

Dopamine Receptor and Hypertension

Chunyu Zeng^{1,*}, Gilbert M. Eisner^{2,4}, Robin A. Felder⁵ and Pedro A. Jose^{2,3}

¹Department of Cardiology, Daping Hospital, The Third Military Medical University, Chongqing, P.R. China,

²Department of Pediatrics, ³Physiology and Biophysics, and ⁴Internal Medicine, Georgetown University Medical Center, Washington, DC, ⁵Department of Pathology, Virginia University for the Health Sciences, Charlottesville, VA, USA

Abstract: Dopamine plays an important role in the pathogenesis of hypertension by regulating epithelial sodium transport and reactive oxygen and by interacting with vasopressin, renin-angiotensin, and the sympathetic nervous system. Decreased renal dopamine production and/or impaired dopamine receptor function have been reported in hypertension. Disruption of any of the dopamine receptors (D₁, D₂, D₃, D₄, and D₅) results in hypertension. In this paper, we review the mechanisms by which hypertension develops when dopamine receptor function is perturbed.

Key Words: Essential hypertension, dopamine receptor, G protein-coupled receptor kinase type 4, protein phosphatase 2A, endocytosis, desensitization, sodium excretion, vasorelaxation.

INTRODUCTION

Essential hypertension affects 29% of the middle-aged adult population [1,2], thirty to 50% of essential hypertension is thought to be heritable in the United States [3,4] but the genetic cause(s) of essential hypertension has been difficult to decipher. It is likely that in any hypertensive individual, more than one effector gene is engaged in a complex network of gene-gene and gene-environment interactions [1,3-6]. However, because the kidney is a major organ involved in the long-term regulation of blood pressure and because abnormal sodium retention is a common finding in subjects with essential hypertension, many studies have focused on abnormal renal handling of sodium chloride in the pathogenesis of essential hypertension [5-9].

In nervous tissue, the catechols, dopamine, norepinephrine, and epinephrine, are synthesized from the same precursors, the amino acid tyrosine and its hydroxylated product L-3, 4-dihydroxyphenylalanine (L-DOPA) [10]. While norepinephrine and epinephrine have been shown to influence blood pressure, over the last two to three decades, the importance of dopamine in the regulation of sodium excretion and blood pressure has become recognized [1,6-10].

Abnormal sodium metabolism is frequently encountered in hypertension. Several forms of monogenic hypertension have been shown to be caused by increased sodium transport in the distal nephron [11]. About 50% of subjects with essential hypertension in United States are sodium chloride sensitive [12-14]. Sodium transport is enhanced in the renal proximal tubule and thick ascending limb of subjects with polygenetic or essential hypertension [1,6-10, 12]. All of the dopamine receptor subtypes have been shown to regulate,

directly or indirectly, renal sodium transport and blood pressure [1, 6-10]. Dopamine receptors and factors that regulate them may be novel targets for antihypertensive therapy. The goals of this review are: (i) to present experimental evidence that has led to the conclusion that dopamine is a major regulator of sodium metabolism, by itself, or by interaction with other blood-pressure-regulating systems; (ii) to present some novel aspects on dopamine signaling pathways.

DOPAMINE METABOLISM

Dopamine is synthesized not only in noradrenergic and dopaminergic nerves but also in non-neural tissues (e.g., kidney, gastrointestinal tract). In neural tissues, dopamine-synthesizing neurons contain tyrosine hydroxylase, which converts tyrosine into L-DOPA; L-DOPA is subsequently decarboxylated to dopamine by aromatic acid decarboxylase (AADC) [15-17]. The main source of dopamine in the kidney is the proximal tubule, which lacks tyrosine hydroxylase but has a high concentration of AADC. Circulating or filtered L-DOPA is transported into the renal proximal tubule via a Na⁺-independent and pH-sensitive type 2 L-type amino acid transporter (LAT2) [18]. Sodium loading causes an increase in the uptake of L-DOPA and hence the synthesis of dopamine. In addition to L-DOPA, 3-*O*-methyldopa may also serve as a precursor of dopamine in the renal proximal tubule [19]. Renal proximal tubules also do not express dopamine β-hydroxylase, and therefore, synthesized dopamine is not converted to norepinephrine [1, 10, 16].

Dopamine produced in the proximal tubule is not stored but transported both to the basolateral membrane and into the tubular lumen where it can act on receptors, locally and in more distal nephron segments. Dopamine can be deaminated to 3, 4-dihydroxyphenylacetic acid (DOPAC) by monoamine oxidases (MAO-A and MAO-B) and methylated to 3-methoxytyramine (3-MT) by catechol-*O*-methyltransferase

*Address correspondence to this author at the Department of Cardiology, Daping Hospital, The Third Military Medical University, Chongqing City, P. R. China; Tel: 011-86-23-68757246; Fax: 011-86-23-68813806; E-mail: cyzeng1@hotmail.com

(COMT) in renal tubule cells. COMT methylates DOPAC while MAO converts 3-MT to homovanillic acid (HVA). MAO-A is more important than MAO-B for deamination of renal dopamine [20,21]. In the intact kidney, COMT appears to play an important role in the physiological regulation of renal dopamine production. Inhibition of COMT leads to a profound dopamine-dependent natriuresis [22,23]. In contrast, MAO inhibition has little effect on urinary sodium excretion [16].

DOPAMINE RECEPTOR INTRACELLULAR MESSENGERS

Dopamine Receptors and G Proteins

The effects of dopamine are exerted by cell surface receptors that belong to the rhodopsin-like family (Family A) [1,6-10]. These receptors are characterized by having seven transmembrane domains and linkage to heterotrimeric G proteins, composed of α , β , and γ subunits [24,25]. Five mammalian dopamine receptors have been cloned since the first dopamine receptor, the D_2 receptor, was cloned in 1988 [26]. Dopamine receptors are classified into D_1 - and D_2 -like subtypes based on their structure and pharmacology [1,6-10, 27].

The two D_1 -like dopamine receptors, D_1 and D_5 , are coupled to the stimulatory G subunit, G_s , while the three D_2 -like receptors, D_2 , D_3 , and D_4 , are coupled to the inhibitory G subunit, G_i ; G_s is stimulatory while G_i is inhibitory of adenylyl cyclase activity [1,6-10]. D_1 and D_5 receptors can also couple to members of the G-family other than G_s [25,27-30]. The D_1 receptor, but not the D_5 receptor, also couples to G_q , and stimulates phospholipase C, in the presence of the adaptor protein, calycon [31-34]. G_{12} and G_{13} , members of the 4th family of G protein subunits, are linked to D_5 and D_3 receptors [35,36], but not to D_1 receptors. G_{12} may also modulate the effects of D_1 -like receptor [37], although the exact D_1 -like receptor involved has not been determined.

Dopamine Receptors and Protein Kinase A and C

The classic signaling pathway for the D_1 -like receptors begins by activation of adenylyl cyclase, resulting in an increase in cAMP levels, and activation of PKA. PKA, in turn, causes phosphorylation and inhibition of NHE3 and Na^+ - K^+ -ATPase [1,6-9]. PKA is also involved in the D_1 -like receptor inhibition of Cl^-/HCO_3^- exchanger, Na^+/HCO_3^- and Na^+/Pi cotransporters. However, cAMP-independent regulation of NHE3 and Na^+/Pi cotransporter has been reported [29, 38]. Thus, the D_1 receptor can regulate NHE3 activity via G_s and G_q in luminal membranes of renal proximal tubules [37,39].

In neural tissue and renal thick ascending limb of Henle [16, 17] but not in renal proximal tubules [40], D_1 -like receptors, via PKA, activate dopamine- and cAMP-regulated phosphoprotein (DARPP-32), inhibit protein phosphatase 1 (PP1) activity and keep Na^+ - K^+ -ATPase in its phosphorylated (inactive) state. Phosphorylated DARPP32 is a potent inhibitor of protein phosphatase 1A, which is dephosphorylated and inactivated by the calcium-dependent protein phosphatase calcineurin [16,41].

