Amelioration of Genetic Hypertension by Suppression of Renal G Protein–Coupled Receptor Kinase Type 4 Expression

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Abstract—Abnormalities in D1 dopamine receptor function in the kidney are present in some types of human essential and rodent genetic hypertension. We hypothesize that increased activity of G protein–coupled receptor kinase type 4 (GRK4) causes the impaired renal D1 receptor function in hypertension. We measured renal GRK4 and D1 receptors and determined the effect of decreasing renal GRK4 protein by the chronic renal cortical interstitial infusion (4 weeks) of GRK4 antisense oligodeoxynucleotides (As-Odns) in conscious-uninephrectomized spontaneously hypertensive rats (SHRs) and their normotensive controls, Wistar-Kyoto (WKY) rats. Basal GRK4 expression and serine-phosphorylated D1 receptors were ≈90% higher in SHRs than in WKY rats and were decreased to a greater extent in SHRs than in WKY rats with GRK4 As-Odns treatment. Basal renal D1 receptor protein was similar in both rat strains. GRK4 As-Odns, but not scrambled oligodeoxynucleotides, increased sodium excretion and urine volume, attenuated the increase in arterial blood pressure with age, and decreased protein excretion in SHRs, effects that were not observed in WKY rats. These studies provide direct evidence of a crucial role of renal GRK4 in the D1 receptor control of sodium excretion and blood pressure in genetic hypertension. (Hypertension. 2006;47:1131-1139.)

Key Words: kidney ■ blood pressure ■ receptors, dopamine ■ rats, spontaneously hypertensive

Dopamine, produced by renal proximal tubules via D1-like receptors, is responsible for >50% of sodium excretion during moderate sodium surfeit.1,2 However, the dopaminergic paracrine regulation of renal tubular sodium handling is defective in salt-sensitive human essential hypertension and rodent models of genetic hypertension, for example, spontaneously hypertensive rats (SHRs).1–3 The renal dopaminergic defect in hypertension has been attributed to a diminished D1-like receptor inhibition of sodium transport in the proximal tubule and the medullary thick ascending limb of Henle. The impairment of D1-like receptor function in the kidney in genetic hypertension is not caused by abnormalities in the expression or primary structure of the 2 D1-like receptors (D1 and D5), G proteins, or effector proteins.4,5 Rather, the D1-like receptor is uncoupled from its G protein/effector protein complex in the kidney. The renal D1-like receptor uncoupling in rodent genetic hypertension is receptor and organ specific and cosegregates with and precedes the onset of hypertension.1,2

The uncoupling of the D1-like receptor from its effector proteins in the kidney in hypertension is associated with increased phosphorylation of the D1 receptor.4,5 In human essential hypertension, single nucleotide polymorphisms of the G protein–coupled receptor (GPCR) kinase 4 (GRK4) are associated with constitutive phosphorylation and desensitization of the D1 receptor in renal proximal tubules.4–6 These lead to sodium retention and hypertension. Indeed, transgenic mice expressing the GRK4 variant, GRK4A142V, develop hypertension that is associated with an impaired D1 receptor–mediated natriuresis.5

To determine whether aberrant GRK4 function contributes to the impaired renal D1 receptor function in SHRs, we studied the renal expression of GRK4 and the effects of decreasing its expression in the kidney by a chronic renal cortical interstitial infusion of GRK4 antisense (As) oligodeoxynucleotides (Odns) in conscious SHRs and their normotensive controls, Wistar–Kyoto (WKY) rats. If an increased GRK4 activity in the kidney is responsible for the increased blood pressure in SHRs, this maneuver should improve D1 receptor–mediated renal tubular handling of sodium and ameliorate the high blood pressure in SHRs without affecting these variables in WKY rats.
Methods

Animals
Four-week–old male WKY rats and SHRs (Japan SLC Inc, Sendai, Japan) were fed 0.26% NaCl chow (Japan CLEA) and tap water. At 5 weeks of age, the diet was changed to 4% NaCl chow. NaCl diet was increased, because the natriuretic effect of D1 receptor stimulation is most evident under conditions of sodium loading.1–3 Unmanipulated 8-week-old WKY rats and SHRs were also studied. All of the animal experimental procedures were approved by the Fuku-shima Medical University School of Medicine Animal Committee.

