

Modulation by neuropeptide Y of parasympathetic nerve-evoked nasal vasodilatation via Y₂ prejunctional receptor

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1 In pentobarbitone anaesthetized dogs, preganglionic stimulation of the superior cervical sympathetic nerve (15 V, 1 ms, 10 Hz) induced marked reduction of nasal arterial blood flow, whereas parasympathetic nerve stimulation (5 V, 1 ms, 10–30 Hz) evoked frequency-dependent vasodilatation.

2 Sympathetic nerve stimulation for 3 min at 10 Hz evoked significant ($P < 0.05$) and prolonged attenuation of the vasodilator response to subsequent parasympathetic stimulation. Pretreatment with phentolamine ($0.5 \text{ mg kg}^{-1} \text{ h}^{-1}$), propranolol (1 mg kg^{-1}) and atropine (0.5 mg kg^{-1}) reduced the vasoconstrictor effect of sympathetic stimulation by $35 \pm 4\%$ whereas the parasympathetic nerve-evoked vasodilatation was not significantly modified. Atropine-resistant parasympathetic vasodilatation remained significantly attenuated for more than 30 min after non-adrenergic sympathetic nerve-evoked vasoconstriction.

3 Vasodilator effects of exogenous vasoactive intestinal polypeptide and peptide histidine isoleucine and vasoconstrictor effects of exogenous neuropeptide Y (NPY) and the NPY analogue [Leu³¹, Pro³⁴] NPY (Y₁-receptor agonist, 8 nmol kg^{-1}), were not altered by adrenoceptor antagonists and atropine whereas the effects of exogenous noradrenaline and acetylcholine were virtually abolished. Attenuation of parasympathetic-evoked vasodilatation could be mimicked by exogenous NPY (8 nmol kg^{-1}) and the NPY analogue, N-acetyl [Leu²⁸, Leu³¹] NPY 24–36 (Y₂-receptor agonist, 20 nmol kg^{-1}) but not by exogenous Y₁-receptor agonist. The Y₂-receptor agonist did not show significant vasoconstrictor action.

4 It is concluded that sympathetic nerve stimulation attenuates parasympathetic vasodilatation via NPY release acting on prejunctional Y₂ receptors.

Keywords: Blood flow; sympathetic; parasympathetic, non-adrenergic non-cholinergic; neuropeptide Y (NPY); Y₁ receptor agonist; Y₂ receptor agonist

Introduction

The nasal mucosa is densely innervated by efferent sympathetic and parasympathetic nerves involved in the regulation of local blood flow and mucus secretion (Eccles & Wilson, 1974). Stimulation of the nasal parasympathetic nerve, i.e. the vidian nerve, causes atropine-sensitive nasal secretion most likely mediated by acetylcholine (ACh, Eccles & Wilson, 1973) and vasodilatation (Tschalussow, 1913) via atropine-resistant mechanisms (Eccles & Wilson, 1973; Malm, 1973). Vasoactive intestinal polypeptide (VIP) is a potent vasodilator agent (Malm *et al.*, 1980) co-localized with ACh in postganglionic parasympathetic neurones supplying exocrine glands and blood vessels in the nasal mucosa (Uddman *et al.*, 1978). VIP is released during parasympathetic stimulation and could be the mediator of the non-cholinergic nasal vasodilatation observed upon stimulation of the vidian nerve in cats (Lundberg *et al.*, 1981). The peptide with N-terminal histidine (H) and C-terminal isoleucine (I) amide (PHI: Tatemoto, 1984) co-exists with VIP in nasal parasympathetic neurones (Lundberg *et al.*, 1984) and have vasodilator action on airway vasculature (Widdicombe, 1990). Both VIP and PHI may be considered as candidates for the atropine-resistant parasympathetic vasodilatation elicited by nerve stimulation (Lundberg *et al.*, 1984).

Electrical stimulation of the preganglionic fibres to the superior cervical sympathetic ganglion reduces nasal mucosa blood flow (Änggård & Edwall, 1974; Eccles, 1978). Noradrenaline (NA) is considered to be the classical mediator of nasal vasoconstrictor effects in postganglionic perivascular sympathetic nerves (Änggård & Densert 1974; Lacroix, 1989). Recent immunohistochemical studies as well

