

Human neuropeptide Y potentiates α_1 -adrenergic blood pressure responses in vivo

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Schuerch, Leander V., Lilly M. Linder, Eric Grouzmann, and Walter E. Haefeli. Human neuropeptide Y potentiates α_1 -adrenergic blood pressure responses in vivo. *Am. J. Physiol.* 275 (Heart Circ. Physiol. 44): H760–H766, 1998.—Human neuropeptide Y (hNPY) potentiates the postjunctional vasoconstrictor effects of α_1 -adrenoceptor agonists in animals and in human hand veins in vivo. We therefore hypothesized that such an interaction might also occur in the human arterial bed. With the present single-blind cross-over study in 12 healthy volunteers, the effect of subpressor doses of hNPY on the blood pressure response to α_1 -adrenoceptor stimulation was evaluated. Dose-response curves were constructed to intravenously infuse phenylephrine with and without coinfusion with two different doses of hNPY (1.4 and 14.3 pmol·kg⁻¹·min⁻¹). Blood pressure, heart rate, and forearm blood flow were recorded, and plasma hNPY was determined. During infusion of the higher hNPY dose, which increased hNPY from 24.0 ± 12.0 to 495.1 ± 12.6 pmol/l, blood pressure curves were 2.4-fold shifted toward lower phenylephrine dose rates ($P < 0.001$). Forearm vascular resistance showed a similar trend, whereas the counter-regulatory decrease of heart rate was similar in both groups. In contrast, the lower hNPY dose rate producing a fourfold increase in hNPY concentrations did not modify the response to phenylephrine. This in vivo study in humans demonstrates that hNPY induced potentiating effects on α_1 -adrenergic constriction also in the systemic arterial circulation and suggests that circulating hNPY may participate in the control of vascular tone.

phenylephrine; hemodynamics; healthy subjects

SINCE THE FIRST ISOLATION of human neuropeptide Y (hNPY) from the porcine brain in 1982 (37) this tyrosine-rich 36-amino acid regulatory peptide has been extensively studied for its central and peripheral actions (for reviews see Refs. 29 and 42). Whereas in the central nervous system hNPY exerts a wide variety of effects (e.g., modulation of eating behavior), the peripheral actions of hNPY are mainly confined to the circulatory system. After being released from synaptic vesicles of perivascular sympathetic nerve fibers, where it is co-stored with norepinephrine (16, 34), hNPY exerts a potent and long-lasting vasoconstriction in animals as well as in humans (27, 30–32), which is not mediated via α_1 -adrenoceptors (30).

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In addition to this direct vasoconstrictor action, hNPY has also been shown to potentiate the vasoconstrictor effects of catecholamines and histamine at low concentrations, which have no constrictor effects on their own (14, 22, 25). We have recently shown in humans that small doses of hNPY increase the venous sensitivity to the α_1 -adrenoceptor agonist phenylephrine fourfold (25). But despite overwhelming experimental evidence from both in vitro and in vivo studies, thus far no published information is available about the potentiating effects of hNPY in the human systemic circulation and about the effect of subpressor hNPY doses on adrenoceptor-mediated blood pressure effects.

With the present single-blind cross-over study in healthy volunteers, we tested the hypothesis that subpressor doses of systemically administered hNPY would potentiate α_1 -adrenoceptor effects using pressor dose-response relationships to phenylephrine as a pharmacodynamic parameter.

METHODS

Subjects. Twelve subjects (six of each gender) with a mean age (±SE) of 27 ± 4.5 yr (range 23–39 yr), participated in this study after giving written informed consent. They were all found to be healthy as assessed by physical examination and routine biochemical and hematological tests, and all had a normal electrocardiogram. None of the subjects was taking any medication other than oral contraceptives (3 women), and none had a history of serious medical disease. All were nonsmokers and refrained from alcohol and caffeine-containing food or beverages for at least 12 h before each study. The study was approved by the Ethics Committee of the Department of Medicine at the University Hospital of Basel (Switzerland).

