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Reactive Oxygen Species and Dopamine Receptor Function in Essential Hypertension

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Abstract

Essential hypertension is a major risk factor for stroke, myocardial infarction, and heart and kidney failure. Dopamine plays an important role in the pathogenesis of hypertension by regulating epithelial sodium transport and by interacting with vasoactive hormones and humoral factors. However, the mechanisms leading to impaired dopamine receptor function in hypertension states are not clear. Compelling experimental evidence indicates a role of reactive oxygen species (ROS) in hypertension, and there are increasing pieces of evidence showing that in conditions associated with oxidative stress, which is present in hypertensive states, dopamine receptor effects, such as natriuresis, diuresis, and vasodilation, are impaired. The goal of this review is to present experimental evidence that has led to the conclusion that decreased dopamine receptor function increases ROS activity and vice versa. Decreased dopamine receptor function and increased ROS production, working in concert or independent of each other, contribute to the pathogenesis of essential hypertension.

Keywords

reactive oxygen species; essential hypertension; dopamine receptor

Introduction

Essential hypertension affects 25% of the adult population and constitutes a major risk factor for stroke, myocardial infarction, and heart and kidney failure (1–4). The etiology of hypertension is complex and involves both genetic and environmental factors. It has been estimated that 30–50% of essential hypertension is heritable. Dopamine has been shown as an important regulator of blood pressure, sodium balance, and renal and adrenal functions through an independent peripheral dopaminergic system (5–8). Dopamine exerts its actions via two families of cell surface receptors that belong to the superfamily of G protein-coupled receptors. D₁-like receptors (D₁ and D₅) stimulate adenylyl cyclases, while D₂-like receptors (D₂, D₃, and D₄) inhibit adenylyl cyclases. Abnormal signaling of D₁-like and D₂-like

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Declaration of Interest

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receptors has been shown to be involved in rodent models of genetic hypertension and in humans with essential hypertension (5–8). However, the precise mechanisms remain to be determined.

Compelling experimental evidence indicates that reactive oxygen species (ROS) play an important pathophysiological role in the development of hypertension (9–11). In states associated with oxidative stress such as aging, diabetes, and hypertension, the functions of the dopamine receptors are impaired (12–14). The goal of this review is to present experimental evidence that has led to the conclusion that decreased dopamine receptor function increases ROS activity and vice versa. Decreased dopamine receptor function and increased ROS production, working in concert or independent of each other, contribute to the pathogenesis of essential hypertension.

ROS and Hypertension

ROS

The term oxidative stress describes a complex phenomenon, that can be defined simplistically as an excess of reactive oxygen species (ROS) in tissues, resulting from either increased Reactive Oxygen Species generation or decreased ROS degradation (9–11). ROS includes superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl anion ($^{\cdot}OH$) formed from H_2O_2 , and hypochlorous acid formed by myeloperoxidase from H_2O_2 and chloride (9–11, 15). Increased production of ROS leads to production of reactive nitrogen species, such as peroxynitrate ($ONOO^-$) which is formed principally by the interaction with nitric oxide (NO), lipid peroxides, such as malondialdehyde, 4-hydroxynonenal (16), oxidized low-density lipoproteins (17), and isoprostanes/isoketals (18), and protein oxidation (8-hydroxydeoxyguanosine) (19). Reactive Oxygen Species is generated by specific oxidases, such as the reduced form of nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase, xanthine/xanthine oxidase, various arachidonic acid monooxygenases, and the mitochondrial respiratory chain. The levels of ROS depend not only on their generation but also on their metabolism by antioxidant enzymes, such as heme oxygenase (HO) and superoxide dismutase (SOD). The major degradative pathway is through SOD, which is expressed as extracellular, intracellular, and mitochondrial isoforms, and peroxidases that metabolize O_2^- to H_2O_2 (20,21); peroxidases such as catalase and glutathione peroxidase (predominantly intracellular) further metabolize H_2O_2 to oxygen (O_2) and water. Heme oxygenase degrades heme, a pro-oxidant, and generates biliverdin, an antioxidant. There are two HO isoforms (HO-1 and HO-2) that are constitutively expressed in the kidney (22,23).

Initial interest in ROS as vasoactive mediators focused particularly on O_2^- and its interaction with NO as a mechanism to explain endothelial dysfunction (24,25). More recent interest has focused on the role of H_2O_2 in the regulation of NADPH oxidase activity (26,27). NADPH oxidase is present not only in phagocytes, but also in many non-phagocytic cells, including endothelial, vascular smooth muscle, mesangial, and renal tubule cells. Nicotinamide-adenine dinucleotide phosphate oxidase is an enzymatic complex comprised of five subunits: membrane components p22^{phox} and Nox proteins (Nox1, Nox2, Nox3, Nox4, Nox5, Duox1, and Duox2); cytosolic components p40^{phox}, p47^{phox}, and p67^{phox}; and a low molecular weight G protein, Rac1 or Rac2. Activation requires either p67^{phox} or Nox1 and phosphorylated p47^{phox} or the organizer Nox1 to translocate them to the catalytically active Nox protein at the plasma membrane. Nox 4 is constitutively active and does not require an activator protein. NADPH is the major source of ROS in vascular and kidney tissues (28–30).

