Angiotensin-II Type 1 Receptor–Mediated Hypertension in D4 Dopamine Receptor–Deficient Mice


Abstract—Dopamine receptors are important in systemic blood pressure regulation. D4 receptors are expressed in the kidney and brain, but their role in cardiovascular regulation is unknown. In pentobarbital-anesthetized mice, systolic and diastolic blood pressures were elevated in sixth-generation D4 receptor–deficient (D4/−/) mice and in tenth-generation D4/−/ mice compared with D2 wild-type (D2+/+) littermates. The conscious blood pressures measured via a chronic arterial (femoral) catheter or telemetry (carotid) were also higher in D4/−/ mice than in D2 littermates. Basal renal and plasma renin concentrations were similar in the 2 mouse strains. The protein expression of angiotensin II type 1 receptor was increased in homogenates of kidney (330±53%, n=5) and brain (272±69%, n=5) of D4/−/ mice relative to D4+/+ mice (kidney: 100±12%, n=5; brain: 100±32%, n=5). The expression of the receptor in renal membrane was also increased in D4/−/ mice (289±28%, n=8) relative to D4+/+ mice (100±14%, n=10). In contrast, the expression in the heart was similar in the 2 strains. Bolus intravenous injection of angiotensin II type 1 receptor antagonist losartan initially decreased mean arterial pressures to a similar degree in D4/−/ and D4+/+ littermates. However, the hypotensive effect of losartan dissipated after 10 minutes in D4/−/ mice, whereas the effect persisted for >45 minutes in D4/−/ mice. We conclude that the absence of the D4 receptor increases blood pressure, possibly via increased angiotensin II type 1 receptor expression. (Hypertension. 2006;47:288-295.)

Key Words: dopamine receptors, angiotensin II mice hypertension angiotensin II endothelin vasopressins

Essential hypertension is a major risk factor for the development of cardiovascular disease.1 It is a heterogeneous disease in which both genetics and environmental influences blood pressure.2 Dopamine affects cardiovascular regulatory mechanisms by its actions on renal hemodynamics and ion and water transport and by its regulation of hormones and humoral agents, such as aldosterone, catecholamines, endothelin, prolactin, proopiomelanocortin, renin, and vasopressin. In addition, dopamine can control blood pressure by acting on neuronal cardiovascular centers, heart, and arterial and venous vessels.3–9 Dopamine exerts its actions by occupation of the D1-like (D1 and D5) and D2-like (D2, D3, and D4) family of cell surface G protein–coupled receptors. We have reported that disruption of the D2, D3, D5, and D4 receptors leads to hypertension in mice, via specific pathophysiologic mechanisms.10–13 The cardiovascular consequences of disruption of the D4 receptor have not been reported. D4 receptors are expressed in the heart, renal collecting ducts, juxtaglomerular cells, and in brain nuclei known to affect blood pressure, but their role in cardiovascular regulation is unknown.14–17 Loci near the D4 receptor gene (11p15.5) have been linked to hypertension,18,19 and polymorphisms of the D4 receptor gene are associated with hypertension.20 Therefore, we tested the hypothesis that the D4/−/ mouse has a cardiovascular phenotype.

Methods

Generation of D4 Dopamine–Receptor Mutant Mice

The original F1 hybrid strain (129/Sv×C57BL/6) carrying a mutant form of the D4 dopamine receptor was initially generated and backcrossed to C57BL/6 mice. Heterozygous (D4+/−) mice were mated to obtain D4/−/ and D4+/+ littermates, and the D4/−/ mice were backcrossed with C57BL/6 mice to obtain sixth- and tenth-generation mice in the Department of Physiology and Pharmacology, Oregon Health and Science University.21 We used sixth-generation mice for acute studies and tenth-generation mice for chronic and immunoblotting studies. All of the animals were genotyped and treated in accordance with National Institutes of Health guidelines for ethical treatment and handling of animals in research.
Blood Pressure Measurement

Blood Pressures Under Anesthesia
Mice were anesthetized with pentobarbital (50 mg/kg IV) and tracheotomized (PE100). Catheters (PE50 heat-stretched to 180-µm tip) were inserted into the femoral vessels for fluid administration and blood pressure monitoring. Blood pressures were recorded (CardioMaxII, Columbus Instrument) after 1 hour of equilibration.

