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Regional heterogeneity in the contractile and potentiating effects of neuropeptide Y in rat isolated coronary arteries: modulatory action of the endothelium

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1 Neuropeptide Y (NPY) induced a concentration-dependent contraction of isolated rings of proximal epicardial (PC) and distal intramural (DC) coronary arteries of the rat, with an EC_{50} of ca. 1×10^{-7} M. The NPY-induced contraction at 3×10^{-7} M was significantly smaller in PC than DC arteries: 34% vs. 55% of the 125 mM K^+-induced response, respectively.

2 NPY (2×10^{-8} M) increased the sensitivity to noradrenaline (NA) and 5-hydroxytryptamine (5-HT) more in PC (4.2 and 2.8 fold, respectively) than in DC arteries (2.2 and 1.4 fold, respectively). The maximal contractile response to NA and 5-HT was increased more in DC (43% and 29%, respectively) than in PC arteries (20% and 12%, respectively).

3 Removal of the endothelium increased the sensitivity and maximal response to NPY as well as the spontaneous myogenic tone in PC but not in DC arteries. NPY had no relaxing effect on PC and DC arteries submaximally contracted with 10^{-6} M prostaglandin $F_{2\alpha}$, suggesting that spontaneous rather than stimulated release of endothelium-derived relaxing factor (EDRF) depresses the contractile action of NPY in PC arteries.

4 The results indicate a heterogeneity in the contractile and potentiating action of NPY in rat coronary arteries depending on size or location in the coronary circulation.

Introduction

Neuropeptide Y (NPY) is one of the most abundant peptides in the cardiac nerves (Gu *et al.*, 1983; 1984) and it is contained and released from sympathetic nerves together with noradrenaline (NA) (Lundberg *et al.*, 1983; 1984). NPY is a potent vasoconstrictor both *in vivo* and *in vitro* in the coronary vascular bed of several species (Aizawa *et al.*, 1985; Rudehill *et al.*, 1986; Franco-Cereceda & Lundberg, 1987; Han & Abel, 1987; Tseng *et al.*, 1988; Franco-Cereceda, 1989; Maturi *et al.*, 1989), and it potentiates catecholamine- and histamine-induced coronary vasoconstriction (Han & Abel, 1987; Macho *et al.*, 1989).

Although there is little information about the actions of NPY on resistance vessels (Owen & Taphorn, 1988; Andriantsitohaina & Stoclet, 1988), a correlation between the vascular effects of NPY and the diameter of the vessels has been proposed: it induces a stronger contraction in small arteries whereas the potentiation of the responses induced by other vasoconstrictors seems to be restricted to larger arteries where NPY has little or no direct contractile effect (Pernow, 1988; Franco-Cereceda, 1989).

There is some controversy about the role of endothelium in the vascular actions of NPY. NPY-induced contractions in human skeletal and pig splenic arteries seem to be endothelium-independent (Pernow, 1988), as is the potentiation of noradrenaline (NA)-induced contractions in rabbit ear artery (Budai *et al.*, 1989). However, Hieble *et al.* (1989) found that NPY had an endothelium-dependent potentiating effect in the same vascular bed.

The aims of the present study: (i) to determine whether or not NPY possesses a direct contractile effect on rat isolated proximal epicardial, and distal intramyocardial, coronary arteries *in vitro*; (ii) to examine how the NPY-induced response in these arteries is modulated by the endothelium; and (iii) to examine the ability of this peptide to enhance NA- and 5-hydroxytryptamine (5-HT)-induced contractions in the coronary arteries.

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Methods

Dissection and mounting

Segments of the proximal (PC) and distal (DC) part of the left coronary artery in hearts from 3 month old male Wistar were isolated as previously described (Nyborg, 1990) and mounted as ring preparations on two 40 μm diameter stainless steel wires on a double myograph (Mulvany & Nyborg, 1980) which allows direct determination of wall tension while the internal circumference of the vessels is controlled.

