentrations of D₁-like and D₂-like receptors agonists act as antioxidants (92,120,290,722).

D₁-like receptors have been reported to decrease oxidative stress in lymphocytes, neural, and vascular smooth muscle cells and the kidney (120, 529). Both the D₁R and D₅R have antioxidant properties. Studies in mice lacking the D₅R and in HEK293 cells expressing the human D₅R (HEK-hD₅R) have indicated that the D₅R has an important role in regulating the production of ROS. Plasma thiobarbituric acid-reactive substances (TBARS), an index of systemic oxidative stress, and the expression of NADPH oxidase proteins (gp91^{phox} and p47^{phox}) and NADPH oxidase activity in the brain and kidney are increased in D₅R^{-/-} mice relative to D₅R wild-type littermates (Table 1). Chronic administration of apocynin, an NADPH inhibitor, normalizes blood pressure, plasma TBARS, and NADPH oxidase activity in the brain and kidney of D₅R^{-/-} mice, suggesting that the D₅R keeps blood pressure in the normal range by preventing excessive ROS production (685). The inhibitory effect of D₅R activation on NADPH oxidase activity may also involve direct and indirect mechanisms. In HEK-hD₅R cells, the D₅R co-localizes with gp91^{phox} in cell surface membranes; D₅R receptor stimulation induces the dissociation of D₅R and gp91^{phox} and impairs the

translocation of p67^{phox}, a cytosolic component of the NADPH oxidase, to the oxidase complex. D₅R may also decrease oxidative stress through a PLD-mediated signal transduction pathway (684,685). Stimulation of PLD increases NADPH oxidase activity and the production of ROS. Renal PLD expression and activity are higher in D₅R^{-/-} mice compared to D₅R^{+/+} mice. Moreover, activation of the D₅R by fenoldopam in HEK-hD₅R cells decreases PLD expression and activity. The increase in mRNA expression α/β hydrolase 1, which can decrease NADPH oxidase activity, in D₅R^{-/-} mice may be a compensatory response (596). The D₅R may also negatively regulate nitrogen reactive species (33).

More recent studies in HEK293 cells expressing the human D₁R but not the human D₅R also indicate that the D₁R has antioxidant properties. The D₁R-mediated inhibitory effect on NADPH oxidase activity is via a PKA and PKC cross-talk that is mediated by increased phosphorylation of PKC θ at serine 676 (698). The redox status of the D₁R^{-/-} mice remains to be determined.

The function of the D₁-like receptors is impaired by oxidative stress. Rat renal proximal tubules treated with hydrogen peroxide or proximal tubules from streptozotocin-treated rats, both of which have increased oxidative stress, have impaired D₁-like receptor function. Apparently, oxidative stress causes the nuclear translocation of NF κ B and subsequent activation of PKC (46) and GRK2, which in turn increases D₁R phosphorylation impairing its activity (26,395). Furthermore, in old rats that also have increased oxidative stress and impaired D₁-like receptor function, exercise or treatment with an antioxidant decreases oxidative stress and restores normal D₁R function (28). In Sprague-Dawley rats, treatment with an oxidant and high salt increases blood pressure and decreases the response to endothelium-dependent and endothelium-independent vasorelaxation by reducing NO levels and signaling (46). In this model, treatment with tempol restores D₁R responses and normalizes blood pressure (48).

The D₂R has also been shown to have antioxidant activity. D₂R agonists have neuroprotective effects in experimental models and show free radical scavenging and antioxidant activity (451). *In vitro* and *in vivo* studies have shown that the protective effects of D₂R are eliminated when they are co-administered with D₂R antagonists, indicating that D₂R activation contributes to the neuroprotective effects (283, 606). The neuroprotective effect of D₂R may be related to its ability to decrease ROS production by the mitochondria (469). D₂R^{-/-} mice are hypertensive and have increased urinary excretion of 8-isoprostane, a parameter of oxidative stress, as well as increased activity and expression of NADPH oxidase and decreased expression of the antioxidant enzyme HO-2 in the kidney, suggesting that the regulation of ROS production by D₂R involves both inhibition of pro-oxidant and stimulation of antioxidant systems (22). Apocynin (an NADPH inhibitor) or hemin (an inducer of HO-1) normalizes blood pressure in D₂R^{-/-} mice. Spironolactone normalizes the blood pressure in D₂R^{-/-} mice but does not normalize the renal expression of NADPH oxidase, indicating that the increased ROS production is only partly mediated by impaired aldosterone regulation (22).

The effect of D₃R receptors on ROS production is controversial. The D₃R has also been reported to increase a dopamine autotrophic factor that has an antioxidant action and thus the D₃R has antioxidant effect, albeit indirectly (92). The selective D₃R agonist pramipexole has also reported to inhibit lipid peroxidation (722). Pramipexole increases the activity of antioxidant enzymes (glutathione peroxidase and catalase) and inhibits the production of ROS by the mitochondria but this effect is not related to its dopamine agonist properties (176, 349). Moreover, the D₃R has been reported to stimulate PLD activity in HEK293 cells heterologously expressing the human D₃R. However, overexpression systems may not always mimic the endogenously expressed proteins. The neuroprotective effect of D₄R agonists is apparently independent of any action on ROS (224).