as functional observations have suggested that both adrenergic and non-adrenergic mechanisms may occur in the peripheral sympathetic control of several vascular beds (Lundberg *et al.*, 1989) including the nasal mucosa (Lacroix, 1989). One candidate for non-adrenergic effects is neuropeptide Y (NPY), a 36 amino acid peptide that is colocalized with noradrenaline (NA) in sympathetic postganglionic perivascular nerves in several organs including the nasal mucosa in various species (Lundberg *et al.*, 1982; Lacroix *et al.*, 1990). In the cardiovascular system, NPY induces vasoconstriction via postjunctional receptors (Potter, 1985). In addition, NPY inhibits its own release as well as other neurotransmitter release such as NA (Edvinsson, 1988) and ACh (Revington *et al.*, 1990; Warner & Levy, 1990) by acting on prejunctional receptors (see Lundberg *et al.*, 1990). NPY probably acts via at least two subtypes of receptors, Y₁ and Y₂, which show differences in sensitivity to various NPY analogues *in vitro* (Wahlestedt *et al.*, 1986; Fuhendorff *et al.*, 1990). Postjunctional NPY receptors have been called Y₁ receptors and prejunctional receptors have been called Y₂ receptors (Wahlestedt *et al.*, 1986; Lundberg *et al.*, 1988). By means of functional experiments *in vivo* combined with binding studies *in vitro*, NPY analogues have recently been developed. The Y₁-selective analogue [Leu³¹, Pro³⁴] NPY has the same vasopressor effect as NPY in rats and shares similar binding *in vitro* to various cell lines expressing only Y₁ receptor (Herzog *et al.*, 1992). In contrast, the recently developed Y₂-receptor agonist N-acetyl [Leu²⁸, Leu³¹] NPY 24–36, mimics the action of NPY in inhibiting cardiac vagal action (a Y₂-receptor-mediated interaction) but has no pressor effect (a Y₁-receptor action) (Potter *et al.*, 1994).

We have recently shown that sympathetic nerve stimulation as well as exogenous NPY, attenuates the vasodilator response to subsequent parasympathetic nerve stimulation in the nasal mucosa of cats via non-adrenergic and non-

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cholinergic mechanisms (Lacroix *et al.*, 1994). The purpose of the present study was to evaluate possible interactions between sympathetic and parasympathetic nerves in the control of canine nasal mucosa blood flow. In order to characterize further the mechanisms underlying these interactions, parasympathetic-nerve evoked vasodilatation was also studied in the presence of exogenous NPY and the Y_1 and Y_2 receptor agonists, [Leu³¹, Pro³⁴] NPY and N-acetyl [Leu²⁸, Leu³¹] NPY 24–36, respectively.

Methods

Experiments were performed on twelve adult mixed breed dogs of either sex weighing between 4 and 9 kg. These experiments were approved by the institutional animal care and ethics committee. The dogs were anaesthetized with pentobarbitone sodium (35 mg kg⁻¹, i.v.). The trachea was cannulated low in the neck and the animals were artificially ventilated. A catheter connected to a Statham P23AC blood pressure transducer was placed in a femoral artery for systemic blood pressure monitoring. Another catheter was inserted in a femoral vein for administration of compounds and further doses of anaesthetic as required (0.5–1 ml of a 1-in-5 dilution of pentobarbitone). The left cervical vagus nerve was dissected high in the neck, the vagal sheath was removed and then the sympathetic nerve was easily separated from the vagal trunk. In some animals the sympathetic nerve was traced to the superior cervical sympathetic ganglion (Berridge & Roach, 1986). The left zygomatic arch was removed and the vidian nerve and the sphenopalatine ganglion were exposed by a procedure similar to the one described by Eccles & Wilson (1973). The proximal portion of the cervical sympathetic nerve as well as the cut peripheral end of the parasympathetic nerve was placed on bipolar platinum electrodes connected to a Grass S 88 stimulator (Grass Instruments, Quincy, U.S.A.). The identification of the cervical sympathetic nerve was confirmed by observing dilatation of the pupil with its electrical stimulation. The preganglionic parasympathetic nature of the vidian nerve was confirmed by the inhibition of vasodilatation evoked by its electrical stimulation after administration of chlorisondamine (2 mg kg⁻¹, i.v.). The left external carotid artery was dissected up to the internal maxillary artery. The main arterial branches located beyond to the superficial temporal artery were ligated as described previously by Lacroix *et al.* (1988), a procedure which leaves the internal maxillary artery flow supplying only the nasal mucosa. The superficial temporal artery was cannulated for selective injection of agents into the main nasal arterial blood supply. The nasal arterial blood flow was recorded with a transonic flow probe (3SB454) placed around the internal maxillary artery and connected to a T206 ultrasonic blood flowmeter (Transonic System Inc., NY, U.S.A.). All parameters were continuously recorded on a Grass polygraph model 7C in all experiments. The animals were allowed a 1 h intervention-free period following completion of surgery.

