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Effects of neuropeptides and capsaicin on the canine tracheal vasculature *in vivo*

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1 The nonadrenergic, noncholinergic nervous system may control the airway vasculature via various neuropeptides. We have perfused the cranial tracheal arteries of the anaesthetized dog and investigated the effects of neuropeptides and capsaicin (which is supposed to release neuropeptides from sensory nerve endings) on the tracheal vasculature by injecting them locally into the perfusion system.

2 Neurokinin A (NKA, 0.02–20 pmol), calcitonin gene-related peptide (CGRP, 2–200 pmol) and peptide histidine isoleucine (PHI, 0.02–2 nmol) dose-dependently decreased tracheal vascular resistance (R_{tv}). NKA was 10 and 100 times more potent than CGRP and PHI, respectively. The duration of the response to CGRP was greatly prolonged with larger doses. Galanin (0.2–2 nmol) had no appreciable effect on R_{tv}.

3 Neuropeptide Y (NPY 0.02–2 nmol) and bombesin (0.02–10 nmol) dose-dependently increased R_{tv}. However, the dose-response curve for bombesin was bell-shaped suggesting the development of tachyphylaxis with larger doses. In smaller doses, bombesin was twice as potent as NPY. The duration of the response to NPY was prolonged with larger doses.

4 With the exception of PHI no neuropeptide altered tracheal smooth muscle tone; PHI (1 and 2 nmol) caused small dilatations of the trachea.

5 The effects of capsaicin (2–100 nmol) were complex. Usually, the vascular response had two dose-dependent phases: a rapid vasoconstriction followed by a small, longer-lasting vasodilatation. The tracheal smooth muscle response was usually biphasic, a contraction followed by a relaxation.

6 According to previous and present data, the order of potency of the neuropeptides on the canine tracheal vasculature is for the vasodilators: NKA > vasoactive intestinal peptide (VIP) > CGRP ⩾ substance P > PHI, and for the vasoconstrictors: bombesin > NPY. The longer-acting neuropeptides (VIP, CGRP and NPY) may be more important than the shorter-acting neuropeptides (substance P, NKA, PHI and bombesin) as regulators of the airway wall blood flow.

Introduction

The tracheobronchial circulation may be involved in asthma in several ways, e.g. by regulating the penetration and clearance of chemical mediators in the airway wall and by controlling water and heat exchange in the tracheobronchial tree (Baier *et al.*, 1985; Deffebach *et al.*, 1987). It is regulated neurally by adrenergic constrictor mechanisms (Daly & Hebb, 1966; Lung *et al.*, 1976) as well as by cholinergic and noncholinergic dilator mechanisms (Martling *et al.*, 1985; Laitinen *et al.*, 1987a). The noncholinergic tracheobronchial vasodilatation in the cat (Martling *et al.*, 1985) and dog (Laitinen *et al.*, 1987a) has two distinct components; one via orthodromic motor pathways and the other via antidromic stimulation of sensory nerve fibres. Both of these pathways may act via neuropeptides postulated to be mediators of the nonadrenergic, noncholinergic (NANC) nervous system in the airways (Barnes, 1986).

Immunohistochemical studies have localized neuropeptides to both efferent and afferent nerves associated with many structures of the mammalian airways, including airway blood vessels (Polak & Bloom, 1985; Uddman & Sundler, 1987). Vasoactive

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intestinal peptide (VIP), peptide histidine isoleucine (PHI; in man peptide histidine methionine) and galanin are mainly in parasympathetic efferent nerves, whereas neuropeptide Y (NPY) is in sympathetic efferent nerves. Tachykinins such as substance P (SP) and the neurokinins (NKA and NKB), and calcitonin gene-related peptide (CGRP) are localized to sensory C-fibres. Bombesin is found in neuroendocrine cells of the airway epithelium. A recent immunohistochemical study confirms this general concept of the neuropeptide distribution in a primate (Ghatei *et al.*, 1987).

Many neuropeptides have potent effects on various vascular beds. VIP dilates the dog hindlimb vasculature (Said & Mutt, 1969) and CGRP and tachykinins dilate blood vessels in the human skin (Brain *et al.*, 1985; Barnes *et al.*, 1986) and forearm (Eklund *et al.*, 1977; Benjamin *et al.*, 1987). NPY constricts blood vessels in the cat submandibular gland (Lundberg & Tatemoto, 1982), the canine spleen (Corder *et al.*, 1987) and in the human forearm (Pernow *et al.*, 1987) and myocardium (Clarke *et al.*, 1987).

