Impaired renal D₁-like and D₂-like dopamine receptor interaction in the spontaneously hypertensive rat

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Departments of 1Pediatrics, 5Physiology and Biophysics, and 4Medicine, Georgetown University Medical Center, Washington, District of Columbia 20007; 2Zambon Group, 20091 Bresso (MI), Italy; and 3Developmental Endocrinology Branch, National Institute of Child Health and Human Development, Bethesda, Maryland 20892

Received 8 March 2000; accepted in final form 22 May 2001

Ladines, Cecilia A., Chunyu Zeng, Laureano D. Asico, Xiaoguang Sun, Felice Pocchiari, Claudio Semeraro, Joseph Pisegna, Stephen Wank, Ikuyo Yamaguchi, Gilbert M. Eisner, and Pedro A. Jose. Impaired renal D₁-like and D₂-like dopamine receptor interaction in the spontaneously hypertensive rat. Am J Physiol Regulatory Integrative Comp Physiol 281: R1071-R1078, 2001.—D₁-like (D₁, D₅) and D₂-like (D₂, D₃, D₄) dopamine receptors interact in the kidney to produce a natriuresis and a diuresis. Disruption of D₁ or D₂ receptors in mice results in hypertension that is caused, in part, by a decreased ability to excrete an acute saline load. We studied D₁-like and D₂-like receptor interaction in anesthetized spontaneously hypertensive rats (SHR) by the intrarenal infusion of Z-1046 (a novel dopamine receptor agonist with rank order potency of D₅>D₃>D₂>D₁>D₁). Z-1046 increased glomerular filtration rate (GFR), urine flow, and sodium excretion in normotensive Wistar-Kyoto rats but not in SHRs. The lack of responsiveness to Z-1046 in SHRs was not an epiphenomenon, because intrarenal cholecystokinin infusion increased GFR, urine flow, and sodium excretion to a similar extent in the two rat strains. We conclude that renal D₁-like and D₂-like receptor interaction is impaired in SHRs. The impaired D₁-like and D₂-like receptor interaction in SHRs is not caused by alterations in the coding sequence of the D₁ receptor, the D₂-like receptor expressed in rat renal tubules that has been shown to be involved in sodium transport. Because the diuretic and natriuretic effects of D₁-like receptors are, in part, caused by an interaction with D₂-like receptors, it is possible that the decreased Z-1046 action in SHRs is secondary to the renal D₁-like receptor dysfunction in this rat strain.

D₁-like receptors; D₂-like receptors; natriuresis; diuresis; cholecystokinin; hypertension

SEVERAL CANDIDATE GENES have been shown to be important in the pathogenesis of hypertension in human and rodent models of genetic hypertension, but the etiology of essential hypertension remains to be determined (22). In several models of hypertension, an impairment in the ability of the kidney to regulate fluid and electrolyte balance is important in the pathogenesis of the high blood pressure (12). There is ample evidence that under conditions of moderate sodium loading, endogenous renal dopamine, acting via D₁-like dopamine receptors with contributions by D₂-like dopamine receptors, is important in the regulation of sodium excretion (13, 17, 18, 29, 37). The five dopamine receptors that have been cloned are expressed in the kidney: two belong to the D₁-like family (D₁ and D₅) and three belong to the D₂-like family (D₂, D₃, and D₄) (17, 18). Although dopamine or the selective D₁-like receptor agonist fenoldopam elicits a decrease in proximal tubular sodium reabsorption in normal humans or in Wistar-Kyoto (WKY) rats, this effect is not seen in the spontaneously hypertensive rat (SHR) and in humans with essential hypertension (1, 7, 10, 26). In mice, disruption of the D₁-receptor gene led to the development of hypertension (1).

However, abnormalities in the D₁-like receptor alone may not explain salt-sensitive hypertension. Although D₂-like receptors exert an antinatriuretic effect when stimulated independently of D₁-like receptors, D₁-like and D₂-like receptors may participate in complex interactions at different levels and through different mechanisms, resulting in a potentially greater inhibition of the sodium pump (4, 5, 14, 17, 18, 33, 34, 36, 39). For instance, in striatal neurons and proximal tubules (but not in medullary thick ascending limbs or cortical collecting ducts), both D₁-like and D₂-like receptors were required to inhibit Na⁺-K⁺-ATPase activity (4, 5, 33). More recently, we reported that D₁-like receptors exerted a renal vasodilatory effect while D₂-like receptors exerted a renal vasoconstrictor effect (16), in agreement with the studies of Siragy et al. (37). We also found that costimulation of D₁-like and D₂-like receptors resulted in a diuresis and a natriuresis greater than stimulation of D₁-like receptors alone, as predicted by combined ability of these receptors to inhibit Na⁺-K⁺-ATPase activity in renal proximal tubules (4, 16, 33).