Protocols. In a single-blind cross-over design, each volunteer was studied on three different days, which were separated by at least 1 wk. On each study day, a pressor dose-response curve to phenylephrine (0.035–11.2 nmol·kg⁻¹·min⁻¹) was constructed as previously described (36). The following three infusion protocols were performed in all volunteers: Pressor dose-response curves were constructed to phenylephrine alone and during coinfusion with either of the two different doses of hNPY (1.4 and 14.3 pmol·kg⁻¹·min⁻¹), which was started 30 min before the first phenylephrine dose and maintained throughout the dose-response curve. In additional control experiments, in four of these volunteers the effect of the higher hNPY dose (14.3 pmol·kg⁻¹·min⁻¹ for 90 min) on supine arterial blood pressure was also studied in the absence of phenylephrine.

Throughout the study period, the subjects remained supine in a quiet room with a constant temperature of 22 ± 1°C to minimize endogenous sympathetic nervous system activity. After the insertion of a cannula into an antecubital vein of

each arm, an infusion of 4% gelatin solution (Physiogel) at a rate of 0.5 ml/min was delivered into the right arm at a constant speed with a Harvard infusion pump. A semiautomated sphygmomanometer (Dinamap) was attached for frequent measurements of blood pressure and heart rate. Once a stable blood pressure baseline was reached (after ≥ 30 min of rest), the phenylephrine or hNPY infusion was started. Phenylephrine was given as a constant intravenous infusion in stepwise incremental doses to construct a cumulative dose-response relationship. Each dose rate was administered for 10 min. Blood pressure was measured after 7 and 9 min, and these readings were averaged for subsequent analysis.

Pharmacological end points consisted of an increase in systolic blood pressure of ≥ 40 mmHg, an increase in diastolic blood pressure of ≥ 25 mmHg (39), or a decrease in heart rate to a resting heart rate of ≤ 30 beats/min. When one of these targets was reached, the administration of vasoactive compounds was stopped. After we discontinued the infusion(s), the subjects were observed for at least 30 more minutes until blood pressure and heart rate had returned to preinfusion values. The total volume of fluid infused was 50–150 ml.

On the left forearm, blood flow was measured using venous occlusion plethysmography with mercury in Silastic strain gauges as previously described (24). During measurements, blood flow to the hand was excluded by a pediatric wrist cuff, which was inflated to 50 mmHg over systolic blood pressure. The collecting cuff on the upper arm was inflated to 40 mmHg. Flows were recorded over 2 min before drug administration, during the last 2 min of each phenylephrine dose rate, and at ~ 8 , 18, and 28 min after the infusions were stopped. When hNPY was administered, additional measurements were performed ~ 8 , 18, and 28 min after the start of the hNPY infusion, i.e., before phenylephrine was administered. Forearm vascular resistance was calculated as mean blood pressure divided by forearm blood flow and is expressed in arbitrary units.

Plasma samples for the determination of hNPY (17) were drawn before and at the end of drug administration. All samples were kept on ice, separated in a refrigerated centrifuge within 60 min, and immediately frozen and stored at -70°C until analysis.

Materials. Phenylephrine (Neo-Synephrine) was obtained from Sanofi-Winthrop (Münchenstein, Switzerland), and hNPY was purchased from Clinalfa (Läufelfingen, Switzerland). To prevent the peptide from sticking to tubing, 4% gelatin (Physiogel, SRK Bern, Switzerland) solutions were used for all studies as solvent.

Statistics. Data are presented as means \pm SE. Semilogarithmic dose-response curves in the forearm and in the systemic circulation were fitted by nonlinear regression to a quadratic equation [change in forearm vascular resistance = $a \cdot (\log \text{dose rate})^2 + b \cdot (\log \text{dose rate}) + c$]. Dose rates inducing a 20-mmHg increase in blood pressure (PD₂₀) and the PD₂₀ ratio (PD₂₀ without hNPY/PD₂₀ with hNPY) were determined and used for statistical analysis (36). ANOVA for repeated measures with Bonferroni correction was used for comparison of dose-response curves to evaluate the effects of the different interventions on blood pressure and forearm vascular resistance. Linear regression analysis was used to assess correlations of hNPY plasma concentrations with PD₂₀ values and the effects of the highest dose rates on changes in blood pressure, heart rate, and forearm vascular resistance, respectively. A two-tailed P value of <0.05 was considered to indicate a significant difference. All calculations were performed using the STATVIEW 4.1 (Abacus) statistical program.

Side effects. hNPY and phenylephrine were well tolerated in all volunteers. However, during the highest administered doses of phenylephrine ($\geq 5.6 \text{ nmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), all subjects reported piloerection and tingling on the scalp.