Uninephrectomy and Renal Cortical Interstitial Catheter Implantation
Under pentobarbital (50 mg/kg, IP) anesthesia, the right kidney was removed, and a catheter (8-mm polyethylene 10 tube connected to a 4-cm polyethylene 60 tube by Bpax epoxy resin glue) was implanted 3 to 4 mm deep from the outer edge of the lower pole of the remaining left kidney, as reported previously.7 At day 0, an osmotic minipump was placed in the space where the right kidney was removed (1 mL/h, Alzet Corporation) for the continuous cortical interstitial infusion of lactated Ringer’s solution. At day 7, the rats were anesthetized and the implanted minipump replaced with another that infused As-Odn, scrambled oligonucleotides (50 nmol per day), or lactated Ringer’s solution (vehicle) at 0.2 mL/h for 4 weeks.

Urinary was collected for 24 hours, twice a week. Sodium concentrations were measured by ion electrode detection. Unanesthetized systolic blood pressures were measured twice a week by the tail-cuff method (Blood Pressure Analyzer model BP-98A, Softron).

After 4 weeks, the rats were anesthetized and perfused with 50 mL of lactated Ringer’s solution. The remaining kidney and heart were quickly removed, weighed, flash frozen, and stored at −70°C. In some rats, the kidneys were fixed with Histochoice and cryoprotected with 30% sucrose.

Design and Synthesis of Odn
The nucleotide sequences of purified rhodamine-conjugated propyne/phosphorothioate–modified rat GRK4 Odn (Greiner) were: As-Odn, 209 5’-CATGAAGTTCTC CAGTTCCAT-3’ 189; and scrambled Odn (Scr-Odn), 5’-ATTITCCATAGGC GCATTAG-3’.8,9 These sequences have no homology with other mammalian GRK4 sequences in GenBank (Accession No X97568).

GRK4 Antibody Design
The GRK4 antibody used in these studies was raised in rabbit (94065) against the peptide EYEDKGLSPLEKHKICSC (Research Genetics, Huntsville, AL), which is 100% homologous to both rat GRK4A (amino acids 526 to 543; GenBank Accession No CAA66180) and GRK4B (amino acids 495 to 512; GenBank Accession No CAA66181).10 The affinity-purified (SulfoLink, product 44895, Pierce) antibodies were used in the experiments.

Immunohistochemistry for GRK4
Three-μm tissue sections were incubated with anti-rat GRK4 antibodies or GRK4 antibodies preadsorbed by the immunizing peptide (10% weight/weight, relative to antibody). Immunostaining was detected with an avidin–biotin immunoperoxidase kit (Vectastain Elite kit or ABC/Peroxidase kit, Vector Laboratories) and diamino-benzidine (Sigma Fast DAB Tablets, Sigma). The kidneys were lightly counterstained with hematoxylin. Some flash-frozen kidney sections were also examined by fluorescence microscopy to verify diffusion of the Odns.

Immunoprecipitation and Immunoblotting
Renal cortical or cardiac ventricular proteins were subjected to immunoblotting or immunoprecipitation, as reported previously.4–7,10,11 The membranes were probed with polyclonal anti-rat GRK4, anti-human GRK4 y8 (Santa Cruz Biotechnology, Inc, Santa Cruz, CA), anti-rat D1 receptor, anti-phosphoserine (Zymed), or monoclonal β-actin antibodies (Santa Cruz Biotechnology, Inc). The specificities of the anti-rat D1 receptor and anti-phosphoserine antibodies have already been established.4–6,10 The bands were visualized by enhanced chemiluminescence reagents (Amersham Corp), and the density of the bands was quantified by densitometry using Quantscan.

Statistical Analysis
The data are expressed as mean±SE. Comparisons within and among groups were made by repeated measures or factorial ANOVA, respectively, followed by Duncan’s test. Student t test was used for 2-group comparison. P<0.05 was considered significant.

Results
There were no differences in body weight, water intake, and sodium output among the groups at the beginning of the study. Systolic blood pressures were higher in SHRs than in WKY rats. Baseline sodium output was similar among the groups, but baseline urine output was greater in WKY rats than in SHRs. The nephrectomized kidney weight, as a percentage of body weight, was similar in all groups. (Table I, available in an online supplement at http://www.hypertensionaha.org).

