MINIREVIEW

Renal Dopamine Receptors and Hypertension

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Dopamine has been recognized as an important modulator of central as well as peripheral physiologic functions in both humans and animals. Dopamine receptors have been identified in a number of organs and tissues, which include several regions within the central nervous system, sympathetic ganglia and postganglionic nerve terminals, various vascular beds, the heart, the gastrointestinal tract, and the kidney. The peripheral dopamine receptors influence cardiovascular and renal function by decreasing afterload and vascular resistance and promoting sodium excretion. Within the kidney, dopamine receptors are present along the nephron, with highest density on proximal tubule epithelial cells. It has been reported that there is a defective dopamine receptor, especially D_1 receptor function, in the proximal tubule of various animal models of hypertension as well as in humans with essential hypertension. Recent reports have revealed the site of and the molecular mechanisms responsible for the defect in D_1 receptors in hypertension. Moreover, recent studies have also demonstrated that the disruption of various dopamine receptor subtypes and their function produces hypertension in rodents. In this review, we present evidence that dopamine and dopamine receptors play an important role in regulating renal sodium excretion and that defective renal dopamine production and/or dopamine receptor function may contribute to the development of various forms of hypertension. Exp Biol Med 228:134–142, 2003

Key words: natriuresis; proximal tubule; sodium transport; dopamine receptor; phosphorylation

Physiologic Role of Dopamine and Dopamine Receptors in the Kidney

Dopamine and Dopamine Receptor in the Kidney. Dopamine produces its biologic effects through five genetically distinct dopamine receptor subtypes: D_1, D_2, D_3, D_4, and D_5 (1). These receptors are categorized into two groups known as D_1-like (D_1 and D_5, whose rat homologs are D_{1A} and D_{1B}) and D_2-like (D_2, D_3, and D_4) dopamine receptors based on their ability to stimulate and inhibit adenylyl cyclase, respectively (Fig. 1). Of the cloned dopamine receptors, D_{1A}, D_{1B}, D_2, and D_3 have been identified in the kidney (1–5). The D_1-like receptors are present on the smooth muscle of blood vessels of most major organs, the juxtaglomerular apparatus, and on renal tubules (4–8). The D_2-like receptor exists on the glomeruli, postganglionic sympathetic nerve terminals, zona glomerulosa cells of the renal cortex, and renal tubules (4–8).

The source of the dopamine that activates tubular dopamine receptors is believed to be nonneuronal. The tubular cells contain abundant dopa decarboxylase, which is necessary for synthesis of dopamine (9). The substrate L-dopa is filtered freely from the glomerulus and is actively transported into tubular cells, where L-dopa is converted to dopamine by the decarboxylation process (10, 11). Once dopamine is synthesized, it is transported out of the cells where it can interact with dopamine receptors (Fig. 2).

Physiologic Role of Peripheral Dopamine Receptors. Since the discovery in 1964 that dopamine produces natriuresis and diuresis (12), a tremendous amount of progress has been made in understanding dopamine-mediated effects on renal and cardiovascular function. Selective D_1-like receptor agonists cause hypotension, reduce afterload, increase blood flow to certain organs, and promote urinary sodium and water excretion. Selective D_2-like receptor agonists produce hypotension, bradycardia, a decrease in afterload, and vasodilation in certain vascular beds (13, 14). The vasodilation and subsequent hypotension caused by D_1-like receptor agonists such as fenoldopam result from activation of D_1 receptors located on various vascular beds (13, 14). On the other hand, compounds such as bromocriptine, a D_2-like receptor agonist, cause vasodilation by activating prejunctional D_2-like receptors located on postganglionic sympathetic nerve terminals and causing inhibition of norepinephrine release (13, 14). Therefore, the magnitude of vasodilation and subsequent hypotension seen