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We previously showed that disruption of the D_3-receptor gene in mice produces renin-dependent hypertension and impairment in the excretion of an acute saline load (3). In the SHR, there is also evidence of a defective interaction between D_1- and D_2-like receptors (42). We, therefore, sought to determine whether the ability of D_1-like and D_2-like receptors to inhibit sodium transport in vivo is impaired in the SHR. We compared the effect of Z-1046 (a novel dopamine receptor agonist with rank order potency of D_3$>$D_2$>$D_1$>$$D_1$) (16) on glomerular filtration rate (GFR), urine flow (V), and absolute (U_NaV) and fractional (FENa) sodium excretion between the WKY rat and its hypertensive counterpart, the SHR. We also studied the coding sequence and expression of the D_3 receptor, the D_2-like receptor expressed in renal tubules involved in sodium transport (17, 23, 27).

**METHODS**

Male WKY and SHRs (12–16 wk old) were maintained on a regular Purina rat chow diet and unlimited water intake. Food but not water was then withheld 24 h before the study. The rats were anesthetized with pentobarbital sodium (50 mg/kg body wt), placed on a heated table to maintain rectal temperature at 37°C, and connected to a tracheostomy (PE-240) (16). Laparotomy was performed to expose the left and right ureters, which were then catheterized (PE-10, heat stretched to 180 μm). In some animals, a Transonic Systems flow probe was secured around the right renal artery (Transonic Systems, Ithaca, NY); the abdomen was closed with surgical clips. Fluid losses throughout the experiment were replaced with 5% albumin at 1% body wt over 30 min. The animals then received an intravenous infusion of saline containing [14C]inulin (0.01 mCi/10 ml; New England Nuclear, Boston, MA) at a rate of 5 ml/h. In some experiments, cholecystokinin was given to achieve a final arterial blood concentration of 10⁻³ mol/l for three periods. After two baseline periods with vehicle infusion, cholecystokinin was given to achieve a final renal arterial blood concentration of 10⁻³ mol/l for three periods. Thereafter, the infusion was changed 10 min before each period to account for the dead space in the renal arterial catheter. All infusions were given at a rate of 40 μl/h.

**Cholecystokinin group.** To determine whether there is receptor selectivity in any differential effect of Z-1046 between WKY and SHRs, we also tested the effect of cholecystokinin. Cholecystokinin receptors, similar to D_1-like receptors, are linked to Gαs and G_q (2, 17). After two baseline periods with vehicle infusion, cholecystokinin was given to achieve a final renal arterial blood concentration of 10⁻³ mol/l for three periods. Thereafter, the infusion was changed to the vehicle during the recovery period as in the Z-1046 group.

Blood samples were obtained before the first collection period, before the fifth collection period, and at the end of the experiment. Radioactivity, sodium, and potassium concentrations were assayed in the blood and urine samples. The position and patency of the intrarenal arterial catheter were verified with lissamine green infusion at the conclusion of the experiment.

**Immunoblotting Studies**

The antipeptide polyclonal affinity-purified rabbit anti-rat D_3 antibody was raised against the specific 19 amino acids in the third cytoplasmic loop of the D_3-dopamine receptor at a concentration of 1 μg/ml (D3R12-A, Alpha Diagnostic International, San Antonio, TX). Membranes derived from kidney homogenates or brush-border membranes (BBM) were mixed with Laemmli sample buffer, boiled for 5 min, subjected to electrophoresis on 7.5% SDS-PAGE, and transferred electrophoretically to nitrocellulose membranes. Non-specific binding was blocked with 10% nonfat dry milk in Tris-HCl-saline-Tween 20 buffer. The membrane was then probed with the D_3 antibody and blood pressure determination, the kidneys were harvested for immunoblotting and RNA studies.