Another signaling pathway of the D_1 receptor involves activation of phospholipase C (PLC), in the presence of the adaptor protein, calycon [42], resulting in the production of inositol phosphates and diacylglycerol, which activates protein kinase C (PKC) [43,44]. In the kidney, D_1 receptors stimulate the β isoform of PLC [45]. D_1 receptors can stimulate PKC- β [44], PKC- δ [46], inhibit PKC- α [44], as well as translocate specific PKC isoforms. Thus, D_1 receptors translocate PKC β , δ , and α from cytosol into membranes and PKC β from membranes to cytosol [47,48]. Long-term (hours) stimulation of D_1 receptors also inhibits PKC β [44]. Activation of the D_1 receptor stimulates phosphatidylinositol 3-kinase activity and inhibits Na^+ - K^+ ATPase activity, via the diacylglycerol/PKC pathway, PKC β can phosphorylate the Na^+ - K^+ ATPase α -subunit in cell-free preparations [49,50]. The effects of D_2 -like receptors, independently of D_1 -like receptor, on Na^+ - K^+ ATPase activities are not consistent; some have reported that the D_2 receptor can activate phosphatidylinositol 3-kinase, which subsequently inhibits Na^+ - K^+ ATPase activity [51], while others have reported opposite results [1,9,10,52,53]. However, our studies and those of others have shown that D_2 -like receptors synergistically act with D_1 -like receptors to increase urinary sodium excretion, in part, by inhibition of Na^+ - K^+ ATPase activity [52].

The physiological effects that follow activation of D_1 receptors in renal proximal tubule are also mediated by phospholipase A2 and subsequent release of arachidonic acid and its metabolites [54]. It is suggested that this pathway is initiated by D_1 -dependent PKA phosphorylation of phospholipase A2; PKC-mediated activation of phospholipase A2 has also been suggested [55]. The predominant arachidonic acid metabolite in the mature kidney is the CYP 450 product 20-HETE, which has a direct inhibitory effect on Na^+ - K^+ ATPase [56,57]. This pathway has been implicated in the D_1 receptor-mediated inhibition of Na^+ - K^+ ATPase activity in proximal tubular cells [49].

PHYSIOLOGIC ROLE OF PERIPHERAL DOPAMINE RECEPTORS

Natriuretic and Diuretic Effects of Dopamine Receptor Activation

Endogenous renal dopamine is a major physiological regulator of renal sodium excretion. During conditions of moderate sodium balance, more than 50% of renal sodium excretion is regulated by D_1 -like receptors [1,6-9]. The natriuretic effect of intrarenal dopamine was initially observed with the administration of the dopamine prodrug gludopa. Gludopa is converted to L-DOPA by γ -glutamyl transpeptidase expressed in the renal brush border membrane; L-DOPA is then converted to dopamine by AADC [58,59]. The D_1 receptor increases cAMP production to a greater extent than the D_5 receptor in renal proximal tubule cells, [60]. It is possible that the natriuretic effect of dopamine is due mainly to the D_1 receptor.

D_2 -like receptors may also act, synergistically, with D_1 -like receptors to increase urinary sodium excretion [52,61]. We have reported that the increase in sodium excretion induced by Z-1046, a dopamine receptor agonist with a rank

order potency $D_4 > D_3 > D_2 > D_5 > D_1$, was blocked by either a D_1 -like or D_2 -like receptor antagonist. D_2 -like receptors may potentiate the inhibitory effect of D_1 -like receptors on Na^+ -Pi co-transport, NHE3, and Na^+ - K^+ ATPase activities in renal proximal tubules [62-64]. Because the major D_2 -like receptor in the renal proximal tubule is the D_3 receptor, we surmised that the dopamine receptors interacting in the proximal tubule to inhibit sodium transport are the D_1 and the D_3 receptors. Indeed, we have found that the D_1 and D_3 receptor can increase each other's expression [63]. We have also reported that D_3 receptor null mice develop hypertension and have an impaired ability to excrete an acute sodium load [65]. Moreover, two different D_3 receptor agonists (7-OH-DPAT and PD128907) produce a natriuresis and a diuresis in anesthetized rats [36,66]. Chronic blockade of D_3 receptors with a D_3 receptor antagonist, BSF 135170, for 29 days induces salt-sensitive hypertension in Dahl salt-resistant rat also supports this D_1/D_3 receptor interaction [66].

The Effect of Dopamine Receptor Activation on Resistance Vessels

Dopamine, at low concentrations, dilates resistance arteries via D_1 -like receptors [1,6-9]. However, the effect of D_3 receptors on arterial vascular tone is not consistent. A D_3 receptor agonist, quinpirole, has been reported not to have any relaxant effect on mesenteric arteries [67]. Another D_3 receptor agonist, pramipexole, decreases vascular resistance, although part of the effect could be accounted for by an interaction with the D_1 receptor [68]. In anesthetized rats, the systemic infusion of 7-OH-DPAT, another D_3 receptor agonist, has been shown to constrict postglomerular vessels [69]. Although the reason for these apparent discrepancies is not clear, the effect of D_2 -like receptors on vascular tone may vary depending upon the resting tone and the arterial segment being studied [10]. For example, a D_1 receptor agonist increases the vascular tone of the rat-tail artery [70]; in all other vessels, including the renal artery, D_1 receptors are vasodilatory [71]. Pre-junctional D_2 -like receptors are vasodilatory, while post-junctional D_2 -like receptors can induce vasoconstriction when resting vascular tone is low and vasodilation when resting vascular tone is high [10].

The simultaneous stimulation of D_1 and D_3 receptors causes a vasorelaxation that is additive rather than synergistic [67,72]. This may indicate that D_1 and D_3 receptors induce vasorelaxation by different mechanisms. We have found that the vasorelaxant effects of fenoldopam and PD128907 are enhanced by calcium channel blockade with nifedipine. The vasodilatory effect of D_3 receptors may also involve potassium channels (small- and/or large-conductance calcium activated potassium) [67,72].

IMPAIRED DOPAMINE RECEPTOR FUNCTION IN HYPERTENSION

Several pieces of evidence support the notion that abnormalities of dopamine function play important roles in the pathogenesis of hypertension. For example, salt-loaded WKY rats develop hypertension when dopamine receptors are blocked by a non-selective dopamine antagonist [73]; inhibition of dopamine synthesis outside the central nervous

system accelerates the development of hypertension in spontaneously hypertensive rats (SHRs) [74]. Chronic administration of the long-acting D_1 receptor antagonist, ecopipam, also increases blood pressure in humans [75]. Moreover, D_1 receptor gene polymorphism A-48G is associated with essential hypertension [76].

Decreased renal synthesis of dopamine may be involved in the pathogenesis of hypertension (not classified according to sensitivity to salt) in some human subjects [77]. Some salt-sensitive subjects, with or without hypertension, do not increase renal dopamine production in response to a NaCl or protein load [74-82]. However, a decreased renal production of dopamine does not explain the impaired function of endogenous dopamine in many cases of essential hypertension. Urinary dopamine and dopamine metabolites are actually increased in young patients with essential hypertension [83,84].

The urinary excretion of dopamine is not decreased in the SHR or in the Dahl salt-sensitive rat, compared with their normotensive controls [85-87]. Increasing renal dopamine production in the SHR does not enhance the ability of D_1 -like agonists to inhibit renal cortical NHE3 activity or sodium excretion to the degree seen in WKY rats [88]. In both SHR and Dahl salt-sensitive rats, dopamine and D_1 -like receptor agonist-mediated natriuretic and diuretic responses are impaired [1,6-9]. The ability of fenoldopam, a D_1 -like agonist, to inhibit renal proximal (but not distal) tubular sodium reabsorption is also impaired in salt sensitive hypertensive humans [89]. In humans with essential hypertension and rodents with genetic hypertension (SHR and Dahl salt sensitive rat), the ability of the renal proximal tubule and thick ascending limb of Henle [90,91] but not the cortical collecting duct [92] to increase cAMP production in response to D_1 -like receptor stimulation is impaired. There is also an impaired D_1 -like receptor inhibition of NHE3, Cl^-/HCO_3^- exchanger, Na^+/HCO_3^- co-transporter and Na^+ - K^+ ATPase activities in genetic hypertension. The impaired D_1 -like receptor function in hypertension is not caused by abnormalities in G proteins, effector, or ion transporting proteins, such as adenylyl cyclase, NHE3 or Na^+ - K^+ ATPase [1,6-9]. Rather, the renal D_1 -like receptor is uncoupled from G protein subunits, leading to decreased D_1 -like receptor interaction with G protein subunits, resulting in decreased production of second messengers and decreased interaction between G protein subunits, ion transporters such as [93,94]. The D_1 -like receptor function in hypertension is receptor specific, because parathyroid hormone and cholecystokinin action is intact. There is organ specificity because D_1 receptor action in the brain striatum is also intact. The impaired D_1 -like receptor function is probably of genetic origin, because it precedes the onset of hypertension and co-segregates with high blood pressure [1,6,9,10].

