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Dopamine and G protein-coupled receptor kinase 4 in the kidney: role in blood pressure regulation

Pedro A. Jose, MD, PhD[1], **Patricio Soares-da-Silva, MD, PhD**[2], **Gilbert M. Eisner, MD**[3], and **Robin A. Felder, PhD**[4]

[1] Center for Molecular Physiology Research, Children's National Medical Center, George Washington University for the Health Sciences, Washington, DC, USA

[2] Institute of Pharmacology and Therapeutics Faculty of Medicine, University of Porto, Porto, Portugal

[3] Department of Medicine, Georgetown University Medical Center, Washington, DC

[4] Department of Pathology, University of Virginia, Charlottesville, VA, USA

Abstract

Complex interactions between genes and environment result in a sodium-induced elevation in blood pressure (salt sensitivity) and/or hypertension that lead to significant morbidity and mortality affecting up to 25% of the middle-aged adult population worldwide. Determining the etiology of genetic and/or environmentally-induced high blood pressure has been difficult because of the many interacting systems involved. Two main pathways have been implicated as principal determinants of blood pressure since they are located in the kidney (the key organ responsible for blood pressure regulation), and have profound effects on sodium balance: the dopaminergic and renin-angiotensin systems. These systems counteract or modulate each other, in concert with a host of intracellular second messenger pathways to regulate sodium and water balance. In particular, the G protein-coupled receptor kinase type 4 (GRK4) appears to play a key role in regulating dopaminergic-mediated natriuresis. Constitutively activated GRK4 gene variants (R65L, A142V, and A486V), by themselves or by their interaction with other genes involved in blood pressure regulation, are associated with essential hypertension and/or salt-sensitive hypertension in several ethnic groups. GRK4γ 142V transgenic mice are hypertensive on normal salt intake while GRK4γ 486V transgenic mice develop hypertension only with an increase in salt intake. GRK4 gene variants have been shown to hyperphosphorylate, desensitize, and internalize two members of the dopamine receptor family, the D_1 (D_1R) and D_3 (D_3R) dopamine receptors, but also increase the expression of a key receptor of the renin-angiotensin system, the angiotensin type 1 receptor (AT_1R). Knowledge of the numerous blood pressure regulatory pathways involving angiotensin and dopamine may provide new therapeutic approaches to the pharmacological regulation of sodium excretion and ultimately blood pressure control.

Corresponding author: Pedro A. Jose, MD, PhD, Center for Molecular Physiology Research, Children's National Medical Center, 111 Michigan Avenue, NW, Washington, DC, USA 10010, Tel: 202-476-5715, Fax: 202-476-6285.

Keywords

dopamine; dopamine receptors; G protein-coupled receptor kinase 4; sodium transport; essential hypertension

1.1 Introduction

Dopamine is important in the regulation of sodium balance and blood pressure via renal mechanisms [1,2] The affinity of dopamine for its receptors is in the nanomolar range; higher concentrations occupy other GPCRs [1,2]. Circulating dopamine concentrations (picomolar range) are not sufficiently high to activate dopamine receptors, but high nanomolar concentrations can be attained in dopamine-producing tissues (e.g., renal proximal tubule, jejunum). Independent of innervation, renal proximal tubules synthesize dopamine that is not converted to norepinephrine [1,2]. Dietary sodium and intracellular sodium are the major determinants for the renal tubular synthesis/release of dopamine [3–9]; the stimulatory effect of increased dietary sodium on renal dopamine production is impaired in some hypertensive humans [10–12]. Locally generated dopamine, which is secreted preferentially into the renal tubular lumen, and acts in an autocrine/paracrine manner [1,2,13], is responsible for over 50% of incremental sodium excretion, especially when sodium intake is increased. The increase in renal sodium excretion due to dopamine is caused by inhibition of sodium transporter and pump activities, in the short-term, and a decrease in the expression of several sodium transporters, in the long-term. The inhibitory effect of dopamine on sodium pump activity is tissue/cell-specific. Indeed, in alveolar epithelial cells, dopamine stimulates rather than inhibits sodium channel and pump [14–16]. The short-term inhibition of sodium transport by dopamine involves interaction at caveolin-1 rich plasma membrane microdomains followed by their internalization, via scaffolding proteins [17–32]. The long-term inhibition of sodium transport by dopamine may involve the regulation of protein expression [33].

