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Dopamine, the Kidney, and Hypertension

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Abstract

There is increasing evidence that the intrarenal dopaminergic system plays an important role in the regulation of blood pressure, and defects in dopamine signaling appear to be involved in the development of hypertension. Recent experimental models have definitively demonstrated that abnormalities in intrarenal dopamine production or receptor signaling can predispose to salt-sensitive hypertension and a dysregulated renin-angiotensin system. In addition, studies in both experimental animal models and in humans with salt-sensitive hypertension implicate abnormalities in dopamine receptor regulation due to receptor desensitization resulting from increased G-protein receptor kinase 4 (GRK4) activity. Functional polymorphisms that predispose to increased basal GRK4 activity both decrease dopamine receptor activity and increase angiotensin II type 1 (AT1) receptor activity and are associated with essential hypertension in a number of different human cohorts.

Keywords

Hypertension; Dopamine; G-protein receptor kinases; GRK4; Angiotensin; Kidney; Dopaminergic system; Blood pressure; Salt-sensitive hypertension

Introduction

In addition to its role as a neurotransmitter, dopamine also serves important physiologic functions outside of the central nervous system. As discussed in this review, dopamine has an important physiologic role in the kidney, regulating net salt and water excretion, and intrarenal activation of dopaminergic pathways serves to prevent or mitigate the development and consequences of hypertension. Furthermore, abnormalities in renal dopaminergic signaling may be an underlying factor in the development of essential hypertension in some individuals.

Dopamine's actions are mediated by activation of one or more of the five members of the family of seven transmembrane G protein-coupled dopamine receptors in mammals. The

dopamine receptors are classified into “D1-like” (D1 and D5) and “D2-like” (D2, D3 and D4) based on G protein subtype coupling, with D1-like receptors coupled to G_s, which stimulates adenylate cyclases, and D2-like receptors coupled to G_i, which serves to inhibit adenylate cyclase. Both D1-like and D2-like dopamine receptors are expressed in the mammalian kidney [1].

Intrarenal Dopaminergic System

The kidney has an intrarenal dopaminergic system that is distinct from any neural dopaminergic input. Circulating concentrations of dopamine are normally in the picomolar range, whereas dopamine levels in the kidney can reach high nanomolar concentrations [2]. The dopamine precursor L-DOPA (L-dihydroxyphenylalanine) is taken up by the proximal tubule via multiple amino acid transporters, including rBat, LAT2, and ASCT2 [3, 4] from the circulation or following filtration at the glomerulus and is then converted to dopamine by aromatic amino acid decarboxylase (AADC), which is also localized to the proximal tubule [5]. Intrarenal dopamine production increases when dietary salt intake increases [6, 7].

Dopamine receptor activation leads to decreases in salt and water reabsorption in the mammalian kidney, mediated at least in part by inhibition of specific tubule transporter activity along the nephron, including NHE3, NaPi-II, NBC, and Na/K-ATPase in the proximal tubule, NKCC2 in TAL, and ENaC and AQP2 in the collecting duct [8–10, 11•, 12•]. A general characteristic of essential hypertension is a relative defect in renal sodium and water handling. Because it is estimated that the intrarenal dopaminergic system is responsible for regulating over 50% of net renal salt and water excretion when salt intake is increased [13], dysfunction of this system could have profound consequences for regulation of intravascular volume and systemic blood pressure.

Dopamine stimulates prostaglandin production in the renal medulla and increases urinary prostaglandin excretion [14–16]. Specifically, increased intrarenal dopamine leads to increased medullary COX-2 expression and activity [17]. Medullary COX-2-mediated prostaglandins promote renal salt and water excretion [18], suggesting that dopamine-mediated effects on natriuresis and diuresis may be at least partly the result of increased renal medullary prostaglandin production.

Dopamine Interactions with the Renin-Angiotensin System

There is also abundant evidence that dopamine interacts with the intrarenal renin-angiotensin system at multiple levels, including at the level of renin production and release and at the level of receptor expression and activation. Although previous studies indicated that dopamine increased renin release in cultured juxtaglomerular cells or renal cortical slices through activation of D1-like receptors [19–21], recent results indicate a more complicated regulation in vivo [22]. The intrarenal dopaminergic system indirectly inhibits renal renin expression as a result of decreased proximal salt reabsorption and modulation of macula densa COX-2 expression and activity [23], which opposes direct stimulation via activation of D1-like receptors [19–21]. The overall effect of dopamine on renal renin expression may be a balance between indirect inhibitory effects and direct stimulatory effects, with indirect inhibition being predominant in normal or volume-depleted conditions but a small direct stimulation becoming evident in volume-expanded conditions [22].

