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Sitagliptin Augments Sympathetic Enhancement of the Renovascular Effects of Angiotensin II In Genetic Hypertension

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Abstract

Dipeptidyl peptidase IV converts neuropeptide Y₁₋₃₆ (Y₁-receptor agonist released from renal sympathetic nerves) to neuropeptide Y₃₋₃₆ (selective Y₂-receptor agonist). Previous studies suggest that Y₁, but not Y₂, receptors enhance renovascular responses to angiotensin II in kidneys from genetically-susceptible animals. Therefore, we hypothesized that inhibition of dipeptidyl peptidase IV with sitagliptin (antidiabetic drug) would augment the ability of exogenous and endogenous neuropeptide Y₁₋₃₆ to enhance renal vascular responses to angiotensin II in kidneys from spontaneously hypertensive rats. This hypothesis was tested using three protocols in isolated, perfused kidneys.

Results from Protocol 1: Exogenous neuropeptide Y₁₋₃₆ enhanced renovascular responses to angiotensin II; This effect of neuropeptide Y₁₋₃₆ was blocked by BIBP3226 (selective Y₁ receptor antagonist); Exogenous neuropeptide Y₃₋₃₆ did not enhance renovascular responses to angiotensin II.

Results from Protocol 2: Sitagliptin augmented the ability of exogenous neuropeptide Y₁₋₃₆ to enhance renovascular responses to angiotensin II; This effect of sitagliptin was blocked by BIBP3226.

Results from Protocol 3: Renal sympathetic nerve stimulation enhanced renovascular responses to angiotensin II; This enhancement was augmented by sitagliptin and abolished by BIBP3226.

Conclusion: Neuropeptide Y₁₋₃₆ via Y₁ receptors enhances renovascular responses to angiotensin II in kidneys from genetically hypertensive animals. Sitagliptin, by blocking dipeptidyl peptidase IV, prevents metabolism of neuropeptide Y₁₋₃₆ and thereby increases the effects of neuropeptide Y₁₋₃₆ released from renal sympathetic nerves on Y₁ receptors leading to augmentation of neuropeptide Y₁₋₃₆-induced enhancement of the renovascular effects of angiotensin II. The renal effects of dipeptidyl peptidase IV inhibitors in hypertensive, diabetic patients merit a closer examination.

Keywords

neuropeptide Y; CD26; receptors, neuropeptide Y; rats, inbred SHR; sympathetic nervous system; kidney; renal circulation

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INTRODUCTION

Our previously published results indicate that activation of renovascular Y₁ receptors (Y₁Rs) markedly enhances renovascular responses to physiological levels of angiotensin II (Ang II) in kidneys of spontaneously hypertensive rats (SHR)¹. In contrast, kidneys from normotensive Wistar-Kyoto rats (WKY) are resistant to this interaction¹. Our studies also show that unlike Y₁Rs, renovascular Y₂ receptors (Y₂Rs) exert little effect on Ang II-induced renovascular responses in kidneys from either SHR or WKY¹. Although we do not know precisely why SHR, but not WKY, kidneys are susceptible to Y₁R-induced enhancement of Ang II-mediated renal vasoconstriction, these findings indicate that endogenous agonists of Y₁Rs, but not Y₂Rs, would potentiate Ang II-induced renal vasoconstriction in genetically-susceptible kidneys, provided Y₁R agonists reach the renal microcirculation.

In this regard, there are two endogenous agonists of Y₁Rs that would be presented to the kidney microcirculation, i.e., peptide YY₁₋₃₆ (PYY₁₋₃₆) and neuropeptide Y₁₋₃₆ (NPY₁₋₃₆). Both are pancreatic polypeptide-fold peptides. A fatty meal releases PYY₁₋₃₆ into the systemic circulation from endocrine L-cells in the small bowel, colon and rectum producing physiologically active levels of PYY₁₋₃₆ in plasma that are 500% to 1000% above basal circulating levels²⁻⁸, and this circulating PYY₁₋₃₆ would be delivered promptly to the renal microcirculation via the blood stream (humoral Y₁R-agonist input to kidney microcirculation). Renal sympathetic nerves release NPY₁₋₃₆ in response to central nervous system-mediated activation of the renal sympathetic nerves (neural Y₁R-agonist input to kidney microcirculation), resulting in high local levels of NPY₁₋₃₆ in sympathetically-innervated renal microvessels during renal sympathetic activation⁹. Because both PYY₁₋₃₆ and NPY₁₋₃₆ are potent Y₁R agonists^{10, 11}, physiological processes that increase PYY₁₋₃₆ release from the gut, NPY₁₋₃₆ release from renal sympathetic nerves or both simultaneously would activate Y₁Rs in the renal microcirculation, which in genetically-susceptible kidneys would enhance Ang II-induced renal vasoconstriction.

