G Protein-Coupled Receptor Kinase 4
Role in Hypertension

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The kidney plays an important role in the long-term control of blood pressure and is the major organ involved in the regulation of sodium homeostasis. The inappropriate sodium retention in hypertension results from enhanced renal sodium transport per se or a failure to respond appropriately to signals that decrease renal sodium transport in the face of increased sodium intake. Humans with polygenic essential hypertension have increased renal sodium transport that is not properly regulated by natriuretic and antinatriuretic hormones and humoral factors, including dopamine and angiotensin II (Ang II). Dopamine and Ang II exert their effects via G protein-coupled receptors (GPCRs).

GPCRs constitute by far the largest receptor family in mammals, which are encoded by >800 genes in the human genome and play a vital role in the regulation of most cellular and physiological functions in the body. On ligand binding, GPCRs regulate and modulate a variety of cell functions by coupling to heterotrimeric G proteins and regulating downstream effectors, such as adenylyl cyclases, phospholipases, protein kinases, and ion channels. Activation of renal GPCRs, including dopamine and Ang II receptors, leads to either natriuresis (sodium excretion) or antinatriuresis (sodium retention), keeping a normal sodium balance, resulting in the maintenance of a normal blood pressure.

GPCR kinases (GRKs) constitute a family of 7 serine/threonine protein kinases characterized by their ability to specifically recognize and phosphorylate agonist-activated GPCRs. GRK-mediated receptor phosphorylation is one of the well-characterized mechanisms for GPCR desensitization. In the process of GPCR desensitization, GRKs phosphorylate agonist-bound receptors, leading to the translocation and binding of arrestins to the receptors and inhibition of subsequent receptor activation by blocking GPCR-G protein coupling. In particular, GRK4 seems to play a vital role in regulating dopamine-mediated natriuresis and renin–angiotensin system (RAS)–mediated antinatriuresis. Increasing number of studies show that GRK4 is associated with hypertension and blood pressure response to antihypertensive medicines and adverse cardiovascular outcomes of antihypertensive treatment.

In this report, we review our evolving understanding of the role of GRK4 in the regulation of dopamine and Ang II receptor function, which advances our understanding of the role of GRK4 in the control of blood pressure and highlights potential and novel strategies for the prevention and treatment of hypertension.

Physiological Role of Intrarenal Dopamine and RAS

Dopamine, via 5 subtypes of receptors, plays an important role in the control of blood pressure by regulating epithelial sodium transport, vascular smooth muscle contractility, inflammation, and production of reactive oxygen species and by interacting with the RAS and sympathetic nervous system. Dopamine receptors are classified into D₁ and D₂-like receptor subtypes: D₁-like receptors (D₁R and D₅R) couple to stimulatory G protein Gₛ and stimulate adenylyl cyclases activity, whereas D₂-like receptors (D₂R, D₃R, and D₄R) couple to inhibitory G protein Gᵢₛ and inhibit adenylyl cyclases activity. Disruption of any of the dopamine receptor genes in mice results in hypertension, the pathogenesis of which is specific for each receptor subtype.

The RAS is classically known as a coordinated hormonal cascade regulating blood pressure, as well as electrolyte and fluid homeostasis. Ang II is a biologically active octapeptide that is considered the main mediator of classic RAS. Ang II exerts its action through 2 major receptor subtypes, namely type 1 (AT₁R) and type 2. AT₁R mediates the vast majority of cardiovascular and renal actions of Ang II, including vasostriction, renal tubule sodium reabsorption, reactive oxygen species generation, and inflammation. In contrast, activation of the Ang II receptor type 2 induces vasodilatation, promotes natriuresis, and lowers blood pressure.

The activity of dopamine receptors and AT₁R is regulated by phosphorylation/dephosphorylation, which is mediated by GRKs and protein phosphatases, respectively. Basal protein phosphatase 2A activity in renal proximal tubules (RPTs) is not different between the normotensive Wistar–Kyoto (WKY) rats and spontaneously hypertensive rats (SHRs), which have impaired D₁R function. D₁-like receptor agonist treatment of RPT membranes from SHRs failed to increase protein phosphatase 2A activity; an impaired ability to increase protein phosphatase 2A activity would result in continued hypertensive response.
phosphorylation and desensitization of the D$_1$R. However, the GRKs have received, by far, the most attention in the regulation of renal dopamine and Ang II receptors in hypertension.