Dopamine and angiotensin II serve counterregulatory functions in the kidney [24, 25]. Dopamine inhibits angiotensin II-mediated proximal tubule reabsorption and AT₁ expression [26–29]. In addition to vasoconstriction of the renal microvasculature and stimulation of salt and water reabsorption mediated by AT₁ receptors, angiotensinogen-derived peptides also mediate counterregulatory vasodilatory and natriuretic/diuretic

pathways through angiotensin II activation of AT₂ receptors and angiotensin 1–7 activation of Mas [30]. Deletion of intrarenal dopamine production in mice by deleting proximal tubule AADC expression leads to increased angiotensinogen and AT₁ expression but decreased AT₂ and Mas expression [31••]. Dopamine's natriuretic effects are mediated in part through AT₂ signaling [32]. Furthermore, deficiency of intrarenal dopamine can lead to augmented responsiveness to angiotensin II, with an accelerated increase in blood pressure and increased renal damage [31••] (Fig. 1). Selective deletion of AT_{1a} increases longevity in mice [33], whereas selective deletion of the intrarenal dopaminergic system markedly decreases their lifespan [31••].

Activation of D1-like or D2-like receptors can also have antioxidant effects [34, 35]. D2 receptor and D5 receptor knockout mice develop hypertension dependent on reactive oxygen species (ROS). In these mice, renal NADPH activity and expression are increased, and inhibition of NADPH oxidase activity normalizes the blood pressure [36, 37]. Conversely, increased intrarenal dopamine decreases oxidative stress in response to deoxycorticosterone acetate (DOCA)/high salt-induced hypertension [17].

Dopamine and Hypertension

Mice deficient in COMT, one of the major dopamine metabolizing enzymes in the kidney, have increased intrarenal dopamine levels and blunted elevations in blood pressure in response to DOCA/high salt [17], as well as increases in nocturnal blood pressure in response to a high-salt diet [38]. Conversely, mice with selective intrarenal deletion of intrarenal dopamine due to AADC deficiency develop salt-sensitive hypertension [31••]. Abnormalities in dopamine production and receptor function have been associated with human essential hypertension and several forms of rodent genetic hypertension [1, 39, 40••, 41]. In animal models of genetic hypertension, the proximal tubule dopaminergic pathway is impaired, along with the ability to increase urinary sodium excretion [42].

Decreased D1-like receptor function in the kidney precedes hypertension development in SHR (spontaneously hypertensive rats) and cosegregates with a genetic predisposition to develop high blood pressure [43]. Studies indicate decreased dopamine production in some experimental models of hypertension such as DOCA-salt hypertension [44]. In addition, dopamine receptor expression is decreased in some experimental models of hypertension [1].

Although abnormalities in dopamine production and/or dopamine receptor expression may play a role in essential hypertension, the most compelling evidence for underlying abnormalities in dopaminergic signaling involves alterations in dopamine D1 receptor function by GRK4 [45]. After ligand binding to a G-protein coupled receptor (GPCR) such as the dopamine receptor, there is uncoupling of the G protein complex from the receptor and activation of GRKs (G protein receptor kinases), which can then phosphorylate serine or threonine residues on intracellular domains of the receptor. These phosphorylated residues serve as binding sites for adaptor proteins such as arrestins. Arrestin binding prevents re-association of the G proteins, thereby inducing desensitization. Receptors are then internalized into endosomes, where they are dephosphorylated and recycle back to the plasma membrane or are trafficked to lysosomes for degradation.

In humans, seven GRKs have been identified to date, which can be divided into three families: the opsin family (GRK1 and GRK7), the β adrenergic receptor family (GRK2 and GRK3), and the GRK4 family (GRK4, GRK5, and GRK6). GRK1 is restricted to the rods and GRK7, to the cones. GRKs 2, 3, 5, and 6 are ubiquitous, but GRK4 has been shown to have a restricted expression pattern, with the highest levels in the testis and myometrium and substantial expression in the kidney proximal tubule, brain, and intestine [45, 46]. GRK4 is

also unique among the GRKs in that it has four different isoforms (α , β , γ and δ) and is constitutively active under basal conditions.

Given the restricted distribution of GRK4, the association of the *GRK4* gene locus with development of essential hypertension [1], and previous work in renal proximal tubules from humans with essential hypertension and from rodents with genetic hypertension indicating that the D1-like receptor is uncoupled from its G protein-effector enzyme complex [25, 47–50], Felder and coworkers examined the potential role of GRK4 in regulating the renal dopaminergic system. They found that basal serine-phosphorylated D1 receptor was increased in renal proximal tubules from genetically hypertensive rodents, as well as from humans with essential hypertension [50]. They subsequently detected three single-nucleotide polymorphisms (SNPs) in GRK4 γ (R65L in exon 3, A142V in exon 5 and A486V in exon 14) that can alter GRK4 function and lead to increased basal activity [45].

