Pancreatic Polypeptide-Fold Peptide Receptors and Angiotensin II–Induced Renal Vasoconstriction

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Abstract—The G\textsubscript{i} pathway augments renal vasoconstriction induced by angiotensin II in spontaneously hypertensive but not normotensive Wistar-Kyoto rats. Because the G\textsubscript{i}-coupled pancreatic polypeptide (PP)-fold peptide receptors Y\textsubscript{1} and Y\textsubscript{2} are expressed in kidneys and are activated by endogenous PP-fold peptides, we tested the hypothesis that these receptors regulate angiotensin II–induced renal vasoconstriction in kidneys from hypertensive but not normotensive rats. A selective Y\textsubscript{1}-receptor agonist [(Leu\textsubscript{31},Pro\textsubscript{34})-neuropeptide Y; 6 to 10 nmol/L] greatly potentiated angiotensin II–induced vasoconstriction in isolated, perfused kidneys from hypertensive but not normotensive rats. A selective Y\textsubscript{2}-receptor agonist (peptide YY\textsubscript{3-36}; 6 nM) only slightly potentiated angiotensin II–induced renal vasoconstriction and only in kidneys from hypertensive rats. Neither the Y\textsubscript{1}-receptor nor the Y\textsubscript{2}-receptor agonist increased basal perfusion pressure. BIBP3226 (1 \mu mol/L, highly selective Y\textsubscript{1}-receptor antagonist) and BIIE0246 (1 \mu mol/L, highly selective Y\textsubscript{2}-receptor antagonist) completely abolished potentiation by (Leu\textsubscript{31},Pro\textsubscript{34})-neuropeptide Y and peptide YY\textsubscript{3-36}, respectively. Y\textsubscript{1}-receptor and Y\textsubscript{2}-receptor mRNAs and protein levels were expressed in renal microvessels and whole kidneys, but the abundance was similar in kidneys from hypertensive and normotensive rats. Both Y\textsubscript{1}-receptor–induced and Y\textsubscript{2}-receptor–induced potentiation of angiotensin II–mediated renal vasoconstriction was completely abolished by pretreatment with pertussis toxin (30 \mu g/kg IV, blocks G\textsubscript{i} proteins). These data indicate that, in kidneys from genetically hypertensive but not normotensive rats, Y\textsubscript{1}-receptor activation markedly enhances angiotensin II–mediated renal vasoconstriction by a mechanism involving G\textsubscript{i}. Although Y\textsubscript{2} receptors can also potentiate angiotensin II–mediated renal vasoconstriction via G\textsubscript{i}, the effect is modest compared with Y\textsubscript{1} receptors. These findings may have important implications for the etiology of genetic hypertension. (Hypertension. 2006;47[part 2]:545-551.)

Key Words: receptors ■ neuropeptides ■ peptides ■ hypertension

The renin–angiotensin system (RAS) is essential for the development and maintenance of genetic hypertension in spontaneously hypertensive rats (SHRs).\textsuperscript{1,2} Moreover, transplantation studies reveal that, in addition to the RAS, the SHR kidney is pivotal to the pathophysiology of hypertension in the SHR.\textsuperscript{3,4} Finally, the renal sympathetic nervous system also appears to importantly contribute to the pathophysiology of hypertension in SHRs. In support of this latter concept, chronic denervation of the SHR kidney both delays the development of hypertension and attenuates the maximum increase in blood pressure in SHR.\textsuperscript{5-8} Thus, there appears to be a coinvolvement of the RAS, the sympathetic nervous system, and the kidney in SHR hypertension.

Many studies have been performed in search of a possible explanation for the coinvolvement of the RAS and the kidney in SHR hypertension. In this regard, studies do not support an increased expression of renal angiotensin II (Ang II) receptors\textsuperscript{9} or increased levels of circulating\textsuperscript{10} or renal\textsuperscript{11} Ang II; also, SHRs do not have altered renal Ang II degradation rates.\textsuperscript{12} However, SHRs do exhibit increased renovascular responses to Ang II,\textsuperscript{13,14} and this appears to be the explanation for the coinvolvement of the RAS and the kidney in SHR hypertension.