After equilibration in oxygenated (5% CO_2 in O_2) physiological saline solution (PSS) for 30 min, pH 7.4, 37°C, the internal circumference, L_0, of the vessels were set to 0.9 times the circumference they would have if relaxed and subjected to transmural pressure of 100 mmHg (Nyborg *et al.*, 1987). The effective normalized lumen diameter, $l_0 = L_0 \pi^{-1}$, ranged between 204 and 300 μm for the DC arteries and between 350 and 525 μm for the PC arteries.

The vessels were subsequently stimulated repetitively with K-PSS until reproducible responses were recorded.

Pharmacology

The direct contractile effect of NPY on the coronary arteries was tested in cumulative concentration-response experiments. The maximal obtainable concentration of NPY was 3×10^{-7} M. The arteries could be used only once because of development of tachyphylaxis to NPY.

The potentiating effect of NPY was studied on cumulative NA and 5-HT concentration-response curves. The vessels were washed in drug-free PSS for 30 min and NPY (2×10^{-8} M) was added. When the response to the peptide had stabilized (5–8 min), cumulative additions of NA or 5-HT were repeated. NPY (2×10^{-8} M) induced an initial contraction of the arteries that was less than 10–15% of that induced by K-PSS. NA-induced contractions were elicited in the presence of 10^{-5} M propranolol.

The role of the endothelium in the contractile effect of NPY was studied on consecutive arterial segments. One was taken as a control and the other had its endothelium removed by guiding a horse hair (PC arteries) or a 40 μm steel stainless

wire (DC arteries) through the vessel lumen and gently pushing the hair/wire back and forth. The function of the endothelium was tested by measuring the relaxation induced by 10^{-5} M acetylcholine in vessels contracted with 10^{-5} M prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$).

Solutions and drugs

The vessels were, unless otherwise stated, dissected and kept relaxed in PSS with the following composition (mM): NaCl 119, NaH_2CO_3 25, KCl 4.7, $CaCl_2$ 1.5, KH_2PO_4 1.18, $MgSO_4$ 1.17, EDTA 0.026 and glucose 11. K-PSS was similar to PSS except that NaCl was exchanged with KCl on an equimolar basis.

Drugs used were neuropeptide Y (NPY) (Peptides, U.K.), (−)-noradrenaline HCl (Sigma), 5-hydroxytryptamine creatinine sulphate complex (Sigma), propranolol (Sigma) and prostaglandin $F_{2\alpha}$ (Dinoprost, UpJohn). Drugs were dissolved in distilled water for stock solutions and they were added in volumes of not more than 0.3% to give the required concentrations.

Statistics

Vessel responses are expressed as either active tension, Nm^{-1}, calculated as increase in vessel wall force divided by twice the vessel segment length, or as percentage of the response elicited by K-PSS. In the potentiation experiments, NA- and 5-HT-induced responses are given as the percentage of the maximal response of the control concentration-response curve. The initial NPY-induced contractions were subtracted from those induced by NA and 5-HT. Sensitivities to the agonist are expressed as pD_2-values. Differences between mean values were analysed by Student's t test for paired and unpaired values where appropriate. A probability less than 0.05 was considered significant for both tests.

Results

Contractile effect of neuropeptide

NPY induced concentration-dependent contractions of both PC and DC arteries (Figure 1) with a threshold concentration between 10^{-10} M and 10^{-9} M for both types of arteries. The contractions were slow in onset and long-lasting compared to those induced by NA, 5-HT and K-PSS. The responses to NPY (3×10^{-7} M) were $0.95 \pm 0.20\,Nm^{-1}$ ($n = 6$) and $0.90 \pm 0.27\,Nm^{-1}$ ($n = 7$) in PC and DC arteries, respectively. The maximal contractions elicited by 5-HT (3×10^{-5} M) and NA (10^{-4} M) in PC arteries were $3.12 \pm 0.30\,Nm^{-1}$ ($n = 9$) and $0.68 \pm 0.10\,Nm^{-1}$ ($n = 7$), respectively (Figure 1a). The maximal contractions evoked by 5-HT and NA were $1.02 \pm 0.16\,Nm^{-1}$ ($n = 8$) and $0.65 \pm 0.19\,Nm^{-1}$ ($n = 7$), respectively in DC arteries (Figure 1b). NPY was the most potent of the 3 constrictor agents in boths kind of vessel. The order of potency: NPY > 5-HT > NA was similar in both PC and DC arteries, the pD_2-values being 6.94 ± 0.25 ($n = 6$), 6.06 ± 0.07 ($n = 9$) and 4.89 ± 0.13 ($n = 7$), respectively in PC arteries and 6.93 ± 0.27 ($n = 7$), 5.54 ± 0.07 ($n = 8$) and 4.91 ± 0.14 ($n = 7$), respectively, in the DC arteries. There was no difference in the sensitivities of PC and DC arteries except to 5-HT ($P < 0.01$).