D1-mediated increases in cAMP were inhibited in proximal tubule cells cultured from hypertensive patients, and GRK4 antisense oligonucleotides decreased the increased D1 serine phosphorylation and increased D1 signaling [45]. The human proximal tubule cell line, HK-2, expresses the three GRK γ SNPs described in essential hypertension and demonstrates uncoupled, hyporesponsive D1 receptors [51].

In addition to modulation of D1 receptors in proximal tubules, there is evidence that *GRK4* also may modulate AT1 receptor activity. The *GRK4* gene variants associated with hypertension increase proximal tubule AT1 receptor expression and activity (Fig. 2) [52].

Basal GRK4 expression and activity and D1 phosphorylation were higher in SHR than in the nonhypertensive WKY rats, and cortical interstitial infusion of GRK4 antisense oligonucleotides to SHR increased urine sodium excretion and decreased blood pressure in SHR while not affecting blood pressure in WKY rats [53]. Transgenic mice overexpressing GRK4 γ SNP A142V were hypertensive and failed to increase urine flow and sodium excretion in response to the D1 receptor agonist, fenoldopam [45]. A subsequent study, only reported in abstract form to date, indicated that transgenic mice overexpressing the GRK4 γ SNPA486V also develop hypertension, but only when given a high-salt diet [52]. Whether this finding indicates differing effects of the different GRK4 variants on dopamine receptor activation and/or downstream signaling is currently unknown and will require further studies.

A number of studies have examined the association of the three GRK4 γ SNPs with human hypertension and report an association with essential hypertension in some, but not all, populations [45]. The locus on the human chromosome containing GRK4, 4p16.3, has been linked to increases in blood pressure from childhood to adulthood and to hypertension in adult populations [54, 55]. Different allele frequencies have been detected among populations, with GRK4 65 L and GRK4 142 V being less frequent and GRK 486 V more frequent in Asians than in African-Americans and GRK4 A486V being more frequent in Hispanic and non-Hispanic whites than in African Americans [56]. Association with essential hypertension was found in an Italian cohort and in an Anglo-Celtic Australian cohort with SNP A486V [57, 58]. However, these three SNPs are in linkage disequilibrium, so they may be co-inherited. Both the A486 variant and the L65/V142/A486 haplotype were associated with hypertension in a Chinese Han cohort [59]. Similarly, in a Japanese cohort, the presence of all three GRK4 variants impaired the natriuretic effect of a dopaminergic agonist and correctly predicted the presence of salt-sensitive hypertension in 94% of cases [60].

There may also be co-association with other SNPs implicated in hypertension; in a Ghanaian population, GRK4 65 L was found to co-associate with angiotensin-converting enzyme

(ACE) isoform expression in hypertensive individuals [61]. In an analysis of the African-American Study of Kidney Disease and Hypertension (AASK), an association of SNP A142V and blood pressure response was found among African American men with early hypertensive nephrosclerosis, and these individuals were less responsive to antihypertensive effects of the beta-blocker metoprolol if they also had a GRK4 L65 variant [62]. However, there is also a report of a negative association of the A486V SNP and hypertension in African Americans, although this study did also see some signal for hypertension with the R65L SNP, in association with NOS3 polymorphisms [63]. In contrast, studies in patients of European ancestry failed to find an association with either SNP A142V or A486V [64, 65]. In addition, no genome-wide association study (GWAS) performed to date has identified *GRK4* as associated with hypertension [66–71].

Conclusions

Dopamine is an important regulator of salt and water excretion by the kidney. The kidney has a robust intrarenal dopaminergic system, and there is increasing evidence that alterations in intrarenal dopamine signaling may underlie essential hypertension in certain human populations. Ongoing studies linking functional polymorphisms in *GRK4* with hypertension in both experimental animals and humans provide a plausible mechanism for dysregulation of proximal tubule dopamine receptor function and signaling that may underlie increased sodium reabsorption and the ultimate development of hypertension (Fig. 2).

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Fig. 1. Renal dopamine deficiency results in salt-sensitive hypertension. **a** Proximal tubule aromatic amino acid decarboxylase (AADC) was deleted in *ptAADC*^{-/-} mice. **b** Salt-sensitive hypertension was observed in *ptAADC*^{-/-} mice. * $P < 0.01$ vs wild type on a normal-salt diet, † $P < 0.05$ vs wild type on a high-salt diet, ‡ $P < 0.005$ vs *ptAADC*^{-/-} on a normal-salt diet ($n = 9$ in each group). (Adapted from Zhang et al. [31•])

Fig. 2.

Dopamine directly inhibits renal sodium reabsorption and decreases activity of the renin-angiotensin system at multiple steps, helping to maintain normal blood pressure. *GRK4* variants decrease dopamine receptor activity and increase *AT1R* activity, with a net effect of increased sodium reabsorption, which predisposes to hypertension. *ACE* angiotensin-converting enzyme, *AT1* angiotensin II type 1, *GRK4* G-protein receptor kinase 4