It is conceivable, however, that renal dipeptidyl peptidase IV (DPP IV, also called CD26) limits stimulation of renal Y₁Rs by physiological processes that increase the exposure of the renal microcirculation to PYY₁₋₃₆ and NPY₁₋₃₆. DPP IV is an ecto-enzyme that is anchored to the cell surface and converts PYY₁₋₃₆ to PYY₃₋₃₆¹² and NPY₁₋₃₆ to NPY₃₋₃₆¹² by cleaving two amino acids from the N-terminus of PYY₁₋₃₆ and NPY₁₋₃₆. Whereas PYY₁₋₃₆ and NPY₁₋₃₆ are potent Y₁R agonists, PYY₃₋₃₆ and NPY₃₋₃₆ are inactive at Y₁Rs but are potent and selective Y₂R agonists^{10, 11}. These facts suggest the hypothesis that DPP IV in the renal vasculature or glomeruli is a determinant of the extent to which PYY₁₋₃₆ and NPY₁₋₃₆ enhance renovascular responses to Ang II in genetically-susceptible kidneys.

In support of this concept, our recently published study¹³ demonstrates that in SHR kidneys: 1) PYY₁₋₃₆ enhances renovascular responses to Ang II, whereas PYY₃₋₃₆ has little effect in this regard; 2) P32/98 (DPP IV inhibitor) augments the ability of PYY₁₋₃₆ to enhance renovascular responses to Ang II; 3) DPP IV is expressed in preglomerular microvessels and glomeruli; 4) kidneys metabolize arterial PYY₁₋₃₆ to PYY₃₋₃₆ via a mechanism blocked by P32/98; and 5) freshly isolated preglomerular microvessels and glomeruli convert PYY₁₋₃₆ to PYY₃₋₃₆, and this conversion is inhibited by P32/98. These results confirm that DPP IV is expressed in the renal microcirculation and that inhibition of this ecto-enzyme causes arterial PYY₁₋₃₆ to more effectively enhance Ang II-induced renal vasoconstriction in genetically-susceptible kidneys.

Although the aforementioned study supports the hypothesis that renal DPP IV importantly modifies the effects of humoral Y₁R-agonist input to the kidney microcirculation, this study

does not address whether renal DPP IV significantly influences the effects of neural Y₁R-agonist input to the kidney. This is an important unanswered question because previously published results indicate that renal sympathetic nerve stimulation enhances renovascular responses to Ang II in the SHR, but not WKY, kidneys via a Y₁R mechanism¹⁴. Therefore, one aspect of the present study was to determine whether inhibition of DPP IV alters the ability of exogenous NPY₁₋₃₆ and endogenous NPY₁₋₃₆ (i.e., that released from renal sympathetic nerves in response to periarterial renal nerve stimulation) to enhance renovascular responses to Ang II.

Another important unanswered question is whether clinically available DPP IV inhibitors affect the ability of exogenous and endogenous Y₁R agonists to enhance renovascular responses to Ang II. P32/98 is a DPP IV inhibitor that is available from chemical supply companies, but is not used clinically, nor is P32/98 as potent as clinically employed DPP IV inhibitors. Another aspect of the present study was to examine the effects of sitagliptin (Januvia®), a potent, selective and recently FDA-approved and marketed DPP IV inhibitor, on the interaction between exogenous and endogenous NPY₁₋₃₆ on Ang II-induced renal vasoconstriction in kidneys from genetically hypertensive rats.

METHODS

Animals

Studies utilized adult (14-16 weeks-of-age) male SHR obtained from Taconic Farms (Germantown, NY). 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 US National Institutes of Health (NIH Publication No. 85-23, revised 1996).

Isolated, Perfused Kidney Preparation

SHR were anesthetized with Inactin (90 mg/kg, i.p.; Sigma-Aldrich, St. Louis, MO), and the left kidney was isolated and perfused with Tyrode's solution using a Hugo Sachs Elektronik-Harvard Apparatus GmbH (March-Hugstetten, Germany) kidney perfusion system as previously described¹⁵. Briefly, all branches of the left renal artery and vein were ligated. A polyethylene-50 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 an 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.

Protocol 1

Kidneys were isolated from adult SHR and perfused in vitro as described above. After a 1-hour stabilization period, renovascular responses (i.e., changes in perfusion pressure) to 0.3 nmol/L of Ang II were assessed by infusing Ang II into the perfusate for 10 minutes and noting the difference between the perfusion pressure just before the Ang II infusion compared to the perfusion pressure at the end of the Ang II infusion. The infusion of Ang II was stopped, and 10 minutes later the kidneys were exposed to NPY₁₋₃₆ or NPY₃₋₃₆ (6 nmol/L) for 20 minutes. Ten minutes into the treatments with either NPY₁₋₃₆ or NPY₃₋₃₆, Ang II was infused once again for 10 minutes to obtain another renovascular response to Ang II, but this time in the presence of either NPY₁₋₃₆ or NPY₃₋₃₆. Some kidneys were treated with BIBP3226 (1 μmol/L), a highly selective Y₁R antagonist¹⁰, beginning 20 minutes before the first renovascular response to Ang II and continuing until the end of the protocol. The effect of NPY₁₋₃₆ or NPY₃₋₃₆ on the renovascular response to Ang II was calculated by subtracting the renovascular response to Ang II before treatment with either NPY₁₋₃₆ or NPY₃₋₃₆ from the renovascular

response to Ang II after treatment with either NPY₁₋₃₆ or NPY₃₋₃₆. Ang II, NPY₁₋₃₆, NPY₃₋₃₆ and BIBP3226 were obtained from Sigma-Aldrich.

