Dopamine plays an important role in the control of renal sodium excretion. Specific receptors for dopamine have been identified in various regions of the nephron, and it is reported that dopamine is synthesized within the renal proximal tubules. Endogenously produced dopamine, as well as exogenously administered dopamine, exerts pronounced effects on renal function. There are reports suggesting that a defect in renal dopamine receptor function and/or dopamine production may play a role in the pathogenesis of hypertension. For example, reduced urinary dopamine/sodium excretion is reported in some forms of human primary hypertension. It is reported that a defect in dopamine receptor function may play a role in hypertension. Furthermore, the therapeutic potential of dopamine and other dopamine receptor agonists in the management of cardiovascular disorders will also be discussed.

Dopamine Receptor Classification and Localization in the Kidney

The biological effects of dopamine are mediated through at least 5 genetically distinct dopamine receptors: D₁, D₂, D₃, D₄, and D₅. These receptors are classified into two major families as D₁-like (includes D₁ and D₃, whose rat homologues are D₁A and D₁B) and D₂-like (includes D₂, D₃, and D₄) dopamine receptors based on the stimulation and inhibition of adenyl cyclase, respectively. With pharmacological means of receptor characterization, the peripheral dopamine receptors were initially classified as DA₁ and DA₂ subtypes. Within the kidney, ligand binding and autoradiographic studies have revealed the presence of both DA₁ and DA₂ receptors. Of the cloned dopamine receptors, D₁A, D₁B, D₂long, and D₃ have been identified in the kidney. In this review, we will use the nomenclature D₁-like receptors and D₂-like receptors to describe the dopamine receptors linked to the stimulation and the inhibition of adenyl cyclase, respectively.
Dopamine receptors are located at various regions within the kidney of both experimental animals and humans, including the renal vasculature, sympathetic nerve terminals innervating different sites, juxtaglomerular cells, and renal tubules.\textsuperscript{10,13,17–19} The D\textsubscript{1}-like receptors are present on the smooth muscle of renal arteries and juxtaglomerular apparatus and on the renal tubules.\textsuperscript{13,19,20} The D\textsubscript{2}-like receptors are expressed in the intimal layer of the renal vasculature, glomeruli, sympathetic nerve terminals, and the renal tubules.\textsuperscript{13,19} The tubular D\textsubscript{1}-like dopamine receptor density is higher in humans than in rats.\textsuperscript{15} Another feature of the tubular dopamine receptors is higher density of D\textsubscript{1}-like receptors in the proximal tubules than in the distal parts of the nephron,\textsuperscript{11} as well as in the renal vasculature.\textsuperscript{15} Also, D\textsubscript{1}-like and D\textsubscript{2}-like receptors are located on both basolateral and brush border membranes of the proximal tubules.\textsuperscript{11}

**Physiological Role of Dopamine in the Kidney**

In 1964 the natriuretic and diuretic effects of dopamine were first observed in humans.\textsuperscript{22} Although the concept of a specific receptor for dopamine had not been proposed at that time, it is now known that dopamine exerts pronounced cardiovascular and renal actions by activating both D\textsubscript{1}-like and D\textsubscript{2}-like dopamine receptors located at various sites within the cardiac, vascular, and renal regions.\textsuperscript{13,18,19} At higher doses, dopamine also activates \(\beta\)- and \(\alpha\)-adrenoceptors.\textsuperscript{23} Several studies have shown that selective agonists at D\textsubscript{1}-like receptors cause hypotension, increase in blood flow to certain organs, diuresis, and natriuresis, whereas D\textsubscript{2}-like receptor agonists produce hypotension, bradycardia, a decrease in afterload, and vasodilation in certain vascular beds (Table).\textsuperscript{24,25} It has been shown that D\textsubscript{1}-like receptor agonists cause an increase in RBF and glomerular filtration rate, as well as increase in urinary excretion of sodium and water.\textsuperscript{24,26} Studies from our laboratory and others have shown that the natriuretic and diuretic response elicited by D\textsubscript{1}-like receptor agonist involves changes in intrarenal hemodynamics and direct tubular action. At lower doses, it is the direct action on the renal tubules that accounts for the natriuresis and diuresis induced by selective D\textsubscript{1}-like receptor agonists.\textsuperscript{13,24,26} These effects of agonists can be antagonized by SCH 23390, a selective D\textsubscript{1}-like receptor antagonist, further substantiating the role of D\textsubscript{1}-like receptors in these actions of dopamine and D\textsubscript{1}-like agonists. A positive correlation has been reported between sodium intake/urinary excretion and renal dopamine production/urinary excretion in both experimental animals and humans.\textsuperscript{27,28} Several studies have shown the role of dopamine in the regulation of sodium excretion during acute volume expansion and during acute increase in sodium intake.\textsuperscript{29–31} For example, we have shown that almost 60% of the natriuresis seen during acute volume expansion (5% of body weight) is accompanied by an increase in urinary dopamine excretion and could be antagonized by SCH 23390.\textsuperscript{26} The increased sodium excretion seen in animals placed on a high sodium diet is accompanied by an increase in urinary dopamine excretion.\textsuperscript{32,33} These results suggest that endogenously formed kidney dopamine plays a pivotal role in maintaining body sodium homeostasis during increases in sodium intake.