Experimental protocol

Group 1 ($n = 8$) Solutions of ACh (5.5×10^{-11} to 5.5×10^{-8} mol), VIP (3×10^{-11} to 3×10^{-9} mol), PHI (3.3×10^{-11} to 1.6×10^{-8} mol) and NA (6×10^{-11} mol to 6×10^{-8} mol) were infused into the superficial temporal artery over a period of 15 s. The administration of saline alone had no measurable effect. An interval of 5 min was allowed between successive injections. Fifteen minutes after the completion of the ACh, VIP, PHI and NA injections, parasympathetic nerve stimulations (5 V, 5 ms) were performed at continuous frequencies of 10, 20 and 30 Hz for 10 s. Each stimulation was performed 3 min after the blood flow in the internal maxillary artery returned to base line from the preceding stimulation. Sympathetic nerve stimula-

tion (15 V, 5 ms) was then performed continuously at 10 Hz for 3 min. Parasympathetic nerve stimulations were repeated 5 min, 30 min and then 1 h after sympathetic nerve stimulation. This entire protocol was repeated after pretreatment with the α -adrenoceptor antagonist, phentolamine (0.5 mg kg⁻¹ h⁻¹), the β -adrenoceptor antagonist, propranolol (1 mg kg⁻¹) and the parasympathetic muscarinic receptor blocker, atropine (0.5 mg kg⁻¹), all delivered by local intra-arterial (i.a.) injection. Stimulations of the parasympathetic nerve were also performed 5 min, 30 min and 1 h after the administration of exogenous NPY (8 nmol kg⁻¹) dissolved in 5 ml of saline and infused into the femoral vein for 1 min.

Group 2 ($n = 4$) The parasympathetic nerve was stimulated at 10, 20 and 30 Hz in animals under control conditions and after pretreatment with phentolamine, propranolol and atropine (same doses as above). Parasympathetic nerve stimulations were repeated 5 min, 30 min and 1 h after the i.v. administration of the NPY analogue, [Leu³¹, Pro³⁴] NPY (Y_1 -receptor agonist, 8 nmol kg⁻¹). Ninety minutes later, parasympathetic nerve stimulation was also performed after the i.v. infusion of the NPY analogue, N-acetyl [Leu²⁸, Leu³¹] NPY 24–36 (Y_2 -receptor agonist, 20 nmol kg⁻¹).

Analysis of results

Changes of the nasal arterial blood flow were expressed in terms of vascular resistance in the maxillary artery (R_{ma}), obtained by dividing the driving mean arterial blood pressure in the femoral artery by the peak value of the blood flow volume rate in the maxillary artery. Before each experiment a zero flow in the maxillary artery was obtained by clamping the artery downstream to the transonic probe for 30 s. The durations of the responses were given in s and calculated from the end of the electrical stimulation until return to former basal values. All data are presented as mean \pm standard error of the mean (s.e.mean). Statistical differences were evaluated by one way ANOVA test.

Drugs used

The following drugs were used: pentobarbitone sodium (Nembutal, Boehringer Ingelheim, Germany), acetylcholine (ACh, acetylcholine chloride, Sigma, U.S.A.), VIP (Peninsula, U.S.A.) and PHI (porcine PHI-27, Bachem, U.S.A.); phentolamine (Regitine, Ciba-Geigy, Switzerland), propranolol (Inderal, ICI, UK), atropine (atropine sulphate, Astra, Sweden), NA (Levophed, Winthrop, Australia) and NPY (h-NPY, Novabiochem Switzerland); the Y_2 -receptor agonist, N-acetyl [Leu²⁸, Leu³¹] NPY 24–36 and the Y_1 -receptor agonist, [Leu³¹, Pro³⁴] NPY (AusPep, Australia); chlorisondamine (Ecolid, Ciba-Geigy, Switzerland).

All solutions were freshly prepared before each experiment by dissolving the compounds in sterile 0.9% w/v NaCl.

Results

The basal blood flow in the internal maxillary artery of the dog was 8.5 ± 2 ml min⁻¹ kg⁻¹. After section of both sympathetic and parasympathetic nerves on the left side the homolateral nasal arterial flow was 9.7 ± 2.5 ml min⁻¹ kg⁻¹ (representing a 14% increase). The femoral arterial blood pressure was not modified by the section of the sympathetic or the parasympathetic nerves.