Our previous research indicates that G\textsubscript{i} mediates, in part, the enhanced renovascular response to Ang II in SHR. For example, pertussis toxin, an inhibitor of G\textsubscript{i}, abolishes the increased renovascular response to Ang II in SHR.\textsuperscript{15,16} Importantly, activation of renal sympathetic nerves leads to the release of neuropeptide Y (NPY).\textsuperscript{17} NPY is an example of a pancreatic polypeptide (PP)-fold peptide,\textsuperscript{18} and NPY binds with high affinity to Y\textsubscript{1}, Y\textsubscript{2}, and Y\textsubscript{5} receptors but not Y\textsubscript{4} receptors,\textsuperscript{18} whereas Y\textsubscript{1} receptors most likely do not exist.\textsuperscript{19} Both Y\textsubscript{1} and Y\textsubscript{2} receptors are expressed in the kidney,\textsuperscript{17,18} whereas Y\textsubscript{5} receptors are expressed predominantly in the central nervous system, not the kidney.\textsuperscript{20} Because Y\textsubscript{1} and Y\textsubscript{2} receptors coupled to G\textsubscript{i} exist in the kidney and are stimulated by NPY, it is conceivable that the coinvolvement of the RAS, sympathetic nervous system, and kidney in SHR hypertension is mediated in part by activation of Y\textsubscript{1} and/or Y\textsubscript{2} receptors leading to a potentiation of Ang II–induced renal vasoconstriction in the SHR kidney.
The purpose of the present study was to test the hypothesis that Y₁ and/or Y₂ receptor activation potentiates renal vascular responses to Ang II selectively in SHR kidneys by a mechanism involving inhibitory G proteins. In this regard, we examined the effects of (Leu31,Pro34)-NPY (LPNPY), a highly selective Y₁ agonist, and peptide YY3-36 (PYY3-36), a highly selective Y₂ agonist, on renovascular responses to Ang II in SHR and Wistar-Kyoto (WKY) kidneys in vitro in the presence and absence of a highly selective Y₁ antagonist (BIBP3226), a highly selective Y₂ antagonist (BIIE0246), or pertussis toxin to inhibit G proteins.

Methods

Animals

Studies used adult (14 to 16 weeks of age) male SHRs or WKY obtained from Taconic Farms (Germantown, NY). Some SHRs were pretreated 3 days before the experiment with an intravenous (tail vein) injection of pertussis toxin (30 μg/kg given as a bolus; Sigma). We have shown previously that this approach blocks G-protein function in vivo.13 The Institutional Animal Care and Use Committee approved all procedures. The investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health (NIH Publication No. 85-23, revised 1996).

Experiments in Isolated, Perfused Kidneys

SHRs and WKY were anesthetized with Inactin (90 mg/kg, IP), and the left kidney was isolated and perfused with Tyrode’s solution using a Hugo Sachs Elektronik-Harvard Apparatus GmbH (March-Hugstetten) kidney perfusion system as described previously. Briefly, all branches of the left renal artery and vein were ligated. A polyethylene-90 cannula was placed into the left renal artery, and a polyethylene-90 cannula was placed into the left renal vein. The left kidney was removed, attached to the perfusion system, and allowed to stabilize for 1 hour before the experimental protocol. Kidneys were perfused (single pass mode) at a constant flow (5 mL/min), and perfusion pressure was monitored with a pressure transducer.

In a study, Ang II (Sigma) was infused at increasing doses to provide concentrations in the perfusate of 0.3, 1, or 3 nmol/L. Each dose of Ang II was infused for 2 minutes, and the perfusion pressure was allowed to return to basal levels over the next 5 minutes before initiating the next higher dose of Ang II. After the highest dose of Ang II and following a rest period of 15 minutes, LPNPY (Sigma) was infused into the kidney to provide a concentration in the perfusate of 0.05 nmol/L. Ten minutes into the infusion of LPNPY, the kidney was restimulated with Ang II. The response to Ang II was taken as the change in perfusion pressure during the Ang II infusion and was calculated as the perfusion pressure recorded at the end of the infusion of Ang II minus the basal perfusion pressure recorded just before the Ang II infusion. Time control experiments demonstrated that concentration-response curves to Ang II were stable over the duration of the experiment as long as the infusion time was kept to 2 minutes, which avoided tachyphylaxis because of multiple infusions of high concentrations of Ang II. Although this experimental design permitted evaluation of multiple concentrations of Ang II while avoiding tachyphylaxis, the response to Ang II did not always achieve steady state in 2 minutes. Therefore, this design permitted an evaluation of the effects of LPNPY on the early response to Ang II.