RESULTS

Baseline characteristics, hemodynamic data, and the results of the curve fittings of individual dose-response curves are shown in Table 1. Individual dose rates exerting PD₂₀ and the ratio of PD₂₀ without hNPY/PD₂₀ with hNPY were not correlated with any of the following baseline parameters: age, plasma hNPY, heart rate, or baseline blood pressure. The phenylephrine dose-response curves obtained after averaging of individual dose-response relationships are shown in Fig. 1.

Infusion of 1.4 and 14.3 pmol \cdot kg⁻¹ \cdot min⁻¹ of hNPY both resulted in significant increases in circulating plasma hNPY concentrations (Table 1). Whereas there was no shift of the systolic blood pressure dose-response curve during infusion of the smaller hNPY dose rate ($P = 0.64$), phenylephrine responses were significantly shifted to the left toward lower dose rates during infusion of the higher hNPY dose ($P < 0.001$) (Fig. 1).

When hNPY was administered alone (14.3 pmol \cdot kg⁻¹ \cdot min⁻¹ for 90 min in four control subjects), the circulating plasma concentrations of hNPY increased from 26.0 ± 19.9 to 459.3 ± 33.3 pmol/l. There was no effect on blood pressure and heart rate in these experiments. Systolic and diastolic blood pressure values before ($117 \pm 2.2/66 \pm 0.8$ mmHg) and after administration of hNPY ($115 \pm 2.5/63 \pm 2.0$ mmHg) were similar, as well as heart rate values (65.6 ± 2.0 before and 62.1 ± 4.0 after infusion of hNPY).

Administration of phenylephrine alone was associated with a slight (24.4%) but significant ($P < 0.001$) increase of circulating hNPY concentrations in all

Table 1. Baseline characteristics and hemodynamic data

	Phenylephrine		
	Control	+hNPY 1.4 pmol \cdot kg ⁻¹ \cdot min ⁻¹	+hNPY 14.3 pmol \cdot kg ⁻¹ \cdot min ⁻¹
hNPY basal, pmol/l	18.0 \pm 5.8	18.0 \pm 7.8	24.0 \pm 12.0
hNPY end, pmol/l	22.4 \pm 6.4†	82.4 \pm 6.3†‡	495.1 \pm 12.6†‡
SBP basal, mmHg	115.8 \pm 2.4	113.4 \pm 2.9*	114.9 \pm 2.3
DBP basal, mmHg	64.6 \pm 1.4	61.6 \pm 1.7*	63.0 \pm 1.2
FVR basal, Units	36.6 \pm 3.6	36.9 \pm 4.6	33.3 \pm 4.1
HR basal, beats/min	58.9 \pm 3.3	59.7 \pm 3.4	62.7 \pm 3.7*
HR end, beats/min	40.9 \pm 1.7†	42.9 \pm 1.3†	41.6 \pm 1.2†
PD ₂₀ , log nmol \cdot min ⁻¹ \cdot kg ⁻¹	0.64 \pm 0.06	0.6 \pm 0.06	0.26 \pm 0.07†
GM, nmol \cdot min ⁻¹ \cdot kg ⁻¹	4.35	4.01	1.81†
PD ₂₀ Phe/PD ₂₀ hNPY		1.09 \pm 0.09	2.35 \pm 0.48

Values are means \pm SE. hNPY, human neuropeptide Y; SBP, systolic blood pressure; DBP, diastolic blood pressure; FVR, forearm vascular resistance; HR, heart rate; PD₂₀, phenylephrine dose inducing a 20-mmHg increase in blood pressure; GM, geometric mean; PD₂₀ Phe/PD₂₀ hNPY, the ratio of PD₂₀ without hNPY/PD₂₀ with hNPY. * $P < 0.05$ compared with control; † $P < 0.001$ compared with control; ‡ $P < 0.001$ compared with baseline (paired t -test).