Electrical stimulation of the parasympathetic nerve induced frequency-dependent reductions of the R_{ma} (Figure 1a) whereas the BP was not significantly modified (not shown). Parasympathetic stimulation at 10 Hz increased the blood flow from 9.7 ± 2.5 ml min⁻¹ kg⁻¹ to 11.35 ± 1.8 ml min⁻¹ kg⁻¹ representing a reduction in R_{ma} of $16.8 \pm 2\%$ (Figure 1a). During stimulation at 30 Hz the blood flow increased to 13.4 ± 1.8 ml min⁻¹ kg⁻¹ corresponding to a R_{ma} reduction of

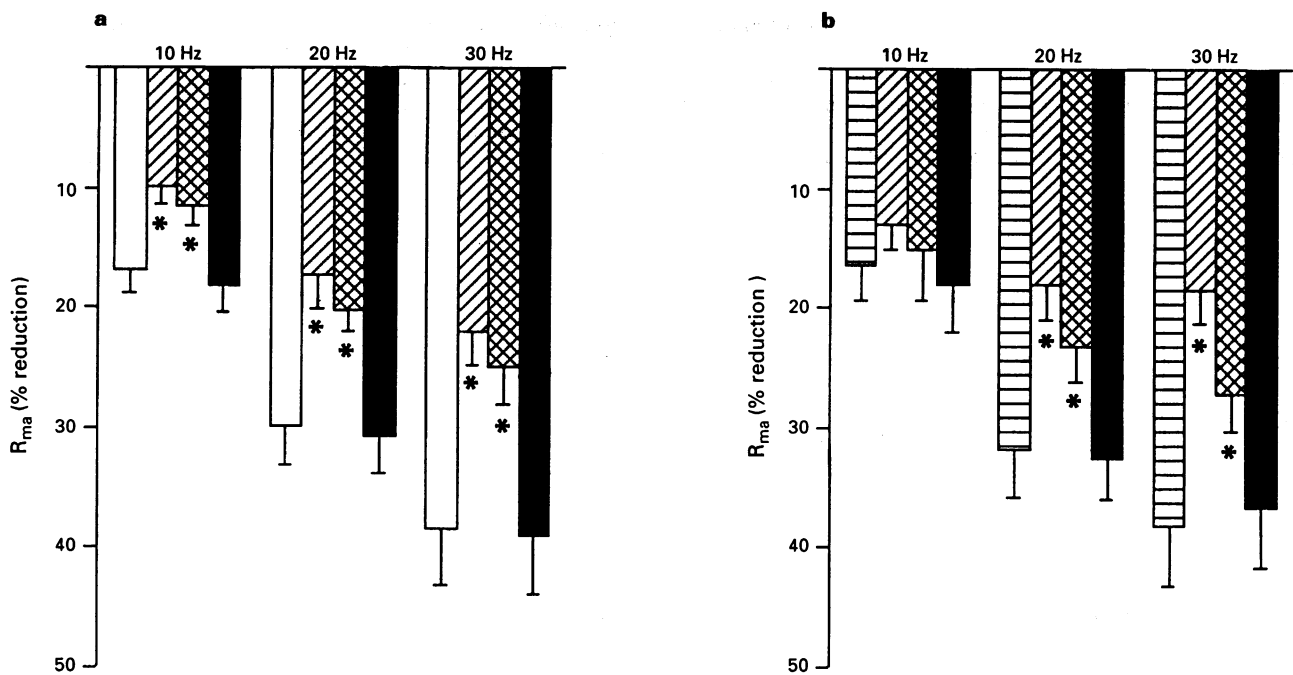


Figure 1 Effects of parasympathetic nerve stimulation (5 V, 5 ms) at different frequencies on the vascular resistance in the internal maxillary artery (R_{ma}) of the dog (a) under control conditions (open column) and (b) after pretreatment with phentolamine ($0.5 \text{ mg kg}^{-1} \text{ h}^{-1}$), propranolol (1 mg kg^{-1}) and atropine (0.5 mg kg^{-1}) (horizontally hatched column). The effects of the same parasympathetic stimulations are also shown just after sympathetic nerve stimulation (15 V, 5 ms, 10 Hz, 3 min) (diagonally hatched column), 30 min after sympathetic stimulation (cross hatched column) and 1 h later (solid column). $n = 8$, $*P < 0.05$ when compared to control (one way ANOVA test).

$38.5 \pm 4.7\%$ (Figure 1a). The blood flow increase lasted for $43 \pm 5 \text{ s}$ after stimulation at 10 Hz and $78 \pm 8.2 \text{ s}$ after 30 Hz stimulation.

Sympathetic nerve stimulation at 10 Hz for 3 min reduced the blood flow in the maxillary artery by $57.5 \pm 7\%$ lasting more than 7 min. The vasodilator responses evoked by electrical stimulations of the parasympathetic nerve were attenuated by an average 40% ($P < 0.05$) after sympathetic nerve stimulation at 10 Hz for 3 min (Figure 1a). Thirty minutes after the SNS the vasodilatation evoked by the stimulation of the parasympathetic nerve was still reduced by $23 \pm 5\%$ (Figure 1a). One hour after the completion of the SNS, the vasodilator effect of parasympathetic nerve stimulation was not significantly different in magnitude to that before sympathetic stimulation (Figure 1a and 3a).