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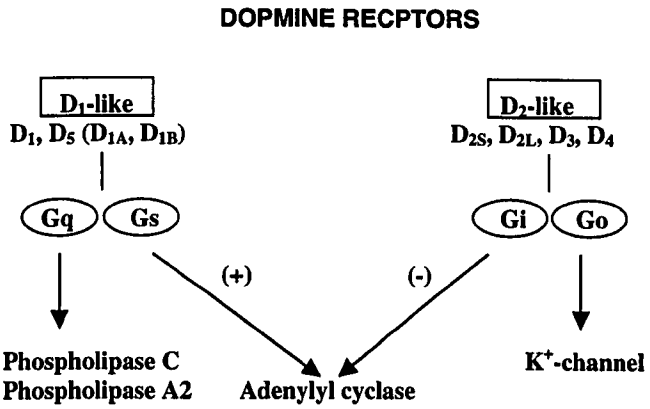

Figure 1. Dopamine receptor subtypes and their second messengers; (+), stimulation; (-), inhibition.

with D_2-like receptor agonists is dependent on existing sympathetic vasoconstrictor tone.

At higher doses dopamine also activates β-adrenoceptors and α-adrenoceptors (15). Studies from our laboratory and others have shown that the natriuretic and diuretic response elicited by D_1-like receptor agonists involves changes in intrarenal hemodymanics (increase in renal blood flow and glomerular filtration rates) as well as a direct tubular action (12, 16). At lower doses it is the direct action on renal tubules that accounts for the natriuresis and diuresis caused by selective D_1-like receptor agonists (8, 13, 16, 17).

A positive correlation has been reported among sodium intake, renal dopamine production, and urinary sodium excretion both in experimental animals and humans (18, 19). Several studies have shown a role for dopamine in the regulation of sodium excretion during acute volume expansion as well as during acute increase in sodium intake (20–25). The increased sodium excretion seen in animals placed on high sodium intake is accompanied by an increase in urinary dopamine excretion (24) and a decrease in Na,K-ATPase activity in the proximal tubules (26). These effects of dopamine can be blocked by D_1-like receptor antagonists (21, 22, 25, 26), suggesting a role for D_1-like receptors in maintaining body sodium homeostasis during increases in sodium intake.

Dopamine Receptor-Linked Cellular Signaling Pathways

Dopamine Receptor-Mediated Regulation of Sodium Transporters. *Role of D_1-like Receptors.* The Na,H-exchanger and the Na,K-ATPase provide a primary mechanism for the regulation of sodium ansport across the proximal tubules in the kidney (Fig. 2). These two sodium transporters have been identified as final effector proteins for the action of dopamine (27–31). Numerous studies in isolated tubular preparations have shown that dopamine produces inhibition in the activities of Na,H-exchanger and Na,K-ATPase, a mechanism by which dopamine reduces tubular sodium reabsorption and thereby increases sodium excretion. Both the D_1-like and the D_2-like receptors are coexpressed in proximal tubules and other parts of the nephron (2–6, 8). It is the activation of D_1-like receptors that causes inhibition in Na,K-ATPase and Na,H-exchanger activity in proximal tubules and in other parts of the nephron such as medullary thick ascending limb (mTAL) and cortical collecting duct (CCD) (28–30). Similar results were reported in fibroblast LTK cells transfected with D_{1A} receptor, where the D_1-like agonist fenoldopam caused inhibition of the Na,K-ATPase activity (32). These results are consistent with the observation that the activation of D_1-like receptors promotes sodium excretion (16, 17, 25). Other studies have shown that simultaneous activation of both dopamine receptors, D_1-like and D_2-like, is required to promote natriuresis and to inhibit Na,K-ATPase activity in proximal tubules (33).