**Renal Function Studies**

**Control group.** The vehicle, normal saline, was infused alone into the right suprarenal artery at a rate of 40 μl/h for eight collection periods for both the hypertensive and normotensive rats. The control group for normotensive rats, concurrently performed with the current studies, was published (16).

**Z-1046 group.** On the basis of previous studies that determined the dose of Z-1046 that produced a natriuresis (16), these groups of rats received the preferential D_3 agonist, Z-1046, at 2 μg·kg⁻¹·min⁻¹ for three periods after two baseline periods where the vehicle, normal saline, was infused. Subsequently, three more collections were made during the recovery period, during which the vehicle alone was again infused. The infusion was changed 10 min before each period to account for the dead space in the renal arterial catheter. All infusions were given at a rate of 40 μl/h.

**Table 1. Effect of vehicle on renal function in the infused right kidney of the SHR**

<table>
<thead>
<tr>
<th>Periods</th>
<th>MAP, mmHg</th>
<th>GFR, ml/g body wt·min⁻¹</th>
<th>V, μl/min</th>
<th>U_NaV, nEq/min</th>
<th>FENa, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>163.0±10.7</td>
<td>1.0±0.1</td>
<td>3.92±0.59</td>
<td>357±98</td>
<td>0.22±0.06</td>
</tr>
<tr>
<td>C2</td>
<td>155.8±6.4</td>
<td>1.7±0.7</td>
<td>4.85±0.70</td>
<td>352±127</td>
<td>0.22±0.08</td>
</tr>
<tr>
<td>C3</td>
<td>157.2±6.8</td>
<td>1.0±0.1</td>
<td>4.27±0.51</td>
<td>407±122</td>
<td>0.29±0.09</td>
</tr>
<tr>
<td>C4</td>
<td>157.8±8.7</td>
<td>1.3±0.2</td>
<td>4.69±0.46</td>
<td>495±131</td>
<td>0.28±0.08</td>
</tr>
<tr>
<td>C5</td>
<td>155.8±8.0</td>
<td>1.2±0.1</td>
<td>4.56±0.49</td>
<td>500±143</td>
<td>0.29±0.09</td>
</tr>
<tr>
<td>C6</td>
<td>157.2±9.3</td>
<td>1.1±0.1</td>
<td>4.39±0.50</td>
<td>505±149</td>
<td>0.29±0.09</td>
</tr>
<tr>
<td>C7</td>
<td>157.2±8.5</td>
<td>1.1±0.1</td>
<td>4.24±0.50</td>
<td>509±174</td>
<td>0.30±0.09</td>
</tr>
<tr>
<td>C8</td>
<td>158.8±7.2</td>
<td>1.1±0.1</td>
<td>4.24±0.51</td>
<td>565±169</td>
<td>0.33±0.08</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SE. SHR, spontaneously hypertensive rats (body wt 342±2 g, n = 5); GFR, glomerular filtration rate; V, volume; C1–8, periods during vehicle infusions; U_NaV, urine Na excretion; FENa, fractional Na excretion; MAP, mean arterial pressure.
primary antibody (1:250) for 1 h. After three washes, the membrane was incubated with peroxidase-labeled anti-rabbit IgG donkey serum (Amersham, Arlington Heights, IL) with 2% normal donkey serum for 60 min. In some studies, the D3 antibodies were preadsorbed with the immunizing peptide D3R12-P (1 μg/5 μg incubated for 24 h at 4°C). Specific bands were visualized using enhanced chemiluminescence (ECL Western Blotting Detection Kit, Amersham, Arlington Heights, IL). Human embryonic kidney cells transfected with the D3-dopamine receptor cDNA and rat olfactory tubercle were used as positive controls. The specific bands were quantified using Quantiscan (Biosoft, Ferguson, MO) with the total area arbitrarily set at 100% (3).

Sequencing Studies
Total RNA was extracted from the kidney of SHR or WKY rats using the RNAzol B (Tel-Test, Friendswood, TX). Total RNA (1 μg) was reverse-transcribed using avian myeloblastosis virus reverse transcriptase (Promega, Madison, WI) at 42°C for 30 min using D3-specific primer 5′-CGAAGTGGG-TAAAGGGAGTG-3′ (complementary to nt 1756–1779). Subsequently, PCR was performed to amplify the coding region of the rat D3-receptor mRNA [5′-ATGCCACCTCTGAGCAGATAAGGGCG-3′ (nt 82–108) and 5′-GCGAGGACAGGATCTGAGGAAGCC-3′ (complementary to nt 1756–1779)]. A set of primers, 5′-GGAGTCTGGAATTTCAGC-3′ (complementary to nt 847–864), was used to confirm the results (GenBank accession number A17753). The PCR products were sequenced using the Applied Biosystems 377 DNA sequencer (Perkin Elmer, Wellesley, MA).

