Adrenergic and Endothelin B Receptor–Dependent Hypertension in Dopamine Receptor Type-2 Knockout Mice

Xiao Xi Li, Martin Bek, Laureano D. Asico, Zhiwei Yang, David K. Grady, David S. Goldstein, Marcelo Rubinstein, Gilbert M. Eisner, Pedro A. Jose

Abstract—Polymorphism of the dopamine receptor type-2 (D₂) gene is associated with essential hypertension. To assess whether D₂ receptors participate in regulation of blood pressure (BP), we studied mice in which the D₂ receptor was disrupted. In anesthetized mice, systolic and diastolic BPs (in millimeters of mercury) were higher in D₂ homozygous and heterozygous mutant mice than in D₂ +/+ littermates. BP after α-adrenergic blockade decreased to a greater extent in D₂ −/− mice than in D₂ +/+ mice. Epinephrine excretion was greater in D₂ −/− mice than in D₂ +/+ mice, and acute adrenalectomy decreased BP to a similar level in D₂ −/− and D₂ +/+ mice. An endothelin B (ET[B]) receptor blocker for both ET(B1) and ET(B2) receptors decreased, whereas a selective ET(B1) blocker increased, BP in D₂ −/− mice but not D₂ +/+ mice. ET(B) receptor expression was greater in D₂ −/− mice than in D₂ +/+ mice. In contrast, blockade of ET(A) and V₁ vasopressin receptors had no effect on BP in either D₂ −/− or D₂ +/+ mice. The hypotensive effect of an AT₁ antagonist was also similar in D₂ −/− and D₂ +/+ mice. Basal Na⁺,K⁺-ATPase activities in renal cortex and medulla were higher in D₂ +/+ mice than in D₂ −/− mice. Urine flow and sodium excretion were higher in D₂ +/+ mice than in D₂ −/− mice before and after acute saline loading. Thus, complete loss of the D₂ receptor results in hypertension that is not due to impairment of sodium excretion. Instead, enhanced vasoreactivity in the D₂ mutant mice may be caused by increased sympathetic and ET(B) receptor activities. (Hypertension. 2001;38:303-308.)

Key Words: dopamine receptors, dopamine receptors, endothelin receptors, Na⁺,K⁺ transporting ATPase kidney

Dopamine can regulate cardiovascular function by its actions on central cardiovascular centers, the pituitary and adrenal glands, kidney, cardiac and vascular smooth muscle, and the sympathetic nervous system.1,2 Effects of dopamine are mediated by dopamine receptor type-1 and type-2 (D₁ and D₂)–like receptors that belong to the G protein–coupled receptor family.1,3 Both D₁ and D₂-like receptors have been shown to regulate arterial blood pressure (BP).1,2 Genetic hypertension in rodents and humans has been shown to be associated with decreased activity of D₁-like receptors in the kidney and central nervous system.1,2 Decreased D₂-like dopaminergic activity in the central nervous system has been reported in essential hypertension.1,4 Several studies in animal models of genetic hypertension also support the notion of altered central D₂-like dopaminergic activity in hypertension.5,6 However, 3 D₂-like dopamine receptors, D₂, D₃, and D₄, exist, and which of the 3 cloned D₂-like receptors participate in the D₂-like regulation of BP is unclear.1,3 Disruption of D₃ receptors in mice produces hypertension mediated, at least in part, by activation of the renin-angiotensin system.7 The D₂ receptor could be involved in D₂-like-mediated hypertension because it is the major D₂-like dopamine receptor.3,8–11 Moreover, BP decreased when a segment of chromosome 8 that contained the D₂ receptor gene was transferred from a normotensive Brown Norway rat to a spontaneously hypertensive rat background.12

Several variants of the human D₂ dopamine receptor have been reported.13 Abnormalities of D₂ receptor genes could play a role in the pathogenesis of essential hypertension, because the association of a D₂ dopamine receptor polymorphism with obesity and hypertension has been reported.14 To determine whether D₂ receptors play a role in the regulation of BP, we measured arterial pressure in congenic B6 mice mutants for the D₂ receptor.8,9 Because D₂-like receptors have been shown to interact with vasopressor systems,1,6,15,16 interactions between D₂ receptors and other vasopressor systems were also studied.