Role of D_2-like Receptors. Unlike the D_1-like receptor, the role of D_2-like receptor in the kidney is not yet well defined. However, there are reports suggesting that the activation of D_2-like receptors produces antidiuresis and antinatriuresis (34, 35). Consistent with this observation, the activation of D_2-like receptors has been reported to cause stimulation of the Na,K-ATPase activity in rat renal proximal tubules as well as in LTK-murine cells transfected with the D_{2Long} receptor cDNA (36, 37). Recently, we have found that D_2-like receptors are linked to the stimulation of MAP kinase in rat renal proximal tubules and opossum kidney (OK) cells (37). Furthermore, we observed that the activation of MAP kinase by D_2-like agonists might be a signaling mechanism responsible for the stimulation of Na,K-ATPase activity as well as mitogenesis, seen in the proximal tubule and OK cells (38). In a recent report, the activation of D_2-like receptors in OK cells is shown to inhibit the Na,K-ATPase activity and to hyperpolarize the epithelial cells, actions associated with the opening of K^+ channels (39). This observation adds to the complicity of the D_2-like receptor signaling and function in the kidney.

Dopamine Receptors and G Proteins. Dopamine receptors belong to the super-family of G-protein-coupled receptors. The D_1-like receptors are coupled with G_s and G_q protein (40, 41). The D_2-like receptors are linked to the pertussis toxin-sensitive proteins, likely with G_i in the proximal tubule (36, 37).

Dopamine Receptors and Adenylyl Cyclase/ Protein Kinase A. A correlation between dopamine infusion and urinary cAMP excretion has initially implicated a role for adenylyl cyclase as one of the second messengers involved in dopamine-mediated cellular effects (Figs. 2 and 3) (42). Later, dopamine was shown to inhibit the Na,H-exchanger via cAMP-dependent as well as cAMP-independent mechanisms in the brush border membrane vesicle preparations (28, 40, 43, 44). Dopamine-mediated increase in cAMP leads to activation of protein kinase A, which, in turn, causes phosphorylation of the Na,H-exchanger and subsequent inhibition of its activity (28, 45, 46). There are also reports implicating the role of the cAMP/PKA pathway in dopamine-mediated inhibition of the