Statistical Analyses
The data are expressed as means ± SE. Comparison within groups was made using ANOVA for repeated measures and comparison among groups was made using ANOVA with Newman Keuls test. Measurements between different periods were compared using paired t-test with Bonferroni correction. Corresponding periods between two different groups were analyzed using independent t-test. A P < 0.05 was considered significant.

RESULTS

Effect of Vehicle on Renal Function in the SHR

Intrarenal arterial infusion of the vehicle on the right kidney of the SHR (n = 5) had no effect on mean arterial pressure (MAP), GFR, V, UNaV, FENa (Table 1), or renal blood flow (not shown). Likewise, the vehicle did not affect renal function in the WKY rats (16).

Effect of Z-1046 Infusion on Renal Function

Intrarenal arterial infusion of Z-1046 at a dose of 2 μg·kg⁻¹·min⁻¹ did not affect the MAP or heart rate in either group of animals. However, Z-1046 increased V, UNaV, FENa, and GFR in WKY rats (Table 2) but not in SHRs (Tables 3 and 4). Z-1046 did not alter these variables in SHRs whether basal sodium excretion was the same as or higher than in the WKY rats.

Effect of Cholecystokinin Infusion on Renal Function

To determine whether the failure of the kidney of the hypertensive rat to respond to Z-1046 was an epiphenomenon, we studied the effects of the intrarenal arterial infusion of cholecystokinin. Cholecystokinin induced a natriuresis and diuresis (Tables 5–7) in both WKY and SHRs. The natriuretic and diuretic effects of Z-1046 were similar to those of Z-1046 and were associated with the same degree of natriuresis and diuresis (Tables 6–7) in both WKY and SHRs.
cholereticokinin were evident in SHRs whether basal sodium excretion was the same as or higher than in the WKY rats. Because the baseline V, UNaV, FENa, and GFR were slightly different between WKY and SHRs, we also expressed the effects of cholereticokinin as percent maximum response compared with baseline period 2. The maximum increases in V, UNaV, FENa, and sodium excretion were the same or higher in SHRs compared with WKY rats. (Fig. 1).

**DISCUSSION**

Our studies show that the ability of Z-1046, a dopamine receptor agonist with the rank order potency D3>D2>D0>D1, to increase V, UNaV, FENa, and GFR in the normotensive WKY rat is not present in its hypertensive counterpart the SHR. Previous studies in our laboratory have shown that the natriuretic and diuretic effects of Z-1046 are D1- and D2-like receptor mediated (16). Thus the infusion of the D1-like antagonist SCH-23390 or the D2-like antagonist domperidone prevented the natriuresis and diuresis caused by Z-1046 alone in the WKY rat. In the same study, it was shown that the increase in GFR with Z-1046 was caused by a D1-like receptor action (16). The inability of Z-1046 to affect renal function in the SHR is consistent with an impaired interaction between D1- and D2-like receptors.

Several studies have shown an impaired function of the D1-like receptor in the kidney in rodent genetic and human essential hypertension (6–10, 17, 18, 24, 26). The defective D1-like function in the kidneys of SHRs is caused by an uncoupling of the D1-dopamine receptor from its G protein/effector complex (see review, Refs. 17, 18). The uncoupling has been suggested to be caused by a “hyper” serine phosphorylation of the D1 receptor (31, 43). An important role of the D1-receptor gene in regulating blood pressure was supported by the development of hypertension in mice in which the D1-receptor gene was deleted (9). The uncoupling has been proposed to be caused by an uncoupling of the D1-dopamine receptor from its G protein/effector complex (see review, Refs. 17, 18). The uncoupling has been suggested to be caused by a “hyper” serine phosphorylation of the D1 receptor (31, 43). An important role of the D1-receptor gene in regulating blood pressure was supported by the development of hypertension in mice in which the D1-receptor gene was disrupted (1). It is possible that the failure of the preferential D2-like agonist Z-1046 to alter GFR or produce a