Effect of neuropeptide Y on noradrenaline- and 5-hydroxytryptamine-induced contractile responses

NPY (2×10^{-8} M) caused a significant leftward shift ($\Delta pD_2 = 0.62 \pm 0.16$, $n = 7$, $P < 0.01$) of the NA concentration-response curve in PC arteries (Figure 2a). The maximal response increased by $20 \pm 8\%$ ($n = 7$, $P < 0.05$). NPY also caused a leftward shift ($\Delta pD_2 = 0.34 \pm 0.10$, $n = 7$, $P < 0.02$) of the NA concentration-response curve in DC arteries (Figure 2b); however, the maximal response was increased by $43 \pm 16\%$ ($n = 7$, $P < 0.05$).

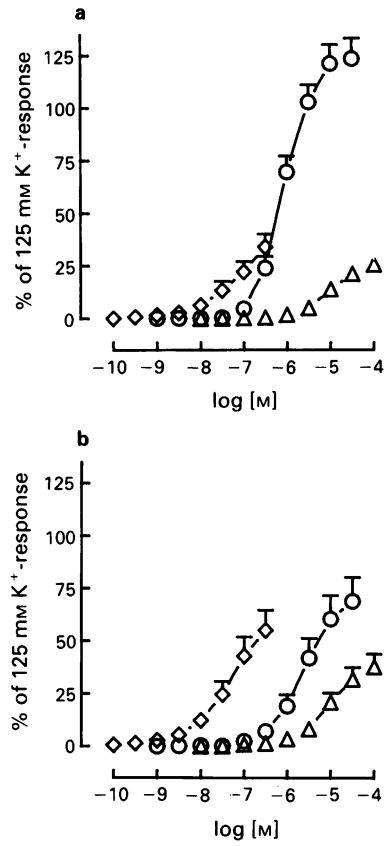

Figure 1 Contractile effects of neuropeptide Y (◇), 5-hydroxytryptamine (○) and noradrenaline (△) in rat PC (a) and DC (b) arteries. Responses are expressed as percentage of the 125 mM K^+-induced response in each vessel. Points represent mean values of 6–9 vessels. Vertical bars indicate s.e.mean where this value exceeds the size of the symbol.

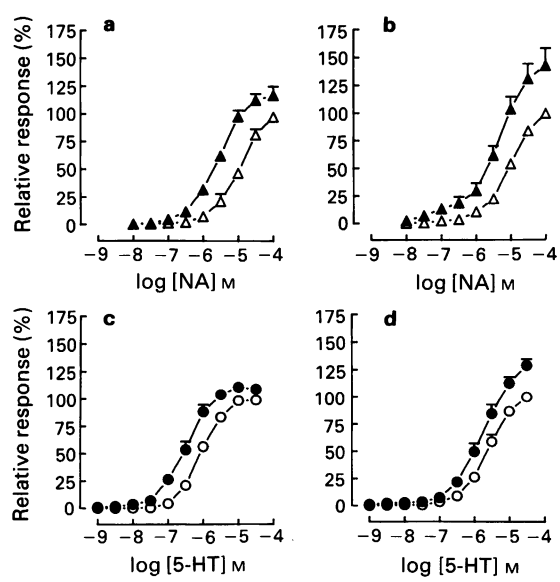

Figure 2 Effects of pretreatment with neuropeptide Y (NPY, ▲) on the noradrenaline (NA, a,b) and 5-hydroxytryptamine (5-HT, c,d) concentration-response curve in rat PC (a,c) and DC (b,d) arteries. NPY (2×10^{-8} M) was added 5–8 min before and was present throughout the construction of the concentration-response curves. Points show mean values from 7–9 observations. Vertical bars indicate s.e.mean where this value exceeds the size of the symbol.