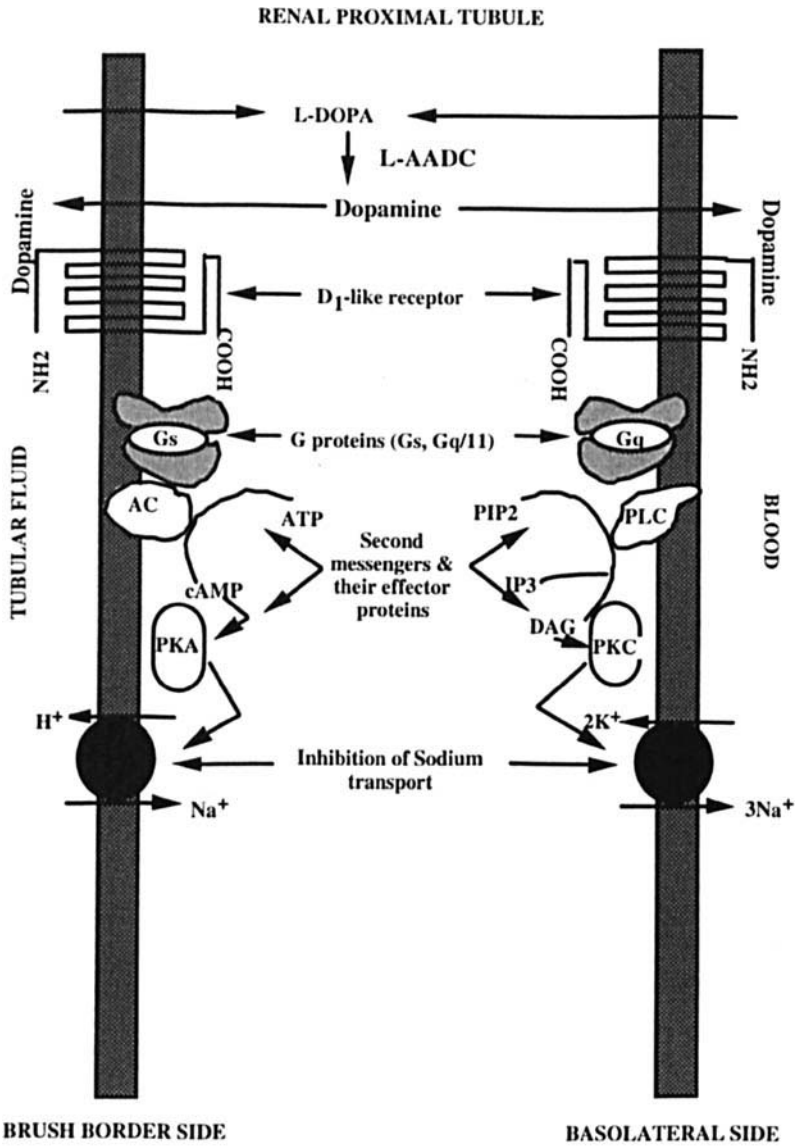

Figure 2. Hypothetical scheme of dopamine synthesis and D_1-like receptor signaling pathway that causes inhibition of sodium transporters in proximal tubles of rat kidney. L-AADC, L-aromatic amino acid decarboxylase; AC, adenylyl cyclase; PLC, phospholipase C; PKA, protein kinase A; PKC, protein kinase C; PIP2, phosphatidylinositol bisphosphate; IP3, inositol trisphosphate; L-DOPA, L-dihydroxyphenylalanine; DAG, diacylglycerol.

Na,K-ATPase activity in proximal tubules (32, 33) and in other parts of the nephron, such as mTAL and CCD (31). Dopamine-related phosphoprotein-32 (DARPP-32), which is present in large quantities in mTAL (47), has also been reported to play a role in dopamine-mediated inhibition of Na,K-ATPase activity in this segment of the nephron (48).

The stimulation of D_2-like receptors causes a decrease in cAMP via the G_i proteins. Studies from our laboratories have shown that a decrease in cAMP is the first biochemical signal that leads to a cascade of events ultimately resulting in the stimulation of Na,K-ATPase (36).

Dopamine D_1-like Receptors and Phospholipase C/Protein Kinase C. Numerous studies have provided evidence for the role of the phospholipase C (PLC) and protein kinase C (PKC) in dopamine-mediated inhibition of the Na,K-ATPase activity in the proximal tubule (Fig. 2) (49–54). Inhibitors of PLC and PKC have been shown to block the inhibitory effects of dopamine and D_1-like agonists on the phosphorylation and activity of Na,K-ATPase (49, 53, 54). Further studies have suggested that the activation of the D_1-like receptors stimulates PLC by regulating the expression and the activity of PLCβ1 and PLCγ1 isoforms in the kidney cortex (55). Dopamine and D_1-like agonists also stimulate the PKC activity in proximal tubules (56, 57). Further studies suggest that it is the PKCδ and especially PKCζ isoforms regulated by D_1 receptors that may be involved in dopamine-mediated inhibition of Na,K-ATPase activity (53, 58). The stimulation of these isoforms of PKC might be causing phosphorylation and, as a result, inhibition of the Na,K-ATPase activity (57, 59). The role of phosphatidyl inositide 3-kinase (PI3-kinase) is also demonstrated by PKC-mediated inhibition of the Na,K-ATPase activity in proximal tubular cells (59). Stimulation of PI3-kinase via activation of D_2 and D_3 receptors has also been reported (60, 61). Additionally, stimulation of PI3-kinase has also been associated with the stimulation of Na,K-ATPase activity (62), and the inhibition of Na,K-ATPase activity is the cause of the increase in PI3-kinase (63).

