Journal of Physiology (1991), **444**, *pp.* 289–302
With 8 figures
Printed in Great Britain

EFFECTS OF NEUROPEPTIDE-Y ON RENAL FUNCTION AND ITS INTERACTION WITH SYMPATHETIC STIMULATION IN CONSCIOUS DOGS

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(*Received 26 November 1990*)

SUMMARY

1. The effects of neuropeptide-Y (NPY) on renal function were investigated in conscious foxhounds.

2. Dose–response curves ($n = 7$) were obtained for NPY by measuring renal blood flow (RBF), glomerular filtration rate (GFR), urine excretion (V_U), sodium excretion (V_{Na}), potassium excretion (V_K) and plasma renin activity (PRA) at different infusion rates. All variables decreased with increasing infusion rates except for PRA, which surprisingly did not change during the different infusion rates.

3. The influence of the non-constrictor dose of NPY at control pressure, and after servo-controlling renal arterial pressure at 80 mmHg, was determined for these parameters ($n = 6$).

4. This was repeated during a reflex sympathetic activation via carotid sinus hypotension, in order to quantify a possible interaction between the sympathetic transmitter and co-transmitter ($n = 6$).

5. The subthreshold NPY dose raised plasma NPY-like immunoreactivity (NPY-LI IR) significantly (renal venous plasma: 54 ± 13 *vs.* 405 ± 117 pg ml^{-1}; $P < 0.05$) and enhanced the pressure-dependent (80 mmHg) antidiuresis (0.48 ± 0.06 *vs.* 0.24 ± 0.02 ml min^{-1}; $P < 0.05$), antinatriuresis (46 ± 11 *vs.* 25 ± 3 μmol min^{-1}; $P < 0.05$), antikaliuresis (19 ± 4 *vs.* 9 ± 0.7 μmol min^{-1}; $P < 0.05$) and pressure-dependent renin release (0.95 ± 0.27 *vs.* 3.0 ± 1.1 ng angiotensin I ml^{-1} h^{-1}; $P < 0.05$). These effects are consistent with a non-uniform vasoconstrictor action of NPY in the renal vascular bed (see accompanying papers).

6. The effects of NPY plus sympathetic activation were less than the sum of the two individual effects, which may rely on a presynaptic mechanism.

INTRODUCTION

Neuropeptide-Y (NPY) is a recently discovered neurotransmitter, which is co-stored and co-released with noradrenaline in sympathetic nerve terminals. This thirty-six amino acid co-transmitter interacts with noradrenaline both pre- and postsynaptically (Pernow & Lundberg, 1989; Wahlestedt, Håkanson, Vaz &

Zukowska-Grojec, 1990). NPY binding sites and NPY immunocytochemical staining have been identified in the kidneys of various species including the rabbit (Leys, Schachter & Sever, 1987), the rat (Allen, Godfrey, Yeats, Bing & Bloom 1986*a*; Ballesta, Lawson, Pals, Ludens, Lee, Bloom & Polak, 1987; Reinecke & Forssman, 1988; Knight, Fabre & Beal, 1989), the guinea-pig and the dog (Reinecke & Forssmann, 1988). Although vascular smooth muscle appears to be a preferential site of action (Leys *et al.* 1987; Ballesta *et al.* 1987; Reinecke & Forssmann, 1988; Knight *et al.* 1989), the nerves supplying the juxtaglomerular apparatus (Ballesta, Polak, Allen & Bloom, 1984; Ballesta *et al.* 1987) reveal NPY staining, and the proximal convoluted tubules have also been shown to contain NPY receptors (Leys *et al.* 1987).

These findings suggest a role of NPY in the control of renal function. A very consistent finding is the dose-dependent vasoconstriction induced by NPY. Interestingly, in the isolated rat kidney, NPY also causes a dose-dependent natriuresis (Allen, Raine, Ledingham & Bloom, 1985) in spite of its vasoconstrictor action, and inhibits renin release (Hackenthal, Aktories, Jakobs & Lang, 1987). The natriuretic and renin-inhibiting influence of NPY has, however, been challenged by a study in anaesthetized and uninephrectomized primates (Echtenkamp & Dandridge, 1989), in which no such effect was found. Experimental conditions and anaesthesia may play an essential role for these discrepancies. Moreover, basal vasomotor tone of the kidney vasculature, which is also altered by anaesthesia and procedures to isolate the kidney, has a profound impact on most renal functions. Thus, it is necessary to investigate the role of NPY in conscious animals at a defined perfusion pressure.

Three issues were investigated in this study: the dose-dependent renal effects of NPY, the pressure-dependent influence of a low dose of NPY, and the interaction of NPY with a sympathetic stimulus.