Blood Pressures Without Anesthesia
Conscious blood pressures were measured in 2 sets of mice. In the first set of studies, blood pressures were measured via a femoral artery catheter, coated with 5% heparin complex, threaded upward and out of a 5-mm incision at the nape of the neck. Catheter was flushed immediately (1/2 mg plasmin and 1000 U heparin/mL of sterile saline) and every 2 days thereafter. One to 3 days after catheter placement, blood pressures were measured in freely moving, unanesthetized mice. In the second set of studies, TA-PAC20 catheter placement, blood pressures were measured in freely moving, sterile saline) and every 2 days thereafter. One to 3 days after

Acute Saline Loading Study
After a 60-minute stabilization period after the catheter insertion and a baseline 60-minute period for blood pressure measurement, a normal saline load equivalent to 5% body weight was infused intravenously for 30 minutes. Urine was collected during saline loading via suprapubic cystostomy for another 30 minutes; 3 more urine collection periods of 60 minutes each were obtained after saline loading. Blood (50 µL) was obtained from the femoral artery before the load and at the end of the last urine collection. The kidneys were homogenized with 0.1 mol/L HClO4 and centrifuged at 6000 g for 20 minutes at 4°C. The supernatant and urine catechol concentrations were determined by high-performance liquid chromatography and electrochemical detection.

Acute Drug Infusion Studies
In additional experiments, several antagonists of receptors known to influence blood pressure were infused via a central venous catheter, and blood pressure and heart rate were monitored. The drugs were α-adrenergic antagonist phentolamine (5 ng/kg per minute), angiotensin II type 1 receptor (AT1) antagonist losartan (3 mg/kg per minute for 10 minutes), endothelin B receptor (ETB) antagonist BQ788 (6.6 µg/kg per minute for 15 minutes), and V1 vasopressin receptor (V1) antagonist [1-(6-mercapto-β, β-cyclopentamethylenepropionic acid)-2-(O-methyl)-tyrosine] arginine vasopressin (10 µg/kg over 30 s). The rationale and dosages of these drugs have been validated.11–13 The dose of losartan had been shown previously to have an effect of limited duration in wild-type mice.12 We also studied the acute effect on blood pressure of varying doses of bolus intravenous injections of angiotensin II (0.1, 0.3, 1, 3, and 10 ng/kg per minute). Mice were euthanized with pentobarbital (100 mg/kg) at the end of the experiments.

Measurement of Renin, Na+ /K+-ATPase Activity, and Catechols
Plasma and renal renin concentrations were assessed by radioimmunoassay measuring the generation of angiotensin 1-12 Na+/K+-ATPase activity in renal cortex or medulla was measured as the ouabain-sensitive dephosphorylation of (tris)-p-nitrophenyl phosphate by K+/p-nitrophenyl phosphatase.11,12 The kidneys were homogenized with 0.1 mol/L HClO4 and centrifuged at 6000 g for 20 minutes at 4°C. The supernatant and urine catechol concentrations were determined by high-performance liquid chromatography and electrochemical detection.

