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The actions of neuropeptide Y and peptide YY on the hepatic arterial and portal vascular beds of the anaesthetized dog

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1 The vascular actions of the two peptides, neuropeptide Y (NPY) and peptide YY (PYY) were compared with the transmitter noradrenaline (NA) on the arterial and portal vascular beds of the *in situ* liver of the anaesthetized dog.

2 The sole vascular response of the hepatic arterial vasculature to intra-arterial administration of either NPY or PYY was vasoconstriction; the duration of these responses was longer than that to NA.

3 The maximum hepatic arterial vasoconstrictor responses to PYY and to NPY were significantly different and they were both significantly less than the maximum to NA ($P < 0.001$).

4 In contrast to its activity on the splenic arterial vasculature PYY was not more potent, on a molar basis, than NPY as an hepatic arterial vasoconstrictor agent. However, both peptides were significantly more potent than NA ($P < 0.005$).

5 Neither peptide, when injected intraportally, caused any change in intrahepatic portal inflow resistance.

6 Both peptides when administered intraportally in doses which were free of systemic effects caused hepatic arterial vasoconstriction.

Introduction

The structurally homologous hexatriacontapeptides peptide YY (PYY) and neuropeptide Y (NPY), originally isolated from extracts of porcine intestine and brain respectively (Tatemoto 1982a,b), were quickly identified as potent vasoconstrictor agents (Lundberg & Tatemoto, 1982). Subsequently, immunohistochemical studies of these two peptides have revealed very marked differences in their anatomical distributions. PYY is located primarily in paracrine cells of the pancreas and intestinal mucosa, with the number of such cells and the tissue concentration showing a gradient which increases distally through the gastrointestinal tract to the colon (Lundberg *et al.*, 1982; Adrian *et al.*, 1987). In contrast, neuropeptide Y has a predominantly neuronal origin with a particularly high density in perivascular noradrenergic nerves (Lundberg *et al.*, 1983; Sundler *et al.*, 1986). It is also abundant in the adrenal medulla of some species (Lundberg *et al.*, 1983; de Quidt & Emson, 1986). In addition to its presence in the sympathetic nervous system, NPY-like immunoreactivity has been demonstrated in a population of non-adrenergic neurones of the gastrointestinal tract which, unlike the majority of noradrenergic NPY neurones, are insensitive to either surgical or chemical sympathectomy (Sundler *et al.*, 1986; Ekblad *et al.*, 1987).

In the liver the precise histological distribution of NPY in relation to the vasculature has yet to be described, although there is evidence for NPY being localized in the innervation of the biliary tract (Allen *et al.*, 1984). Physiologically, the sympathetic innervation to the liver does not appear to be of paramount importance in the control of hepatic haemodynamics in the dog, although both direct and reflex sympathetic activation can lead to the concomitant vasoconstriction of the hepatic arterial and portal vascular beds (Carneiro & Donald, 1977).

The aim of the present experiments was to characterize the actions of the two peptides, PYY and

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NPY, on both the hepatic arterial and portal inflow resistances in separate perfusion experiments in anaesthetized dogs. This may be functionally important, firstly because of the presence of NPY in sympathetic nerves and, secondly, on account of the postprandial secretion of PYY from the gut which enters the liver vasculature in the portal inflow (Adrian *et al.*, 1987), and may alter hepatic haemodynamics in a manner of physiological significance (Withrington & Richardson, 1986).

Methods

The experiments were performed on 12 greyhounds (mean weight 25.1 ± 1.4 kg; range 18.5–32.0 kg) anaesthetized with an intravenous mixture of chloralose and urethane (50 and 500 mg kg^{-1} respectively) after induction with methohexitone sodium (6 mg kg^{-1}). The trachea was cannulated although respiration was always spontaneous. The right femoral vein was cannulated to administer additional anaesthetic when appropriate. The right femoral artery was cannulated to provide hourly blood samples for analysis of pH, Po_2 and Pco_2 (Blood Gas Analyser, Instrumental Laboratory, Model 1302); $NaHCO_3$ was administered i.v. (1.0 mmol min^{-1}) if considered necessary, to maintain a normal arterial pH. The left carotid artery was cannulated and connected to a strain gauge transducer (Statham P23Gb), to provide a continuous registration of phasic systemic blood pressure from which a continuous recording of heart rate was derived electronically. Body temperature was maintained within normal limits, as indicated by a buccal thermometer, by either table heaters or overhead lamps. The animals were treated with heparin (500 iu kg^{-1}) once perfusion had commenced and half this dose administered hourly.