Regulation of inflammation

Dopamine and dopaminergic drugs have regulatory functions on the immune response and the inflammatory reaction (61,317,720). Treatment with dopaminergic agonists increases the expression of macrophage receptors important in the host defense reaction and in immune-mediated disorders (222). Dopamine inhibits the release of interleukin-2 (IL-2), interferon (IFN) γ and IL-4 (197, 445), and the lipopolysaccharide-stimulated production of IL-12 p40 (251), but stimulates the production of the anti-inflammatory IL-10 (251) in immune cells. *In vivo* administration of dopamine or dopexamine decreases the number of splenic IFN γ producing cells (87), the tumor necrosis factor (TNF) α response to endotoxin and reduces leukocyte activation in experimental sepsis (74). Conversely, treatment with a dopaminergic antagonist stimulates macrophage constitutive and inducible gene expression of IL-1 β , IL-6, and TNF α (720). Dopamine treatment in brain-dead rats, a condition that is associated with profound inflammation in end-organs, reduces renal monocytes infiltration and expression of IL-6 (264), and improves renal function after transplantation (264). Inflammatory cells may also regulate dopamine secretion. Adult female rats exposed to IL-6 *in utero* have decreased dopamine excretion and increased renal renin, angiotensinogen and AT₁R expression but decreased AT₂R expression (532).

The anti-inflammatory effects of dopamine and dopaminergic agonists are mediated at least in part by the D₂R. The D₂R regulates the inflammatory reaction (56, 387). The D₂R is expressed in lymphocytes, monocytes, neutrophils, macrophages, and other immunocompetent cells (358). Dopamine or the D₂-like receptor agonist, bromocriptine, inhibits lymphocyte proliferation (415), decreases the antigen-induced macrophage activation and the secretion of IL-2, IL-4, and IFN γ (197). Bromocriptine also decreases the severity of experimental autoimmune encephalomyelitis, a T-cell-mediated disease (509). In contrast, the D₂-like receptor antagonist haloperidol induces macrophage activation as a consequence of a direct action on macrophage dopamine receptors (374). In normal human lymphocytes, dopamine through the D₂R induces the secretion of the anti-inflammatory cytokine IL-10, but not of IFN γ and IL-4, by *de novo* gene expression (73). TNF α release from activated rat mast cells is inhibited by a mixed D₁-like receptor antagonist and D₂R agonist (342).

D₂Rs also regulate cytokine and chemokine production in the kidney. Renal tubule cells produce both proinflammatory cytokines and chemokines IL-1 β , TNF α , IL-12, and

macrophage chemoattractant protein (MCP)-1 and anti-inflammatory cytokines IL-10 and TGF β (208,241,518,649). Both pro-inflammatory and anti-inflammatory cytokines are secreted by tubular cells across their apical or basolateral membranes (649); the pro-inflammatory cytokines contribute to the development and progression of glomerular and tubular injury (208, 241, 518, 649). Silencing the D₂R in renal proximal tubule cells increases the expression of TNF α and MCP-1(24); expression of TNF α , MCP- 1, IL-6, and IL-10 are increased in renal cortex of D₂^{-/-} mice. These mice show renal injury and increased urinary albumin, suggesting that altered D₂R function results in renal inflammation and injury (24).

Infiltration of inflammatory cells and oxidative stress in the kidney play a role in the development of renal injury and in the induction and maintenance of hypertension that may be related to dysfunction of D₁-like receptor function (27, 28). Obesity, via the associated hyperinsulinemia and other as yet unidentified factors, may also contribute to D₁-like receptor dysfunction (47). Whether this effect is mediated by D₁R or D₅R remains to be determined. The role of other dopamine receptors in inflammation is not clear. Pramipexole, a D₃R selective agonist, has been shown to protect dopaminergic neurons against lipopolysaccharide-induced dopaminergic cell death without affecting the inflammatory response (288).

Regulation of Dopamine Receptor Function

The generally accepted paradigm for GPCR trafficking starts with the binding of a ligand to its GPCR followed by receptor desensitization—or the waning of receptor responsiveness to subsequent stimulation—through a change in receptor conformation, modification and/or phosphorylation by G protein-coupled receptor kinases (GRKs), association with β -arrestin and other adaptor proteins, uncoupling from G proteins, and by receptor endocytosis/internalization. Internalized GPCRs, however, can continue to be active, prior to their eventual desensitization (84, 298). The internalized GPCR is dephosphorylated/demodified, dissociates from β -arrestin and the resensitized GPCR is recycled back to the plasma membrane. GPCRs that are not recycled back to the plasma membrane are directed to lysosomes or proteasomes for degradation. Some GPCRs, for example, D₂R, are not desensitized by phosphorylation, but rather by association with β -arrestin and phosphorylation is required for its recycling (109). In addition, some GPCRs may not undergo internalization, for example, AT₂R (259), A_{2A}R (712), and D₄R (588), are resistant to desensitization, for example, β_3 -adrenergic receptor (304), or to degradation, for example, β_1 -adrenergic receptor (367). Although the D₄R has been shown to induce β -arrestin translocation to the plasma membrane (110), a more recent study has shown that D₄R does not bind to arrestin (588).

At least three families of regulatory molecules contribute to GPCR desensitization, namely, second messenger-dependent protein kinases, GRKs, and arrestins (172,189,192, 468,501,615). Homologous desensitization, in response to agonist stimulation, occurs via the action of a member(s) of the GRK family (172,189,192,468,492,501,615). Heterologous desensitization, mediated by second messenger-dependent kinases, occurs when a decrease in receptor responsiveness is induced by a ligand other than its own specific ligand. The

internalized receptors are sorted into divergent pathways, that is, the receptors are: (i) sorted into recycling endosomes for their return to the cell membrane (recycling and resensitization); (ii) accumulate in late endosomes and are passed on to the lysosomes or proteasomes for subsequent degradation; or (iii) transported to the perinuclear endosomes (trans-Golgi network, TGN) and to the late endosomes for eventual lysosomal degradation) (142, 199, 383, 674). The GPCR-associated sorting protein (GASP) is involved in the sorting of certain GPCRs (not D₁R) to the lysosome (614,663). Additional proteolytic mechanisms, such as proteasomes or cell-associated endopeptidases, are also implicated in downregulating certain GPCRs (363,639). For example, while angiotensin II trafficks the AT₁R to lysosomes, stimulation of the D₅R trafficks AT₁R to proteasomes (199,363).