GRK4 Antibody Characterization
Several bands at 65, 60, and 54 kDa were detected in rat renal cortex membranes, probably representing GRK4A, B, and E, respectively, according to their molecular sizes. The 54- and 60-kDa bands were no longer visible or diminished (65 kDa) when the antibody was preadsorbed by its immunizing peptide (peptide+; Figure 1A). Bands of similar sizes were

![Image](316x197 to 546x390)
detected by the antibody, as well as by an antibody to the V5 tag in HEK-293 cells, heterologously expressing V5/His-tagged rat GRK4A (∼65 kDa) and rat GRK4B (∼60 kDa), confirming the specificity of the GRK4 antibody (Figure 1B). Faint bands were seen in the empty vector-transfected HEK 293 cells, indicating minimal endogenous expression of GRK4 in these cells (Figure 1B).

**Distribution of GRK4 in the Kidney**

In both WKY and SHRs, GRK4 expression was most evident in subapical membranes of renal proximal tubules and thick ascending limbs of Henle and arteries. There was much less staining in glomeruli. The expression of GRK4 in renal arterioles suggests regulation of the D1 receptor in rat renal resistance vessels (Figure 2A and 2B).12,13

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**Figure 2.** Renal GRK4 immunohistochemistry. GRK4 is expressed in renal proximal tubules, especially in the subluminal area, and medullary thick ascending limbs of Henle in WKY rats (A) and SHRs (B). There is also staining of renal arteries, but there is minimal staining in glomeruli. No staining is seen when the anti-rat GRK4 94065 antibody is preadsorbed by its immunizing peptide, negative control. Immunostaining was visualized with an avidin–biotin immuperoxidase and VIP kit. These studies were done ≥3 times.
Expression of GRK4, D1, and Serine-Phosphorylated D1 Receptors in Renal Cortex

Renal cortical GRK4 protein was increased in unmanipulated SHRs compared with unmanipulated WKY rats (Figure 3A and Figure I, available online), as well as in vehicle-treated SHRs compared with vehicle-treated WKY rats (Figure 3B). These results were confirmed using another antibody (anti-human GRK4 γδ; Figure II, available online). Although GRK4 Scr-Odn slightly increased GRK4 expression in WKY rats, GRK4 expression was still less than in vehicle or Scr-Odn–treated SHRs. However, GRK4 As-Odn decreased GRK4 expression in both WKY rats and SHRs such that there was no longer any difference between them. Cardiac GRK4 expression was similar in the 2 rat strains (Figure 3C), indicating that the increased GRK4 expression in hypertension has organ specificity. Cardiac GRK4 expression was not affected by Odn treatment, indicating confinement of the intrarenal Odn treatment to the kidney.

Renal cortical D1 receptor protein was similar in vehicle-treated WKY rats and SHRs (Figure 4A). In contrast, levels of serine-phosphorylated D1 receptors were increased in membranes of vehicle-treated SHRs, as reflected by the increased ratio of serine-phosphorylated/total D1 receptor protein (Figure 4B).
Effect of Treatment With GRK4 Odn
At the end of the study, WKY rats weighed more than SHRs. After 4 weeks of infusion of vehicle or Odns, the weight of the remnant left kidney in the As-Odn–treated SHRs was similar to other groups except for Scr-Odn–treated WKY rats (Table). As-Odn–treated SHR kidneys weighed less than Scr-Odn–treated and WKY rat kidneys. The heart weight was greater in SHRs than in WKY animals and was unaffected by any of the treatments. Food and water intake, urinary output, blood urea nitrogen, and serum creatinine were similar in all of the groups. At the end of the study, protein excretion was higher in SHRs than in WKY rats regardless of the treatment. However, SHRs treated with As-Odn excreted significantly less protein than SHRs treated with vehicle or with Sdr-Odns (Table).

Effect of GRK4 Odn on Blood Pressure
In WKY rats, blood pressure did not increase with age and was not affected by vehicle or Odn treatment. In SHRs, blood pressures increased with age. However, GRK4 As-Odn treatment caused a marked attenuation in the increase in blood pressure (relative to vehicle- and Sc-Odn–treated SHRs) that started at 6.5 weeks of age and persisted until the end of the study (9.5 weeks of age). Nevertheless, SHR blood pressures were still higher than age-matched WKY rats (Figure 5A).