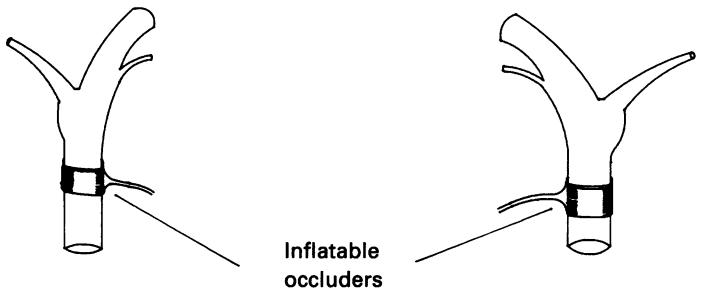
Our findings suggest that NPY enhances antidiuresis, antinatriuresis and antikaliuresis while servo-controlling renal arterial pressure (RAP) at 80 mmHg (RAP_{80}). Renin release was unaffected by increasing doses of NPY, but renin release increased during NPY infusion with RAP_{80}. These findings are compatible with a preferential action of NPY on larger renal vessels, as suggested by the accompanying papers (Dietrich, Fretschner, Nobiling, Persson & Steinhausen, 1991; Nobiling, Gabel, Persson, Dietrich & Bührle, 1991). The infusion of NPY did not augment the response to the sympathetic stimulus.

METHODS

Twenty-five experiments were performed in conscious foxhounds of either sex, which had free access to water and received a standard dog diet (Alma H5003, Kempten, Germany; Na^+: 4 g kg^{-1}). Foxhounds were chosen on account of their tame and docile temperament. The mean body weight was $21 \pm 0{\cdot}3$ kg. The experimental kidneys weighed on average $80 \pm 4{\cdot}4$ g; the contralateral right kidneys had a mean weight of $81 \pm 4{\cdot}7$ g. Experiments were made at least 14 days after implanation surgery.

Surgical procedures (*Fig. 1*). Anaesthesia was induced by sodium pentobarbitone (20 mg kg^{-1} I.V.) and maintained with halothane and N_2O. Polyurethane catheters were placed into the abdominal aorta and renal artery. A Silastic catheter was implanted into the left renal vein after ligation of the spermatic, or ovarian, vein. The left renal pelvis was catheterized retrogradely from a small incision made into the ureter. The three renal catheters allowed a selective infusion and sampling of the experimental kidney only. No surgery was performed on the right kidney.

An electromagnetic flowprobe was positioned around the renal artery close to the bifurcation from the aorta. A reinforced inflatable vascular occluding cuff was placed around the renal artery further downstream. The tip of the renal artery catheter was placed distal to the occluder in order to measure RAP. The renal artery catheter and the constricting cuff were connected to an external electro-pneumatic pressure-control system, which allowed us to reduce RAP and keep it constant at a pre-set level (control precision of $< \pm 1$ mmHg).



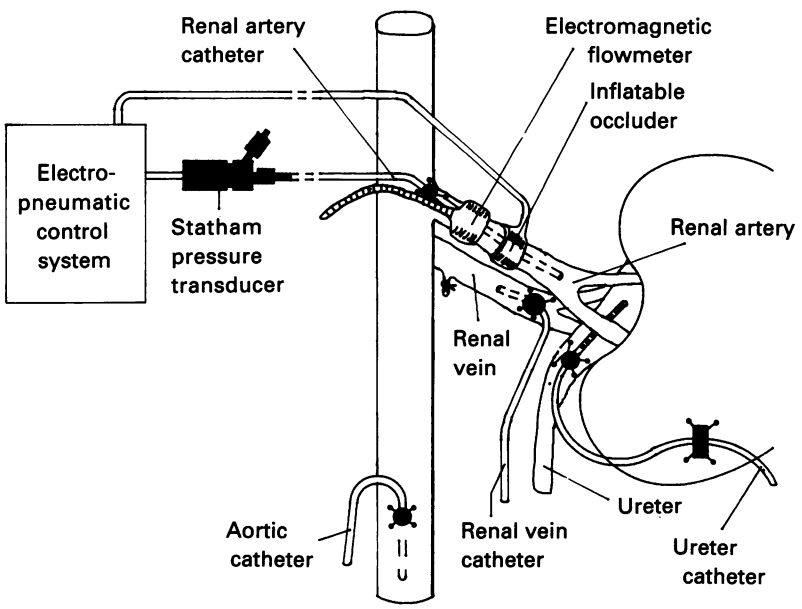


Fig. 1. Schematic illustration of implants. Chronic catheters were inserted into the renal artery, renal vein, aorta and ureter. An electromagnetic flowprobe was placed around the renal artery distal to a pneumatic occluder which controlled RAP.

A sympathetic reflex stimulus was achieved via bilateral common carotid occlusion (CCO). Two occlusive cuffs were implanted around the common carotid arteries. All catheters, cables and cuff-leads were fed subcutaneously to the dog's neck where they were brought out through the skin. All catheters were filled with a heparin solution (Braun, Melsungen, Germany).

Circulatory measurements. Blood pressure was measured in the abdominal aorta and renal artery (Statham pressure transducers: P23Db and Gould pressure processors). An analog recorder (Gould

2600) was used to record mean and pulsatile aortic pressures as well as RAP. Heart rate (HR) was recorded instantaneously with a rate meter (Gould pressure processor). Renal blood flow (RBF) was measured by precalibrated electromagnetic flow probes (Zepeda Instruments, Seattle, USA). Zero flow was determined 10 min prior to the experiments by a short maximal inflation of the renal artery cuff.

