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Dopamine, kidney, and hypertension: studies in dopamine receptor knockout mice

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Abstract

Dopamine is important in the pathogenesis of hypertension because of abnormalities in receptor-mediated regulation of renal sodium transport. Dopamine receptors are classified into D_1-like (D_1, D_5) and D_2-like (D_2, D_3, D_4) subtypes, all of which are expressed in the kidney. Mice deficient in specific dopamine receptors have been generated to provide holistic assessment on the varying physiological roles of each receptor subtype. This review examines recent studies on these mutant mouse models and evaluates the impact of individual dopamine receptor subtypes on blood pressure regulation.

Keywords

Dopamine receptor; Hypertension; Knockout mice; Renal function

Introduction

Hypertension, which affects a quarter of all middle-aged adults, is one of the most common risk factors of cardiovascular disease. High blood pressure is a phenotype expressed by several disorders, and results from an aberrant interaction between genetic and environmental factors. Hypertension occurs because of the increased activity of pro-hypertensive systems and/or decreased activity of anti-hyrtensive systems [1–4], one of

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which is the dopaminergic system [1, 2]. Therefore, a dysfunction in the dopaminergic pathway may be a mechanism in the development of essential hypertension.

Mammalian dopamine receptors are G protein-coupled receptors (GPCRs) belonging to the α group of the rhodopsin family (Class A, Family A, or Family 1) and include five subtypes identified by molecular cloning [5, 6]. The D_1 and D_5 receptor subtypes are known as D_1-like receptors and couple to G proteins G_s and G_{olf} to stimulate adenylyl cyclase activity. The D_2, D_3, and D_4 receptor subtypes are known as D_2-like receptors and couple to G_I and G_o to inhibit adenylyl cyclase activity [1, 2]. D_1-like receptors are typically expressed post-synaptically/post-junctionally, whereas D_2-like receptors are also expressed pre-synaptically/pre-junctionally. Distinct cells within the same organ may co-express different receptor subtypes, rendering cell-specific assignment of receptor subtypes difficult [2, 7–14]. Dopamine receptor agonists and antagonists have poor selectivity for individual dopamine receptors and, consequently, hinder investigation of the specific roles of each dopamine receptor subtype. To circumvent this problem, gene-targeted mutant mouse models lacking one or more dopamine receptor subtypes [8–13, 15–26] have been generated. Studies using these mouse models have shed light on the specific physiological role of each receptor at the cell, organ, and whole animal level.

The long-term regulation of blood pressure is accomplished by both renal and non-renal mechanisms [1, 2, 27– 31]. Abnormalities in renal epithelial ion transport play important roles in the pathogenesis of essential hypertension, especially in salt-sensitive hypertension. In this review, we summarize the role of the dopamine receptor subtypes in the regulation of blood pressure in humans and rodents.

Renal distribution of the dopamine receptors

D_1 receptor

Human—D_1 receptor mRNA is expressed in cultured human renal proximal tubule cells [32]. In the human kidney [33], D_1 receptor immunostaining is found in the apical and basolateral membrane of the proximal and distal convoluted tubules, medullary thick ascending limb of Henle, macula densa, and cortical collecting duct, but not in the glomerulus and juxtaglomerular cell. D_1 receptor protein is also present in the large intrarenal arteries in humans [33], but not in renal veins. Immunoblotting studies have revealed the presence of several forms of D_1 receptors, varying in size from 50 to 210 kDa, in rat and human renal proximal tubules [34], which is in agreement with data obtained in brain tissue [35].

Rat—Radioligand binding studies of the rat have shown the presence of D_1-like receptors in the renal cortex, but not in glomeruli or medulla [36–41]. However, ligands to both D_1-like receptors have similar affinities and, therefore, cannot pharmacologically distinguish the D_1 from the D_5 receptor. D_1 receptor mRNA is expressed in the rat proximal and distal tubule, arteriole, juxtaglomerular apparatus, but not in the glomerulus or medulla [42–44]. It is also expressed in cultured renal proximal tubule cells from the rat [45], mouse (unpublished studies), opossum [46], human [32], and pig [47]. D_1 receptor immunostaining is present in the rat apical and basolateral membrane of the proximal and distal convoluted tubules, medullary thick ascending limb of Henle, macula densa, and cortical collecting duct [7, 48]. Most of the D_1 receptors in the rat proximal tubules are located in the S3 segment (unpublished observations, 2007). The protein expression of D_1 receptors in the inner medullary collecting duct has not been documented, but dopamine does not stimulate cyclic adenosine monophosphate (cAMP) production in this nephron segment [49]. The expression of D_1 receptors in the juxtaglomerular cell [7, 44, 48] has been reported in the rat, but not in the human or mouse kidney. Consistent with the results from mRNA studies and adenylyl

cyclase activation in response to D_1-like receptor agonist [2], D_1 receptor proteins are not expressed in the rat glomerulus.

Mouse—The distribution of D_1 receptor protein in the renal tubular segments in the mouse ([2], unpublished studies) is similar to that in the human and rat kidney.

D_2 receptor

There are two D_2 receptor isoforms, D_{2short} and D_{2long}, which have been suggested to function pre- and post-synaptically, respectively [50]. The D_{2short} receptor is expressed more in pre- than in post-synaptic junctions [51, 52].

Rat—D_{2long} mRNA is expressed in renal tubules and glomeruli [53]. Immunoblotting [54] revealed that D_2 receptor protein is expressed in rat kidney cortex at a major band of 63 kDa and a minor protein band of 95 kDa (probably a D_2 receptor dimer). By indirect immunofluorescence microscopy, D_2 receptor immunostaining is found in the rat renal cortical proximal tubule, collecting duct, and the mesangial cell of the glomerulus [54]. The D_2 receptor is expressed in the intercalated—but not in the principal cell— of the medullary collecting duct. D_2 receptor protein is also expressed in an opossum proximal tubule cell line, which also exhibits distal tubular cell characteristics [55]. There are no reports of renal tubular D_2 receptor expression in the human and mouse.