**GPCR Kinase Family**

**Classification of GRKs**

There are over 800 known GPCRs in the human genome, but only 7 GRKs have been identified. All GRKs have a similar general structure: a highly conserved central protein kinase domain, inserted in the regulator of G protein signaling homology domain that keeps the ability of the kinase domain to phosphorylate activated GPCRs. The first 20 or so amino acids of GRKs are highly conserved, whereas the carboxyl tail region is GRK subtype-specific; prenylated in the GRK1 subfamily; binds to G$\beta$$\gamma$ and contains a pleckstrin homology domain in the GRK2 subfamily; and has a C-terminal helix/palmitylation site in the GRK4 subfamily. The GRK1 subfamily (opsin kinase family) consists of GRK1 and GRK7; GRK2-like subfamily (β-adrenergic receptor kinase family) consists of GRK2 and GRK3; and the GRK4-like subfamily consists of GRK4, GRK5, and GRK6. GRK1 and GRK7 are found almost exclusively in the retina and modulate opsins. GRK2, GRK3, GRK5, and GRK6 are ubiquitously expressed, whereas GRK4 is expressed in only a few organs (vide infra).

**GRKs and Hypertension**

GRKs have multiple physiological effects on the regulation of blood pressure. Vascular smooth muscle overexpression of GRK2 in transgenic mice attenuates β-adrenergic receptor–induced vasodilation and increases resting blood pressure. GRK2 expression and GRK activity are increased in both the lymphocytes and vascular smooth muscles of patients with essential hypertension and in SHRs. GRK2 hemizygous knockout mice have increased nitric oxide bioavailability that protects against Ang II–induced hypertension. The transgenic mice with vascular smooth muscle–specific GRK5 overexpression are hypertensive. By contrast, GRK3 expression in human lymphocytes has been reported to be inversely correlated with blood pressure, suggesting a protective role for GRK3 in the regulation of blood pressure that is supported by the findings in transgenic mice. Overexpression of GRK2, GRK3, and GRK5 in human embryonic kidney (HEK293) cells desensitizes the D$_1$R. Inhibition of GRK6 prevents intestinal D$_1$R desensitization. However, renal GRK6 levels are lower in hypertensive subjects and SHRs than their normotensive controls.

**Role of GRK4 in Hypertension**

**GRK4 Isoforms**

GRK4 has some inherent characteristics. For example, GRK4 has constitutive activity under basal conditions, which may, in part, be because of its ability to bind to inactive G$_{\alpha}$ and G$_{\alpha_1}$ subunits. It is the only GRK subtype that is capable of phosphorylating unstimulated GPCRs. GRK4 is expressed in a limited number of tissues, for example, artery, bone, cerebellum, heart, kidney, myometrium, small intestines, and testes, unlike GRK2, GRK3, GRK5, and GRK6, which are ubiquitously expressed. Moreover, 4 splice variants (GRK4$\alpha$, β, γ, and δ) of GRK4 have been identified in humans. Alternative splicing generates 4 isoforms of human GRK4 mRNA that differ in the presence or absence of exon 2 and exon 15: GRK4$\alpha$ is the longest isoform and contains all of the 16 exons; GRK4β, which lacks exon 2, has a 32-codon-deletion that encompasses the phosphatidylinositol bisphosphate–binding domain near the amino terminus; GRK4γ, which lacks exon 15, has a 46-codon-deletion near the carboxyl terminus; and GRK4δ lacks both exons 2 and 15. The human GRK4 gene locus at 4p16.3 is linked to hypertension. Numerous studies show that abnormal GRK4 function has the potential to affect GPCR (such as D$_1$R, D$_3$R, and AT$_1$R)–regulated biological responses in many physiological and pathological conditions, such as hypertension, which makes GRK4 as an attractive candidate for a genetic determinant for essential hypertension.