Chronic Sodium Balance Study With Ration Feeding in Metabolic Cages
The mice were maintained in metabolic cages to allow quantitative urine collections and ration feeding, modified from a rat-diet protocol.25,26 The baseline sodium diet (5 g/25 g body weight per day, TD.90228, Harlan Teklad) consisted of a gelled mixture of distilled water (10 mL/5 g of mouse chow), agar (0.04 g/10 mL of water), and 0.4% NaCl (added before gelation). The sodium replete diet was the same, except for the addition of 0.8% NaCl. All of the animals received the same amount of gelled food, determined by weighing the gelled mixture. On day 3, the mice were ration-fed 0.4% NaCl gelled food. On day zero, the ration was changed to 0.8% NaCl for 1 week. Seven days later, the mice were euthanized after blood pressures were recorded with anesthesia. Serum and urinary samples were analyzed for Na, K, Cl (E4A Electrolyte system, Beckman) and creatinine concentrations (Creatinine Analyzer2,
Beckman). After sacrifice, kidneys, brains, and hearts were homogenized, as reported previously. In additional studies, mouse kidney homogenates were centrifuged at 42 000g to obtain membrane fractions.

### Statistical Analysis

Data expressed as mean±SE were analyzed by repeated-measures ANOVA for comparisons within groups and 1-way factorial ANOVA for comparisons among groups. Student t test was used for 2-group comparison, with Bonferroni correction as indicated. *P*<0.05 was considered significant.

### Results

#### Blood Pressure and Other Physiological Data in D1/−/− Mice

Figure 1A shows that the systolic (SBP), diastolic (DBP), and mean arterial (MAP) blood pressures (mm Hg) measured under anesthesia in sixth-generation mice were higher in D1/−/− mice (SBP, 128±2; DBP, 98±1; MAP, 108±1; n=27) than in D1+/+ littermates (SBP, 104±1; DBP, 79±1; MAP, 87±1; n=18; 8- to 12-months old, mixed gender). No differences in MAP between genders were found in D1+/+ mice (female: 93±1, n=10; male: 90±1, n=8) and D1/−/− mice (female: 113±4, n=10; male: 110±2, n=18). Body weights were the same in D1+/+ and D1/−/− mice (28±1 g in both groups). However, heart weights (% body weight) were greater in D1+/+ than in D1/−/− mice (0.50±0.02 versus 0.43±0.01; *P*<0.05), whereas kidney weights (1.15±0.08 versus 1.23±0.06) were similar. The heart rates (447±6 versus 430±8 bpm) were not different between the 2 mouse strains.

In pentobarbital-anesthetized tenth-generation (4- to 6-months old, mixed gender), the blood pressures of D1/−/− mice were also higher than in D1+/+ littermates (Figure 1B). Conscious blood pressures were also higher in the tenth-generation D1/−/− mice than in D1+/+ mice (4- to 6-months old, mixed gender) measured via the femoral artery (Figure 2A) or by telemetry (Figure 2B and 2C). SBPs measured by telemetry were lower than those measured via the femoral catheter, presumably because there were no distractions in the mice studied by telemetry.

#### Arterial Blood Pressure, Renal Function, and Catechol Excretions in Response to an Acute Sodium Load

SBP, DBP, and MAP were not affected by an acute sodium load in D1/−/− and D1+/+ mice (data not shown). Glomerular filtration rate was not different between the 2 mouse strains and was not affected by saline loading (Table 1). Urine flow and sodium excretion, which were increased by saline loading, were also similar in the 2 mouse strains. Urinary catechol excretions were similar in D1/−/− and D1+/+ mice. Saline loading increased dopamine excretion in both mouse strains without affecting the excretion of other catechols (Table 2).