D_3 receptor

Human—There are no published studies on the location of the D_3 receptor in non-embryonic human kidney.

Rat—Radioligand binding of 7-OH-DPAT, a selective D_2 and D_3 receptor ligand, has been reported in rat cortical tubules and mesangial cells [56]. D_3 receptor mRNA is expressed in the glomeruli, renal cortical and medullary tubular, and intrarenal vascular tissues [53]. In renal proximal tubules, D_3 receptor protein is mainly located in the apical and subapical areas, but not in the basolateral membrane [57]. However, results on the expression of the rat D_3 receptor along the nephron and blood vessels have not been consistent. Nurnberger et al. [57] found D_3 receptor protein to be limited to the proximal tubule, whereas O'Connell et al. [58] found the receptor protein in the glomerulus, renal blood vessel, renal proximal tubule, the apical membrane of the distal convoluted tubule, in the intercalated cell of the cortical collecting duct, and in the macula densa of the rat kidney, but not in juxtaglomerular apparatus. However, D_3 receptor mRNA and functional D_3 receptors have been described in primary cultures of rat juxtaglomerular cells [59]. The discrepancy between the findings in the kidney in situ and juxtaglomerular cells in vitro suggests that the expression of D_3 receptors is conditional (e.g. culturedependent). Two species of D_3 receptor (45 and 90 kDa) are expressed in rat renal proximal tubule brush border membranes [60] and cells [61], as detected by immunoblotting studies.

Mouse—D_3 receptor immunostaining is observed at the apical membrane of the S1 segment of the proximal convoluted tubule. The staining is also found in the macula densa, cytoplasm of the thick ascending limb of Henle, distal convoluted tubule, and the glomerulus, but not in the medullary collecting duct [62].

D_4 receptor

Human—D_4 receptor mRNA is expressed in the human kidney [63].

Rat—D_4 receptor mRNA is not expressed in the glomerulus or the loop of Henle [63], but the D_4 receptor protein is found in cultured rat juxtaglomerular cells [59]. Immunoblotting analysis of the renal cortex has revealed a minor protein band of 49 kDa and a major protein band of 38 kDa [54]. D_4 receptor immunostaining is present in the S_1 segment of the proximal tubule, the distal convoluted tubule [64], and especially in the cortical and medullary collecting ducts, where it is more prominent at the basolateral area than at the luminal areas. D_4 receptor staining is weak in the glomerulus [54].

Mouse—There are no reports on the expression of the D_4 receptor in the mouse kidney. Our unpublished studies indicate that the D_4 receptor is expressed throughout the nephron, except at the thick ascending limb of Henle (Fig. 1).

D_5 receptor

Human—D_5 receptor protein is expressed in cultured proximal tubule cells from the human kidney [65].

Rat—The D_5 receptor protein is expressed in the proximal and distal convoluted tubules, and arteriole, but not in the juxtaglomerular cell, glomerulus, or macula densa [7, 66– 68]. The D_5 receptor may be expressed preferentially over the D_1 receptor in the thick ascending limb of Henle and the cortical collecting duct, while the D_1 receptor is preferentially expressed in the proximal tubule [69, 70]. Immortalized rat renal proximal tubule cells express D_5 receptors of molecular sizes similar to those of the D_1 receptor [71, 72]. The D_5 receptor is also expressed in the opossum kidney, but not in the opossum kidney cell line [46].

Mouse—The D_5 receptor immunostaining is located in the apical and brush border membrane of mouse renal cortical tubule [72].

Role of the dopamine receptors in renal physiology

The D_1-like receptors

Dopamine produced by the renal proximal tubule plays an important role in the regulation of sodium excretion, especially when there is a surfeit of sodium in the system [1, 2]. The D_1-like dopamine receptors, D_1R and D_5R, account for 50–70% of renal sodium excretion [1, 2] during moderate sodium intake. The inhibition of sodium transport exerted by endogenous renal dopamine is due mainly to renal tubular effects [2, 38, 73], in contrast to exogenously administered dopamine and D_1-like receptor agonists which regulate sodium excretion by both hemodynamic and tubular mechanisms [1, 2, 14, 38, 74–76].

As aforementioned, there are no available ligands that can distinguish the D_1 from the D_5 receptor. However, it is likely that the natriuretic effect of dopamine is exerted mainly through the D_1 receptor in renal proximal tubule cells since the cAMP production caused by dopamine in these cells is mostly due to D_1 receptor activity [77]; the inhibition of renal ion transport by D_1-like receptors is, in part, mediated by cAMP. Chronic intrarenal cortical infusion of D_1 receptor antisense oligodeoxynucleotides, which selectively decrease D_1 receptor protein expression without affecting the D_5 receptor expression [78], provides direct evidence of the specific D_1 receptor role in the inhibition of renal sodium transport. In this study, the selective renal cortical inhibition of D_1 receptor expression decreased sodium excretion during a normal or high salt intake.