The source of dopamine that activates tubular dopamine receptors is believed to be nonneuronal. The tubular cells contain dopa-decarboxylase in abundance.\textsuperscript{26} The substrate L-dopa is filtered freely from glomerulus and is actively transported into the tubular cells where L-dopa is converted to dopamine by decarboxylation process.\textsuperscript{35,36} Once dopamine is synthesized, it is transported out of the cells where it can interact with dopamine receptors.

**Dopamine Receptor–Linked Cellular Signaling Mechanisms**

Regulation of sodium transport across the proximal tubules occurs through the involvement of two key proteins: Na,H-
exchanger, located on the brush border membrane, and Na,K-ATPase, located on the basolateral membrane of the proximal tubule. 

These two proteins have been identified as the target for the action of dopamine. Dopamine produces inhibition in the activities of these proteins, a mechanism by which dopamine affects tubular sodium transport. In the proximal tubules, both D_{1}-like and D_{2}-like receptors are coexpressed. 12,13 The activation of D_{1}-like receptors by dopamine produces inhibition in Na,K-ATPase activity in the proximal tubules and in other parts of the nephron, such as mTAL and CCD.40,41 Also, using in vitro transfection of D_{1A} receptor in fibroblast LTK^- cells, Horiiuchi et al42 showed inhibition of Na,K-ATPase activity by fenoldopam, a D_{1}-like receptor agonist. The activation of D_{1}-like receptor by dopamine and D_{1}-like agonist also produces inhibition of Na,H-exchanger activity in the proximal segments of the nephron, as well as in brush border membrane vesicle preparations.57,58 As it relates to the effects of D_{2}-like receptor activation, according to one study, the inhibition of Na,K-ATPase activity by dopamine requires simultaneous activation of D_{1}-like and D_{2}-like receptors in the proximal tubules. 43 On the other hand, we and others recently demonstrated in vitro that D_{1}-like receptor activation may lead to the stimulation of Na,K-ATPase activity in the proximal tubules44 and the LTK^- murine cells transfected with D_{2aLong} cDNA.45 The stimulation of Na,K-ATPase activity by the D_{2}-like receptor agonists involves pertussis toxin-sensitive, G protein–linked inhibition of cAMP. Although it is suggested that activation of D_{2}-like receptors produces anti-diuresis and anti-natriuresis,46 whether tubular D_{2}-like receptors are directly involved in the regulation of tubular sodium absorption and contribute to the basal level of sodium transport through the mechanism of Na,K-ATPase is yet to be determined. The activation of D_{2}-like receptor does not affect the activity of Na,H-exchanger in the proximal tubule. 58

The process from the activation of D_{1}-like dopamine receptors to the inhibition of Na,K-ATPase and Na,H-exchanger activity involves multiple cellular signaling pathways that despite a great deal of work appear to be complex and are yet to be completely understood. Initially, a positive correlation between dopamine infusion and urinary cAMP excretion implicated adenylyl cyclase as one of the second messengers in the action of dopamine.47 Later, in the brush border vesicle preparations, the inhibition of Na,H-exchanger by dopamine was shown to be linked to cAMP-dependent as well as cAMP-independent mechanisms.57–58. In mTAL and CCD, accumulation of cAMP and activation of PKA by dopamine also leads to the inhibition of Na,K-ATPase activity.41 In addition, dopamine-related phosphoprotein-32 (DARPP-32), present in high amounts in mTAL, has also been implicated in dopamine-mediated inhibition of Na,K-ATPase in mTAL.49 In the proximal tubules, most investigators believe that the cAMP pathway is not the mechanism that mediates the inhibition of Na,K-ATPase activity by dopamine. However, one study43 has suggested the role of dopamine stimulation of cAMP in the inhibition of Na,K-ATPase activity in the proximal tubules. The inhibition of Na,K-ATPase activity through the mechanism of PKA activation has been shown to result from the agonist occu-

