Comparison of the effects of neuropeptide Y and noradrenaline on rat gastric mucosal blood flow and integrity

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- 1 The effects of neuropeptide Y (NPY) and noradrenaline on rat gastric mucosal blood flow, as estimated by laser Doppler flowmetry (LDF), have been examined. In addition, the ability of NPY and noradrenaline to induce acute mucosal haemorrhagic damage has also been assessed.
- 2 Close-arterial infusion of NPY ($0.05\text{--}0.2\text{ nmol kg}^{-1}\text{ min}^{-1}$) for 10 min in the anaesthetized rat induced a dose-dependent fall in LDF, but had minimal effects on systemic arterial blood pressure. Higher doses of NPY did not produce any further reduction in LDF.
- 3 Close-arterial infusion ($0.1\text{--}0.4\text{ nmol kg}^{-1}\text{ min}^{-1}$) of the structurally related peptide YY (PYY) or pancreatic polypeptide (PP), had inconsistent actions in decreasing LDF.
- 4 Close-arterial infusion of noradrenaline ($30\text{--}90\text{ nmol kg}^{-1}\text{ min}^{-1}$) dose-dependently reduced gastric LDF.
- 5 Local infusion of NPY (0.1 and $0.2\text{ nmol kg}^{-1}\text{ min}^{-1}$) or noradrenaline (45 and $60\text{ nmol kg}^{-1}\text{ min}^{-1}$) resulted in dose-related increases in the area of mucosal hemorrhagic damage.
- 6 Pretreatment with the α_1 -adrenoceptor antagonist, prazosin (0.1 mg kg^{-1} , i.v.) significantly reduced the effect of noradrenaline, but not NPY, on both LDF and mucosal damage.
- 7 These findings indicate that NPY and noradrenaline act directly on the gastric microvasculature to induce vasoconstriction and both can induce acute mucosal damage. Therefore endogenous NPY, like noradrenaline could play a modulatory role in regulating vascular tone and may influence mucosal integrity.

Introduction

In addition to their classical neurotransmitters, sympathetic neurones may also synthesize and release one or more biologically active peptides (Loren *et al.*, 1979; Hokfelt *et al.*, 1980). Among the many peptides which have been identified in these nerves is the 36 amino acid peptide, neuropeptide Y (NPY; Lundberg & Tatemoto, 1982).

NPY has been identified in postganglionic nerves supplying arteries and veins (Sundler *et al.*, 1983). In these nerves, the peptide co-exists with noradrenaline and is released together with noradrenaline by sympathetic stimulation (Lundberg *et al.*, 1984). In the gastrointestinal tract, NPY-like immunoreactivity has been found in sympathetic nerves associated with blood vessels (Lee *et al.*, 1985; Ekblad *et al.*, 1985) and in enteric neurones originating from the myenteric and submucosal plexus (Furness *et al.*, 1983; Lee *et al.*, 1985; Su *et al.*, 1987). In addition, peptides that are structurally similar to NPY including pancreatic polypeptide (PP) and polypeptide YY (PYY) have also been found in the gut, although these peptides have been identified primarily in endocrine cells (Lundberg *et al.*, 1982; El-Salhy *et al.*, 1983; Bottcher *et al.*, 1984).

The physiological role of NPY is as yet unclear. Exogenous administration of NPY has been reported to produce a direct pressor response in the systemic circulation which was not attenuated by α -adrenoceptor blockade (Lundberg & Tatemoto, 1982; Dahlof *et al.*, 1985). In addition, NPY has been found to enhance the contractile response of arterial segments to α -adrenoceptor stimulation both *in vitro* (Edvinsson *et al.*, 1984; Wahlestedt *et al.*, 1985) and *in vivo* (Aubert *et al.*, 1988). However, in the gastro-intestinal tract, investigations on the possible physiological role of NPY have been directed primarily at effects on non-vascular smooth muscle tone (Allen *et al.*, 1987; Hellstrom, 1987; Holzer *et al.*, 1987) or intestinal ion and water transport (Saria & Beubler, 1985).

In the present study, we have now compared the effects of NPY and noradrenaline on gastric mucosal blood flow using laser Doppler flowmetry in the anaesthetized rat. Furthermore, since adequate perfusion of the gastric microvasculature is necessary for maintaining mucosal integrity (see Whittle, 1989), we have also examined the effects of NPY and noradrenaline in inducing acute mucosal haemorrhagic damage.