The perfusion circuits and surgery required for hepatic arterial and portal perfusion have been described in detail previously (Richardson & Withrington, 1978a) and in all essential details the same procedures were adopted for the present experiments. Briefly, the hepatic artery was cannulated after ligation of major side tributaries, and perfused with arterial blood from the cannulated left femoral artery. The hepatic periarterial innervation remained intact. Incorporated into the arterial perfusion circuit was a strain gauge pressure transducer (Statham P23Gb) and a cannulating electromagnetic flow probe (Cardiovascular Instruments) to measure perfusion pressure and flow, respectively. These signals were heavily damped electronically to provide mean values which were continuously monitored on a chart recorder (Devices M19). In addition the signals were digitized (Data Translation DT-2801) and processed by an IBM PC-XT computer programmed to calculate and store the absolute values of hepatic arterial vascular resistance (mean pressure/mean flow) and the changes induced by any experimental procedure. A 'T' piece was included in the perfusion circuit so that vasoactive substances could be administered, by either bolus injection or infusion, directly into the hepatic arterial circuit without necessarily entering the systemic circuit. This avoided either altering the conditions of the perfusion (i.e. constant pressure) or eliciting reflex changes in hepatic sympathetic tone. In some of the arterial perfusion experiments the spleen was removed after cannulation of the splenic vein with a long polythene catheter which was then pushed down into the portal vein. Its position was verified by manual examination and by the withdrawal of blood which subsequent analysis (Po_2 and Pco_2) verified as portal venous composition. Vasoactive substances could then be administered intraportally to assess their actions on hepatic arterial blood flow and hepatic arterial inflow resistance.

In the portal perfusion experiments the hepatic portal vein was cleared of all attachments and principal side branches ligated. The spleen was removed and a wide bore polythene tube passed retrogradely down the splenic vein to the portal vein. The portal vein was then tied cranially just beyond the entrance of the superior mesenteric and splenic veins, so that the venous drainage from the gastrointestinal tract was diverted along the splenic vein cannula to a reservoir. The hepatic end of the portal vein was then cannulated and blood from the mesenteric drainage reservoir pumped, by means of a roller pump (Watson-Marlow MHRE 1000), into the intrahepatic portal vascular bed. The pump was set to deliver the same volume flow as the mesenteric venous drainage and, once set, remained constant throughout any experiment. Incorporated into the portal perfusion circuit between the pump and liver was a low pressure strain-gauge transducer and an electromagnetic flow probe to measure hepatic portal venous pressure (HPVP) continuously and to check the pump outflow (HPVF), respectively. A long, narrow bore, polythene cannula was passed up the inferior vena cava (IVC) from the right femoral vein to a point just below the diaphragm and opposite the entry of the hepatic veins. After suitable electronic damping this provided a continuous recording of IVC pressure (IVCP). The signals from these pressure transducers were heavily damped electronically to provide mean values which were continuously monitored on a pen recorder. Again the values were digitized and fed into a personal IBM computer programmed to calculate hepatic portal mean inflow resistance (HPVP – IVCP/HPVF) and also to store the maximum changes in portal pres-

sure and portal inflow resistance induced by any experimental procedure. Incorporated into the portal circuit was a 'T' piece for injection of vasoactive substances directly into the portal inflow.

The flow probes were calibrated with whole blood at the end of each experiment. The liver was weighed at the end of each experiment so that hepatic arterial and portal flows and resistances could be expressed in terms of 100 g liver weight.

Drugs used and vehicles

Vasoactive substances (noradrenaline, NPY, PYY) were washed in with saline (0.9% w/v NaCl solution) to give a total injectate of 2.0 ml. NPY and PYY were purchased from Bachem and made up in sterile saline which contained human serum albumin (10 mg ml^{-1}; Elstree) and polypep (2.5 mg ml^{-1}; low viscosity; Sigma). Close arterial or intraportal injection of this vehicle did not alter either hepatic arterial or portal inflow resistance. The human serum albumin and polypep were used to reduce non-specific binding of NPY and PYY onto plastic surfaces. Noradrenaline acid tartrate (Levophed; Winthrop) was diluted immediately before injection in normal saline and the containers maintained in ice.

Statistics

Results are presented as mean ± s.e.mean. Tests for significance were either by Student's unpaired *t* test or paired *t* test.