Few of the neuropeptides have been studied on the airway vasculature. VIP and SP are potent dilators of the nasal (Lung *et al.*, 1984) and tracheal (Laitinen *et al.*, 1987b) vascular beds of the anaesthetized dog. We have used the *in vivo* perfused trachea preparation described by Laitinen *et al.* (1987a) to investigate the effects of NKA, CGRP, PHI, galanin, NPY and bombesin. The effect of capsaicin was also studied, because it releases neuropeptides from sensory nerve endings (Saria *et al.*, 1984; Zaidi *et al.*, 1985). Some of the results have been presented in abstract form (Salonen *et al.*, 1987).

Methods

Experiments were carried out with thirteen greyhounds (body weight 27.2 ± 0.9 kg, mean $\pm$ s.e.mean) of either sex. The animals were anaesthetized with pentobarbitone sodium (30 mg kg^{-1} i.v.), and additional anaesthetic was given as required to maintain surgical anaesthesia. Body temperature was monitored with a rectal thermometer and maintained between 37 and 39°C without supplemental heating sources. Both femoral arteries were catheterized (8 FG, Portex). One catheter was connected to a pressure transducer (P23 Db, Gould) for the measurement of systemic arterial blood pressure; the other was used to supply blood to the tracheal perfusion circuits. A similar catheter was inserted into the left femoral vein for the administration of heparin and supplemental doses of anaesthetic.

A low cervical tracheostomy was performed and a tracheal cannula inserted and connected to a pneumotachograph (Fleisch) to give airflow. The animals breathed spontaneously during the whole experiment.

Assessment of tracheal vascular resistance

This method has been described recently by Laitinen *et al.* (1987a). The common carotid arteries were exposed on both sides of the trachea at the level of the superior thyroid arteries, which were isolated; arteries to skeletal muscles, larynx and thyroid glands were tied off. Catheters (8 FG, Portex) were inserted orthogradely into both common carotid arteries 1–1.5 cm below the superior thyroid arteries to be connected to the perfusion circuits, and the common carotid arteries were tied off about 1 cm cranial to the superior thyroid arteries. To ensure an intact blood flow to the brain and a normal pressure in the carotid sinuses, the occluding catheterizations in the common carotid arteries were bypassed with plastic tube loops.

Perfusions of the tracheal mucosa on the left and right sides were via the short segments of common carotid arteries and the tracheal branches of the superior thyroid arteries, with blood from the reservoir filled from the femoral artery; perfusions were at constant rates by two peristaltic pumps (MHRE Mk 4, Watson-Marlow). The perfusion pressures were measured by two pressure transducers (P23 ID, Gould) from points between the peristaltic pumps and the carotid catheters. Each perfusion flow rate was adjusted to give tracheal perfusion pressure close to systemic arterial pressure (range 150–200 mmHg); pentobarbitone-anaesthetized greyhounds tend to have high blood pressure (Laitinen *et al.*, 1987a). Perfusion flow rates (range 3–15 ml min^{-1}) needed readjustment usually 2–3 times during the experiment. Each dog was given heparin sodium (25,000 iu, i.v.) before perfusion).

Tracheal vascular resistances (R_{tv}) were calculated from measurements of tracheal arterial pressures at constant perfusion flow. Inflow pressure was divided by flow to give R_{tv}. Distribution of perfused circulation was tested by close arterial injections of 0.2 ml Evans Blue (0.5% w/v in phosphate buffered saline) into both perfusion circuits. This always appeared in the mucosa of the upper part of the trachea, around the cranial 4–12 cartilaginous rings; only a little dye appeared in adjacent tissues such as the cranial part of the oesophagus.

Assessment of changes in tracheal smooth muscle tone

Changes in tracheal smooth muscle tone were assessed either by recording pressure changes (pressure