Methods

D₂ Receptor–Deficient Mice

The original F₂ hybrid strain (129/SvXC57BL/6J, Oregon Health Sciences University, Portland) that contained the mutated D₂ recep-
tor allele was backcrossed to wild-type C57BL/6J for 5 generations and genotyped. These mice acquired normal motor skills without tremor, ataxia, or abnormal stance or posture but had decreased initiation of movement. All studies were approved by the Georgetown University Animal Care and Use Committee.

**BP and Renal Function Studies**

Mice were anesthetized with pentobarbital 50 mg/kg IP, placed on a heated board to maintain body temperature at 37°C, and tracheotomized. Mice were euthanized (pentobarbital 100 mg/kg) at the conclusion of the study.

**Effect of Agonists and Antagonists on BP**

Because preliminary studies indicated that arterial pressures were higher in D2−/− than D2+/+ mice, we determined the mechanism of increase in BP by intravenous infusion of antagonists of pressor agents. After a 60-minute stabilization period, drugs were infused in random order: [1-(β-mercaptopo-β,β-cyclopentamethylenenepropionic acid)-2-(O-methyl)-tyrosine] arginine vasopressin (V1 vasopressin antagonist; Peninsula Laboratories, Inc) 10 μg/kg IV over 30 seconds[1]; BQ-610 (endothelin receptor antagonist, ET[A]; Peninsula) 5 ng · kg−1 · min−1 for 10 minutes[5]; BQ-788 (endothelin B ET[B1]/ET[B2] antagonist; Peninsula) 6.6 μg · kg−1 · min−1 for 15 minutes[6]; RES-701-1 (ET[B1] antagonist; American Peptide) 100 μg · kg−1 · min−1 for 1 hour[7]; phenolamine (α-adrenergic antagonist; Research Biochemicals International) 5 ng · kg−1 · min−1 for 30 minutes[3]; and losartan (AT1 antagonist) 3 mg/kg IV over 30 seconds. BP was allowed to stabilize at preinfusion values for 30 to 60 seconds 17; BQ-610 (endothelin receptor antagonist, ET[A]; Peninsula) 6.6 μg · kg−1 · min−1 for 1 hour 19; RES-701-1 (ET[B1] antagonist; American Peptide) 100 μg · kg−1 · min−1 for 1 hour 20; phenolamine (α-adrenergic antagonist; Research Biochemicals International) 5 ng · kg−1 · min−1 for 30 minutes[2]; and losartan (AT1 antagonist) 3 mg/kg IV over 30 seconds. BP was allowed to stabilize at preinfusion values for 30 to 60 minutes before new drug administration. These antagonists block the vasopressor effects of their respective agonists; 40 μL of various concentrations of vasopressin, phenylephrine, endothelin-1 (ET-1), and angiotensin II, respectively, given over 30 seconds. Effects on BP of bolus injections of ET(B1) agonist sarafotoxin S6 0.01 to 1.0 nmol/kg (American Peptide) and ET-1 0.1 to 1.3 pmol/kg were also studied.

**Adrenalectomy**

Effect of adrenalectomy on BP was also studied in some mice. After a midline abdominal incision, adrenal gland was separated from kidney, ligated, crushed with forceps, and excised. BP readings were obtained after a 20-minute stabilization period.

**Immunoblotting Studies**

Because blockade of ET(B) receptors normalized BP in D2−/− mice (see Results), we immunoblotted for ET(B) receptors (Maize Technology Services, Inc) of liver; ET-1 has been reported to induce (see Results), we immunoblotted for ET(B) receptors (Maine Bio- tech Services, Inc) of liver; ET-1 has been reported to induce

**Determination of Na+,K+-ATPase Activity**

Na+,K+-ATPase activity is as described previously.23

**Determination of Catecholamines**

Kidneys were homogenized with 0.1 mol/L HClO4, and centrifuged at 6000g for 20 minutes at 4°C. Supernatant, urine, and plasma were flash-frozen and stored at −70°C until assay.24

**Determination of Plasma Endothelin-Immunoreactive Levels**

Fifty microliters of plasma was diluted with 1% TCA and centrifuged at 14 000 rpm for 20 minutes at 4°C. Supernatants were loaded into separation columns preequilibrated with 100% acetonitrile and washed with 1% TCA. Peptides were eluted (60% acetonitrile in 1% TCA), lyophilized, and quantified by ELISA (Peninsula).