The stimulation of D_1-like receptors decreases sodium transport in the proximal tubule by inhibiting the activity of several sodium transporters, including the sodium hydrogen

exchanger 3 (NHE3, SLC9A3), sodium phosphate cotransporter (NaPi-IIa/SLC34A1 and NaPi-IIc/SLC34A3), and Cl^-/ HCO_3^- exchanger (SLC26A6) at the apical membrane, and electrogenic Na^+/HCO_3^- co-transporter (NBCe1A, SLC4A4), and Na^+-K^+ ATPase at the basolateral membrane [16, 75, 79–86]. In the medullary thick ascending limb of Henle, D_1-like receptors decrease sodium transport [87] by inhibiting Na^+–K^+ ATPase activity, although dopamine increases NKCC2 (SLC12A1) activity in this nephron segment [88]. We have suggested that the D_1-like receptor stimulation of NKCC2 may be important in K^+ recycling. Eicosanoids (20-hydroxyeicosatetraenoic acid, 20-HETE) may act synergistically with D_1-like receptors to inhibit NKCC2 activity. G protein-dependent, cAMP/protein kinase A (PKA)-dependent, and protein kinase C (PKC)-independent mechanisms are involved in the D_1-like receptor inhibition of Na^+/Pi_2, NHE3, Na/HCO_3^- co-transporter and Cl^-/HCO_3^- exchanger activity, including their translocation out of the brush border membranes [82, 89–94]. On the other hand, D_1-like receptors inhibit Na^+–K^+ ATPase activity via cAMP/PKA, certain PKC isoforms, and 20-HETE that internalizes Na^+–K^+ ATPase subunits [2, 83, 95–104]. The mechanism of the inhibitory effect of D_1-like receptors on Na^+–K^+ ATPase is nephron-segment specific. Protein kinase A is involved in D_1-like receptor-mediated inhibition of sodium transporters in the cortical collecting duct, while PKC is involved in the proximal convoluted tubule, and the eicosanoids are involved in all nephron segments [1, 95–98, 100–103, 105–107]. D_1-like receptors inhibit NHE3 activity via PKA in rat renal proximal tubule cells [91], while PKC may also be involved in opossum kidney cells [107]. Interestingly, the ability of D_1-like receptors to stimulate calcium uptake in renal proximal tubule cells, via cAMP and PKC, may play a role in the inhibition of NHE3 activity [108].

In addition to the direct inhibition of sodium excretion by the D_1-like receptors per se, these receptors interact with the D_2-like receptors to enhance their inhibitory effect. We have reported that the increase in sodium excretion induced by Z-1046, a dopamine receptor agonist with a rank order potency $D_4 \geq D_3 > D_2 > D_5 > D_1$, is blocked by either a D_1-like or D_2-like receptor antagonist [60]. D_2-like receptors may potentiate the inhibitory effect of D_1-like receptors on Na^+-Pi co-transport, NHE3, and Na^+-K^+ ATPase activities in renal proximal tubules (see below).

D_1 receptor and renal function—The D_1 receptor interacts with other systems, such as the renin–angiotensin–aldosterone and the sympathetic nervous systems, to tightly regulate renal and cardiovascular functions. Angiotensin II exerts its effects on angiotensin II type I receptors (AT_1R) and opposes the effects of dopamine exerted mainly through the D_1-like receptors. D_1-like and AT_1 receptors have contrasting effects on the generation of second messengers, i.e. D_1-like receptors stimulate adenylyl cyclases, while the AT_1 receptor inhibits them. Both D_1-like and AT_1 receptors stimulate phospholipase C activity; however, they stimulate different PKC isoforms [1, 2]. Activation of AT_1 receptors stimulates all renal proximal tubular ion-transporting proteins that are inhibited by the D_1-like dopamine receptors [106, 109–111]. Thus, the effect of the D_1-like receptors on natriuresis is enhanced when angiotensin II production is decreased or when AT_1 receptors are blocked [112, 113]. The D_1-like receptors can also counteract the renal vasoconstrictor effect of angiotensin II [114]. Activation of the D_1-like receptors decreases AT_1 receptor expression and the number of angiotensin II binding sites in renal proximal tubule cells from normotensive Wistar–Kyoto (WKY) rats [72, 115]. The use of antisense oligonucleotides against D_1 or D_5 receptors points to D_5R as the major negative regulator of AT_1R expression [65]. However, the D_1 receptor can also inhibit AT_1 receptor function by direct physical interaction [116]. In contrast to AT_1 receptors, AT_2 receptors participate in the natriuresis mediated by the D_1-like receptors [117].

D_5 receptor and renal function—Activation of D_1-like receptors induces diuresis and natriuresis in WKY rats [1, 2, 38, 39, 117]. Due to the lack of selective D_1 and D_5 receptor ligands, the relative contribution of D_1 and D_5 receptors on natriuresis in response to D_1-like receptor agonist stimulation is not known. It is presumed that both D_1 and D_5 receptors are involved because both receptors increase cAMP production and cAMP mediates the D_1-like receptor-mediated inhibition of ion transport [77]. However, as aforementioned, cAMP production is increased to a greater extent by the D_1 receptor than by the D_5 receptor in renal proximal tubule cells [77] and, thus, the D_1 receptor, conceivably, mediates most of the natriuretic effect of dopamine [78].

D_2-like receptors and renal function

The D_2-like receptor family consists of the D_2, D_3, and D_4 dopamine receptors. These receptors variably regulate sodium transport [1, 2]. The D_2-like receptors can modulate renal function by regulating dopamine transporter activity [118] and renal dopamine production [119]. Bromocriptine, a D_2-like receptor agonist with a tenfold greater affinity for D_2 over D_3 receptors, stimulates Na^+–K^+ ATPase activity by increasing its alpha subunit in the plasma membrane [120, 121]. Bromocriptine also increases chloride transport in the medullary thick ascending limb of Henle in rat renal proximal tubules [122]. LY171555, a D_2-like receptor agonist with a higher affinity to the D_2 receptors, stimulates Na^+–K^+ ATPase activity in murine fibroblasts heterologously expressing D_{2Long} [123]. Interestingly, dopamine engenders antinatriuresis in sodium-depleted women [124]. Sulpiride, a D_2-like receptor antagonist with equal affinity to all D_2-like receptors, impairs the dopamine-mediated natriuresis in volume-expanded women [125]. Thus, activation of D_2-like receptors results in an antinatriuresis in conditions of volume depletion or in a natriuresis in volume-expanded states. Whether this is a direct effect of the D_2-like receptors or due to their interaction with the D_1-like receptors remains to be determined. D_2-like receptors have also been shown to possess vasodilatory effects, presumably by a pre-junctional inhibition of catecholamine release [2].