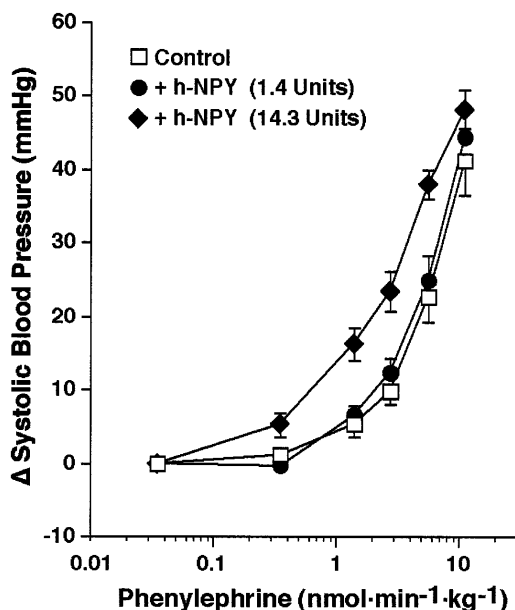


Fig. 1. Log-linear systolic pressor dose-response relationships to phenylephrine obtained after data of all 12 dose-response curves were averaged. Fitted values of dose rates exerting a 20-mmHg increase (PD_{20}) of these summary curves for phenylephrine alone and in combination with 1.4 and 14.3 $\text{pmol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ hNPY were 0.63, 0.57, and 0.27 $\log \text{nmol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$, respectively. Only dose response during coadministration of 14.3 $\text{pmol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ was significantly different from experiments where phenylephrine was administered alone ($P < 0.001$).

volunteers (Table 1). Whereas the measurements of total plasma protein concentrations in these experiments showed also a slight (6.1%) increase in all volunteers (from 64.0 ± 0.7 to 67.9 ± 0.8 g/l; $P < 0.001$), total plasma protein concentrations showed no increase when the higher dose of hNPY (14.3 $\text{pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) was given alone (64.1 ± 1.3 to 62.6 ± 1.7 g/l). In these control experiments, the final hNPY plasma concentrations were 5.6% lower than the final hNPY plasma concentrations in the corresponding experiments with phenylephrine in the same four volunteers (459.3 ± 33.3 and 484.9 ± 24.4 pmol/l, respectively).

The effects of the administered vasoconstrictors on forearm vascular resistance are shown in Fig. 2. The dose-response relationships to phenylephrine alone and in combination with 1.4 and 14.3 $\text{pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ hNPY were obtained after data of all dose-response curves were averaged. There was a trend of a shift similar to that of the systolic pressure dose-response, but it did not reach statistical significance (Fig. 2).

The increase in blood pressure resulted in a decrease in heart rate (Table 1). The corresponding heart rate dose-response curves obtained after data of all dose-response curves were averaged are shown in Fig. 3. Whereas during infusion of the potentiating hNPY dose (14.3 $\text{pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), heart rate dose-response curves were significantly ($P < 0.05$) shifted to the left (Fig. 3), pressure-rate products (heart rate \times systolic blood pressure, Fig. 4) were similar ($P = 0.91$). During infusion of the lower hNPY dose rate (1.4 $\text{pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), both heart rate dose-response curves and pres-

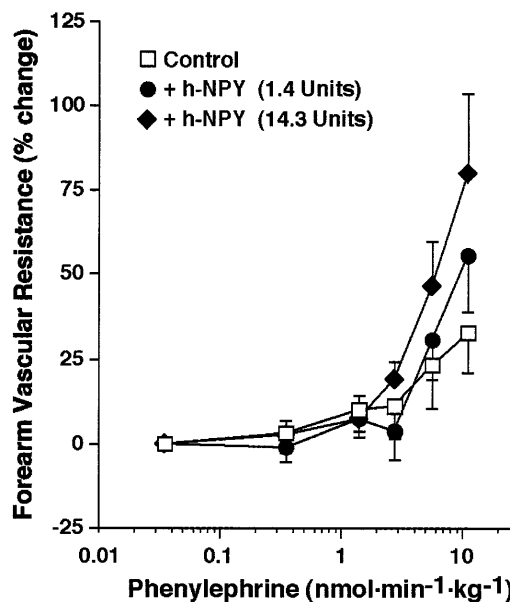


Fig. 2. Changes in forearm vascular resistance during systemic administration of phenylephrine alone and in combination with 1.4 and 14.3 $\text{pmol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ hNPY in 12 volunteers. Log-linear dose-response curves were obtained after data of all individual dose-response curves were averaged.

sure-rate products were similar compared with the experiments where phenylephrine was administered alone (P values were 0.17 and 0.79, respectively) (Fig. 4).

