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REVIEW

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Dopamine Receptor D_1R and D_3R and GRK4 Interaction in Hypertension

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Essential hypertension is caused by the interaction of genetic, behavioral, and environmental factors. Abnormalities in the regulation of renal ion transport cause essential hypertension. The renal dopaminergic system, which inhibits sodium transport in all the nephron segments, is responsible for at least 50% of renal sodium excretion under conditions of moderate sodium excess. Dopaminergic signals are transduced by two families of receptors that belong to the G protein-coupled receptor (GPCR) superfamily. D_1-like receptors (D_1R and D_5R) stimulate, while D2-like receptors (D_2R, D_3R, and D_4R) inhibit adenylyl cyclases. The dopamine receptor subtypes, themselves, or by their interactions, regulate renal sodium transport and blood pressure. We review the role of the D_1R and D_3R and their interaction in the natriuresis associated with volume expansion. The D_1R- and D_3R-mediated inhibition of renal sodium transport involves PKA and PKC-dependent and -independent mechanisms. The D_3R also increases the degradation of NHE3 via USP-mediated ubiquitinylation. Although deletion of *Drd1* and *Drd3* in mice causes hypertension, *DRD1* polymorphisms are not always associated with human essential hypertension and polymorphisms in *DRD3* are not associated with human essential hypertension. The impaired D_1R and D_3R function in hypertension is related to their hyper-phosphorylation; GRK4γ isoforms, R65L, A142V, and A486V, hyper-phosphorylate and desensitize D_1R and D_3R. The *GRK4* locus is linked to and *GRK4* variants are associated with high blood pressure in humans. Thus, *GRK4*, by itself, and by regulating genes related to the control of blood pressure may explain the "apparent" polygenic nature of essential hypertension.

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Abbreviations: AT_1R, angiotensin II receptor type 1; AT_2R, angiotensin II receptor type 2; D_1R, dopamine receptor D1; D_2R, dopamine receptor D2; D_3R, dopamine receptor D3; D_4R, dopamine receptor D4; D_5R, dopamine receptor D5; *DRD1/Drd1*, dopamine D1 receptor gene; *DRD3/Drd3*, dopamine D3 receptor gene; ETBR, endothelin receptor type B; GPCR, G protein-coupled receptor; GRK4, G protein-coupled receptor kinase 4; NHE3, sodium hydrogen exchanger type 3; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; PM, plasma membrane; RAS, renin-angiotensin system; USP48, ubiquitin-specific peptidase 48.

Keywords: dopamine receptor, D_1R, D_3R, G protein-coupled receptor kinase 4, hypertension

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INTRODUCTION

Essential hypertension is caused by the interaction of genetic, behavioral, and environmental factors [1,2]. Renal and nonrenal mechanisms participate in the long-term regulation of blood pressure. The abnormalities in the regulation of renal ion transport, as well as in other systems, intrinsic and extrinsic to the kidney, have been proposed to cause essential hypertension [1,3-5]. The nephron segments responsible for the bulk of sodium retention in human polygenic/essential hypertension are the renal proximal tubule and medullary thick ascending limb of Henle [6-9]. However, renal distal tubular mechanisms also contribute to the increased sodium retention in hypertension [10,11] especially in monogenic forms of hypertension [12,13].

ROLE OF THE RENAL DOPAMINERGIC SYSTEM IN ESSENTIAL HYPERTENSION

Hormones and humoral factors, such as those involved in the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system, are pre-eminent in promoting elevated blood pressure [1,14-33]. Angiotensin II (Ang II) is essential in increasing renal tubule reabsorption of sodium and blood pressure [1,14,28]. Germline, global deletion of *Agtr1a* in mice decreases blood pressure [1,14,16,24,29]. These mice have greater urine volume on a low and normal salt diet than their wild-type littermates, but urinary sodium excretion only tended to be increased in the *Agtr1a* knockout mice [29]. However, renal proximal tubule-specific deletion of *Agtr1a* increases basal sodium excretion and decreases blood pressure [33], indicating confounding effects of global gene deletion. However, the high blood pressure in the F1 offspring (normotensive Wistar-Kyoto (WKY) mated with spontaneously hypertensive rats (SHRs)) transplanted with kidneys from parental SHRs is not caused by abnormalities of the RAAS and the sympathetic nervous system or by increased vascular reactivity to vasopressin [34]. Increased activity of pro-hypertensive systems and defects in anti-hypertensive systems result in high blood pressure and eventually hypertension. Nevertheless, in the above studies, vascular reactivity to acetylcholine and nitroprusside are not impaired, indicating a normal nitric oxide system. Therefore, aberrations in other counter-regulatory pathways, (eg, dopaminergic pathway, eicosanoids), participate in the pathogenesis of essential hypertension [25,26,35-43].