These abnormalities, first demonstrated in genetically hypertensive rats, appear to be present in a subset of human subjects with hypertension. Although total D_1 receptor expression is not different between renal proximal tubule cells from normotensive humans and humans with essential hypertension and from WKY and SHRs [95,96], D_1 receptor cell surface expression is lower in hypertensives than in normotensives. The degree of D_1 receptor phosphorylation in

renal proximal tubule cells is also greater in hypertensive humans and rats suggesting that the D₁ receptor is desensitized in the hypertensive state [87,97]. Under normal conditions the initial process of G protein-coupled receptor (GPCR) desensitization is caused by the phosphorylation or some other action by G protein related kinases (GRKs) [1,98,99]. GRKs are serine and threonine kinases that phosphorylate GPCRs, including the D₁ receptor, in response to agonist stimulation. The binding of phosphorylated or modified D₁ receptor to arrestin and other adaptor proteins results in uncoupling from its G-protein complex, and leads to a decrease in function [1,99]. The modified/phosphorylated D₁ receptor and arrestin/adaptor protein complex undergo internalization via clathrin-coated pits [100, 101]. The internalized D₁ receptor is transported into a sorting endosome and subsequently to a recycling endosome where the D₁ receptor is dephosphorylated by protein phosphatases and recycled back to the plasma membrane. The sorting of modified GPCRs to lysosomes or proteasomes results in their degradation. The sorting protein for the D₁ receptor remains to be determined; synexin 1 may be the sorting protein for D₅ receptor degradation [102]. Ubiquitination of β -arrestin results in the internalization of the α_2 adrenergic receptor, while of the α_2 adrenergic receptor ubiquitination results in its degradation [103]. There may be similarities in the trafficking between the D₁ and the α_2 adrenergic receptor because they belong to Class A GPCRs, which bind to β 2-arrestin2 with higher affinity than β 2-arrestin1 and do not interact with visual arrestin [104]. It should be noted, however, that desensitization of the D₁ receptor may not always correlate with phosphorylation and internalization may not be necessary for resensitization [99,105].

The notion that GRKs are important in the impaired renal D₁-like receptor function is supported by studies showing that inhibition of GRK activity (by heparin) in human renal proximal tubule cells from hypertensive subjects normalizes D₁ receptor function [106]. There are seven members of the GRK4 family. GRKs 1 and 7 belong to the rhodopsin family, GRKs 2 and 3 belong to the β -adrenergic receptor kinase family, and GRKs 4, 5 and 6 belong to the GRK4 family [1]. We have reported that GRK4 plays a more important role than GRK2 in the desensitization of the human D₁ receptors in renal proximal tubules [107,108]. However, the first 20 minutes of homologous desensitization of the human D₁ receptor is GRK independent, the mechanism of which remains to be determined. In the early and late stages of desensitization, sucrose, which prevents endocytosis [109,110], has no effect on total GRK expression, but prevents the desensitization of the D₁ receptor response [unpublished data]. These data indicate that the desensitization of the D₁ dopamine receptor appears to involve the formation of endocytic vesicles and GRK-dependent and -independent mechanisms in human proximal tubule cells. This pathway, however, may be different in other cells, indicating cell or tissue-specific D₁ receptor desensitization [41,111].

In human embryonic kidney cells (HEK-293), GRK2, GRK3, and GRK5 are involved in the desensitization of the D₁ receptor [99]. In SHR, however, the increases in GRK

activity and expression (GRK2 and GRK5) follow rather than precede the hypertensive process [112]. The limited expression of GRK4 and the fact that the GRK4 gene locus (chromosome 4p16.3) is linked to hypertension make GRK4 an attractive candidate for a pathogenetic mechanism in human hypertension [113]. Moreover, GRK4 variants (R65L, A142V, A486V), by themselves, or in association with genes that regulate the renin-angiotensin system, are associated with hypertension [114-116]. However, there are at least four isoforms of GRK4 (, , ,) [117-119]. We found that GRK4 variants impair D₁ receptor function in renal proximal tubule cells; GRK4 variants co-expressed with the human D₁ receptor in Chinese hamster ovary (CHO) cells replicate the D₁ receptor defect noted in renal proximal tubules [94]. Inhibition of GRK4 function or expression normalizes D₁ receptor function in CHO cells expressing GRK4 variants and in renal proximal tubule cells from humans with essential hypertension [94,119,120]. Over-expression of GRK4A142V variant in mice produces hypertension and impairs the natriuretic but not the acute vasodepressor effect of D₁ receptors, similar to that found in humans with essential hypertension [94]. Over-expression of GRK4 R65L and A486V in mice also produces hypertension. However, GRK4 A486V transgenic mice develop hypertension only after being fed high NaCl diet [121].

As stated above, dephosphorylation of GPCRs results in restoration of potential function. We also found that the diminished responsiveness of D₁ receptor in renal proximal tubules from SHR is associated with decreased activation of protein phosphatase 2A, that may be the result of a decreased recruitment of its regulatory subunit, B56 in cell surface membrane [122, 123].

As mentioned, the natriuretic effect of dopamine may be the result of a synergistic action between D₁ receptor and D₃ receptors [52,58, 62-64]. This effect is seen in WKY rats but not in SHR [97,124,125]. Intrarenal artery infusion of D₃ receptor agonist increases sodium excretion in WKY rats, not in SHR [36]. Although it is not clear whether the D₃ receptor impairment in genetic hypertension is secondary or independent of D₁ receptors, we have found that D₃ receptor mRNA and protein expression are lower in cortical membrane of kidney and renal proximal tubule in SHR. In addition, the physical interaction between D₁ and D₃ receptors in renal proximal tubules is decreased in SHR compared with WKY rats [97,124,125].

In general, the renal and non-renal vasodilatory effects of D₁-like receptors in hypertension are not impaired [89,126]. There are, however, reports of impaired renal vasodilatory effect of D₁-like receptor agonist in humans with essential hypertension [127] and in SHR [93,128]. Indeed, the ability of D₁-like receptors in renal arteries of SHR to stimulate adenylyl cyclase is impaired [93]. D₃ agonist-induced vasorelaxation is similar in WKY and SHR except at the highest concentrations. In contrast, the mesenteric arteries from SHR are less sensitive and less reactive than WKY rats to the vasorelaxant effect of a D₁-like agonist. Whereas pretreatment of mesenteric arteries with PD128907 enhances the vasorelaxant effect of fenoldopam in WKY rats, no additional vasorelaxant effect is noted in SHR [67, 72].

These data are reminiscent of the absence of an additive natriuretic effect of D₁ and D₃ receptors in SHR [124].

INTERACTION WITH OTHER SYSTEMS

Interaction with the Renin-angiotensin-aldosterone System

Dopamine and angiotensin II are two important regulators of sodium and water transport in the kidney serving counteracting functions, via the D₁-like and AT₁ receptors, respectively. AT₁ receptors stimulate all proximal tubular ion-transporting-proteins that are inhibited by D₁-like receptors [64, 88, 90, 129, 130]. The natriuretic effect of D₁-like receptors is enhanced when angiotensin II production is decreased or when AT₁ receptors are blocked [131,132]. The renal vasoconstrictive effect of angiotensin II can also be antagonized by D₁-like receptor agonists [10, 93]. D₁ receptors stimulate renin production and thus, may counteract the blood pressure-lowering effect of D₁ receptors working via renal sodium transport inhibition, while D₃ receptors inhibit renin secretion [65,133,134]. D₁-like and AT₁ receptors have opposing effects on the generation of second messengers and PKC isoforms [135,136]. In addition, dopamine, via D₁-like and D₃ receptors, also decreases AT₁ receptor expression and angiotensin II binding sites in renal proximal tubule cells from normotensive WKY rats [131,137,138].