As with other GPCRs, the signal transduction that follows dopamine receptor occupation by its ligand is highly regulated (172,189,192,468,501,615) to ensure the specificity of cellular response, both temporally and spatially. Early in the exposure of cells to dopamine, dopamine recruits its own receptors specifically D₁R (80, 200, 696) and D₃R (634) to caveolin-1-containing microdomains of the plasma membrane (198, 331). An intact microtubulin network has been shown to be important in the recruitment of D₁R (332). In addition, wild-type GRK4 is important in D₁R and D₃R recruitment in human renal proximal tubule cells (198,634).

Following receptor occupation by the ligand, the cognate trimeric G protein dissociates into G α and G $\beta\gamma$ subunits (Fig. 6). The G α subunit either activates or inhibits the enzyme adenylyl cyclase to either increase or decrease the production of cAMP, depending on the dopamine receptor subtype. The G $\beta\gamma$ subunit recruits GRKs, which then modify and/or selectively phosphorylate serine and threonine residues at the third intracytoplasmic loop and carboxy terminus to promote the binding of arrestins, thus disrupting the interaction between the dopamine receptor and G protein subunits (295, 324, 619). The phosphorylated/modified GPCR binds to arrestin and the GPCR/ β -arrestin complex undergoes endocytosis/internalization via clathrin-coated pits into a series of endosomal units, where it is dephosphorylated/demodified and recycled back to the plasma membrane, or degraded. The rapidity in which the GPCR is recycled back to the plasma membrane is dependent upon the stability of the association of a particular GPCR with arrestin. There are four members of the mammalian arrestin family; arrestin1 expressed in retinal rods, arrestin 4 expressed in retinal cones, and arrestin 2 (or β -arrestin 1) and arrestin 3 (or β -arrestin 2) which are ubiquitously expressed. Once internalized, the dopamine receptors are sorted into recycling endosomes for their return to the cell membrane (recycling and resensitization) or in late endosomes for subsequent lysosomal degradation. The dichotomous fates of internalized dopamine receptors play a critical role in dictating the signaling response after the initial “desensitization” event, underscoring the critical function of GPCR trafficking in signal termination or propagation and in receptor resensitization (391).

There are two classes of GPCRs based on their binding to arrestins. Class A receptors bind to arrestin 3 to a greater extent than arrestin 2 and do not bind to arrestin 1 or 4. Class A receptor binding to arrestin is unstable, dissociates at or near the plasma membrane, and not endocytosed. Class B receptors bind to arrestin 2 and 3 with similar affinities and also interact with visual arrestin (442). Class B receptor binding with arrestin is stable, and the

GPCR/arrestin complex is internalized in endocytic vesicles. Dopamine receptors have been classified as Class A receptors because they are rapidly recycled back to the plasma membrane after agonist stimulation. However, D₁R and D₃R are also endocytosed (198,324,634). Moreover, arrestin 3 binds to agonist-stimulated D₂R preferentially over the D₃R (343). The recycling of dopamine receptors to the plasma membrane involves protein phosphatases and sorting nexins, among others; sorting nexin 1 for D₅R (262), the isoform for the other dopamine receptor subtypes remains to be identified. We have reported that protein phosphatase 2A is important in D₁R recycling, at least in renal proximal tubule cells (697). In the neurocortex, D₁R has been reported to be linked to both protein phosphatase 2A and protein phosphatase 2B (5). Postsynaptic density-95 (PSD-95) is also involved in D₁R recycling (601); PSD-95 also constitutively interacts with D₂R and D₅R but its role in D₂R and D₅R recycling remains to be determined. Other proteins reported to affect the trafficking of D₁R include COPI, which associates with D₁R to transport it to the cell surface (65), and DRiP78, which leads to the retention of D₁R in the endoplasmic reticulum, reduced ligand binding, and a decrease in D₁R glycosylation (66). DRiP78 may act via G protein γ subunit (145),

G protein-coupled receptor kinase and dopamine receptors

There are seven members of the GRK family. GRKs 1 and 7 belong to the rhodopsin family, GRKs 2 and 3 belong to the β -adrenergic receptor kinase (β ARK) family, and GRKs 4, 5, and 6 belong to the GRK4 family. The tissue distribution of GRK4 is different from the other GRKs. GRKs 1 and 7 are expressed in rods and cones, respectively. GRKs 2, 3, 5, and 6 are ubiquitously expressed, while GRK4 is expressed to a greater extent in the testes and myometrium and to a lesser extent in specific brain areas and the kidney (171,172).