Methods

Measurement of gastric mucosal blood flow

Male Wistar rats (230–260 g body weight) were deprived of food but not water for 18–20 h before the experiment. Animals were anaesthetized with sodium pentobarbitone (60 mg kg^{-1} , i.p.) and the stomach exposed by a mid-line incision. The left gastric artery was cannulated with a short 23 g teflon cannula as described by Esplugues & Whittle (1988). A small bore (8.5 mm o.d.) plastic cannula was then inserted via a small incision in the forestomach and tied in place, to allow free access to the gastric lumen. Gastric blood flow was recorded continuously with a laser Doppler blood flow monitor (Model MBF3D, Moor Instruments Ltd, Devon).

The principle of laser Doppler flowmetry for assessment of gastric blood flow has been described previously (Kiel *et al.*, 1985; Holm-Rutili & Berglin, 1988). A stainless steel laser optic probe (1.65 mm o.d.; Moor Instruments) was inserted into the gastric lumen via the plastic cannula and was allowed to rest gently on the gastric fundic mucosa. Changes in laser Doppler flow (LDF) were assessed in response to intra-arterial infusions ($10\text{ }\mu\text{l min}^{-1}$) of isotonic saline or the compounds under investigation. Isotonic saline was infused for 5–10 min until LDF had stabilized, and NPY, related peptides or noradrenaline were then infused for 10 min. Average LDF values were determined for the 3 min period of saline infusion just prior to NPY or noradrenaline infusion. Similarly the average LDF was calculated for the final 3 min of the drug infusion period when values of LDF had stabilized. Furthermore, LDF values in the absence of blood flow were recorded after clamping the vascular pedicle. The small LDF value observed as a

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result of non-specific light reflectance was subtracted from average LDF levels calculated for the control and test periods. In control experiments, saline infusion was continued throughout the experimental period.

In some experiments, agents were infused via the intravenous route with a 25 g hypodermic needle and 0.3 mm polyethylene cannula inserted into a tail vein. Furthermore, to evaluate any interaction between these vasoconstrictors, NPY and noradrenaline were infused simultaneously into the left gastric artery and LDF changes were monitored.

The mean systemic arterial blood pressure (BP) was also measured in some rats from a cannula inserted into a carotid artery and connected to a pressure transducer (Bell & Howell, Ashford, U.K.) and a chart recorder (Grass model 7D polygraph).

In a further series of studies, the α_1 -adrenoceptor antagonist, prazosin (0.1 mg kg^{-1}), was injected intravenously 5 min before infusion of NPY or noradrenaline and the changes in LDF were subsequently determined. This dose was selected from preliminary dose-response studies with prazosin (0.05 – 0.5 mg kg^{-1}) on LDF and BP changes induced by noradrenaline.

Assessment of gastric mucosal damage

Gastric mucosal damage was assessed in further groups of rats in response to local arterial infusions of NPY or noradrenaline. The left gastric artery was cannulated as described above and after ligating the oesophagus and pylorus, 2.0 ml of 0.1 M HCl in saline was instilled into the gastric lumen by injection through the non-glandular portion of the stomach. Either NPY or noradrenaline were then infused for 10 min via the left gastric artery. At the end of the infusion period the arterial cannula was clamped and 20 min later, the stomach was removed and opened along the greater curvature. The stomach was pinned out, mucosal side up, to a wax block and immersed in neutral buffered formalin and then photographed on colour transparency film. The extent of macroscopically visible damage, involving regions of both haemorrhagic lesions and visible exfoliation, was determined from these projected transparencies via computerized planimetry in a randomized manner. Damage was also assessed in NPY- or noradrenaline-treated rats which had also received an intravenous bolus injection of prazosin (0.1 mg kg^{-1}) 5 min prior to challenge.

For histological confirmation of the nature of the mucosal injury, two samples of the fundus were excised from standardized regions and were processed by routine techniques before embedding in paraffin. Sections ($4 \mu\text{m}$) were stained with haematoxylin and eosin and examined under a light microscope. Each section was assessed histologically for epithelial cell injury, glandular disruption, vasocongestion, and haemorrhagic damage.

Drugs

Neuropeptide Y (human, rat), pancreatic peptide (rat) and polypeptide YY (human), from Peninsula Labs (St Helens, Merseyside) were dissolved in distilled water and stored frozen in aliquots (-20°C). An aliquot was freshly thawed and diluted with isotonic saline when required. Noradrenaline (Sigma Chemical Co. Dorset) was freshly dissolved in isotonic saline. Prazosin (Pfizer, Sandwich, Kent) was freshly dissolved in a small volume of N,N-dimethylacetamide (Sigma; 10% of final volume) then brought up to volume with isotonic saline. This vehicle alone had no effect on BP or the response to noradrenaline.