DOPAMINE RECEPTORS

The renal dopaminergic system inhibits sodium transport in all the nephron segments, including the renal proximal tubule and thick ascending limb of Henle [39]. The intrarenal arterial infusion of the D_1-like receptor antagonist SCH23390 in uninephrectomized conscious dogs on a sodium intake of 40 mEq/day decreased the fractional sodium excretion from 25% to 75% depending upon the dose [42]. In anesthetized Wistar-Kyoto rats, the intrarenal arterial infusion of SCH23390 decreased sodium excretion by 28% [41]. In anesthetized Sprague-Dawley rats, relative to vehicle-treated rats, the intravenous infusion of SCH23390 impaired the natriuretic effect of a 2% isotonic volume expansion by 60%, and the natriuretic effect of a 5% isotonic volume expansion by 56%. By contrast the natriuretic effect of a 10% isotonic volume expansion was not different between vehicle- and SCH23390-treated rats. Systemic blood pressure was not a confounding variable in these studies [44]. The importance of the renal dopaminergic system in the regulation of renal sodium transport and blood pressure regulation was proved by studies in mice with renal proximal tubule-selective deletion of aromatic amino acid decarboxylase (pt*Aadc*$^{-/-}$) which is needed for the synthesis of dopamine. These pt*Aadc*$^{-/-}$ mice had increased blood pressure and decreased renal and urinary dopamine and decreased urine volume and sodium excretion, relative to wild-type mice [23]. Thus, these studies show the critical role of the intrarenal dopaminergic system in the regulation of sodium excretion, especially under conditions of sodium excess [23,39-46]. The ability of dopamine to control sodium excretion may be lost during sodium restriction [45] and other factors may become more important than dopamine in the increase in sodium excretion with marked sodium loading [44]. Thus, the decreased ability to excrete a moderate sodium load in hypertension is due to enhanced sodium transport *per se* and/or the dysfunction of systems that decrease sodium transport (ie, a failure to respond appropriately to signals that decrease sodium transport) [46].

Dopaminergic signals are transduced by two families of receptors that belong to the GPCR superfamily [35-37,39,46,47]. The D_1-like receptors cloned in mammals (D_1R and D_5R) are linked to the stimulatory G-protein, $G\alpha_s$, and stimulate adenylyl cyclases. By contrast, the D_2-like receptors (D_2R, D_3R and D_4R) inhibit adenylyl cyclases, via $G\alpha_i$, and calcium channels and activate/modulate potassium channels.

D_1R AND RENAL SODIUM HANDLING

Low doses of dopamine or D_1-like receptor stimulation increases fractional sodium excretion [48-51] while D_1-like receptor inhibition [40-44] decreases fractional sodium excretion. The latter study indicates that at least one D_1-like receptor is constitutively active. In the renal proximal tubule, D_1-like receptors inhibit luminal ion

transport (NHE3, NaPi-IIc, Cl^-/HCO_3^-) via protein kinase A (PKA)-dependent [52-55] and -independent mechanisms [56-60] and basolateral transport by inhibition of Na^+/HCO_3 cotransporter [61] which is transduced by PKA [62]. The second messengers mediating the D_1-like receptor-mediated inhibition of Na^+/K^+ ATPase are nephron segment-specific. PKA [63-65], protein kinase C (PKC) [63,65-67], and phosphoinositide 3-kinase [68] are involved in the renal proximal tubule and PKA in the medullary thick ascending limb of Henle [67,69] and cortical collecting duct [64,67,70]; eicosanoids are involved in regulation of sodium transport in all these segments [64,66,67,71].