D_2 receptor and renal function—In the LTK2 cells expressing the D_{2Long} receptor, activation of D_2-like receptors decreases cAMP levels, resulting in increased Na^+–K^+ ATPase activity [123]. The selective agonists for the D_2 receptor, bromocriptine, and LY171555 inhibit adenylyl cyclase activities. The resulting decrease in cAMP production/PKA activation probably mediates the stimulation of Na^+–K^+ ATPase activity [120, 123]. The D_2 receptor can inhibit adenylyl cyclase activity even in the absence of adenylyl cyclase V [126], the isoform not expressed in the kidney [127]. D_1 receptor-mediated activation of PKC could lead to a D_{2long}-mediated sensitization of adenylyl cyclase VI [128]. In Chinese hamster ovary (CHO) cells heterologously expressing tenfold more D_2 receptors than D_1 receptors, stimulation of either receptor results in the potentiation of arachidonic acid release compared to those cells expressing either receptor only [129, 130]; arachidonic acid cytochrome P-450 products have been shown to inhibit renal sodium transport [83, 98, 131, 132]. This synergism between D_1 and D_2 receptors in the production of cAMP, phospholipase C, and arachidonic acid products might explain the observed D_2 receptor-mediated natriuretic effect. The D_1 and D_2 receptors can heterodimerize [133] and interact with each other [130, 134] to increase c-fos [135] and inhibit Na^+-K^+ ATPase activity [136]. It is conceivable that the D_2-like receptors stimulate sodium transport under conditions of "low" sodium intake and inhibit Na^+-K^+ ATPase activity in renal proximal tubules cells under conditions of "moderate" sodium excess (in concert with D1-like receptors) to synergistically increase sodium excretion [124, 125, 137–139].

D_3 receptor and renal function—The ability of D_3 receptors to mediate natriuresis is supported by the decreased ability of D_3 receptor-deficient mice to excrete an acute saline

load [17] and corroborated by several pharmacological studies. The D_3 receptor agonists 7-OH-DPAT and PD128907 [140] have been shown to decrease renal sodium transport [141]. Acute intravenous administration of 7-OH-DPAT in salt-resistant Dahl rats increases glomerular filtration rate and sodium and water excretion without affecting blood pressure [141]. PD128907, a selective D_3 receptor agonist with a 120-fold selectivity over the D_2 receptor, infused directly into the renal artery, dose-dependently increases fractional sodium excretion in WKY rats [but not in spontaneously hypertensive rats (SHR)] fed a normal or high salt diet [142]. Quinerolane, a D_2-like receptor agonist with 21-fold selectivity for the D_3 over the D_2 receptor, opens K^+ channels, resulting in hyperpolarization and inhibition of Na^+–K^+ ATPase activity [143]. The renal effects of D_3 receptor activation are mediated by actions on post-junctional glomerular and tubular receptors, and pre-synaptic modulation of norepinephrine release because renal denervation attenuates the effects of 7-OH-DPAT [144].

D_4 receptor and renal function—The D_4 receptor exerts an antagonistic effect on vasopressin- and aldosterone-dependent water and sodium reabsorption in the cortical collecting duct [145, 146]. In the rabbit cortical collecting duct, the D_4 receptor-mediated decrease in sodium transport is exerted mainly at the basolateral membrane despite of greater expression of D_4 receptors at the luminal membrane [146].

The distribution of dopamine receptors and apical sodium transporters in rat renal tubules is summarized in Fig. 1.

Aberrant dopamine receptor function and hypertension

D1-like receptors and hypertension

The diuretic and natriuretic responses to administration of D1-like receptor agonists are impaired in rodents with polygenic hypertension (Dahl salt-sensitive rats and SHRs) [1, 2, 38, 75, 147]. The natriuretic effect of parathyroid hormone and cholecystokinin is not impaired in the SHRs, indicating that the impaired D1-like receptor effect is receptor-specific [60]. More importantly, the natriuretic effect of dopamine synthesized in the kidney is also impaired in rodent polygenic hypertension [38, 60, 147]. In human essential hypertensive subjects, the actions of D_1-like receptors on renal hemodynamics and distal renal tubule function (see below) are preserved [148, 149], and for this reason, the overall natriuretic effect of administered D1 receptor agonists may be similar or even greater than that in normotensive subjects, even when the ability of D_1-like receptor agonists to inhibit proximal tubular reabsorption is impaired [148].

The ability of D1-like receptors to inhibit NHE3, Cl^-/ HCO3- exchanger, Na^+/HCO3- cotransporter, and Na^+–K^+ ATPase activities is decreased in rodent genetic hypertension which is due, in part, to decreased production of second messengers (e.g. cAMP, diacylglycerol, eicosanoids) in the renal proximal tubule [16, 37, 71, 75, 86, 92, 93, 98, 150–153] and the thick ascending limb of Henle [75]. The D1-like receptor-mediated stimulation of cAMP production, however, is not impaired in the cortical collecting duct of SHRs [154].

The impaired ability of D1-like receptors to stimulate cAMP production in renal proximal tubules is receptor specific, since the ability of parathyroid hormone to stimulate cAMP production or stimulate G proteins is intact [153, 155, 156] and, at least in young SHRs, β-adrenergic function is also intact [157]. Increased serine phosphorylation and decreased expression of D1 receptors at the plasma membrane [71, 158], are responsible for the impaired ability of D1-like receptors to stimulate cAMP production in renal proximal tubules in genetic hypertension. However, the impairment of D1-like receptor function is organ specific because D1-like receptor function in the brain striatum is intact [37]. The D1-

like receptor defect is genetic because it co-segregates with high blood pressure and precedes the onset of hypertension [16, 37, 159, 160].