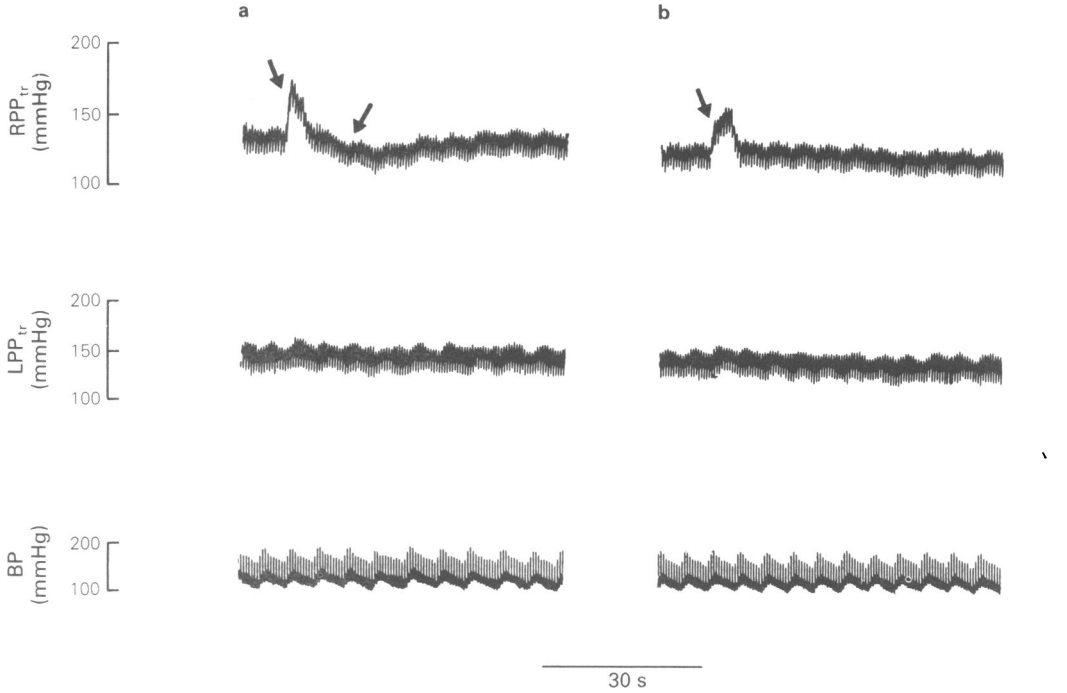

Figure 1 The tracheal vascular responses to 0.2 ml of saline (a) and blood (b) injected into the arterial catheter supplying the right side of the tracheal vascular bed. In both cases there was an abrupt increase in perfusion pressure due to injection (pressure artifact) which only after saline was followed by a transient decrease (lowered blood viscosity). From above down: right and left perfusion pressures (RPP_{tr} and LPP_{tr}) and systemic arterial blood pressure (BP).

transducer PM5, Statham) from an air-filled, thin-walled balloon (basal pressure $\sim 50\,mmH_2O$; response range -50 to $+100\,mmH_2O$) inserted into the cranial trachea (Laitinen *et al.*, 1987a), or by recording changes in the external diameter of the cranial trachea. To determine external diameter, a fixed bar was placed on one side of the trachea and a thin lever connected to a force-displacement transducer (FT03 C, Grass) was gently placed on the other side using a micromanipulator. Changes in force were read against a standard calibration curve to give the displacement of the lever tip (range $\pm$ 1.6 mm) indicating changes in external tracheal diameter.

Administration of drugs

NKA (0.02–20 pmol), CGRP (2–200 pmol), PHI (0.02–2 nmol), NPY (0.02–2 nmol), galanin (0.02–2 nmol) and bombesin (0.02–10 nmol) were dissolved and administered in isotonic saline. Capsaicin (2–100 nmol) was given in 5% ethanol/saline solution. Neuropeptides and capsaicin as well as control injections of saline and 5% ethanol/saline were administered in a volume of 0.2 ml into the arterial catheters supplying the tracheal vascular bed. The doses of each drug were given singly and allocated randomly to the left and right perfusion circuits. The time-interval between doses was at least 15 min to allow the vascular bed to recover fully from the preceding drug effects. Full dose-response curves for two drugs were constructed for each dog.

Calculation of results

Injections of 0.2 ml saline, drug solutions and blood into the perfusion circuits caused an abrupt (duration 5–10 s) increase (pressure artifact) in perfusion pressure (range 20–50 mmHg) which always preceded the response to drugs (Figure 1). With saline solutions but not with blood this was followed by a transient decrease (due to lowered perfusion viscosity) in perfusion pressure (Figure 1); this decrease in pressure occasionally (especially at low doses of drugs) overlapped with the responses to drugs and was then subtracted. Both the magnitude