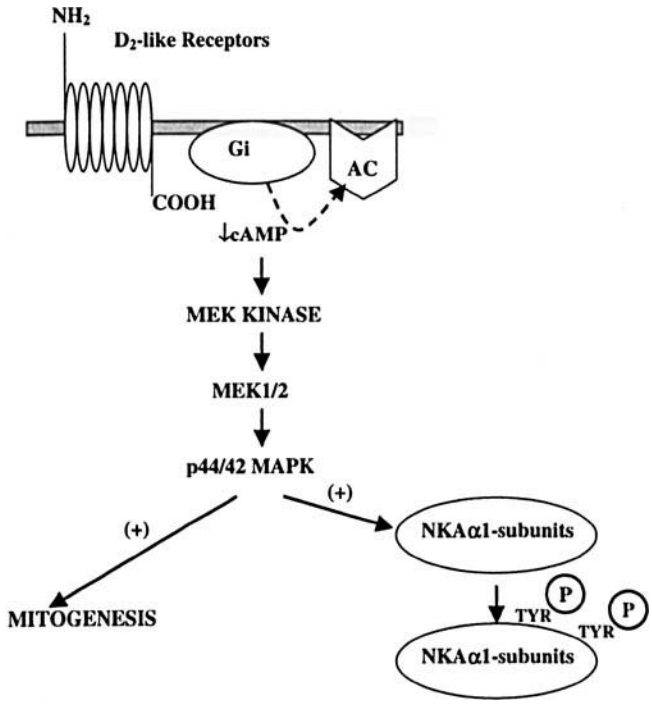

Figure 3. Hypothetical scheme of dopamine D_2-like receptor signaling that causes stimulation of the MEK1/2–p44/42 MAPK pathway leading to the stimulation of the Na,K-ATPase activity and the mitogenic response in proximal tubules of the kidney.

Dopamine D_1-like Receptors and Phospholipase A_2. The role of PLA_2 has also been suggested in dopamine-mediated inhibition of Na,K-ATPase in the renal proximal tubule (64, 65). It is likely that D_1-like receptor-mediated activation of PKC stimulates PLA_2, which in turn releases arachidonic acid from membrane lipids. Arachidonic acid is further metabolized by cytochrome P450 to produce various metabolites, including 20-hydroxyeicosatetraenoic acid (20-HETE), which utilizes PKC to inhibit the Na,K-ATPase activity (66). In mTAL and CCD, the PLA_2 pathway interacts with PKA to inhibit Na,K-ATPase activity (31). In regard to the role of these signaling pathways, a recent study reported sequential activation of PKC/PLA_2 and PKA/PLA_2 pathways in the inhibition of Na,K-ATPase by dopamine (67). Early inhibition of Na,K-ATPase activity by dopamine involves the activation of PKC/PLA_2 pathways, whereas the late inhibition involves activation of PKA/PLA_2 pathways (67).

Although dopamine receptor-mediated regulation of sodium-transporting proteins is present throughout the nephron length, dopamine receptors located at the proximal tubule and CCD (compared to other segments of the nephron) seem to play an important role in the natriuretic response to exogenously administered or endogenously produced dopamine (26, 68). It is likely that the proximal portion of the nephron is of greater importance because it is the site of major fluid and sodium reabsorption, and it is this site at which dopamine receptor-mediated signaling is selectively defective and unable to regulate Na,K-ATPase and Na,H-exchanger activity in various forms of hypertension in humans and animal models; this is discussed below.

Dopamine D_2-like Receptors and Tyrosine Kinase. Dopamine D_2-like receptor activation causes stimulation of Na,K-ATPase activity (Fig. 3) (36, 37). Recent studies from our laboratory designed to investigate the cellular signaling mechanism for this response have revealed the involvement of a tyrosine kinase pathway. Inhibitors of tyrosine kinase as well as MAP kinase blocked the stimulatory effect of bromocriptine on Na,K-ATPase activity in renal proximal tubules. Also, bromocriptine increased phosphorylation of p44/42 MAPK in proximal tubules, suggesting that D_2-like receptor activation causes stimulation of Na,K-ATPase via a tyrosine kinase-p44/42 MAPK pathway in renal proximal tubules (69). Whereas D_2-like receptors activate the p44/42 MAPK pathway and promote mitogenesis, D_1-like receptors activate the p38 MAPK pathway, which is involved in apoptosis (70).