GRK regulation of dopamine receptors

The D₁R (but not D₅R) endogenously expressed in human (171, 172, 198, 657) and rat renal proximal tubule cells (45, 537, 618) is regulated to a lesser extent by GRK2 and to a greater extent by GRK4 in human kidneys, (171, 657) but the converse may be true in rat kidneys (245, 618); endogenously and heterologously expressed GRK4 and D₁R colocalize and interact in human renal proximal tubule cells (Fig. 7). GRK6 may not be important in the regulation of D₁R in the kidney (677), but is important in D₁R desensitization in intestinal crypt cells, emphasizing the importance of cell type in D₁R regulation (183). GRK3 also can desensitize rat D₁R expressed in HEK 293 cells (615). The GRK regulating renal D₂R is not known but D₂R in other cells is regulated by GRK2, GRK3, GRK5, and GRK6 (292, 293, 427) with D_{2S}R affected to a greater extent than D_{2L}R (110). However, GRK2 or GRK3 but not GRK5 or GRK6 is involved in the desensitization of the calcium signal mediated by the interaction of D₁R/D₂R heterologously expressed in HEK293TSA cells (572). The desensitization of D₃R is weakly regulated by GRK2 and GRK3 (323), but robustly by GRK4 (GRK4 γ > GRK4 α) (634); GRK4 and D₃R colocalize and interact in human renal proximal tubule cells (Fig. 8). The GRK regulating D₄R is not clear but does not seem to involve either GRK2 or GRK3. The GRK regulating D₅R is also not clear but does not seem to involve GRK4.

GRK4 and renal dopamine receptors

GRK4 is constitutively active which may be due to its ability to bind to inactive G_{α_S} and G_{β} subunits (319). Unlike the other GRKs, GRK4 has several splice variants; four (α , β , γ , and δ) have been reported in humans, five (A, B, C, D, E) in rats, and one in mice (493,494,527,537,637). The GRK α in humans, GRK4A in rats, and the only GRK4 reported in mice are closely homologous, sharing about 70% sequence identity. (493,494). GRK4 has several single nucleotide polymorphisms (Fig. 9) in its coding region that predispose to essential hypertension and salt sensitivity.

The GRK4 isoform that desensitizes D_1R and D_3R is cell specific; GRK4 γ desensitizes both D_1R and D_3R , heterologously expressed in Chinese hamster ovary cells and endogenously expressed human renal proximal tubule cells (172, 634); GRK4 α desensitizes the rat D_1R in HEK 293 cells (501) and D_3R in human renal proximal tubule cells (634). There is also GRK4 isoform-specific regulation of other GPCRs. GRK4 α desensitizes the metabotropic glutamate receptor, G protein-coupled calcium-sensing receptor (482), GABA $_B$, (310,477) luteinizing hormone/human chorionic gonadotropin receptor (422, 494), FSH receptor (347), rhodopsin, (527), and mutant (Y326A) β_2 adrenergic receptor (405).

GRK4 α does not desensitize the AT_1R (461), formyl peptide receptor (500), mGlu4 metabotropic glutamate receptor (278), mGlu5 metabotropic glutamate receptor (585), parathyroid hormone receptor (172,182), wild-type β_2 adrenergic receptor (461, 567) and m1 to m5 muscarinic receptors (621); GRK4 α is also not linked to G_{α_q} (483). GRK4 β desensitizes the luteinizing hormone/human chorionic gonadotropin receptor (279) and maybe the V_2 vasopressin receptor (629). GRK4 δ , in the presence of GRK5 and GRK6, desensitizes the m2 muscarinic receptor (637) and luteinizing hormone/human chorionic gonadotropin receptor (279) but sensitizes the m3 muscarinic receptor (621). GRK4 δ does not desensitize D_1R (unpublished data). As stated above, GRK4 γ , especially its variants, desensitizes the D_1R (172, 533) and D_3R (634) and only at high concentrations does GRK4 γ minimally desensitize the luteinizing hormone/human chorionic gonadotropin receptor (494). GRK4 γ wild-type does not desensitize the parathyroid hormone receptor (172) and AT_1R but GRK4 γ 142V may actually increase, directly or indirectly, AT_1R expression and function (653). Human GRK4 γ 142V transgenic mice on normal salt diet have increased AT_1R expression, while renal AT_1R expression in GRK4 γ 486V transgenic mice have increased renal AT_1R expression on high but not normal salt diet (651).

GRK and sodium transporters

GRK2 maintains ENaC in the active state and decreases its degradation by phosphorylating the C terminus of the β subunit (25,140,538). GRK2 and GRK3 phosphorylate and may aid in the internalization of $Na^+/K^+ATPase$ (326). How this effect of GRK2 on D_1R desensitization and decreased internalization of $Na^+/K^+ATPase$ affects sodium transport is unclear (70,72,198,321,332,470). NKCC1 colocalizes with GRK3 in rodent olfactory epithelia but its regulation by GRK3 in the kidney has not been demonstrated (406).

GRK and essential hypertension

Hypertension, which causes 50% of reversible heart disease and 75% of strokes, is the most expensive disease in the United States, with the economic burden in excess of \$69 billion in 2008. Hypertension affects a third of middle-aged individuals but the prevalence is higher (65%) in individuals above 60 years of age (539, 590). About 30% to 50% is thought to be heritable but the genetic causes of essential hypertension have been difficult to identify (249). More than 1 gene is undoubtedly involved, because Mendelian dominant and recessive traits are not readily discernible in hypertensive subjects, except in those with monogenic forms of hypertension. Indeed, recent genome-wide association studies (GWAS) have been able to identify 2% of genetic factors believed to influence blood pressure (4,111,248,359,435,648). However, the GWAS were not designed to identify predisposing genes engaged in a complex network of gene-gene and gene/environment interactions (412), for example, salt sensitivity, a dietary sodium-induced increase in blood pressure that may or may not be in the hypertensive range. Several criteria have been suggested to link gene(s) to complex diseases such as hypertension and salt sensitivity but the definitive evidence is swapping one phenotype for another (i.e., transgenic studies) (205). Many genes have been proposed to be causal of hypertension, however, their gene variants, including those identified in the GWAS, have not been shown to produce hypertension in mice. Many gene overexpression and deletion studies are performed in mice without taking into account the salt sensitivity of the strain. C57BL/6 mice from Jackson Laboratories, Bar Harbor, Maine, USA have an impaired ability to excrete a salt (NaCl) load with a resultant increase in blood pressure, while others are salt-resistant (e.g., SJL mice) (163). We have recently reported that the renal D₁-like receptor function is impaired in C57BL/6 Jackson mice and is associated with increased expression of GRK4 upon salt loading (163). Deletion of *Grk4* gene in C57BL/6 mice prevents the development of salt-sensitive hypertension (20). Renal D₁-like receptor function is also impaired in the SHR. The impaired renal D₁-like receptor function in the SHR is not due to increased renal nerve activity (31), but may be related to increased expression of GRK4E; renal cortical silencing of *Grk4* attenuates the increase in blood pressure with age in SHRs but not in normotensive WKY rats (537). The mechanism for the increased GRK4 expression in C57BL/6 and SHR is not known. Aging and obesity are associated with decreased D₁-like receptor or dysfunction (29, 47, 312, 632). In obese rats, the D₁-like receptor dysfunction is acquired and has been related to increased GRK4 expression and membrane translocation of GRK2 due to insulin resistance (618).