Dopamine may modulate the secretion of aldosterone secretion [139-142]. The effects of dopamine on aldosterone secretion depends on the sodium balance state. Dopamine, which has no significant effects on angiotensin II -induced aldosterone secretion in sodium-replete subjects, inhibits the hormonal response to angiotensin II infusion in sodium-depleted normal subjects [139-141]. Metoclopramide, a non-selective antagonist for D₂-like receptors, increases both basal plasma aldosterone levels and the aldosterone response to angiotensin II in rats and humans on a high sodium intake [141,142]. Dihydroergotamine, a non-selective D₂-like agonist, suppresses the aldosterone secretion induced by sodium depletion in hypertensive patients, an effect blocked by a non-selective D₂-like antagonist, sulpiride [143]. In contrast, in rats on a high K⁺ or low Na⁺ diet, D₂-like receptors facilitate aldosterone effects [144]. Subsequent studies have shown that D₂ receptors mediate the inhibitory effect while D₄ receptors mediate the stimulatory effect of dopamine on aldosterone secretion [145]. This dual effect of dopamine receptors could be used to modulate aldosterone secretion and aldosterone effects in the treatment of hypertension.

Interaction with the Sympathetic Nervous System

The D₂ receptor mutant mouse develops hypertension, in part, due to increased vasoconstrictive activity of the sympathetic nervous system [146]. Moreover, the increased blood pressure in D₂, D₄ and D₅ receptor-deficient mice may involve the central nervous system [146-148]. Abnormal function of central nervous D₂-like receptors in human essential hypertension has been documented both in SHR and human subjects with essential hypertension [149,150]. Similar to the negative interaction between AT₁ and D₁-like receptors, D₁-like receptors and adrenergic receptors have

opposite effects on vascular smooth muscles and sodium transport [49]. In OK cells, the dopamine regulation of the proximal sodium phosphate transporter is potentiated by treatment with α -adrenergic receptor antagonists [151].

Interaction with Reactive Oxygen Species (ROS)

Many physiological and pathological conditions, such as aging and hypertension, have been ascribed to ROS. ROS include singlet oxygen, superoxide, hydrogen peroxide, hydroxyl radical and hypochlorous acid [152]. Dopamine has different effects on ROS depending on dopamine concentrations, at low concentration <500 μ M, decreases ROS formation; in contrast, at concentrations more than 1mM, dopamine even acts as a pro-oxidant [153]. The low concentration may reflect the real physiological function of dopamine in kidney, for concentrations in non-neural tissues are low μ M or high nM. In nerve cells, where dopamine is produced in higher concentrations, oxidation of dopamine is prevented when stored in synaptic vesicles [154]. Besides the direct action of dopamine on ROS, the production of ROS can also be enhanced by the oxidation of dopamine or generated by enzymes that degrade dopamine [155].

D₅ receptors have antioxidant functions. Phospholipase D expression, specifically, PLD₂, is increased in the kidney of D₅ receptor deficient mice. D₅ receptors expressed in HEK-293 cells inhibit, an enzyme that produces phosphatidic acid [156]. Phosphatidic acid activates NADPH oxidase; a major enzyme involved in the production of ROS in vascular smooth muscle and renal proximal tubule cells [157,158]. A variant of D₅ receptor gene (D5F173L), which cannot stimulate adenylyl cyclase, increases formation of ROS [156]. The deficiency of D₅ receptors in mice, which increases blood pressure, is associated with increased expression and activity of phospholipase D and NADPH oxidase in brain and kidney [159]. A superoxide dismutase mimetic, Tempol, decreases blood pressure in D₅ receptor deficient but not in wild-type mice [159]. Impaired antioxidant function of D₁-like receptors has been demonstrated in vascular smooth muscles of SHR [160]. However, increased ROS activity in the SHR has been reported to derive from nitric oxide synthase rather than the other sources of ROS, e.g., NADPH oxidase [161,162]. Therefore, oxidative stress may be an important pro-hypertensive mechanism that enforces the maintenance of a high blood pressure initiated by other primary processes.

Dopamine Interaction with Atrial Natriuretic Peptide (ANP)

Both ANP and dopamine have natriuretic effects; some data show that the natriuretic effect of ANP requires the presence of dopamine receptors [163-166]. Furthermore, the inhibitory effect of dopamine on the NHE3 in the proximal tubule is potentiated by ANP [162]. The above-mentioned phenomenon is ascribed to the ability of ANP to recruit intracellularly located D₁ receptors to the plasma membrane.

Dopamine Interaction with Nitric Oxide

Dopamine and nitric oxide have similar effects in kidney [167]. Both of them are vasodilators, both are synthesized in

renal proximal tubule cells and both inhibit $\text{Na}^+\text{-K}^+\text{ATPase}$ and NHE3 activities [1,6-10,168,169]. Abnormalities of nitric oxide synthesis and degradation have also been implicated in hypertension [171]. Stimulation of the nitric oxide system increases D_1 receptor expression. Nitric oxide may be involved in the stimulation of urinary dopamine excretion and vice versa, phenomena well described in neurons [166-172]. Nitric oxide can also increase D_1 receptor expression [171]. D_2 -like receptor blockade enhances the increase in sodium reabsorption when nitric oxide synthesis is inhibited [173].

Dopamine Interaction with Endothelin B (ETB) Receptor

The ETB receptor and dopamine receptors can interact to regulate renal function and blood pressure. In D_2 receptor null mice with hypertension, ETB receptor expression is greater than in control mice [146]. An ETB receptor blocker for both ETB_1 and ETB_2 receptors decreases, whereas a selective ETB_1 blocker increases blood pressure in D_2 receptor null mice but not in control mice, indicating ETB receptor, at least in part, is involved in the pathophysiology of hypertension of D_2 receptor null mice.

Dopamine Interaction with Prostaglandins

Prostaglandin E2, produced in the collecting duct, has a diuretic and natriuretic effect. The natriuretic effect may be accomplished by inhibition of several sodium transporters, including $\text{Na}^+\text{-K}^+\text{ATPase}$. Dopamine, probably via D_2 receptor, increases the production of prostaglandin E2 in rat inner medullary collecting duct cells; phospholipase A2 takes part in signal pathway of this action [16,174,175].

Dopamine Interaction with Arginine Vasopressin

Vasopressin has been implicated in the pathogenesis of essential hypertension. Water permeability of the collecting ducts is bidirectionally regulated; the increase in water permeation due to arginine vasopressin can be opposed by several hormonal factors, including dopamine [176]. D_2 -like receptors are expressed in the collecting duct, and a D_2 -like receptor (most likely a D_4 receptor) inhibits arginine vasopressin-dependent sodium and water transport and osmotic water permeability in isolated perfused rat cortical collecting ducts [177, 178]. Moreover, dopamine also inhibits aquaporin-4, an aquaporin that plays an important role in the basolateral movement of water in the collecting duct [179].

Both D_1 receptors and D_2 -like receptors have been reported to increase vasopressin secretion [180-182]. However, at low concentrations, D_1 -like receptors inhibit vasopressin secretion *in vitro* [181]. Because dopamine has a higher affinity for D_5 than D_1 receptors [183], it is possible that the D_1 -like receptor inhibition of vasopressin release is mediated by the D_5 receptor.

In summary, there is clear evidence that dopamine is an important modulator of renal function and blood pressure. Impairment of renal dopamine production or receptor function and interaction with other blood pressure-regulating systems contribute to various forms of hypertension in both

humans and animal models. If, as it appears, that abnormalities of the dopamine system are major causes of idiopathic (hereditary) hypertension, early detection of these abnormalities might allow utilization of strategies not simply to treat but to prevent the development of hypertension.

ACKNOWLEDGEMENT

These studies were supported in part by grants from the National Institutes of Health, HL 23081, DK 39308, HL68686, DK52612, HL41618, and National Natural Science Foundation of China 30470728.