The data were stored on-line (IBM PC-AT) after analog-to-digital conversion of 10 s increments.

Urine sampling. To guarantee free urine flow to the bladder when no sampling was done, a small diameter was chosen for the ureter catheter (outer diameter: 0·9 mm). The anatomical and ureter catheter dead-space was on average 1·2 ml.

Urine was collected into a fraction sampler. The suction used for complete collection of urine (-40 cmH_2O) was determined prior to the experiments. Urine excretion (V_U) was complete at a suction of -20 cmH_2O.

Urine and blood analysis. All blood samples were collected in tubes containing 3·8% ethylenediaminetetraacetate (EDTA). Creatinine concentrations in urine and in plasma were determined by an automatic creatinine analyser (Beckman, Munich, Germany). Sodium and potassium concentrations were measured by an automatic analyser using ion-selective electrodes (Nova Biomedical, Darmstadt, Germany).

Glomerular filtration rate. An oral dose of 3 g creatinine was given 90 min before each experiment. Arterial (C_A) and renal–venous (C_V) plasma creatinine concentrations had the highest values (600–900 μmol l^{-1}) at the beginning of the experiments and fell to values of 200–250 μmol l^{-1} at the end of each experiment. Blood samples (1 ml each) were taken simultaneously from the renal venous and aortic catheters during the last 30 s of each pressure step for the measurement of creatinine extraction. The simultaneous sampling alleviates possible artifacts due to the elimination of creatinine.

Glomerular filtration rate (GFR) was determined by combining RBF and creatinine extraction with the measurement of haematocrit (Hct, microtube centrifugation). In contrast to humans, creatinine is not subjected to tubular secretion in dogs (Smith, 1951). GFR was calculated according to the equation

$$\mathrm{GFR} = (C_A - C_V)\, C_A^{-1}\, \mathrm{RBF}\,(1\text{-Hct}).$$

Plasma renin activity (PRA) and NPY. For the measurement of PRA plasma samples were incubated in the presence of 6 mM-EDTA, 1·6 mM-dimercaptopropanol and 100 mM-tris-hydroxymethyl-aminoethane-sulphonate (TES–NaOH) at pH 7·30 and at 37 °C for 60 min. Then the amount of angiotensin I formed was estimated by radioimmunoassay. Similarly, NPY-like immunoreactivity (NPY-LI IR) was measured by radioimmunoassay. Due to minor cross-reactivity of the antiserum to the structurally related peptides peptide YY and pancreatic polypeptide, the concentration is referred to as NPY-LI IR.

Experimental protocols. All experiments were done between the 14th day and the 5th week after implantation surgery. The experiments were started between 9.00 and 11.30 am. Only one experiment was made during one experimental day. All catheters were flushed with a 0·1% bovine serum albumin solution. The dogs were trained to rest on a padded bench for the time of an experimental period.

Two experimental protocols were used. In both protocols the following variables were determined: mean arterial pressure (MAP), RAP, HR, RBF, GFR, V_U, V_{Na}, V_K, PRA and plasma NPY-LI IR.

Dose–response curves (Fig. 2). A control measurement was made, then increasing concentrations of NPY (Sigma, Germany) were infused into the renal artery. The doses were 60 ng min^{-1}, 600 ng min^{-1}, 3 μg min^{-1}, 6 μg min^{-1} and 15 μg min^{-1}. Each step including the control measurement was maintained for 8 min (3 min for ureter dead-space elimination and 5 min sampling). For reasons of costs, the last dose was maintained for only 3 min. Thus, a satisfactory ureteral dead-space elimination was not always guaranteed. Therefore, the last step was only analysed for RBF and NPY-LI IR.

Pressure dependence and sympathetic interaction of NPY. Each measuring period lasted 10 min. Five minutes were allowed for equilibration and dead-space clearance; the other 5 min were used for sampling. The following steps were made: a control measurement was made, then RAP was reduced to 80 mmHg in order to determine the renal parameters at a defined pressure above the lower RBF autoregulation limit, which is 65–70 mmHg in our dogs (Persson, Ehmke, Nafz &

TABLE 1. A diagram of the protocol steps

(1*a*) Control	(1*b*) NPY
(2*a*) Control + RAP_{80}	(2*b*) NPY + RAP_{80}
(3*a*) CCO	(3*b*) CCO + NPY
(4*a*) CCO + RAP_{80}	(4*b*) CCO + NPY + RAP_{80}

Kirchheim, 1990*a*, *b*). To obtain a reflex sympathetic activation, CCO was performed 10 min prior to the next sampling period. A measurement was made and then the RAP was again maintained at 80 mmHg during the CCO. These four steps were repeated during the continuous, intrarenal NPY infusions. Thus, four steps were made for control (*a*) and NPY (*b*) (see Table 1).