ROS and Hypertension

A plethora of evidence shows the important role of ROS in the development of hypertension (9–11). Generation of ROS is increased in animal models of genetic and experimental hypertension (31–35). Inhibition of ROS generation with apocynin (NADPH oxidase inhibitor) or allopurinol (xanthine oxidase inhibitor) and radical scavenging with antioxidants or SOD mimetics decrease blood pressure and prevent the development of hypertension in rodent models of hypertension (20,35–44). These beneficial effects have been attributed to the normalization of endothelial function, regression of vascular remodeling, and reduced vascular inflammation.

High oxidative stress in the kidney variably affects sodium reabsorption by direct or indirect mechanisms. O_2^- has been reported to stimulate NaCl absorption by the renal thick ascending limb of Henle (36). However, H_2O_2 may decrease Na^+ /glucose cotransporter, Na^+ /Pi cotransporter, and Na^+ / H^+ antiporter activities in renal proximal tubule cells (37). Oxidant injury in renal cells also decreases sodium transport in renal proximal tubule cells (38). However, H_2O_2 activation by angiotensin II, via the angiotensin type 1 (AT_1) receptor, increases Cl^-/HCO_3^- exchanger activity in renal proximal tubule cells (39). In addition, high oxidative stress impairs D_1 dopamine receptor function by disrupting the D_1 receptor/G protein coupling in renal proximal tubule cells, resulting in a failure of D_1 -like receptor agonist to inhibit sodium potassium ATPase (Na^+ - K^+ ATPase) activity (40). Thus, the overall effect of ROS on overall renal sodium transport is difficult to assess because ROS can decrease or increase sodium transport (41). However, mouse models deficient in ROS-generating enzymes have lower blood pressure and angiotensin II infusion fails to induce hypertension in these mice compared to wild-type counterparts (24). Increased renal superoxide anion production is associated with the inactivation of NO, which influences afferent arteriolar tone, tubuloglomerular feedback responses, and sodium reabsorption, all of which are important mechanisms in the long-term regulation of blood pressure (10). In cultured vascular smooth muscle cells (VSMCs) and isolated arteries from hypertensive rats and humans, ROS production is enhanced, redox-dependent signaling is amplified, and antioxidant bioactivity is reduced (45).

Clinical studies demonstrate increased ROS production in patients with essential hypertension, renovascular hypertension, malignant hypertension, and preeclampsia (46–48). These findings are, in general, based on increased levels of plasma thiobarbituric acid-reactive substances and 8-epiisoprostanes, which are biomarkers of lipid peroxidation and oxidative stress (49). Accumulation of ROS byproducts from oxidized genomic and mitochondrial DNA has also been demonstrated in hypertensive individuals (50). Polymorphonuclear leukocytes and platelets, which are rich sources of O_2^- , also participate in vascular oxidative stress and inflammation in hypertensive patients (51). In never-treated subjects with mild-to-moderate hypertension, lipid peroxidation and oxidative stress are not increased, suggesting that ROS may not be critical in the early stages of human hypertension, but could be more important in severe hypertension (52). Increased ROS activity in the spontaneously hypertensive rat (SHR) has also been reported to occur after the development of hypertension (53).

Role of ROS in the Dopamine Receptor Defect in Hypertension

D_1 Receptor

Activation of D_1 -like receptors induces natriuresis and diuresis, relaxation of resistance arteries, and inhibition of proliferation of conduit arteries (5–8,54). Because of the lack of specific agonists that can discriminate between D_1 and D_5 receptors, it is not clear which D_1 -like receptor subtype mediates the effects of D_1 -like receptors. However, it has been shown that the D_1 receptor is expressed in blood vessels and the kidney. In the kidney, the

D₁ receptor protein is expressed in the juxtaglomerular cell, proximal tubule, distal convoluted tubule, macula densa, cortical collecting duct, and renal vasculature. In the proximal tubule, D₁ receptor staining is localized both at the brush border and basolateral membranes. The D₁ receptor is also expressed in the tunica media of the aorta, common carotid artery, vertebral artery, pulmonary artery, pial, renal, mesenteric artery branches, and superior vena cava (55–57).

Physiology of the D₁ Receptor—Endogenous renal dopamine is a major physiological regulator of renal ion transport (5–8,58). During conditions of moderate sodium balance, more than 50% of renal sodium excretion is regulated by the D₁-like receptors. Direct evidence of the involvement of the D₁ receptor in the natriuresis comes from the chronic selective intrarenal cortical infusion of D₁ receptor antisense oligodeoxynucleotides, which selectively decreases D₁ receptor protein without affecting D₅ receptors. Selective inhibition of D₁ receptor decreases sodium excretion during a normal or high sodium chloride intake (59). Since the inhibition of renal ion transport by the D₁-like receptors is mediated by increased cyclic adenosine monophosphate (cAMP) and since the D₁ receptor increases cAMP production to a greater extent than the D₅ receptor in renal proximal tubule cells (60), it is possible that the natriuretic effect of dopamine is exerted mainly through the activation of the D₁ receptor in this nephron segment. D₁-like receptors decrease ion transport in many segments of the nephron, i.e., proximal tubule, medullary thick ascending limb of Henle, and cortical collecting duct, by inhibiting the activities of sodium hydrogen exchanger 3 (NHE3), sodium phosphate cotransporter and Cl[−]/HCO₃[−] exchanger at the apical membrane, and Na⁺/HCO₃[−] co-transporter and sodium potassium ATPase (Na⁺-K⁺ ATPase) at the basolateral membrane (61–65).