**Distribution of GRK4 in Kidney and Artery**

GRK4 is expressed in the rat renal cortex. In both WKY and SHRs, GRK4 is expressed in the subapical membranes of the RPT, thick ascending limb of Henle, and renal artery, with much less expression in the glomerulus. Renal cortical GRK4 expression is increased in SHRs compared with WKY rats, whereas cardiac GRK4 expression is similar in the 2 rat strains, indicating that the increased GRK4 expression in hypertension has organ specificity. In mice, the renal expression of GRK4 is strain-dependent and influenced by salt intake, for example, lower on normal but higher on high-salt diet in C57BL/6J than in SJL/J mice. C57BL/6 mice are salt-sensitive and have an impaired ability to excrete a NaCl load that is associated with an increase in blood pressure, whereas SJL/J mice are salt-resistant. All 4 GRK4 isoforms are expressed abundantly in human RPT cells; GRK4 is localized at the RPT cell surface membrane and cytoplasm and internalized after stimulation of dopamine receptors.

GRK4 activity is increased in kidneys of hypertensive humans. Antisense GRK4 oligonucleotides completely blocked the constitutive serine phosphorylation of the D$_1$R and restored the ability of the D$_1$-like receptor agonist, fenoldopam, to stimulate cAMP accumulation in RPT cells from hypertensive subjects, which suggests that the major GRK involved in the phosphorylation of the D$_1$R in hypertension is GRK4 and not the other GRKs. However, there are no differences in the expression of the GRK4 isoforms (α/β, γ/δ) in kidneys or cultured RPT cells between hypertensive and normotensive subjects. Therefore, we assume that the increased activity of GRK4 in the kidney of hypertensive subjects is not caused by increased renal GRK4 protein expression but rather by constitutively active variants of GRK4.

In Sprague–Dawley rats and C57BL/6J mice, GRK4 is well-expressed in large and small arterial vessels, including the carotid arteries, thoracic aorta, superior mesenteric artery, and renal artery. In the aorta, GRK4 is expressed in the tunica media and adventitia. However, removal of the adventitia does not affect the Ang II–mediated vasoconstriction, suggesting that GRK4 in the adventitia does not participate in Ang II–mediated vasoconstriction.
Regulation of GRK4

As a regulator of GPCRs, GRK4 per se is regulated by transcription factors and signaling molecules. The GRK4 promoter region, containing 1851 bp of the 5’-flanking region and 275 bp of the 5’-untranslated region, is reported to be highly active. The GRK4 core promoter resides in the first 1851 bp upstream of its transcription start site, suggesting that the complex DNA–protein and protein–protein interaction patterns at this portion may affect the transcriptional and expression capacities of GRK4. The transcription factor c-Myc, binding to the promoter of GRK4, positively regulates GRK4 protein expression in human RPT cells, which connects aberrant Ang II activation to D1R–adenylyl cyclases uncoupling. The GRK4 subfamily, including GRK4, is potently inhibited by ubiquitous calcium-binding protein calmodulin, which has little or no effect on members of other GRK subfamilies. Sorting nexins are involved in receptor endocytosis and trafficking through the endosomes. Sorting nexin 5 directly interacts with GRK4 and prevents GRK4 from targeting the phosphorylation sites of the D1R, which is enhanced after D1R interacts with GRK4 and prevents GRK4 from targeting the D1R. Hence, GRK4 has the ability to constitutively phosphorylate the D1R in the absence of agonist activation, whereas depletion of GRK4 blunts the increased renal D1R function in hypertensive hGRK4γ142V transgenic mice, not in the hypertensive hGRK4γ142V transgenic mice. Additional studies showed that the higher blood pressure in hGRK4γ142V transgenic mice is not because of the transgene integration sites, flanking genes, or copy numbers, but due mainly to the effect of hGRK4γ142V transgene acting via D1R. This is confirmed by in vitro studies: in the transfected Chinese hamster ovary cells, GRK4γ142V increases GRK activity and causes D1R phosphorylation, which may explain, in part, the decreased responsiveness of the D1R in hypertensive hGRK4γ142V transgenic mice. There is, however, cell specificity of the ability of GRK4γ142V to regulate D1R function; GRK4γ142V regulates D1R function in human RPT, Chinese hamster ovary cells, and HEK293 cells (vide supra), whereas it is GRK4α in HEK293T cells. We also found that the function of D1R is also impaired in the hGRK4γ142V-transfected human RPT cells (J. Yang, V.A.M. Villar, and P.A. Jose, unpublished data, 2015). The hypertension in hGRK4γ142V transgenic mice is also associated with increased AT1R expression and function in both kidney and artery. GRK4γ142V transgenic mice have increased renal AT1R expression and function, for example, increased blood pressure response to Ang II infusion and AT1R blockade. By contrast, GRK4γ142V transgenic mice that are deficient of AT1R have normal blood pressure. We have reported that both AT1R expression and AT1R-mediated
Variants Transduced Cell Studies