The highest subthreshold dose for reducing RBF by NPY (600 ng min^{-1}–1 μg min^{-1}) was infused into the kidney in protocols *b*. This avoided artifacts due to changes in total renal vascular resistance. All steps were performed according to a randomly distributed chronology.

All data provided refer to the means ± the standard error of the means. Statistical significances were calculated between corresponding interventions before and after NPY (e.g. step 1*a* *vs.* step 1*b*). The Wilcoxon Rank Test was applied to determine significant differences between these groups.

RESULTS

Dose–response curves

An 11·5% reduction of RBF was found during the 3 μg min^{-1} infusion of NPY, which increased systemic plasma NPY-LI IR to a level of seven times control (Fig. 2). The control levels of canine NPY-LI IR were slightly below 50 pg ml^{-1}, which is somewhat higher by comparison to human NPY concentrations (Pernow, 1988).

The GFR response was similar to that of RBF. At 3 μg min^{-1}, GFR decreased from 33 ± 4 to 30 ± 7 ml min^{-1}. Urine and sodium excretions were reduced from 0·59 ± 0·08 to 0·51 ± 0·1 ml min^{-1} and from 69 ± 12 to 53 ± 12 μmol min^{-1}, respectively. The maximal responses were in the same range as for RBF (GFR, 27 ± 4 ml min^{-1}; V_U, 0·49 ± 0·1 ml min^{-1}; V_{Na}, 45 ± 11 μmol min^{-1}).

Intriguingly, PRA did not change in response to the NPY infusion. As seen in Fig. 3, neither the renal venous nor the arterial plasma levels of PRA changed in response

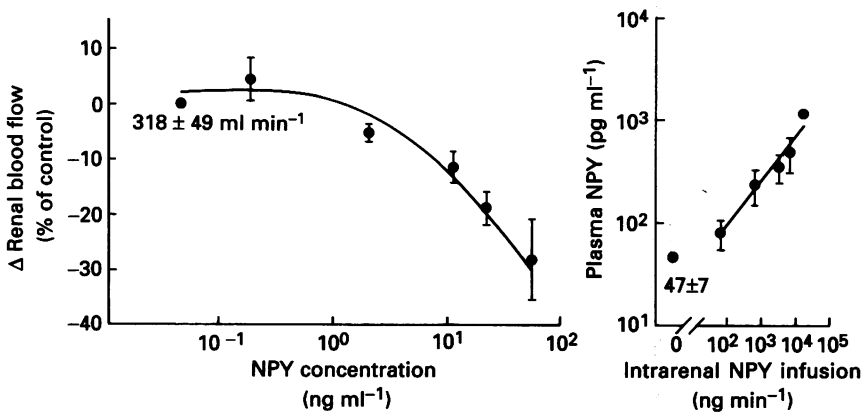


Fig. 2. Dose–response curve for renal blood flow (RBF): dependence of RBF on estimated intrarenal NPY-LI IR concentration (left). The right panel shows the increase of plasma NPY-LI IR concentration during the corresponding NPY infusions. The numbers refer to baseline values.

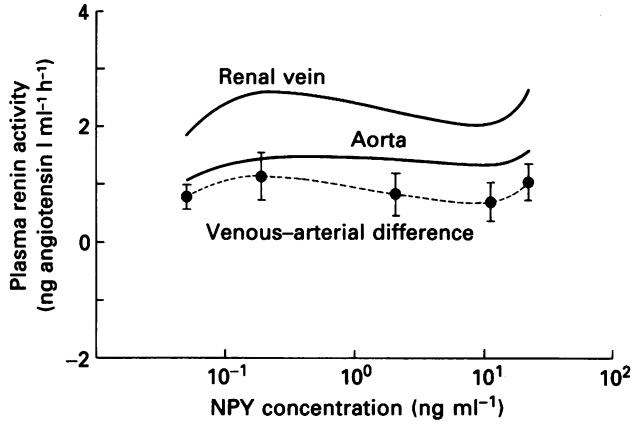


Fig. 3. Renal venous and aortic plasma renin activities were not significantly changed by the increasing NPY infusions. The venous–arterial difference is similarly unaffected.

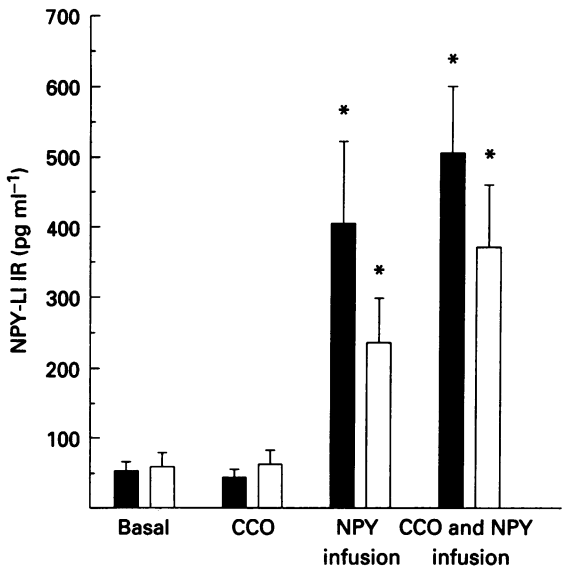


Fig. 4. NPY-LI IR during basal conditions and carotid occlusion. The subthreshold NPY infusion increased the plasma levels significantly. Asterisks refer to a significance of $P < 0{\cdot}05$. Significance was calculated for basal *vs.* NPY and for CCO *vs.* CCO and NPY. ■, renal vein; □, aorta.

to NPY. Thus, only minor variation was found in the venous–arterial difference, which can be taken as an index for renin secretion.