The GRK4 locus on human chromosome 4p16.3 is linked to the increase in blood pressure from childhood to adulthood and to hypertension (13, 105, 719). Interestingly, adolescents with GRK4 65L, 142V, and A486 haplotype have a greater increase in blood pressure with age than those with the wild-type GRK4 haplotype (718). GRK4 gene variants (65L, 142V, and 486V) are associated with essential hypertension in several ethnic groups: Caucasians, Chinese, Ghanaians, and Japanese (62, 232, 536, 587, 670). In salt-sensitive hypertensive Japanese, the presence of three GRK4 variants impaired the natriuretic effect of a dopaminergic drug and predicted salt-sensitive hypertension correctly in 94% of cases (536). In Ghanaians, the combination of angiotensin-converting enzyme insertion/deletion polymorphism and GRK4 65L has an estimated predictive accuracy for hypertension of 70% (669, 670). A meta-analysis revealed a significant association of GRK4 486V with

hypertension with an odds ratio of 1.5 (95% CI: 1.2–1.9). One study, however, did not find an association of GRK4 486V with the top fifth percentile of diastolic blood pressure of subjects with white European ancestry; the authors did not test the association of GRK4 gene variants with hypertension (499). Another study did not find an association between GRK4 142V and hypertension, but did find an association between variants of the promoter region of D₁R and hypertension (589). The discordance of this report in European Caucasians (589) with other populations may be the influence of ethnicity in the phenotypic expression of a quantitative trait such as essential hypertension. Interestingly, low-renin hypertension is less frequent in Caucasians (15–20%) (223) than in other ethnic groups (e.g., 40–60% in Japanese) (598). In the Japanese, the single best genetic model for low-renin hypertension included only GRK4 A142V, by itself, or GRK4 A142V and aldosterone synthase gene, CYP11B2, with an estimated predictive accuracy of 78% (536). Ethnicity may also explain some of the discordances. GRK4 65L and GRK4 142V are less frequent, while GRK4 486V is more frequent in Asians than in African-Americans. GRK4 486V is also more frequent in Hispanic and non-Hispanic whites than in African-Americans (371). Recent GWAS did not identify GRK4 as associated with hypertension (4, 111, 248, 249, 359, 435). This is probably because salt sensitivity was not taken into account and because previous studies have shown that it was critical to assess the role of GRK4 in conjunction with other GRK4 SNPs and genes, for example, ACE with GRK4 65L (669,670), *ADRB2*, *TH*, and with *GRK4 486V* (232). Also, GRK4 A142V is not included in the Affymetrix platform, Fremont, CA, USA.

Early in the stage of D₁R (80,200,332,696) and D₃R stimulation (634), D₁R and D₃R increase their respective function, in part, by recruiting intracellular D₁R and D₃R to the plasma membrane. This is afforded, in part, by GRK4 γ wild-type that increases the initial response to agonist stimulation (200,634). However, as indicated above, sustained stimulation results in desensitization and subsequent resensitization, which allows these receptors to respond to subsequent stimuli. The GRK4 γ wild-type (but not GRK4 α wild-type) desensitizes the AT₁R and decreases AT₁R expression in the kidney (651,653) (Fig. 10). GRK4 wild-type is necessary for D₁R and D₃R (200,634) to exert their renal autocrine/paracrine natriuretic function and inhibit the antinatriuretic effect AT₁R (651, 653). While GRK4 γ 142V transgenic mice are hypertensive even on a normal salt diet (650,653), GRK4 γ 486V transgenic mice develop hypertension only when stressed by a high salt diet (652). Depending upon the genetic background of the mouse, overexpression of human GRK4 γ wild-type converts a salt-sensitive phenotype to a salt-resistant phenotype, while overexpression of human GRK4 γ 486V converts a salt-resistant phenotype to a salt-sensitive phenotype (651, 652). These phenotypic changes may be related to differential expression of human GRK4 γ and regulation of D₁R and other GPCRs and could be taken as evidence of the “apparent polygenicity” of hyper-tension. GRK4 γ 65L transgenic mice are normotensive on a normal and high salt diet (unpublished data) but whether or not some form of stress is needed for the hypertensive phenotype to develop is not known. It is known, however, that adolescent African-Americans expressing GRK4 65L exposed to mental stress respond with an increase in blood pressure and a decrease in sodium excretion (718).