**Table 5. Effect of cholereticokinin on renal function in the infused right kidney of the WKY**

<table>
<thead>
<tr>
<th>Periods</th>
<th>MAP, mmHg</th>
<th>GFR, ml·g kidney⁻¹·min⁻¹</th>
<th>V, μl/min</th>
<th>UNaV, nEq/min</th>
<th>FENa, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td>97.0 ± 3.0</td>
<td>1.5 ± 0.1</td>
<td>4.54 ± 0.57</td>
<td>175 ± 27</td>
<td>0.08 ± 0.01</td>
</tr>
<tr>
<td>B2</td>
<td>96.9 ± 2.5</td>
<td>1.2 ± 0.2</td>
<td>4.52 ± 0.64</td>
<td>211 ± 44</td>
<td>0.11 ± 0.02</td>
</tr>
<tr>
<td>CCK1</td>
<td>97.9 ± 2.0</td>
<td>1.5 ± 0.1</td>
<td>7.86 ± 0.73</td>
<td>427 ± 91</td>
<td>0.19 ± 0.05</td>
</tr>
<tr>
<td>CCK2</td>
<td>100.4 ± 2.0</td>
<td>1.6 ± 0.1*</td>
<td>8.96 ± 1.19</td>
<td>647 ± 183*</td>
<td>0.27 ± 0.08*</td>
</tr>
<tr>
<td>CCK3</td>
<td>99.6 ± 2.1</td>
<td>1.5 ± 0.1*</td>
<td>8.54 ± 0.98</td>
<td>710 ± 184*</td>
<td>0.29 ± 0.07*</td>
</tr>
<tr>
<td>R1</td>
<td>99.9 ± 2.6</td>
<td>1.4 ± 0.1</td>
<td>7.60 ± 1.17</td>
<td>805 ± 285</td>
<td>0.35 ± 0.10</td>
</tr>
<tr>
<td>R2</td>
<td>100.2 ± 2.2</td>
<td>1.3 ± 0.1</td>
<td>7.05 ± 1.44</td>
<td>749 ± 274</td>
<td>0.33 ± 0.11</td>
</tr>
<tr>
<td>R3</td>
<td>98.4 ± 2.6</td>
<td>1.2 ± 0.1</td>
<td>5.90 ± 0.88</td>
<td>582 ± 195</td>
<td>0.33 ± 0.11</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SE. WKY body wt 426 ± 11 g, n = 8. Periods CCK1–CCK3, cholereticokinin infusion periods. *P < 0.05 vs. B1 or B2, ANVR, Newman Keuls test. †P < 0.05 vs. other periods, ANVR, Newman Keuls test.
D1- AND D2-LIKE RECEPTORS IN SPONTANEOUS HYPERTENSION

Table 6. Effect of cholecystokinin on renal function in the infused right kidney of the SHR

<table>
<thead>
<tr>
<th>Periods</th>
<th>MAP, mmHg</th>
<th>GFR, ml·g kidney⁻¹·min⁻¹</th>
<th>V̇, μl/min</th>
<th>UNaV, nEq/min</th>
<th>FENa, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td>162.6 ± 3.8</td>
<td>1.0 ± 0.1</td>
<td>4.40 ± 0.45</td>
<td>412 ± 72</td>
<td>0.31 ± 0.06</td>
</tr>
<tr>
<td>B2</td>
<td>158.4 ± 6.1</td>
<td>1.2 ± 0.1</td>
<td>4.61 ± 0.48</td>
<td>398 ± 86</td>
<td>0.25 ± 0.06</td>
</tr>
<tr>
<td>CCK1</td>
<td>159.4 ± 4.9</td>
<td>1.6 ± 0.1*</td>
<td>7.49 ± 1.01*</td>
<td>887 ± 212</td>
<td>0.44 ± 0.11</td>
</tr>
<tr>
<td>CCK2</td>
<td>160.4 ± 5.3</td>
<td>1.5 ± 0.1</td>
<td>7.95 ± 1.07*</td>
<td>1,077 ± 253*</td>
<td>0.51 ± 0.12*</td>
</tr>
<tr>
<td>CCK3</td>
<td>156.6 ± 4.9</td>
<td>1.6 ± 0.1*</td>
<td>6.86 ± 0.69*</td>
<td>845 ± 179</td>
<td>0.39 ± 0.08</td>
</tr>
<tr>
<td>R1</td>
<td>155.6 ± 4.8</td>
<td>1.5 ± 0.2</td>
<td>6.08 ± 0.64</td>
<td>804 ± 249</td>
<td>0.39 ± 0.11</td>
</tr>
<tr>
<td>R2</td>
<td>156.0 ± 5.5</td>
<td>1.5 ± 0.3</td>
<td>5.72 ± 0.80</td>
<td>817 ± 230</td>
<td>0.41 ± 0.10</td>
</tr>
<tr>
<td>R3</td>
<td>155.1 ± 4.7</td>
<td>1.3 ± 0.2</td>
<td>4.95 ± 0.56</td>
<td>696 ± 209</td>
<td>0.39 ± 0.11</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SE. SHR body wt 329 ± 12 g, n = 8. *P < 0.05 vs. B1 or B2, ANVR, Newman Keuls test. †P < 0.05 vs. R3, ANVR, Newman Keuls test.