Dopamine can also affect sodium balance by regulating fluid and sodium intake via the “appetite” centers in the brain [34–36] and gastrointestinal transport [37]. Dopamine regulates the secretion/release of other hormones and humoral agents [38–44] that also regulate sodium balance and blood pressure (1). These hormones may interact with dopamine to increase (e.g., atrial natriuretic peptide [45], prolactin [46]) or decrease its inhibitory effect on sodium transport (e.g., angiotensin II [47–50], insulin [51,52]). Oxidative stress and inflammation also impair dopamine receptor function [53–58]. This article reviews the role of dopamine and dopamine receptor subtypes and their regulation by G protein-coupled receptor kinase (GRK4), with especial emphasis on GRK4 type 4 (GRK4), in essential hypertension.

2.1 Renal dopamine receptor subtypes

In mammals, dopamine exerts its actions via two receptor classes, D_1-like and D_2-like, that belong to the α group of the rhodopsin-like family of GPCRs[1,2,59]. The D_1-like receptors, D_1 (D_1R) and D_5 (D_5R) subtypes (also called $D_{1A}R$ and $D_{1B}R$ in rodents), stimulate adenylyl cyclases [1,2,60]. The D_1R, but not D_5R, couples to G_O [61]. In contrast, D_5R, but not D_1R, couples to Gz and $G\alpha_{12/13}$ [62,63]. The D_1-like receptors are also linked to Gαq [64–67]. The linkage of G protein subunits to the specific D_1-like receptor is tissue-specific. In fibroblasts, the D_1R couples to Gαq and phospholipase C [68]. More recently, the D_5R has also been linked to stimulation of phospholipase C activity of neural tissue (hippocampus, cortex, and striatum) [69]. In neural (striatal) cells, D_1R mediated-stimulation of phospholipase C requires the presence of D_2R, while D_5R, by itself, increases calcium mobilization that is inhibited by D_2R [70]. However, in a pituitary adenoma rat cell line, GH4C1, transfected with the D_5R, the

D_5R actually decreases inositol phosphate production [71]. Therefore, the linkage between D_1R and D_5R to phospholipase C activation is cell-specific.

The D_2-like receptors, D_2R, D_3R, and D_4R, couple to G-proteins $G\alpha_i$ and G_o, inhibit adenylyl cyclase and calcium channel activities, and modulate potassium channel activity [1,2,60]. There are two isoforms of D_2R; postsynaptic D_2R effects are mediated by the long isoform, $D_{2L}R$, while presynaptic D_2R effects are mediated by the short isoform, $D_{2S}R$ [60]. There could be seven distinct alternatively spliced D_3R variants. The full-length D_3R and a shorter receptor isoform, the $D_{3S}R$, bind to dopamine. There are five other alternatively spliced D_3R variants that do not bind dopamine, including D_3Rnf, but regulate receptor dimerization [72]. Different numbers of 16 amino acid repeats in the third cytoplasmic loop cause several human D_4R isoforms (e.g., D4-2, D4-4, and D4-7) [73]. The role of these D_4R isoforms remains to be determined. However, the D_4R long (at least one 7 to 10 repeat) has been reported to be associated with higher diastolic and systolic blood pressure [74].

The D_3R may also couple to Gαq in renal proximal tubule cells [75]. As stated above, the D_1R and D_2R heterodimer stimulates phospholipase C but the $D_{2S}R$ can stimulate phospholipase D, independent of D_1R [76]; the latter enzyme is inhibited by D_5R [57]. These effects need not negate each other because, as mentioned earlier, the $D_{2S}R$ is presynaptic, while the inhibition of phospholipapse D by D_5R occurs in renal proximal tubule cells. The D_4R may also regulate phospholipase C-coupled D_1-like receptor action, e.g., D_1-like receptor-mediated grooming [77].