### Table 1. The Effect of Saline Loading on Renal Function in D1+/+ (n=6) and D1/−/− (n=18) Mice

<table>
<thead>
<tr>
<th>Collection Periods</th>
<th>GFR (nL/g kidney weight per minute)</th>
<th>V (µL/min)</th>
<th>UNaV (nEq/min)</th>
<th>FENa (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1+/+</td>
<td>D1/−/−</td>
<td>D1+/+</td>
<td>D1/−/−</td>
<td>D1+/+</td>
</tr>
<tr>
<td>Baseline</td>
<td>1225±256</td>
<td>198±123</td>
<td>1.21±0.09*</td>
<td>1.11±0.07*</td>
</tr>
<tr>
<td>Loading</td>
<td>1390±107</td>
<td>1823±136</td>
<td>2.94±0.27</td>
<td>4.28±0.84</td>
</tr>
<tr>
<td>Postload 1</td>
<td>1240±77</td>
<td>1493±203</td>
<td>1.72±0.33*</td>
<td>3.36±0.72</td>
</tr>
<tr>
<td>Postload 2</td>
<td>1146±167</td>
<td>1304±80*</td>
<td>1.32±0.06*</td>
<td>2.53±0.52</td>
</tr>
<tr>
<td>Postload 3</td>
<td>1260±133</td>
<td>1247±102*</td>
<td>1.19±0.10*</td>
<td>1.32±0.21*</td>
</tr>
</tbody>
</table>

Data are mean±SE. Each period lasted 60 minutes. MAgs were not affected by time or saline infusion. GFR, glomerular filtration rate; V, urine flow; UNaV, sodium excretion; FENa, fractional sodium excretion.

### Table 2. The Effect of Saline Loading on Urinary Catechols (pg/min) in D1+/+ (n=5) and D1/−/− (n=17) Mice

<table>
<thead>
<tr>
<th>Collection Periods</th>
<th>L-DOPA (pg/min)</th>
<th>DOPAC (pg/min)</th>
<th>Dopamine (pg/min)</th>
<th>Epinephrine (pg/min)</th>
<th>Norepinephrine (pg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1+/+</td>
<td>D1/−/−</td>
<td>D1+/+</td>
<td>D1/−/−</td>
<td>D1+/+</td>
<td>D1/−/−</td>
</tr>
<tr>
<td>Baseline</td>
<td>10.6±2.3</td>
<td>15.2±2.4</td>
<td>105±26</td>
<td>82±9</td>
<td>498±87*</td>
</tr>
<tr>
<td>Loading</td>
<td>15.1±4.0</td>
<td>18.0±3.9</td>
<td>231±61</td>
<td>149±31</td>
<td>884±107</td>
</tr>
<tr>
<td>Postload 1</td>
<td>14.0±4.5</td>
<td>20.5±5.5</td>
<td>183±67</td>
<td>143±37</td>
<td>606±112*</td>
</tr>
<tr>
<td>Postload 2</td>
<td>12.5±3.7</td>
<td>31.3±14.0</td>
<td>131±51</td>
<td>144±44</td>
<td>492±37*</td>
</tr>
<tr>
<td>Postload 3</td>
<td>9.0±2.3</td>
<td>33.7±9.7</td>
<td>140±59</td>
<td>151±43</td>
<td>518±86*</td>
</tr>
</tbody>
</table>

Data are mean±SE. Each period lasted 60 minutes. DOPA indicates dihydroxyphenylalanine; DOPAC, dihydroxyphenylacetic acid.

*P*<0.05 vs loading period or postload 1, ANVR, Newman Keuls test.

#P<0.05 vs baseline, ANVR, Newman Keuls test.
Renal and Plasma Renin Concentrations in D4−/− Mice

Renal renin concentrations (μg A/g kidney per hour) were similar in D4−/− mice (57.5±7.2, n=18) and D4+/+ mice (70.2±18.3, n=5). Plasma renin concentrations were also not significantly different between D4−/− (3835±2097 ng A/g/mL per hour, n=18) and D4+/+ (3540±2881, n=5) mice.

Na+/K+-ATPase Activity

Renal cortical and medullary Na+/K+-ATPase activities were not significantly changed in D4−/− mice (cortex = 34.2±0.5 mmol Pi/mg protein per minute, medulla = 33.2±0.5, n=17) compared with D4+/+ mice (cortex = 33.4±2.0 mmol Pi/mg protein per minute, medulla = 31.5±2.6, n=5). The D4 receptor agonist, SKF81297 (1 μmol/L), decreased Na+/K+-ATPase activity to a similar extent in cortex (D4−/− = 25.98±2.91%, D4+/+ = 21.60±1.41%) and medulla (D4−/− = 23.17±3.34%, D4+/+ = 20.02±1.37%; P<0.05, ANOVA) in the 2 mouse strains.