D_3R AND RENAL SODIUM HANDLING

The systemic or intrarenal administration of highly selective D_3R agonists (eg, PD128907, pramipexole, 7-OH-DPAT) [72-76] in rats increases absolute and fractional sodium excretion. In opossum kidney cells, which have characteristics of renal proximal tubule cells, a preferential D_3R agonist (quinerolane) opens K^+ channels, resulting in hyperpolarization and inhibition of Na^+/K^+-ATPase activity [77]. D_2-like receptors also decrease luminal ion flux (Na^+ and K^+) in the cortical collecting duct of mice and rabbits [78,79]. In rat renal proximal tubule cells, the D_3R-mediated inhibition of Na^+/K^+-ATPase activity has been related to D_3R interaction with $G\alpha_{12}/G\alpha_{13}$ [80]. The D_3R, linked to $G\alpha_i3$, also inhibits NHE3 activity in rat renal proximal tubule cells [81,82], via a phospholipase C (PLC)-PKC-mediated event, and modulated by intracellular Ca^{2+}. Interestingly, a D_3R agonist, pramipexole, increases PLC β1 expression in renal cortical membranes, as do other D_1-like receptor agonists [83]. The effect of D_3R, via $G\alpha_i3$, is not due to inhibition of adenylyl cyclase because the inhibition of adenylyl cyclases by D_3R is weak and often undetectable, except in the presence of the adenylyl cyclase 5 isoform [84]. However, adenylyl cyclase 5 is not expressed in renal proximal tubule cells [85]. D_3R stimulation, as with D_1R stimulation, can also inhibit NHE3, via PKA, in opossum kidney cells [77]. The D_3R agonist also decreases NHE3 expression in human renal proximal tubule cells and rat renal cortices [86], similar to the effect observed with D_1-like receptor stimulation [55,56]. In human renal proximal tubule cells and rat renal cortices, D_3R decreases NHE3 expression by increasing its degradation caused by the inhibition of the deubiquitinylating activity of ubiquitin-specific peptidase 48 (USP48) [86] (Figure 1). The D_3R may also inhibit NaCl cotransporter activity because in mouse distal convoluted tubule cells, the D_3R agonist PD128907 induces the internalization of NaCl cotransporter (unpublished data). Thus, the D_3R may inhibit the activity of renal sodium transporters by short-term (trafficking) and long-term (protein expression) mechanisms.

D_1R AND D_3R INTERACTION

D_1-like and D_2-like receptors [87] (specifically, D_3R [75]) interact to enhance the natriuretic effect of dopamine. In sodium-replete states [40-44], D_1-like receptors (D_1R, D_5R) act synergistically with D_2-like receptors (D_2R, D_3R, D_4R) to increase sodium excretion by inhibiting NHE3 [88] and Na^+/K^+ ATPase [89-93] activities; the synergistic interaction between D_1R and D_3R [93] occurs in renal proximal tubules [94,95]. D_1R and D_3R also interact to inhibit vascular smooth muscle cell proliferation [96] and induce vascular smooth muscle relaxation [97]. D_1R and D_3R heterodimerize in expression systems [98]. Interestingly, $G\alpha_S$, which by itself can decrease NHE3 activity, independently of PKA [99] is normally linked to D_1R [35-37,39,46,47,99] but can also be linked to D_3R [100]. Gαq/11, which engages in the D_1-like receptor inhibition of Na^+/K^+ATPase [101], can also be linked to D_3R [102]. The natriuretic action [75] and PLC [83]-stimulating effect of a D_3R selective agonist, pramipexole, are also blocked by a D_1R antagonist. The D_3R co-localizes and interacts with the D_1R in immortalized renal proximal tubule cells from normotensive WKY rats. In these cells, stimulation of D_3R increases both the co-immunoprecipitation of D_1R with D_3R and the protein expression of D_1R [95] and endothelin B receptor (ETBR) [72]. The D_3R also co-localizes and interacts with the AT_1R but unlike its positive effect on D_1R and ETBR expression, D_3R has a negative effect on AT_1R expression [103]. Thus, the D_3R promotes natriuresis, in the short-term, by its own action [72] and also by interacting with the D_1R [95], D_4R [104], D_5R [105], ETBR [72], AT_2R [76], and in the long-term, by increasing the expression of pro-natriuretic D_1R [95] and ETBR [72], and by down-regulating the expression of the anti-natriuretic AT_1R [103,105], via D_3R/AT_1R interaction [103,106]. These receptor-receptor interactions and the inhibition of sodium transporter activity [81,82] and expression [92,105] promote sodium excretion by inhibiting transport in proximal and distal nephron segments.