DISCUSSION

Overwhelming experimental evidence from animal studies suggests that hNPY may selectively potentiate

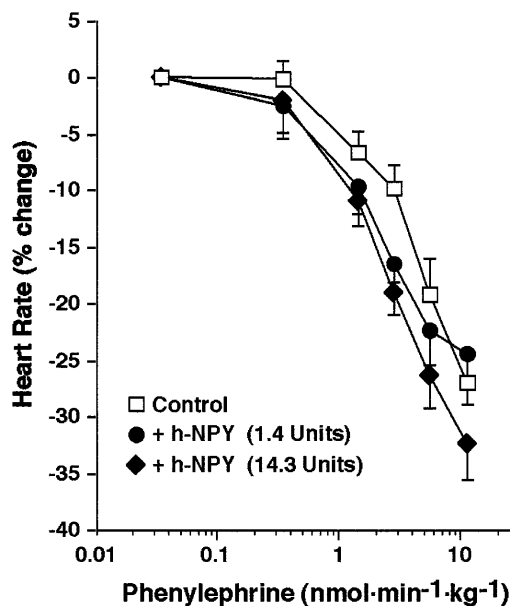


Fig. 3. Log-linear heart rate dose-response relationships to phenylephrine obtained after data of all 12 dose-response curves were averaged. Whereas during infusion of the potentiating hNPY dose (14.3 $\text{pmol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$), heart rate dose-response curves were significantly ($P < 0.05$) shifted to the left, phenylephrine responses during infusion of 1.4 $\text{pmol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ hNPY were similar ($P > 0.1$) compared with experiments where phenylephrine was given alone.

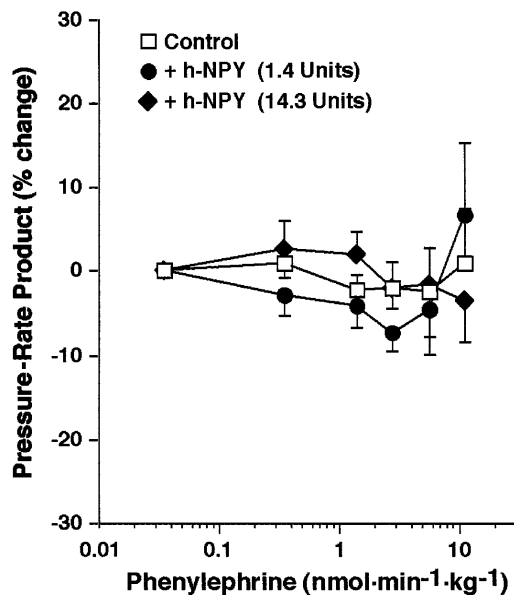


Fig. 4. Effects of phenylephrine alone and in combination with 1.4 and 14.3 $\text{pmol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ hNPY on pressure-rate products. All log-linear pressure-rate curves were similar ($P > 0.5$).

the postjunctional vasoconstrictor effects of catecholamines (11, 13, 19, 22, 40), angiotensin II (10), histamine (13), and ATP (41), whereas endothelin-1-induced vasoconstriction remains unaffected (21). We were recently able to show that small doses of hNPY increase the venous sensitivity to the α_1 -adrenoceptor agonist phenylephrine fourfold also in superficial hand veins in humans (25).

In this study we have evaluated the effect of subpressor doses of hNPY on the blood pressure response to α_1 -adrenoceptor stimulation. This study for the first time showed a synergistic interaction also in the arterial circulation, resulting in a 2.4-fold shift of the pressor dose-response curve toward lower dose rates. In accordance with *in vitro* studies in isolated blood vessels (13), this shift occurred in a concentration-dependent fashion and was observed at circulating hNPY concentrations of ~ 500 pmol/l. In contrast, the lower hNPY dose rate, which resulted in a fourfold increase in circulating hNPY concentrations, did not increase the blood pressure response to phenylephrine. Hence, at normal or slightly elevated concentrations, intravascular hNPY appears not to potentiate α -adrenoceptor agonists in healthy subjects. This is further supported by the absence of any correlation between phenylephrine responsiveness and baseline hNPY plasma concentrations.