Protocol 2

Kidneys were isolated from adult SHR and perfused in vitro as described above. After a 1-hour stabilization period, the renovascular response (as defined above) to Ang II (0.1 nmol/L) was assessed by infusing Ang II into the perfusate for 10 minutes. The infusion of Ang II was stopped, the kidney was exposed to 0.1 nmol/L of NPY₁₋₃₆ for 20 minutes, and 10 minutes into the treatment with 0.1 nmol/L of NPY₁₋₃₆, the renovascular response to Ang II was again obtained by infusing Ang II (0.1 nmol/L) for 10 minutes. The infusion of Ang II was again stopped, and the concentration of NPY₁₋₃₆ was increased to 0.3 nmol/L for 20 minutes, and 10 minutes into this higher concentration of NPY₁₋₃₆, the renovascular response to Ang II (0.1 nmol/L) was again obtained by infusing Ang II (0.1 nmol/L) for 10 minutes. This procedure was repeated as the concentration of NPY₁₋₃₆ was increased to 1 nmol/L and finally to 3 nmol/L. Some kidneys were pretreated for 10 minutes before the first response to Ang II with either sitagliptin (1 μmol/L) or sitagliptin + BIBP3226 (1 μmol/L), and these treatments were maintained throughout the experiment. The fold-increase in the renovascular response to Ang II was calculated by dividing the renovascular response before administering NPY₁₋₃₆ into the renovascular response to Ang II in the presence of each concentration of NPY₁₋₃₆.

Protocol 3

Kidneys were isolated from adult SHR and perfused in vitro as described above. Care was taken not to damage the periarterial renal sympathetic nerves during isolation by leaving as much tissue as possible around the artery and avoiding trauma to the nerves. Immediately after initiating perfusion of the kidney, a platinum bipolar electrode was positioned around the renal artery close to the kidney for renal nerve stimulation, and the electrode was connected to a Grass stimulator (model SD9E; Grass Instruments, Quincy, MA). The tissues around the electrode were kept moist with Tyrode's solution. After a 1-hour stabilization period, prazosin (30 nmol/L) was infused into the renal artery to block α₁-adrenoceptors so that renal nerve stimulation would not cause direct vasoconstriction and would not increase basal renovascular tone¹⁴. Some kidneys also were pretreated with sitagliptin (1 μmol/L). The infusions of prazosin or prazosin plus sitagliptin were continued for the duration of the experiment. Ten minutes after initiating the infusions of prazosin or prazosin plus sitagliptin, a sham periarterial renal nerve stimulation was performed by going through the motions of activating the stimulator while not actually activating the stimulator. Two minutes into the sham renal nerve stimulation, Ang II (0.1 nmol/L) was infused into the renal artery for 7 minutes to obtain a renovascular response to Ang II (as defined above). This first renovascular response to Ang II was designated the period 1 response, which was a basal/control response. At the end of the Ang II infusion, kidneys were allowed to recover for 10 minutes, and then were subjected to renal nerve stimulation (biphasic, 5 Hz, 1-ms pulse duration, 35 V) for 9 minutes. Two minutes into the renal nerve stimulation, Ang II (0.1 nmol/L) was infused once again for 7 minutes to obtain another renovascular response to Ang II. This second renovascular response to Ang II was designated the period 2 response, which was a response to Ang II in the presence of renal nerve stimulation. At this point, both the Ang II infusion and the renal nerve stimulation were discontinued, and an infusion of BIBP3226 (1 μmol/L) was initiated and continued until the end of the protocol. After a 20-minute stabilization period, the kidneys were once again subjected to renal nerve stimulation (biphasic, 5 Hz, 1-ms pulse duration, 35 V) for 9 minutes. Two minutes into the renal nerve stimulation, Ang II (0.1 nmol/L) was infused again for 7 minutes to obtain a third renovascular response to Ang II. This third response to Ang II was designated the period 3 response, which was a response to Ang II in the presence of renal nerve stimulation plus BIBP3226.

Extraction of Sitagliptin

Sitagliptin is not available from chemical supply companies. However, because sitagliptin phosphate monohydrate is highly water soluble, we purchased Januvia® tablets containing 100 mg of sitagliptin phosphate monohydrate from the University of Pittsburgh Medical Center hospital pharmacy and dissolved these tablets in Tyrode's solution. In this regard, we added a 100-mg Januvia® tablet to 10 ml of Tyrode's solution, and placed this preparation in the refrigerator for 1 hour to allow tablet dissolution to occur. The preparation was then vortexed at room temperature and then centrifuged to remove any particulates. An appropriate volume of this preparation (based on the labeled amount of sitagliptin in the tablet) was then diluted in Tyrode's solution to give the desired final concentration of sitagliptin in the perfusate. The solution was then tested by ion-trap mass spectrometry. The mass spectrum of the extract was characterized by a single peak at 408 m/z corresponding to protonated sitagliptin ($407 + 1 = 408$).