D_1R AND D_3R IN HYPERTENSION

Global disruption in mice of the D_1R gene, *Drd1* (C57BL/6J and B129 background) [107] or the D_3R gene, *Drd3* (C57BL/6J background) [84,106] increases arterial blood pressure. $D_3^{-/-}$ mice are hypertensive even on a normal NaCl diet and the hypertension is aggravated by a high NaCl diet [105,106,108]. The hypertension in $D_3^{-/-}$ mice is mitigated by an increase in D_5R receptor activity [105] and by genetic background [106,109]. Another strain of $D_3^{-/-}$ mice on C57BL/6J background is

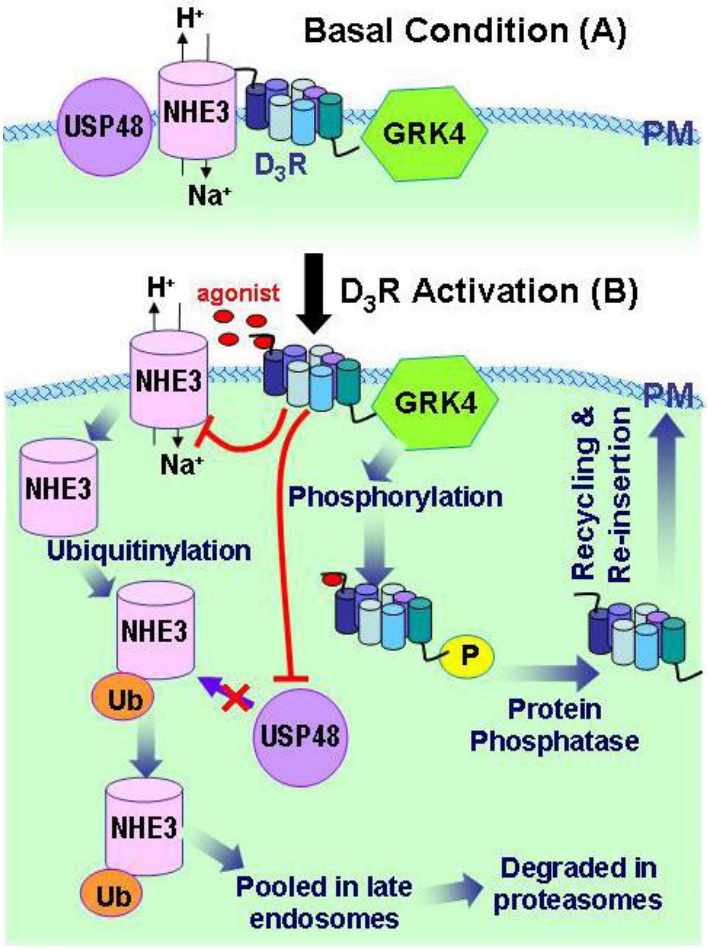

Figure 1. The D_3R, GRK4, NHE3, and USP48 in human renal proximal tubule cells in the basal state (**A**) form a cohesive signaling network capable of selective GPCR activation and efficient signal propagation and amplification to target specific effector systems. D_3R stimulation (**B**) causes the: (1) inhibition of the activity of membrane-bound NHE3, via PLC/ PKC and via protein-protein interaction that results in the internalization, ubiquitinylation (aka ubiquitination) and trafficking of NHE3 into sorting endosomes, to late endosomes, and eventually into proteasomes where it is degraded; and (2) inhibition of the activity of internalized and cytoplasmic USP48. The agonist-occupied D_3R, homologously desensitized by GRK4γ and to a lesser extent, by GRK4α, is internalized and directed to the late recycling endosome dephosphorylated and re-inserted to the plasma membrane (PM). Not shown are the constitutively active GRK4γ variants (eg, GRK4γ 124V) which impair D_3R function, resulting in increased expression and activity of NHE3 (and other Na^+ transporters), increased renal Na^+ transport and balance, and increased blood pressure (hypertension).

