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Dose-related effects of pharmacological mediators on tracheal vascular resistance in dogs

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1 Various doses of mediators were tested on tracheal vascular resistance in dogs anaesthetized with pentobarbitone. Tracheal vascular resistance was determined by perfusing the cranial tracheal arteries at constant flows and measuring inflow pressures.

2 All drugs produced dose-related changes in vascular resistance.

3 The peptides bradykinin, substance P and vasoactive intestinal peptide (VIP) each had similar vasodilator potencies and were much more powerful than histamine, methacholine and salbutamol.

4 Platelet activating factor (Paf) was a weaker dilator than the peptides. Prostaglandins D_2, E_1 and $F_{2\alpha}$ had wide dilator potency ranges, PGE_1 being very effective even at low concentrations.

5 Phenylephrine, an α-adrenoceptor agonist, was the only drug tested that always increased vascular resistance.

6 All the drugs studied also had effects on the contralateral tracheal vascular resistance.

Introduction

In addition to providing nutrition to the lungs, the bronchial vessels play significant roles in controlling the clearance of chemical mediators, in regulating the development of airway wall oedema, and in controlling heat exchange in the tracheobronchial tree (Baier *et al.*, 1985). The bronchial vessels can also function as a haemodynamic and gas-exchange system due to anastomoses with the pulmonary arteries. Studies of the pharmacology of the tracheobronchial circulation have been largely restricted to the bronchial vessels.

Studies dealing with lower airway vasculature have concentrated on the effects of pharmacological agents either acting on bronchial vascular resistance or affecting microvascular permeability (Laitinen *et al.*, 1987b). Histamine, methacholine and isoprenaline increase bronchial blood flow in sheep when administered directly into the bronchial artery; adrenaline injected similarly reduces bronchial blood flow, and nicotine has a variable effect (Parsons *et al.*, 1985). Histamine (Bruner & Schmidt, 1947; Yamatake & Yanaura, 1978), methacholine (Lakshminarayanan *et al.*, 1985), isoprenaline (Yamatake & Yanaura, 1978) and prostaglandins E_2 (Yamatake & Yanaura, 1978) and $F_{2\alpha}$ (Lakshminarayanan *et al.*, 1985) increase bronchial blood flow in dogs, although one report (Yamatake & Yanaura, 1978) describes a vasoconstriction with prostaglandin $F_{2\alpha}$. Aerosolised histamine increases both bronchial blood flow and airflow resistance, and it is suggested that the action of histamine on bronchial arterioles is mediated by H_2-receptors (Long *et al.*, 1985). None of these studies has included dose-response curves, and even qualitatively their interpretation is complicated because the majority of the bronchial circulation drains via bronchopulmonary anastomoses into the pulmonary circulation.

Anatomically the tracheal circulation is simpler than that to the bronchi, lacking 'tracheopulmonary' anastomoses (Laitinen *et al.*, 1986a, 1987a). Qualitatively, bradykinin, histamine and methacholine have large tracheal vasodilator effects and also increase the thickness of the canine tracheal mucosa (Laitinen *et al.*, 1986b). Substance P, VIP and prostaglandins $F_{2\alpha}$ and E_1 also cause large decreases in tracheal vascular resistance, but they only have small effects in increasing tracheal mucosal thickness. Phenylephrine increases tracheal vascular resistance and decreases mucosal thickness (Laitinen *et al.*, 1986b).

The effects of drugs on the tracheobronchial circulation have so far been studied mainly qualitatively. The present study was undertaken to establish dose-related

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effects of various mediators on vascular resistance in the canine trachea.

Methods

Experiments were carried out with 14 greyhounds (body weight 27.3 ± 0.5 kg, mean ± s.e.mean) of either sex. The animals were anaesthetized with intravenous sodium pentobarbitone (30 mg kg^{-1}) and additional anaesthetic was given as required. Body temperature was monitored with a rectal thermometer and was maintained between 37°C and 39°C without supplemental heating sources. Both femoral arteries were catheterized (8 FG, Portex). One catheter was connected to a pressure transducer (P23ID, Gould) for the measurement of systemic arterial blood pressure; the other was used to supply blood to the tracheal perfusion circuit. A femoral venous catheter (6 FG, Portex) was inserted for administration of heparin, relaxant and supplemental doses of anaesthetic.