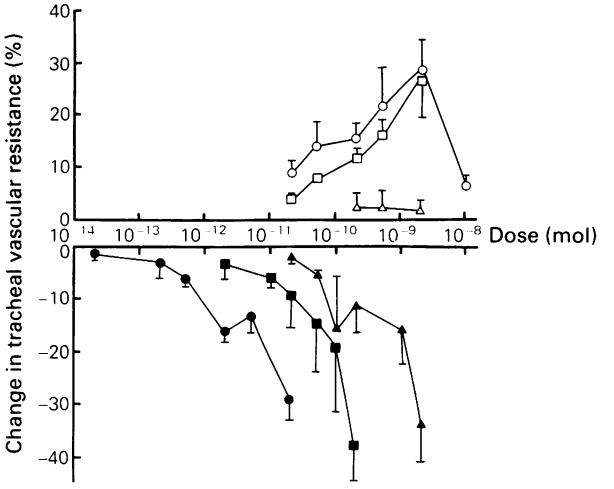

Figure 2 Dose-response curves showing the effects of the neuropeptides on tracheal vascular resistance. Five to six doses of each neuropeptide (only three doses of galanin) were injected into the arterial catheters supplying the tracheal vascular bed. (○) Bombesin, (□) neuropeptide Y, (△) galanin, (●) neurokinin A, (■) calcitonin gene-related peptide, (▲) peptide histidine isoleucine. The values presented are mean percentage changes from control values in 3–4 separate dogs; vertical lines indicate s.e.mean.

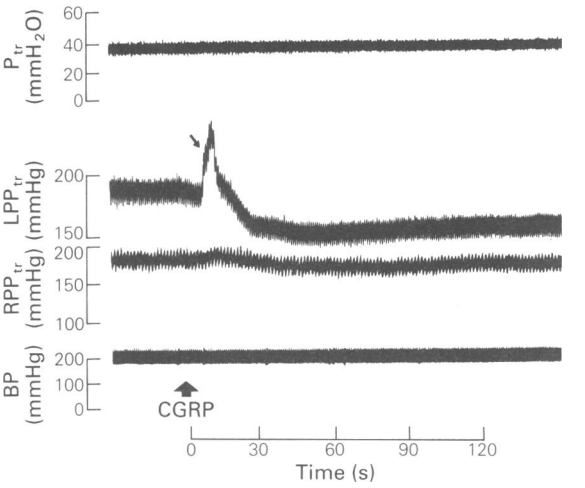

Figure 3 The tracheal vascular response to calcitonin gene-related peptide (CGRP; 0.1 nmol) injected into the arterial catheter supplying the left side of the tracheal vascular bed. A long-lasting decrease in left arterial perfusion pressure (LPP_{tr}) is seen after a transient increase in perfusion pressure caused by the injection (small arrow). A second potential artifact (lowered viscosity of blood) is masked and followed by CGRP-induced vasodilatation. A small decrease is also seen in the right arterial perfusion pressure (RPP_{tr}). There is no change in systemic arterial blood pressure (BP) or intratracheal pressure (P_{tr}).

(13.6 ± 0.7%, mean ± s.e.mean; basal pressure 167.7 ± 2.8 mmHg, $n = 43$) and the duration (10–40 s) of the decrease in perfusion pressure caused by lowered viscosity of blood greatly depended on the perfusion flow rate. Therefore, a control injection with saline was done after every change in perfusion flow rate.

Table 1 The potencies of the neuropeptides in the canine tracheal vasculature

Neuropeptide	*Dose for 25% change in R_{tv}* (nmol)
Vasodilators	
NKA	0.014
VIP*	0.044
CGRP	0.13
SP*	0.15
PHI	1.5
Vasoconstrictors	
Bombesin	0.92
NPY	1.5

A dose causing a 25% change (decrease or increase) in tracheal vascular resistance (R_{tv}) was determined for each neuropeptide from the dose-response curves in Figure 2.
* Data from Laitinen *et al.* (1987b).

Dose-response curves (molar dose vs % change in R_{tv}) were plotted for each neuropeptide and capsaicin. To compare the potencies, a dose causing a 25% change (decrease or increase) in R_{tv} was determined for each neuropeptide from the dose-response curves. The results could not be expressed as percentages of the maximal available effect, because drug doses that changed R_{tv} by more than 30–40% were liable to affect systemic arterial blood pressure (which may evoke various reflex actions) and thus were avoided.

To compare the time-courses of the vascular responses to the neuropeptides, two time-intervals were determined; the time from the injection to the maximal response (T_{max}) and the half-time of the vascular response (the time from the maximal effect to the half-maximal recovery).

Drugs

All neuropeptides were synthetic and supplied by Sigma: bombesin, CGRP (human), galanin, NKA,

NPY (porcine) and PHI (porcine). The other drugs were capsaicin (Sigma), Evans Blue (Sigma Diagnostics), heparin sodium (CP Pharmaceuticals) and pentobarbitone sodium (May & Baker).