To address the effects of PP-fold agonists on the steady-state effects of Ang II, in another study, Ang II was infused to achieve a concentration in the perfusate of 0.3 nmol/L. After 10 minutes, the infusion of Ang II was stopped, and the perfusion pressure was allowed to return to basal levels over the next 10 minutes, then LPNPY or PYY3-36 (Tocris Cookson Inc) was infused into the kidney to provide a final concentration in the perfusate of 6 nmol/L. Twenty minutes into the infusion of LPNPY or PYY3-36, the kidney was restimulated with Ang II for 10 minutes. By using only a low concentration of Ang II and by limiting the experiment to 2 challenges with Ang II, tachyphylaxis to Ang II was avoided, and responses to Ang II were stable. Changes in perfusion pressure in response to Ang II were calculated as described above. Some of these experiments were conducted in kidneys obtained from SHRs pretreated with pertussis toxin. Also, some of these experiments were conducted in kidneys in which BIBP3226 (Tocris) or BIIE0246 (Tocris) was infused into the perfusate to provide a concentration in the perfusate of 1 μmol/L. The infusions of BIBP3226 or BIIE0246 were initiated at the beginning of the 1-hour rest period and continued until the end of the protocol.

RT-PCR for Y₁ and Y₂ Receptor mRNA and Western Blotting for Y₁ and Y₂ Receptor Protein

Y₁ or Y₂ receptor mRNA was obtained from SHR and WKY pregglomerular microvessels (PGMVs) and whole kidneys and measured as described previously for other receptors. Briefly, PGMVs were obtained by iron oxide injection into the renal artery followed by magnetic retrieval of PGMVs. Total RNA was isolated from PGMVs or whole kidney with TRIzol reagent. RNA was reverse transcribed and amplified using a Titanium One-Step RT-PCR kit. For the Y₁ receptor, the forward primer was 5′-CTGATCGTG-AACCTCTCCTTCT-3′, and the reverse primer was 5′-GTC-GTGAAGACAGCCTGTTG-3′. For the Y₂ receptor, the forward primer was 5′-GGTCTGGCAGCATTGAG-AAC-3′, and the reverse primer was 5′-GGTTGTTTGTGCTCCTCC-3′. Each PCR cycle consisted of denaturing at 94°C for 30 seconds, annealing at 65°C for 30 seconds, and extension at 72°C for 60 seconds. RT-PCR products were separated on a 1.2% agarose gel, and gels were stained with ethidium bromide.

Y₁ or Y₂ receptor protein was obtained from PGMVs and whole kidneys and measured as described previously for other receptors. Briefly, protein samples from whole kidneys and PGMVs were loaded onto a 7.5% acrylamide gel and subjected to SDS-PAGE using the BioRad mini gel system. Proteins were electroblotted onto polyvinylidene fluoride membranes. Membranes were blocked with 5% milk and then incubated with primary antibody to either the Y₁ or Y₂ receptor (Sigma). After washing, the membrane was incubated with horseradish peroxidase-conjugated donkey anti-rabbit IgG secondary antibody. Membranes were then exposed to films, and the signals were detected by a Supersignal Substrate kit. Band densities were quantitatively measured using Scion Image software.

Statistical Analysis

Data were analyzed by paired or unpaired 2-tailed Student t test or 1-factor or 2-factor ANOVA, as appropriate. The Fisher least significant difference (LSD) test was used for post-hoc analyses if a significant ANOVA was obtained. The criterion of significance was P<0.05. All of the data are presented as mean±SEM.

Results

Basal Renal Perfusion Pressures

In this study, baseline renal perfusion pressures were similar (60±3 and 52±2 mm Hg) in WKY and SHR kidneys, respectively, and were not affected by any of the various treatments or combinations of treatments. Although the perfusion flow rate was physiological (5 mL/min), baseline perfusion pressures were below the normal renal perfusion pressure in vivo because of the low viscosity of Tyrode’s solution compared with whole blood. However, despite the low basal perfusion pressure, the kidneys were very responsive to Ang II.