not hypertensive or salt-sensitive [109]. However, blood pressures of C57BL/6J mice from Jackson Laboratories may [110] or may not [111] be salt-sensitive. The blood pressures of C57BL/6J mice from Charles Rivers [112] are salt-sensitive while the blood pressures of C57BL/6 mice from Taconic Farms may be salt-resistant [113] or salt-sensitive [114]. SJL/J [115] and male BALB/c mice [116-118] are salt-resistant; female BALB/c mice are salt-sensitive [118]. Acute treatment with newer D_3R antagonists, R-VK4-40 and R-VK4-116, does not increase blood pressure in Long-Evans rats [119]. However, chronic D_3R antagonist treatment of salt-loaded Dahl salt-resistant rats produces hypertension [73] and potentiates the hypertensive effect of cocaine in conscious dogs [120]. These D_3R pharmacological studies support the *Drd3* knockout studies in mice and can be taken as evidence to rule out compensatory mechanisms that may have developed in mice with global germline deletion of *Drd3*.

The hypertension in $D_3^{-/-}$ mice is caused by both vascular and renal mechanisms [93]. As aforementioned, in $D_3^{-/-}$ mice, the RAS is activated; renal renin activity is increased [106] and acute AT_1R blockade decreases blood pressure [106]. In addition to the involvement of impaired D_3R function and expression in Dahl salt-sensitive rats [73], these may also be involved in the hyper-

tension in SHRs [94,121]. $D_3^{-/-}$ mice have an impaired ability to excrete an acute [106] and a chronic sodium load [109]. Moreover, an impaired ability to excrete a NaCl load in genetic hypertension can be explained, in part, by dysfunction of the D_1R [62,107,115,122,123] and D_3R [72,82,104,124,125]. The D_3R, by itself or via its interaction with the D_1R, is vasodilatory [94] and this effect is impaired in SHRs [97].

GRK4, D_1R, D_3R, AND HYPERTENSION

The increase in blood pressure and the development of hypertension in $D_1^{-/-}$ [107] and $D_3^{-/-}$ [105,106] mice show the importance of these genes in blood pressure regulation. However, polymorphisms in the non-coding region of the human D_1R gene, *DRD1*, have been associated with a decrease [126,127], increase [128,129], or no effect on blood pressure [130,131]. Furthermore, there are no polymorphisms in the coding region of *DRD3* [132,133] that are associated with human essential hypertension, except in one report among Hani Chinese. Polymorphisms in *DRD1* (rs1799914 and rs4867798) and *DRD3* (rs9880168) are associated with essential hypertension in Hani Chinese but not in Han or Yi Chinese [134]. The failure to replicate the association of *DRD1* and *DRD3* polymorphisms and human essential hypertension could be related to ethnicity.