Dopamine, at low concentrations, dilates resistance arteries via D₁-like receptors (5–8). The vasorelaxant effect of dopamine in the rabbit pulmonary artery has been reported to be both endothelium-dependent and -independent (66). However, in the mesenteric artery, the vasodilatory effect of the D₁ receptor agonist is endothelium independent, and the calcium channel is involved in its signaling pathway (67,68). cAMP may also mediate the vasodilatory effect of D₁-like receptor; inhibition of Na⁺-K⁺ ATPase activity results in vasoconstriction. Dopamine dilates coronary arteries via cAMP cross-activation of cyclic guanosine monophosphate (cGMP)-dependent protein kinase and subsequent stimulation of BK_{Ca} channels (69). This may be exerted via the D₅ rather than the D₁ receptor (70).

D₁ Receptor and Hypertension—D₁ receptor null mice have elevated blood pressure (61). Although the underlying mechanisms are not completely understood, D₁-like receptor agonist stimulation does not increase renal cAMP accumulation in these mice, which may provide a reasonable correlation between deficient D₁ receptor/signal transduction, abnormal renal sodium handling, and the development of hypertension.

In rodents with genetic hypertension (SHRs; Dahl salt-sensitive [DSS] rats), D₁-like receptor agonist-mediated diuretic and natriuretic responses are impaired (5–8, 58, 62–64, 71–73), resulting from diminished D₁-like receptor inhibition of NHE3, Cl[−]/HCO₃[−] exchanger, and Na⁺/HCO₃[−] cotransporter and Na⁺-K⁺ ATPase activities. The impaired inhibitory effects of D₁-like receptor on epithelial sodium transport is not always due to decreased total cellular expression of D₁ receptor, but is consistently associated with decreased expression of D₁ receptors at the plasma membrane (74,75) and increased serine phosphorylation, leading to the uncoupling of the D₁ receptor from its G protein/effector complex (5–7,12,58,64,76,77). The uncoupling is receptor-specific, organ-selective, nephron segment-specific, precedes the onset of hypertension, and co-segregates with the hypertensive phenotype (58,61,75,76).

In general, the renal and non-renal vasodilatory effects of D₁-like receptors in hypertension are not impaired (78). There are, however, reports of impaired renal vasodilatory effect of D₁-like receptor agonist in humans with essential hypertension and in SHR (79,80). Indeed, the ability of D₁-like receptors in renal arteries of SHR to stimulate adenylyl cyclase is impaired (80). We have also reported an impaired ability of D₁-like receptor agonists to vasodilate mesenteric arteries of SHR (67).

Dysfunction of the D₁ receptor could be involved in human essential hypertension. The human D₁ gene locus at chromosome 5q35.1 is linked to human essential hypertension (81). More recently, D₁ receptor A-48, G-94, and C-800 haplotype has been reported to be associated with lower blood pressure in a Flemish population (82). This study complements the report of an association of the D₁ receptor polymorphism, -48G with essential hypertension in a Japanese population (83). However, the D₁ receptor -48G allele was also reported to be associated with lower blood pressure in white and African-American adolescents (84).

Role of Oxidative Stress in the Anti-Hypertensive Effect by D₁ Receptor—As previously mentioned, D₁-like receptor agonist-mediated natriuretic and diuretic effects are impaired in humans with essential hypertension and rodents with genetic hypertension (5–7,58, 61,62,71,72). This is accompanied by increased oxidative stress, which can be replicated in normotensive rats after treatment with oxidative reagents. H₂O₂ treatment of proximal tubules from Wistar-Kyoto (WKY) rats induces an increase in lipid peroxidation, an indicator of oxidative stress, and results in the loss of D₁/G protein coupling. However, treatment of WKY rat proximal tubules with an antioxidant, ascorbic acid, or a reducing agent, dithiothreitol, restores the D₁ receptor/G protein coupling, suggesting that D₁ receptor/G protein coupling may be modulated by changes in redox states. Therefore, the D₁ receptor/G protein coupling in SHR may have been impaired by reactive oxygen species produced during elevated oxidative stress in the proximal tubules (12). Treatment of rats on a high salt diet with buthionine sulfoximine, an oxidant, causes severe hypertension that is associated with impaired renal D₁ receptor function. The addition of the superoxide dismutase mimetic, tempol, normalizes blood pressure and renal D₁ receptor function (85).