pency of D_{1A} receptors expressed in fibroblast LTK^- cells. In the proximal tubules, the role of PLC in the inhibition of Na,K-ATPase activity by dopamine is well documented and supported by several studies.39,50–52 The animals placed on a high sodium diet showed an increase in urinary dopamine excretion, increase in PLC activity,43 and decrease in Na,K-ATPase activity.33 In vitro, an analogue of diacylglycerol (1-oleoyl-2-acetyl-racglycerol) and a direct activator of PKC mimic the inhibitory effects of dopamine on Na,K-ATPase activity, and U73122, a PLC inhibitor, abolishes the effect of dopamine.39 These studies suggest the involvement of PLC and PKC in the D_{1}-like receptor signaling system that leads to the inhibition of Na,K-ATPase activity. Dopamine and D_{1}-like receptor agonists stimulate PLC activity in kidney cortex that has been shown to be independent of the adenylyl cyclase pathway.50,51 We have reported the direct stimulation of PKC activity by dopamine and the D_{1}-like receptor agonist fenoldopam.53 Thus, the activation of D_{1}-like receptors causes the stimulation of PLC with resulting generation of inositol triphosphate and diacylglycerol. Diacylglycerol stimulates PKC, which in turn induces inhibition of Na,K-ATPase activity.54 Interestingly, α_{1}-receptor activation also leads to the stimulation of PLC activity but activates Na,K-ATPase activity in the proximal tubules.55 This phenomenon is explained by the differential regulation of PLC activity and isoform expression by D_{1}-like and α_{1}-receptors. 56 D_{1}-like receptor and α_{1}-receptor agonists were intrarenally infused in rats, and the expression and activity of various PLC isoforms in the cortical membranes were studied. The intrarenal infusion of D_{1}-like receptor agonist increased PLC-β1 expression and activity but decreased PLC-γ1 expression and activity in the membranes of renal cortex.56 Similar observations on the changes in PLC-β1 and PLC-γ1 expression and activity by D_{1}-like receptor agonist were also made in LTK^- cells heterologously expressing the rat D_{1A} receptor.57 Similar to D_{1}-like agonist, phenylephrine (α_{1}-adrenoceptor agonist) also increased the expression of PLC-β1 protein but had no effect on the expression of PLC-γ1 in the cortical membranes. The two signaling pathways, adenylyl cyclase and PLC, were proposed to be linked to D_{1}-like receptors through the coupling of G_{i} and G_{q,i1} proteins in the proximal tubules.50–52 More direct evidence came from our recent study using [35S]GTPγS binding stimulated by fenoldopam (a D_{1}-like receptor agonist) and antagonism by specific anti-G_{i} in the basolateral membranes.5 Bertorello et al58 have reported that pertussis toxin–sensitive G proteins (G_{i}/G_{q} family) also play a role in dopamine-mediated inhibition of Na,K-ATPase activity. This supports their study showing that simultaneous activation of both D_{1}- and D_{2}-like receptors is required to inhibit Na,K-ATPase by dopamine.59 D_{2}-like receptors have been shown to be linked to pertussis toxin–sensitive proteins.64,65 Despite the evidence based on the transfection of cells with D_{1A} receptor and showing that activation of D_{1A} receptors could stimulate both adenylyl cyclase and PLC, recent studies suggest the existence of two different molecular entities that are linked independently to adenylyl cyclase and PLC in the brain.66 Recently, with the use of D_{1A} knockout mice, it was reported that the D_{1}-like receptor agonist SKF 38393 and dopamine clearly did not generate
Renal Dopamine Receptors in Hypertension

Schematic hypothetical presentation of D₁-like dopamine receptor and associated cellular signaling mechanisms in the nephron that mediate the inhibition of sodium-transporting proteins and thereby increase in renal sodium excretion. PKC (same or different isoforms), directly or via the stimulation of PLA₂, may phosphorylate Na,K-ATPase. D₁-like receptor and its coupling with G proteins are believed to be defective, which leads to diminished renal sodium excretion in hypertension. IP₃ indicates inositol triphosphate; DAG, diacylglycerol; Cyt P450, cytochrome P450 monooxygenase; and Pi, phosphorylation.

cAMP but stimulated inositol phosphate production in the brain regions (striatum and frontal cortex). This suggested that the inositol formation (PLC-linked pathway) is independent of D₁A receptor. However, similar studies have yet to be performed in the kidney to investigate whether adenylcyclase and PLC are linked to the same D₁A receptor or to two different D₁-like receptor proteins. Of the D₁-like receptors, D₁B dopamine receptors are also expressed in the proximal tubules. It is also possible that D₁B receptors are linked to the PLC pathway. However, such a plausible explanation may not be tested using the conventional approach because of the unavailability of selective agonist or antagonist. D₁B receptor knockout animals may provide a model to resolve the issue.

The role of the PLA₂ pathway has also been reported in the cellular signaling systems involved in dopamine-induced inhibition of Na,K-ATPase activity in the proximal tubules, which is distinct compared with other segments of the nephron. According to the scheme proposed by Satoh et al in the PLC/PKC-dependent mechanisms of dopamine action (via D₁-like receptors), PKC leads to the activation of PLA₂, which in turn releases arachidonic acid from membrane lipids. Arachidonic acid is further metabolized by cytochrome P450 producing various metabolites. Recently, it was reported that one of the metabolites of arachidonic acid, 20-HETE, inhibits Na,K-ATPase activity via a PKC-dependent pathway. In mTAL and CCD, the PLA₂ pathway interacts with PKA to inhibit Na,K-ATPase activity. Although there is ample evidence for the role of a PLA₂ pathway in dopamine receptor signaling, the link between the receptor and PLA₂ is not known. The Figure shows a hypothetical diagram of dopamine receptor-mediated cellular signaling mechanisms in the nephron.