diuresis and natriuresis in the SHR was caused by a defective D1 receptor that prevented a normal interaction with the D2-like receptor (4, 16, 19, 23, 34, 42). In the current studies, Z-1046 also had no effect on renal blood flow in the SHR (data not shown).

D2-like receptors have been shown in cells and in tissues in vitro to increase the inhibition of the sodium pump via synergistic interactions with D1-like receptors (4, 5, 30, 33). In vivo, in the WKY rat, the D2-like antagonist domperidone prevented the expected Z-1046-stimulated natriuresis and diuresis seen, indicating participation of D2-like receptors (16). The major D2-like receptor expressed in rat renal proximal tubules and renal vessels is the D2 receptor (17, 23, 27). D2 receptors in the kidney appear to be located prejunctionally in dopaminergic nerves (11, 17), and the D4 receptor is mainly expressed in collecting ducts (17, 40). D3 but not D3-like receptors have been identified in rat juxtaglomerular cells, and there is evidence that the D3 receptor may be the dopamine receptor subtype responsible in regulating renin release (32). Mice whose D3-receptor gene has been disrupted exhibit renin-dependent hypertension (3). Increased activity of the renin-angiotensin system resulting in increased reabsorptive action in the kidney has been reported in the SHR (41). Thus a defective action of D3 receptors in the kidney of the SHR may play a role in the pathogenesis of the hypertension in this rat strain. The exact defect in the D3 receptor is not clear from these studies. However, it is not due to differences in D3-receptor sequence between WKY and SHRs. Two molecular sizes, ~45 and ~90 kDa, were observed in the renal BBM of both WKY and SHRs. There were no differences in the ~90-kDa protein between WKY and SHR. However, less ~45-kDa D3-receptor protein was found in the BBM of SHRs. The cause of the differences in one size but not in another was not determined in these studies.

The apparent lack of responsiveness of the SHR to Z-1046 infusion is not an epiphenomenon, because the diuretic and natriuretic effects of cholecystokinin seen in the WKY rats were also observed in the SHRs. The effects of parathyroid hormone on cAMP and phosphate excretions were also similar in WKY and SHRs (28). Cholecystokinin-A receptors and parathyroid hormone receptors, similar to D1-like receptors, are linked to Gs and Gq/11 (2, 17). Polymorphisms in Gsα and Gβ-subunits have been reported in some populations with essential hypertension (15, 35). However, of these receptors, only D1-like receptor function is impaired in the kidney in genetic hypertension, suggesting that G protein dysfunction is probably not a critical component in the rodent models of genetic hypertension and human essential hypertension (17, 32).

In conclusion, we showed that the natriuresis and diuresis caused by Z-1046, a dopamine receptor agonist with preferential affinity at D2-like more than D1-like receptors, are abrogated in the SHR. This deficiency was receptor specific, because renal functional effects of cholecystokinin acting at another G protein-coupled receptor, were intact in the SHR.