Results

Effects of neuropeptides on tracheal vasculature

Dose-response curves showing the tracheal vascular effects of the neuropeptides are presented in Figure 2. NKA, CGRP and PHI dose-dependently decreased R_{tv}. On a molar basis, NKA was 10 and 100 times more potent than CGRP and PHI, respectively (Table 1). The contralateral vascular responses to these vasodilators were usually 10–30% of the ipsilateral responses. Figure 3 shows the vascular response to CGRP.

NPY and bombesin dose-dependently increased R_{tv} (Figure 2). Bombesin was about twice as potent as NPY (Table 1), but had a bell-shaped dose-response curve. The contralateral vascular responses to NPY and bombesin were usually 20–40% of the ipsilateral responses. Figure 4 shows the vascular response to NPY. Galanin had no effect on R_{tv}.

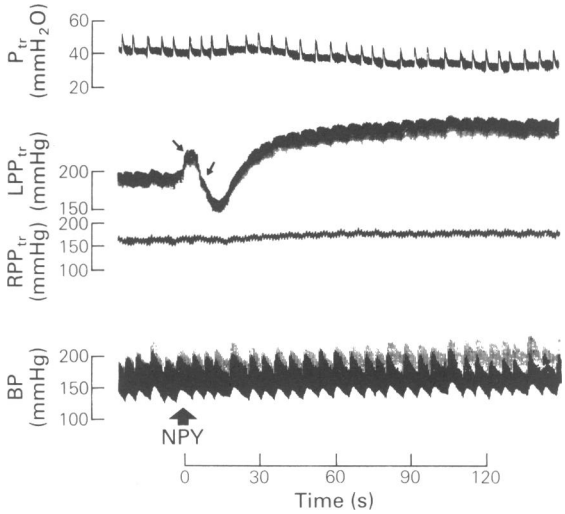

Figure 4 The tracheal vascular response to neuropeptide Y (NPY, 2 nmol) injected into the arterial catheter supplying the left side of the tracheal vascular bed. A long-lasting increase in left arterial perfusion pressure (LPP_{tr}) is seen after two transient artifacts (small arrows); the initial increase in perfusion pressure is due to injection and the subsequent decrease is caused by lowered viscosity of blood. There are also a small increase in right arterial perfusion pressure (RPP_{tr}) and a decrease in intra-tracheal pressure (P_{tr}; not seen in two other dogs) but no change in systemic arterial blood pressure (BP).

Time-courses of the tracheal vascular responses

The time-courses of the vascular responses to the neuropeptides are compared in Table 2. In general, both the T_{max} values and the half-times of the vascular responses were longer for the vasoconstrictors than for the vasodilators. There was very little difference between T_{max} values for the small and large

Table 2 The time-courses of the tracheal vascular response to the neuropeptides

Neuropeptide	*Dose* (nmol)	*Control* PP_{tr}	*Change in* R_{tv} (%)	T_{max} (s)	*Half-time* (s)
Vasodilators					
NKA	0.005	161.9 ± 9.7	−12.9 ± 3.3	34 ± 10	27 ± 5
	0.02	178.3 ± 14.2	−23.8 ± 3.6	24 ± 4	43 ± 13
CGRP	0.02	163.4 ± 6.8	−9.0 ± 5.9	25 ± 9	26 ± 10
	0.2	176.5 ± 14.4	−37.2 ± 6.9	41 ± 2	>600
PHI	0.2	162.7 ± 5.5	−10.4 ± 5.7	27 ± 7	16 ± 6
	2.0	169.7 ± 14.7	−32.9 ± 7.1	30 ± 3	37 ± 11
Vasoconstrictors					
Bombesin	0.02	161.1 ± 3.3	+9.1 ± 1.9	78 ± 11	147 ± 37
	2.0	165.4 ± 8.1	+29.3 ± 5.1	51 ± 10	145 ± 9
NPY	0.2	170.2 ± 15.3	+11.7 ± 2.3	106 ± 40	66 ± 34
	2.0	187.3 ± 10.6	+27.0 ± 7.3	81 ± 16	>600

The onset and duration of the effect on tracheal vascular resistance (R_{tv}) are described by two time-intervals; the time from the local arterial injection to the maximal response (T_{max}) and the half-time of the vascular response (the time from the maximal effect to the half-maximal recovery). The values (mean ± s.e.mean; n = 3–4) were determined for neuropeptide doses causing about 10% (small dose) and 30% (large dose) changes in R_{tv}. Control perfusion pressures (PP_{tr}) are given.