Statistical Analysis

Data were analyzed by one-factor analysis of variance, repeated measures two-factor analysis of variance, Fisher's Least Significant Difference (LSD) test or Mann-Whitney U test as appropriate. The criterion of significance was $p < 0.05$. All data are presented as means \pm SEM.

RESULTS

Protocol 1

As shown in Figure 1, the Ang II-induced change in perfusion pressure was enhanced by 47 ± 7 mm Hg ($n=7$) by NPY₁₋₃₆ (6 nmol/L). Unlike NPY₁₋₃₆, NPY₃₋₃₆ ($n=7$) had little effect on Ang II-induced changes in perfusion pressure (Figure 1). Moreover, the ability of NPY₁₋₃₆ to potentiate renovascular responses to Ang II was blocked by pretreating the kidneys for 20 minutes with BIBP3226 (1 μ mol/L; $n=6$; Figure 1), a highly selective Y₁-receptor blocker¹⁰.

Protocol 2

In this protocol, we examined the effects of increasing concentrations of NPY₁₋₃₆ (0.1, 0.3, 1 and 3 nmol/L) in the absence and presence of sitagliptin (1 μ mol/L) or sitagliptin plus BIBP3226 (1 μ mol/L) on vasoconstrictor responses to a very low, physiologically-relevant concentration (100 pmol/L) of Ang II. The basal response to 100 pmol/L of Ang II was similar in all three groups and averaged 7 ± 1 mm Hg ($n=23$). As shown in Figure 2, at concentrations of 1 nmol/L or less, NPY₁₋₃₆ had little effect on the vasoconstrictor response to Ang II, and at 3 nmol/L the renovascular response to Ang II was enhanced by only 1.90-fold ($n=8$). In marked contrast, in sitagliptin-treated kidneys (Figure 2), the vasoconstrictor response to Ang II was concentration-dependently (from 0.1 to 3 nmol/L) enhanced by NPY₁₋₃₆ and at 3 nmol/L the renovascular response to Ang II was enhanced by 2.83-fold ($n=8$). The relationship between concentration of NPY₁₋₃₆ and fold-enhancement was statistically-significantly greater in sitagliptin-treated kidneys ($n=8$) compared with the non-sitagliptin-treated kidneys ($p=0.0168$). Importantly, in kidneys treated with both sitagliptin and BIBP3226, NPY₁₋₃₆ had little effect on Ang II-induced renovascular responses regardless of the concentration of NPY₁₋₃₆ (Figure 2; $n=7$). The relationship between concentration of NPY₁₋₃₆ and fold-enhancement was statistically-significantly less in BIBP3226 plus sitagliptin-treated kidneys ($n=7$) compared with sitagliptin-treated kidneys ($p=0.0061$).

Protocol 3

In the third protocol, we examined the effects of renal nerve stimulation in control kidneys ($n=11$) versus kidneys pretreated with sitagliptin (1 μ mol/L; $n=12$) on renovascular responses to a very low, physiologically-relevant concentration of Ang II (100 pmol/L) before and after

BIBP3226 (1 $\mu\text{mol/L}$). The basal response to 100 pmol/L of Ang II was similar in both groups and averaged 6 ± 1 mm Hg ($n=23$). Renal nerve stimulation did not influence basal renal perfusion pressure because the kidneys were pretreated with prazosin to block the α_1 -adrenoceptor-mediated effects of norepinephrine. As shown in Figure 3, in both non-sitagliptin-treated control kidneys and in sitagliptin-treated kidneys, renal nerve stimulation significantly ($p<0.05$) enhanced Ang II-induced renovascular responses. Also, in both non-sitagliptin-treated control kidneys and in sitagliptin-treated kidneys BIBP3226 blocked all effects of renal nerve stimulation on Ang II-induced renovascular responses. Notably, the fold-enhancement of Ang II-induced renovascular responses was significantly ($p=0.0227$) greater in sitagliptin-treated versus non-sitagliptin-treated kidneys (3.60-fold versus 1.51-fold).

DISCUSSION

The results from the first protocol of the present study demonstrate that a high concentration of exogenous NPY₁₋₃₆ markedly enhances renovascular responses to Ang II in SHR kidneys. This finding supports the concept that if endogenous concentrations of NPY₁₋₃₆ achieve a high enough level, endogenous NPY₁₋₃₆ also should enhance renovascular responses to Ang II in kidneys from genetically-susceptible kidneys. Importantly, BIBP3226, a selective Y₁R antagonist, abrogates the effects of a high concentration of exogenous NPY₁₋₃₆ on renovascular responses to Ang II. This finding implies that the effect of NPY₁₋₃₆ on renovascular responses to Ang II is mediated by activation of Y₁Rs and not by other Y-receptor subtypes. Consistent with this interpretation, a high concentration of exogenous NPY₃₋₃₆, a peptide that selectively activates Y₂Rs and is inactive at Y₁Rs, is not efficacious with regard to enhancing Ang II-induced renal vasoconstriction. Because DPP IV metabolizes NPY₁₋₃₆ to NPY₃₋₃₆¹², this latter finding implies that renovascular DPP IV has the potential to minimize the renovascular impact of endogenous NPY₁₋₃₆ in genetically-susceptible kidneys by converting the efficacious NPY₁₋₃₆ to the non-efficacious NPY₃₋₃₆.