Effect of GRK4 Odn on Urine Flow, Sodium Excretion, and Sodium Balance
Sodium excretion increased to a greater extent in WKY rats than in vehicle or Scr-Odn–treated SHRs. After 2.5 weeks of Odn or vehicle infusion, sodium output of As-Odn–treated SHRs was greater than vehicle- or Odn-treated SHRs and similar to the vehicle- and Odn-treated WKY rats (Figure 5B). Daily sodium balance (sodium intake minus urine sodium) from 7.5 to 9.5 weeks of age (age when the study ended) was significantly less (P<0.05 ANOVA, Duncan’s test) in As-Odn–treated SHRs than in Scr-Odn- or vehicle-treated SHRs and approximated those observed in vehicle and Odn-treated WKY rats (Table).

Effect of GRK4 Odn on Renal and Cardiac Expression of GRK4 and D1 Receptor
Treatment with GRK4 As-Odn but not with GRK4 Scr-Odn decreased the levels of immunoreactive GRK4 in renal cortical homogenates (Figure 3B) without affecting the levels of immunoreactive GRK2 (Figure III, available online). GRK4 As-Odns also seemed to reduce GRK4 immunostain-
transport and increase urinary sodium excretion is impaired in serine-phosphorylated D1 receptors in both WKY rats and from SHRs.14 In the renal cortex, GRK4 As-Odn decreased to our preliminary report using renal proximal tubule cells greater in vehicle-treated and GRK4 Scr-Odn–treated SHRs.

The renal dopaminergic system participates in the pathogenesis of genetic hypertension.1–5,10–18 Thus, the ability of dopamine and D1-like agonists to decrease renal proximal tubular sodium transport and increase urinary sodium excretion is impaired in human essential hypertension and rodent models of genetic hypertension.3,15–17 A defective coupling of the D1 dopamine receptor to its G protein effector enzyme complex in renal proximal tubules and medullary thick ascending limbs causes the impaired renal dopaminergic action in genetic rodent and human essential hypertension.1–5,14–18

The uncoupling of the renal D1 receptor from its G protein/effector protein complex in genetic hypertension1–5,12–18 is akin to but different from homologous desensitization.6,10,19–22 After agonist stimulation, phosphorylation-dependent and -independent mechanisms initiated by GRKs lead to the binding of GPCRs with adaptor proteins (eg, arrestin), an uncoupling of the receptor from its G protein complex, and a decrease in functional response. The phosphorylated GPCR and arrestin complex undergoes internalization into endosomes where the GPCR is dephosphorylated by protein phosphatases and recycled back to the plasma membrane or degraded by lysosomes.6,19–22

Whereas homologous desensitization is ligand dependent, the desensitization of the D1 receptor in the kidney in hypertension is ligand independent.1,4,5,14–15 We have reported that the uncoupling of the D1 receptor from its G protein/effector complex in renal proximal tubules from humans with essential hypertension is caused by activating variants of GRK4.5 The GRK4γ variants, R65L, A142V, and A486V, to wild type, increase the phosphorylation and impair the ability of D1 receptors to stimulate cAMP in Chinese hamster ovary cells heterologously expressing these genes. Transgenic mice expressing GRK4γA142V but not wild-type GRK4γ have increased arterial blood pressure and have an impaired diuretic and natriuretic response to a nonhypotensive dose of the D1-like agonist, fenoldopam.5

We now report that in SHRs, as in humans with essential hypertension, GRK4 participates in the impaired function of the D1 receptor in the kidney. The increased activity of GRK4

