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Abnormalities in Renal Dopamine Signaling and Hypertension: The Role of GRK4

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Abstract

Purpose of review—This review will highlight recent findings concerning the role of the intrarenal dopaminergic system in hypertension, especially the role of alterations in GRK4 activity.

Recent findings—Recent studies highlight the importance of the intrarenal dopaminergic system in blood pressure regulation and how defects in dopamine signaling are involved in the development of hypertension. There are recent experimental models that definitively demonstrate that abnormalities in intrarenal dopamine production or receptor signaling can predispose to salt-sensitive hypertension and a dysregulated renin-angiotensin system. Furthermore, studies in 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 AT1 receptor activity and are associated with essential hypertension in a number of different human cohorts.

Summary—The ongoing elucidation of this important regulatory pathway further emphasizes the importance of the kidney in maintenance of blood pressure control and may help to delineate underlying mechanisms predisposing individuals or populations to increased risk for development of hypertension.

Keywords

hypertension; dopamine; G-protein receptor kinases; angiotensin

Introduction

There is increasing evidence that the intrarenal dopaminergic system plays an important role in blood pressure regulation. Furthermore, new evidence in both experimental systems and in human studies is elucidating the role that abnormalities in intrarenal dopamine production or receptor signaling can predispose to salt-sensitive hypertension and dysregulation of the renin-angiotensin system. This review will highlight recent studies and findings in this area.

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Physiologic regulation of renal function by dopamine

Although dopamine is a well-characterized neurotransmitter, extraneural dopamine also serves important physiologic functions. Dopamine's actions are transduced by a family of 5 seven transmembrane G protein-coupled receptors. They 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 and D2-like receptors coupled to G_i. Both D1-like and D2-like dopamine receptors are expressed in the mammalian kidney [1], and exogenous administration of dopamine is known to modulate solute and water transport 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 proximal tubule, NKCC2 in TAL, and ENaC and AQP2 in collecting duct [2-6].

The intrarenal dopaminergic system

The kidney possesses an intrarenal dopaminergic system that is distinct from any neural dopaminergic input. Circulating concentrations of dopamine are normally in the picomolar range, while dopamine levels in the kidney can reach high nanomolar concentrations [7]. The dopamine precursor L-DOPA (L-dihydroxy-phenylalanine) is taken up by the proximal tubule via multiple amino acid transporters, including rBat, LAT2 and ASCT2 [8, 9] 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 [10]. There is evidence that intrarenal dopamine production is modulated by alterations in dietary salt intake [11, 12].

Dopamine serves as a counterregulatory factor to angiotensin II in the kidney [13, 14]. Dopamine inhibits renal renin expression [15] and inhibits angiotensin II-mediated proximal tubule reabsorption and AT₁ expression [16-19].

A general characteristic of essential hypertension is a relative defect in renal sodium and water handling. Since 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 [20], dysfunction of this system could have profound consequences for regulation of intravascular volume and systemic blood pressure.

The association of dysfunction of the intrarenal dopaminergic system and hypertension

Abnormalities in dopamine production and receptor function have been associated with human essential hypertension and several forms of rodent genetic hypertension [1, 21-23]. In animal models of genetic hypertension, there is impairment of the proximal tubule dopaminergic pathway such that the ability to increase urinary sodium excretion is impaired [24].

Decreased D1-like receptor function in the kidney have been reported to precede the development of hypertension in SHR (spontaneously hypertensive rats) and to cosegregate with the genetic predisposition of high blood pressure. Although there have been studies indicating decreased dopamine production in some experimental models of hypertension such as DOCA-salt hypertension, other studies have indicated that dopamine signaling in proximal tubule is also dysfunctional, due to abnormalities in GRK4 coupling to D1 receptors (see below). In addition, in certain experimental models of hypertension, dopamine receptor expression is decreased.

Previous studies have not been able to discriminate completely between intrarenally vs. extrarenally produced dopamine in the mediation of kidney function. Recent studies reported the effect of selectively inhibiting intrarenal dopamine production in mice by

deleting proximal tubule AADC expression [25]. These studies demonstrated the importance of the intrarenal dopaminergic system in maintenance of renal function, modulation of the renin-angiotensin system and regulation of blood pressure. Even with central and other peripheral sites of dopamine production intact, selective deletion of the kidney's ability to generate dopamine led to profound phenotypic alterations, characterized by increased expression of salt and water transporters along the nephron, altered salt and water homeostasis, hypertension and markedly decreased life span [25]. These studies emphasized that a dysfunctional intrarenal dopaminergic system may have profound consequences for regulation of intravascular volume and systemic blood pressure.

The potential role of altered GRK4 and hypertension

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 involve alterations in dopamine receptor function by GRK4. After ligand binding to a G-protein coupled receptor (GPCR) such as the dopamine receptors, there is uncoupling of the G protein complex from the receptor and activation of GRKs (G protein receptor kinases), which can 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. There is then subsequent internalization of receptors into endosomes, where they are dephosphorylated and recycle back to the plasma membrane or are trafficked to lysosomes for degradation.