Physiological and biochemical interactions between angiotensin II and dopamine receptors have been reported in the kidney. It is reported that dopamine increases renin release by activating D₁-like receptors probably located on juxtaglomerular cells, which in turn has been shown to attenuate fenoldopam-induced natriuresis. With use of an in vitro system, it was reported that the pretreatment of proximal tubular preparations with dopamine decreased the expression of AT₁ receptors at the AT₁ mRNA level, an effect likely mediated by increased intracellular cAMP levels. This suggested that the activation of dopamine receptors may also reset the sensitivity of the proximal tubules to angiotensin. Similar to D₁-like receptors, the pretreatment of renal brush border membranes with D₂-like receptor agonist has been reported to lower [¹²⁵I]angiotensin II binding sites. We have shown that pretreatment of proximal tubules with bromocriptine, a D₂-like receptor agonist, antagonized the stimulatory effect of angiotensin II on Na,K-ATPase activity and attenuated the inhibitory effect of angiotensin II on cAMP accumulation. These effects of bromocriptine appear to be due to reduced [¹²⁵I]angiotensin II binding sites and an imbalance of G₂ and G₃ protein ratio in the proximal tubules (T.H., M.F.L., unpublished observations, 1998).

Renal Dopaminergic System in Hypertension

Human Primary Hypertension

There are reports of a deficiency in the renal dopamine synthesis and/or secretion in various forms of human hypertension. Depressed urinary dopamine excretion has been reported in salt-sensitive hypertensive patients compared with normal subjects or non–salt-sensitive patients, as well as in low-renin primary hypertension compared with normotensive normal-renin and high-renin hypertensive patients. The depressed renal dopamine in low-renin primary hypertension is commonly associated with increase in renal vascular resistance, decrease in renal plasma flow, and expansion of extracellular fluid volume. Suppressed dopaminergic activity has also been shown in the prehypertensive stage of primary hypertension. Because endogenous kidney dopamine plays
an important role in maintaining body sodium homeostasis, renal dopaminergic deficiency may contribute to the development and maintenance of high blood pressure, at least in a subpopulation of humans with essential hypertension. Suppression of dopaminergic activity was also observed in young normotensive subjects with an apparent family history of hypertension before any evidence of hypertension emerged.\textsuperscript{69,70} The infusion of exogenous dopamine leads to the augmentation of sodium excretion in the subjects with low-renin hypertension and in the subjects with family history of hypertension.\textsuperscript{70,71} In another study, increased urinary sodium excretion in response to exogenous dopamine infusion in patients with essential hypertension was accompanied by increased urinary and nephrogenous cAMP contents compared with the normotensive control subjects.\textsuperscript{72} These studies are in agreement with the hypothesis of an upregulation of dopamine receptor and/or change in receptor affinity in patients with essential hypertension, secondary to decreased endogenous intrarenal dopamine production.\textsuperscript{72,73,74}

The notion of D\textsubscript{1}-like receptor upregulation has been recently supported by another study.\textsuperscript{75} According to this study in hypertensive subjects,\textsuperscript{75} the upregulation of D\textsubscript{1}-like receptor function takes place in the distal tubules and not in the proximal tubules, and such an upregulation in the distal tubules D\textsubscript{1}-like receptor offsets the defect in the proximal tubule, leading to natriuresis and diuresis in response to the D\textsubscript{1}-like agonist fenoldopam. However, thus far, direct measurements of renal dopaminergic receptor population or agonist affinity in subjects with primary hypertension have not been reported. A defect in the coupling of D\textsubscript{1}-like receptors and adenylyl cyclase system was recently reported in primary hypertensive animals.\textsuperscript{76} This defect is receptor specific, since adenylyl cyclase stimulation by parathyroid hormone was found to be similar in the cells from both normotensive and hypertensive subjects. Furthermore, a D\textsubscript{1}-like receptor/adenylyl cyclase defect in human cells was suggested to be similar to the defects found in the proximal tubules from animal models of genetic hypertension (discussed below).

The exact mechanism for the renal dopaminergic deficiency in 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 suggested in subjects with a family history of hypertension,\textsuperscript{69,77,78} whereas in a subgroup of salt-sensitive hypertensive patients a decrease in both renal tubular uptake of L-dopa and its conversion to dopamine has been reported.\textsuperscript{79} Because the suppression of renal dopaminergic activity has been observed in young normotensives with a family history of hypertension before the manifestation of hypertension, it has been suggested that renal dopaminergic suppression may contribute to the development of hypertension.\textsuperscript{80}