Results

Control values

The mean liver weight was 571 ± 31 g representing 2.29 ± 0.06% of the body weight. In the 9 hepatic arterial perfusion experiments the initial mean hepatic arterial blood flow was 191 ± 12.6 ml min^{-1} or 34.0 ± 2.2 ml min^{-1} 100 g^{-1}. Since the mean hepatic arterial perfusion pressure was 151 ± 7.3 mmHg then the mean calculated hepatic arterial vascular resistance was 0.81 ± 0.05 mmHg ml^{-1} min or 4.78 ± 0.44 mmHg ml^{-1} min 100 g liver weight. These agree with previous values from this laboratory.

In the three hepatic portal perfusion experiments the mean initial systemic blood pressure, once portal perfusion had started, was 136 ± 11 mmHg. The mean hepatic portal blood flow was 146.7 ± 8.7 ml min^{-1} or 26.2 ± 2.7 ml min^{-1} 100 g^{-1}. The mean hepatic portal venous pressure was 10.1 ± 0.43 mmHg and the mean inferior vena caval pressure 1.77 ± 0.23 mmHg; therefore the mean portal/IVC pressure gradient was 8.3 ± 0.29 mmHg. The mean calculated hepatic portal inflow resistance was 0.057 ± 0.0045 mmHg ml^{-1} min or 0.37 ± 0.04 mmHg ml^{-1} min 100 g liver weight. These values are similar to those obtained previously from this laboratory.

Hepatic arterial vascular responses to close arterial injections

Noradrenaline In all nine hepatic arterial perfusion preparations graded bolus doses of noradrenaline (NA) were made directly into the hepatic arterial perfusion circuit over the dose range 0.1–100 μg to construct most of the dose-response curve. The characteristic response (Figures 1 and 3) was a rapid and brief reduction in hepatic arterial blood flow followed by a more prolonged increase in flow. At constant perfusion pressure, these changes in arterial flow represent an increase and then a decrease in hepatic arterial inflow resistance and, therefore, hepatic arterial vasoconstriction and a secondary hepatic arterial vasodilatation, respectively. The hepatic arterial vascular changes to NA have been analysed extensively (Richardson & Withrington, 1977) and represent the overlapping time courses of an initial predominantly α-adrenoceptor activation followed by predominantly β_2-adrenoceptor activation. These two phases of the hepatic arterial vascular response to NA were always present but their magnitude and time course were related to dose in a complex manner.

In the present series of perfusions the maximum hepatic arterial vascular response to intra-arterial NA was, in 4 of the 9 experiments, to shut down completely hepatic arterial inflow. The mean maximum percentage reduction in flow, achieved at a bolus dose of either 50 or 100 μg was 72.6 ± 2.9%. The mean dose of NA to cause a 50% reduction in hepatic arterial blood flow was 52.5 ± 9.4 nmol.

Neuropeptide Y In all nine hepatic arterial perfusion preparations NPY was injected close-arterially in graded bolus doses over the range 0.1–10 nmol to construct, in each experiment, the majority of the dose-response curve. Three distinct differences to the hepatic arterial vascular response to NA were observed.

In all the preparations the only hepatic arterial vascular response to any injection of NPY, was a