After combined pretreatment with phentolamine, propranolol and atropine the driving mean arterial blood pressure was reduced by $18 \pm 6\%$. In parallel, the blood flow in the internal maxillary artery was reduced by the same magnitude so the R_{ma} was not significantly modified. The vascular effects of exogenous NA and ACh were virtually abolished in pretreated animals (not shown). The peak of the vasodilator responses to parasympathetic nerve stimulation was not significantly different from that observed before the administration of the adrenoceptor blockers and atropine (Figure 1). In contrast the responses were slower in onset and prolonged by 55% (Figure 3b).

After adrenoceptor blockade, the vasoconstriction evoked by sympathetic stimulation at 10 Hz for 3 min was reduced by an average 35% when compared to control (Figure 3b). The subsequent atropine-resistant vasodilatation evoked by parasympathetic nerve stimulation at 20 Hz and 30 Hz was reduced by more than 40% ($P < 0.05$) (Figure 1b). Thirty minutes after the sympathetic nerve stimulation, the vasodilatation evoked by the stimulation of the parasympathetic nerve was still reduced by $28 \pm 5\%$ (Figure 1b). After 1 h, the effects of parasympathetic stimulations were similar in magnitude to those before the sympathetic stimulation (Figure 1b and 3b).

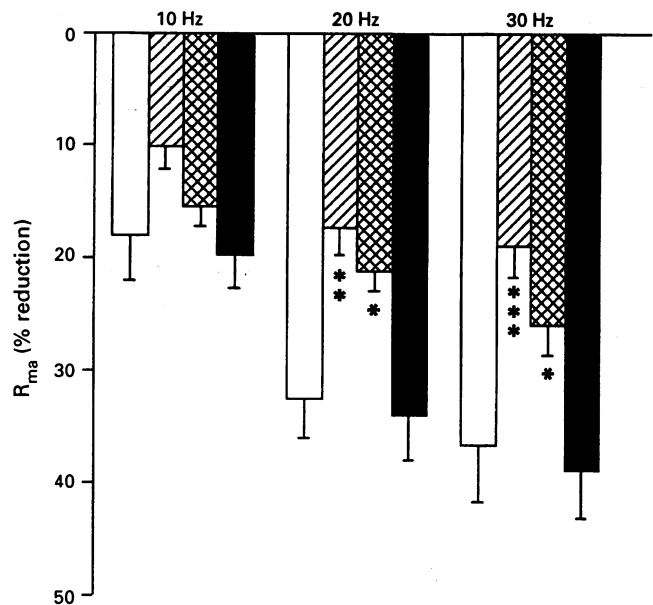


Figure 2 Effects of parasympathetic nerve stimulation (5 V, 5 ms) at different frequencies on the vascular resistance in the internal maxillary artery (R_{ma}) of the cat pretreated with phentolamine ($0.5 \text{ mg kg}^{-1} \text{ h}^{-1}$), propranolol (1 mg kg^{-1}) and atropine (0.5 mg kg^{-1}) (open column), just after the administration of exogenous neuropeptide Y (NPY, 8 nmol kg^{-1} , i.v.) (diagonally hatched column), 30 min after the administration of NPY (cross hatched column) and 1 h later (solid column). $n = 8$, $*P < 0.05$ and $P < 0.01$ when compared to the first column (one way ANOVA test).

The administration of exogenous NPY (8 nmol kg^{-1} , i.v.) increased arterial blood pressure by $25 \pm 7 \text{ mmHg}$ lasting $7.4 \pm 1.8 \text{ min}$. In parallel the blood flow in the internal maxillary artery was reduced by $43 \pm 8\%$. Atropine-resistant

vasodilatations evoked by parasympathetic stimulations at 20 and 30 Hz were reduced by more than 45% ($P < 0.05$) after the administration of exogenous NPY (Figure 2 and 3c). The vasodilatation induced by parasympathetic stimulation at 20 and 30 Hz remained significantly reduced ($P < 0.05$) 30 min after the administration of exogenous NPY (Figure 2). One

hour after the completion of the NPY infusion, stimulation of the parasympathetic fibres evoked increases in nasal blood flow similar in magnitude to those before the NPY administration (Figure 2 and 3c).