Deficiency of the expression of D1-like receptors could be involved in human essential hypertension. The human D1 gene locus on chromosome 5 at q35.1 is linked to human essential hypertension [161]. Although there are as yet no reports of the association of polymorphisms of the coding region of the D1 receptor and essential hypertension, a polymorphism, A-48G, in the 5′-untranslated region is associated with essential hypertension in Japanese [162]— but not in Caucasians [163]. However, the D1 receptor A-48G polymorphism has been reported to be associated with albuminuria [164].

The D_5 receptor gene locus (chromosome 4p15.1–16.1) is also linked to essential hypertension [165]; the human D_5 receptor gene has polymorphisms that code for receptors abnormally coupled to adenylyl cyclase [166]. The role of the D_5 receptor in hypertension has been difficult to determine, mostly due to the fact that the D_1 and D_5 receptors are pharmacologically indistinguishable. As mentioned above, the lack of selective ligands makes it impossible to activate or block only the D_1 or D_5 receptor in vivo. For this reason, genetic approaches to this problem have been employed by investigators who used gene silencing techniques to inhibit D_1 or D_5 receptor expression and generate D_1 or D_5 receptor-deficient mice [9, 12, 16, 22, 23].

D_1 receptor mutant mice—D_1 receptor knockout (D_1−/−) mice were generated by targeted mutagenesis with 7.0 kb of the 129/Sv-derived D_1 receptor genomic construct in pPNT [16, 22]. The homozygous D_1−/− mice have no binding sites for D_1-like receptor antagonists, and in response to D_1-like receptor agonist stimulation, they do not increase cAMP accumulation although their response to parathyroid hormone is intact. Systolic, diastolic, and mean arterial pressures are higher in both homozygous and heterozygous mice than in wild-type mice. These data indicate that defective D_1 receptor/signal transduction results in increased blood pressure in mice [16]. However, there is no report available on the renal function or the activity of the renin-angiotensin II–aldosterone system in D_1−/− mice. It is also unknown whether the hypertension of the null mice is salt-dependent.

D_5 receptor-deficient mice—D_5 receptor deficient (D_5−/−) mice were generated by injecting into C57BL/6 mouse blastocysts 129/SV embryonic stem cells containing the targeting construct generated by ligating the neomycin resistance gene in reverse orientation at the unique *Sfi*I site in the second intracellular loop of the D_5 receptor. D_5−/− mice are viable, develop normally, and have normal expression of the other dopamine receptors, including the D_1 receptor [23, 167].

Congenic D_5−/− mice are hypertensive and salt-sensitive. Blood pressure is also increased in D_5+/− mice (Table 1, unpublished data). D_5−/− mice have a greater epinephrine/norepinephrine ratio and a greater hypotensive response to the acute administration of an α-adrenergic blocker [23] than their D_5+/+ littermates, indicating that increased sympathetic activity plays a role in the elevated blood pressure. However, the percentage decrease in systolic blood pressure, after adrenalectomy, is similar in D_5−/− and D_5+/+ mice, indicating that central nervous system mechanisms are involved in the hypertension of D_5−/− mice [23, 168]. In addition, these central nervous system mechanisms, AT_1 receptors, and the increased production of reactive oxygen species (ROS) are also involved in the hypertension of D_5−/− mice [14, 66, 72, 169]. However, renal renin protein expression and serum aldosterone level are not altered in D_5−/− mice (unpublished data). D_5−/− mice also exhibit proteinuria [170].

D_2-like receptors and hypertension

Abnormalities of D_2-like receptor function have been reported in hypertension. One of the polymorphisms of the D_2 receptor, which results in decreased D_2 receptor expression, is associated with hypertension [171, 172]. Moreover, transfer of the segment of chromosome 8 containing the D_2 receptor gene from the normotensive Brown-Norway rat onto an SHR background decreases blood pressure [173].

The D_3 Ser9Gly receptor variant heterologously expressed in CHO cells impairs D_3 receptor-mediated inhibition of cAMP production, although these cell do possess the ability to decrease prostaglandin E2 (PGE2) production [174]. However, there is no association between the D_3 Ser9Gly, or other D_3 receptor gene variants with hypertension [175], despite the chromosome locus of the D_3 receptor gene (3q13.3) having been linked to human essential hypertension [176, 177]. Several studies have demonstrated that D_3 receptor deficiency may be important in the development of salt-sensitive hypertension. Salt-resistant Dahl rats on a high sodium diet and chronically treated with a highly selective D_3 receptor antagonist have increased blood pressure [178]. The natriuretic effect of a D_3 agonist is not evident in hypertensive salt-sensitive Dahl rats [178]. The same research group did not find differences in the natriuretic effect of a D_3 agonist between WKY rats and SHRs [179]. In this study, however, the D_3 agonist is given systemically, and activation of D_3 receptors outside the kidney may have had compensating role, thereby obscuring a differential effect on sodium excretion between WKY and SHRs. When the selective D_3 receptor agonist, PD128907, is infused directly into the renal artery in WKY rats and SHRs fed a high salt diet, fractional sodium excretion is dose-dependently increased in WKY rats but not in SHRs [142]. The mechanisms causing the impaired D_3 receptor function in the kidney in hypertension are not completely known. The stimulatory effect of the D_3 receptor agonist, PD128907, on D_3 receptor expression is no longer evident in renal proximal tubule cells from the SHRs [180]. It is possible that mechanisms which impair D_1 receptor function in SHR also impair D_3 receptor—for example, by increased G protein-coupled receptor-related kinase 4 (GRK4) activity [181]—or that impaired D_1 receptor function results in impaired synergistic interaction between the D_1 and D_3 receptor. In addition, the impaired natriuretic function of the D_3 receptor in SHRs may, in part, be related to the aberrant D_3 and AT_1 receptor interaction in renal proximal tubule cells [180]. D_3 receptor stimulation decreases AT_1 receptor expression in renal proximal tubule cells from the WKY rat, while D_3 receptor stimulation increases AT_1 receptor expression in the SHR [180].