Pressure-dependent effects of NPY

The individual subthreshold NPY infusion rate for reducing RBF (600 ng min^{-1}–1 μg min^{-1}) of each dog was chosen for the experiments of protocols *b*. As depicted in Fig. 4, the average increase of plasma NPY was roughly eight times that of the control levels.

No difference was detected between the control arterial and renal venous NPY-LI IR concentrations. During NPY infusion, the renal venous levels were higher than the arterial concentration. However, the venous–arterial NPY-LI IR difference was lower than expected. Although bovine serum albumin was added to the NPY

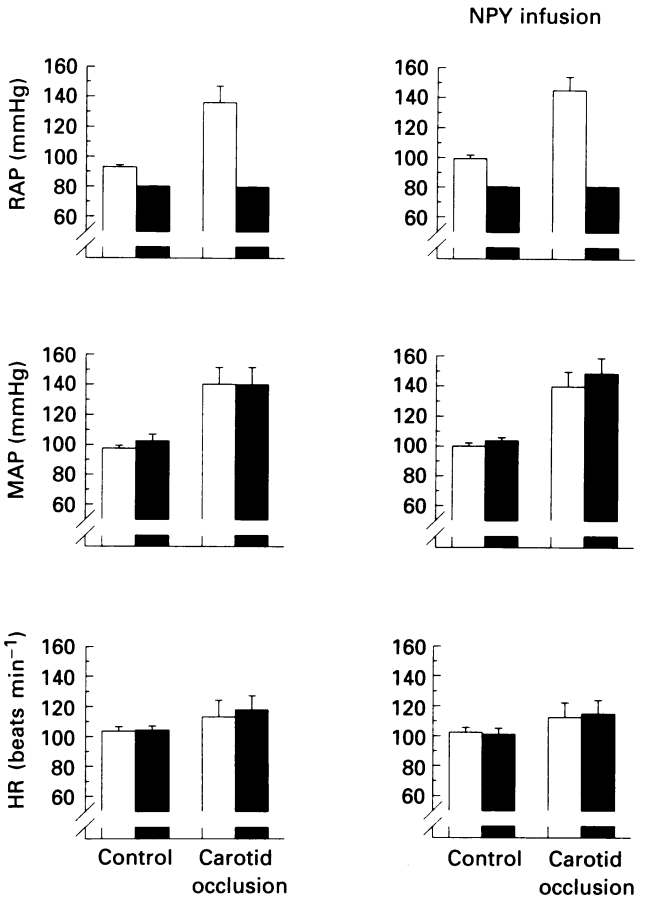


Fig. 5. Left panel, haemodynamic parameters during control and during carotid occlusion. Mean arterial pressure (MAP) and heart rate (HR) increased in response to the occlusion. The servo-controlling of RAP to 80 mmHg (■) had no effect on these parameters (□, no servo-control). Right panel, these systemic haemodynamic parameters were not different during the intrarenal subthreshold NPY infusion. $n = 6$.

solution in order to prevent adhesion to the surfaces, there appears to be a rather low NPY recovery and/or a very high renal binding of NPY. This should be considered in studies where plasma NPY-LI IR is not measured.

The intrarenal infusion of NPY (protocol 1*b*) did not induce systemic effects *per se* as indicated by MAP and HR (Fig. 5). In accordance with the dose–response experiments, RBF and GFR did not change during the subthreshold NPY infusion

in this protocol (Fig. 6). Furthermore, the measured excretory functions were unaffected (Fig. 7).

RAP_{80} alone (protocol 2*a*) also does not have any effect on MAP or HR (Fig. 5), which agrees with previous studies (Ehmke, Persson, Seyfarth & Kirchheim, 1990;