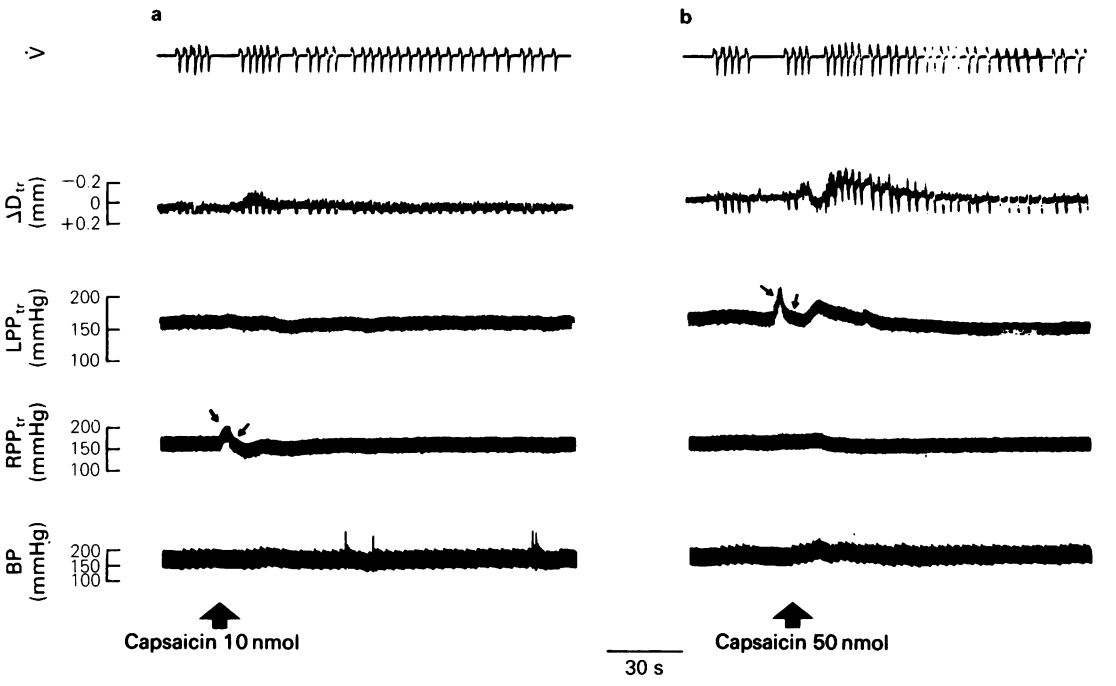

Figure 5 The tracheal vascular responses to 10 nmol (a) and 50 nmol (b) of capsaicin injected into the arterial catheters supplying the tracheal vascular bed. After the two transient artifacts (small arrows), there is a biphasic change in ipsilateral perfusion pressure which is seen best in response to the larger capsaicin dose (b). Also note the decrease in contralateral perfusion pressure, the complex changes in external tracheal diameter (ΔD_{tr}) and the increases in respiration frequency (airflow ($\dot{V}$) recording) and systemic arterial blood pressure (BP). For abbreviations used see Figure 4.

doses of any neuropeptide, whereas the half-time values for the large doses of CGRP and NPY were more than 10 and 20 times longer than those for the small doses of these drugs (Table 2).

Effects of neuropeptides on tracheal smooth muscle, respiration and systemic blood pressure

In general, the neuropeptides failed to change appreciably tracheal smooth muscle tone. The only exceptions were the two largest doses of PHI (1 and 2 nmol) which consistently decreased intratracheal pressure (-16.1 ± 8.5 and $-21.6 \pm 11.8\,mmH_2O$; mean ± s.e.mean) in three dogs indicating small tracheal dilatations. During saline injections ($n = 29$) intratracheal pressure shifted no more than $\pm 8\,mmH_2O$ ($0.3 \pm 1.8\,mmH_2O$; mean ± s.e.mean). Control injections of methacholine (0.25–1 μg) increased ($+40$ to $+100\,mmH_2O$) and those of salbutamol (0.5–2 μg) decreased (-20 to $-50\,mmH_2O$) intratracheal pressure.

The neuropeptides did not affect either respiration rate or systemic arterial blood pressure.

Effects of capsaicin

The effects of capsaicin were complex. Usually, the tracheal vascular effect had two dose-dependent phases; a rapid increase in R_{tv} followed by a slow, small decrease (Figures 5 and 6). The onset and duration of the latter response depended on the capsaicin dose (Figure 5); the larger the dose (10–100 nmol), the slower the onset (T_{max} = 28–110 s) and the longer the duration (half-time = 16–600 s) of the vasodilator effect.