Dopamine and Dopamine Receptors in Hypertension

Dopamine Deficiency in Human Hypertension. Deficiency in renal dopamine synthesis and/or secretion has been reported in various forms of human hypertension. Urinary dopamine excretion is lower in salt-sensitive hypertensive patients than in normal subjects or non-salt-sensitive patients on high sodium intake (71). Suppressed dopaminergic activity has also been shown in the prehypertensive stage of primary hypertension (72, 73). Reduced dopaminergic activity has also been observed in young normotensive subjects with an apparent family history of hypertension before any evidence of hypertension emerged (73, 74). The exact mechanism for the renal dopaminergic deficiency in the human primary hypertension is not known. However, a defect in L-dopa-decarboxylase, the enzyme that catalyzes the conversion of L-dopa to dopamine, has been reported in a subject with a family history of hypertension (73–76). Other studies have shown a decrease in both the renal tubular uptake of L-dopa and the conversion of L-dopa to dopamine in a subgroup of salt-sensitive hypertensive patients (77). Because the suppression of renal dopaminergic activity has been observed in young normotensives with a family history of hypertension before any manifestation of the disease, it has been suggested that renal dopaminergic deficiency may contribute to the development of hypertension (78).

Defective Dopamine Receptors in Human Hypertension. Recently, a defective D_1-like dopamine receptor (more specifically D_{1A} subtype) has been reported in primary cells cultured from hypertensive human proximal tubules (79). The D_1-like receptor agonist stimulated adenylyl cyclase activity in normotensive cells but was unable to stimulate the enzyme activity in hypertensive proximal tubule cells. Further studies suggest that the defect was receptor specific because adenylyl cyclase stimulation by parathyroid hormone was found to be similar in the cells

from both normotensive and hypertensive subjects (79). Furthermore, the D_1-like receptor or adenylyl cyclase defect in human cells was suggested to be similar to the defects found in proximal tubules from animal models of genetic hypertension. The detailed molecular mechanism of the defect is discussed below. Interestingly, despite a defective D_{1A} receptor in the proximal tubule, an exogenous dopamine infusion in essential hypertensive patients caused a natriuretic response (80). This suggested that the dopamine receptors located on the distal part of the nephron are upregulated (81) and therefore offset the defective dopamine receptor function at the level of the proximal tubule. A recent study suggested that D_1 receptor gene polymorphism is associated with essential hypertension (82). In a group of essential hypertensive and normotensive patients, polymerase chain reaction was used to amplify the A-48G polymeric site in the D_1 receptor gene, and restriction analysis of the polymerase chain reaction product was used to score A and G alleles. This analysis showed that essential hypertensive patients possessing the G allele had a higher diastolic pressure than those lacking the G allele, suggesting that such a polyphosphism in the D_1 receptor gene may account for the higher diastolic blood pressure of essential hypertensive patients (82).

In another study reported by Felder *et al.* (83), they measured G protein-coupled receptor kinase 4 gene variants (GRK4γA142V) in the renal proximal tubular cells obtained from essential hypertensive patients. They found that single-nucleotide polymorphism of GRK4γ, resulting in increased GRK activity, caused serine phosphorylation and subsequent uncoupling of the D_1 receptor from its G protein–effector enzyme complex in renal proximal tubule (83). Moreover, expressing GRK4γA142V produced hypertension and impaired diuretic and natriuretic effects of D_1-like agonist stimulation. These results led the authors to suggest a novel mechanism for the D_1-receptor-coupling defect in the kidney that may explain the inability of the kidney to properly excrete sodium in genetic hypertension (83).