<table>
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<th>Variables</th>
<th>Vehicle (n=3)</th>
<th>Scr-Odn (n=3)</th>
<th>As-Odn (n=3)</th>
<th>Vehicle (n=3)</th>
<th>Scr-Odn (n=7)</th>
<th>As-Odn (n=6)</th>
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<tr>
<td>Remnant kidney weight, %BW</td>
<td>260±6*</td>
<td>245±14</td>
<td>246±7</td>
<td>231±5</td>
<td>218±5+</td>
<td>221±7†</td>
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<td>Heart weight, %BW</td>
<td>0.61±0.03</td>
<td>0.71±0.04</td>
<td>0.65±0.04</td>
<td>0.67±0.05</td>
<td>0.61±0.02</td>
<td>0.57±0.01§</td>
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<td>BUN, mg/dL</td>
<td>19.2±0.7</td>
<td>18.1±0.7</td>
<td>18.1±1.1</td>
<td>19.2±0.8</td>
<td>19.8±1.3</td>
<td>18.5±0.8</td>
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<td>Serum creatinine, mg/dL</td>
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<td>0.20±0.01</td>
<td>0.20±0.01</td>
<td>0.21±0.01</td>
<td>0.24±0.01</td>
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<td>Systolic BP, mm Hg</td>
<td>126±6*</td>
<td>129±3*</td>
<td>125±1*</td>
<td>224±8</td>
<td>230±4</td>
<td>183±2</td>
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<tr>
<td>Water intake, mL/d</td>
<td>55.0±4.0</td>
<td>60.7±4.2</td>
<td>56.7±3.9</td>
<td>54.0±5.0</td>
<td>53.3±3.8</td>
<td>54.5±2.7</td>
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<td>Food intake, g/d</td>
<td>19.3±2.8</td>
<td>17.3±0.3</td>
<td>16.7±0.7</td>
<td>17.3±2.6</td>
<td>16.7±0.9</td>
<td>17.5±0.7</td>
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<tr>
<td>Urine output, mL/d</td>
<td>43.3±5.3</td>
<td>43.3±5.6</td>
<td>38.1±3.1</td>
<td>37.5±0.9</td>
<td>36.2±1.8</td>
<td>40.2±2.7</td>
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<tr>
<td>Sodium output, mEq/d</td>
<td>11.5±0.5</td>
<td>10.1±1.0</td>
<td>11.8±0.9</td>
<td>8.5±1.1†</td>
<td>8.2±0.5‡</td>
<td>10.7±0.4‡</td>
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<tr>
<td>Protein excretion, mg/d</td>
<td>24.5±2.5*</td>
<td>23.4±1.0*</td>
<td>38.0±1.1*</td>
<td>88.4±6.8</td>
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<tr>
<td>Average daily sodium balance (mEq/day) during the last 2 weeks of the study</td>
<td>1.14±0.53</td>
<td>1.40±0.29</td>
<td>0.93±0.50</td>
<td>3.78±0.49</td>
<td>3.51±0.64</td>
<td>1.88±0.35</td>
</tr>
</tbody>
</table>

BW indicates body weight; BUN, blood urea nitrogen; BP, blood pressure. *P<0.05 vs SHR, †P<0.05 vs others, ‡P<0.05 vs others except SHR vehicle and WKY Scr-Odn, §P<0.05 vs WKY Scr-Odn, ¶vs others within own group, ||P<0.05 vs others at the same time point, ANOVA, Duncan’s test.
in humans with essential hypertension is not caused by GRK4 protein abundance. However, SHRs have increased renal cortical membrane GRK4 expression relative to WKY rats. GRK4 polymorphisms (called FJ1 in Reference 24) are associated with hypertension in humans, but there are no differences in the coding region of GRK4 in WKY rats and SHRs (unpublished data).

We do not know the mechanism of the increased expression of GRK4 in the renal cortex of SHRs; however, there is ample evidence to suggest that GRK4 is important in the regulation of renal sodium handling and blood pressure in these rats. In SHRs, the selective decrease of renal GRK4 expression with GRK4 As-Odn reduces the increased D1 receptor serine phosphorylation. The increased serine phosphorylation is receptor specific, because angiotensin type 1 (AT1) receptor serine phosphorylation, but not AT1 tyrosine phosphorylation, is decreased in SHRs (unpublished data). Moreover, GRK4 does not participate in the desensitization of the AT1 receptor.27

The intrarenal cortical administration of GRK4 As-Odn in SHRs prevents by >50% the increase in blood pressure with age and slightly reduces the age-related increase in urinary protein excretion. The concomitant reduction in protein excretion and blood pressure suggests that the decrease in proteinuria could be related to the decrease in blood pressure. GRK4 As-Odn treatment also produces a 50% decrease in