The results from the second protocol of the present study are consistent with the hypothesis that renovascular DPP IV minimizes the renovascular impact of endogenous NPY₁₋₃₆ in genetically-susceptible kidneys. In this regard, we observe that very low concentrations of exogenous NPY₁₋₃₆ have little effect on renovascular responses to Ang II in genetically-susceptible kidneys. In contrast, when very low concentrations of exogenous NPY₁₋₃₆ are administered to kidneys pretreated with sitagliptin, a potent and clinically useful DPP IV inhibitor, even these minute concentrations of exogenous NPY₁₋₃₆ enhance renovascular responses to Ang II. This finding strongly suggests that renovascular DPP IV inactivates NPY₁₋₃₆ so that low concentrations cannot enhance the renovascular effects of Ang II; however, when DPP IV is inhibited, this inactivation is impaired and so even low concentrations of NPY₁₋₃₆ potentiate renovascular responses to Ang II.

Although the first and second protocols are consistent with the concept that endogenous NPY₁₋₃₆ may regulate renovascular responses to Ang II in genetically-susceptible kidneys, these experiments do not directly address this critical issue. As discussed above, the main source of renal NPY₁₋₃₆ is neural, i.e., NPY₁₋₃₆ is a co-transmitter in renal sympathetic nerve varicosities⁹. Therefore, a straightforward approach to test the role of endogenous NPY₁₋₃₆ with regard to its interaction with Ang II is to examine renovascular responses to Ang II in the absence and presence of renal sympathetic nerve stimulation. However, renal nerve stimulation normally increases renovascular tone, and increases in renovascular tone would be expected to enhance responses to any vasoconstrictor. Therefore, such experiments would be impossible to interpret. However, an experimental design around the confounding variable of changes in basal renovascular tone is to conduct the renal nerve stimulation in the presence of an α_1 -adrenoceptor antagonist, such as prazosin, so that NPY₁₋₃₆ is released upon nerve stimulation but the co-released norepinephrine cannot increase basal renovascular tone.

Protocol three demonstrates that renal nerve stimulation in the presence of prazosin does indeed enhance the renovascular response to Ang II without changing basal renovascular tone. Moreover, this protocol shows that the effect of renal nerve stimulation on the renovascular response to Ang II is entirely blocked by BIBP3226. Thus it is clear that Y₁Rs mediate the effect of renal nerve stimulation on renovascular responses to Ang II, a finding consistent with our previously published results¹⁴. Because NPY₁₋₃₆ is the only known Y₁R agonist released from renal sympathetic nerves, it is nearly certain that the enhancement of renovascular responses to Ang II by renal nerve stimulation is mediated entirely by endogenous NPY₁₋₃₆ activating Y₁Rs.

As mentioned above, an implication of protocols one and two is that renovascular DPP IV inactivates NPY₁₋₃₆ so that low concentrations cannot enhance the renovascular effects of Ang II; however, when DPP IV is inhibited, this inactivation is impaired and so even low concentrations of NPY₁₋₃₆ potentiate renovascular responses to Ang II. If this conclusion can be applied to endogenous NPY₁₋₃₆, then sitagliptin, a DPP IV inhibitor, should augment the effects of renal nerve stimulation on renovascular responses to Ang II. Importantly, the results of protocol three are entirely consistent with this hypothesis, i.e., renal nerve stimulation enhances renovascular responses to Ang II more so in kidneys treated with sitagliptin compared with kidneys not treated with sitagliptin. The fact that BIBP3226 blocks the ability of sitagliptin to augment the interaction between renal nerve stimulation and Ang II is entirely consistent with the effects of sitagliptin being mediated by reducing metabolism of endogenous NPY₁₋₃₆.

In the present study does not examine the interaction between NPY₁₋₃₆ and Ang II in WKY rats because such an interaction cannot be demonstrated. In this regard, our previous studies show that activation of Y₁Rs, even with high concentrations of potent Y₁R agonists such as (Leu31,Pro34)-NPY¹ or PYY₁₋₃₆¹³, has little or no ability to enhance renovascular responses to Ang II in WKY kidneys. Our previous results also demonstrate that renal nerve stimulation does not enhance renovascular responses to Ang II in WKY kidneys¹⁴. Thus, with respect to the interaction between Ang II and NPY₁₋₃₆, it is a moot point as to whether DPP IV regulates the levels of NPY₁₋₃₆ in WKY kidneys because the peptide cannot significantly alter Ang II-induced renal vasoconstriction regardless of whether or not it is metabolized by DPP IV. The ability of Y₁Rs to enhance renovascular responses in SHR kidneys, but not WKY kidneys, is due to the fact that Y₁Rs signal via the Gi pathway. In this regard, activation of the Gi pathway enhances renovascular responses to Ang II in SHR, but not WKY, kidneys¹⁵. Why this is the case is presently unknown, but under investigation. Nonetheless, whether renovascular or glomerular DPP IV expression is increased in hypertension is an interesting and important question that deserves investigation because DPP IV has many substrates and alters the levels of a large array of polypeptides.