Similar to those observed in human essential hypertension and SHR, D₁ receptor function is also impaired in the metabolic syndrome, which is characterized by insulin resistance with hyperglycemia, hypertension, and abdominal obesity (86–90). There is increasing evidence that oxidative stress is associated with this cluster (86–90). The obese Zucker rat, a model of type 2 diabetes, exhibits a moderate degree of hypertension and an increased oxidative stress. Moreover, these animals have a defect in dopamine D₁ receptor function. Tempol decreases D₁ receptor phosphorylation and restores receptor/G protein coupling and the natriuretic response to D₁-like receptor agonists (91). In another animal model of diabetes, the streptozotocin (STZ)-treated rat, similar to the hyperglycemic Zucker rats, has impaired renal D₁-like receptor-G protein coupling and function. Tempol supplementation restores D₁-like receptor/G protein coupling and D₁-like receptor natriuretic effect in this rodent model. Another study shows that the uncoupling of D₁ receptor and G protein is due to the phosphorylation of D₁ receptor by activation of the protein kinase C (PKC)-G protein coupled receptor kinase 2 (GRK2) pathway (92). Marwaha and Lokhandwala found that nuclear factor (NF)-κB is the upstream signal of PKC and GRK2. H₂O₂ induces the nuclear translocation of NF-κB, increases PKC activity, and triggers the translocation of GRK2 to renal proximal tubular membranes. Pretreatment with pyrrolidine dithiocarbamate, an NF-κB inhibitor, blocks the H₂O₂-induced nuclear translocation of NF-κB, the increase in PKC activity, GRK2 translocation, and hyperphosphorylation of D₁ receptors, and restores D₁ receptor/G protein coupling and D₁ receptor agonist-mediated inhibition of the Na⁺-K⁺ ATPase activity (93) (Figure 1). These *in-vivo* studies have been replicated and confirmed

in studies *in vitro*. Treatment of freshly prepared renal proximal tubule cells from Sprague-Dawley rats with H₂O₂ increases D₁ receptor phosphorylation and impairs D₁ receptor inhibition of Na⁺-K⁺ ATPase activity (94). We also have preliminary data indicating that the D₁ receptor inhibits NADPH oxidase activity in human kidney cells (95).

D₅ Receptor

The D₅ receptor, like the D₁ receptor, is expressed in the brain, renal proximal, and distal tubules, thick ascending limb of Henle, cortical collecting ducts, and tunica media of arterioles (96,97). Because of the lack of specific ligand that can distinguish the D₅ from the D₁ receptor, it has been difficult to distinguish D₁ from D₅ receptor function. The D₅ receptor has generated significant interest because of its relatively high affinity for dopamine, compared to the other dopamine receptors. Moreover, the D₅ receptor can be activated in the absence or presence of low concentrations of its endogenous ligand (98).

Physiology of the D₅ Receptor—There is increasing evidence showing the importance of the D₅ receptor in regulating blood pressure. Activation of D₁-like receptors induces diuresis and natriuresis via inhibition of renal sodium transporters and Na⁺-K⁺ ATPase activities in WKY rats (5–8). The D₁-like receptor inhibition of renal sodium transport is, in part, related to cAMP production. Both the D₁ and the D₅ receptor stimulate cAMP production, although the D₁-like receptors stimulation of cAMP production in renal proximal tubules is predominantly a D₁ receptor mediated effect (determined by gene silencing using antisense oligonucleotides) (60). As aforementioned, due to the lack of selective D₁ and D₅ receptor agonists or antagonists, the contribution of D₅ receptor on natriuresis is not known. In D₅ receptor deficient mice (D₅^{−/−}) mice, high salt diet further increases blood pressure (99,100), suggesting that the renal D₅ receptor plays an important role in the control of blood pressure by regulating renal sodium chloride transport. While the nephron segments in which the D₅ receptor regulates ion transport remain to be determined, the more D₅ than D₁ receptors are expressed in distal nephron segments (101), indicating that the D₅ receptor exerts a greater regulatory effect than the D₁ receptor on sodium excretion in these nephron segments.

The proliferation of VSMCs is believed to play a key role in hypertension (102). The D₁-like receptors have been shown to inhibit VSMC proliferation induced by hormones, such as platelet-derived growth factor BB (103). This inhibition is reversed by the transfection of D₅ receptor antisense oligonucleotides, indicating that the D₅ receptor has an anti-proliferative effect on VSMCs.

D₅ Receptor and Hypertension—The D₅ receptor gene locus (chromosome 4p15.1–16.1) is linked to essential hypertension (104) and the human D₅ receptor gene has polymorphisms that encode for receptors with abnormal coupling to adenylyl cyclase (105). D₅^{−/−} mice are hypertensive (106), which is aggravated by a high salt diet (99,100). D₅^{−/−} mice have an elevated epinephrine/norepinephrine ratio and a greater reduction in mean arterial pressure after adrenalectomy, or with α-adrenergic blockade compared to control mice. These studies indicate that the hypertension is caused, in part, by increased sympathetic activity. However, because the percentage decrease in systolic blood pressure after adrenalectomy is similar in both D₅^{−/−} mice and wild-type littermates, the increased sympathetic activity in D₅^{−/−} mice has been ascribed to central rather than peripheral nervous system mechanisms (106).

Role of Oxidative Stress in the Anti-Hypertensive Effect by D₅ Receptor—Low concentrations of dopamine or dopamine agonists acting on D₁-like receptors have been reported to decrease oxidative stress in VSMCs, peripheral blood lymphocytes and the

kidney (103,107,108) through a phospholipase D (PLD)-mediated signal transduction pathway (100,109). Phospholipase D is a ubiquitous enzyme stimulated by many cell surface receptors that hydrolyze phospholipids, such as phosphatidylcholine, to form phosphatidic acid and the free polar head group of the phospholipid substrate, which is believed to be involved in the pathophysiology of hypertension by increasing oxidative stress (110). In the brain and liver of the SHR, PLD activity is higher than those observed in WKY rats (111).