Defective Dopamine Receptor in Hypertensive Animal Models. There are several lines of evidence suggesting a defective dopaminergic system in the kidneys of Dahl salt-sensitive and spontaneously hypertensive rats (SHR). Similar to human hypertension, Dahl salt-sensitive rats produce less kidney dopamine and have a poor natriuretic and diuretic response in the event of sodium load (84–86). In addition to the dopamine production deficiency, defective D_1-like receptor function has been reported in proximal tubules of Dahl salt-sensitive rats. The defect in D_1-like receptors results in a loss of the ability of dopamine to regulate adenylyl cyclase activity (87, 88) and Na,K-ATPase activity in proximal tubules of salt-sensitive rats (89, 90). The SHR, as a model, has been extensively used to elucidate the mechanisms of the defective D_1-like receptor function in proximal tubules. Dopamine production in SHR is normal or even increased (91, 92), but dopamine and D_1-like receptor agonist-mediated natriuretic and diuretic responses are diminished compared to normotensive control Wistar Kyoto (WKY) rats (93, 94). In 1989, Kinoshita *et al.* (95) reported that despite equal numbers of D_1-like receptors and intact G protein-adenylyl cyclase complexes, dopamine and D_1-like agonists stimulated adenylyl cyclase activity in proximal tubules of SHR to a lesser extent than in normotensive WKY rats. This suggested that the defect resided in the coupling of the receptor with adenylyl cyclase and that the G proteins and adenylyl cyclase were not themselves defective. The defect was specific to D_1-like receptor because parathyroid hormone stimulated adenylyl cyclase equally in SHR and WKY rats (95). Also, it has been reported that D_1 receptors in the proximal tubule membrane from SHR were resistant to activation by the agonist, and this was most likely a result of the inability of the receptor to associate with $G_{s\alpha}$ (41, 96).

In another study, the coupling of D_1 receptor to $G_{s\alpha}$ and to Na,H-exchanger (NHE3) was examined in brush border membranes obtained from SHR and WKY rats (97). It was found that the inhibitory effect of D_1 receptor agonist on NHE activity in SHR was less than that seen in WKY rats and that GTPγS enhanced the inhibitory effect of a D_1 receptor agonist on NHE activity in WKY but not in SHR, suggesting an uncoupling of D_1 receptor from $G_{s\alpha}$/NHE3 in SHR (97). It is also reported that the defect in D_1-like receptor/adenylyl cyclase was organ (only in the kidney) and nephron segment (only in the proximal tubule) specific (98, 99). The major consequence of the decrease in the ability of dopamine to stimulate adenylyl cyclase in SHR is the subsequent failure to inhibit Na,H-exchanger in the hypertensive animals (100, 101). The decreased inhibitory effect of D_1-receptor stimulation on Na,H-exchanger in SHR precedes the development of hypertension (101). These results led the authors to speculate that D_1-like receptor genes or genes that regulate their function probably participate in raising the blood pressure in genetic hypertension (101). The stimulation of PLC and PKC by dopamine and D_1-like agonist was also reduced in SHR, suggesting a defect in the coupling of D_1-like receptor with $G_{q/11}$ proteins (102, 103). As a result of the defective coupling of D_1-like receptor with G proteins and subsequent decreased stimulation of the associated second-messenger systems (adenylyl cyclase–PKA, PLC–PKC), dopamine and D_1-like agonist failed to inhibit Na,H-exchanger and Na,K-ATPase activities in proximal tubules (49, 100, 101). The failure of dopamine and D_1-like agonist to inhibit sodium transporters provides a mechanism responsible for the diminished natriuresis and diuresis in SHR in response to dopamine as well as the inability of SHR to excrete sodium in response to volume expansion (93, 94). The impaired D_1-like receptor inhibition of Na,H-exchanger activity in the SHR preceded the establishment of hypertension (104).

Further studies in SHR revealed that they had lost high-affinity binding to the agonist (105, 106), and as a result, D_1-like receptors were unable to interact with G proteins in

response to the agonist (41, 96). Limited sequencing of the D1AmRNA (equivalent to the third cytoplasmic loop of cloned D_{1A} receptor, which is believed to be the G protein-interacting domain) revealed no mutation in the protein in SHR (99). However, there are a number of studies that provide a sequence of events suggesting a molecular basis for the defect in the D_{1A} receptor (a D_1-like receptor). The titration of the sulfhydryl groups present on D_{1A} receptors revealed that sulfhydryl groups may be buried inside the receptor protein (107), which may be the result of posttranslational modifications or conformational changes in the receptor protein. In a recent study, Felder *et al.* (83) reported a greater agonist-independent phosphorylation of D_{1A} receptor caused by the higher constitutive activity of GRK4. Furthermore, the greater phosphorylation of D_{1A} receptor may also be contributed to by the decreased ability of the D_{1A} receptor agonist (fenoldopam) to increase the dephosphorylating enzyme, protein phosphatase 2A, activity in the proximal tubule membrane of SHR (108).