Perspective

The FDA recently approved sitagliptin, a potent inhibitor of DPP IV, for the treatment of type 2 diabetes, and other similar compounds are in the development and approval pipeline. Given the epidemic of type 2 diabetes and the emerging controversy regarding the safety of PPAR (agonists (the thiazolidinediones) in type 2 diabetics, it is likely that DPP IV inhibitors will become widely used in type 2 diabetics, many of whom will have hypertension as a co-morbidity. The results of the present study support the hypothesis that DPP IV inhibitors, in the appropriate genetic setting, may augment the ability of endogenously released NPY₁₋₃₆ to enhance renovascular responses to Ang II. In this highly vulnerable patient population, this could impair renal function, increase arterial blood pressure and inadvertently lead to an increased risk of stroke and myocardial infarction. Counteracting this possible adverse effect of DPP IV inhibitors on renal function is the fact that, as shown by Girardi and colleagues,

DPP IV forms a physical complex with the sodium hydrogen exchanger type 3 (NHE3) in the proximal tubular brush border so that inhibition of DPP IV leads to a reduction in NHE3-mediated transport¹⁶⁻¹⁸. Thus, the renal effects of DPP IV inhibitors in hypertensive, diabetic patients will be complicated and perhaps strongly dependent on the genetic predisposition of the patient. Certainly, the renal effects of DPP IV inhibitors in various patient populations merit a closer examination. In the meanwhile, it may be prudent to consider the concomitant use of an angiotensin receptor blocker or renin inhibitor (but perhaps not an angiotensin converting enzyme inhibitor which possibly could increase the risk of angioedema in patients treated with DPP IV inhibitors¹⁹) in type 2 diabetics treated with DPP IV inhibitors until this issue is resolved.

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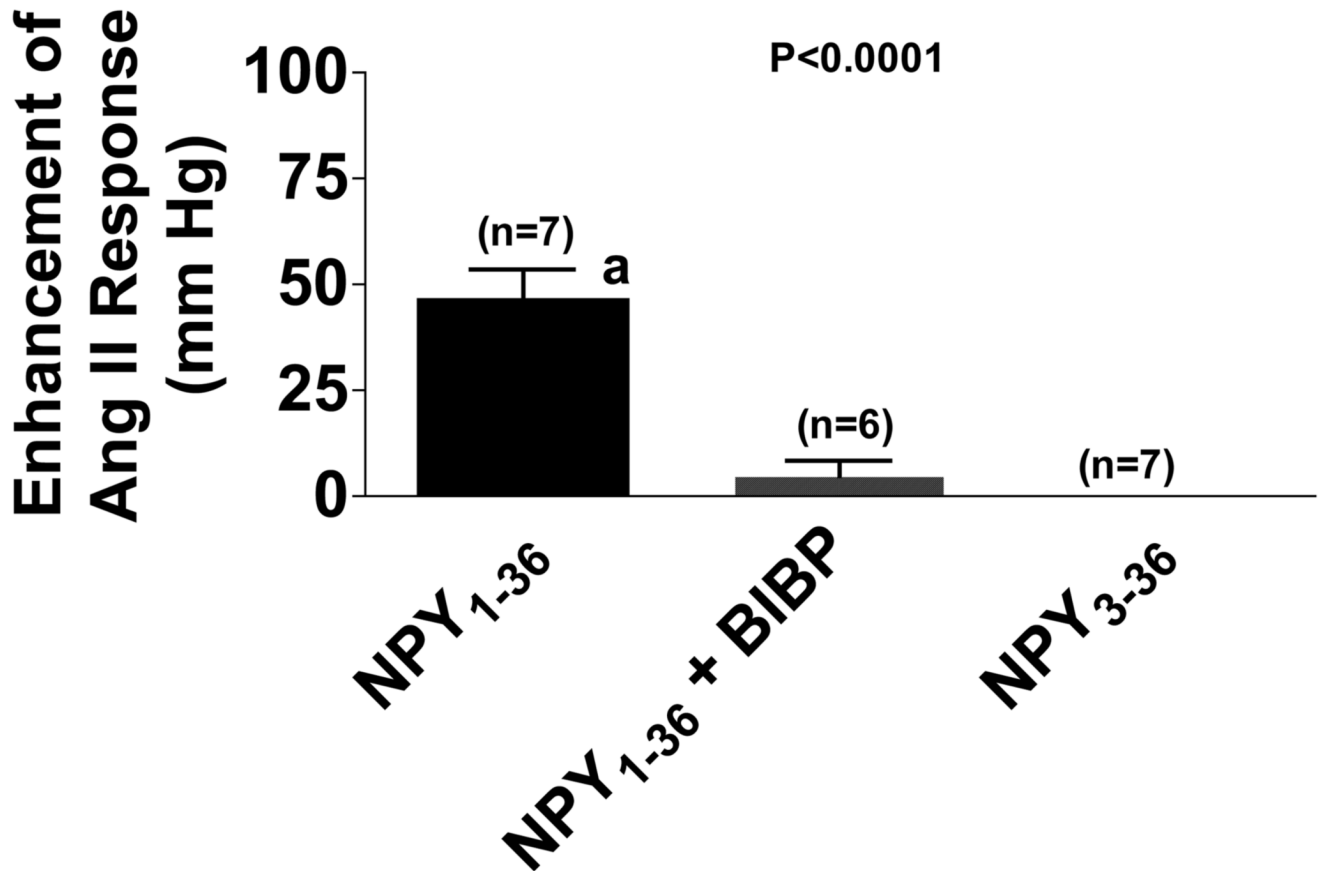