Perspectives

Abnormal regulation of blood pressure by dopamine receptor subtypes has been reported in genetic hyper-

Table 7. Effect of cholecystokinin on renal function in the infused right kidney of the SHR with a lower basal sodium excretion than those observed in Table 6

<table>
<thead>
<tr>
<th>Periods</th>
<th>MAP, mmHg</th>
<th>GFR, ml·g kidney⁻¹·min⁻¹</th>
<th>V̇, μl/min</th>
<th>UNaV, nEq/min</th>
<th>FENa, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td>191.3 ± 3.1</td>
<td>1.1 ± 0.1</td>
<td>2.60 ± 0.13</td>
<td>165 ± 22</td>
<td>0.31 ± 0.06</td>
</tr>
<tr>
<td>B2</td>
<td>188.3 ± 4.0</td>
<td>1.2 ± 0.1</td>
<td>2.74 ± 0.20</td>
<td>145 ± 7</td>
<td>0.25 ± 0.06</td>
</tr>
<tr>
<td>CCK1</td>
<td>187.2 ± 5.1</td>
<td>1.6 ± 0.2*</td>
<td>5.10 ± 0.52*</td>
<td>391 ± 102</td>
<td>0.44 ± 0.11</td>
</tr>
<tr>
<td>CCK2</td>
<td>189.5 ± 4.4</td>
<td>1.7 ± 0.2*</td>
<td>5.36 ± 0.39*</td>
<td>521 ± 163*</td>
<td>0.51 ± 0.12</td>
</tr>
<tr>
<td>CCK3</td>
<td>184.8 ± 5.8</td>
<td>1.7 ± 0.2*</td>
<td>5.49 ± 0.38*</td>
<td>689 ± 196*</td>
<td>0.39 ± 0.08*</td>
</tr>
<tr>
<td>R1</td>
<td>184.8 ± 5.2</td>
<td>1.3 ± 0.1</td>
<td>4.95 ± 0.62*</td>
<td>705 ± 198*</td>
<td>0.39 ± 0.11*</td>
</tr>
<tr>
<td>R2</td>
<td>185.5 ± 4.5</td>
<td>1.4 ± 0.1</td>
<td>4.82 ± 0.44*</td>
<td>740 ± 204*</td>
<td>0.41 ± 0.10*</td>
</tr>
<tr>
<td>R3</td>
<td>180.6 ± 4.6</td>
<td>1.5 ± 0.1</td>
<td>4.50 ± 0.21*</td>
<td>575 ± 150</td>
<td>0.39 ± 0.11*</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SE. SHR body wt 344 ± 7 g, n = 5. *P < 0.05 vs. B1 or B2, ANVR, Newman Keuls test.
tension (17, 18). In the SHR, we have reported that the uncoupling of the D1-like receptors, specifically the D1 subtype, in renal proximal tubules from its G protein/effector complex is important in the pathogenesis of hypertension (17, 18, 31). However, abnormalities of D2-like receptors have also been described in genetic hypertension (21, 38). D1- and D2-like receptors may interact to regulate cardiovascular and renal function (4, 5, 16, 33). We now report that there is an impaired interaction in the kidney of D1- and D2-like receptors in the SHR, resulting in impaired renal vasodilatory, diuretic, and natriuretic effects of a dopamine receptor agonist with selectivity to all the dopamine receptor subtypes but not to other G protein-coupled receptors (16). The major renal tubular D2-like receptor is the D3 receptor (reviewed in Refs. 17, 18, 23, 27). The absence of any differences in D3 sequence between WKY and SHRs suggests a primary abnormality of the D1-like receptor. There is also a possibility that the D3 receptor shares a similar posttranslational modification with the D1 receptor that results in impaired renal dopamine receptor function. D3 receptors can form homooligomers depending on where the receptors are expressed: the brain striatum expresses oligomers, whereas only monomers are expressed in the ventral midbrain (19, 25). Jung et al. (19) suggested that the D3 autoreceptors may be expressed only as monomers. The significance of the decreased expression of monomeric D3 receptors in the SHR remains to be determined. However, a decreased D3-autoreceptor function...
may be a mechanism for an increased sympathetic activity in the SHR. D1 receptors have been reported to upregulate D3 receptors but not vice versa (20). Whether the defective D1-receptor function in the SHR has a role in the differential expression of the 45-kDa D3-receptor protein remains to be determined. It is also not known whether the renal D3 receptor shares with the renal D1 receptor the same abnormalities in post-translational modification (e.g., serine phosphorylation) seen in genetic hypertension (31, 43).

These studies were supported in part by Grant HL-58536 from the National Heart, Lung, and Blood Institute and by a National Kidney Foundation Grant, National Capital Affiliate.

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