All of the dopamine receptor subtypes are expressed in the renal tubule and renal vasculature. However, dopamine receptors are not distributed evenly along the mammalian nephron. All members of the dopamine receptor family are present in the renal proximal tubule. The medullary thick ascending limb of Henle expresses D_1R, D_3R, and D_5R while the cortical thick ascending limb expresses D_3R only. The distal convoluted tubule expresses D_1R and D_3R, while the collecting duct expresses all members of the dopamine receptor family except D_2R [1,78,79].

Dopamine inhibits sodium transport at multiple sites along the renal tubule and acts on multiple targets (NHE1 [80], NHE3 [22,75,81,82], Na/PiIIa[24,31,83,84], Na^+/HCO_3^- cotransporter [30], Cl^-/HCO_3^- exchanger [85], Na^+/K^+ATPase [17–19,23,27,[28],37,50,86–91], and probably NCC [92]. Dopamine, via the D_4R, may also inhibit ENaC [93,94] and arginine vasopressin-dependent sodium transport and water permeability [94]. Dopamine stimulates NKCC2 in medullary thick ascending limb, but because Na^+/K^+ATPase is inhibited, overall transport is decreased [95]. There is tissue specific regulation of sodium transport by dopamine. For example, in pulmonary alveolar cells, dopamine stimulates Na^+/K^+ATPase [91], and $D_{2L}R$ stimulates Na^+/K^+ATPase in murine fibroblasts [96]. D_1R and D_2R, on the one hand, and Na^+/K^+ATPase, on the other, can also negatively regulate each other in HEK293T cells by direct protein-protein interaction [97]. While the inhibition of Na^+/K^+ATPase in the kidney by dopamine under conditions of NaCl excess is beneficial, inhibition of Na^+/K^+ATPase activity in neuronal cells by high concentrations of dopamine can lead to cell death [98]. Inhibition of Na^+/K^+ATPase activity in vascular smooth muscle cells would increase vascular resistance, as has been reported in the rat tail [99]. Low concentrations of dopamine, however, decreases systemic vascular resistance, probably by other mechanisms [100–102], e.g., opening of potassium channels [103] that is mediated by D_5R but not D_1R, at least in human coronary arteries [104].

The autocrine/paracrine regulation of renal tubular sodium transport, via D_1-like receptors, is mediated by **tubular** and **not by hemodynamic** mechanisms [105–108]. Thus, systemically administered dopaminergic drugs may not mimic the autocrine/paracrine function of

dopamine. However, D_3R may regulate glomerular dynamics [109]. The quantitative contribution of a particular dopamine receptor subtype to renal sodium transport and glomerular dynamics has not been studied. However, the D_1R is responsible for ≈80% of D_1-like receptor activity in renal proximal tubules [110] while the D_5R may be more important in the distal nephron [92,111]. Each of the dopamine receptor subtypes, alone, or via interaction with the other dopamine receptor subtypes or other GPCRs regulate sodium transport in a unique fashion [1,2,78]. Indeed, disruption of any of the dopamine receptor genes in mice results in hypertension, the pathogenesis of which is specific for each subtype [1,78].

3.1 Regulation of dopamine receptor function

As with other GPCRs, dopamine receptor signal transduction is regulated precisely [112–119]. Loss of receptor responsiveness (desensitization) is a mechanism that dampens short-term agonist effects following repeated agonist exposure. At least three families of regulatory molecules contribute to GPCR desensitization: second messenger-dependent protein kinases, GRKs, and arrestins [112–119]. Desensitization of GPCRs involves phosphorylation, sequestration/internalization, and degradation of receptors.