REFERENCES

- [1] Jose, P.A.; Eisner, G.M.; Felder, R.A. *Nephron. Physiol.*, **2003**, *95*, 19.
- [2] Hajjar, I.; Kotchen, T.A. *JAMA*, **2003**, *290*, 199.
- [3] Ward, R. In *Hypertension: Pathophysiology, Diagnosis and Management*, Laragh, J.H.; Brenner, B.M. Eds., Raven Press: New York, 2nd edition, **1995**; pp. 67-88.
- [4] Hunt, S.C. In *Hypertension Primer*. Izzo, J.L.Jr.; Black, H.R. Eds.; Lippincott Williams & Wilkins: Philadelphia, **2003**, pp. 218-221.
- [5] Hall, J.E.; Brands, M.W.; Henegar, J.R. *J. Am. Soc. Nephrol.*, **1999**, *10*(suppl. 12), 258.
- [6] Jose, P.A.; Eisner, G.M.; Drago, J.; Carey, R.M.; Felder, R.A. *Am. J. Hypertens.*, **1996**, *9*, 400.
- [7] Hussain, T.; Lokhandwala, M.F. *Hypertension*, **1998**, *32*, 187.
- [8] Carey, R.M. *Hypertension*, **2001**, *38*, 297.
- [9] Jose, P.A.; Eisner, G.M.; Felder, R.A. *Curr. Hypertens. Rep.*, **2002**, *4*, 237.
- [10] Jose, P.A.; Eisner, G.M.; Felder, R.A. *Pharmacol. Ther.*, **1998**, *80*, 149.
- [11] Lifton, R.P.; Wilson, F.H.; Choate, K.A.; Geller, D.S. *Cold Spring. Harb. Symp. Quant. Biol.*, **2002**, *67*, 445.
- [12] Aviv, A.; Hollenberg, N.K.; Weder, A. *Hypertension*, **2004**, *43*, 707.
- [13] Weinberger, M.H. *Hypertension*, **1996**, *27*, 481.
- [14] Weinberger, M.H.; Fineberg, N.S.; Fineberg, S.E.; Weinberger, M. *Hypertension*, **2001**, *37*, 429.
- [15] Vieira-Coelho, M.A.; Gomes, P.; Serrao, M.P.; Soares-da-Silva, P. *Clin. Exp. Hypertens.*, **1997**, *19*, 43.
- [16] Aperia, A.C. *Annu. Rev. Physiol.*, **2000**, *62*, 621.
- [17] Soares-da-Silva, P.; Fernandes, M.H.; Pinto-do-O, P.C. *Br. J. Pharmacol.*, **1994**, *112*, 611.
- [18] Pinho, M.J.; Serrao, M.P.; Gomes, P.; Hopfer, U.; Jose, P.A.; Soares-da-Silva, P. *Kidney Int.*, **2004**, *66*, 216.
- [19] Ibarra, F.R.; Aguirre, J.; Nowicki, S.; Barontini, M.; Arrizurieta, E.E.; Armando, I. *Am. J. Physiol.*, **1996**, *270*, F862.
- [20] Pestana, M.; Soares-da-Silva, P. *Br. J. Pharmacol.*, **1994**, *113*, 1269.
- [21] Guimaraes, J.T.; Soares-da-Silva, P. *Life Sci.*, **1998**, *62*, 727.
- [22] Eklöf, A.C.; Holtbäck, U.; Sundelöf, M.; Chen, S.; Aperia, A. *Kidney Int.*, **1997**, *52*, 742.
- [23] Hansell, P.; Odlind, C.; Mannisto, P.T. *Acta. Physiol. Scand.*, **1998**, *162*, 489.
- [24] Gether, U. *Endocr. Rev.*, **2000**, *21*, 90.
- [25] Ho, M.K.; Yung, L.Y.; Chan, J.S.; Chan, J.H.; Wong, C.S.; Wong, Y.H. *Br. J. Pharmacol.*, **2001**, *132*, 1431.
- [26] Bunzow, J.R.; Van, Tol, H.H.; Grandy, D.K.; Albert, P.; Salon, J.; Christie, M.; Machida, C.A.; Neve, K.A.; Civelli, O. *Nature*, **1988**, *336*, 783.
- [27] Sibley, D.R. *Annu. Rev. Pharmacol. Toxicol.*, **1999**, *39*, 313.
- [28] Uh, M.; White, B.H.; Sidhu, A. *J. Hypertens.*, **1998**, *16*, 1307.
- [29] Albrecht, F.E.; Xu, J.; Moe, O.W.; Hopfer, U.; Simonds, W.F.; Orłowski, J.; Jose, P.A. *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, **2000**, *278*, R1064.
- [30] Jose, P.A.; Eisner, G.M.; Felder, R.A. *Curr. Opin. Nephrol. Hypertens.*, **2003**, *12*, 189.
- [31] Felder, C.C.; Jose, P.A.; Axelrod, J. *J. Pharmacol. Exp. Ther.*, **1989**, *248*, 171.
- [32] Bertorello, A.; Aperia, A. *Am. J. Physiol.*, **1989**, *256*, F370.