A locus near the D_4 receptor gene (11p15.5) has been linked to hypertension. The most intensively studied D_4 receptor polymorphism is a 48-bp repeat located in exon 3 of the D_4 receptor gene. This variant codes for a 16-amino acid sequence located in the third intracellular loop of the D_4 receptor protein, a region that appears to interact with G proteins and influence intracellular levels of cAMP [182]. The number of repeats at the D_4 site varies from two to ten, but the four and seven repeat lengths are the most common in Caucasians in whom the long variant of the D_4 gene is associated with increased systolic and diastolic blood pressures [183].

The effects of D_4 agonists and antagonists on cardiovascular and renal function in genetically hypertensive rats have not been reported. The D_4 receptor protein is increased in the renal cortex—but not in the inner medulla—of SHRs relative to WKY rats [54].

D_2 receptor mutant mice—The D_2 receptor gene deficient ($D_2-/-$) mice were generated by homologous recombination in embryonic stem cells with deletion of exon 7 and the 5′ half of exon 8. These regions encode the majority of the putative third intracellular loop, the last two transmembrane domains, and the carboxy terminus [24]. $D_2-/-$ mice have decreased initiation of movement but otherwise normal basic motor skills without tremor,

ataxia, or abnormal stance or posture. D_2−/− and D_2−/+ mice have higher systolic and diastolic blood pressures than D_2 wild-type (D_2+/+) mice. The ability of D_2−/− mice to excrete an acute saline load is similar to that of D_2+/+ mice regardless of the elevated blood pressure, indicating that D_2−/− mice have a blunted pressure-natriuresis response. α-Adrenergic blockade decreases blood pressure to a greater extent in D_2−/− mice than in D_2+/+ mice. Epinephrine excretion is greater in D_2−/− mice than in D_2+/+ mice, and acute adrenalectomy decreases blood pressure to a similar level in D_2−/− and D_2+/+ mice. Endothelin B (ETB) receptor expression is greater in D_2−/−mice than in D_2+/+ mice, and an ETB receptor blocker decreases blood pressure in D_2−/− mice but not D_2+/+ mice. D_2−/− mice may be hypertensive because of enhanced vascular reactivity caused by increased sympathetic and ETB receptor activities [24] as well as by increased ROS production [184]. The D_2−/− mice also have increased production of aldosterone, and treatment with a mineralocorticoid receptor blocker normalizes blood pressure in these mice [184]. In contrast, D_2+/− mice have normal urinary aldosterone levels [185].

In another strain of D_2−/− mice, blood pressure is only increased when the animals are fed a high-salt diet, and this condition is associated with a decrease in renal aromatic L-amino acid decarboxylase (AADC) activity and renal dopamine production [26]; AADC converts L-DOPA (levodopa), which is taken up by renal brush border membranes, to dopamine. Sympathetic activity is not increased in these D_2−/− mice. Basal urine flow and sodium excretion are lower in D_2−/− mice than in D_2+/+ mice. However, administration of dopamine increases urine volume and sodium excretion in D_2−/− mice to levels similar to those found in D_2+/+ mice [118]. The differences between the two strains of D_2−/− mice could be related to differences in their genetic backgrounds.

D_3 receptor mutant mice—D_3 receptor gene deficient (D_3−/−) mice have been generated by targeted mutagenesis. The targeting construct has a 7-kb 129/sv-derived D_3 receptor genomic sequence in the GKNeo cassette in antisense orientation at the *SalI* site in exon 2 [15]. The locomotor phenotype of D_3 mutants does not resemble that of D_2 mutants. D_3−/− mice develop normally, are fertile, and may show a transient locomotor hyperactivity in a novel environment. D_3−/− and D_3-/+ mice have higher systolic and diastolic blood pressures than their wild-type littermates, either on a mixed C57BL/6 and B129 background [17] or in congenic C57BL/6 background [62]. In contrast, Staudacher et al. reported that D_3−/− mice in a congenic C57BL/6 background and on a low, normal, or high salt intake have normal blood pressure [186]. This report has to be interpreted with caution because C57BL/6 mice from Jackson Laboratories develop hypertension when fed a high NaCl diet [187], while those from Taconic [169] do not. The two strains of D_3−/− mice, however, have a decreased ability to excrete an acute or a chronic sodium chloride load [17, 186], which may lead to an expansion of the extracellular fluid volume. Thus, disruption of the D_3 receptor results in sodium retention, but the hypertension is also related to increased renal renin production. Renal renin activity and AT_1 receptor expression are greater in D_3−/−than in wild-type mice, and blockade of AT_1 receptors decreases systolic blood pressure more effectively in D_3−/−mice than in wild-type ones [17]. Urinary aldosterone levels are not altered in D_3−/− mice (unpublished data).

D_4 receptor mutant mice—D_4 receptor deficient (D_4−/−) mice backcrossed to C57BL/6J mice for more than six generations have increased systolic and diastolic blood pressures that are increased yet further with increased sodium intake [20]. D_4−/− mice do not have altered circulating or renal renin levels [20] although juxtaglomerular cells in culture also express D_4 receptors [59]. Serum/urinary aldosterone levels are not different between D_4−/− and D_4+/+ mice on a normal or increased sodium chloride diet (unpublished data). The expression of AT_1 receptors is increased in homogenates of kidney and brain of D_4−/− mice relative to that shown by similar homogenates of 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 losartan, an AT_1 receptor antagonist, dissipates after 10 min in D_4+/+ mice, whereas the effect has been found to persist for more than 45 min in D_4−/− mice. Thus, hypertension brought about by the absence of the D_4 receptor is mediated, in part, by increased AT_1 receptor expression [20]. While on a normal salt diet (unpublished data), the heterozygote mutant D_1, D_2, D_3, and D_5 receptor mice have increased blood pressure, while D_4+/− mice have normal blood pressure.

Some phenotypes related to renal function in dopamine receptor deficient mice are summarized in Table 1.