**Rat Models of Hypertension**

**Dahl Salt-Sensitive Rats**

There are several lines of evidence suggesting a defective dopaminergic system in the kidneys of the Dahl salt-sensitive strain of rats. Dahl salt-sensitive rats excrete sodium poorly with increased sodium load.\textsuperscript{81} There is decreased kidney dopamine content in salt-sensitive rats fed a high salt diet,\textsuperscript{82} a lack of increased urinary dopamine excretion in salt-sensitive rats subjected to acute volume expansion,\textsuperscript{83} and reduced urinary dopamine and cAMP excretion in young normotensive salt-sensitive rats compared with control Wistar rats fed a normal salt diet.\textsuperscript{2} In addition to a decreased urinary dopamine excretion, a defect in the D\textsubscript{1}-like receptor has been reported in the proximal tubules of Dahl salt-sensitive rats. In an experimental study, endogenous dopamine was allowed to accumulate by inhibition of its conversion to norepinephrine by a dopamine \(\beta\)-hydroxylase inhibitor. This led to down-regulation of proximal tubular D\textsubscript{1}-like receptors and complete ablation of D\textsubscript{1}-like agonist stimulation of adenylyl cyclase activity in the normotensive rats, while the D\textsubscript{1}-like receptors in salt-sensitive rats were resistant to such regulation.\textsuperscript{84,85} In another study,\textsuperscript{85} high salt intake (10 days) downregulated Na,K-ATPase activity in the proximal tubules of salt-resistant rats that was reversed by benserazide (dopamine synthesis inhibitor), suggesting a role of endogenous dopamine in the regulation of Na,K-ATPase. In contrast, high salt intake did not affect Na,K-ATPase activity, and benserazide also had no effect on the enzyme in salt-sensitive rats. This suggested the inability of the D\textsubscript{1}-like receptor to regulate the Na,K-ATPase activity that results from a defective D\textsubscript{1}-like receptor-mediated cellular signaling mechanism in salt-sensitive rats. The notion of defective coupling of D\textsubscript{1}-like receptor with adenylyl cyclase is supported by another study.\textsuperscript{86} It was discovered that D\textsubscript{1}-like receptor agonists were unable to stimulate adenylyl cyclase in the proximal tubules from Dahl salt-sensitive rats, whereas forskolin (a direct stimulator of adenylyl cyclase) stimulation of the enzyme was not different between Dahl salt-sensitive and salt-resistant rats.\textsuperscript{86} A defective coupling would be expected to lead to a reduced D\textsubscript{1}-like receptor-mediated inhibition of Na,H-exchanger and hence a reduced sodium excretion, which has yet to be demonstrated in Dahl salt-sensitive rats.

**Spontaneously Hypertensive Rats**

In SHR, dopamine production and excretion is normal or even increased,\textsuperscript{87,88} but dopamine- and fenoldopam-mediated natriuretic and diuretic responses are diminished under normal conditions, as well as during acute volume expansion (5% body weight), compared with those in normotensive control WKY.\textsuperscript{83,89,90} We and others have performed extensive studies to investigate the site(s) of defect in the D\textsubscript{1}-like receptor system in the SHR.\textsuperscript{4,39,91-93}

Because proximal tubular dopamine receptors (D\textsubscript{1}-like receptors) contribute to 60% of the sodium excretion under acute volume expansion, a phenomenon that is impaired in SHR, studies have been conducted on the D\textsubscript{1}-like receptor system in the proximal tubules to investigate the site of impairment. In 1989, Kinoshita et al\textsuperscript{10} reported that D\textsubscript{1}-like receptor agonists stimulated adenylyl cyclase activity to a lesser extent in the proximal tubules of SHR compared with normotensive WKY. The D\textsubscript{1}-like receptor numbers and the affinity to antagonist measured by [\(125\text{I}\)]SCH 23982, as well as forskolin- and GTP-stimulated adenylyl cyclase activities, were similar in SHR and WKY. This suggests that the defect resided in the coupling of the receptor with adenylyl cyclase.
and that the G proteins and adenylyl cyclase per se were not defective. The defect is specific to D₁-like receptor as well as nephron segment (only in the proximal part) and is organ specific (only in the kidney and not in the brain striatum of SHR). The stimulation of another signaling system, PLC, by dopamine and D₁-like agonist was also reduced in SHR, suggesting a defect in the D₁-like receptor and PLC coupling. Because adenylyl cyclase and PLC serve as the primary signaling pathways in the inhibition of Na,H-exchanger and Na,K-ATPase caused by dopamine, it was found that dopamine failed to inhibit the activities of these sodium-transporting proteins in the proximal tubules of SHR. The defect in the D₁-like receptor/adenylyl cyclase and PLC may explain the decreased natriuretic effect of dopamine and D₁-like agonists in SHR.

Further studies on the solubilized D₁-like receptors in SHR revealed that the agonist displacement of [¹²⁵I]SCH 23982 showed both high and low affinity in WKY but only low affinity in SHR, suggesting a defect in the high-affinity coupling between D₁-like receptor and G proteins. Other evidence for the reduction in the agonist binding comes from the agonist displacement of photoaffinity labeling by [¹²⁵I]SCH 23982 of D₁-like receptors. One reason could be a difference in the biochemical/physical nature of D₁-like receptor between WKY and SHR. The sulfhydryl groups are present on D₁-like receptors and regulate ligand-binding properties of the receptor. The concentration of N-ethylmaleimide (NEM, a sulfhydryl blocking agent by alkylation) required to reduce the ligand binding ([¹²⁵I]SCH 23982) by 50% was much lower (5.2 μM/L) in WKY than in SHR (1200 μM/L). Whether the defect in the agonist binding domain is in the primary structure because of mutation or in the tertiary structure because of improper folding of the receptor protein is not yet clear. Limited sequence of the D₃ mRNA (equivalent to the third cytoplasmic loop of cloned D₁A receptor, which is believed to be G protein–interacting domain) revealed no mutation in the protein in SHR compared with WKY.