Experiments in Isolated, Perfused Kidneys With LPNPY

As shown in Figure 1, 0.3 (Figure 1A), 1 (Figure 1B), and 3 (Figure 1C) nmol/L of Ang II caused a concentration-
dependent increase in renal perfusion pressure in both WKY (left graphs) and SHRs (right graphs). Ang II–induced increases in renal perfusion pressure were significantly greater in SHR compared with WKY kidneys (right versus left graphs in Figure 1). In SHR kidneys and at all concentrations of Ang II, LPNPY (10 nmol/L) significantly potentiated Ang II–induced increases in renal perfusion pressure (Figure 1, right graphs). In contrast, in WKY kidneys, LPNPY did not augment Ang II–induced increases in renal perfusion pressure regardless of the concentration of Ang II (Figure 1, left graphs). Two-factor ANOVA demonstrated a significant interaction between rat strain and LPNPY on Ang II–induced changes in perfusion pressure (P = 0.003, P < 0.001, and P = 0.004 for 0.3, 1, and 3 nmol/L Ang II, respectively).

In a separate set of experiments using naïve SHR kidneys, LPNPY (6 nmol/L) again markedly and significantly potentiated the ability of Ang II (at 0.3 nmol/L infused to a steady-state response) to increase renal perfusion pressure (Figure 2A). The ability of LPNPY to potentiate Ang II–induced renal vasoconstriction was greatly suppressed by both BIBP3226 (Figure 2B) and pertussis toxin (Figure 2C); however, there remained a statistically significant, albeit small, residual potentiation. LPNPY enhanced Ang II–induced changes in perfusion pressure by 54 ± 8, 8 ± 3, and 13 ± 6 mm Hg in untreated, BIBP3226-treated and pertussis toxin–treated kidneys, respectively, and the ability of LPNPY to enhance Ang II–induced changes in perfusion pressure was statistically significantly suppressed by both BIBP3226 and pertussis toxin.

RT-PCR for Y1 Receptor mRNA and Western Blotting for Y1 Receptor Protein

As shown in Figure 3, mRNA and protein expression for Y1 receptors was detected in whole kidney and PGMVs from both WKY and SHRs. However, the expression of Y1...
receptor mRNA and protein, when normalized to β-actin and quantified by densitometry, did not differ between WKY and SHR tissues (Figure 4).

Experiments in Isolated, Perfused Kidneys With PYY3-36
As shown in Figure 5A, PYY3-36 caused a very small but statistically significant and reproducible potentiation of renal vasoconstriction induced by Ang II (0.3 nmol/L infused to steady-state response; 32 ± 5 and 41 ± 5 mm Hg, change in perfusion pressure in response to Ang II before and during PYY3-36, respectively). However, in WKY, PYY3-36 did not significantly alter Ang II–induced renal vasoconstriction (17 ± 5 and 14 ± 3 mm Hg, change in perfusion pressure in response to Ang II before and during PYY3-36, respectively).

As shown in Figure 5, BIIE0246 (Figure 5B) and pertussis toxin (Figure 5C) completely blocked PPY3-36-induced potentiation of Ang II–induced changes in perfusion pressure. PPY3-36 enhanced Ang II–induced changes in perfusion pressure by 9 ± 2, −2 ± 2, and −1 ± 3 mm Hg in untreated, BIIE0246-treated, and pertussis toxin–treated kidneys, respectively, and the ability of PPY3-36 to enhance Ang II–induced changes in perfusion pressure was statistically significantly suppressed by both BIIE0246 and pertussis toxin.

RT-PCR for Y2 Receptor mRNA and Western Blotting for Y2 Receptor Protein
As shown in Figure 6, mRNA and protein expression for Y2 receptors was detected in whole kidney and PGMVs from both WKY and SHRs. However, the expression of Y2 receptor mRNA and protein, when normalized to β-actin and quantified by densitometry, did not differ between WKY and SHR tissues (data not shown).

Discussion
The PP-fold family of peptides consists of 4 members, NPY, PYY3-36, PYY3-36, and PP.18,19 Four active PP-fold peptide receptors have been cloned in primate species, namely Y1, Y2, Y4, and Y5.18,19 Although, as confirmed in the present study, Y1 and Y2 receptors are expressed in the kidney, Y4 and Y5 receptors are expressed predominantly in the intestines and brain,18 not the kidney. Therefore, in the present study, we focused on the role of Y1 and Y2 receptors as regulators of Ang II–induced renal vasoconstriction.

Figure 3. RT-PCR products for Y1 receptor mRNA and β-actin mRNA in WKY and SHR kidneys (top left) and in prerglomerular microvessels (PGMV; bottom left). Western blot analysis of Y1 receptor and β-actin in WKY and SHR kidneys (top right) and preglomerular microvessels (PGMV; bottom right).