- [33] Hussain, T.; Lokhandwala, M.F. *Am. J. Physiol.*, **1997**, *272*, F339.
- [34] Lezcano, N.; Mrzljak, L.; Eubanks, S.; Levenson, R.; Goldman-Rakic, P.; Bergson, C. *Science*, **2000**, *287*, 1660.
- [35] Zheng, S.; Yu, P.; Zeng, C.; Wang, Z.; Yang, Z.; Andrews, P.M.; Felder, R.A.; Jose, P.A. *Hypertension*, **2003**, *41*, 604.
- [36] Zeng, C.; Asico, L.D.; Zheng, S.; Hopfer, U.; Eisner, G.M.; Felder, R.A.; Jose, P.A. *Am. J. Hypertens.*, **2004**, *17*, 96A (abstract).
- [37] Li, X.X.; Albrecht, F.E.; Robillard, J.E.; Eisner, G.M.; Jose, P.A. *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, **2000**, *278*, R931.
- [38] Baines, A.D.; Drangova, R. *J. Am. Soc. Nephrol.*, **1998**, *9*, 1604.
- [39] Albrecht, F.E.; Xu, J.; Moe, O.W.; Hopfer, U.; Simonds, W.F.; Orłowski, J.; Jose, P.A. *Am. J. Hypertens.*, **1998**, *11*, 156A (abstract).
- [40] Slobodyansky, E.; Aoki, Y.; Gaznabi, A.K.; Aviles, D.H.; Fildes, R.D.; Jose, P.A. *Am. J. Physiol.*, **1995**, *268*, F279.
- [41] Hemmings, H.C.Jr.; Greengard, P.; Tung, H.Y.; Cohen, P. *Nature*, **1984**, *310*, 503.
- [42] Tang, T.S.; Bezprozvanny, I. *J. Biol. Chem.*, **2004**, Aug 2 [Epub ahead of print].
- [43] Felder, C.C.; Blecher, M.; Jose, P.A. *J. Biol. Chem.*, **1989**, *264*, 8739.
- [44] Yao, L.P.; Li, X.X.; Yu, P.Y.; Xu, J.; Asico, L.D.; Jose, P.A. *Hypertension*, **1998**, *32*, 1049.
- [45] Yu, P.Y.; Asico, L.D.; Eisner, G.M.; Jose, P.A. *J. Clin. Invest.*, **1995**, *95*, 304.
- [46] Efendiev, R.; Bertorello, A.M.; Pedemonte, C.H. *FEBS Lett.*, **1999**, *456*, 45.
- [47] Asghar, M.; Hussain, T.; Lokhandwala, M.F. *Am. J. Physiol. Renal. Physiol.*, **2003**, *285*, F1100.
- [48] Nowicki, S.; Kruse, M.S.; Brismar, H.; Aperia, A. *Am. J. Physiol. Cell. Physiol.*, **2000**, *279*, C1812.
- [49] Chibalin, A.V.; Ogomoto, G.; Pedemonte, C.H.; Pressley, T.A.; Katz, A.I.; Feraille, E.; Berggren, P.O.; Bertorello, A.M. *J. Biol. Chem.*, **1999**, *274*, 1920.
- [50] Feschenko, M.S.; Stevenson, E.; Sweadner, K.J. *J. Biol. Chem.*, **2000**, *275*, 34693.
- [51] Nair, V.D.; Sealfon, S.C. *J. Biol. Chem.*, **2003**, *278*, 47053.
- [52] Jose, P.A.; Asico, L.D.; Eisner, G.M.; Pocchiari, F.; Semeraro, C.; Felder, R.A. *Am. J. Physiol.*, **1998**, *275*, R986.
- [53] Hussain, T.; Abdul-Wahab, R.; Lokhandwala, M.F. *Eur. J. Pharmacol.*, **1997**, *321*, 259.
- [54] Satoh, T.; Cohen, H.T.; Katz, A.I. *J. Clin. Invest.*, **1993**, *91*, 409.
- [55] Hussain, T.; Lokhandwala, M.F. *Clin. Exp. Hypertens.*, **1997**, *19*, 131.
- [56] Lin, F.; Abraham, N.G.; Schwartzman, M.L. *Ann. NY Acad. Sci.*, **1994**, *744*, 11.
- [57] Nowicki, S.; Chen, S.L.; Aizman, O.; Cheng, X.J.; Li, D.; Nowicki, C.; Nairn, A.; Greengard, P.; Aperia, A. *J. Clin. Invest.*, **1997**, *99*, 1224.
- [58] Lee, M.R. *Clin. Sci.*, **1993**, *84*, 357.
- [59] Wilk, S.; Mizoguchi, H.; Orłowski, M. *J. Pharmacol. Exp. Ther.*, **1978**, *206*, 227.
- [60] Sanada, H.; Xu, J.; Watanabe, H.; Jose, P.A.; Felder, R.A. *Am. J. Hypertens.*, **2000**, *13*, 156A (abstract).
- [61] Eklof, A.C. *Acta Physiol. Scand.*, **1997**, *160*, 311.
- [62] Bertorello, A.M.; Hopfeld, J.F.; Aperia, A.; Greengard, P. *Nature*, **1990**, *347*, 386.
- [63] Perrichot, R.; Garciaocana, A.; Couette, S.; Comoy, E.; Amiel, C.; Friedlander, G. *Biochem. J.*, **1995**, *312*, 433.
- [64] Sheikh-Hamad, D.; Wang, Y.P.; Jo, O.D.; Yanagawa, N. *Am. J. Physiol.*, **1993**, *264*, F737.
- [65] Asico, L.D.; Ladines, C.; Fuchs, S.; Accili, D.; Carey, R.M.; Semeraro, C.; Pocchiari, F.; Felder, R.A.; Eisner, G.M.; Jose, P.A. *J. Clin. Invest.*, **1998**, *102*, 493.
- [66] Luippold, G.; Zimmermann, C.; Mai, M.; Kloor, D.; Starck, D.; Gross, G.; Muhlbauer, B. *J. Am. Soc. Nephrol.*, **2001**, *12*, 2272.
- [67] Zeng, C.; Wang, D.; Yang, Z.; Wang, Z.; Asico, L.D.; Wilcox, C.S.; Eisner, G.M.; Welch, W.J.; Felder, R.A.; Jose, P.A. *Hypertension*, **2004**, *43*, 654.
- [68] Kaneko, S.; Eisner, G.M.; Jose, P.A. *J. Auton. Pharmacol.*, **1990**, *10* (Suppl. 1), S53.
- [69] Muhlbauer, B.; Kuster, E.; Luippold, G. *Acta. Physiol. Scand.*, **2000**, *168*, 219.
- [70] Rashed, S.M.; Songu-Mize, E. *Eur. J. Pharmacol.*, **1995**, *284*, 289.
- [71] Ventura, H.O.; Messerli, F.H.; Frohlich, E.D.; Kobrin, I.; Oigman, W.; Dunn, F.G.; Carey, R.M. *Circulation*, **1984**, *69*, 1142.
- [72] Zeng, C.; Wang, D.; Asico, L.D.; Welch, W.J.; Wilcox, C.S.; Hopfer, U.; Eisner, G.M.; Felder, R.A.; Jose, P.A. *Hypertension*, **2004**, *43*, 673.
- [73] Shigetomi, S.; Ueno, S.; Tosaki, H.; Suenaga, K.; Hashimoto, S.; Fukuchi, S. *Nippon. Naibunpi. Gakkai. Zasshi*, **1986**, *62*, 26.
- [74] Yoshimura, M.; Kambara, S.; Okabayashi, H.; Takahashi, H.; Ijichi, H. *Clin. Exp. Hypertens. [A]*, **1987**, *9*, 1141.
- [75] Haney, M.; Ward, A.S.; Foltin, R.W.; Fischman, M.W. *Psychopharmacology (Berl.)*, **2001**, *155*, 330.
- [76] Sato, M.; Soma, M.; Nakayama, T.; Kanmatsue, K. *Hypertension*, **2000**, *36*, 183.
- [77] Kuchel, O.G.; Kuchel, G.A. *Hypertension*, **1991**, *18*, 709.
- [78] Clark, B.A.; Rosa, R.M.; Epstein, F.H.; Young, J.B.; Landsberg, L. *Hypertension*, **1992**, *19*, 589.
- [79] Damasceno, A.; Santos, A.; Serrao, P.; Caupers, P.; Soares-da-Silva, P.; Polonia, J. *J. Hypertens.*, **1999**, *17*, 1995.
- [80] Gill, J.R.Jr.; Grossman, E.; Goldstein, D.S. *Hypertension*, **1991**, *18*, 614.
- [81] Gill, J.R.Jr.; Gullner, G.; Lake, C.R.; Lakatua, D.J.; Lan, G. *Hypertension*, **1988**, *11*, 312.
- [82] Sowers, J.R.; Zemel, M.B.; Zemel, P.; Beck, F.W.; Walsh, M.F.; Zawada, E.T. *Hypertension*, **1988**, *12*, 485.
- [83] Saito, I.; Takeshita, E.; Saruta, T.; Nagano, S.; Sekihara, T. *J. Hypertens.*, **1986**, *4*, 57.
- [84] Saito, I.; Itsuji, S.; Takeshita, E.; Kawabe, H.; Nishino, M.; Wainai, H.; Hasegawa, C.; Saruta, T.; Nagano, S.; Sekihara, T. *Clin. Exp. Hypertens.*, **1994**, *16*, 29.
- [85] Grossman, E.; Hoffman, A.; Tamrat, M.; Armando, I.; Keiser, H.R.; Goldstein, D.S. *J. Hypertens.*, **1991**, *9*, 259.
- [86] Stier, C.T.Jr.; Itskovitz, H.D.; Chen, Y.H. *Clin. Exp. Hypertens.*, **1993**, *15*, 105.
- [87] Kambra, S.; Yoshimura, M.; Takahashi, H.; Ijichi, H. *Jpn. Heart. J.*, **1987**, *28*, 594.
- [88] Hussain, T.; Abdul-Wahab, R.; Kotak, D.K.; Lokhandwala, M.F. *Hypertension*, **1998**, *32*, 1054.
- [89] O'Connell, D.P.; Ragsdale, N.V.; Boyd, D.G.; Felder, R.A.; Carey, R.M. *Hypertension*, **1997**, *29*, 115.
- [90] Pedrosa, R.; Jose, P.A.; Soares-da-Silva, P. *Am. J. Physiol. Renal. Physiol.*, **2004**, *286*, F1120.
- [91] Ohbu, K.; Kaskel, F.J.; Kinoshita, S.; Felder, R.A. *Am. J. Physiol.*, **1995**, *268*, R231.
- [92] Schafer, J.A.; Li, L.; Sun, D. *Acta. Physiol. Scand.*, **2000**, *168*, 239.
- [93] Chatziantoniou, C.; Ruan, X.; Arendshorst, W.J. *Proc. Natl. Acad. Sci. USA*, **1995**, *92*, 2924.
- [94] Felder, R.A.; Sanada, H.; Xu, J.; Yu, P.Y.; Wang, Z.; Watanabe, H.; Asico, L.D.; Wang, W.; Zheng, S.; Yamaguchi, I.; Williams, S.M.; Gainer, J.; Brown, N.J.; Hazen-Martin, D.; Wong, L.J.; Robillard, J.E.; Carey, R.M.; Eisner, G.M.; Jose, P.A. *Proc. Natl. Acad. Sci. USA*, **2002**, *99*, 3872.
- [95] Horiuchi, A.; Albrecht, F.E.; Eisner, G.M.; Jose, P.A.; Felder, R.A. *Am. J. Physiol.*, **1992**, *263*, F1105.
- [96] Kinoshita, S.; Sidhu, A.; Felder, R.A. *J. Clin. Invest.*, **1989**, *84*, 1849.
- [97] Zeng, C.; Yu, P.; Asico, L.D.; Hopfer, U.; Eisner, G.M.; Jose, P.A. *Am. J. Hypertens.*, **2002**, *15*, 11A (abstract).
- [98] Yu, P.Y.; Dirami, G.; Hopfer, U.; Carey, R.M.; Felder, R.A.; Jose, P.A. *Pediatr. Res.*, **1996**, *39*, 372A (abstract).
- [99] Tiberi, M.; Nash, S.R.; Bertrand, L.; Lefkowitz, R.J.; Caron, M.G. *J. Biol. Chem.*, **1996**, *271*, 3771.
- [100] Perry, S.J.; Baillie, G.S.; Kohout, T.A.; McPhee, I.; Magiera, M.M.; Ang, K.L.; Miller, W.E.; McLean, A.J.; Conti, M.; Houslay, M.D.; Lefkowitz, R.J. *Science*, **2002**, *298*, 834.
- [101] Rapacciuolo, A.; Suvarna, S.; Barki-Harrington, L.; Luttrell, L.M.; Cong, M.; Lefkowitz, R.J.; Rockman, H.A. *J. Biol. Chem.*, **2003**, *278*, 35403.
- [102] Heydorn, A.; Sondergaard, B.P.; Hadrup, N.; Holst, B.; Haft, C.R.; Schwartz, T.W. *FEBS Lett.*, **2004**, *556*, 276.
- [103] Shenoy, S.K.; McDonald, P.H.; Kohout, T.A.; Lefkowitz, R.J. *Science*, **2001**, *294*, 1307.
- [104] Oakley, R.H.; Laporte, S.A.; Holt, J.A.; Caron, M.G.; Barak, L.S. *J. Biol. Chem.*, **2000**, *275*, 17201.
- [105] Gardner, B.; Liu, Z.F.; Jiang, D.; Sibley, D.R. *Mol. Pharmacol.*, **2001**, *59*, 310.