The defect in the D₁A receptor/signal transduction coupling is believed to exist before the development of hypertension in SHR. The stimulation of adenylyl cyclase by D₁-like agonist is greater in WKY than in SHR at the prehypertensive age of 3 weeks and increases with age in WKY but not in SHR. Similarly, G protein stimulation (measured by [³⁵S]GTPγS binding) by D₁-like agonist was reduced in the basolateral membranes from 3-week-old SHR compared with WKY. Compelling evidence showing a relationship of defective D₁A receptor/signaling system with hypertension comes from two sets of experiments published recently: one on the cross-breeds of normotensive and hypertensive rats and the second on mice lacking functional D₁A receptors. In the F₂ generation from female WKY and male SHR crosses, the inability of D₁-like receptor to inhibit Na,H-exchanger in the proximal tubules cosegregated with increased systolic blood pressure (>160 mm Hg) and decreased ability of renal sodium excretion in response to D₁-like agonist infused in the renal arteries of the rats. The activation of D₁-like receptors was able to inhibit the Na,H-exchanger in rats of the same F₂ generation with systolic blood pressure <140 mm Hg. In another set of experiments, mutant mice lacking functional D₁A receptors were generated. Compared with control mice, both homozygous and heterozygous mice had greater systolic, diastolic, and mean arterial pressures. The renal tubules from homozygous mice had no [¹²⁵I]SCH 23982 (a D₁-like ligand) binding sites and had no stimulation of cAMP by dopamine. In addition to the observation made with D₁A receptor, the disruption of D₁ receptor (a member of D₁-like receptors present on proximal tubules) has also been shown recently to cause renin-dependent hypertension. However, the mechanism of hypertension caused by the disruption of D₁ receptors is different than that caused by D₁A receptors. The renal renin activity was much greater in the mice lacking D₁ receptors (both homozygous and heterozygous) than in the wild-type control group. A single-bolus dose of the AT₁ receptor antagonist losartan decreased systolic blood pressure to a greater extent and for a longer time in the homozygous mice than in the wild-type mice. During acute volume expansion, blood pressure was unchanged, glomerular filtration rates were similar, and urine flow was increased to similar extents in the wild-type and the mutant mice (both homozygous and heterozygous). However, increase in sodium excretion was attenuated in homozygous mice compared with control. There is evidence showing that a physiological and biochemical interaction exists between dopamine and angiotensin II receptors in the kidney. Intrarenally produced angiotensin has been shown to counteract fenoldopam-induced sodium excretion. Also, it has been shown that both D₁-like and D₂-like receptor agonists cause a decrease in AT₁ receptor binding sites in proximal tubular preparations. Although the AT₁ receptor binding sites have not been measured in the D₂ mutant mice, it is possible that the absence of D₁ receptors might have caused an increase in AT₁ receptors in the proximal tubules along with the higher renin production. Recently, we reported that fenoldopam stimulated [³⁵S]GTPγS binding to a lesser extent in the basolateral membranes of SHR than WKY. Moreover, of the two coupled G proteins (G₃ and Gq/11), a reduction in the quantities of Gq/11 was found in the basolateral membranes of SHR compared with WKY. In another study, dopamine and cholera toxin (G protein activator) were reported to inhibit Na,K-ATPase activity in the proximal tubules from WKY but had no effect in SHR. When the proximal tubules were pretreated with pertussis toxin (G protein inactivator), both dopamine and cholera toxin produced significant inhibition in Na,K-ATPase activity in SHR. Because arachidonic acid metabolites mediate dopamine-induced inhibition of Na,K-ATPase activity in the proximal tubules, a reduced inhibition in Na,K-ATPase activity by arachidonic acid was observed in SHR compared with WKY. As we discussed earlier, the response of adenylyl cyclase and Na,H-exchanger to D₁-like agonist undergoes ontogenesis in WKY but not in SHR; a similar ontogenesis takes place with the action of cAMP on Na,H-exchanger in WKY but not in SHR. Horiiuchi et al have shown that the effect of cAMP on Na,H-exchanger activity is lost with maturation in the proximal tubules of SHR. On the basis of these studies, it is reasonable to propose that the alterations in these signaling components may also contribute to the failure of dopamine and D₁-like agonists to
inhibit Na,K-ATPase and Na,H-exchanger activity in the proximal tubules from SHR.