Homologous desensitization, in response to agonist stimulation, occurs via action of a member (s) of the GRK family [112–119]. Heterologous desensitization, mediated by second messenger-dependent kinases, occurs when a decrease in receptor responsiveness is induced by a ligand other than its own specific ligand. The phosphorylation of GPCRs, including the D_1R, leads to the binding of a member(s) of the arrestin family, uncoupling of the receptor from its G protein complex, and a decrease in its functional response. The phosphorylated GPCR/β-arrestin complex undergoes endocytosis/internalization via clathrin-coated pits into a series of endosomal units, where the GPCR is dephosphorylated, and recycled back to the plasma membrane. The unrecycled GPCRs are degraded in proteasomes and/or lysosomes.

3.2 G protein-coupled receptor kinase (GRK) and dopamine receptors

There are seven GRKs in humans: GRKs 1 and 7 belong to the opsin kinase family, GRKs 2 and 3 belong to the β-adrenergic receptor kinase (βARK) family, and GRKs 4, 5, and 6 belong to the GRK4 family [116]. The tissue distribution of GRK4 is different from the other GRKs [117]. GRKs 1 and 7 are expressed in rods and cones, respectively. GRKs 2, 3, 5, and 6 are ubiquitously expressed while GRK4 is expressed to a greater extent in the testes and myometrium and to a lesser extent in specific brain areas [119], intestines [120], and the kidney [112,117].

3.3 GRK2 and GRK4 and renal D_1R

The D_1R (but not D_5R), expressed endogenously in human [19,112,121] and rat renal proximal tubule cells [52,122,123], is regulated to a lesser extent by GRK2 and to a greater extent by GRK4 in human kidneys [121], but the converse may be true in rat kidneys [53,123]. In a human embryonic kidney cell line (HEK293), overexpression of GRK3 also desensitizes the rat D_1R [114]; a role for GRK5 in the desensitization of the rat D_1R is not settled (113, 114). GRK6 is not be important in the regulation of D_1R in the kidney [124] but it is important in the desensitization of the D_1R in intestinal crypt cells [120], emphasizing the importance of cell type in D_1R regulation.

3.4 GRK4 isoforms and renal dopamine receptors

GRK4 is constitutively active. This may be due to its ability to bind to inactive $G\alpha_S$ and Gβ subunits [125]. Unlike the other GRKs, GRK4 has several splice variants. Four GRK4 (GRK4α, β, γ, and δ) splice variants have been reported in humans, five in rats, and one in mice

[117,119,121,122,126–128]. Only the GRKα in humans, GRK4A in rats, and the only GRK4 reported in mice are closely homologous (approximately 70%) [119,126,127].

The GRK4 isoform that desensitizes D_1R and D_3R is cell-specific; GRK4γ in CHO and human renal proximal tubule cells [112,129]. GRK4α also desensitizes D_1R in HEK-293 cells [113, 114], and D_3R in human renal proximal tubule cells [129]. There is also GRK4 isoform-specific regulation of other GPCRs. GRK4α **desensitizes** the metabotropic glutamate receptor [130], G protein-coupled calcium-sensing receptor [131], $GABA_B$ [132,133], luteinizing hormone/human chorionic gonadotropin receptor [119,134], FSH receptor [135], and mutant (Y326A) β2 adrenergic receptor [135].

GRK4α does not desensitize the angiotensin type 1 receptor (AT_1R) [137], formyl peptide receptor [138], mGlu4 metabotropic glutamate receptor [139], mGlu5 metabotropic glutamate receptor [140], parathyroid hormone receptor [112,141], wild-type β_2 adrenergic receptor [137,142], and m1, m2, m3, m4, and m5 muscarinic receptors [143]. GRK4α is also not linked to Gαq [144]. GRK4β desensitizes the luteinizing hormone/human chorionic gonadotropin receptor [139], and possibly the V_2 vasopressin receptor [145]. GRK4δ, in the presence of GRK5 and GRK6, desensitizes the m2 muscarinic receptor [143] and luteinizing hormone/human chorionic gonadotropin receptor [119], but sensitizes the m3 muscarinic receptor [143]. GRK4δ **does not** desensitize D_1R (unpublished data). As mentioned earlier, GRK4γ, especially its gene variants, desensitizes the D_1R [112], and D_3R [129], and only at high concentrations does GRK4γ minimally desensitize the luteinizing hormone/human chorionic gonadotropin receptor [119]. GRK4γ wild type **does not** desensitize the parathyroid hormone receptor [122], and AT_1R but GRK4 142**V** and GRK4 486V may actually **increase,** directly or indirectly, AT_1R expression and function [146,147]. GRK4 142V increases AT_1R expression in mice on normal salt diet [146], while GRK4 486V increases AT_1R expression in mice on high salt diet [147].