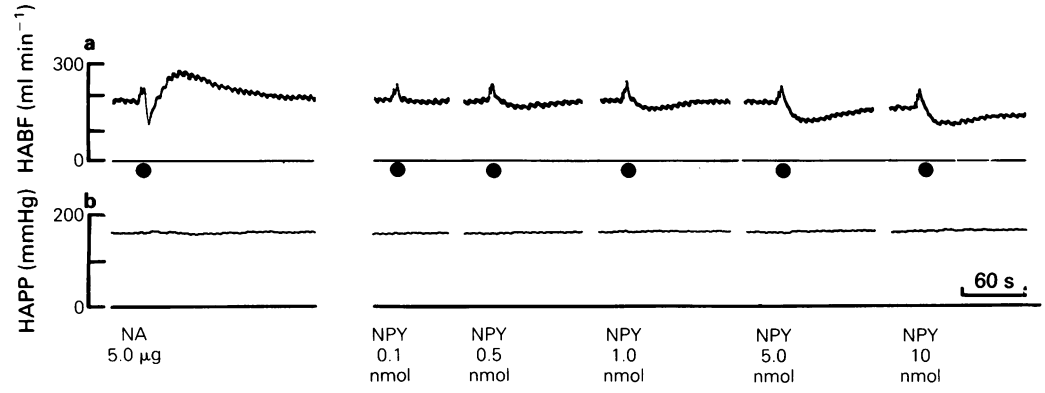

Figure 1 Records are (a) HABF, hepatic arterial mean blood flow; (b) HAPP, hepatic arterial mean perfusion pressure. The six panels illustrate the changes in response to the intra-arterial injections of noradrenaline (NA, 5.0 μg) and 5 increasing doses of neuropeptide Y (NPY, 0.1, 0.5, 1.0, 5.0 and 10 nmol). The initial upward deflection on the flow record, concomitant with each bolus injection, is an injection artifact. (Liver 754 g).

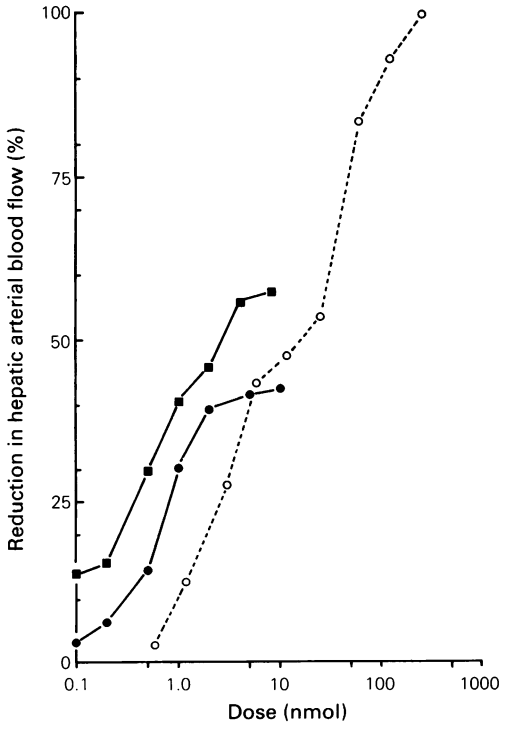

Figure 2 Dose-response curves relating the hepatic arterial vasoconstrictor response (reduction in hepatic arterial mean blood flow, expressed as a percentage of the maximum response to noradrenaline) to intra-arterial injections of noradrenaline (○), neuropeptide Y (●) and peptide YY (■). All the points were obtained in the same experiment under comparable conditions of vascular tone; mean hepatic arterial vascular resistance was 0.79 ± 0.019 mmHg ml^{-1} min. (Liver 590 g).

reduction in hepatic arterial blood flow (Figure 1) representing, in the absence of any changes in perfusion pressure, an increase in hepatic arterial vascular resistance and therefore hepatic arterial vasoconstriction. This vasoconstrictor response was graded with dose. Hepatic arterial vasodilatation was never seen.

The time course of the hepatic arterial vasoconstrictor response to NPY was much more prolonged than to NA. A comparison of hepatic arterial responses to NPY and NA, equieffective in terms of their maximum vasoconstrictor effect but irrespective of dose, revealed that the time to half recovery from the start of the vascular response was approximately 5–8 times longer for NPY.

In individual experiments the threshold dose for the hepatic arterial vasoconstrictor effect to NPY was usually less than 0.1 nmol, less than for NA, whilst the maximum decrease in hepatic arterial blood flow to NPY (5.0 or 10 nmol) was always less than the maximum to NA in that experiment (Figure 2). Considering all the hepatic arterial perfusion experiments the mean maximum reduction in hepatic arterial blood flow to NPY was 32.9 ± 1.62% of control flow, highly significantly less than the maximum to NA ($P < 0.001$). The mean maximum hepatic arterial vasoconstrictor response to NPY was 45.6 ± 2.7% of the mean maximum to noradrenaline.