Figure 1.

Bar graph shows enhancement of angiotensin II (Ang II)-induced changes in renal perfusion pressure by neuropeptide Y₁₋₃₆ (NPY₁₋₃₆; 6 nmol/L), without and with BIBP3226 (BIBP; 1 μmol/L), and by neuropeptide Y₃₋₃₆ (NPY₃₋₃₆; 6 nmol/L). The effect of NPY₁₋₃₆ or NPY₃₋₃₆ on the renovascular response to Ang II was calculated by subtracting the renovascular response to Ang II before treatment with either NPY₁₋₃₆ or NPY₃₋₃₆ from the renovascular response to Ang II after treatment with either NPY₁₋₃₆ or NPY₃₋₃₆. The concentration of Ang II was 0.3 nmol/L. Basal perfusion pressure (48 ± 2 mm Hg) was similar among the three groups and was not affected by NPY₁₋₃₆, NPY₃₋₃₆ or BIBP3226. The basal response to Ang II (before treatments) was similar among the three groups and was 31 ± 3 mm Hg. The p-value is from 1-factor analysis of variance. ^aIndicates $p < 0.05$ versus NPY₁₋₃₆ (Fisher's LSD test). Values represent means \pm SEM for the indicated sample size.

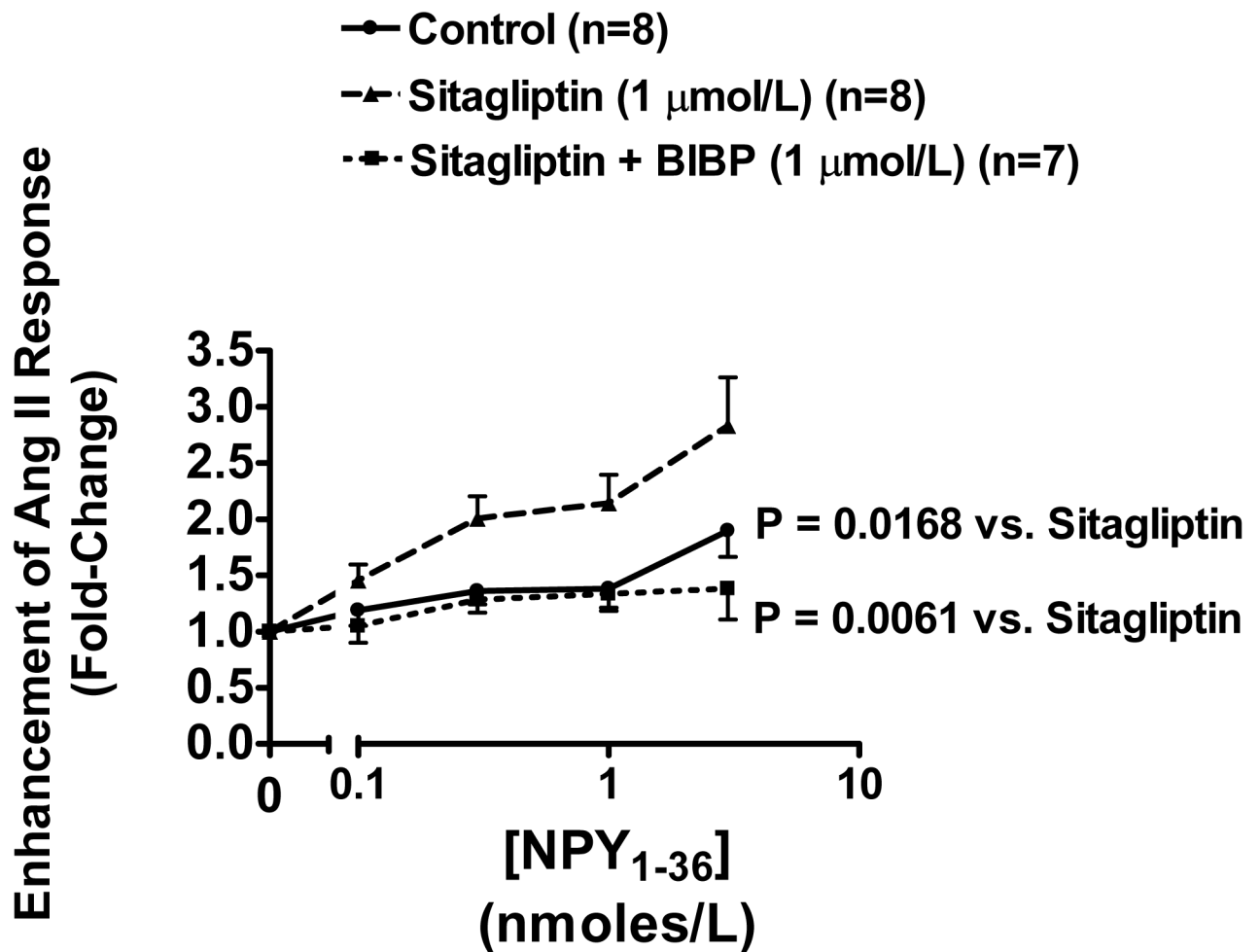


Figure 2.

Line graph illustrates the fold-increase in the renovascular response to Ang II (100 pmol/L) induced by increasing concentrations of NPY₁₋₃₆. The fold-increase was calculated by dividing the renovascular response to Ang II before administering NPY₁₋₃₆ into the renovascular response to Ang II in the presence of each concentration of NPY₁₋₃₆. Experiments were performed in the absence and presence