Statistical analysis

Changes in mucosal blood flow were determined as % change in LDF from the initial control period during local infusion of isotonic saline. Mucosal injury was expressed as % of the total

mucosal area. All data are expressed as mean $\pm$ s.e.mean. Comparisons between two groups were made by Student's *t* test for unpaired data, while multiple comparisons between different groups was by analysis of variance and Duncan's multiple range test. *P* values of less than 0.05 were taken as significant.

Results

Effects of neuropeptide Y and noradrenaline on laser Doppler flow

Close-arterial infusion of NPY (0.5 – $0.2 \text{ nmol kg}^{-1} \text{ min}^{-1}$) resulted in a dose-dependent significant reduction in LDF (Figure 1). LDF was observed to decline within 3–5 min of the start of infusion and nadir values were achieved within 7 min, after which LDF stabilized at this level. The maximal fall in LDF ($41 \pm 5\%$, $n = 4$, $P < 0.05$) was obtained with NPY at $0.2 \text{ nmol kg}^{-1} \text{ min}^{-1}$, and there was no further significant decrease in LDF with higher doses (0.4 and $0.6 \text{ nmol kg}^{-1} \text{ min}^{-1}$) of this peptide (Figure 1). In contrast, close-arterial infusion of noradrenaline produced a progressive reduction in LDF over the entire narrow dose-range examined in the present study (30 – $90 \text{ nmol kg}^{-1} \text{ min}^{-1}$), with a maximum fall of $84 \pm 6\%$ of control ($n = 5$; $P < 0.05$). The reduction in LDF was well-maintained throughout the infusion of these doses of noradrenaline. In control studies, close-arterial infusion of saline at $10 \mu\text{l min}^{-1}$ over similar periods of time did not result in significant changes in LDF ($n = 4$).

In contrast to local administration, intravenous administration of NPY ($0.2 \text{ nmol kg}^{-1} \text{ min}^{-1}$), in a dose significantly elevating BP (see below), did not significantly reduce LDF ($5.5 \pm 3.2\%$ of control, $n = 4$). In other studies, simultaneous intra-arterial administration of near-threshold doses of NPY ($0.05 \text{ nmol kg}^{-1} \text{ min}^{-1}$) and noradrenaline ($10 \text{ nmol kg}^{-1} \text{ min}^{-1}$) produced no greater reduction in mean LDF than with each agent alone ($n = 3$).

Effects on systemic arterial blood pressure

Infusion of NPY (0.1 – $0.2 \text{ nmol kg}^{-1} \text{ min}^{-1}$) via the gastric intra-arterial or intravenous routes resulted in small, dose-dependent increases in mean BP (Figure 2). At each dose examined, the increases in BP were significantly ($P < 0.05$) greater when NPY was infused intravenously than when given by the intra-arterial route.

Noradrenaline was less active than NPY in producing threshold increases in BP, when infused either by the gastric intra-arterial or intravenous route (Figure 2). As with NPY,

Figure 1 Effects of close-arterial infusion of neuropeptide Y (●, 0.05 – $0.8 \text{ nmol kg}^{-1} \text{ min}^{-1}$) or noradrenaline (○, 30 – $90 \text{ nmol kg}^{-1} \text{ min}^{-1}$) on gastric mucosal blood flow in the anaesthetized rat, as determined by laser Doppler flowmetry. Results are expressed as mean % reduction from control of (*n*) values, where vertical bars represent s.e.mean. All groups, except the lowest dose of noradrenaline, were significantly different ($P < 0.05$) from control.

Figure 2 Effect of intravenous (●) or close-arterial (○) infusion of (a) neuropeptide Y ($0.1\text{--}0.4\text{ nmol kg}^{-1}\text{ min}^{-1}$) or (b) noradrenaline ($10\text{--}90\text{ nmol kg}^{-1}\text{ min}^{-1}$) on mean systemic arterial blood pressure (BP) in the anaesthetized rat. Results, expressed as BP (mmHg), are shown as the mean of (*n*) values, where vertical bars represent s.e.mean. All groups, except the lowest intra-arterial dose of NPY or noradrenaline, were significantly different ($P < 0.05$) from control.

noradrenaline was more active ($P < 0.05$) when infused intravenously and significant changes in BP were evident only when noradrenaline was infused intra-arterially in a dose greater than $30\text{ nmol kg}^{-1}\text{ min}^{-1}$. The observed maximal increase in BP in response to intra-arterial infusion of NPY ($0.4\text{ nmol kg}^{-1}\text{ min}^{-1}$) was $15 \pm 3\text{ mmHg}$, whereas intra-arterial infusion of noradrenaline ($90\text{ nmol kg}^{-1}\text{ min}^{-1}$) resulted in an increase in BP of $61 \pm 4\text{ mmHg}$ ($n = 4$).