Role of Blood Pressure–Regulating Systems in the Hypertension of D4−/− Mice

Bolus intravenous injection of losartan decreased MAP promptly and to a similar degree initially in the 2 strains. However, the effect dissipated quickly with recovery toward baseline 10 minutes after the injection in D4−/− mice, whereas the hypotensive effect of losartan persisted for >45 minutes in D4+/+ mice (Figure 3a). In contrast, the V1 vasopressin receptor antagonist, [1-(β-mercapto-β-b-cyclopentamethylenepropionic acid)-2-(O-methyl)-tyrosine] arginine vasopressin, was given intravenously (D4−/−, n=6; D4+/+, n=6). A slight decrease in blood pressure was noted in D4−/− mice 8 minutes after the start of BQ 788 infusion (P<0.05, ANOVA, Newman Keuls test). Differences between D4−/− and D4+/+ mice became evident at 9 minutes (*P<0.05 vs D4−/−, t test). (b) V1 vasopressin receptor antagonist, BQ 610, decreased blood pressure in both D4−/− and D4+/+ mice immediately after the injection (P<0.05, ANOVR, Newman Keuls test). However, a significantly longer duration of BP suppression was observed in D4−/− mice compared with D4+/+ mice beginning 8 minutes after losartan administration and lasting as long as 45 minutes. (c) ETA receptor antagonist, ETB receptor antagonist, (d) ETA receptor antagonist, losartan (Figure 4a), 20.02

Figure 3. Effect of antagonists to α-adrenergic, AT1, endothelin (A and B), and V1 vasopressin receptors on MAP in anesthetized D4−/− and D4+/+ mice. (a) AT1 receptor antagonist, losartan, was given as an intravenous bolus injection (D4−/−, n=6; D4+/+, n=5). A decrease in blood pressure was noted in both D4−/− and D4+/+ mice immediately after the injection (P<0.05, ANOVR, Newman Keuls test). However, a significantly longer duration of BP suppression was observed in D4−/− mice compared with D4+/+ mice immediately after the infusion of phenolamine in D4−/− mice and 7 minutes in D4+/+ mice (P<0.05, ANOVR, Newman Keuls test). Differences between D4−/− and D4+/+ mice became evident at 8 minutes (*P<0.05, t test). (c) ETB receptor antagonist, BQ 788, was infused intravenously (D4−/−, n=6; D4+/+, n=6). A slight increase in blood pressure was noted in D4−/− but not in D4+/+ mice, 8 minutes after the start of BQ 788 infusion (P<0.05, ANOVR, Newman Keuls test). Differences between D4−/− and D4+/+ mice became evident at 9 minutes (*P<0.05, t test). (d) ETA receptor antagonist BQ 610 or the α-adrenergic antagonist phentolamine was infused intravenously (D4−/−, n=6; D4+/+, n=4). There were no effects of BQ 610 on blood pressure, but a significant decrease in blood pressure was noted 5 minutes after the infusion of phentolamine in D4−/− mice and 7 minutes in D4+/+ mice (P>0.05, ANOVR, Newman Keuls test).

Figure 4. Effect of angiotensin II on MAP in anesthetized D4−/− and D4+/+ mice. Angiotensin II dose-dependently (0.1, 0.3, 1, 3, and 10 ng/kg per mouse) increased the blood pressure in both D4−/− [Yc=16.45+ (5.6×dose), n=5] and D4+/+ mice [Yc=13.89+ (3.37×dose), n=4; P<0.05]. Although, a higher MAP was found in D4−/− mice than in D4+/+ mice.
mice at any dose, the MAP tended to increase to a greater extent in D₄⁺/⁺ than in D₄⁻/⁻ mice, reaching significance at 10 ng (ΔMAP, mm Hg, D₄⁺/⁺: 67 ± 4, n = 5; D₄⁻/⁻: 44 ± 4, n = 4; P < 0.05; t test; Figure 4).