**Results**

**General Characteristics**

D2+/− mice were heavier than either D2+/+ or D2−/− mice (Table 1). Heart and kidney weights as a percentage of body weight were similar among the groups. Heart rate was significantly elevated in D2−/− mice versus D2+/+ mice. Furthermore, systolic, diastolic, and mean arterial pressures were also higher in mice heterozygous and homozygous for mutated D2 receptor allele compared with wild-type mice. D2 receptors (47 and 98 kDa) were detected in rat striatal tissues (positive control) but not in renal cortical or medullary tissue from rats or from D2−/− or D2+/+ mice (data not shown).

**Effect of Saline Loading**

Basal urine flow rate and sodium excretion were greater in D2−/− mice than in D2+/+ mice (Figure 1). Saline loading increased urine flow and absolute (Figure 1) and fractional sodium (data not shown) excretion in all the mice. However, the increase was greater in D2−/− mice than in D2+/+ mice.

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**Table 1. Characteristics of D2 Mutant Mice**

<table>
<thead>
<tr>
<th>Variable</th>
<th>D2+/+ Mice (n=13)</th>
<th>D2+/− Mice (n=11)</th>
<th>D2−/− Mice (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mo</td>
<td>6−12</td>
<td>6−12</td>
<td>6−12</td>
</tr>
<tr>
<td>Body weight, g</td>
<td>25±1</td>
<td>31±2</td>
<td>25±1</td>
</tr>
<tr>
<td>Heart weight, % body weight</td>
<td>0.45±0.01</td>
<td>0.42±0.01</td>
<td>0.44±0.02</td>
</tr>
<tr>
<td>Kidney weight, % body weight</td>
<td>1.21±0.08</td>
<td>1.22±0.10</td>
<td>1.20±0.05</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>418±8</td>
<td>439±13</td>
<td>452±8†</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>104±2‡</td>
<td>129±4</td>
<td>128±2</td>
</tr>
<tr>
<td>Diastolic</td>
<td>77±1‡</td>
<td>98±3</td>
<td>97±2</td>
</tr>
<tr>
<td>Mean</td>
<td>85±1‡</td>
<td>108±3</td>
<td>107±2</td>
</tr>
</tbody>
</table>

Data are mean±SE. *P<0.05 vs D2+/+ or D2−/− mice; †P<0.05 vs D2+/+ mice; ‡P<0.05 vs mutant mice by ANOVA, Newman-Keuls test.

**Statistical Analyses**

Data (mean±SE) were analyzed by 1-way or repeated ANOVA or t test as indicated.

**Figure 1.** Urine flow (V) and sodium excretion (UNaV) in D2+/− and D2−/− mice. Natriuresis and diuresis before (Basal) and during (Load) but not after (Post 1, 2, and 3) saline loading were greater in D2−/− mice than in D2+/+ mice. *P<0.05, D2−/− vs D2+/+ mice, t test; †P<0.05 vs basal, ANOVA for repeated measures, Newman-Keuls test; n=6 to 9 per group. Each period lasted 60 minutes.
Glomerular filtration rate was similar in D2−/− and D2+/+ mice and was not affected by saline loading. Arterial pressures were not affected by the acute saline load (data not shown).

**Na⁺,K⁺-ATPase Activity**

In agreement with reports that D2-like agonists stimulate Na⁺,K⁺-ATPase activity in renal tubules, Na⁺,K⁺-ATPase activity was lower (P<0.05, t test) in both cortical and medullary regions in D2−/− mice (cortex, 22.97±3.26; medulla, 22.09±2.07 nmol of inorganic phosphate per milligram of protein per minute, n=5) than in D2+/+ mice (cortex, 33.45±2.01; medulla, 31.52±2.62 nmol of inorganic phosphate per milligram of protein per minute, n=7).

**Effect of Receptor Ligands on BPs**

**Effects of AT1 and V1 Receptor Antagonists**

AT1 receptor antagonist decreased BP in D2+/+ and D2−/− mice, which indicated that AT1 receptors maintain a tonic control of BP in anesthetized wild-type and mutant mice. In the first 5 minutes after AT1 antagonist administration, however, decrease in BP was greater in D2+/+ than D2−/− mice (Figure 2A). V1 vasopressin antagonist [1-(β-mercaptopropionyl)-β-cyclopentamethylenepropionic acid]-2-(O-methyl)-tyrosine] arginine vasopressin had minimal effects on BP (Figure 2A).