Role of Other GRKs in hypertension

GRK activity and GRK2 expression are increased in lymphocytes of patients with essential hypertension and SHRs (117, 174). The impaired β -adrenergic vasodilation in hypertensive patients (294) and SHRs (455) may be due to enhanced GRK2 expression. GRK2 regulates myocardial contractility via its regulation of β_1 -adrenergic receptors (635); the improved myocardial β -adrenergic responsiveness with exercise in hypertension is associated with decreased GRK2 abundance (384). ETA receptor responsiveness in resistance arteries is regulated by GRK2 but not by GRK3, GRK5, or GRK6 (417). Overexpression of GRK2 in vascular smooth muscles in mice produces hypertension and impairs the vasodilatory action of β -adrenergic receptors (148). The vasoconstrictor response to angiotensin II is also impaired in these mice, which is at odds with the increased reactivity and sensitivity to angiotensin II in essential hypertension (617). Interestingly, GRK2 activates the ENaC by phosphorylating the C terminus of its β subunit, making it insensitive to the ubiquitin protein ligases Nedd4 and Nedd2 (25,140,538). Although GRK2 polymorphisms have not been associated with human essential hypertension, renal expression of GRK2 is increased with aging (30), and by insulin/obesity/metabolic syndrome (45, 50, 618), and by oxidative stress (2, 46, 49) that impair D₁R function in rats. More importantly, increased GRK2 expression (but not GRK5) in lymphocytes of African-Americans correlates with hypertension (117).

Transgenic mice selectively expressing a competitive inhibitor of GRK3 (carboxyl-terminal plasma membrane targeting domain of GRK3) in the heart have increased blood pressure that is related to the regulation of endothelin and α_1 -adrenergic receptors (635, 636). GRK5 overexpression in vascular smooth muscle cells in mice also increases blood pressure. The hypertension in male GRK5 transgenic mice is, in part, because of decreased β_1 -adrenergic receptor activity, whereas the high blood pressure in female mice is because of increased activity of AT₁Rs (320). The increase in GRK5 in hypertension may be secondary not primary; angiotensin II-induced GRK5 upregulation in rat aortae may be due to hypertension *per se* (291).

In summary, there is GPCR specificity of GRK4, especially the human GRK4 γ isoform, in the regulation of D₁R and D₃R. The human GRK4 locus is linked to hypertension and the human GRK4 gene variants, either alone or in conjunction with variants of other genes, are associated with essential hypertension, especially the association of human GRK4 486V with salt sensitivity. Human GRK4 γ 142V transgenic mice are hypertensive even on a normal sodium intake and human GRK4 γ 486V transgenic mice are salt-sensitive. The ability of humans with salt-sensitive essential hypertension to excrete a chronic sodium load is inversely correlated with the number of human GRK4 allelic variants (536). Salt sensitivity may be imparted by the GRK4 gene variants, and this effect seems to be dependent on the number of allelic variants present. Additional genes contribute to the predictive value of GRK4 single nucleotide polymorphisms for hypertension and salt sensitivity, suggesting that epistasis is responsible for the etiology of this complex polygenic disorder. GRK4 gene variants may not only be predictive of hypertension phenotypes (e.g., salt sensitivity, low plasma renin), but may also predict drug response.

Conclusion

Dopamine controls water and electrolyte balance and blood pressure by regulating the secretion/release of hormones and humoral agents that affect water and electrolyte balance, salt “appetite” centers in the brain, and ion and water transport in the kidney and gastrointestinal tract. Independent of innervation, the kidney and intestines synthesize dopamine from circulating or filtered L-DOPA that is not metabolized to norepinephrine. Sodium intake and intracellular sodium are probably the major determinants of the renal tubular synthesis/release of dopamine. The physiological effects of dopamine occur by occupation of two families of cell surface receptors, D₁-like receptors comprising D₁R and D₅R, and D₂-like receptors, comprising D₂R, D₃R, and D₄R, interacting among themselves and with other GPCRs and hormones and humoral agents. D₁-like receptors are linked to vasodilation, while the effect of D₂-like receptors on the renal vasculature is probably dependent upon the state of renal nerve activity. The dopamine-induced increase in renal blood flow is not consistently associated with an increase in glomerular filtration rate. The autocrine/paracrine regulation of renal tubular sodium transport, mainly via D₁-like receptors, is mediated by tubular and not by hemodynamic mechanisms. The dopamine receptors are differentially expressed along the nephron; all the five dopamine receptor subtypes are expressed in the proximal tubule, distal convoluted tubule, and cortical collecting duct, D₁R, D₃R, D₄R, and D₅R in the mTAL, only D₃R in the cTAL, D₂R, D₃R, D₄R and D₅R in the outer medullary collecting duct, and only the D₂-like receptors D₂R, D₃R, and D₄R in the inner medullary collecting duct. Dopamine inhibits ion transport in the proximal and distal nephron. D₁-like receptors inhibit NHE3, NaPi2, and Cl⁻/HCO₃⁻ exchanger, ENaC at the apical membrane, and electrogenic Na⁺/HCO₃⁻ co-transporter and Na⁺/K⁺ATPase at the basolateral membrane. Dopamine may also inhibit NCC but stimulates NKCC2, the latter effect for K⁺ recycling. Dopamine and its receptors are important in the regulation of ion transport under conditions of euolemia and moderate volume expansion but have a minor role under marked volume expansion. D₂-like receptors participate in the inhibition of ion transport during conditions of euolemia and moderate volume expansion but may increase ion transport in hypovolemic states. Dopamine also controls sodium transport and blood pressure by regulating the production of ROS and the inflammatory response. Aging, obesity, metabolic syndrome, and essential hypertension are associated with abnormalities in dopamine production, receptor number, or posttranslational modifications.