Development of renal dopamine

Development of renal dopamine synthesis

Dopamine-mediated natriuresis and renal vascular effects are less in younger animals than in older ones. An inverse correlation between urinary dopamine and age has been reported in adults [188, 189]. The excretion of dopamine is higher in the pediatric population than in elderly subjects [190]. However, urinary dopamine increases postnatally in very low birth weight infants [191, 192]. In rats, intrarenal levels of dopamine have a tendency to increase between 3 and 20 days after birth, but significantly decrease between 20 to 80 days after birth [193]. Urinary excretions of dopamine and its deaminated metabolite 3,4-dihydroxyphe-nylacetic acid (DOPAC) [194], as well as dopamine formation in kidney slices, are markedly decreased in old rats, which have been attributed to decreased uptake of L-DOPA by tubular brush-border membranes [194, 195]. The uptake of L-DOPA is the rate-limiting step in the renal synthesis of dopamine [194]. The activity of aromatic AADC, the enzyme involved in the renal synthesis of dopamine, however, increases with age [195]. The activity of AADC is higher in the adult dog kidney than in 10-day or 2-month-old dogs [196]. In the rat, AADC immunore-activity can be observed in renal tubule cells as early as gestational day 18 and is present in proximal tubules in the outer and inner cortex 5 days after birth. Aromatic L-amino acid decarboxylase mRNA is present in the entire cortex by the sixth post-natal day [193].

Development of renal dopamine receptors

In the rat, renal dopamine D_1-like and D_2-like receptor densities approach adult values by 3 weeks of age [197, 198]. Rat renal D_1 receptors are present by the 15th day of gestational age and increase with maturation [199]. Renal D_1 receptors are also expressed in fetal sheep [200]. However, in the sheep, the renal cortical affinity or maximum receptor of D_1-like receptors, as determined by radioligand binding, does not change with maturation [201].

In rats, renal D_2-like receptor binding does not change within the first 2 weeks of life but increases after 3 weeks [202]. In contrast, renal D_2-like receptor binding decreases with age in sheep [201].

Renal effects of dopaminergic agonists—The decreased natriuretic action of dopamine and D_1-like receptor agonists in the young and the aged has been attributed to a decreased renal generation of cAMP and inhibition of NHE3 and Na^+/K^+ ATPase activity in response to D_1-like receptor stimulation [198, 201–208]. Even though renal D_1-like receptor densities are not different between 3- and 10-week-old rats, there is an impaired ability of the D_1-like agonist fenoldopam to stimulate adenylyly cyclase activity in the young [198, 203]. The decreased inhibitory effect of D_1-like receptors on NHE activity in young rats is caused, in part, by the increased expression and activity of the G protein subunit G β/γ [208].

In neonatal dogs, pigs, and sheep, the intravenous or intrarenal arterial administration of dopamine alone may not always increase renal blood flow or decrease renal vascular resistance [209–213]. The systemic or intrarenal arterial infusion of dopamine alone, even in low doses, may result in a renal vasoconstriction that is more pronounced in the fetal and neonatal animals [209, 211, 213]. This is due to the occupation of renal α adrenergic receptors that increase in number in the perinatal dog and sheep. A low dose of dopamine injected into the renal artery increases renal blood flow and decreases renal vascular resistance in adult dogs [214], but not in young puppies [215]. Even in the presence of α- and β-adrenergic blockade, dopamine does not increase renal blood flow in 1- to 2-week-old puppies, but it does increase renal blood flow and glomerular filtration rate in older puppies [215]. Similar results are observed following intravenous dopamine administration in young piglets [211]. In spite of the absence of any change in renal blood flow following intrarenal arterial infusion of dopamine, sodium excretion increases, but this effect is less evident in the younger puppy than in the older one [215]. Dopamine also increases sodium excretion in the fetal sheep without increasing renal blood flow [213, 216]. Thus, in the very young, the natriuretic effect of dopamine is probably due mainly to tubular factors.

The effects of the D_2-like receptor agonist are not well studied. However, in the developing animal, selective D_2-like receptor agonists increase glomerular filtration rate to a similar extent as that found in younger and older rats [217]. In premature infants, in contrast to the findings in adults, a predominantly D_2-like receptor antagonist increases urine flow, sodium excretion, and osmolar clearance, suggesting that D_2-like receptor effects may predominate in the human infant [218].

Ability to excrete a salt load in human neonates

Pre-term infants have a decreased ability to retain sodium, but both full-term and pre-term infants have a decreased ability to excrete a salt load [219]. In the pediatric age group, a decrease in sodium intake results in an increase in urinary dopamine, while in adults, a high salt intake results in an increase in urinary dopamine [212, 218]. Low doses of dopamine, however, can induce a natriuresis in preterm infants, but it is not known if the magnitude of the response is different from that reported in the adult [220]. Deficits in renal dopamine function may be responsible for the diminished ability of the aged kidney to excrete a salt load [221]. Whether this is also true in the neonate has not been determined.

Overall summary

In summary, dopamine receptors are important players in the regulation of renal function and blood pressure. Each dopamine receptor subtype exerts a unique regulatory function and interacts with other GPCRs, especially those related to angiotensin II. All dopamine receptor subtypes are present in the kidney, showing a distinct distribution along the nephron. Renal sodium transport is regulated by all subtypes, either directly or indirectly by interaction with other GPCRs, to maintain sodium balance. Deletion of any of the dopamine receptor subtypes results in elevated blood pressure and impaired pressure natriuresis in the mutant mice. Abnormalities of dopamine receptors in their genes/ proteins or in their regulation of renal function play an important role in the pathogenesis of hypertension.