**Effect of α-Adrenergic Antagonist**

Phentolamine, an α-adrenergic antagonist, markedly decreased BP in D2 mutant and wild-type mice. The magnitude of the decrease in BP was greater in D2−/− than D2+/+ mice (Figure 2B), ultimately resulting in similar BPs at the nadir of the phentolamine effect. Moreover, acute adrenalectomy decreased BP in D2−/− (mean BP in mm Hg before adrenalectomy, 101±5; after adrenalectomy, 52±14; n=3), D2+/− (mean BP before adrenalectomy, 101±2; after adrenalectomy, 61±4; n=4) and D2+/+ (mean BP before adrenalectomy, 82±2; after adrenalectomy, 47±8; n=2) mice, such that BPs were no longer different among groups.

**Effects of ET(A) and ET(B) Antagonists**

ET(A) antagonist BQ-610 had minimal effects on BP in D2+/+ and D2−/− mice (Figure 2A). In contrast, ET(B1)/ET(B2) antagonist BQ-788 decreased BP in D2−/− but not D2+/+ mice, which indicated that increased activity of ET(B) receptors contributes to elevation of BP in D2 mutant mice (Figure 3A). Because ET(B) receptor subtypes have differential vascular effects (ET[B1] decreases and ET[B2] increases BP), additional studies were performed with ET(B1) antagonist RES-701-1 (Figure 3A). RES-701-1 increased BP to a greater extent in D2−/− than D2+/+ mice.

**Effects of ET-1 and ET(B) Agonist**

Because ET(B1) and ET(B2) effects were increased in D2 mutant mice, we determined the effect of ET-1 on BP. ET-1 (0.1 to 1.3 nmol/kg) tended to increase BP to a greater extent in D2+/+ than D2−/− mice (maximum increase, 23±5% and 17±5%, respectively; n=3 to 6 per group), but significant differences were not found. ET(B) agonist sarafotoxin S6c also tended to increase BP to a greater extent in D2+/+ than D2−/− mice (maximum increase, 33±10% and 30±4%, respectively) but reached significance only at 0.3 nmol/kg (D2+/+, 21±5% versus D2−/−, 10±1%; P<0.05 by t test; n=3 to 6 per group).

**Endothelin Receptor Protein and Endothelin-Like Immunoreactive Levels**

Immunoreactive ET(B) receptors were 3-fold greater in D2−/− than D2+/+ mice (Figure 3B). Plasma immunoreactive endothelin levels were not different between D2+/+ (1.20±0.42 ng/mL) and D2−/− (0.75±0.24 ng/mL) mice, although a trend occurred toward lower values in D2−/− mice. These values are 5 to 100 times greater than that previously reported in mice, because the antibody used cross-reacts with ET-1, ET-2, and big endothelin (Peninsula).

**Catechol Levels**

Renal catechol levels were similar in D2+/+ and D2−/− mice (data not shown). Urinary catechols were also similar except for urinary epinephrine. Epinephrine excretion rates were generally higher before (baseline, urine period 1), during (urine period 2), and after saline loading (urine periods 3 through 5) in D2−/− versus D2+/+ mice (Table 2). Urinary dopamine and norepinephrine tended to increase with saline loading.
loading in D2+/+ mice and reached statistical significance in D2−/− mice; the percentage increases in urinary dopamine (85%) and urinary norepinephrine (108%) with saline loading (compared with baseline) were similar in D2+/+ and D2−/− mice. These changes were associated with increased urine flow but not with glomerular filtration rate (data not shown).

Discussion

Our data suggest that disruption of the D2 dopamine receptor, a member of the family of D2-like receptors, increases systolic and diastolic BPs in D2+/- mice and D2−/− mice. No gender effect occurred. Presence of hypertension in D2+/- mice may be taken to be an indication that few spare D2 receptors regulate this phenotype, similar to what has been reported for locomotor and pituitary lactotroph function.7,8 The hypertensive phenotype was unlikely to be caused by genetic heterogeneity, because mice have been inbred to the fifth generation.7