While it is still not clear which of the D₁-like receptor subtype(s) inhibits PLD activity, the D₅ receptor may play an important role in this action. Activation of D₁ and D₅ receptors result in contrasting effects on PKC activity, which has been suggested to be the upstream signal of PLD; D₁ receptors stimulate, whereas D₅ receptors inhibit PKC activity (112,113). Due to the lack of a specific agonist for D₅ receptor, we used D₅^{-/-} mice and human embryonic kidney (HEK)-293 cells heterologously expressing human D₅ receptor to determine the effect of the D₅ receptor on PLD activity. We found that renal PLD expression and activity are higher in D₅^{-/-} mice than in D₅^{+/+} mice. Moreover, activation of the D₅ receptor by fenoldopam in HEK-hD₅ cells decreases PLD expression and activity, indicating that the anti-oxidative effects of D₅ receptors are, in part, via PLD (109) (Figure 2).

Stimulation of PLD increases NADPH oxidase activity. It is possible that the agonist-activated, PLD-mediated D₅ receptor inhibition also inhibits NADPH oxidase activity, and thus, the production of ROS. We explored this issue in D₅^{-/-} mice and found that, in these mice, plasma thiobarbituric acid-reactive substances (TBARS), an index of systemic oxidative stress, are increased and that the expression of NADPH oxidase proteins (gp91^{phox} and p47^{phox}) and NADPH oxidase activity are increased in the brain and kidney compared to wild-type littermates. Furthermore, the chronic administration of apocynin, a drug with antioxidant activity, normalizes blood pressure, plasma TBARS, and NADPH oxidase activity in the brain and kidney of D₅^{-/-} mice, suggesting that the D₅ receptor may act to keep the systemic blood pressure in the normal range by preventing excessive ROS production (100). The results culled from D₅^{-/-} mice have been confirmed in D₅ receptor transfected cells (100). In HEK-hD₅ cells, fenoldopam decreases the expression of one of NADPH oxidase subunits (gp91^{phox}), NADPH oxidase activity, and ROS production. The inhibitory effect of D₅ receptor activation on NADPH oxidase activity may involve direct and indirect mechanisms. We also reported in a preliminary communication that, in HEK-hD₅ cells, the D₅ receptor co-localizes with gp91^{phox} in the cell surface membrane and that D₅ receptor stimulation induces the dissociation of D₅ receptor and gp91^{phox} and impairs the translocation of p67^{phox}, a cytosolic component of the NADPH oxidase component, to the oxidase complex (114). Similar results were obtained in renal proximal tubule cells from WKY rats (115). We also found that stimulation of D₅ receptors in HEK-hD₅ cells increases HO-1 activity (116). HO-1 converts heme to carbon monoxide, iron, and biliverdin. Carbon monoxide can inhibit NADPH oxidase activity, and bilirubin, which is converted from biliverdin via biliverdin reductase, has antioxidant activity. Thus, D₅ receptor activation may indirectly inhibit ROS production via these metabolic products. However, the D₅ receptor can also interfere with the plasma membrane distribution and assembly of NADPH oxidase components, causing the inhibition of NADPH oxidase activity (100) (Figure 2).

D₂-Like Receptor

Physiology of the D₂-Like Receptors

D₂ receptor: The D₂ receptor is expressed as D_{2short} and D_{2long} receptors (117). It has been suggested that the D_{2short} receptor functions as the presynaptic receptor, while the D_{2long} receptor functions as the postsynaptic receptor (118,119). In the kidney, D_{2long} mRNA is

expressed in renal tubules and the glomeruli (120), whose protein product has been described in the opossum kidney cell, a proximal tubule cell line that has some distal tubular cell characteristics (121). However, D₂ receptor expression in the intact kidney is not well documented but it has been found in the heart and coronary artery (122,123).

The D₂ receptor can affect renal function by regulating dopamine production and dopamine transporter activity (124,125). Deletion of the D₂ receptor gene in mice causes a decrease in renal dopamine production, impaired excretion of a chronic (but not acute) salt load, and salt-sensitive elevation of blood pressure (126–127).

The mechanisms by which the D₂ receptor inhibits sodium reabsorption are not known. The effects of D₂ receptor on Na⁺-K⁺ ATPase activity are not consistent. Both inhibitory and stimulatory effects have been reported, and which effect predominates may depend on sodium balance. D₂-like receptor stimulation increases Na⁺-K⁺ ATPase activity in renal proximal tubules from normotensive rats fed a normal salt diet (128). Stimulation of the D_{2Long} receptor heterologously expressed in murine fibroblasts also increases Na⁺-K⁺ ATPase activity (129). In contrast, D₂-like receptors, in concert with D₁-like receptors, inhibit Na⁺-K⁺ ATPase activity in neostriatal neurons (130) and renal proximal tubule cells (131). It is possible that the stimulatory effect of D₂-like receptors on Na⁺-K⁺ ATPase activity changes to a synergistic inhibition in the presence of D₁-like receptors. Indeed, co-stimulation of D₁ and D₂ receptors results in a synergistic increase in arachidonic acid production (132,133). The D₂-like receptor mediated inhibition of Na⁺-K⁺ ATPase, in the presence of D₁-like receptors may be related to increased production of eicosanoids, specifically, 20 hydroxytetraenoic acid (134). The synergism of D₁- and D₂-like receptors on the inhibition of Na⁺-K⁺ ATPase activity may be the reason why a D₁-like and D₂-like receptor interaction increases sodium excretion in WKY rats under conditions of *moderate* sodium excess (135,136).