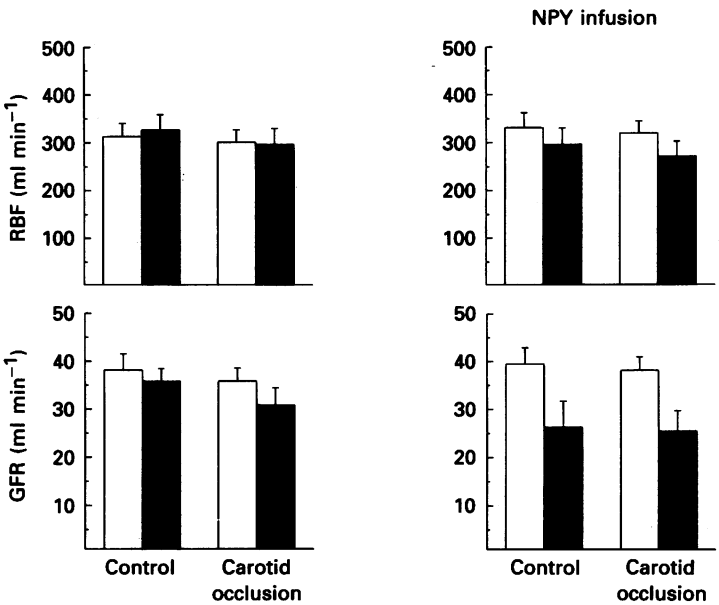


Fig. 6 Measurements of renal blood flow (RBF) and glomerular filtration rate (GFR) according to Fig. 5. □, no servo-control; ■, servo-control (RAP = 80 mmHg). $n = 6$.

Persson *et al.* 1990*a*). Eighty mmHg is above the lower limit for RBF autoregulation in conscious foxhounds (Persson *et al.* 1990*a*, *b*), so RBF did not change, as seen in Fig. 6. In contrast, diuresis and electrolyte secretion (which are pressure-dependent processes) decreased in response to RAP_{80} (Fig. 7). The venous–arterial PRA difference increased during pressure reduction (Fig. 8), due to pressure-dependent renin release (Ehmke, Persson, Fischer, Hackenthal & Kirchheim, 1989).

NPY infusion enhanced the pressure-dependent processes (protocol 2*b*). As illustrated in Fig. 7, diuresis was less than half during NPY and servo-control in comparison to servo-control alone (2*a* *vs.* 2*b*: $P < 0{\cdot}05$). Basically, the same result was found for natriuresis ($P < 0{\cdot}05$) and kaliuresis ($P < 0{\cdot}05$). Pressure-dependent renin release increased threefold compared to control (Fig. 8, $P < 0{\cdot}05$). There was a slight reduction of RBF and GFR during NPY in protocol 2*b* (Fig. 6). However, these differences were not significant.

Sympathetic interaction of NPY

A reflex sympathetic stimulus was achieved by CCO (protocol 3*a* and *b*). In response, MAP increased from 98 ± 2 to 140 ± 5 mmHg. HR increased from 104 ± 3 to 113 ± 11 beats min^{-1} (Fig. 5). In spite of this clear-cut evidence for a sympathetic activation, only a slight tendency for an increase in NPY-LI IR was found (Fig. 4).

The CCO does not alter baseline RBF and GFR (Fig. 6). However, CCO did lower GFR at 80 mmHg (protocol 4*a*), which is consistent with the shifting of autoregulation by this reflex sympathetic activation (Persson *et al.* 1990*a*, *b*).

V_U, V_{Na} and V_K by contrast increased significantly in response to CCO (Fig. 7). Since a sympathetic stimulus without a concomitant pressure increase has the reverse

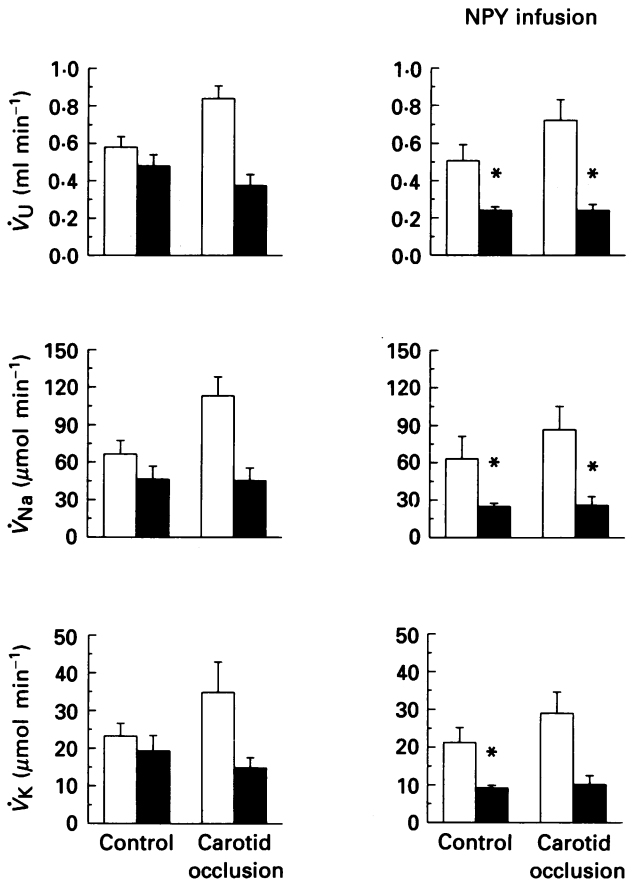


Fig. 7. Measurements of urine excretion (V_U), sodium excretion (V_{Na}) and potassium excretion (V_K) according to Fig. 5. Servo-controlling RAP reduces diuresis, natriuresis and kaliuresis. This effect is significantly stronger in the presence of NPY. Asterisks refer to a significance level of $P < 0{\cdot}05$. Significance was only calculated for the comparison of the two corresponding interventions before and after the NPY infusion. □, no servo-control; ■, servo-control (RAP = 80 mmHg). $n = 6$.

effect on these parameters (Persson, Ehmke, Kögler & Kirchheim, 1989; Ehmke *et al.* 1990), a pressure-dependent mechanism is proposed.