Both α2-adrenergic and D2 dopamine receptors are involved in prejunctional inhibition of catecholamine release.3,15,16 α2-adrenergic receptor has been shown to inhibit sympathetic outflow, and disruption of this receptor in mice increased BP.26 Stimulation of prejunctional D2-like receptors also inhibited sympathetic outflow.3,15,16 In contrast, stimulation of postsynaptic D2-like receptors in the nervous system and arterial vessels increased vascular resistance or BP.6,27 The pressor effect of intravenously administered D2-like drugs was transient, whereas the peripheral vasodilator effect, presumably caused by actions at prejunctional D2-like receptors, was persistent.16 The decrease in BP after α-adrenergic blockade in D2−/− mice suggests that sympathetic activity may have increased as a result of withdrawal of D2 receptor actions at prejunctional receptors. Thus, acute adrenalectomy decreased BP such that BPs were no longer different among groups. Moreover, urinary epinephrine levels were elevated in D2−/− compared with D2+/- mice; D2 receptors in the adrenal medulla inhibit epinephrine release.27 Similar renal and urinary norepinephrine levels in D2+/- and D2−/− mice may be explained by observations of catecholamine metabolism in striatum of D2−/− mice. Monoamine levels in striatum were similar in D2−/− and D2+/- mice, although dopamine metabolites were increased.9,10

An unexpected finding in these studies was the ability of BQ-788, an ET(B1)/ET(B2) antagonist, to decrease and normalize BP, whereas ET(B1) antagonist RES-701-1 increased BP in D2−/− mice without affecting BP in D2+/- mice. ET(A) antagonist BQ-610 had no effect on BP in either D2−/− or D2+/- mice. The endothelins (ET-1, ET-2, and ET-3), which are generally vasoconstrictors, exert their actions by means of ET(A) and ET(B) receptors.18–20,25,28 However, endothelins can also mediate vasodilation.19,20,25,28 On the basis of pharmacological evidence, 2 types of ET(B) receptors have postulated: ET(B1), which is a relaxant, and ET(B2), which is a vasoconstrictor.

**Table 2.** Catechol Excretion in D2+/- and D2−/− Mice

<table>
<thead>
<tr>
<th>Urine Catechols, pg/min</th>
<th>D2+/- Mice (n=7)</th>
<th>U1</th>
<th>U2</th>
<th>U3</th>
<th>U4</th>
<th>U5</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHPG</td>
<td>148±23</td>
<td>299±156</td>
<td>166±56</td>
<td>201±100</td>
<td>220±139</td>
<td></td>
</tr>
<tr>
<td>DOPA</td>
<td>65±41</td>
<td>181±112</td>
<td>163±118</td>
<td>99±49</td>
<td>228±193</td>
<td></td>
</tr>
<tr>
<td>DOPAC</td>
<td>35±6</td>
<td>56±18</td>
<td>52±17</td>
<td>39±14</td>
<td>36±12</td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td>437±79</td>
<td>810±264</td>
<td>513±139</td>
<td>516±197</td>
<td>631±408</td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>9±3</td>
<td>24±7</td>
<td>31±13</td>
<td>11±5</td>
<td>7±3</td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>131±43</td>
<td>273±77</td>
<td>164±56</td>
<td>128±39</td>
<td>146±87</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>U1</th>
<th>U2</th>
<th>U3</th>
<th>U4</th>
<th>U5</th>
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<tr>
<td>173±19</td>
<td>213±21</td>
<td>11.8±14</td>
<td>87±14*</td>
<td>71±12*</td>
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<td>75±66</td>
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<td>14±26</td>
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<tr>
<td>353±55†</td>
<td>656±118</td>
<td>498±50</td>
<td>400±74</td>
<td>386±67†</td>
</tr>
<tr>
<td>63±23</td>
<td>156±49‡</td>
<td>125±36‡</td>
<td>73±19‡</td>
<td>113±50</td>
</tr>
</tbody>
</table>

U indicates urine periods 1-5: U1, baseline; U2, saline loading; and U3 through U5, after saline loading. DHPG indicates dihydroxyphenyl glycol; DOPA, dihydroxyphenylalanine; and DOPAC, dihydroxyphenylacetic acid.