Effects of pancreatic polypeptide and peptide YY on laser Doppler flow

The effects of peptides which are structurally similar to NPY were also examined following close-arterial administration. PP infusion (0.1 , 0.2 and $0.4\text{ nmol kg}^{-1}\text{ min}^{-1}$) resulted in small decreases in LDF of $10 \pm 6\%$ ($P > 0.05$), $19 \pm 5\%$ ($P < 0.05$), and $13 \pm 8\%$ ($P > 0.05$) of control, respectively ($n = 3$ for each), which were significantly smaller than those with equivalent doses of NPY. Close-arterial infusion of PYY ($0.1\text{--}0.4\text{ nmol kg}^{-1}\text{ min}^{-1}$) reduced LDF to a comparable maximal level as NPY, although the dose-response relationship was less consistent. Thus, the changes in LDF with NPY (0.1 , 0.2 and $0.4\text{ nmol kg}^{-1}\text{ min}^{-1}$) were $41 \pm 2\%$ ($P < 0.05$), $40 \pm 6\%$ ($P < 0.05$) and $28 \pm 13\%$ ($P < 0.05$) of control, respectively ($n = 3$ for each).

Gastric damage by neuropeptide Y and noradrenaline

Local intra-arterial infusion of NPY (0.1 and $0.2\text{ nmol kg}^{-1}\text{ min}^{-1}$) or noradrenaline (45 and $60\text{ nmol kg}^{-1}\text{ min}^{-1}$) resulted in significant dose-related increases in the area of mucosal damage when compared to control animals (Figure 3). The damage was observed as areas of exfoliation of surface tissue and distinct regions of haemorrhagic necrosis. Mucosal damage in response to NPY ($0.2\text{ nmol kg}^{-1}\text{ min}^{-1}$) was not significantly different from that produced by noradrenaline ($45\text{ nmol kg}^{-1}\text{ min}^{-1}$).

On histological examination, the mucosal injury induced by NPY ($0.2\text{ nmol kg}^{-1}\text{ min}^{-1}$) involved loss of surface epithelial cells with deep glandular damage involving up to 50% of the length of the section, with areas of vasocongestion and haemorrhage, as shown in Figure 4. The mucosal damage induced by noradrenaline ($45\text{ nmol kg}^{-1}\text{ min}^{-1}$) likewise involved distinct epithelial and glandular disruption (Figure 4).

Effect of α_1 -adrenoceptor antagonist, prazosin

The effects of α_1 -adrenoceptor blockade with prazosin (0.1 mg kg^{-1}) on LDF responses to NPY and noradrenaline

Figure 3 Induction of gastric mucosal damage following close-arterial infusion of neuropeptide Y (0.1 and $0.2\text{ nmol kg}^{-1}\text{ min}^{-1}$) or noradrenaline (45 and $60\text{ nmol kg}^{-1}\text{ min}^{-1}$) for 10 min in the anaesthetized rat. Results, expressed as macroscopic damage, % of total mucosal area, are the mean of (*n*) values, where vertical bars represent s.e.mean and significant difference from control is shown as * $P < 0.05$, ** $P < 0.01$.

were investigated. In these studies, prazosin was evaluated against doses of noradrenaline ($60\text{ nmol kg}^{-1}\text{ min}^{-1}$) and NPY ($0.2\text{ nmol kg}^{-1}\text{ min}^{-1}$) which produced statistically similar changes in LDF (Figure 1). Whereas prazosin did not significantly alter the effect of NPY infusion on LDF, the reduction in LDF observed after intra-arterial infusion of noradrenaline was eliminated, as shown in Figure 5. Prazosin administration alone did not significantly influence LDF ($n = 3$).

The effects of prazosin on the extent of mucosal haemorrhagic damage induced by intra-arterial infusion of NPY ($0.2\text{ nmol kg}^{-1}\text{ min}^{-1}$) or noradrenaline ($60\text{ nmol kg}^{-1}\text{ min}^{-1}$) were also investigated. Prazosin substantially ($P < 0.05$) reduced the extent of haemorrhagic damage induced by noradrenaline ($69 \pm 5\%$ inhibition), yet did not significantly reduce the area of mucosal damage induced by NPY (Figure 6).