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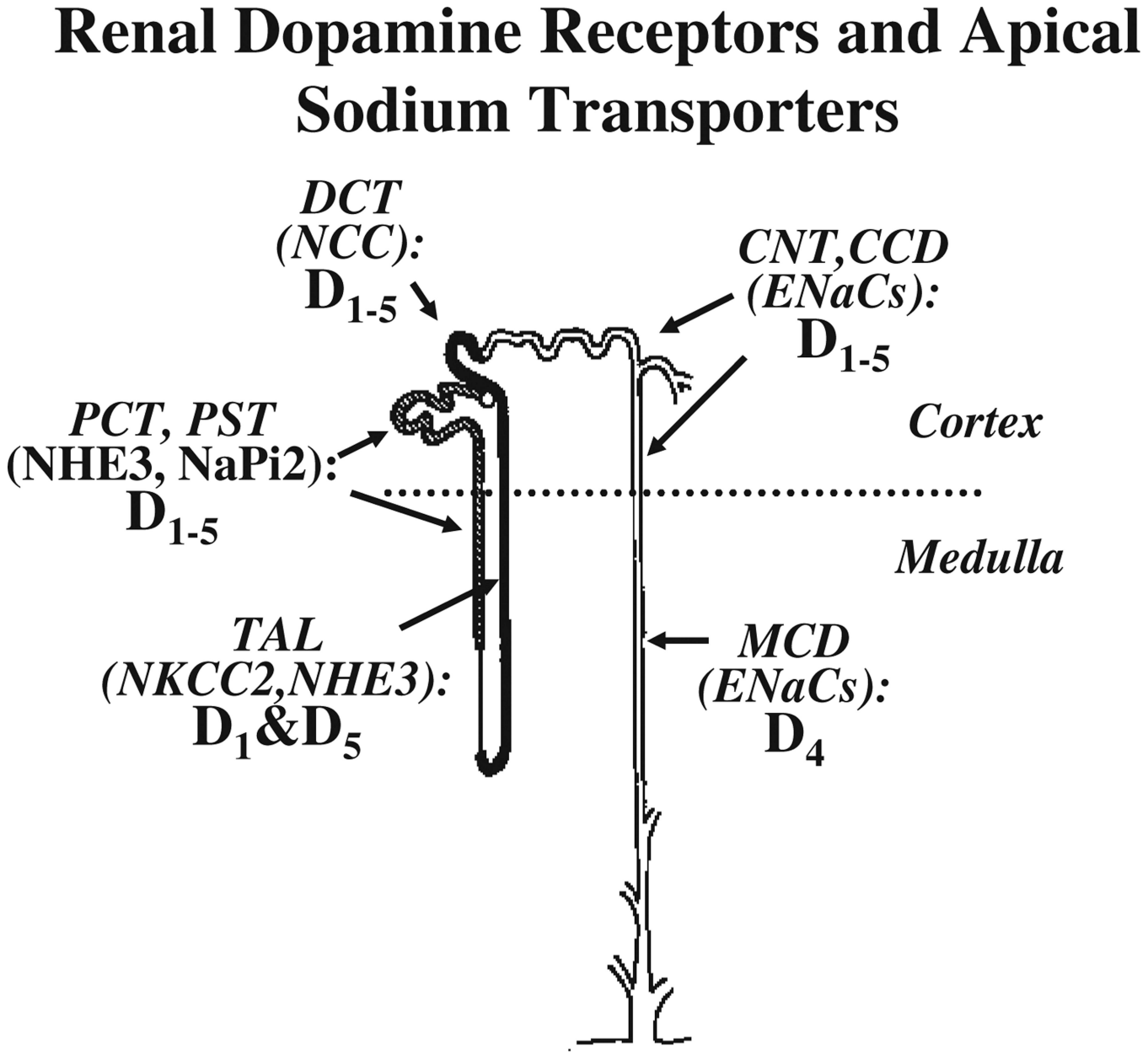

Fig. 1.

Distribution of dopamine receptor subtypes ($D_{1–5}$) and apical sodium transporters in rat tubules. *PCT* Proximal convoluted tubule, *PST* proximal straight tubule, *TAL* thick ascending limb of Henle's loop, *DCT* distal convoluted tubule, *CNT* cortical connecting tubule, *CCD* cortical collecting duct, *MCD* medullar collecting duct, *NHE3* sodium hydrogen exchanger type 3, *NaPi2* sodium phosphate cotransporter type 2, *NKCC2* sodium potassium two chloride cotransporter, *NCC* sodium chloride cotransporter, *ENaC* epithelial sodium channel

Table 1

Phenotypes of dopamine receptor (DR)-deficient mice and renal mechanism(s) involved in the pathogenesis of hypertension

Mouse genotypes	D_1R		D_5R		D_2R		D_3R		D_4R	
	−/−	+/−	−/−	+/−	−/−	+/−	−/−	+/−	−/−	+/−
Blood pressure on 0.8% NaCl diet	Increased [16]	Increased [16]	Increased [23,168, 169]	Increased #	Increased [24]	Increased [24]	Increased [17]	Increased [17]	Increased [20]	Normal #
Blood pressure on 4–6% NaCl diet			Increased [68, 169]		Increased #		Increased #		Increased #	
Kidney deformities	None #		None		None #		None #		None #	
Creatinine clearance	&#		Normal #		Normal [184]		Normal #		Normal [20]	
Ability to excrete an acute NaCl load			Not impaired #		Not impaired [24]	Not impaired #	Impaired [17]	Not impaired [17]	Not Impaired #	Not impaired #
Ability to excrete a chronic NaCl load					Not impaired #	Not impaired #	Impaired [186]		Impaired #	
Proteinuria Plasma/Kidneyrenin			Yes [170] Normal #		No #		No # Increased [17]	Increased [17]	No # Normal [20]	
Serum/Urine aldosterone			Normal #		Increased [184]	Normal [185]	Normal#		Normal #	
Renal AT_1R			Increased [72]		Normal #		Increased [17]		Increased [20]	

Blank cell indicates no report available;

& indicates normal blood urea nitrogen (BUN);

# indicates unpublished