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mice only when salt intake is increased remains unclear. An increase in blood pressure in GRK4 γ hGRK4 an increase in basal D1R phosphorylation and impairment of (65L/486V)-transfected Chinese hamster ovary cells, there is showed that in single (65L or 486V) or double variant GRK4 Asico and P.A. Jose, unpublished data, 2015). In vitro studies diet, but have increased blood pressure on high-salt diet (L.D. transgenic mice, have normal blood pressure on a normal-salt genetic mice. Moreover, infusion of Ang II causes a greater increase in blood pressure, whereas infusion of the AT1R antagonist candesartan causes a greater decrease in blood pressure in hGRK4γ 142V transgenic mice than GRK4 wild-type transgenic mice.46 AT1R mRNA and protein expression and function are higher in hGRK4γ142V than in hGRK4γ wild-type cells, but the opposite is true for AT1R phosphorylation and degradation,22 indicating that the regulation of AT1R expression by hGRK4γ occurs at both transcriptional and post-translational levels.

Depending on the genetic background and sodium intake, hGRK4γ 486V transgenic mice may develop increased blood pressure. hGRK4γ 486V transgenic mice have increased renal AT1R expression and develop hypertension only after an increase in sodium intake, in contrast to GRK4γ 142V transgenic mice, which have increased AT1R expression and develop hypertension even on a normal-salt diet.46,50 Depending on the genetic background of the mouse, hGRK4γ wild-type prevents salt-sensitive hypertension, whereas hGRK4γ 486V converts a salt-resistant phenotype to a salt-sensitive phenotype.50 hGRK4γ 65L transgenic mice, similar to hGRK4γ 486V transgenic mice, have normal blood pressure on a normal-salt diet, but have increased blood pressure on high-salt diet (L.D. Asico and P.A. Jose, unpublished data, 2015). In vitro studies showed that in single (65L or 486V) or double variant GRK4 (65L/486V)-transfected Chinese hamster ovary cells, there is an increase in basal D1R phosphorylation and impairment of D1R-mediated cAMP production.20 The mechanism for the increase in blood pressure in GRK4γ 65L or 486V transgenic mice only when salt intake is increased remains unclear.

**GRK4 Polymorphisms and Hypertension**

The GRK4 gene polymorphisms have different allele frequencies among different populations. GRK4 486V is more frequent in Asians and less frequent in blacks than in other populations (Hispanics and whites).51 The GRK4 locus on human chromosome 4p16.3 is linked to essential hypertension and salt sensitivity.35 The first report in 2002 by Bengra et al found a significant association between GRK4 A486V variant and an Italian population of mildly hypertensive patients.52 Subsequent studies showed that GRK4 gene variants R65L, A142V, and A486V are each associated with essential hypertension in several ethnic groups (Table 2). In Euro-Australians, GRK4 486V is associated with essential hypertension, whereas the 65L and 142V variants track with elevation in diastolic blood pressure only in male hypertensives.54 In a Chinese Han population, GRK4 A486V is also associated with hypertension in additive, dominant, and recessive model, whereas GRK4 142V is associated with hypertension in an additive model only.59,60 However, there are reports that do not show the association between GRK4 variants and hypertension.53,64 In a population of blacks 18 to 49 years of age, GRK4 A486V variant was found to be negatively associated with hypertension.61 Although the reasons leading to the differences among studies are not known, the negative studies could be the consequence of not taking into account salt sensitivity (particularly for GRK4 R65L and A486V) or assessing the role of GRK4 in conjunction with other single nucleotide polymorphisms of GRK457 and other genes.53,60,65