*P<0.05 vs U1 or U2 in D−/− mice by ANOVA, Newman-Keuls test; †P<0.05 vs U1 in D−/− mice by ANOVA, Newman-Keuls test; ‡P<0.05 vs D2+/- mice, t test.
and ET(B2) which is a constrictor. In ET(B) knock-out mice, both vasodilatory and vasoconstrictor effects of ET(B) receptors were eliminated, which suggests that ET(B1) and ET(B2) receptors are the same receptor. The difference in their actions may be related to the sites at which these receptors are expressed. For example, ET(B) (ET(B1)) receptors expressed in endothelial cells are vasodilatory because of their linkage to nitric oxide and prostaglandin; the ability of prejunctional ET(B) (ET(B1)) receptors to inhibit catecholamine release may also contribute to decreasing vascular resistance. Elimination of the ET(B1)-mediated stimulation of endothelial prostacyclin production has been suggested to be the cause of hypertension in ET(B)-deficient mice. If an ET(B1)-mediated increase in endothelial or prostacyclin production does not occur, however, then the vasoconstrictor effect of ET(B2) would become unopposed, which would result in hypertension. The anticipated inhibitory effect of ET(B1) on catecholamine release would partially offset the usual inhibitory effect of ET(B1) receptors on catecholamine release in this model. This occurrence may explain the modest changes in urinary catechol levels in mice.

Interestingly, ET(B) expression was 3 times greater in than ET(B+) mice. Absence of ET(B) receptors conceivably could have led to increased vasodilatory ET(B1) receptors and vasoconstrictor ET(B2) receptors. Because ET(B) receptors are expressed at the junction of adventitia and tunica media, disruption of ET(B) receptors should affect expression of ET(B1) and ET(B2) receptors in the tunica media–adventitia but not ET(B1) in the tunica intima because no dopamine receptors are expressed in this blood vessel layer.

Minimal differential effect of ET-1 and the ET(B1) agonist sarafotoxin S6c occurred on BP in ET(B1−/− mice, presumably because ET(B1) expression in tunica media was not altered in ET(B1−/− mice. The predominant effect in ET(B1−/− mice was an increase in ET(B2) action, however, because the ET(B1−/− mice were hypertensive. Hence, the BP-lowering effect of ET(B1)/ET(B2) antagonist BK-788 in ET(B1−/− mice and the greater increase in BP in ET(B1−/− mice than ET(B1+) mice after the ET(B1) antagonist RES-101-1. Although renin levels were not measured in these studies, the greater hypertensive response to AT1 blockade in ET(B1−/− wild-type versus ET(B1−/− mice is suggestive of decreased activity of the renin-angiotensin system in ET(B1−/− mice. ET(B) receptors have been reported to inhibit renin gene expression in mouse jugular body cells.

The site of interaction between ET(B) dopamine receptors and ET(B) receptors was not determined in the present studies. Dopamine, dopamine receptors, endothelin, and ET(B) receptors have been found in brain and spinal regions known to control cardiovascular function. Depletion of dopamine production in the striatum has been reported to decrease ET receptors. Decreased clearance of dopamine in ET(B−/− mice may have led to upregulation of vasoconstricting ET(B2) receptors in the tunica media of resistance vessels. Another explanation may be that the absence of inhibitory effect of ET(B) receptors on ET(B1) receptors in adrenal medulla of ET(B−/− mice could have led to the increase in circulating epinephrine.

We have reported that disruption of the D2 receptor in mice leads to development of renin-dependent hypertension and decreased ability to excrete sodium load. In the present studies, D2−/− mice not only had a greater basal urine flow rate and sodium excretion than D2+/+ mice but also responded to saline loading with greater natriuresis and diuresis than the D2+/+ mice. Increased sodium excretion in the D2−/− mice was associated with lower Na+K+-ATPase activity, the cause of which remains to be determined. However, ET(B) receptors have been reported to decrease chloride transport at the thick ascending limb of Henle. Pressure natriuresis also may have contributed to increased sodium excretion in the D2−/− mice.

In summary, on the basis of our examination of D2 receptor–deficient mice, we conclude that D2 dopamine receptors expressed on sympathetic neurons normally act to inhibit sympathetic outflow from the nervous system. When 50% of the D2 receptor population is depleted, concomitant increases occur in sympathetic outflow and expression of ET(B) receptors in several tissues, including liver and, presumably, vascular smooth muscle cells as well. The absence of inhibitory tone on sympathetic outflow mediated by the D2 dopamine receptor coupled with increased ET(B) activity may predispose the animal to hypertension.

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