3.5 GRK regulation of dopamine receptors other than D_1R (Table 1)

The D_2R is regulated by GRK2, GRK3, GRK5, and GRK6 [148,149], with $D_{2S}R$ affected to a greater extent than $D_{2L}R$ [73]. However, GRK2 or GRK3, but not GRK5 or GRK6, is involved in the desensitization of the calcium signal mediated by D_1R/D_2R interaction [150]. The D_3R is regulated by GRK2, GRK3 [151], and GRK4 (GRK4γ>GRK4α) [129]. The GRK regulating D_4R is not clear but does not seem to involve either GRK2 or GRK3 [73]. The GRK regulating D_5R is also not clear but does not seem to involve GRK4 [47]. These studies show that the GRK regulation of dopamine receptor subtypes is GRK isoform-specific.

3.6 GRK and sodium transporters

GRK2 decreases the degradation of ENaC [152,153]. GRK2 and GRK3 phosphorylate and may aid in the internalization of Na^+K^+ ATPase [154]. It is unclear how this effect of GRK2 on D_1R desensitization and decreased internalization of Na^+K^+ ATPase is modulated [17–19,23,27,[28],37,50,86–91]. NKCC1 colocalizes with GRK3 in rodent olfactory epithelia, but its regulation by GRK3 has not been demonstrated [155].

4.1 GRK4 and essential hypertension

Hypertension is the most expensive disease in the USA. It affects 73 million Americans, causes 50% of heart diseases and 75% of strokes, and costs in excess of $69 billion in 2008. Hypertension affects a third of middle-aged adults, but the prevalence is higher (65%) in individuals above 60 years of age [156,157]. About 30% to 50% of essential hypertension is thought to be heritable, but the genetic causes of essential hypertension have been difficult to identify [158]. More than one gene is undoubtedly involved, because Mendelian dominant and

recessive traits are not readily discernible in hypertensive subjects, except in those with monogenic forms of hypertension. Indeed, recent genome-wide association studies (GWAS) have been able to identify only 2% of genetic factors believed to influence blood pressure [159–164]. However, the GWAS were not designed to identify predisposing genes engaged in a complex network of gene-gene and gene/environment interactions [165], e.g., the genes (or factors) underlying salt sensitivity, a dietary sodium-induced increase in blood pressure that may or may not be in the hypertensive range.

Several criteria have been suggested to link gene(s) to complex disorders such as salt sensitivity and hypertension, but the definitive evidence is provided by swapping one phenotype for another (i.e., transgenic studies) [166]. Many genes have been proposed to be causal of hypertension. Their gene variants, including those identified in the GWAS, however, have not been shown to produce hypertension in mice. Furthermore, gene overexpression and deletion studies performed in mice must take into account the salt sensitivity of the strain. C57BL/6 mice from Jackson Laboratories have an impaired ability to excrete a NaCl load which results in an increase in blood pressure when their salt intake is increased; others are salt-resistant (e.g., SJL mice) [167]. We have reported recently that the renal D_1-like receptor function is impaired in salt-sensitive C57BL/6 Jackson mice. Renal GRK4 expression is increased in salt-loaded C57BL/6 Jackson mice [167]. Deletion of Grk4 in C57BL/6 mice prevents the development of salt-sensitive hypertension [168]. Renal D_1-like receptor function is also impaired in the spontaneously hypertensive rat (SHR), a strain with increased expression of GRK4E. Renal cortical silencing of GRK4 attenuates the increase in blood pressure with age in the SHR but not in normotensive Wistar-Kyoto rats whose blood pressures minimally increase with age [121].