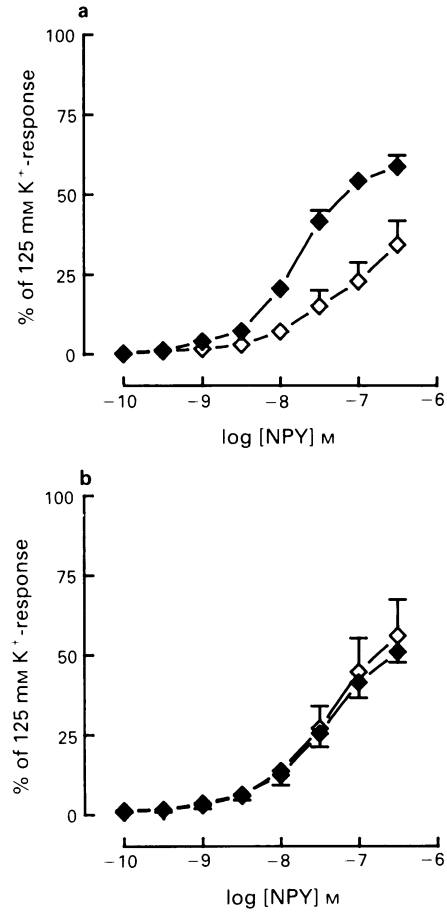

Figure 3 Concentration-response curves showing the contractile effects on neuropeptide Y (NPY) in rat PC (a) and DC (b) arteries with endothelium (◇) and after removal of the endothelium (◆). The contractile effect is expressed as a percentage of that induced by 125 mM K^+.

NPY (2×10^{-8} M) also had a potentiating effect on the 5-HT concentration-response curve in PC arteries ($\Delta pD_2 = 0.44 \pm 0.05$, $n = 9$, $P < 0.001$) (Figure 2c). The maximal response was slightly but significantly increased by $12 \pm 3\%$ ($n = 9$) ($P < 0.01$). In contrast, NPY had no potentiating effect on the 5-HT concentration-response curve in DC arteries ($\Delta pD_2 = 0.16 \pm 0.07$, $n = 8$) (Figure 2d), although the maximal response was increased by $29 \pm 6\%$ ($n = 8$) ($P < 0.01$).

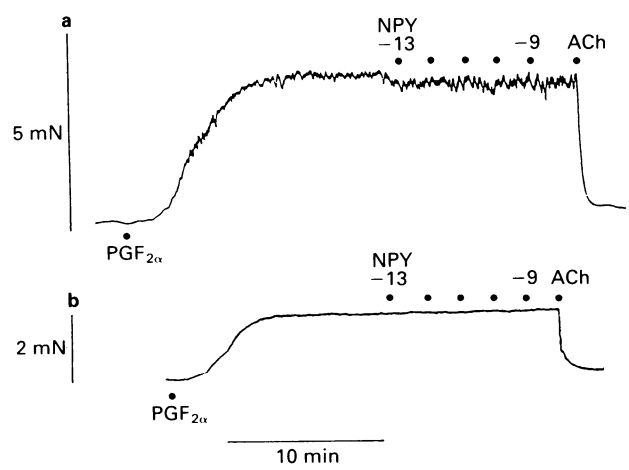

Figure 4 Tracings showing the effect of neuropeptide Y (NPY, 10^{13}–10^{-9} M) on a 390 μm PC (a) and a 282 μm DC (b) artery, submaximally contracted with 10^{-6} M prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). Presence of endothelium is demonstrated by the relaxation induced by acetylcholine (ACh) 10^{-5} M. Vertical and horizontal scales show force (mN) and time, respectively.