- [106] Zeng, C.; Sanada, H.; Watanabe, H.; Eisner, G.M.; Felder, R.A.; Jose, P.A. *Physiol. Genomics*, **2004**, in press.
- [107] Watanabe, H.; Xu, J.; Bengra, C.; Jose, P.A.; Felder, R.A. *Kidney Int.*, **2002**, *62*, 790.
- [108] Casari, G.; Barlassina, C.; Cusi, D.; Zagato, L.; Muirhead, R.; Righetti, M.; Nembr, P.; Amar, K.; Gatti, M.; Macciardi, F.; et al. *Hypertension*, **1995**, *25*, 320.
- [109] Ng, G.Y.-K.; Trodradis, J.; Stephens, J.; Bouvier, M.; O'Dowd, B.F.; George, S.R. *Proc. Natl. Acad. Sci. USA*, **1995**, *93*, 10157.
- [110] Vickery, R.G.; von Zastrow, M. *J. Cell Biol.*, **1999**, *144*, 31.
- [111] Kim, O.J.; Gardner, B.R.; Williams, D.B.; Marinac, P.S.; Cabrera, D.M.; Peters, J.D.; Mak, C.C.; Kim, K.M.; Sibley, D.R. *J. Biol. Chem.*, **2004**, *279*, 7999.
- [112] Gros, R.; Chorazyczewski, J.; Meek, M.D.; Benovic, J.L.; Ferguson, S.S.; Feldman, R.D. *Hypertension*, **2000**, *35*, 38.
- [113] Allayee, H.; de Bruin, T.W.; Michelle Dominguez, K.; Cheng, L.S.; Ipp, E.; Cantor, R.M.; Krass, K.L.; Keulen, E.T.; Aouizerat, B.E.; Lusic, A.J.; Rotter, J.I. *Hypertension*, **2001**, *38*, 773.
- [114] Speirs, H.J.; Katyk, K.; Kumar, N.N.; Benjafield, A.V.; Wang, W.Y.; Morris, B.J. *J. Hypertens.*, **2004**, *22*, 931.
- [115] Williams, S.M.; Ritchie, M.D.; Phillips, J.A.^{3rd}; Dawson, E.; Prince, M.; Dzhura, E.; Willis, A.; Semenya, A.; Summar, M.; White, B.C.; Addy, J.H.; Kpodonu, J.; Wong, L.J.; Felder, R.A.; Jose, P.A.; Moore, J.H. *Hum. Hered.*, **2004**, *57*, 28.
- [116] Williams, S.M.; Addy, J.H.; Phillips, J.A.^{3rd}; Dai, M.; Kpodonu, J.; Afful, J.; Jackson, H.; Joseph, K.; Eason, F.; Murray, M.M.; Epperson, P.; Aduonum, A.; Wong, L.J.; Jose, P.A.; Felder, R.A. *Hypertension*, **2000**, *36*, 2.
- [117] Salles, M.; Mariggio, S.; Colodel, G.; Moretti, E.; Piomboni, P.; Baccetti, B.; De Blasi, A. *J. Biol. Chem.*, **1997**, *272*, 10188.
- [118] Premont, R.T.; Macrae, A.D.; Aparicio, S.A.; Kendall, H.E.; Welch, J.E.; Lefkowitz, R.J. *J. Biol. Chem.*, **1999**, *274*, 29381.
- [119] Dale, L.B.; Bhattacharya, M.; Anborgh, P.H.; Murdoch, B.; Bhatia, M.; Nakanishi, S.; Ferguson, S.S. *J. Biol. Chem.*, **2000**, *275*, 38213.
- [120] Watanabe, H.; Xu, J.; Jose, P.A.; Felder, R.A. *Hypertension*, **2002**, *40*, 65.
- [121] Wang, Z.; Asico, L.D.; Zeng, C.; Felder, R.A.; Robillard, J.E.; Jose, P.A. *J. Am. Soc. Nephrol.*, **2003**, *14*, 362A. (abstract).
- [122] Yu, P.; Asico, L.D.; Eisner, G.M.; Hopfer, U.; Felder, R.A.; Jose, P.A. *Hypertension*, **2000**, *36*, 1053.
- [123] Yang, Z.; Yu, P.; Asico, L.D.; Felder, R.A.; Jose, P.A. *Clin. Exp. Hypertens.*, **2004**, *26*, 243.
- [124] Ladines, C.A.; Zeng, C.; Asico, L.D.; Sun, X.; Pocchiari, F.; Semeraro, C.; Pisegna, J.; Wank, S.; Yamaguchi, I.; Eisner, G.M.; Jose, P.A. *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, **2001**, *28*, R1071.
- [125] Zeng, C.; Asico, L.D.; Eisner, G.M.; Hopfer, U.; Jose, P.A.; Felder, R.A. *Am. J. Hypertens.*, **2003**, *16*, 104A. (abstract).
- [126] Murphy, M.B.; Murray, C.; Shorten, G.D. *N. Engl. J. Med.*, **2001**, *345*, 1548.
- [127] Bughi, S.; Horton, R.; Antonipillai, I.; Manoogian, C.; Ehrlich, L.; Nadler, J. *J. Clin. Endocrinol. Metab.*, **1989**, *69*, 1116.
- [128] de Vries, P.A.; Navis, G.; de Jong, P.E.; de Zeeuw, D.; Kluppel, C.A. *J. Cardiovasc. Pharmacol.*, **1999**, *34*, 191.
- [129] de Hurtado, M.C.; Alvarez, B.V.; Ennis, I.L.; Cingolani, H.E. *Circ. Res.*, **2000**, *86*, 622.
- [130] Kunimi, M.; Seki, G.; Hara, C.; Taniguchi, S.; Uwatoko, S.; Goto, A.; Kimura, S.; Fujita, T. *Kidney Int.*, **2000**, *57*, 534.
- [131] Zeng, C.; Yu, P.; Zheng, S.; Eisner, G.M.; Jose, P.A. *J. Am. Soc. Nephrol.*, **2001**, *12*, 477A. (abstract).
- [132] Chen, C.; Lokhandwala, M.F. *Naumyn. Schmiedeberts. Arch. Pharmacol.*, **1995**, *352*, 194.
- [133] Yamaguchi, I.; Yao, L.; Sanada, H.; Ozono, R.; Mouradian, M.M.; Carey, R.M.; Jose, P.A.; Felder, R.A. *Hypertension*, **1997**, *29*, 962.
- [134] Sanada, H.; Yao, L.; Jose, P.A.; Carey, R.M.; Felder, R.A. *Clin. Exp. Hypertens.*, **1997**, *19*, 93.
- [135] Houillier, P.; Chambrey, R.; Achard, J.M.; Froissart, M.; Poggioli, J.; Paillard, M. *Kidney Int.*, **1996**, *50*, 1496.
- [136] Efendiev, R.; Budu, C.E.; Cinelli, A.R.; Bertorello, A.M.; Pedemonte, C.H. *J. Biol. Chem.*, **2003**, *278*, 28719.
- [137] Zeng, C.; Asico, L.D.; Jones, J.E.; Hopfer, U.; Eisner, G.M.; Felder, R.A.; Jos, P.A. *Circulation*, **2003**, *108*, IV-214. (abstract).
- [138] Cheng, H.F.; Becker, B.N.; Harris, R.C. *J. Clin. Invest.*, **1996**, *97*, 2745.
- [139] Carey, R.M.; Sen, S. *Rec. Prog. Horm. Res.*, **1986**, *42*, 251.
- [140] Carey, R.M.; Thorne, M.O.; Ortt, E.M. *J. Clin. Invest.*, **1980**, *66*, 10.
- [141] Missale, C.; Lombardi, C.; De Cotiis, R.; Memo, M.; Carruba, M.O.; Spano, P.F. *J. Cardiovasc. Pharmacol.*, **1989**, *14* (Suppl. 8), S29.
- [142] Rizzi, C.A.; Mierau, J.; Ladinsky, H. *Neuropharmacology*, **1997**, *36*, 763.
- [143] Missale, C.; Liberini, P.; Memo, M.; Carruba, M.O.; Spano, P. *Endocrinology*, **1986**, *119*, 2227.
- [144] Adam, W.R.; Goland, G. *Clin. Exp. Pharmacol. Physiol.*, **1979**, *6*, 631.
- [145] Wu, K.D.; Chen, Y.M.; Chu, T.S.; Chueh, S.C.; Wu, M.H.; Bor-Shen, H. *J. Clin. Endocrinol. Metab.*, **2001**, *86*, 4460.
- [146] Li, X.X.; Bek, M.; Asico, L.D.; Yang, Z.; Grandy, D.K.; Goldstein, D.S.; Rubinstein, M.; Eisner, G.M.; Jose, P.A. *Hypertension*, **2001**, *38*, 303.
- [147] Hollon, T.R.; Bek, M.J.; Lachowicz, J.E.; Ariano, M.A.; Mezey, E.; Ramachandran, R.; Wersinger, S.R.; Soares-da-Silva, P.; Liu, Z.F.; Grinberg, A.; Drago, J.; Young, W.S.^{3rd}; Westphal, H.; Jose, P.A.; Sibley, D.R. *J. Neurosci.*, **2002**, *22*, 10801.
- [148] Bek, M.; Zheng, S.; Asico, L.D.; Grandy, D.K.; Rubinstein, M.; Carey, R.M.; Eisner, G.M.; Jose, P.A. *Am. J. Hypertens.*, **2001**, *14*, 157A. (abstract).
- [149] Sowers, J.R.; Nyby, M.; Jasberg, K. *Hypertension*, **1982**, *4*, 431.
- [150] Linthorst, A.C.; De Jong, W.; De Boer, T.; Versteeg, D.H. *Brain Res.*, **1993**, *602*, 119.
- [151] Lederer, E.D.; Sohi, S.S.; McLeish, K.R. *J. Am. Soc. Nephrol.*, **1998**, *9*, 975.
- [152] Kitiyakara, C.; Wilcox, C.S. *Curr. Opin. Nephrol. Hypertens.*, **1998**, *7*, 531.
- [153] Wang, H.; Joseph, J.A. *Free. Radic. Biol. Med.*, **1999**, *27*, 612.
- [154] Conway, K.A.; Rochet, J.C.; Bieganski, R.M.; Lansbury, P.T. Jr. *Science*, **2001**, *294*, 1346.
- [155] Bianchi, P.; Seguelas, M.H.; Parini, A.; Cambon, C. *J. Am. Soc. Nephrol.*, **2003**, *14*, 855.
- [156] Yang, Z.; Asico, L.D.; Yu, P.; Wang, Z.; Jones, J.E.; Bai, R.K.; Sibley, D.R.; Felder, R.A.; Jose, P.A. *Am. J. Physiol. Heart Circ. Physiol.*, **2004**, in press.
- [157] Touyz, R.M. *Braz. J. Med. Biol. Res.*, **2004**, *37*, 1263.
- [158] Bek, M.J.; Reinhardt, H.C.; Fischer, K.G.; Hirsch, J.R.; Hupfer, C.; Dayal, E.; Pavenstadt, H. *J. Immunol.*, **2003**, *170*, 931.
- [159] Yang, Z.; Yu, P.; Asico, D.L.; Wang, Z.; Bek, M.; Sibley, D.R.; Jose, P.A. *J. Am. Soc. Nephrol.*, **2003**, *14*, 553A. (abstract).
- [160] Yasunari, K.; Kohno, M.; Kano, H.; Minami, M.; Yoshikawa, J. *Circulation*, **2000**, *101*, 2302.
- [161] Cosentino, F.; Patton, S.; d'Uscio, L.V.; Werner, E.R.; Werner-Felmayer, G.; Moreau, P.; Malinski, T.; Luscher, T.F. *J. Clin. Invest.*, **1998**, *101*, 1530.
- [162] Kerr, S.; Brosnan, M.J.; McIntyre, M.; Reid, J.L.; Dominiczak, A.F.; Hamilton, C.A. *Hypertension*, **1999**, *33*, 1353.
- [163] Marin-Grez, M.; Briggs, J.P.; Schubert, G.; Schnermann, J. *Life Sci.*, **1985**, *36*, 2171.
- [164] Petterson, A.; Hedner, J.; Hedner, T. *Acta Physiol. Scand.*, **1986**, *126*, 619.
- [165] Katoh, T.; Sophasan, S.; Kurokawa, K. *Am. J. Physiol.*, **1989**, *257*, F300.
- [166] Israel, A.; Torres, M.; Barbella, Y. *Cell. Mol. Neurobiol.*, **1989**, *9*, 369.
- [167] Velasco, M.; Contreras, F.; Cabezas, G.A.; Bolivar, A.; Fouilloux, C.; Hernandez, R. *J. Hypertens.*, **2002**, *20* (suppl. 3), S55.
- [168] Turban, S.; Wang, X.Y.; Knepper, M.A. *Am. J. Physiol. Renal. Physiol.*, **2003**, *285*, F843.
- [169] Haynes, W.G.; Hand, M.F.; Dockrell, M.E.; Eadington, D.W.; Lee, M.R.; Hussein, Z.; Benjamin, N.; Webb, D.J. *Am. J. Physiol.*, **1997**, *272*, F364.
- [170] Lonart, G.; Cassels, K.L.; Johnson, K.M. *J. Neurosci. Res.*, **1993**, *35*, 192.
- [171] Venkatakrishnan, U.; Chen, C.; Lokhandwala, M.F. *Clin. Exp. Hypertens.*, **2000**, *22*, 309.
- [172] Yuasa, S.; Li, X.; Hitomi, H.; Hashimoto, M.; Fujioka, H.; Miyamoto, H.; Uchida, K.; Shoji, T.; Takahashi, N.; Miki, S.; Miyatake, A.; Mizushige, K.; Matsuo, H. *Clin. Exp. Pharmacol. Physiol.*, **2000**, *27*, 18.