The GRK4 locus on human chromosome 4p16.3 is linked to the increase in blood pressure from childhood to adulthood [169] and to hypertension in adults [170]. Interestingly, adolescents with GRK4 65L/142V/A486 haplotype have a greater increase in blood pressure with age than those with the wild-type GRK4 haplotype [171]. We have reported [172–174] with subsequent confirmation by others [175,176] that GRK4 gene variants (65L, 142V, and 486V) are associated with essential hypertension in several ethnic groups: Caucasians, Chinese, Ghanaians, and Japanese. In salt-sensitive hypertensive Japanese the presence of three GRK4 variants impaired the natriuretic effect of a dopaminergic drug and predicted salt-sensitive hypertension correctly in 94% of cases [174]. In Ghanaians, multilocus genotype combinations of angiotensin-converting enzyme insertion/deletion, and GRK4 65L had an estimated predictive accuracy for hypertension of 70% [173], confirming an earlier study [177].

A meta-analysis revealed a significant association of GRK4 486V with hypertension, with an odds ratio of 1.5 (95% CI: 1.2 to 1.9) [117]. One study however, did not find an association of GRK4 486V with the top fifth percentile of diastolic blood pressure of subjects with white European ancestry [178]. However, the authors did not test the association of GRK4 gene variants with hypertension [178]. Another study did not find an association between GRK4 142V and hypertension but did find an association between variants of the promoter region of D_1R and hypertension [179]. The discordance between this report in European Caucasians [179] and other reports involving other populations may be a result of the influence of genetic background in the phenotypic expression of a quantitative trait essential hypertension. Interestingly, low renin hypertension is less frequent in the Caucasian (15–20%) [180] than in other populations (40–60% in Japanese) [181]. In our Japanese study, the single best genetic model for low-renin hypertension included only GRK4 A142V, by itself, or GRK4 A142V and CYP11B2, with an estimated predictive accuracy of 78% [174]. Ethnicity may also explain some of the discordances. GRK4 65L and GRK4 142V are less frequent while GRK4 486V is more frequent in Asians than in African-Americans. GRK4 486V is also more frequent in Hispanic and non-Hispanic whites than in African-Americans [182]. Recent GWAS did not

identify GRK4 as associated with hypertension [158–164]. This is probably because salt sensitivity and gene-gene interaction were not taken into account. Previous studies have shown that it was critical to assess the association of GRK4 with hypertension, in conjunction with other GRK4 SNPs [174] and genes, e.g., ACE with GRK4 65L [173,177], *ADRB2, TH*, and *GRK4 486V* [176]. GRK4 A142V and GRK4 A486V are, moreover, not included in the Affymetrix or Illumina platforms, respectively.

Early in the process of D_1R [20,86,183,184] and D_3R stimulation [129], D_1R and D_3R increase their respective activities, in part, by the recruitment of intracellular D_1R and D_3R to the plasma membrane. This recruitment of D_1R and D_3R to the plasma membrane requires the presence of GRK4γ wild-type [129,184]. However, as indicated above [117], sustained D_1R and D_3R stimulation results in desensitization caused by their phosphorylation and internalization. Resensitization occurs by receptor dephosphorylation, caused by protein phosphatase 2A in D_1R [183], and recycling to the plasma membrane. Sorting nexins also help in the recycling of GPCRs to the plasma membrane. The GRK4γ wild-type (but not GRK4α wild-type) desensitizes the AT_1R and decreases AT_1R expression in the kidney [146,147]. Therefore, GRK4 wild-type is necessary for D_1R and D_3R [129,184] to exert their renal autocrine/paracrine natriuretic function, in part by inhibiting the antinatriuretic effect of AT_1R [146, 147]. However, GRK4 gene variants constitutively modify, phosphorylate, and internalize D_1R [112] and presumably the D_3R also, preventing their recycling to the plasma membrane. GRK4 gene variants also increase AT_1R expression in mice. This involves GRK4γ 142V on normal salt diet and by GRK4γ486V on high salt diet [146,147]. While GRK4γ 142V transgenic mice are hypertensive even on a normal salt diet [112,146,185], GRK4γ 486V transgenic mice develop hypertension only when stressed by a high salt diet [147,186]. Depending upon the genetic background of the mouse, overexpression of human GRK4γ wild-type converts a salt-sensitive phenotype to a salt-resistant phenotype, while overexpression of human GRK4γ 486V converts a salt-resistant phenotype to a salt-sensitive phenotype [146,186]. These phenotype changes, related to differential actions of human GRK4γ variants and their regulation of D_1R and other GPCRs, could be taken as evidence of the “apparent polygenicity” of hypertension.