of sitagliptin (1 $\mu\text{mol/L}$) or sitagliptin plus BIBP3226 (1 $\mu\text{mol/L}$). Basal perfusion pressure was 48 ± 2 mm Hg and was similar among the three groups and was not affected by NPY₁₋₃₆, sitagliptin or BIBP3226. The basal renovascular response to Ang II was 7 ± 1 mm Hg and was not affected by sitagliptin or sitagliptin plus BIBP3226. The p-value is for the treatment (sitagliptin or sitagliptin plus BIBP3226) term in the repeated measures 2-factor analysis of variance. Values represent means \pm SEM for the indicated sample size.

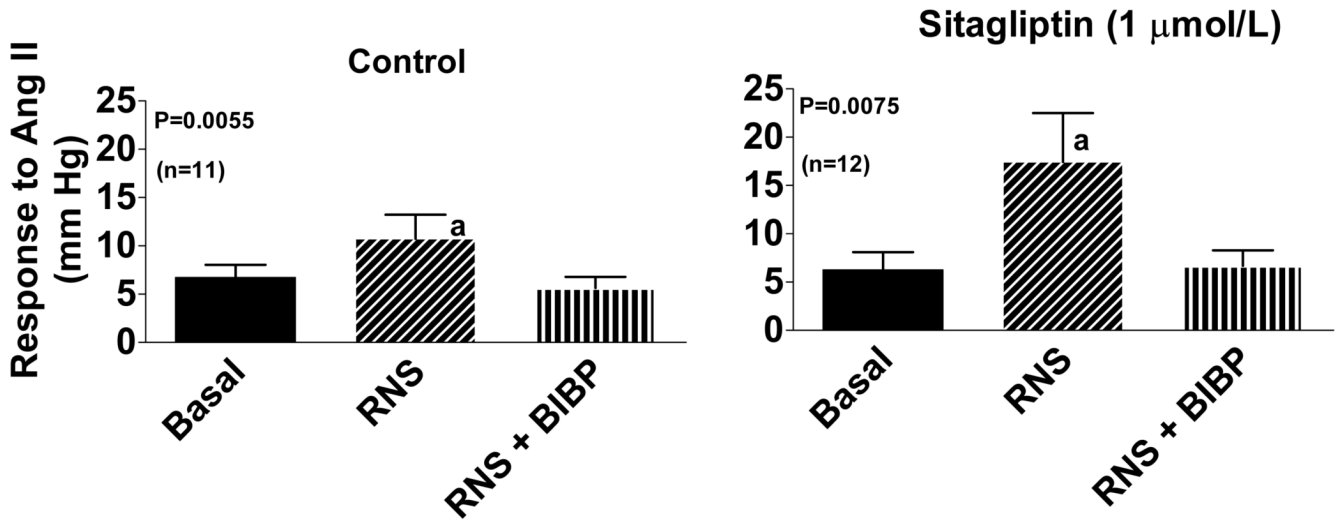


Figure 3.

Bar graph shows the renovascular response to angiotensin II (Ang II) in the absence of renal nerve stimulation and BIBP3226 (Basal), during periarterial renal nerve stimulation (RNS; 5 Hz, 1-ms pulse duration, 35 V) and during RNS in the presence of BIBP3226 (RNS + BIBP; 1 μmol/L). In the left panel, kidneys were not pretreated with sitagliptin, whereas in the right panel, kidneys were pretreated with sitagliptin (1 μmol/L) throughout the experiment. The concentration of Ang II was 0.1 nmol/L. Basal perfusion pressure in the presence of prazosin (42 ± 2 mm Hg) was similar among the three groups and was not affected by RNS or BIBP3226. The p-values are from 1-factor analysis of variance. ^aIndicates $p < 0.05$ versus Basal (Fisher's LSD test). Values represent means \pm SEM for the indicated sample size.