Discussion

The results of the present study indicate that NPY is a potent vasoconstrictor in the gastric mucosal microcirculation, as assessed by laser Doppler flowmetry. This finding extends previous studies demonstrating vasoconstrictor actions of NPY on splenic, renal, testicular, skeletal muscle, and large or small intestinal vascular beds (Lundberg & Tatemoto, 1982; Lundberg *et al.*, 1982; Hellstrom, 1987; Westfall *et al.*, 1987; MacLean & Hiley, 1990). The present study also demonstrates that local intra-arterial infusion of noradrenaline will reduce gastric mucosal blood flow in the rat. The vasoconstrictor activity of noradrenaline in the rat gastric microcirculation has been previously demonstrated by *in vivo* microscopy techniques (Guth & Smith, 1975; Oren-Wolman & Guth, 1984) following local application to the submucosal vessels. While that study demonstrated the phenomenon of vascular escape from the vasoconstriction, such an effect was not evident under the conditions of the present study, which may reflect the different methodologies used to measure the microvascular responses, the region of measurement, or the route of administration of noradrenaline.

NPY appeared to be more active in producing threshold vasoconstrictor responses in the gastric microcirculation than

Figure 4 Histological appearance of the corpus region of the rat gastric mucosa following local intra-arterial infusion of (a) neuro-peptide Y ($0.2 \text{ nmol kg}^{-1} \text{ min}^{-1}$) or (b) noradrenaline ($45 \text{ nmol kg}^{-1} \text{ min}^{-1}$) for 10 min. Sections ($4 \mu\text{m}$) were stained with haematoxylin and eosin. The upper arrows denote epithelial disruption while the lower arrows denote areas of deeper damage and vasocongestion. Marker bar represents $40 \mu\text{m}$.

noradrenaline, although noradrenaline did produce a significantly greater maximal reduction in LDF. Similarly, Lundberg & Tatemoto (1982) have demonstrated that NPY was a more potent vasoconstrictor than noradrenaline in the cat submandibular gland. These authors have also demonstrated that the structurally-related peptides PP and PYY were effective vasoconstrictors in that vascular bed. In that study, the relative molar potencies were found to be $\text{PYY} > \text{NPY} > \text{PP}$ (Lundberg & Tatemoto, 1982). In other studies on the rabbit isolated femoral artery, the vasoconstrictor potencies of NPY and PYY have been found to be approximately equivalent, while PP appeared to be less potent (Wahlstedt *et al.*, 1985). In the present study, NPY and PYY produced similar maximal reductions in gastric mucosal blood flow although the responses to PYY were less consistent, while PP induced minimal changes following close-arterial infusion. In doses reducing LDF, local infusion of NPY induced small changes in systemic arterial BP. Furthermore, intravenous infusion of NPY induced significantly greater increases in BP than following close-arterial infusion, yet did not significantly alter mucosal blood flow. Likewise, in recent studies in the pithed rat, intravenous infusion of four fold greater doses of NPY which elevated BP and induced vasoconstriction in the mesenteric bed, did not increase vascular resistance in the stomach,

as estimated by radiolabelled microspheres (MacLean & Hiley, 1990). The changes in gastric mucosal blood flow observed during local intra-arterial infusion of NPY are thus unlikely to be due primarily to alterations in systemic arterial BP.

Close-arterial infusion of NPY or noradrenaline both resulted in dose-dependent increases in the area of haemorrhagic damage to the oxyntic mucosa. Previous studies have shown that reduction in microvascular perfusion either by direct vasoconstriction or by removal of endogenous vasodilator tone can induce or enhance the development of mucosal damage, erosion or ulceration (Whittle, 1989). Thus, intravenous infusion of noradrenaline in the rat or intra-arterial infusion of vasopressin in the dog, potentiated mucosal damage induced by topical application of bile salts (Whittle, 1983; Ritchie, 1975). The possible role for endogenous NPY in the pathogenesis of mucosal damage is as yet unknown. However, Morris *et al.* (1987) and Lundberg *et al.* (1987) have shown that plasma NPY levels are increased after haemorrhage in both rats and pigs. Since haemorrhagic shock is often followed by gastric damage and bleeding (Guth & Leung, 1987), it could be speculated that NPY release plays some role in this type of gastric injury.