The infusion of the putative Y_1 receptor agonist, [Leu³¹, Pro³⁴] NPY increased femoral blood pressure by

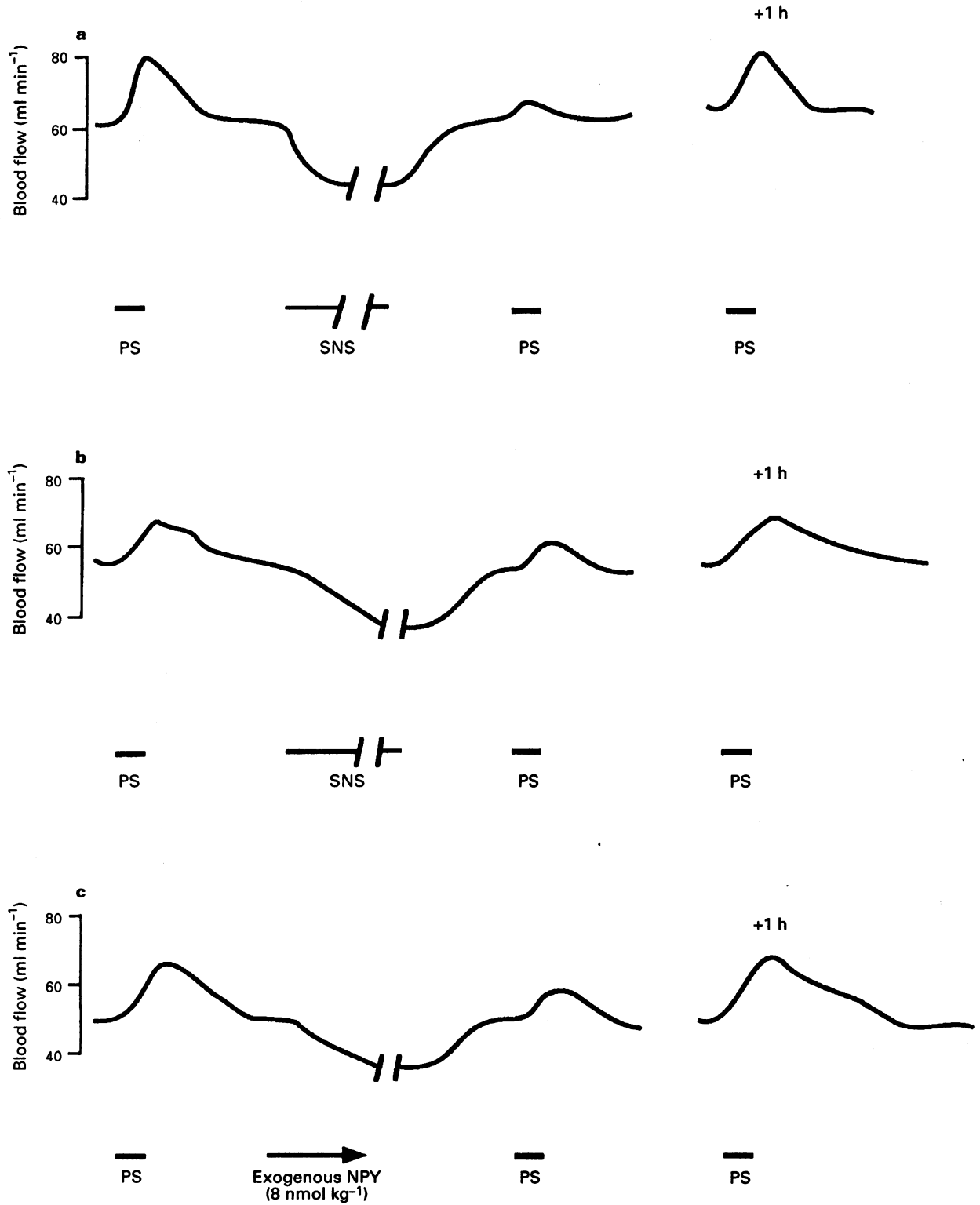


Figure 3 Recording from an anaesthetized dog showing changes in blood flow in the internal maxillary artery upon stimulation of the parasympathetic nerve (PS, 5 V, 5 ms) at 30 Hz for 10 s, during sympathetic nerve stimulation (SNS, 15 V, 5 ms, for 3 min) and the effect of subsequent parasympathetic stimulations. Note that 1 h later, the effect of the parasympathetic stimulation is of the same magnitude as that before sympathetic nerve stimulation: (a) under control conditions, (b) after pretreatment with phenolamine (0.5 mg kg⁻¹ h⁻¹), propranolol (1 mg kg⁻¹) and atropine (0.5 mg kg⁻¹). In (c) the vasoconstrictor effect of exogenous NPY (8 nmol kg⁻¹, i.v.) is similar to the sympathetic stimulation shown in (b) as well as the inhibition of the subsequent parasympathetic vasodilatation. Time scale is given by the PS stimulation for 10 s.