GRK4γ 65L transgenic mice are normotensive on a normal salt diet (unpublished data) but whether or not some form of stress is needed for the hypertensive phenotype to develop is not known [173,177]. It is known however, that adolescent African-Americans expressing GRK4 65L, when exposed to mental stress, respond with an increase in blood pressure and a decrease in sodium excretion [187].

4.2 Role of other GRKs in hypertension

GRK activity and GRK2 expression are increased in lymphocytes of patients with essential hypertension and SHRs [188]. Overexpression of GRK2 in vascular smooth muscle in mice produces hypertension and impairs the vasodilatory action of β-adrenoceptors [189]. The vasoconstrictor response to angiotensin II is also impaired in these mice, which is at odds with the increased reactivity and sensitivity to angiotensin II in essential hypertension [190]. Interestingly, GRK2 activates the epithelial sodium channel by phosphorylating the C terminus of its β subunit, making it insensitive to the inactivating effects of ubiquitin protein ligases Nedd4 and Nedd2 [191]. Although GRK2 polymorphisms have not been associated with human essential hypertension, increased renal expression of GRK2, which is increased with aging [87], in the insulin/obesity/metabolic syndrome [52,58,123], and by oxidative stress [32,53,58], impairs D_1R function in rats. More importantly, increased GRK2 expression (but not GRK5) has been reported in lymphocytes of African-Americans with hypertension [192]. GRK5 overexpression in vascular smooth muscle cells in mice also increases blood pressure. The hypertension in male GRK5 transgenic mice is caused, in part, by decreased β_1-adrenergic receptor activity, whereas the high blood pressure in female mice is caused, in part, by increased

AT_1R activity [193]. The increase in GRK5 expression in hypertension may be secondary not primary; angiotensin II-induced GRK5 up-regulation in the rat aorta may be due to hypertension per se [194].

5.1 GRK4 and pharmacogenomics in essential hypertension

GRK4 polymorphisms may provide predictive pharmacogenetic insight into therapeutic antihypertensive strategies. In hypertensive African- Americans, the GRK4 65L/A142 haplotype is predictive of a poor response to β-adrenergic blockade [195]. Our preliminary studies in hypertensive Japanese suggest that the absolute decrease in blood pressure in response to angiotensin receptor blockers (ARBs) is associated with GRK4 142V [196]. (Interestingly, ARBs also normalize the blood pressure of GRK4γ 142V transgenic mice [146].) The addition of a diuretic to the non-responders of ARBs decreased blood pressure in hypertensive Japanese with the GRK4 486V gene variant. These studies suggest that the pharmacogenetics of GRK4 can be important in guiding the therapy for hypertension.