**Dopamine Receptor Agonists in Treatment of Cardiovascular Diseases**

Dopamine receptors located at various regions within the cardiovascular system, including the kidneys, serve as important target sites for the actions of several compounds acting at either D1-like and/or D2-like receptors. The location and cardiovascular changes caused by the activation of these receptors are shown in the Table.

The therapeutic application of dopamine is somewhat limited by the fact that in addition to activating D1-like receptors, at higher doses it also activates D2-like, β-, and α-adrenergic receptors. However, at low doses ranging from 1 to 3 μg · kg⁻¹ · min⁻¹, dopamine predominantly activates D1-like receptors and causes increases in RBF, glomerular filtration rate, and sodium and water excretion. Dopamine in low doses is used in acute treatment of heart failure in patients to promote natriuresis and diuresis via selective D1-like dopamine receptor stimulation. It was shown in another study that in patients with renal disease, while the renal vasodilatory response to dopamine was reduced compared with that in healthy volunteers, the natriuretic response in these patients was still evident. In a recent study, dose-response analysis of dopamine in water-loaded individuals was performed. It was found that the natriuretic and renal vasodilating effect of dopamine was maximal at a dose of 3 μg · kg⁻¹ · min⁻¹. At higher doses, increased α-adrenergic stimulation caused attenuation of the renal vasodilation seen with D1-like receptor stimulation. Therefore, while dopamine is effective as a renal vasodilator and natriuretic agent, its clinical use is limited because of its ability to activate α-adrenoceptors, and this effect may sometimes be exaggerated depending on the clinical condition of the patient.

Fenoldopam is a preferential D1-like dopamine receptor agonist that has been used in patients with hypertension and heart failure. In patients with congestive heart failure, fenoldopam increases cardiac index and decreases systemic vascular resistance and blood pressure. Intravenous administration of fenoldopam to hypertensive patients leads to an immediate lowering of blood pressure that is accompanied by increases in RBF as well as sodium and water excretion, and these effects of the compound are maintained throughout the infusion period. A comparative study of fenoldopam with nitroprusside in patients with hypertensive crisis revealed that while both of these compounds caused a prompt lowering of blood pressure, the additional beneficial effect seen with fenoldopam was that it promoted natriuresis and diuresis in these patients. Because RBDF was not measured in this study, it is not clear whether natriuretic response was secondary due to an increase in RBF or whether it resulted from the direct tubular action of fenoldopam on D1-like dopamine receptors. It is reported that activation of D1-like receptors located on the juxtaglomerular cells causes an increase in renin release, and we have shown in animal experiments that the natriuretic and diuretic effect of fenoldopam is markedly potentiated by pretreatment with angiotensin-converting enzyme inhibitors and losartan. Therefore, the renin-releasing effect of fenoldopam and subsequent formation of angiotensin II counteracts the natriuretic and diuretic effects of fenoldopam. The clinical significance of this finding in hypertensive patients remains to be determined. Recently, fenoldopam (Corlopam) has been approved by the Food and Drug Administration for use in hospitalized patients for short-term management of hypertension when rapid but quickly reversible emergency reduction of blood pressure is clinically indicated, including malignant hypertension with deteriorating end-organ function. Although fenoldopam is orally active and effective in lowering blood pressure, because of its poor bioavailability, which necessitates frequent dosing, it is not used for the chronic treatment of hypertension.

Dopexamine is a dopamine analogue with a complex pharmacological profile. In therapeutic dose range, it activates D1-like receptors and β₂-adrenoceptors and inhibits neuronal reuptake of norepinephrine. The latter two effects account for the mild positive inotropic effect seen in patients with congestive heart failure. Dopexamine is reported to be effective in the treatment of acute heart failure, during cardiac surgery, and in general intensive care. Also, as it relates to its dopaminergic action, it is reported that dopexamine is effective for the protection of renal function in patients undergoing orthotopic liver transplantation, in patients suffering chronic renal dysfunction, dopexamine infusion caused increases in total cortical and medullary RBF and in renographic clearance rate. These actions of dopexamine at the level of the kidney are most likely due to the action of the compound on D1-like dopamine receptors located at various regions within the kidney, including the blood vessels and renal tubules. However, because of its action at multiple receptors and the fact that it must be administered intravenously, it is likely that dopexamine will be used only in intensive care. This compound is approved for use in acute cardiac failure patients in certain European countries, but it is not yet approved for use within the United States.