Capsaicin (10–100 nmol) also had a small, biphasic effect on tracheal smooth muscle (Figure 5). Both components of the response were dose-dependent; at first external tracheal diameter decreased (-0.05 to -0.13 mm; range of mean changes) indicating tracheal constriction and then increased ($+0.03$ to $+0.24$ mm; range of mean changes) indicating tracheal dilatation. During saline injection ($n = 6$) tracheal diameter shifted no more than ± 0.03 mm. Control injections of methacholine (0.25–1 μg) decreased (-0.6 to -1.2 mm) and those of salbutamol (0.5–2 μg) increased ($+0.6$ to $+1.2$ mm) tracheal diameter.

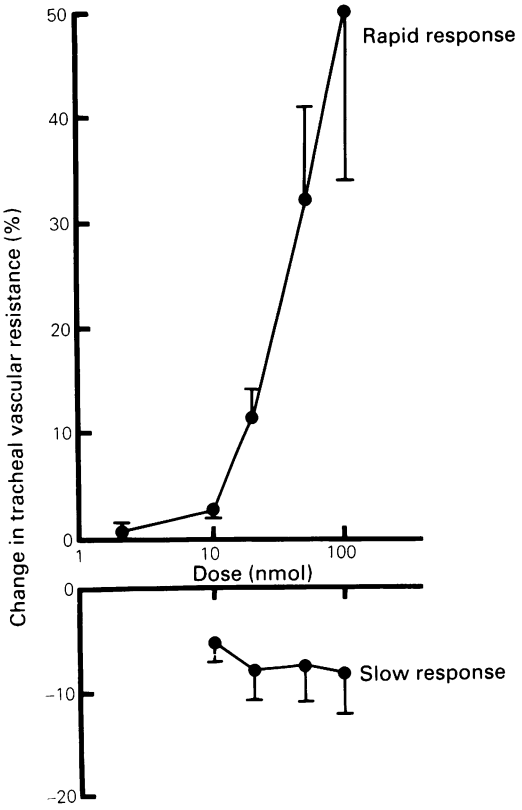

Figure 6 Dose-response curves showing the biphasic effect of capsaicin on tracheal vascular resistance. Five doses of capsaicin were injected into the arterial catheters supplying the tracheal vascular bed. The values presented are mean percentage changes from control values in three separate dogs; vertical lines indicate s.e.mean.

The two largest doses of capsaicin (50 to 100 nmol) usually had a biphasic effect on systemic arterial blood pressure (4.0–19.0% increase followed by 5.0–28.6% decrease), and they transiently increased respiration rate (7–71%) (Figure 5).

Discussion

We have used an auto-perfusion of the cranial tracheal arteries in the anaesthetized dog and investigated effects of locally injected neuropeptides and capsaicin. Changes in R_{tv} probably mainly reflect changes in the calibre of small arteries and arterioles in the tracheal wall, because the tracheal vasculature unlike the bronchial vasculature seems to lack systemic-pulmonary and arteriovenous anastomoses (Laitinen *et al.*, 1986). Many of the neuropeptides used in this study and in that of Laitinen *et al.* (1987b) have been immunohistochemically identified in the canine cervical trachea; so far, there is positive evidence for the existence of SP, CGRP, VIP and NPY (Laitinen, L.A., Laitinen, A., Pelto-Huikko, M., Partanen, M. & Widdicombe, J.G.; unpublished results).

With the exception of galanin, all the neuropeptides had potent effects on the canine tracheal vasculature. In general, the vasodilator neuropeptides were effective at lower doses than the vasoconstrictor peptides (Figure 2 and Table 1). Their vascular responses were quicker and shorter-lasting than the responses to the vasoconstrictor peptides (Table 2). However, this kind of *in vivo* comparison may be biased by several underlying factors, e.g. differences in the basal vascular tone and release of endogenous dilator or constrictor agents. NKA was the most potent vasodilator; in the study of Laitinen *et al.* (1987b), the doses of VIP and SP causing a 25% decrease in R_{tv} were about 3 and 10 times higher than that of NKA in the present work. On the assumption that the disappearance rates for SP and NKA from the tracheal tissue are similar, this suggests that the neurokinin receptors in the resistance vessels of the canine trachea may be mainly those of the NK-A (NK_2) subtype (Regoli *et al.*, 1987).