6.1 Summary

In summary, there is GPCR specificity of GRK4, especially the human GRK4γ isoform, in the regulation of human D_1R and D_3R (Figure 1). The human GRK4 locus is linked to hypertension and the human GRK4 gene variants, either alone or in conjunction with variants of other genes, are associated with essential hypertension. The ability of humans with salt-sensitive essential hypertension to excrete a chronic sodium load is inversely correlated with the number of human GRK4 allelic variants. Therefore, salt sensitivity may be imparted by the GRK4 gene variants, and this effect seems to be dependent on the number of allelic variants present. Human GRK4γ 142V transgenic mice are hypertensive even on a normal sodium intake while human GRK4γ 486V transgenic mice develop hypertension only when given a high salt diet. Additional genes contribute to the predictive value of GRK4 single nucleotide polymorphisms for salt sensitivity and hypertension, suggesting that epistasis is responsible for the etiology of this complex polygenic disorder. GRK4 gene variants may not only be predictive of hypertension phenotypes (e.g., salt sensitivity, low plasma renin) but may also predict response to antihypertensive drugs.

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Abbreviations

AT_1R	angiotensin type 1 receptor
D_1R	D_1 dopamine receptor
D_2R	D_2 dopamine receptor
D_3R	D_3 dopamine receptor
D_4R	D_4 dopamine receptor
D_5R	D_5 dopamine receptor
ENaC	epithelial sodium channel
GPCR	G protein-coupled receptor
GRK	G protein-coupled receptor kinase

GRK2	G protein-coupled receptor kinase type 2
GRK3	G protein-coupled receptor kinase type 3
GRK4	G protein-coupled receptor kinase type 4
GRK5	G protein-coupled receptor kinase type 5
GRK6	G protein-coupled receptor kinase type 6
GWAS	genome-wide association studies
Na/PiIIa	sodium phosphate cotransporter type Iia
NCC	sodium chloride cotransporter
NHE1	sodium hydrogen exchanger type 1
NHE3	sodium hydrogen exchanger type 3
NKCC2	sodium potassium 2 chloride cotransporter

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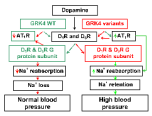

Figure 1.

GRK4 and renal dopamine and angiotensin type 1 receptor interaction During conditions of moderately increased NaCl intake, the renal D_1R is stimulated by dopamine produced in the kidney. The D_1R or D_3R, whose **coupling to G protein subunits** is regulated by G protein-coupled receptor kinase type 4 (GRK4), inhibits sodium reabsorption in several nephron segments. This results in an increase in sodium excretion and maintenance of normal blood pressure. GRK4 wild-type (GRK4 WT) also negatively regulates AT_1R transcription. The decrease in AT_1R expression, caused by GRK4 WT, facilitates the inhibitory effect of D_1R on renal sodium transport. In essential hypertension, constitutively active variants of GRK4 not only **uncouple D_1R and D_3R from G protein subunits**, but also increase AT_1R transcription in the kidney. These effects impair the ability of the kidney to excrete the excess sodium load, resulting in sodium retention, and ultimately hypertension.

Green = normal coupling of D_1R and D_3R to G protein subunits, Red = uncoupling of D_1R and D_3R from G protein subunits

Green arrows = stimulatory, Red arrows = inhibitory

Table 1

G protein-coupled receptor kinases involved in specific dopamine receptor signaling.

Dopamine Receptor Subtype	G protein-coupled receptor kinase	References
D_1R (in differentiated kidney cells) (in embryonic kidney cells)	GRK2, GRK4 (GRK4α and GRK4γ in humans[#], GRK4E in rats) GRK2, GRK3, GRK4α but not GRK4γ, GRK5[*]	53,112,121_123 113,114
(in intestines but not kidney cells)	GRK6	120,124
D_2R	GRK2, GRK3, GRK5, GRK6	73,148,149
D_3R (in kidney cells)	GRK2, GRK3, GRK4γ>GRK4α	129,151
D_4R	GRK2 or GRK3?	73
D_5R	?	

[*] GRK5 increased agonist-dependent phosphorylation of rat D_1R one report (114), but not in another report (113). GRK4α and GRK4γ desensitize the human D_1R (112) while GRK4α but not GRKγ desensitizes the rat D_1R (113).

?unknown or not definite