Ibopamine is an orally active diisobutyrate ester of N-methyl dopamine or epinephrine. Ibopamine is a prodrug, and after absorption it is hydrolyzed in plasma to its active metabolite, epinephrine. Epinephrine has a pharmacological and receptor profile similar to that of dopamine, but the main advantage is that ibopamine, the prodrug, has oral bioavailability and hence is administered orally. While ibopamine was initially shown to be effective in patients with congestive heart failure during short-term administration lasting for a few days, its effects were not persistent in patients when administered for 8 weeks. However, a recent clinical trial with ibopamine in patients with heart failure had to be terminated early because of the excess mortality seen in the ibopamine group (25%) compared with the placebo group (20%). Although the reasons for the excess mortality are not clear, a mechanism involving increased extracellular calcium resulting from β-adrenoceptor stimulation may play a role in the increased mortality in the ibopamine group. These findings have led to restrictions on the use of ibopamine in patients with severe heart failure in countries where the drug is approved as a therapeutic agent. It should be noted that ibopamine is not approved for use in the United States.
Compounds acting on D2-like dopamine receptors have been shown to lower blood pressure and heart rate in experimental animals.117 As shown in the Table, activation of D2-like receptors located on sympathetic nerve terminals and ganglia leads to inhibition of norepinephrine release; the subsequent reduction in afterload and vasodilation is what accounts for the antihypertensive action of compounds such as bromocriptine and quinpirole. However, these compounds are not used in hypertensive patients because of several unwanted and complicating effects. For example, because these agents enter the brain, activation of D2-like receptors in this region produces many undesirable effects, including emesis and endocrine changes. Also, a reduction in sympathetic tone leads to conditions such as postural hypotension. Therefore, although D2-like dopamine receptor agonists have contributed to our understanding of the pharmacology of peripheral prejunctional dopamine receptors and their role in the regulation of sympathetic neurotransmission under pathological conditions, they do not offer any therapeutic potential in the treatment of cardiovascular diseases, including hypertension.

Summary and Future Directions

Several physiological, biochemical, and molecular studies suggest the importance of endogenous dopamine and renal D1A receptor in the regulation of sodium and body volume homeostasis. Although there is evidence that a defective renal dopaminergic system contributes to the development and maintenance of hypertension, it is not yet clear what is the triggering factor that causes the defect selectively in the renal dopaminergic system. In the animal model of genetic hypertension, the precise defect in D1A receptor leading to reduced affinity to the agonist and impaired signal transduction has not yet been defined. Certain biochemical properties of renal D1A receptor in SHR, such as buried sulfhydryl groups, indicate that a defect may lie in the posttranslational and receptor-folding machinery. Similar to β-adrenoceptor, various phosphorylation sites and palmitoylation site (at cys348) are present on the D1A receptor which may play an important role in the coupling with G proteins and activation of second messenger systems. Therefore, in addition to investigating the defects in D1A receptor protein per se, it will be equally important to focus on the biochemistry of posttranslational steps involved in D1A receptor folding and expression of the receptor protein on the cell membrane in SHR. Although the development of hypertension in mice lacking D1A receptor (by general knockout) suggested a causal relationship of the D1A receptor gene with hypertension, the effect of kidney-specific knockout of D1A receptor gene is yet to be investigated. The question of whether D1A receptor is the only D1-like dopamine receptor that is linked to both signaling pathways (PLC/PKC and adenylyl cyclase/PKA) and inhibits Na,K-ATPase and Na,H-exchanger, respectively, in the proximal tubules remains to be answered. The recent report using D1A knockout mice shows that D1-like receptors mediating stimulation of PLC are not D1A dopamine receptors stimulating adenylyl cyclase in the brain striatum. It is not known whether the dopamine receptors linked to adenylyl cyclase and PLC in the kidney are D1A subtypes or whether two different molecular entities of D1-like receptors are expressed. Binding of [125]I[SCH 23390 in the brain striatum and kidney proximal tubules of D1A knockout mice suggested a heterogeneity of D1A receptors.74,86 Brain striatum of D1A knockout mice (homozygous) had the remaining sites that bound to [125]I[SCH 23390 and were suggested to be linked to inositol hydrolysis, whereas the proximal tubules from D1A knockout mice (homozygous) exhibited no [125]I[SCH 23390 binding sites.7 Further biochemical and molecular characterization of dopamine receptors in the kidney will allow us to better understand their role in the regulation of sodium excretion and the cause of defective dopamine receptors and associated signal transduction mechanisms in hypertension.

As related to the relationship between increased renin-angiotensin activity and disruption of D1 receptors in mice, it will also be important to examine whether the disruption of D1 receptors led to an increase in AT1 receptors in the kidney. In light of the reported interactions between angiotensin and dopamine receptors, the findings could be relevant to further explanations for the mechanism of hypertension seen in mice lacking D1 receptors.

The therapeutic potential of dopamine and D1-like receptor agonists in the treatment of cardiovascular diseases is currently limited to the treatment of hypertensive emergencies only, because of the lack of availability of compounds that have extended bioavailability after oral administration. However, compounds such as fenoldopam, in addition to causing rapid lowering of blood pressure during hypertensive emergencies, are also found to be effective in animal experiments in preserving and protecting RBF and renal function under various pathological conditions.121,122 Dopexamine also has been reported to improve blood flow to several important organs and protect organ function during hemorrhagic shock and injury caused by oxygen free radicals.123,124 Therefore, it is likely that the therapeutic potential of currently available dopamine receptor agonists lies in the area of protection and preservation of blood flow to vital organs such as the heart, mesentery, and kidney, and eventually the function of these organs, for patients receiving treatment in intensive care units.

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