In each experiment the dose-response curve for NPY was always to the left of that for NA, i.e. NPY is more potent than NA (Figure 2). The mean results in 6 (Figure 4) experiments revealed that, taking as an index for comparison of molar potency the molar dose to increase hepatic arterial vascular resistance by 30% (ED_{30}) (a point which lies on the linear part

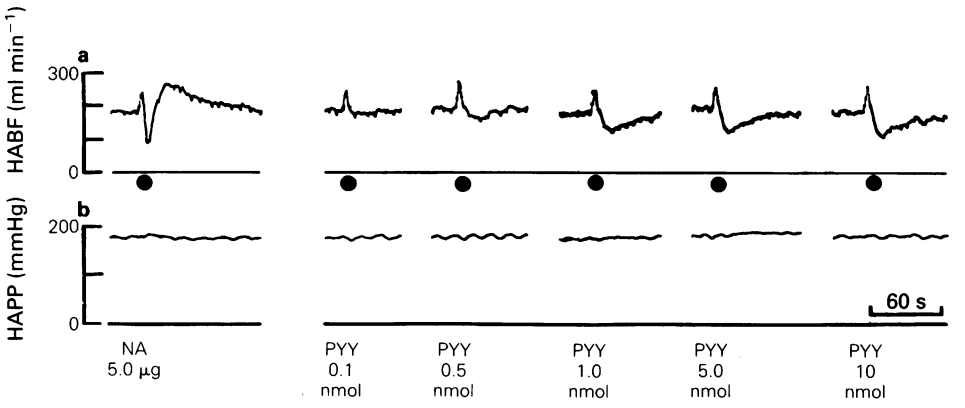

Figure 3 Records are as for Figure 1; (a) HABF, hepatic arterial mean blood flow; (b) HAPP, hepatic arterial mean perfusion pressure. The 6 panels represent the responses to close arterial injections of noradrenaline (NA, 5.0 μg) and 5 increasing doses of peptide YY (PYY; 0.1, 0.5, 1.0, 5.0, and 10 nmol). (Liver 613 g).

of the dose-response curve for all three vasoconstrictor agents examined here), the ED_{30} for NPY and NA was 1.24 ± 0.13 and 3.85 ± 0.92 nmol, respectively. These values are significantly different ($P < 0.005$, paired t test).

Peptide YY Peptide YY (PYY) was administered as a bolus injection into six hepatic arterial preparations to construct nine complete dose-response curves. in all of these preparations dose-response curves to both NA and NPY were also established for comparative purposes and illustrated in Figure 4.

Qualitatively the hepatic arterial vascular response to PYY was very similar to that of NPY (Figure 1). It consisted of graded reductions in hepatic arterial blood flow (Figure 3) of long duration compared with NA. Hepatic arterial vasodilatation was never observed.

Quantitatively there were important differences from NPY. In individual experiments the threshold dose for the hepatic arterial vasoconstrictor response was lower for PYY than NPY and was always less than 0.1 nmol. In addition the maximum hepatic arterial vasoconstrictor response to PYY was always larger than that to NPY (Figure 2) but less than the response to NA. The mean maximum reduction in hepatic arterial blood flow to PYY, which was usually apparent at 5.0 nmol, was $38.5 \pm 2.1\%$ of control flow or $53.4 \pm 3.3\%$ of the maximum reduction in flow to NA. Both of these values are significantly greater ($P < 0.05$) than the corresponding mean values for NPY.

In individual experiments, the molar dose-response curve for PYY always lay to the left of that for both NPY and NA (Figure 2). Using the ED_{30} again as an index for comparison the mean ED_{30} for PYY was, in the six experiments, 0.95 ± 0.15 nmol, a value significantly less than that for NA ($P < 0.005$, t test) but not significantly different from the ED_{30} for NPY ($P > 0.05$).

Hepatic arterial vascular responses to intraportal injections

In three of the hepatic arterial perfusion preparations NA, NPY and PYY were injected intraportally over the same bolus dose range as that administered by direct intra-arterial injection for each substance. The form of the hepatic arterial responses to intraportal injections of NA have been described previously (Richardson & Withrington 1978a) and analysed in terms of the adrenoceptors involved, and the probable routes of access from the portal to arterial resistance sites. In the present series of experiments, intraportal injections of NA were made over the range 1–20 μg and the characteristic biphasic changes in hepatic arterial vascular resistance observed in all three experiments in the absence of any systemic effects. In these experiments the form of the hepatic arterial response to intraportal NPY or PYY remained monophasic, i.e. solely vasoconstrictor.