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Figure 1.
Distribution of the dopamine receptor subtypes along the nephron. OS: outer stripe; IS: inner stripe (composite from several mammals, including humans).

Figure 2.

D₁R and D₃R colocalization in renal proximal tubule cells from WKY rats. The cells were washed, fixed, and immunostained for D₁R and D₃R receptors. Basal colocalization appears as discrete yellow areas in the merge image of FITC-tagged D₁R (pseudocolored green) and Alexa 568-tagged D₃R (pseudocolored red).

Figure 3.

Proposed schema of dopamine signaling in renal proximal tubule cells during salt-replete states. The dopaminergic response to conditions of salt repletion presumably involves both D_1R and D_3R acting synergistically; other dopamine receptors may take part in the physiological response, as well. During these conditions, the dopaminergic system is activated and the intrarenally produced dopamine occupies both D_1 and D_3 receptors (dopamine affinity for the dopamine receptors: $D_3R > D_4R > D_5R > D_2R > D_1R$). The D_1R , mediated by G_{α_s} , activates adenylyl cyclase, leading to increased intracellular cAMP/PKA, which, in turn, inhibits sodium transport in the renal proximal tubule cells and promotes natriuresis. Concurrently, the occupation of D_3R by dopamine leads to increased $G\beta\gamma$, which targets the C1b domain of adenylyl cyclases (other than adenylyl cyclase V, the preferred target of D_3R -associated G_{α_i}) to augment the synthesis of cAMP mediated by D_1R (and thus, the inhibition of sodium transport, green arrow), and to G_{α_i} to directly inhibit NHE3 activity (G_{α_s} can also directly inhibit NHE3). Adenylyl cyclase isoforms IV, V, and VIII are not expressed in the proximal tubules. D_3R can also couple to G_{α_s} to abet the adenylyl cyclase activity by itself (green arrow). During prolonged periods of salt repletion (blue arrow), the D_3R upregulates the expression of D_1R and ETB to ensure continued natriuresis, and downregulates AT_1R expression, directly by itself and indirectly through D_1R , to attenuate its anti-natriuretic effects. Hence, the D_1R and D_3R work in concert to promote natriuresis during salt-replete states. Dopamine may work in the same manner in other nephron segments, however, the processes involved in these segments are still not completely worked out.

Figure 4.

AT₁R is ubiquitinated and the ubiquitination of AT₁R is initiated at the plasma membrane. Ubiquitination of the enhanced green fluorescence (EGF)-tagged human AT₁R is initiated at the plasma membrane in HEK293 cells heterologously expressing the human AT₁R and human D₅R. In vehicle-treated cells, AT₁R (pseudocolored green) is mainly at the membrane but is also observed in the cytoplasm. Ubiquitin (pseudocolored blue) and the proteasome marker, p44S¹⁰ (pseudocolored red) are scattered throughout the cytoplasm. The D₅R agonist fenoldopam promotes the colocalization of AT₁R, p44S¹⁰, and ubiquitin at the plasma membrane. The changes in color indicate colocalization: yellow = colocalization of AT₁R and p44S¹⁰; cyan = colocalization of AT₁R and ubiquitin; magenta = colocalization of p44S¹⁰ and ubiquitin; white = colocalization of AT₁R, ubiquitin, and p44S¹⁰. The merging of the line drawings, red, green, and/or blue also depicts the colocalization of the different proteins. Scale bars are shown in vehicle-treated cells.

Figure 5.

D₃R and ETB interaction in Wistar-Kyoto (WKY) rat renal proximal tubule cells. Renal proximal tubule cells from WKY rats grown on cover slips were treated for 30 min with a D₃R agonist (PD128907), D₃R antagonist (GR103691), ETB antagonist (BQ788), vehicle (PBS), or a combination of the D₃R agonist with either antagonist after a 1-h serum starvation. The cell membrane was labeled with the cell-impermeant EZ-link sulfo-NHS-SS-Biotin for 30 min on ice. The cells were then fixed and permeabilized, double-immunostained for D₃R and ETB, and counterstained with FITC-conjugated avidin to label the cell membrane. Images were obtained for D₃R (pseudocolored red), ETB (pseudocolored green), cell membrane (pseudocolored blue) and the nucleus (pseudocolored magenta), via laser confocal microscopy. Under basal condition, both receptors are found at the cell membrane, with negligible colocalization. D₃R activation results in the internalization of both receptors and in increased colocalization (yellow punctate areas in inset image; white arrows). No changes in the distribution or extent of colocalization are observed with either D₃R or ETB antagonist treatment alone, or as co-treatment.

Figure 6.

Signal transduction of a dopamine receptor. Upon ligand binding to the dopamine receptor (DR), the cognate G protein dissociates into $G\alpha$ and $G\beta\gamma$ subunits. The $G\beta\gamma$ recruits G protein-coupled receptor kinase that then phosphorylates/modifies the receptor. This covalent modification of the receptor prevents it from interacting with G proteins and allows it to associate with other proteins, for example, β -arrestins, clathrin, and dynamin, to facilitate its endocytosis. Depending on the receptor subtype, the $G\alpha$ subunit either activates or inhibits adenylyl cyclase to increase or decrease cAMP levels to promote specific downstream signaling pathways.

Figure 7.