Salt-sensitive hypertension is associated with GRK4 gene variants. The Italian patients whose hypertension is associated with GRK4 A486V are actually salt-sensitive.52 In a Japanese population, the GRK4 variants (R65L, A142V, and A486V) are more frequent in salt-sensitive than salt-resistant hypertensive patients.57 A genetic model of GRK4 R65L, A142V, and A486V is 94.4% predictive of salt sensitivity. By contrast, the single-locus model with only GRK4 A142V is 78.4% predictive, whereas a 2-locus model of GRK4 A142V

**Table 1. GRK4 Variant Transgenic Mice and In Vitro Studies**

<table>
<thead>
<tr>
<th>GRK4 Variants</th>
<th>Mouse Phenotype</th>
<th>Functional Deficit(s)</th>
<th>Receptor Defect(s)</th>
<th>Cell Line</th>
<th>Receptor Defect(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R65L</td>
<td>Salt-sensitive hypertension (high-salt diet)</td>
<td>Not determined</td>
<td>Not determined</td>
<td>CHO</td>
<td>Increased renal D1R phosphorylation and impaired renal D1R function, R65L alone, or combined with 486V variant</td>
</tr>
<tr>
<td>A142V</td>
<td>Hypertension (normal-salt diet)</td>
<td>Decreased urine flow and sodium excretion20</td>
<td>Decreased renal expression and responsiveness of D1R,20</td>
<td>CHO</td>
<td>Increased renal D1R phosphorylation; Impaired renal D1R function</td>
</tr>
<tr>
<td>A486V</td>
<td>Salt-sensitive hypertension (high-salt diet)</td>
<td>Impaired pressure-natriuresis plot50</td>
<td>Increased AT1R expression50</td>
<td>CHO</td>
<td>Increased renal D1R phosphorylation and impaired renal D1R function</td>
</tr>
</tbody>
</table>

AT1R indicates angiotensin type 1 receptor; CHO, Chinese hamster ovary; D1R, D1-like receptors; GRK4, GPCR kinase 4; and RPT, renal proximal tubules.
and aldosterone synthase CYP11B2 is 77.8% predictive of low-renin hypertension. The ability to excrete a salt load is inversely related to the number of GRK4 variant alleles (R65L, A142V, and A486V) in hypertensive Japanese. GRK4 variants are also associated with salt sensitivity in normotensive subjects. In black normotensive adolescents, the GRK4 65L allele is associated with a reduced urinary sodium excretion in response to stress. In young normotensive twins, GRK4 65L was associated with the steepest increase in blood pressure; the GRK4 65L-142V-A486V haplotype had a 1.05 mm Hg steeper increase in systolic blood pressure per year increase in age, relative to those with GRK4 R65, A142, and A486 haplotype. Therefore, genetic variations of GRK4 may contribute to variations of blood pressure in normotensive individuals, potentially influencing the development of hypertension.

As indicated earlier, GRK4 variants interact with other genes in the pathogenesis of hypertension. Multilocus analyses have shown association between GRK4 variants and other gene variants with high blood pressure. In an African population from Ghana, the combination of angiotensin-converting enzyme and GRK4 R65L is the best genetic model to predict hypertension (70.5% prediction of hypertension). Among Japanese subjects, the best combination that is predictive of hypertension, not classified according to salt sensitivity, is GRK4, angiotensin-converting enzyme, and CYP11B2, with an estimated prediction success of 63%; however, for low-renin hypertension in Japanese, the single best genetic model includes only GRK4 A142V and CYP11B2, with an estimated prediction success of 77.8%. Normotensive Japanese with GRK4 polymorphisms were reported to have increased serum N-terminal pro-B-type natriuretic peptide levels. A recent study among African-derived Brazilian populations reported that an interaction between GRK4 A486V and endothelial nitric oxide synthase is associated with increased diastolic blood pressure.

There are currently 2 meta-analyses on the associations of GRK4 polymorphisms with hypertension risk. Our previous meta-analysis showed that GRK4 486V increases the risk for essential hypertension with an odds ratio of 1.5 (95% confidence interval, 1.2–1.9). A more recent meta-analysis showed that GRK4 486V is inversely associated with hypertension among East Asians (odds ratio =0.39, 95% confidence interval, 0.28–0.55), but positively associated with hypertension among Europeans (odds ratio =2.38, 95% confidence interval, 1.38–4.10); GRK4 65L was also associated with hypertension among Europeans.