In one experiment complete dose-response curves for the hepatic arterial vasoconstrictor responses to both NPY and PYY were constructed after both intra-arterial and intra-portal bolus injection. Again hepatic arterial vasoconstriction only was observed with each peptide; the threshold for vasoconstriction was higher following intraportal than after intra-arterial injection. However, once this threshold had been reached, as the dose of NPY or PYY was

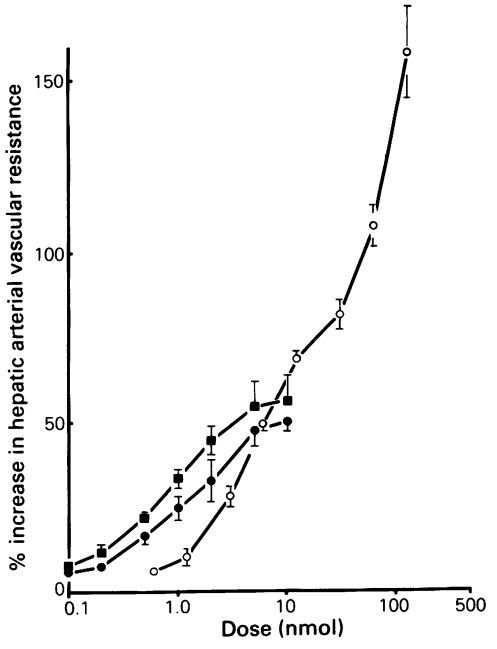

Figure 4 The relationship obtained in 6 separate hepatic arterial perfusions between the intra-arterial molar dose of noradrenaline (○); neuropeptide Y (●) and peptide YY (■); and the increase in hepatic arterial vascular resistance (hepatic arterial vasoconstriction) expressed as a percentage of the control value prior to each injection. The points represent the means, and vertical lines s.e., of at least six observations.

increased, an increasingly higher proportion of the response to direct arterial injection was achieved by the same dose of either peptide when administered intraportally. The mean hepatic arterial response ratio to intraportal/intra-arterial administration for all the doses of NPY and PYY, above threshold, was 62.6 ± 2.9%. These hepatic arterial responses to intraportal NPY were obtained in the absence of systemic effects, such as a rise in systemic blood pressure (Corder *et al.*, 1986).

Hepatic portal responses to intraportal injections

Noradrenaline In three experiments of portal perfusion alone NA was injected intraportally over the dose range 1–50 μg. In contrast to the biphasic vascular response of the hepatic arterial vascular bed the portal response was monophasic consisting of a rise in portal pressure (Figure 5), which at constant inflow volume, reflects a rise in portal inflow resistance or portal vasoconstriction. This portal vascular response has been analysed previously (Richardson & Withrington, 1978b) and reflects the sole distribution of α-adrenoceptors in the portal resistance sites. In the current series the response was graded with dose (Figure 5). At the dose levels used no systemic effects were observed.

Peptides NPY and PYY Both NPY and PYY were injected as bolus doses of 0.1–10 nmol, intraportally. There were no significant or consistent changes in portal pressure in either direction, clearly indicating a lack of direct action by either NPY (Figure 5) or PYY on the intrahepatic portal inflow resistance sites.

Discussion

The systemic pressor actions of NPY and PYY have been described in earlier publications (Lundberg & Tatemoto, 1982), and in the case of NPY this effect has been attributed to increased total peripheral vascular resistance (Corder *et al.*, 1986). Nevertheless very little is known about changes in regional blood flow following i.v. administration of these peptides. *In vitro*, it is evident that some blood vessels are sensitive to the vasoconstrictor activity of NPY (Edvinsson, 1985; Wahlestedt *et al.*, 1986), while other vascular smooth muscle preparations are unresponsive (Edvinsson *et al.*, 1984; Wahlestedt *et al.*, 1986). However, irrespective of whether NPY can

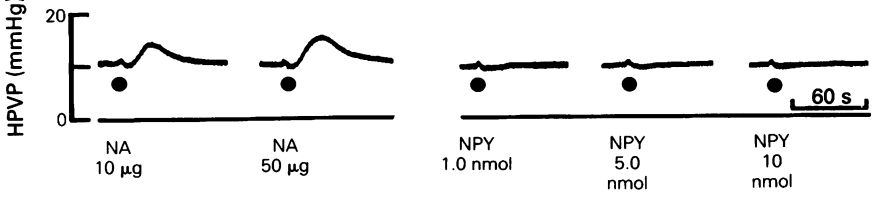

Figure 5 Records of the hepatic portal venous mean perfusion pressure (HPVP) when the portal circuit was perfused at constant flow (146 ml min^{-1}). The 5 panels illustrate the changes in portal pressure, and therefore portal inflow vascular resistance, in response to intraportal injections of 2 doses of noradrenaline (NA, 10 and 50 μg) and 3 doses of neuropeptide Y (NPY, 1.0, 5.0 and 10 nmol). (Liver 588 g).

elicit vascular smooth muscle contractions of a particular preparation, it causes a general enhancement of the vasoconstrictor actions of noradrenaline (Edvinsson *et al.*, 1984; Wahlestedt *et al.*, 1986). From the available data this would also appear to be the case for PYY (Wahlestedt *et al.*, 1986). It is unclear whether the two peptides act on the same receptor. However, based on their actions and structural similarity such a conclusion would not be inappropriate.