Figure 4. Top: densitometry results (normalized to β-actin signal) from Western blot analysis of Y1 receptor protein in WKY vs SHR kidneys (left) and prerglomerular microvessels (PGMV; right). Bottom: densitometry results (normalized to β-actin signal) from RT-PCR products for Y1 receptor mRNA in WKY vs SHR kidneys (left) and prerglomerular microvessels (PGMV; right).
The results of the present study strongly support the concept that Y₁ receptors enhance renal vasoconstrictor responses to Ang II and that the potentiation of Ang II responses by Y₁ receptors is greater in SHR compared with WKY rats. In this regard, our results show that LPNPY, a highly selective Y₁-receptor agonist, greatly enhances the renovascular response to Ang II in the SHR kidney, yet does not potentiate responses to Ang II in the WKY kidney. Moreover, our findings demonstrate that BIBP3226, a highly selective Y₁ receptor antagonist, blocks the ability of LPNPY to enhance renovascular responses to Ang II. This latter finding confirms that the effects of LPNPY are, indeed, mediated mostly by the Y₁ receptor.

The results of the present study also indicate that Y₂ receptors enhance (albeit only slightly) renal vasoconstrictor responses to Ang II and that the potentiation of Ang II responses by Y₂ receptors is greater in SHR compared with WKY rats. In this regard, PYY₃₋₃₆, a highly selective Y₂-receptor agonist, slightly enhances the renovascular response to Ang II in the SHR kidney, yet does not potentiate responses to Ang II in the WKY kidney. The observation that BIIIE0246, a highly selective Y₂-receptor antagonist, completely abrogates the ability of PYY₃₋₃₆ to enhance Ang II–induced renal vasoconstriction confirms that the effects of PYY₃₋₃₆ are, indeed, mediated by the Y₂ receptor with no involvement of other PP-fold peptide receptors.

The findings of the current study have important implications regarding the pathophysiology of genetic hypertension. Renal sympathetic nerves release 2 major neurotransmitters, norepinephrine and NPY. Norepinephrine causes direct vasoconstriction by α₁-adrenoceptors that reside within the...
neuroeffector junction. Importantly, NPY can bind to and activate Y₁ and Y₂ receptors. Our findings indicate, therefore, that an important contributing cause to genetic hypertension could be corelease of NPY from renal sympathetic nerves with subsequent activation of postjunctional Y₁ receptors and, perhaps to a much lesser extent, Y₂ receptors, leading to significant potentiation of the renal vasoconstrictor responses to Ang II. The fact that acute blockade of Y₁ receptors does not lower arterial blood pressure in SHRs does not disprove this hypothesis, because only chronic treatment with a Y₁ receptor antagonist would be expected to lower arterial blood pressure in SHRs by causing a leftward shift in the renal-pressure natriuresis relationship.

It has long been known that chronic treatment of SHR with α₁-adrenoceptor blockers, for example, terazosin, does not alter the course of hypertension in SHRs. Because α₁-adrenoceptors are primarily responsible for sympathetically mediated direct vasoconstriction in the kidney, these data would appear to rule out the involvement of renal sympathetic nerves in the pathophysiology of genetic hypertension. However, chronic denervation of the SHR kidney both delays the development of hypertension and attenuates the maximum increase in blood pressure in SHRs, findings consistent with a role for the renal sympathetic nerves in hypertension, yet inconsistent with the results of studies with α₁-adrenoceptor blockers. Moreover, the profound effects of renal denervation on the natural history of hypertension in SHRs are seemingly at odds with the important role of the RAS in genetic hypertension. Our hypothesis would unify these facts by postulating that the problem is not over-activation of α₁-adrenoceptors or over-activation of the RAS, but rather normal levels of stimulation of Y₁ receptors and, perhaps to a lesser extent, Y₂ receptors, leading to potentiation of the renal vasoconstrictr responses to normal levels of Ang II in SHR, but not WKY, kidneys. It would appear that Y₁ receptors would take the leading role in this scenario, because the efficacy of Y₁ receptors with regard to potentiating Ang II–induced renal vasoconstriction seems quite low.