Hypertension in Dopamine Receptor Knockout Animals. Compelling evidence showing a relationship between defective D_{1A} receptors or signaling system and hypertension comes from two sets of experiments: one on cross-breeds of normotensive and hypertensive rats and the second on mice lacking functional D_{1A} receptors (109). In the F_2 generation from female WKY rats and male SHR crosses, the defective D_1-like receptor function (inability of dopamine to inhibit Na,H-exchanger) in the proximal tubules cosegregated with the increased systolic blood pressure (>160 mmHg) and decreased ability to excrete sodium in response to a D_1-like agonist infused into the renal arteries of the rats. The activation of D_1-like receptors inhibited the Na,H-exchanger in rats of the same F_2 generation with systolic blood pressure <140 mmHg (109).

In another set of experiments, mutant mice were generated that were lacking functional D_{1A} receptors. Compared to the control mice, both homozygous and heterozygous mice had greater systolic, diastolic, and mean arterial pressure. Renal tubules from homozygous mice had no binding sites for [^{125}I]SCH23982, a D_1-like ligand, and showed no stimulation of cAMP by dopamine (109). This provides a reasonable correlation between defective D_{1A} receptor/signal transduction and the development of hypertension in mice. In addition to the observation made with D_{1A} receptors, the disruption of D_3 receptors has also recently been shown to cause renin-dependent hypertension (110). However, the mechanism of hypertension caused by disruption of D_3 receptors is different from that caused by D_{1A} receptors. The renal renin activity was much greater in mice lacking D_3 receptors (both homozygous and heterozygous) than in a wild-type control group. A single bolus dose of losartan, an angiotensin II AT_1 receptor antagonist, causes a decrease in systolic blood pressure in the homozygous mice to a greater extent and for a longer time than in the wild-type mice. During acute volume expansion, blood pressure was unchanged, GFRs were similar, and urine flow increased to a similar extent in the wild-type and the mutant mice (both homozygous and heterozygous). However, the increase in sodium excretion was attenuated in homozygous mice compared to the control (110). There is evidence that shows that a physiologic and biochemical interaction exists between dopamine and angiotensin II receptors in the kidney (111–113). Intrarenally produced angiotensin has been shown to counteract fenoldopam-induced sodium excretion (111).

Also, it has been shown that both D_1-like and D_2-like receptor agonists cause a decrease in AT_1 receptor binding sites in proximal tubular preparations (112–114). Although the AT_1 receptor binding sites have not been measured in the D_3 mutant mice, it is possible that the absence of D_3 receptors might have caused an increase in AT_1 receptors in the proximal tubules along with the higher renin production. Recently, effects of D_2 receptor disruption has also been reported (115). The disruption of D_2 receptors caused higher systolic and diastolic blood pressure in mutant mice. Further study revealed that hypertension in D_2 receptor mutant mice resulted from an increase in α-adrenergic and endothelin B (ETB) receptor activities, which produces vasoconstriction (115).

Concluding Remarks

There is clear evidence that dopamine is an important modulator of cardiovascular and renal function. A deficiency in dopamine production and/or a dysfunction in dopamine receptor contributes to various forms of hypertension in both humans and animal models. Recently, a study (83) revealed the molecular nature and the cause of the defect in D_1 receptor protein in proximal tubular cells of animals and hypertensive patients. This study further demonstrated that the defect in D_1 receptors might be corrected, in the proximal tubule cells obtained from hypertensive patients, by removing the cause of defect, namely, *in vitro* treatment of the cells with antisense GRK4 oligonucleotides (83). However, it is yet to be determined whether correction of the dopamine receptor, especially D_1 receptor, function would lead to a reduction in blood pressure in humans and experimental models of hypertension.

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