In this paper we demonstrated that NPY and PYY are significantly more potent than noradrenaline in producing hepatic arterial vasoconstriction, but neither peptide was able to produce more than one third the maximum vasoconstrictor response at that site obtained with noradrenaline (Figure 4). A comparison of these results obtained in the liver arterial circulation with our previous findings on the arterial vasculature of the dog spleen (Corder *et al.*, 1987) reveals several important differences between the vasoconstrictor responses in these tissues. In the spleen NPY and PYY were as efficacious as noradrenaline in causing vasoconstriction, and indeed were able to arrest splenic arterial blood flow completely. Moreover, the ratio of molar potencies of the three substances was very different. In the splenic arterial vasculature PYY was significantly more potent as a vasoconstrictor than NPY; both peptides were significantly more potent than NA. In the porcine spleen, although reserpine treatment produces a total depletion of noradrenaline, the vascular response to nerve stimulation remains suggesting that another mediator such as NPY is able to fulfill the role of the endogenous vasoconstrictor (Lundberg *et al.*, 1986). In contrast, the absence of maximal hepatic arterial vasoconstrictor responses to these peptides comparable to those obtained with noradrenaline may indicate that, in the liver only a population of the arterioles forming the hepatic arterial resistance vessels are sensitive to NPY and PYY. Alternatively, the hepatic arterial vessels are analogous to those blood vessels which show only a weak response to NPY and where an enhancement of the actions of noradrenaline becomes the more important effect (Edvinsson *et al.*, 1984). It may be that the physiological role of NPY in the liver is to enhance the effects of sympathetic transmission during co-release from perivascular noradrenergic nerves, without having marked intrinsic vasoconstrictor actions.

Neither PYY nor NPY produced, on intraportal injection, any change in portal vascular resistance (Figure 5), although increases in hepatic arterial resistance comparable with those obtained by direct administration into the hepatic artery were produced by intraportal injection. A number of other vasoactive agents also have similar differential effects on hepatic arterial and portal circuits (Withrington & Richardson, 1986). In the case of PYY this effect could be of functional significance since PYY is a candidate gut hormone (Tatemoto, 1982a; Pappas *et al.*, 1986) released postprandially (Adrian *et al.*, 1987) and after infusion of fatty acids. Circulating PYY shows marked increases 15 min after feeding, with significantly higher levels measured in the portal vein than in peripheral vessels (Adrian *et al.*, 1987). Feeding produces a generalized gastrointestinal hyperaemia which may be the result of a combination of neurogenic and humoral events (Bond *et al.*, 1979). However, using the radioactive microsphere method to monitor the vascular response, blood flow throughout the gastrointestinal tract after a meal in the conscious dog was found either to increase or show no change (Gallawan *et al.*, 1980). An exception was the mucosa of the distal colon where a significant reduction in blood flow was observed 30 min after ingestion of a meal; it is here that the highest tissue PYY concentrations are found. A direct involvement of PYY in this colonic mucosal vasoconstriction has yet to be ascertained.

A consistent finding of the postprandial changes of hepatic blood flow in the dog is no change in arterial flow with an almost doubling of portal blood flow (Hopkinson & Schenk, 1968; Gallawan *et al.*, 1980). Whether, in the dog, the portal vein concentration of PYY is sufficient to inhibit hepatic arterial vasodilatation in response to vasodilator substances present in the portal and systemic inflows, and thus play a dominant role in postprandial liver haemodynamics requires further analysis. If hepatic arterial blood flow is related, in a sequential manner, to gastrointestinal segmental activity, then perhaps hepatic arterial vasoconstriction is the appropriate response to some aspect of colonic activity. For example, it is established that hepatic arterial vasoconstriction will induce a lowering of hepatic portal pressure and hence reduce the pressure gradient in a direction favourable for enhanced water absorption.

However, the interactions between gastrointestinal activity, vasoactive peptide levels in the portal vein and liver haemodynamics requires much further examination.

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