### Table 2. Association Studies of GRK4 Variants in Hypertensive or Normotensive Subjects

<table>
<thead>
<tr>
<th>GRK4 Variants</th>
<th>Ethnic Group (Year)</th>
<th>Single or Multilocus Analyses</th>
<th>Hypertension Phenotype</th>
<th>Ethnic Group (Year)</th>
<th>Single or Multilocus Analyses</th>
<th>Blood Pressure or Sodium Excretion</th>
</tr>
</thead>
</table>

ACE indicates angiotensin-converting enzyme; GRK4, GPCR kinase 4; NOS, nitric oxide synthase; SBP, systolic blood pressure; and UNaV, urinary sodium excretion.
is the absence of some genes in the chips. For example, GRK4 was not linked to hypertension in the GWAS probably because the GRK4 polymorphisms are not consistently present in the Affymetrix and Illumina chips; GRK4 65L, 142V, and 486V are present only in the Illumina Human 1 mol/L beadchip, and GRK4 142V is not present in any of the Affymetrix Chips. These limitations may also be found in GWAS for pharmacogenomics of essential hypertension.69

There are several classes of antihypertensive medicines used in clinic and include calcium channel blockers, drugs that target the RAS (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, direct renin inhibitor), diuretics (thiazides and thiazide-like diuretics, loop diuretics, potassium sparing diuretics), and drugs that target the sympathetic nervous system (β-adrenergic receptor blockers, α-adrenergic receptor blockers, direct vasodilators, central α-adrenergic receptor agonists, and adrenergic depleters [e.g., reserpine, probably not used any longer]). The treatment of hypertension is currently not based on pharmacogenetics, but rather based on consensus guidelines.70,71

Current evidence shows that the presence or absence of GRK4 gene variants may be important in guiding therapeutic antihypertensive strategies. In the African American Study of Kidney Disease and Hypertension Study, male (but not female) blacks with GRK4 A142 were found to have a faster decrease in blood pressure response to the β1-adrenoceptor blocker metoprolol, but were less responsive to metoprolol in the presence of GRK4 65L.7 The Pharmacogenomic Evaluation of Antihypertensive Responses study involving hypertensive black and Euro-Americans showed that the presence of GRK4 65L, 142V, and 486V variant alleles in Euro-Americans was associated with reduced response to the β1-adrenergic receptor blocker, atenolol.11 Our studies in hypertensive Japanese subjects show that GRK4 142V is associated with greater decrease in both systolic blood pressure and diastolic blood pressure in response to angiotensin receptor blockers (H. Sanada and P.A. Jose, unpublished data, 2015), which also normalize the increased blood pressure response of GRK4γ142V transgenic mice.46 The lowering of blood pressure with a decrease in dietary salt intake among South African blacks was observed in those with no GRK4 variants or one variant GRK4 65L or GRK4 142V allele; the effect of GRK4 486V was not evaluated.4 However, in a small cohort of Japanese hypertensive subjects, those with GRK4 486V had a good antihypertensive response to low-salt diet or diuretics.72 Patients homozygous to 65L and 142V have been reported to need more antihypertensive treatment, especially diuretics.73 These results suggest that the presence of GRK4 variant alleles may be important determinants in the blood pressure response to antihypertensive drugs or dietary intervention and risk for adverse cardiovascular events.

Conclusions and Perspectives

In summary, increasing evidence shows that constitutively active GRK4 variants, specifically the human GRK4γ 65L, 142V, and 486V variants, play a crucial role in regulating the function of the dopamine receptors and AT1R and are, therefore, involved in the pathogenesis of hypertension (Figure). Genetic association has been found between GRK4 gene variants and hypertension. Antihypertensive medicines have different responses in patients with individual GRK4 variants, indicating that GRK4 variants may be important in choosing the initial antihypertensive medication. Increased understanding of GRK4 in the genetics and pharmacogenetics of hypertension may provide therapeutic targets for hypertension in the future.

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Disclosures

Dr Jose, who is the Scientific Director of Hypogen, Inc, owns US Patent Number 6,660,474 for G protein–related kinase mutants in essential hypertension. The other authors report no conflicts.

References

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Current generation of angiotensin II and the pathogenesis of hypertension.


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