The impaired D_1R and D_3R function in hypertension cannot always be related to their decreased expression [48,135,136]. GRK4 may regulate D_1R and D_3R function without altering their total cellular expression [35]. Human GRK4α and GRK4γ phosphorylate the ligand-occupied D_1R [48] and D_3R [137]. Although non-GRK-mediated phosphorylation, via arrestins [138,139], has been reported for the D_3R, the role of this pathway in its dysfunction in hypertension has not been reported. However, increased GRK4 activity *per se* may impair D_1R [140] and D_3R function [137]. The *GRK4* locus 4p16.3 is linked to hypertension [141] and *GRK4* polymorphisms (rs2960306, rs1024323, rs1801058, rs1644731, and rs1557213) are associated with hypertension and the response to anti-hypertensive medications in several ethnic groups [141-150]. The positive association of *GRK4* polymorphisms and hypertension is not found in all reports, which may be related to not testing for all the aforementioned *GRK4* polymorphisms or their interactions with other genes, eg, *NOS3* and *GRK4* rs2960306 [151,152], *GNB3*, *AGT*, and *GRK4* rs1801058 [152], and *GRK4* rs1801058 and *ADD1* rs4961 [142]. These associations are found in Euro-Americans, African Americans, and Africans (reviewed in [35]), in Chinese and Japanese in some studies ([reviewed in [35]), but not Koreans [153,154] in whom *GRK4* rs2960306 is inversely associated with hypertension risk [154]. However, *GRK4* rs1801058 is associated with obesity risk among Korean children [155]. A meta-analysis in 2016 showed that *GRK4* rs1024323 is associated with hypertension in Euro-Americans/Whites but not East Asians (Chinese and Japanese) while *DRD1* rs5432 (A-48G) is associated with hypertension in East Asians (Chinese and Japanese) but not in Euro-Americans/Whites [156]. The ethnic differences is not related to differences in minor allele frequencies of these *GRK4* polymorphisms. Among Euro-Americans and Europeans (eg, Italians) the minor allele frequencies of the *GRK4* polymorphisms mentioned above are about 0.4 [157,158]. However, among African Americans, the rs1801058 minor allele frequency is about 0.2 [157], a similar frequency found among African Brazilians [152]. The expression of human *GRK4* gene variants R65L (rs2960306) [35], A142V (rs1024323) [35,48,159-162] or A486V (rs18010058) [35,163] in mice causes hypertension.

CONCLUSION

In summary, abnormalities of the renal dopaminergic system, which inhibits sodium transport in all nephron segments, have been shown to be causal of hypertension. In this review, we discussed the role of the D_1R and D_3R, by themselves, or by their interaction in the natriuresis associated with "moderate" degrees of volume expansion. The D_1R-mediated inhibition of renal NHE3, NaPi-IIc, Cl^-/HCO_3, Na^+/HCO_3 cotransporter, and Na^+/K^+ ATPase activity and/or expression involves PKA and PKC-dependent and -independent mechanisms. The D_3R-mediated inhibition of NHE3 also involves PKA and PKC-dependent mechanisms and $G\alpha_i3$ while that of Na^+/K^+ ATPase involves interaction with $G\alpha_{12}/G\alpha_{13}$. The D_3R also decreases NHE3 expression by increasing its degradation caused by ubiquitinylation with USP48. The D_3R also interacts with D_1R, D_4R, D_5R, ETBR, and AT_2R, in the short-term, and by increasing the expression of D_1R and ETBR, and down-regulating the expression of the AT_1R, in the long-term. D_1R and D_3R functions in the kidney are impaired in animal models of hypertension, as well as in renal cells from humans with essential hypertension. Although global deletion of *Drd1* and *Drd3* in mice causes hypertension, polymorphisms of *DRD1* are not always associated with human essential hypertension. Only one *DRD1* polymorphism has been associated with human essential hypertension. The impaired D_1R and D_3R function in hypertension cannot always be related to their decreased expression. However, GRK4γ isoforms, R65L (rs2960306), A142V (rs1024323), and A486V (rs1801058) desensitize the D_1R and D_3R by increasing their phosphorylation. The *GRK4* gene locus is linked to and *GRK4* gene variants are associated with high blood pressure in humans. Of all the genes whose variants are

associated with hypertension, only variants of the *GRK4* gene have been shown to produce hypertension in mice. Thus, *GRK4* is one of the few candidate genes of essential hypertension that fulfills the criteria of a gene as causal of a complex trait (hypertension in this instance) as suggested by Glazier et al. [164] and the complex trait consortium [165]. *GRK4*, a gene whose product affects the function or expression of many other genes (or gene products) makes it an attractive candidate as the causative agent of a polygenic disease, like hypertension. It plays a critical role on D_1R and D_3R signaling. Thus, the *GRK4* gene, by itself, may explain the "apparent" polygenic nature of essential hypertension.

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