Bombesin was the only peptide giving a bell-shaped dose-response curve in the tracheal vasculature (Figure 2). This may be due to development of tachyphylaxis which has been observed with bombesin in other tissues (Erspamer *et al.*, 1972). Galanin had virtually no effect on the canine tracheal vasculature, which accords well with previous results showing its negligible potency in rabbit blood vessels and guinea-pig airways (Ekblad *et al.*, 1985).

In addition to the differences between the potencies of the neuropeptides, we also found major differences between the time-courses of their tracheal vascular effects. The responses to both CGRP and NPY were greatly prolonged as the doses of the two neuropeptides were increased (Table 2), whereas no such changes were seen with NKA, PHI and bombesin.

Analysis of the results of Laitinen *et al.* (1987b) suggests that VIP can also have long-lasting vascular actions in larger doses. With regard to CGRP, our results are consistent with those of Brain *et al.* (1985) and Barnes *et al.* (1986) who have shown a similar dose-dependent prolongation of its vascular effect in the human skin. In many vascular beds, NPY is a slow-acting, long-lasting vasoconstrictor (Lundberg & Tatemoto, 1982; Corder *et al.*, 1987; Pernow *et al.*, 1987) which probably elicits its effects mainly on

the small, peripheral arteries and arterioles (Clarke *et al.*, 1987). In the absence of any detailed knowledge of the enzymatic breakdown and receptor binding characteristics of individual neuropeptides in the airways, possible mechanisms of the dose-related prolongation of the tracheal vascular responses to CGRP and NPY remain unknown. In principle, however, a slow dissociation from receptor sites or a saturation of some enzymatic pathway, or both, could be involved.

From an *in vivo* study like this, it is impossible to draw any conclusions on the cellular mechanisms of the tracheal vascular responses to the neuropeptides. However, *in vitro* studies in other tissues suggest that, in certain conditions, the vasodilator effects of CGRP (Brain *et al.*, 1985) and some other neuropeptides (Vanhoutte *et al.*, 1986) may depend on the presence of an intact vascular endothelium.

Surprisingly, the effects of neuropeptides on tracheal smooth muscle were either small or absent both in our study and in that of Laitinen *et al.* (1987b); only PHI showed weak dilator activity. *In vitro*, the neuropeptides are active on mammalian airway smooth muscles (Barnes, 1986). However, for asthmatic patients Bundgaard *et al.* (1983) and Barnes & Dixon (1984) have shown that VIP, irrespective of its high *in vitro* potency, is a weak bronchodilator when given by inhalation. A possible explanation of the weak *in vivo* activity of the neuropeptides on the airway smooth muscle is that, while crossing tissue barriers, they are effectively metabolized by vascular endothelial (Johnson & Erdös, 1977; Ryan 1986) and airway epithelial cells (Barrowcliffe *et al.*, 1986).

Our results with capsaicin show that its actions on the tracheal vasculature are complex and do not support the concept of a high selectivity for afferent C-fibres (Buck & Burks, 1986). The initial vasoconstriction (Figure 5) could be due to a release of noradrenaline (Kaufman *et al.*, 1982) or constrictor neuropeptides such as NPY from sympathetic motoneurones, or a local release of 5-hydroxytryptamine (5-HT; Skofitsch *et al.*, 1983). However, the later slow vasodilator effect of capsaicin could be caused by SP, neurokinins or CGRP released locally from sensory nerve endings (Saria *et al.*, 1984; Zaidi *et al.*, 1985). The finding that a local injection of capsaicin into the canine tracheal circulation altered systemic arterial blood pressure and increased respiration rate (Figure 4) supports a central reflex involvement at least in some of the responses to capsaicin.

In conclusion, many of the airway neuropeptides are potent agents on the canine tracheal vasculature. According to the present study and that of Laitinen *et al.* (1987b), the order of potency of the vasodilator neuropeptides is: NKA > VIP > CGRP $\geqslant$ SP > PHI. Bombesin is about twice as potent as NPY as a vasoconstrictor but a tachyphylaxis to larger doses of bombesin develops readily. Galanin has no appreciable effect. The lack of action of the neuropeptides (with the exception of larger doses of PHI) on tracheal smooth muscle may indicate that the physiological role of the neuropeptides is more important on airway vascular beds than on smooth muscle, although the relative responses may be influenced by the experimental and natural routes of access to target cells. Finally, the long duration of action of some neuropeptides—VIP, CGRP and NPY—may make them more important than the shorter-acting ones (NKA, SP, PHI, bombesin) in the regulation of the airway wall blood flow.

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