D₁R and GRK4 interaction in human renal proximal tubule cells. The interaction between D₁R and GRK4 was evaluated through confocal microscopy and bimolecular fluorescence complementation (BiFC) assay in human renal proximal tubule cells (hPTCs). Top: serum-starved hPTCs grown on cover slips were treated with the D₁-like receptor agonist fenoldopam (1 μ M, 5 min), fixed and permeabilized, double immunostained for D₁R and GRK4, and observed via laser scanning confocal microscopy. At basal conditions, the receptor (red) is distributed mostly at the cytoplasm and partially at the plasma membrane, while GRK4 (green) is localized in both the cytoplasm and cell membrane. Fenoldopam treatment promotes the redistribution of both proteins to the perinuclear area, where colocalization (yellow) is observed the most. Bottom: to confirm these observations, BiFC

assay was performed in hPTCs. This technique is based on the *in situ* formation of a fluorescent complex when two nonfluorescent fragments of a fluorophore are brought together by the interaction between the proteins tagged with the fragments and thus allows the visualization of protein-protein interaction in cells with neither the need to disrupt subcellular compartmentalization nor the use of exogenous fluorophore-labeled antibodies. hPTCs heterologously expressing D₁R tagged with the n-terminus of EYFP and GRK4 tagged with the c-terminus of the same fluorophore shows minimal fluorescent signal (pseudocolored green) at the basal state. Fenoldopam treatment markedly increases the signal at the perinuclear area.

Figure 8.

D₃R and GRK4 interaction in human renal proximal tubule cells. Top: human renal proximal tubule cells (hPTCs) grown on cover slips were serum-starved for 1 h and treated with the D₃R agonist PD128907 (1 μM) at the indicated duration of treatment. The cell membrane was labeled with a membrane-impermeant biotin, after which the cells were fixed and permeabilized, and double immunostained for D₃R (pseudocolored red) and GRK4 (pseudocolored green). The membrane (pseudocolored blue) was probed with Cy3-conjugated avidin. The distribution and co-localization of the proteins of D₃R (pseudocolored red) and GRK4 (pseudocolored green) were evaluated by laser scanning confocal microscopy. Both the receptor and GRK4 are distributed in both the cell membrane

(CM, pseudocolored blue) and the cytoplasm under basal conditions. Receptor activation promoted the internalization and colocalization (yellow in merge and inset images) of D₃R and GRK4 at the perinuclear area. Bottom: hPTCs were double-transfected with D₃R and GRK4 tagged with the c- and n-termini of the fluorescent protein EYFP, respectively. The cells were grown for 48 h post-transfection, serum-starved for 2 h, stimulated with the D₃R agonist PD128907 (1 μ M) at the indicated time points, and then prepared for confocal microscopy. The cell membrane (CM) was biotinylated with a membrane-impermeant biotin to allow visualization (pseudocolored red) and co-localization with the BiFC signal (pseudocolored green). Colocalization of the BiFC signal with the CM is indicated by yellow punctate areas in merge images. An overlay of the BiFC signal and the nucleus (pseudocolored blue) is shown to indicate intracellular distribution. Under basal conditions, minimal BiFC signal is observed at the CM and cytoplasm. D₃R stimulation markedly enhanced the interaction of the receptor and GRK4, which is observed in both the CM and perinuclear area. Untransfected cells treated with the D₃R agonist for 5 min were used as negative control (control). Scale bar = 10 μ m.

Figure 9.

GRK4 Structure. Schematic representation of the structure of GRK4 with the polymorphisms. The positions of the GRK4 gene variants associated with hypertension are shown in red. The numbers represent amino acid residues in GRK4.

Figure 10.

Differential effect of GRK4 wild-type versus variants on blood pressure regulation. Stimulation of D₁R and D₃R by dopamine leads to receptor phosphorylation/modification by wild-type GRK4, which in turn results in decreased sodium reabsorption in the proximal tubule (and other nephron segments) and increased sodium excretion (natriuresis) and normal blood pressure. The D₃R keeps the AT₁R expression in check. In the presence of GRK4 sequence variants, there is inherent uncoupling of the dopamine receptors with their cognate G proteins and hyperphosphorylation of the receptors, resulting in increased sodium reabsorption and retention, and consequently to high blood pressure. A dysfunction of the D₃R could presumably lead to increased AT₁R expression, which further exacerbates the retention of sodium in the body.

Table 1**Phenotypes of the Dopamine Receptor Knockout Mice**

	D₁^{-/-}	D₂^{-/-}	D₃^{-/-}	D₄^{-/-}	D₅^{-/-}
Blood Pressure	↑ (10)	↑ (365)	↑ (32,365)	↑ (58)	↑ (265)
Renal Na⁺ transporters					
NHE3	ND	↑ (#)	↑ (471)	↑ (644)	= (#)
NaPi2	ND	= (#)	= (#)	= (#)	↓ (#)
NKCC2	ND	= (#)	= (#)	↑ (646)	↑ (646)
NCC	ND	↑ (645)	↑ (#)	↑ (645)	↑ (645)
α ENaC	ND	= (#)	= (#)	↑ (#)	↑ (645)
Renin-angiotensin-aldosterone system					
Plasma/kidney renin	ND	ND	↑ (32)	= (58)	= (363)
Serum/urine aldosterone	ND	↑ (22)	= (32)	= (#)	= (#)
Renal AT ₁ R	ND	= (#)	↑ (32)	↑ (58)	↑ (363,711)
Oxidative stress					
Urine 8-isoprostane	ND	↑ (22)	= (#)	= (#)	↑ (684,685)
Renal NADPH oxidase	ND	↑ (22)	= (#)	= (#)	↑ (684,685)
Sympathetic nervous system					
Response to α -adrenergic blockade	ND	↑ (365)	= (#)	= (#)	↑ (265)
Renal/urine norepinephrine	ND	= (365)	= (#)	= (#)	= (265)

Increased (↑), decreased (↓) or similar (=) to their wild-type littermates.

Reference numbers are in parenthesis.

(#) Unpublished observations.

ND, not determined.