D₃ receptor: Previous studies have shown that the D₃ receptor is expressed in the kidney, specifically in renal proximal tubules, the apical membranes of distal convoluted tubules, cortical collecting ducts (intercalated cells), glomeruli, and renal blood vessels (137,138). We have also reported that the D₃ receptor is expressed in both the tunicae intima and media from rat mesenteric artery (67,68).

The acute intravenous administration of 7-OH-DPAT, which has 65-fold greater selectivity for D₃ receptors over the other D₂-like receptors, increases glomerular filtration rate and sodium and water excretion without affecting blood pressure in Dahl salt resistant rats (139). The intrarenal arterial infusion of PD128907, a selective D₃ receptor agonist with a 120-fold selectivity over the D₂ receptor, on normal or high salt diet dose-dependently increases fractional sodium excretion in WKY rats (140). Systemic administration of D₃ receptor agonists also decreases systemic blood pressure (141). The post-junctional D₃ receptor-mediated vasodilation is more manifest when renal vascular resistance is increased (142). In our studies in the isolated, relaxed mesenteric artery, two different D₃ receptor agonists, PD128907 and 7-OH-DPAT, have no effect on basal vascular contractility. However, when the mesenteric rings are precontracted with potassium or norepinephrine, both PD128907 and 7-OH-DPAT induce vasorelaxation. The vasorelaxant effect of PD128907 is increased by a calcium channel blocker, indicating that the vasorelaxant effect of the D₃ receptor is, in part, caused by a decrease in intracellular calcium. The vasodilatory effect of D₃ receptors may also involve small and/or large conductance, calcium-activated potassium channels (67,68).

D₄ receptor: D₄ receptor is expressed in the kidney to a greater extent in the cortical and medullary collecting ducts (143), and to a lesser extent in the proximal tubule and distal

convoluted tubule (144). In the cardiovascular system, the D₄ receptor has been reported to be expressed in the adventitia and adventitia-media border of pulmonary (145), pial and mesenteric arteries (146). D₄ receptors may be expressed pre- and post-junctionally (146). D₄ receptors are expressed in the atria but not in the ventricles of rats and humans (147). In contrast, the right and left ventricles of guinea pig express D₄ receptors (148).

D₄ receptors have been shown to antagonize vasopressin- and aldosterone-dependent water and sodium reabsorption in the cortical collecting duct (149,150). In the rabbit cortical collecting duct, the D₄ receptor-mediated decrease in sodium transport is exerted mainly at the basolateral membrane in spite of a greater expression of D₄ receptors at the luminal membrane (150).

D₂-Like Receptor and Hypertension

D₂ receptor: Several D₂ receptor polymorphisms have been reported and one has been reported to be associated with hypertension (151,152). Transfer of a segment of chromosome 8, which contains the D₂ receptor gene, from the normotensive Brown-Norway rat onto SHR background decreases blood pressure (153). Disruption of the D₂ receptor gene in mice produces hypertension; the hypertension in D₂ receptor knockout mice is caused by increased activity of the adrenergic nervous system and decreased dopamine production (126,127). However, in another strain of D₂^{-/-} mice, blood pressure is normal on a normal salt diet, but is increased on a high-salt diet (127). Sympathetic activity is not different between these D₂^{-/-} mice and their wild-type littermates. However, renal aromatic amino acid decarboxylase activity and dopamine synthesis are reduced in these D₂^{-/-} mice (124). The differences between the two strains of D₂^{-/-} mice could be related to genetic background.

D₃ receptor: D₃ receptor deficiency may be important in the development of salt-sensitive hypertension. In salt-resistant Dahl rats on high sodium diets and chronically treated with the highly selective D₃ receptor antagonist BSF 135170, the blood pressure is increased by almost 40 mmHg (141). Although several investigators have not found an association between D₃ receptor polymorphisms (-707 G/C, Ser9Gly, Ala17Ala) and blood pressure, the chromosome locus of the D₃ receptor gene (3q13.3) has been linked to human essential hypertension (154–156). Disruption of the D₃ receptor gene in mice produces hypertension (157,158), although the mechanisms are not completely understood. We have reported that D₃^{-/-} mice have renin-dependent hypertension that is associated with an inability to excrete an acute (157) or chronic sodium load (159). Another strain of D₃^{-/-} mice also cannot excrete a sodium load but the blood pressure is not different from the D₃ receptor wild type mice (158). Differences in the environmental and procedures employed, including the manner of duration of salt loading, the surgical conditions (anesthetized vs. conscious state), and the blood pressure measurement (intra-arterial catheter vs. tail-cuff plethysmography) may explain the differences between these two D₃^{-/-} mice. The disparity in the observed effect on blood pressure may also be due to genetics.

We have shown that selective renal D₃ receptor activation increases fractional sodium excretion in WKY rats, but not in SHRs (140). The impaired D₃ receptor-mediated diuresis and natriuresis in SHRs is associated with lower expression of D₃ receptor in renal cortex (160). In isolated mesenteric arterial rings, D₃ agonist-induced vasorelaxation is similar in WKY and SHRs, except at very high concentrations. There is an additive vasodilatory effect between D₁ and D₃ receptors in WKY rats, which is lost in SHRs (67,68). Thus, D₃ receptor deficiency plays a role in the pathogenesis of hypertension.