Effects of neuropeptide Y on endothelium-denuded arteries

The sensitivity to NPY was significantly greater in PC arteries without than with endothelium (Figure 3a), the pD_2 value being 6.93 ± 0.30 ($n = 5$) and 7.70 ± 0.14 ($n = 5$) ($P < 0.05$) in endothelium-intact and denuded arteries, respectively. The response to NPY (3×10^{-7} M) was also significantly greater in the endothelium-denuded arteries than in the control arteries: $59 \pm 4\%$ ($n = 5$) vs. $34 \pm 7\%$ ($n = 5$) ($P < 0.02$) of the K-PSS-induced response. Removal of the endothelium in DC arteries did not change the pD_2-value or the maximal response to NPY (3×10^{-7} M) (Figure 3b).

Relaxation of PC and DC arteries with 10^{-5} M acetylcholine was $85 \pm 5\%$ ($n = 5$) and $97 \pm 2\%$ ($n = 6$) in endothelium-intact arteries and $8 \pm 4\%$ and $7 \pm 3\%$ in endothelium-denuded arteries, respectively. The K-PSS-induced responses were not significantly different, $1.67 \pm 0.24\,Nm^{-1}$ ($n = 6$) and $1.70 \pm 0.49\,Nm^{-1}$ ($n = 6$), in DC arteries with and without endothelium, respectively. However, there was a decrease in the responses to K-PSS in PC arteries from $2.88 \pm 0.35\,Nm^{-1}$ ($n = 5$) before to $1.91 \pm 0.22\,Nm^{-1}$ ($n = 5$, $P < 0.01$) after removal of the endothelium. The lower response to K-PSS was compensated by a greater spontaneous tone, which increased $0.57 \pm 0.15\,Nm^{-1}$ ($n = 5$) after the endothelium was removed, giving a total active tension (spontaneous tone plus K-PSS-induced) of $2.48 \pm 0.21\,Nm^{-1}$ ($n = 5$) after removal of the endothelium. The increase in spontaneous tone in the distal arteries following removal of endothelium was not significant: $0.17 \pm 0.10\,Nm^{-1}$ ($n = 6$).

Cumulative addition of NPY (10^{-13} M–10^{-9} M) did not induce relaxation in any of 6 PC and DC arteries with intact endothelium submaximally contracted with 10^{-6} M $PGF_{2\alpha}$ (Figure 4).

Discussion

NPY induced a potent contraction both in large epicardial and small intramural arteries of the rat left coronary vascular bed. These findings are consistent with previous results obtained in rabbit (Han & Abel, 1987) and human (Franco-Cereceda & Lundberg, 1987; Tseng *et al.*, 1989) isolated epicardial coronary arteries, as well as with *in vivo* studies in the dog (Allen *et al.*, 1986; Macho *et al.*, 1989; Martin & Patterson, 1989; Maturi *et al.*, 1989) and pig (Rudehill *et al.*, 1986).

The contraction induced by the highest obtainable concentration of NPY (3×10^{-7} M) was similar in PC and DC arteries. However, NPY induced a greater relative contraction at all concentrations in DC arteries than PC arteries indicating that NPY would increase the vascular resistance more in DC than in PC arteries *in vivo*. This is in agreement with perfusion studies in the dog coronary (Macho *et al.*, 1989; Maturi *et al.*, 1989) and rabbit renal vasculature (Owen & Taphorn, 1988). The direct constrictor effect of NPY in PC arteries contrasts with findings in human epicardial arteries (Franco-Cereceda, 1989) where NPY has no direct contractile effect. The origin of this discrepancy is unknown but may be attributed to differences in basic properties of the arteries, NPY receptor density, or level of spontaneous EDRF release.

NPY was about 50–100 fold more potent than NA and 5-HT; NPY also induced contractions that were sustained following washout with drug-free PSS in contrast to those induced by 5-HT or NA. These results are in agreement with those reported for human (Franco-Cereceda & Lundberg, 1987) and dog (Macho *et al.*, 1989) coronary arteries and also

for other vascular preparations, such as cat cerebral (Edvinsson *et al.*, 1984) and human skeletal muscle (Pernow, 1988) arteries. NPY-induced contractions were of the same magnitude as those evoked by NA or 5-HT in DC arteries but 5-HT evoked much larger responses in rat PC than in DC arteries as previously demonstrated (Nyborg & Mikkelsen, 1988).