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Figure 5. Effect of GRK4 Odn on systolic blood pressure and sodium excretion in WKY rats and SHRs. (A) tail-cuff blood pressures of conscious in WKY rats and SHRs. Data are mean±SE; *P<0.05 vs other SHRs or WKY rats at the same time point. All SHR values are different from WKY values, except at 5 weeks when vehicle-treated SHRs are not different from Scr-Odn–treated WKY rats. ANOVA, Duncan’s test, for number of rats per group, refer to Table. V indicates vehicle. (B) sodium excretion in WKY rats and SHRs. Sodium excretion in GRK4 As-Odn–treated SHRs begins to be significantly different from GRK4 Scr- and vehicle–treated SHRs at 7.5 weeks of age. ##P<0.05 vs others except SHR Scr-Odn, ###P<0.05 vs others except SHR vehicle and WKYScr-Odn, $P<0.05 vs others except SHR As-Odn, ANOVA, Duncan’s test, *P<0.05 vs SHR As-Odn, ANOVA; Duncan’s test (see Table for number of rats per group).
sodium balance that is associated with a 25% increase in sodium excretion. These data indicate that facilitation of sodium excretion by inhibition of GRK4 expression may, in part, be responsible for the amelioration of the increase in blood pressure with age in SHRs. However, it is not clear why the increase in sodium excretion is less than the decrease in sodium balance. Although the GRK4 As-Odn infusion affects GRK4 expression only in the kidney, the consequences of renal GRK4 inhibition may have affected renal hormonal secretion with consequences on intestinal sodium transport. Nonetheless, the increase in sodium excretion with GRK4 As-Odn treatment in SHRs is consistent with the impaired natriuretic effect of fenoldopam in transgenic mice expressing the GRK4 variant A142V.5

The failure of GRK4 As-Odn to completely normalize the blood pressure in SHRs may be because of several reasons. Antisense methods for posttranslational gene silencing may not be completely efficient.28 However, GRK4 As-Odn decreases renal GRK4 expression and D1 receptor phosphorylation in SHRs to levels similar to those noted in WKY rats. One possibility is that other GRKs may also regulate dopamine receptors. We have reported that GRK2 modestly contributes to the desensitization of D1 receptors in human renal proximal tubules.6 Overexpression of GRK2, GRK3, and GRK5 in HEK cells desensitizes the D1 receptor.19 GRK activity and GRK2 expression are increased in human essential hypertension and SHRs.20,29 and overexpression of GRK2 in vascular smooth muscles in mice induces hypertension and impairs the vasodilatory action of β-adrenergic receptors.30 However, in SHRs, the increase in GRK activity and GRK2 expression follows rather than precedes the hypertensive process.29 Moreover, in the current studies, GRK4 As-Odn does not affect GRK2 expression.

There is another possible explanation for the failure of GRK4 As-Odn to completely normalize blood pressure in the SHR. Because the infusion of the ODNs is limited to the kidney, nonrenal factors important in the pathogenesis of hypertension would have not been affected.31–33 GRK4 is expressed outside the kidney,8,9 including the brain, where blood pressure can also be regulated by GRK4 independent of the kidney.

In summary, in SHRs, the intrarenal infusion of GRK4 Asn-Odn decreases GRK4 expression and D1 receptor phosphorylation, increases sodium excretion, and attenuates the increase in blood pressure with age. In WKY rats, the intrarenal infusion of GRK4 Asn-Odn also decreases GRK4 expression and serine-phosphorylated D1 receptor but does not affect sodium excretion or blood pressure. GRK4 regulation of renal D1 dopamine receptors is important in the pathogenesis of genetic hypertension.

Perspectives

These studies provide direct evidence of a crucial role of renal GRK4 in the D1 receptor control of sodium excretion and blood pressure in genetic hypertension. The renal D1-like receptor uncoupling in rodent genetic hypertension is receptor and organ specific and cosegregates with and precedes the onset of hypertension.2 In human essential hypertension, GRK4 gene variants are associated with constitutive phosphorylation and desensitization of the D1 receptor in renal proximal tubules, sodium retention, and hypertension. In vitro treatment of renal proximal tubular cells from hypertensive patients with antisense GRK4 ODNs corrects the D1 receptor/G protein–coupling defect.5 Our findings that the selective reduction in renal GRK4 activity decreases blood pressure and increases sodium excretion in SHRs suggest the possibility of the use of GRK4 inhibitors in the treatment of hypertension.

Acknowledgments

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References


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