Importance of the genetic background in phenotype expression: $D_3^{+/+}$ congenic mice on C57BL/6J background have normal blood pressure on a normal NaCl intake and is modestly elevated with increased NaCl intake, while their $D_3^{-/-}$ littermates, which are hypertensive on a normal NaCl intake, have a marked aggravation of their hypertension with an increase in NaCl intake (161). Wild-type C57BL/6J mice from the Jackson Laboratory have normal blood pressure on a normal NaCl diet but their blood pressures modestly increase on a high NaCl diet (162). In contrast, the blood pressures of C57BL/6T mice from Taconic Farms are salt-resistant (100). $D_3^{-/-}$ mice on a C57BL/6 Germany genetic background, similar to our congenic C57BL/6J $D_3^{-/-}$ mice, have a decreased ability to excrete a sodium load (158), yet our $D_3^{-/-}$ mice are hypertensive (157,161), while C57BL/6 Germany $D_3^{-/-}$ are not (158). This is reminiscent of C57BL/6T Taconic mice which do not develop hypertension on an increased NaCl intake and yet have a decreased ability to excrete a salt load (100). These studies suggest that in some mouse strains, extra renal factors mitigate an increase in blood pressure even when salt excretion is impaired. It should also be noted that Luippold et al. (141) have reported the importance of the D_3 receptor in regulating renal sodium handling and blood pressure. They showed that Dahl salt-resistant rats fed a high salt intake and chronically received a D_3 receptor antagonist have an impaired ability to excrete a sodium load and develop hypertension (141). Interestingly, renal D_3 receptor expression, measured by ^3H -7-OH-DPAT binding, is also decreased Dahl salt-sensitive rats fed a high sodium diet (141). The influence of genotype on the blood pressure phenotype is not exclusive to the D_3 receptor. $D_2^{-/-}$ on C57BL/6J background are hypertensive even on a normal NaCl diet (31,126), while a different $D_2^{-/-}$ mouse (background unspecified) develops hypertension only when fed a high salt diet (127).

D_4 receptor: Loci near the D_4 receptor gene (11p15.5) have been linked to hypertension, and a D_4 receptor polymorphism, located in exon 3 of the D_4 receptor gene, is associated with a 3-mmHg higher systolic and 2-mm Hg higher diastolic blood pressure among Caucasians (163). Disruption of the D_4 receptor gene in mice produces hypertension (164), which is due in part to increased AT_1 receptor expression. Bolus intravenous injection of the AT_1 receptor antagonist losartan initially decreases mean arterial pressure to a similar degree in $D_4^{-/-}$ mice and $D_4^{+/+}$ littermates. However, the hypotensive effect of losartan persists longer in $D_4^{-/-}$ mice than in control mice (164).

Role of Oxidative Stress in the Anti-Hypertensive Effect of D_2 -Like Receptor

D_2 receptor: The antioxidative effects of the D_2 receptor play a role in blood pressure regulation, as suggested by studies on $D_2^{-/-}$ mice. $D_2^{-/-}$ mice have increased urinary excretion of 8-isoprostane, an index of oxidative stress, increased activity and expression of NADPH oxidase, and decreased expression of the antioxidant enzyme HO-2 in the kidneys, indicating that the regulation of ROS production by the D_2 receptor involves both pro-oxidant and antioxidant systems (31). Apocynin, an NADPH oxidase inhibitor, or hemin, an inducer of HO-1, normalizes the high blood pressure of $D_2^{-/-}$ mice. Urinary aldosterone is increased in $D_2^{-/-}$ mice and remains higher in $D_2^{-/-}$ mice than in their wild-type littermates after 7 days of a high salt diet. Spironolactone normalizes the blood pressure in $D_2^{-/-}$ mice and the renal expression of NADPH oxidases Nox 1 and Nox 4 but does not normalize Nox2 expression or 8-isoprostane excretion. Therefore, increased ROS may not always result in increased blood pressure (31).

D_3 receptor: The effect of D_3 receptors on ROS is controversial. One report has shown that the D_3 receptor stimulates PLD activity in HEK 293 cells heterologously expressing the human D_3 receptor (165). However, the D_3 receptor has also been reported to increase a dopamine autotrophic factor which has an antioxidant action and thus the D_3 receptor has antioxidant effect, albeit indirectly (166). Our preliminary study found that D_3 receptor is

expressed in tunica intima (68). Activation of D₃ receptor also inhibits superoxide production in human brain endothelium cells (unpublished data). The role of oxidative stress in the hypertension of D₃^{-/-} mice remains to be determined.

D₄ receptor: Oxidative stress is thought to be the cause of nerve cell death in central nervous pathology, including ischemia, trauma, and neuro-degenerative disease (167). Glutamate induces neuronal death by initiating the oxidative stress cell death pathway. Administration of dopamine and dopamine receptor agonists, such as apomorphine and apocodine, or PD168077, a D₄ receptor agonist, partially inhibits the glutamate-induced ROS production, and blocks nerve cell death. These protective effects are inhibited by U101958, a dopamine D₄ antagonist (168). However, whether the D₄ receptor has antioxidative effect in the kidney is still unknown.