Why does Y₁ and Y₂ receptor activation potentiate Ang II–induced renal vasoconstriction in SHR, but not WKY, kidneys? One possibility is that Y₁ and Y₂ receptor levels are elevated in the kidneys of SHRs. However, we are unable to detect an increase in either Y₁ or Y₂ receptor mRNA or protein in either whole kidneys or preglomerular microvessels freshly isolated from whole kidneys. Thus, it appears that the mechanism for the enhanced Y₁ and Y₂ receptor activation does not involve overexpression of receptors, but rather enhanced coincidence signaling between Ang II and Y₁ and Y₂ receptor signal transduction pathways in SHR kidneys. In this regard, previous work from our laboratory indicates that the Gᵢ pathway mediates potentiation of Ang II–induced renal vasoconstriction by α₂-adrenoceptors in SHRs. The present study shows that pertussis toxin, which ADP ribosylates and inactivates Gᵢ, blocks the potentiation of Ang II–induced renal vasoconstriction by Y₁ and Y₂ receptors in the SHRs. Thus, like α₂-adrenoceptors, Y₁ and Y₂ receptors appear to enhance renovascular responses to Ang II in the SHRs by activating the Gᵢ pathway. Several studies implicate overexpression of Gᵢ proteins in some tissues in SHRs. However, our studies suggest normal levels of Gᵢ proteins in SHR preglomerular microvessels and indicate a role for the Gᵢ protein/phospholipase C/protein kinase Cε/src/phosphatidylinositol 3-kinase pathway in the interaction between Ang II and the Gᵢ signal transduction pathway in SHRs. Although we do not know why coincidence signaling between the Ang II signal transduction pathway and the Gᵢ signal transduction pathway is enhanced in SHR kidneys, it appears to be because of a downstream event in the aforementioned signal transduction pathway. Additional studies are required to more precisely identify the involved mechanisms.

To the best of our knowledge, this study represents the first investigation of the interaction between Ang II and Y₁ and Y₂ receptors on renovascular resistance in either normotensive or hypertensive animals. However, Mohy El-Din and Malik have examined the effects of high concentrations of NPY on WKY kidneys obtained from normotensive Sprague-Dawley rats. Their studies showed that NPY at the concentration used transiently increased basal renal perfusion pressure by ~58% and potentiated the changes in renal perfusion pressure induced by bolus injections of Ang II by ~32%. Thus, the work by Mohy El-Din and Malik indicates that high concentrations of a “broad-spectrum” PP-fold peptide receptor agonist enhance Ang II–induced renal vasoconstriction in normotensive animals. In the present study, we did not examine the interaction between Ang II and concentrations of LNPY >10 nmol/L, because at higher concentrations LNPY caused a marked and sustained increase in basal renal perfusion pressure that would have confounded interpretation of the interaction between LNPY and Ang II.

The focus of the present study was on the interaction between Y₁ and Y₂ receptors and Ang II. It is well known that in many vascular preparations, including the isolated, perfused rat kidney, NPY enhances norepinephrine-induced vasoconstriction. Whether this interaction is greater in SHR compared with WKY kidneys is an important and open question that should be addressed in future studies. Along these lines, a very recent study by Vonend et al indicates that Y₁-receptor activation enhances purinergic, nonadrenergic renal vasoconstriction in isolated, perfused kidneys from young and adult WKY and young stroke-prone SHRs but not in kidneys from adult stroke-prone SHRs. Thus, the greater enhancement of vasoconstrictor responses in SHR compared with WKY kidneys by Y₁ receptors may occur with only some (eg, Ang II) vasoconstrictors. Indeed, our previous studies demonstrate that activating the Gᵢ pathway with the α₂-adrenoceptor agonist UK14,304 potentiates renovascular responses to Ang II but not to the α₁-adrenoceptor agonist methoxamine in the SHR kidney.

Perspectives

There are 2 known sources of endogenous agonists of renal Y₁ and Y₂ receptors. The sympathetic nervous system releases NPY at renal neuroeffector junctions, and enterocytes in the intestines release PYY₁₋₃₆ and PYY₃₋₁₆ into the circula-
tion in response to food. Thus, there is amply opportunity for endogenous agonists to activate Y₁ and Y₂ receptors. The present study demonstrates that activation of Y₁ and, to a much lesser extent, Y₂ receptors potentiates Ang II–induced renal vasoconstriction in the SHR but not the WKY. These findings indicate that, in genetically susceptible subjects, endogenous agonists of Y₁ receptors and, to a much lesser extent, Y₂ receptors, may facilitate Ang II–induced renal vasoconstriction and thereby contribute to the pathophysiology of hypertension. This work, therefore, suggests that, in genetically susceptible subjects, interactions among the RAS, renal sympathetic nervous system, and perhaps even the intestines may contribute to the pathophysiology of hypertension by vasoconstricting the renal vasculature.

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