In agreement with previous studies (Ehmke *et al.* 1989), the pressure-dependent renin release seems to be enhanced by CCO (protocol 3, Fig. 8).

NPY (protocol 2*b*) produced a slight reduction of RBF and GFR in protocols 2*b* and 4*b*. NPY significantly reduced V_U and V_{Na} in the protocol with RAP_{80} and CCO (protocol 4*a* *vs.* 4*b*, $P < 0{\cdot}05$, Fig. 7).

Although CCO and NPY both enhance pressure-dependent antidiuresis and antinatriuresis, there is no further decrease in excretory function when combining the two interventions (protocol 4*b*): V_{Na}, V_U and V_K are equally low during NPY infusion at 80 mmHg as when CCO is added (Fig. 7). Thus, the combined effects of NPY and CCO are less than their individual sum (inhibitory summation).

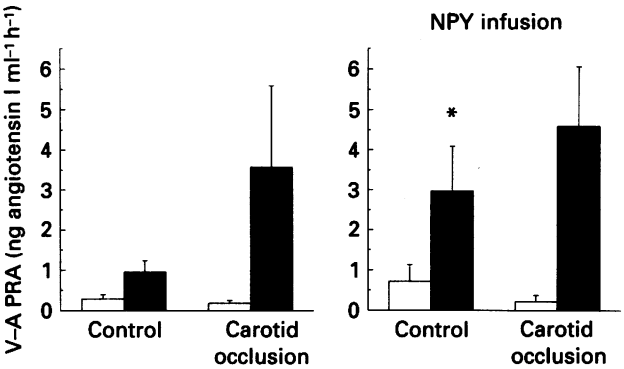


Fig. 8. The venous–arterial plasma renin activity difference (V–A PRA) according to Fig. 5. Carotid occlusion and NPY increased the estimated pressure-dependent renin release. The asterisk refers to a significance level of $P < 0{\cdot}05$. Significance was only calculated for the comparison of the two corresponding interventions before and after the NPY infusion. □, no servo-control; ■, servo-control (RAP = 80 mmHg). $n = 6$.

This also applies to renin release (Fig. 8). Both NPY and CCO enhanced the pressure-dependent renin release, but the combination of both stimuli (protocol 4*b*) is much less than the sum of their individual effect.

DISCUSSION

NPY can exert direct postsynaptic effects and potentiates the postsynaptic noradrenaline responses. Furthermore, NPY inhibits noradrenaline release via a prejunctional mechanism (Wahlestedt, Edvinsson, Ekblad & Håkanson, 1985; Lundberg, Pernow, Tatemoto & Dahlöf, 1985; Minson, McRitchie & Chalmers, 1989). This study was undertaken to determine the renal actions of NPY in the conscious animal under standardized conditions. Dose–response relationships were obtained for intrarenal NPY infusions. The subthreshold dose for an increase of total renal vascular resistance was chosen for further experimentation.

Dose–response relationship

The dose–response curves obtained in our resting foxhounds most likely reflect the direct, postsynaptic actions of NPY since with increasing NPY concentrations the postsynaptic effects dominate over the presynaptic mechanisms.

There is a threshold dose for NPY vasoconstriction (Fig. 2). Along with the decrease in RBF and GFR, V_U and V_{Na} also diminish. These findings are in part

contradictory to previous studies on the effect of NPY on renal function. Allen and colleagues (Allen *et al.* 1985) reported a natriuresis in spite of a reduction of RBF and GFR in the isolated rat kidney. However, as Allen and co-workers pointed out, there may be a difference between the isolated perfused rat kidney and the intact rabbit, in which no natriuresis was found (Allen, Hanson, Lee, Mattin & Unwin, 1986*b*). Our results suggest an antinatriuretic action only at higher doses, which agrees with a study by Echtenkamp & Dandridge (1989) in the uninephrectomized and anaesthetized non-human primate. It is of importance that the intrarenal NPY administration in Echtenkamp & Dandridge's as well as our study did not increase MAP. This avoids pressure natriuresis and prevents inhibition of renal nerve activity by arterial baroreceptors.

Intriguingly, the venous–arterial PRA difference, which can be taken as an estimate for renin secretion, did not change during the different infusion rates (Fig. 3). Again this is in disagreement with findings in the isolated rat kidney and rat kidney tissue pieces. Hackenthal and colleagues found an inhibition of renin release by NPY (Hackenthal *et al.* 1987). Similar observations have been obtained for anaesthetized cats, (Corder, Vallotton, Lowry & Ramage, 1989). In some rat preparations, however, NPY has been found to have no effect on PRA (Aubert, Burnier, Waeber, Nussberger, Dipette, Burris & Brunner, 1988; Waeber, Evéquoz, Aubert, Flückiger, Juillerat, Nussberger & Brunner, 1990) unless PRA levels are elevated by a renal clip (Waeber *et al.* 1990). These conflicting findings are not readily reconciled. The reduction of PRA in the two-kidney, one-clip hypertension model may also rely on a secondary mechanism. In any event it must be kept in mind that alterations of RAP, anaesthesia and surgical trauma all have a profound impact on renin release.