A Complex Association Among ROS, Dopamine Receptor, and Hypertension

Dopamine has contrasting, concentration-dependent effects on ROS production. It acts as a pro-oxidant at high concentrations (169); high concentrations of dopamine (2–100 μM) and D₁-like receptors agonists increase the generation of ROS (170–172). Excessive stimulation of D₂-like receptors (e.g., D₂ and D₃ receptor) can also increase ROS production (165,173). However, D₁-like and D₂-like receptors act as antioxidants at physiologically relevant concentrations of dopamine and low concentrations of their respective agonists (12,100,109,166,168,174,175). It should also be noted that renal tubules do not normally synthesize dopamine at the high concentrations shown to induce oxidative stress (176).

Defects in dopamine receptor expression and/or function, oxidative stress, and hypertension co-exist. However, the hypertension that results from a defect in the dopamine receptor may not always be via oxidative stress. It is possible that two consequences of a defect in dopaminergic function are hypertension and oxidative stress. For example, the hypertension in GRK4γ A142V mice is not dependent on increased ROS production, possibly because of compensatory mechanisms that increase antioxidant activity, e.g., HO-1 (177). The cause of the increase in HO-1 activity is not readily apparent but could be due to increased expression or activity of other G protein-coupled receptors. Although D₁ receptor function is decreased, D₅ receptor and D₂ receptor function may not have been affected in these animals and may have been able to effectively downregulate ROS production (31).

Disruption of the D₂ receptor gene in mice results in hypertension, oxidative stress, and increased production of aldosterone. Although anti-oxidants (hemin or apocynin) normalize blood pressure in D₂^{-/-} mice, an aldosterone antagonist (spironolactone) also normalizes the blood pressure but does not normalize the expression of all the NADPH oxidase subunits or the excretion of 8-isoprostane. These studies suggest that oxidative stress need not be associated with an increase in blood pressure.

Oxidative stress can negatively regulate dopamine receptor expression and function in the kidney. Oxidative stress can then aggravate the defect in dopamine function (85). The increase in the activity of the renin-angiotensin system as a result of decreased dopamine function (157,164) can then further aggravate the hypertension and oxidative stress. In rats, the effect of oxidative stress, per se, on blood pressure is not marked unless there is an increase in sodium intake. Oxidative stress, plus a high sodium intake, results in a marked increase in blood pressure, probably as a result of an inability of dopamine, via D₁ receptors, to increase sodium excretion in response to the salt load. Increased oxidative stress leads to dopamine receptor dysfunction

Whether or not the adverse effect of oxidative stress on dopamine receptor expression and function precedes the onset of hypertension is not known. According to Banday, Lau, and Lokhandwala (85), oxidative stress in Sprague-Dawley rats on normal salt intake impairs D₁ receptor expression and function but the increase in blood pressure is modest and not different from the mild increase in blood pressure with high salt intake alone. However, oxidative stress plus a high salt intake results in a marked increase in blood pressure. These observations plus the fact that ROS production can be elevated without increasing blood pressure suggest that oxidative stress is not a prerequisite for the hypertension caused by dopamine receptor dysfunction. However, ROS may amplify downstream signaling events (178,179). Aldosterone, in concert with H₂O₂, increases NHE-1 activity by enhancing NHE-1 transcription renal proximal tubule cells from spontaneously hypertensive rats (180), akin to the increase in NF- κ B with oxidative stress (93). However, the time course of the development of hypertension and the increase in oxidative stress associated with dopamine receptor dysfunction need to be examined systematically.

In summary, dopamine plays an important role in the regulation of blood pressure by affecting renal sodium transport or by interacting with vasoactive hormones and humoral factors (5–8). In the hypertensive state, the dopamine receptor function is impaired (5–8). However, the mechanisms that impair dopamine receptor function in hypertension are not clear. Dopamine receptor function is regulated by a many factors, including GRKs, especially GRK2 and GRK4, and ROS (12–14,181). Oxidative stress, dopamine receptor defect, and hypertension can coexist and are interrelated with one another. In conditions associated with oxidative stress, e.g., hypertension, and dopamine receptor effects such as natriuresis, diuresis and vasodilation are impaired. This phenomenon can be replicated in normotensive WKY rats by treatment with oxidative reagents. Hydrogen peroxide treatment of proximal tubules from WKY rats induces an additional increase in lipid peroxidation and resulting in a loss of D₁/G protein coupling. However, co-treatment of WKY rat proximal tubules with antioxidants (e.g., apocynin, ascorbic acid, Tempol) or a reducing agent, dithiothreitol, restores the D₁ receptor/G protein coupling, suggesting that dopamine receptor function may be modulated by changes in redox states. Reactive Oxygen Species could be an attractive anti-hypertensive target.

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Figure 1.

A schematic representation of the role of oxidative stress on the D₁ receptor-G protein uncoupling in the kidney. Green and yellow lines indicate stimulatory effects, whereas the red underline indicates the uncoupling of D₁-like receptors from G protein subunits and effector proteins leading to a failure to inhibit (red arrow) Na⁺,K⁺ATPase activity. ROS, reactive oxygen species; NF-κB, nuclear factor-κB; PKC, protein kinase C; GRK2: G protein coupled receptor kinase 2.

Figure 2.

The signal pathway of D₅ receptor-mediated inhibition of reactive oxygen species in the kidney. The broken lines indicate inhibitory effects, whereas the solid lines indicate stimulatory effects; PLD: phospholipase D; PKC: protein kinase C; SOD: superoxide dismutase.