### Chronic Sodium Balance Study

Age- and gender-matched D₄⁻/⁻ mice and D₄⁺/⁺ littermates (tenth-generation) and C57/BL6 mice (Taconic, Germantown, NY) were housed in the animal facility under the same conditions for >1 month before use. Backcrossing to the sixth generation or to more than the tenth generation results in a C57/BL6 genetic background >98% or >99% congenic, respectively. In agreement with data shown in Figure 1A and 1B, SBP and DBP under pentobarbital anesthesia were higher in D₄⁻/⁻ than in D₄⁺/⁺ mice (female, 6 months old). D₄⁻/⁻ mice weighed less than D₄⁺/⁺ mice possibly because of the ration feeding (sodium intake = 0.8% NaCl) in metabolic cages. Sodium and water excretions (normalized by body weight) tended to be lower in D₄⁻/⁻ than in D₄⁺/⁺ mice, but the differences did not reach statistical significance. Creatinine clearance and serum sodium concentration were similar in D₄⁻/⁻ and D₄⁺/⁺ mice (Table 3).

#### AT₁ Receptor Protein Expression

To determine a mechanism for the involvement of the AT₁ receptor in the hypertension of D₄⁻/⁻ mice, we measured AT₁ receptor protein expression in the ration-fed tenth-generation D₄⁻/⁻ mice and C57/BL6 mice. AT₁ receptor expression (45 kDa) in whole-kidney homogenates of D₄⁻/⁻ mice was increased (330 ± 53%, normalized by the band density of D₄⁺/⁺ set to 100%, n = 5; P < 0.05) compared with D₄⁺/⁺ mice (100 ± 12%, n = 5; Figure 5A). AT₁ receptor expression was also increased in whole-brain homogenates of D₄⁻/⁻ mice (272 ± 69%; P < 0.05) compared with D₄⁺/⁺ mice (100 ± 32%; Figure 5B). In contrast, there were no differences in AT₁ expression in whole heart homogenates between the 2 mouse strains (Figure 5C).

In additional experiments, tenth-generation D₄⁻/⁻ and D₄⁺/⁺ mice littermates (mixed gender, 4 to 5 months old) were studied to achieve a >99% C57/BL6 genetic background. There were no differences in body weight between D₄⁻/⁻ mice (31 ± 2 g, n = 10) and D₄⁺/⁺ littermates (27 ± 2 g, n = 8), whereas blood pressures were higher in D₄⁻/⁻ mice than in D₄⁺/⁺ littermates (Figure 1B). AT₁ receptor expression was measured in kidney membrane fractions; receptors in the cytosol would not be responsive to angiotensin II stimulation. AT₁ receptor expression in kidney membrane fractions was increased in D₄⁻/⁻ mice relative to D₄⁺/⁺ littermates (D₄⁻/⁻ mice: 100 ± 14%; D₄⁺/⁺ mice: 289 ± 28; % of D₄⁺/⁺; P < 0.05; Figure 6), in agreement with studies using renal homogenates.