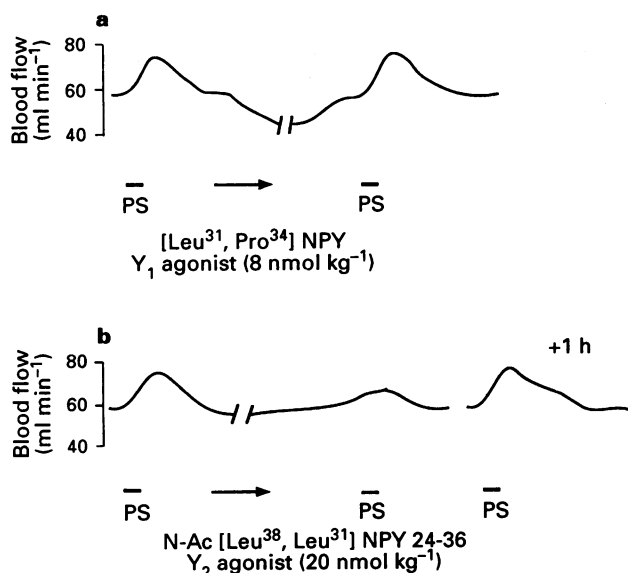


Figure 4 Recording from an anaesthetized dog showing changes in blood flow in the internal maxillary artery upon stimulation of the parasympathetic nerve (PS, 5 V, 5 ms) at 30 Hz for 10 s after pretreatment with phentolamine ($0.5 \text{ mg kg}^{-1} \text{ h}^{-1}$), propranolol (1 mg kg^{-1}) and atropine (0.5 mg kg^{-1}). In (a) the vasoconstrictor effect of the NPY analogue $[\text{Leu}^{31}, \text{Pro}^{34}] \text{ NPY}$ (Y_1 -receptor agonist, 8 nmol kg^{-1}) is similar to those of exogenous NPY shown in Figure 3c but has no influence on the subsequent parasympathetic vasodilatation. In (b) the administration of the NPY analogue N-acetyl $[\text{Leu}^{28}, \text{Leu}^{31}] \text{ NPY 24-36}$ (Y_2 -receptor agonist, 20 nmol kg^{-1}) has no significant vasoconstrictor effect. However, the subsequent parasympathetic vasodilatation is reduced. One hour later, the effect of the parasympathetic stimulation is of the same magnitude as that before the administration of the Y_2 -receptor agonist. Time scale is given by the PS stimulation for 10 s.

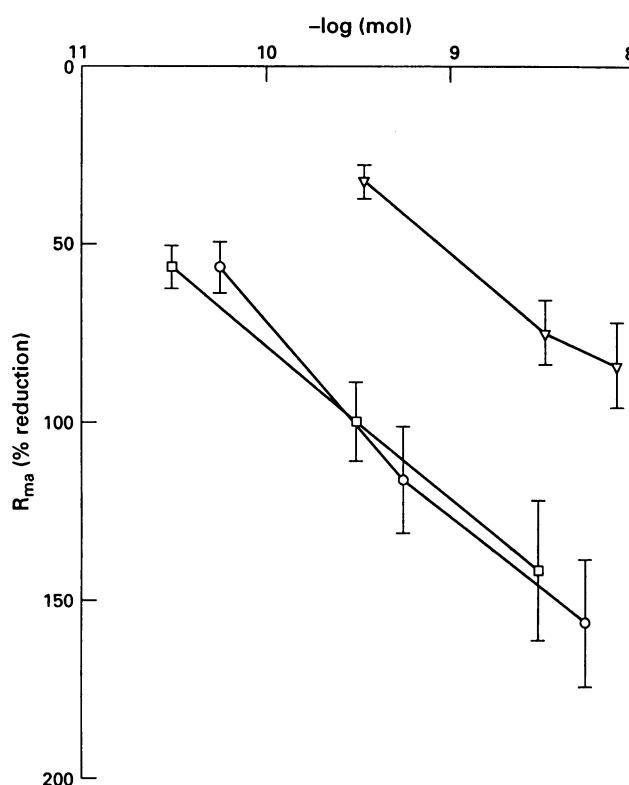


Figure 5 Effects of local intra arterial-injection of acetylcholine (Δ), vasoactive intestinal polypeptide (\circ) and peptide histidine isoleucine (\square) on the vascular resistance in the internal maxillary artery (R_{ma}) of the dog.

$23 \pm 2.8 \text{ mmHg}$ lasting more than 7 min (not shown). In parallel, the nasal mucosa blood flow was reduced by an average of 20% (Figure 4a). The vasodilator response to parasympathetic nerve stimulation was not modified after the administration of $[\text{Leu}^{31}, \text{Pro}^{34}] \text{ NPY}$ (Figure 4a).