The determination of plasma concentrations in studies addressing the effect of exogenously administered peptides is helpful for several reasons. Many peptides may be lost during the process of administration because they may stick to containers, tubing, and syringes, and doses may therefore only loosely reflect the final concentrations achieved in the subjects. Indeed, considerable amounts of hNPY may be lost during filtration procedures and during infusion even when the peptide is administered together with a carrier

protein such as albumin (32). It is therefore more meaningful to establish concentration-response curves than to rely on dosing information. However, determination of hNPY concentrations is demanding because the plasma concentrations of hNPY are very low, usually in the picomolar range. Most of the published analytical procedures for hNPY determination in plasma require immunologic methods. The accuracy of these assays depends on the sensitivity, specificity, and binding properties of the antibodies used, which vary considerably. In addition, different extraction procedures may yield substantially differing amounts of peptide. Hence, whereas intra-assay reproducibility may be very good, concentrations determined with different analytical procedures may yield differing results. It is therefore of little surprise that published normal ranges for hNPY plasma concentrations may vary by more than an order of magnitude. Hence, whereas Corder and Lowry (8) reported values of <5 pmol/l in healthy volunteers, mean normal concentrations in other studies were 12 (32), 32 (33), and 55 pmol/l (1). The most valuable way to compare the results obtained with different assays is therefore to compare ratios of hNPY concentrations observed in the study population and control population or severalfold changes of circulating hNPY observed within the same population.

In our study, administration of a low and a high dose rate of hNPY resulted in a 4- and 20-fold increase in hNPY plasma concentrations, respectively. For comparison, several interventions and diseases are associated with the following mean increases in plasma hNPY: acute inhalation of cigarette smoke with 1.5-fold (33); physical exercise with 1.5- to 2.8-fold (26, 43); septic shock with 8.6-fold (3); obesity with up to 9.6-fold (4); congestive heart failure, depending on its severity with up to 10.7-fold (23); and hNPY-releasing tumors with 10–95-fold (9, 18). Moreover, interpatient variability of hNPY concentrations is large, and for instance, in the study by Hulting and co-workers (23), hNPY concentrations varied between 9.7 and 2,000 pmol/l (i.e., 206-fold) in patients with congestive heart failure with the highest value being 62.5-fold above the mean of controls without heart failure. Interestingly, both hNPY (23) and circulating catecholamine concentrations are increased in some (23, 38) but not all (12, 28) patients with congestive heart failure. It is therefore likely that the severalfold increase induced in our study is in a range of circulating hNPY concentrations that can be observed not only in patients with neuroendocrine tumors but possibly also in some patients with heart failure. It is well established that in these patients peripheral vascular resistance is increased and that these patients benefit from therapeutic measures that lower cardiac afterload (35). To date the role of hNPY in congestive heart failure is unknown, but the findings of this study could indicate that the observed interaction between the α -adrenoceptor agonist and hNPY may indeed reach clinical significance. Thus future studies addressing the participation of hNPY in the maintenance of vascular tone are needed and will require

specific inhibitors of hNPY receptors, which are currently being developed.

Whereas it is generally accepted that an interaction between hNPY and α -adrenergic responses occurs in a paracrine fashion, it is less well investigated whether hNPY also modulates α -adrenoceptor responses after reaching the circulating blood. In this study, we have carefully avoided the release of endogenous sympathetic neurotransmitters and have mimicked circulating hNPY levels similar to those observed in certain pathological conditions. However, in interpreting the data of this study, one important difference between our subjects and the patients of the earlier studies should be considered. Whereas in this study exogenous hNPY was applied intraluminally and only had to pass through the monocellular endothelial lining to reach the site of action, in all the other studies (possibly with the exception of release from tumors), circulating hNPY originated from the vascular adventitia and reached the plasma only after diffusion through the much thicker media (spillover). From studies with norepinephrine, it is well known that only a small fraction of the catecholamine penetrates media and endothelium to reach the systemic circulation and, although not studied, similar limitations for the much larger hNPY must be assumed. Plasma hNPY concentrations are therefore only indirect measures for endogenous hNPY release and are likely to underestimate the actual release from nerve endings when hNPY originates from endogenous sources. These values are therefore not necessarily comparable with concentrations measured after intravascular peptide administration, and to achieve comparable circulating plasma concentrations after endogenous release, substantially higher peptide amounts in the adventitia are most probably required. Hence, whereas the results of this study clearly show that hNPY potentiates the vasopressor effects of phenylephrine at the severalfold increases observed in this study, it cannot exclude that already smaller increases of endogenous hNPY may be sufficient to potentiate the effect of α -adrenoceptor agonists. To answer this question, studies using specific Y_1 -receptor antagonists will be useful.