- [173] Montanari, A.; Tateo, E.; Fasoli, E.; Donatini, A.; Cimolato, B.; Perinotto, P.; Dall'Aglio, P. *Hypertension*, **1998**, *31*, 277.
- [174] Huo, T.; Healy, D.P. *Am. J. Physiol.*, **1991**, *261*, F647.
- [175] Huo, T.; Grenader, A.; Blandina, P.; Healy, D.P. *Am. J. Physiol.*, **1991**, *261*, F655.
- [176] Muto, S.; Tabei, K.; Asano, Y.; Imai, M. *Eur. J. Pharmacol.*, **1985**, *114*, 393.
- [177] Sun, D.; Schafer, J.A. *Am. J. Physiol.* **1996**, *271*, F391.
- [178] Li, L.; Schafer, J.A. *Am. J. Physiol.*, **1998**, *275*, F62.
- [179] Zelenina, M.; Zelenin, S.; Bondar, A.A.; Brismar, H.; Aperia, A. *Am. J. Physiol. Renal. Physiol.*, **2002**, *283*, F309.
- [180] Nagahama, S.; Ann, H.S.; Chen, Y.F.; Lindheimer, M.D.; Oparil, S. *J. Pharmacol. Exp. Ther.*, **1987**, *242*, 143.
- [181] Racke, K.; Meuresch, J.; Trapp, B.; Muscholl, E. *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **1986**, *332*, 332.
- [182] Rossi, F. *Am. J. Physiol.*, **1998**, *275*, E687.
- [183] Sunahara, R.K.; Guan, H.-C.; O'Dowd, B.F.; Seeman, P.; Laurier, L.G.; Ng, G.; George, S.Jr.; Torchia, J.; van Tol, H.H.M.; Niznik, H.B. *Nature*, **1991**, *350*, 614.

Received: 20 August, 2004

Accepted: 28 September, 2004