Both blood pressure and nasal blood flow remained unchanged after the infusion of the NPY analogue, N-acetyl $[\text{Leu}^{28}, \text{Leu}^{31}] \text{ NPY 24-36}$ (Figure 4b). However, the vasodilator responses to parasympathetic nerve stimulation at 10, 20 and 30 Hz were significantly reduced by an average 50% ($P < 0.05$) after the administration of the Y_2 -receptor agonist (Figure 4b). Thirty minutes later the response to parasympathetic nerve stimulation remained significantly reduced (not shown). One hour after the infusion of the Y_2 -receptor agonist, the vasodilatations evoked by the parasympathetic stimulations remained smaller but were not significantly different in magnitude from those obtained before the infusion of the Y_2 -receptor agonist (Figure 4b).

Local intra-arterial injections of ACh, VIP and PHI evoked dose-dependent reductions of the R_{ma} (Figure 5) without significant modification of the arterial blood pressure. On a molar basis the rank order potency was $\text{VIP} > \text{PHI} > \text{ACh}$. Exogenous NA induced dose-dependent increases in R_{ma} (not shown). The vasodilator effect of ACh was rapid whereas those of VIP and PHI were slow in onset and long lasting (not shown). The effects of ACh and NA were abolished after pretreatment with the α -adrenoceptor blockers and atropine whereas the vasodilator effects of VIP and PHI persisted (not shown).

Discussion

The results of the present study show that sympathetic nerve stimulation attenuates subsequent parasympathetic nerve-

evoked nasal vasodilatation in anaesthetized dogs. Similar interactions between the sympathetic and parasympathetic system in the vascular control of the nasal mucosa have been recently described in cats (Lacroix *et al.*, 1994).

In dogs *in vivo*, NPY released upon strong sympathetic nerve stimulation, inhibits ACh release from postganglionic parasympathetic nerve and reduces vagal effectiveness at the heart (Potter, 1988; Revington *et al.*, 1990; Warner & Levy, 1990). Similar mechanisms may be involved in the inhibitory interactions which occur between sympathetic and parasympathetic nasal perivascular nerves during their successive activation. According to the observations reported here, it is likely that sympathetically released NPY attenuates cholinergic vasodilatation in the dog nasal mucosa under control conditions.

Parasympathetically-evoked vasodilatation was not modified after pretreatment with adrenoceptor blockers and atropine, suggesting the involvement of non-adrenergic non-cholinergic mechanisms. As reported earlier by Malm *et al.* (1980), the atropine-resistant nasal vasodilatation evoked by stimulation of the vidian nerve could be mimicked by exogenous VIP and to a lesser extent by PHI. Since VIP is present in perivascular postganglionic parasympathetic neurones in the nasal mucosa (Uddman *et al.*, 1978) and VIP is released during parasympathetic stimulation (Lundberg *et al.*, 1981), this neuropeptide is a probable candidate for mediator of the non-adrenergic, non-cholinergic parasympathetic vasodilatation observed in the present study.

After the administration of both adrenoceptor and cholinceptor antagonists, the attenuation of the parasympathetic vasodilatation remained intact, whereas the effects of both NA and ACh were abolished. The recently developed NPY analogue, N-acetyl $[\text{Leu}^{28}, \text{Leu}^{31}] \text{ NPY 24-36}$, has functional specificity for the prejunctional Y_2 receptor since it attenuates cardiac vagal action without a significant post-junctional Y_1 -mediated pressor effect (Potter *et al.*, 1994). In the present study, the attenuation of the atropine-resistant

parasympathetic vasodilatation was mimicked by both NPY and the Y₂-receptor agonist, N-acetyl [Leu²⁸, Leu³¹] NPY 24–36. In agreement with a recent report by Potter *et al.* (1994) this new NPY analogue has no pressor effects in dogs. In contrast, the Y₁-receptor agonist, [Leu³¹, Pro³⁴] NPY, has shown similar vasopressor effects to exogenous NPY but has no influence on the parasympathetic nerve-evoked vasodilatation. Taken together, these observations strongly suggest that sympathetically released NPY has a prolonged inhibitory effect on parasympathetic vasodilatation via prejunctional Y₂ receptors.

In conclusion, the present observations show that sympathetic nerve stimulation and exogenous NPY have long-lasting inhibitory effects on parasympathetic nerve-evoked

vasodilatation in the dog nasal mucosa. These sympathetic-parasympathetic interactions could be mimicked by N-acetyl [Leu²⁸, Leu³¹] NPY 24–36, a specific Y₂-receptor agonist, suggesting that NPY attenuates parasympathetic vasodilatation by an action on Y₂ presynaptic NPY receptors.

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