During our baseline experiments with phenylephrine administration alone, circulating hNPY concentrations increased slightly but significantly. This increase is most likely the result of a decrease in total blood volume due to phenylephrine administration, since α -adrenoceptor stimulation has been reported to induce a loss of circulating protein-free fluid into the extracellular space (15). This is further supported by the observed increase of total plasma protein concentrations after phenylephrine administration. In accordance with this interpretation, hNPY plasma concentrations at the end of phenylephrine administration were also higher than the levels in control experiments in the same volunteers without phenylephrine administration. However, this finding is in apparent contrast to the findings of a recent study in patients undergoing open heart surgery (20). In these patients, perioperative increases in blood pressure and systemic vascular

resistance were negatively correlated with circulating hNPY concentrations, suggesting that the release of catecholamines decreases hNPY levels in these conditions (20). However, whereas in this previous study sympathetic outflow was undoubtedly increased, in our study the opposite was the case. The results in surgical patients may, therefore, illustrate a negative feedback between blood pressure and hNPY release, which becomes detectable only when the sympathetic nervous system is stimulated.

It is well established that more than one transmitter is stored in neuromuscular junctions and that several transmitters may be coreleased from sympathetic nerve endings (for review see Ref. 6). Indeed upon activation of the sympathetic nervous system, norepinephrine is released together with variable amounts of hNPY and ATP, which may both potentiate postjunctional α_1 -adrenoceptor responses (6). To avoid activation of the sympathetic nervous system and the subsequent release of unknown amounts of endogenous cotransmitters (including ATP), our experiments were performed in a quiet environment in a supine, resting position. Hence, these study conditions were selected to minimize the release of endogenous sympathetic neurotransmitters. In all volunteers, hNPY concentrations at baseline were quite low, confirming that the activity of the sympathetic nervous system was indeed kept low in these experiments. It is, therefore, likely that the observed interaction is caused by phenylephrine and exogenous hNPY and that such an interaction occurs without simultaneous administration of ATP. These results, however, cannot rule out that ATP also is modulating α -adrenoceptor responses in humans.

Our studies were not designed to evaluate at what level of the cardiovascular system the interaction between α_1 -adrenoceptors and hNPY occurs. However, the observation that the pressure-rate product remained constant throughout the different protocols suggests that the interaction is caused by a change in peripheral vascular resistance rather than direct effects on the heart. Interestingly, the change in forearm vascular resistance during elevated hNPY plasma concentrations (~ 500 pmol/l) was smaller than the shift of blood pressure curves. The reason could be due to activation of counterregulatory mechanisms in response to the blood pressure elevation or to the well-known differences in the vasoconstrictor sensitivity of various blood vessels to hNPY (heterogeneity) (2, 13, 27). The potentiating effect of hNPY could therefore be higher in other (e.g., splanchnic) vascular beds than in the limb, which is in accordance with the findings of another *in vivo* study in humans (2). This would also explain the disappearance of a correlation between PD_{20} values and forearm vascular resistance with increasing plasma hNPY concentrations.

The findings of this *in vivo* study in humans are in accordance with our earlier study in superficial hand veins in which hNPY potentiated phenylephrine effects on venous distensibility. However, both studies are in apparent contrast to an earlier study in the human forearm (7), which found no such interaction in forearm

resistance vessels. As discussed earlier (25), the design of the study by Clarke et al. (7) with three sequential dose-response curves to hNPY, norepinephrine, and the combination of both appears not suitable to evaluate this interaction, since the long-lasting effects of hNPY may have influenced subsequent dose-response curves constructed after a hNPY washout phase of only 30 min. Another reason for the lack of any interaction in these experiments might be a lower potency and efficacy of hNPY in forearm resistance vessels. Therefore a larger study group would be needed to detect smaller differences.

In conclusion, this study demonstrates that hNPY induces potentiating effects on α_1 -adrenergic constriction also in the systemic arterial circulation. This effect occurred at circulating hNPY concentrations similar to those reported in numerous disorders with increased peripheral vascular resistance, suggesting although not proving that hNPY may indeed play a pathophysiological role under these conditions.

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