#### Discussion

The present studies show that the complete lack of D₄ dopamine receptors resulted in increased blood pressure. Furthermore, the increased blood pressure in the mutant mice was associated with a prolonged depressor response caused by the AT₁ receptor antagonist losartan. The transient effect of losartan in the D₄⁺/⁺ mice was related to the dose and similar to the hypotensive effect in D₄⁻/⁻ mice. The prolonged hypotensive effect of losartan in the D₄⁻/⁻ mice is also
Evidence has accumulated that the increase in blood pressure caused by central AT1 activation is mediated with37–40 or without41–44 activation of the sympathetic nervous system. In the present study, α-adrenergic blockade with phentolamine decreased blood pressure to a similar extent in D4−/− and D4+/+ mice. This observation may be specific to the D4−/− mice, because the α-adrenergic blockade decreased blood pressure to a greater extent in D4−/− and D4+/+ mice than in their wild-type counterparts.11,13 There were also no differences in renal or urinary catechol excretion between D4+/+ and D4−/− mice. The pressor effect mediated by AT1 receptors expressed in the central nervous system has also been shown to be mediated, in part, by activation of central V1 receptors.38,45,46 The increased blood pressure caused by disruption of the D4 dopamine receptor is characterized by activation of central V1 vasopressin receptors.13 However, in the current study, V1 vasopressin receptor blockade did not decrease but actually produced a slight increase in blood pressure in D4−/− mice, suggesting a different mechanism to be involved.

Endothelin receptors may mediate pressor and depressor effects.37–49 We have reported that disruption of the D2 dopamine receptor in mice increased blood pressure possibly via the vasoconstrictor ETB2 (presumably in vascular smooth muscle or in brain centers).11 The D2 receptor, like the D3 receptor, is not expressed in endothelial cells.50 Thus, neither D2 nor D3 receptors can activate the vasodilatory ETB1 receptors in endothelial cells. The modest increase in blood pressure by blockade of ETB receptors might be mediated via vasoconstrictor ETB2 in the D4−/− mice.

Dopamine has been shown to act as a potent intrarenal natriuretic hormone in humans and rodents.3,4 D4 receptors have been shown to antagonize vasopressin- and aldosterone-dependent sodium reabsorption in the cortical collecting duct.51,52 In the present study, we did not find significant differences in renal Na+K+-ATPase activity and urinary dopamine excretion between D4−/− and D4+/+ mice. The D4+/+ mice did not have an impaired ability to excrete an acute saline load. There are also no differences in sodium excretion between conscious D4−/− mice and D4+/+ littermates in spite of an increase in AT1 receptors in the kidney of D4−/− mice. Possibly, the high blood pressure may have elicited a pressure natriuresis through other mechanism that obfuscated any deficits in the renal handling of sodium in D4−/− mice.53,54

In summary, we have found that disruption of the D4 dopamine receptor in mice causes hypertension that is associated with increased expression of AT1 receptors in the brain and kidney but not in the heart. The mechanism by which D4 receptors regulate AT1 receptor expression remains to be determined.

**Perspectives**
This study demonstrates that disruption of the D4 dopamine receptor results in increased blood pressure that may be related to activation of AT1 receptors in the brain. However, determination of AT1 receptor expression and function in specific brain nuclei are needed to understand how the D4...
receptor interacts with the AT$_1$ receptor in the central regulation of blood pressure. AT$_1$ receptors are also increased in the kidneys of D$_4^{-/-}$ mice, but these mice do not have an impaired ability to excrete an acute sodium load. It is possible that D$_4^{-/-}$ mice may not be able to excrete a chronic sodium load, but that remains to be determined. Because the D$_3$ receptor gene locus is linked to and D$_3$ receptor variants are associated with hypertension, the relevance of the D$_3$ receptor in the pathogenesis of human essential hypertension needs to be evaluated.

Acknowledgments

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References

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In the article by Bek et al in the February 2006 issue of *Hypertension* (Bek MJ, Wang X, Asico LD, Jones JE, Zheng S, Li X, Eisner GM, Grandy DK, Carey RM, Soares-da-Silva P, Jose PA. Angiotensin-II type 1 receptor–mediated hypertension in D4 dopamine receptor–deficient mice. *Hypertension* 2006;47:288–292) the symbols in the legend for Figure 2B were incorrect. The correct Figure 2 appears below. The authors regret the error.

![Figure 2](image-url)