In humans there have been seven GRKs identified, which can be divided into three families: the opsin family (GRKs 1 and 7) the β adrenergic receptor family (GRKs 2 and 3) and the GRK4 family (GRKs 4, 5 and 6). GRKs 1 and 7 are restricted to the rods and cones, respectively while GRKs 2,3,5, and 6 are ubiquitous, but GRK4 has been shown to have a restricted expression pattern, with highest levels in the testis and myometrium and substantial expression in kidney proximal tubule, brain and intestine [26] [27]. 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 indication that the GRK4 gene locus had been associated 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.[14, 28-31], Felder and coworkers examined the potential role of GRK4 in regulation of 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 [31]. They subsequently detected three single nucleotide polymorphisms 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 (Table 1)[27].

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 [27]. Of interest, Gildea et al. have recently reported that the widely used human proximal tubule cell line, HK-2, expresses the three GRK γ SNPs described in essential hypertension and have uncoupled, hyporesponsive D1 receptors [32].

In addition to modulation of D1 receptors in proximal tubule, there is also evidence that GRK4 may modulate AT1 receptor activity in proximal tubule. The GRK4 gene variants

associated with hypertension increase proximal tubule AT1 receptor expression and activity (Figure 1) [33].

Basal GRK4 expression and activity and D1 phosphorylation were higher in SHR than in the non-hypertensive 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 [34].

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 [27]. A subsequent study, only reported in abstract form to date, indicated that transgenic mice overexpressing the GRK4 γ SNP, A486V, also develop hypertension, but only when placed on a high salt diet [34]. Whether this 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 they have found them to be associated with essential hypertension in some, but not all, populations [27]. 4p16.3, the locus on the human chromosome containing GRK4, has been linked to increases in blood pressure from childhood to adults and to hypertension in adult populations [35, 36]. Different allele frequencies have been detected among populations, with GRK4 65L and GRK4 142V being less frequent and GRK486V more frequent in Asians than in African-Americans and GRK4 A486V being more frequent in Hispanic and non-Hispanic whites than in African-Americans [37]. In this regard, association with essential hypertension was found in an Italian cohort and in an Anglo-Celtic Australian cohort with SNP A486V [38, 39]. 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 [40]. 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 [41].

There may also be co-association with other SNPs implicated in hypertension; in a Ghanaian population, GRK4 65L was found to co-associate with ACE isoform expression in hypertensive individuals [42]. In an analysis of the AASK study, an association of SNP A142V and blood pressure response was found among African-American men with early hypertensive nephrosclerosis, and they were found to be less responsive to metoprolol if they also had a GRK4 L65 variant [43]. 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 [44]. In contrast, studies in patients of European ancestry failed to find association with either SNP A142V or A486V [45] [46]. In addition, no GWAS performed to date has identified GRK4 as associated with hypertension [47][48, 49] [50-52].

Potential involvement of other GRKs in hypertension

Other GRKs have also been linked to hypertension. GRK2 has been seen as a possible candidate, in part because it is known to activate the sodium channel, ENaC by phosphorylation of the β subunit, thereby preventing ubiquitination by Nedd4-2 [53]. In mice, GRK2 overexpression in smooth muscle interferes with β -adrenergic vasodilation and induces hypertension [55]. Although GRK2 polymorphisms have yet to be linked to a hypertensive population, increased GRK2 has been found in lymphocytes of individuals with essential hypertension [54], and increased GRK2 activity has also been noted in lymphocytes of African Americans with hypertension [56]. GRK5 overexpression in mouse

smooth muscle also induces hypertension [57], but there is no association with human hypertension to date.

Conclusion

In summary, there is increasing evidence that abnormalities in renal dopamine signaling play an important role in development and maintenance of essential hypertension. The 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.

- Dopamine is an important regulator of salt and water excretion by the kidney.
- The kidney has a robust intrarenal dopaminergic system, and alterations in either dopamine production or signaling can predispose to hypertension in experimental animals.
- There is increasing evidence that alterations in dopamine signaling, due to altered GRK4-mediated dopamine receptor function, may underlie essential hypertension in certain human populations.

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Effects of GRK4 variants to mediate hypertension. Coupling of wild type GRK4 to dopamine receptors stimulates their activity and inhibits salt reabsorption, while wild type GRK4 inhibits AT1 receptor activity. Conversely, GRK4 variants increase AT1R activity and decrease dopamine receptor activity, with a net effect of increased sodium reabsorption, which predisposes to hypertension.

Table 1

GRK4 polymorphisms

<u>Polymorphism</u>	<u>exon</u>	<u>site of polymorphism</u>
R65L	exon 3	GPCR binding domain
A142V	exon 5	GPCR binding domain
A486V	exon 14	Autophosphorylation site in membrane targeting domain