Prazosin treatment did not significantly reduce the effects of

Figure 5 Effect of the α_1 -adrenoceptor antagonist, prazosin (0.1 mg kg^{-1} , i.v., hatched columns) on the fall in gastric mucosal blood flow induced by close-arterial infusion of neuropeptide Y or noradrenaline (0.2 and $60 \text{ nmol kg}^{-1} \text{ min}^{-1}$ respectively), as determined by laser Doppler flowmetry; control, open columns. Results are shown as mean % reduction from control of (n) values, where vertical bars represent s.e.mean, and significant difference from the corresponding control groups is shown as *** $P < 0.01$.

NPY on either gastric mucosal blood flow or the induction of mucosal damage, in doses that substantially attenuated the responses to noradrenaline. The inability of α_1 -adrenoceptor antagonism to overcome the effect of NPY in the gastric circulation is consistent with other findings in the mesenteric circulation of the rat (Westfall *et al.*, 1987) and circular muscle of guinea-pig intestine (Holzer *et al.*, 1987). While we have not investigated the effects of α_2 -adrenoceptor antagonism on NPY-induced reduction in gastric mucosal blood flow, others have demonstrated that activation of α_2 - or β -adrenoceptors does not seem to be a prerequisite for NPY vasoconstrictor activity (Aubert *et al.*, 1988; Westfall *et al.*, 1987). The present data demonstrate that NPY and noradrenaline potently affect the gastric microcirculation, probably by an action directly on gastric vascular smooth muscle, through activation of different receptor types.

Previous studies have demonstrated the close anatomical relationship between NPY and noradrenergic neurones in the rat stomach (Wang *et al.*, 1987). After treatment with 6-hydroxydopamine to deplete noradrenergic nerves, NPY-containing fibres around blood vessels also disappeared. Furthermore, it has been demonstrated that in some preparations, NPY may also modulate the actions of noradrenaline by acting prejunctionally to suppress noradrenaline release or postjunctionally to potentiate the noradrenaline response (Wahlstedt *et al.*, 1985; Hakanson *et al.*, 1988; Aubert *et al.*, 1988). However, in our preliminary studies, we have not been able to confirm a significant postjunctional interaction between exogenously administered threshold doses of NPY and noradrenaline in the gastric microcirculation, at least under the present experimental conditions. Much of the

Figure 6 Effect of the α_1 -adrenoceptor antagonist, prazosin (0.1 mg kg^{-1} i.v., hatched columns) on the gastric mucosal damage induced by a 10 min close-arterial infusion of neuropeptide Y or noradrenaline (0.2 and $60 \text{ nmol kg}^{-1} \text{ min}^{-1}$ respectively); control, open columns. Results, expressed as macroscopic damage, % of the total mucosal area, are shown as mean of (n) values, where vertical bars represent s.e.mean and significant difference from corresponding control is given as * $P < 0.05$.

data in favour of such interactions between NPY and noradrenaline in different vascular beds has been obtained from *in vitro* studies, although facilitation of the systemic pressor actions of α -adrenoceptor agonists *in vivo* by NPY has been observed in pithed and unanaesthetized rats (Dahlof *et al.*, 1985; Aubert *et al.*, 1988). Such NPY-noradrenaline interactions have not been observed in all vascular tissue studied; NPY did not potentiate the vasoconstrictor effects of noradrenaline in segments of gastro-epiploic vein in contrast to its actions on gastro-epiploic artery (Wahlstedt *et al.*, 1985). Moreover, suppression of noradrenaline release by NPY in rabbit gastro-epiploic artery could not be demonstrated (Ekblad *et al.*, 1984). However, we cannot yet exclude the possibility that endogenous NPY does interact with noradrenaline under physiological conditions in the rat gastric microvasculature.

It is of interest that the cardiovascular profile of NPY shares some similarities to that of the endothelium-derived vasoconstrictor peptide, endothelin-1 (see MacLean & Hiley, 1990), and previous studies have shown that endothelin-1 can also induce damage to the rat gastric mucosa following local intra-arterial infusion (Whittle & Esplugues, 1988). The interaction of NPY with locally released endothelin-1 and other vasoactive mediators in the gastric microcirculation thus warrants investigation. The present findings that NPY induces vasoconstriction and damage in the gastric mucosa, therefore suggest that endogenous NPY, like noradrenaline may have a modulatory role in the regulation of gastric mucosal blood flow and mucosal integrity under physiological and pathological conditions.

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