NPY potentiates NA-induced smooth muscle contraction in several vascular beds (Edvinsson *et al.*, 1984; Wahlestedt *et al.*, 1985; Neild 1987; Owen & Taphorn, 1988; Pernow, 1988; Oshita *et al.*, 1989), including rabbit epicardial arteries (Han & Abel, 1987) and resistance arteries in the guinea-pig (Franco-Cereceda & Lundberg, 1985) and dog isolated hearts (Macho *et al.*, 1989). NPY has also been shown to potentiate NA-induced contractions of rat mesenteric resistance arteries (Andriantsitohaine & Stoclet, 1988), although NPY has no direct contractile effect in these vessels. Despite the latter data, there is a general tendency for the potentiation of NA-induced vasoconstriction by NPY to be more pronounced in larger arteries, where it has a weak direct contractile action (Pernow *et al.*, 1987; Pernow, 1988) than in smaller arteries (Owen & Taphorn, 1988; Macho *et al.*, 1989; Maturi *et al.*, 1989). Our results showing a 2 fold greater increase in NA sensitivity of PC and DC arteries are thus consistent with this view; however, the maximal response was increased more in the small than in the large arteries. It must be noted that β-adrenoceptor function dominates in rat small flow-regulating coronary arteries under normal physiological conditions (Nyborg & Mikkelsen, 1985; Nyborg, 1990). The potentiating effect of NPY was not restricted to NA, but occurred also with 5-HT. This supports the idea that NPY sensitizes vascular smooth muscle in a non-specific way (Edvinsson *et al.*, 1984; Wahlestedt *et al.*, 1985; Neild, 1987; Han & Abel, 1987; Andriantsitohaina & Stoclet, 1988; Oshita *et al.*, 1989). The sensitization may be mediated through a partial smooth muscle cell membrane depolarization and an increased calcium entry through voltage-dependent calcium channels (Neild, 1987; Andriantsitohaina & Stoclet, 1988).

Studies concerning the specific role of the endothelium in mediating the vascular effects of NPY seem to be contradictory; both endothelium-dependence (Daly & Hieble, 1987; Hieble *et al.*, 1989) and endothelium-independence (Andriantsitohaina & Stoclet, 1988; Budai *et al.*, 1989) have been described. The direct contractile effect of NPY on human skeletal and pig splenic arteries, both regarded as small arteries, occurs via an endothelium-independent mechanism (Pernow & Lundberg, 1988; Pernow, 1989), but coronary constriction may involve formation of a cyclo-oxygenase product (Martin & Patterson, 1989). NPY seems also capable of releasing EDRF in human coronary arteries (Tseng *et al.*, 1988) and perhaps also in the rat kidney vascular bed (Carter & Halliday, 1989). Our results exclude a major involvement of endothelium-derived substances in the overall vascular response to NPY in the distal part of the rat coronary circulation. The increased responses and sensitivity of endothelium-denuded PC arteries to NPY would indicate a NPY-induced EDRF release in these vessels. However, NPY in low concentrations did not relax endothelium-intact PC arteries suggesting that EDRF release is unlikely to have occurred. Furthermore, PC arteries are characterized by a high basal spontaneous release of EDRF which suppresses spontaneous myogenic tone (Nyborg, 1990; present study). The potentiation of NPY-induced contraction after endothelium removal is probably explained by suppression of basal release of EDRF rather than by stimulation of EDRF release.

In summary, this work shows that NPY can regulate rat coronary vascular tone directly and indirectly. NPY caused a greater contraction in the smaller DC than larger PC arteries whereas NPY increased the sensitivity to NA and 5-HT more in PC than DC arteries. The contractile responses to NPY were differentially affected by the presence of vascular endothelium: it had no effect on NPY responses in DC arteries but depressed contractions to NPY in PC arteries through basal release of EDRF. The present results therefore confirm that the coronary vascular bed is highly heterogeneous in its response to vasoactive substances (Miwa & Toda, 1984; Nyborg & Mikkelsen, 1988; Maturi *et al.*, 1989; Nyborg, 1990).

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