Pressure-dependent effects of NPY

Effects on renin release may only become apparent below the threshold pressure for its secretion, that is roughly 95 mmHg for the conscious dog (Ehmke *et al.* 1989). The effect of NPY on pressure-dependent renin release was quite surprising. There was a clear augmentation of the venous–arterial PRA difference during the servo-control of RAP (Fig. 8). Several hypotheses can be put forward for this mechanism. Vasoconstriction at the site of renin release is implausible, since this would have the reverse effect. Furthermore, a direct action on NPY receptors located at the juxtaglomerular apparatus (Ballesta *et al.* 1984, 1987) appears unlikely in the face of a lack of effect in the dose–response relationship (Fig. 3). Thus, another mechanism is proposed: the local, intrarenal effects of NPY might be unevenly distributed. If NPY were to act in a preferential manner on the larger preglomerular vessels, a vasoconstriction in these segments would occur as a result of NPY infusion. The autoregulating kidney would compensate for this vasoconstriction by a subsequent dilatation in the vascular beds further downstream. This is a very strong stimulus for renin release. Of course, this mode of action is speculative, because we have no means of testing a non-uniformly distributed effect of NPY in our preparation. Thus, we attempted a totally different approach in the accompanying paper by Nobiling *et al.* (1991). The hydronephrotic kidney model allows direct assessment of the renal vascular bed. Roughly 80% of the smooth muscle cells, which were further

than 200 μm upstream from the glomerulus, responded to NPY with a clear-cut depolarization. In the close neighbourhood (< 50 μm) of the glomerulus no response was obtained. Similarly, as indicated by intravital microscopy, the larger vessels constricted in response to low doses of NPY (see accompanying paper of Dietrich *et al.* (1991)). The corresponding preglomerular arterioles did not react or dilate in response to this upstream vasoconstriction. Hence, these findings support the concept of a differential effect of NPY on the renal vascular bed. Of course, reservations must be kept in mind; NPY binding differs between various species (Schachter, Miles, Leys & Sever, 1986; Leys *et al.* 1987), and the tubuloglomerular feedback mechanism is absent in the hydronephrotic kidney.

As observed with renin release, NPY also enhanced the antidiuresis and antinatriuresis which occurs as a consequence of pressure reduction (Fig. 7). This again may have several reasons. In the rabbit kidney, NPY binding has been attributed to the proximal tubules (Schachter *et al.* 1986; Leys *et al.* 1987), and NPY also has antisecretory effects in the intestinal epithelia, albeit without any apparent effect on sodium movement (Cox & Cuthbert, 1988; Cox, Cuthbert, Håkanson & Wahlestedt, 1988). In the face of the lack of effect on sodium transport, it seems more likely to be due to a secondary mechanism. The proposed vasoconstrictor effect on the larger vessels along with the concomitant dilatation of the vessels further downstream leads to a reduction of GFR (Fig. 6) and a change in peritubular Starling forces, which both can decrease V_{Na}. Thus, the enhanced antidiuresis and antinatriuresis are consistent with the proposed pattern of renal vasoconstriction.

Sympathetic interaction

A reflex sympathetic activation via CCO increases toal renal vascular resistance below a RAP of 100 mmHg (Persson *et al.* 1990*a*). This is an α-adrenergic effect, which is independent of renin formation (Persson *et al.* 1990*b*). In analogy to NPY, an α-adrenergic stimulus also enhances pressure-dependent antinatriuresis (Persson *et al.* 1989; Ehmke *et al.* 1990) as well as renin release (Ehmke *et al.* 1989). Thus, there is a considerable analogy between NPY- and α-adrenergic-mediated effects. Due to this analogy, along with the well-known postsynaptic potentiation of noradrenergic effects by NPY (Lundberg *et al.* 1985; Linton-Dahlöf, 1989), one may anticipate a synergism of both stimuli. This is not supported by this study. The effects of NPY with a servo-controlled RAP are not enhanced by CCO (Figs 7 and 8). Therefore, in our protocols, we find an inhibitory summation (i.e. the sum of the individual effects is greater than the combined effect). This is not necessarily a contradiction to other studies, which reveal a postsynaptic potentiation of the sympathetic effects by NPY (Lundberg *et al.* 1985; Linton-Dahlöf, 1989), since the presynaptic mechanism inhibits the release of noradrenaline (Linton-Dahlöf, 1989). Hence this presynaptic effect impairs noradrenaline release during CCO. Furthermore, α_2-adrenergic receptors may be involved.

We thank Mrs B. Collins, I. Keller and L. Mahl for their expert technical assistance. This study was supported by the German Research Foundation (Forschergruppe Niere, Heidelberg).

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