A low cervical tracheostomy was performed and a tracheal cannula was connected to a Fleisch pneumotachograph to give airflow. In about half the experiments a thin-walled balloon was inserted into the cranial trachea, filled with 10–15 ml air, and pressure changes (1–5 cmH_2O) were recorded to indicate changes in tracheal muscle contraction. To minimize skeletal muscular artefacts on tracheal pressure, these animals were paralysed with an intravenous injection of gallamine triethiodide (1 mg kg^{-1}, May & Baker Ltd.) and ventilated with a tidal volume of 12–16 ml kg^{-1} at a constant rate of 12–18 breaths per min. Arterial blood gas partial pressures were sometimes monitored with an automated blood gas analyzer (Instrumentation Laboratories IL 413) to ensure a P_{O_2} between 60 and 85 Torr, P_{CO_2} between 31 and 43 Torr and a pH between 7.40 and 7.43.

The common carotid arteries were exposed at the level of the superior thyroid arteries, which were isolated; arteries to skeletal muscles, larynx and thyroid gland were tied off. Catheters (8 FG, Portex) were inserted orthogradely into both common carotid arteries below the superior thyroid arteries for connection to the perfusion circuit, and the common carotid arteries were tied off above the superior thyroid arteries. To ensure intact blood flow to the brain and a normal pressure in the carotid sinuses, the occluding catheterisations in the common carotid arteries on both sides were by-passed with plastic tube loops.

Perfusions of the tracheal mucosa were on one side in early experiments, and subsequently on both sides (hence *n*-values for ipsi- and contralateral sides are often different). Blood was from a reservoir filled from the femoral artery; perfusions were at constant rates by peristaltic pumps (MHRE Mk 4, Watson-Marlow). The perfusion pressures were measured by pressure transducers (P23ID, Gould) from points between the peristaltic pumps and the carotid arterial catheters. Each perfusion flow rate was initially adjusted so that tracheal perfusion pressure was close to systemic arterial pressure. Greyhounds anaesthetized with pentobarbitone tend to be hypertensive (control mean blood pressure about 125–150 mmHg), and initial perfusion pressures were similar. Each dog was given heparin (25,000 u, i.v., Leo Laboratories Ltd.) before perfusion.

Tracheal vascular resistances were calculated from measurements of tracheal arterial pressure at constant perfusion flow, usually 3–15 ml min^{-1}. Inflow pressure was divided by flow to give vascular resistance. Flow/pressure curves were constructed for some animals; Figure 1 gives a representative example. They were near-linear but showed a standing pressure of about 50 mmHg at zero flow, presumably due to anastomoses with more caudal systemic vessels; there was a small contralateral influence of flow/pressure changes.

Distribution of perfused circulation was tested by close arterial injection of Evans Blue. This always appeared in the mucosa of the upper part of the trachea, around the cranial 4–6 cartilaginous rings; only a little dye appeared in adjacent tissues such as the cranial part of the oesophagus. Thus it was concluded that the great majority of the perfused circulation was to the tracheal wall. For the sheep, 92% of the tracheal circulation goes to the mucosa and only 8% to the tracheal muscle (Lindsey *et al.*, 1986).

Drugs were dissolved in isotonic (155 mmol l^{-1}) NaCl solution as close as possible to time of use. Contact with glass surfaces was avoided. The drugs were injected directly into the arterial catheter supplying the tracheal vascular bed in 0.2 ml isotonic saline. From the perfusion rates and the catheter volumes we estimate that the drugs were in the blood for 4–20 s before they reached the tracheal vasculature, and we cannot say whether any may have been partially inactivated in this time. Drugs included phenylephrine hydrochloride (Boehringer Ingelheim), salbutamol sulphate (Ventolin, Allen & Hanburys), bradykinin triacetate (Sigma), histamine dihydrochloride (Sigma), methacholine chloride (Sigma), substance P (Sigma), vasoactive intestinal peptide (VIP; Sigma), prostaglandins D_2, E_1 and $F_{2\alpha}$ (Sigma), and platelet-activating factor (Paf-acether, Sigma). Doses of drugs are expressed as mol. At least three dose levels of each drug were injected in order to obtain a dose-response curve. Doses were kept below those that caused appreciable systemic vascular effects, which limited the range of dose-response curves (see later). As far as possible drugs and their doses were randomised.

Controls were carried out as injections of 0.2 ml saline into the perfusion circuit. These usually caused brief increases in pressure during the injection (10–

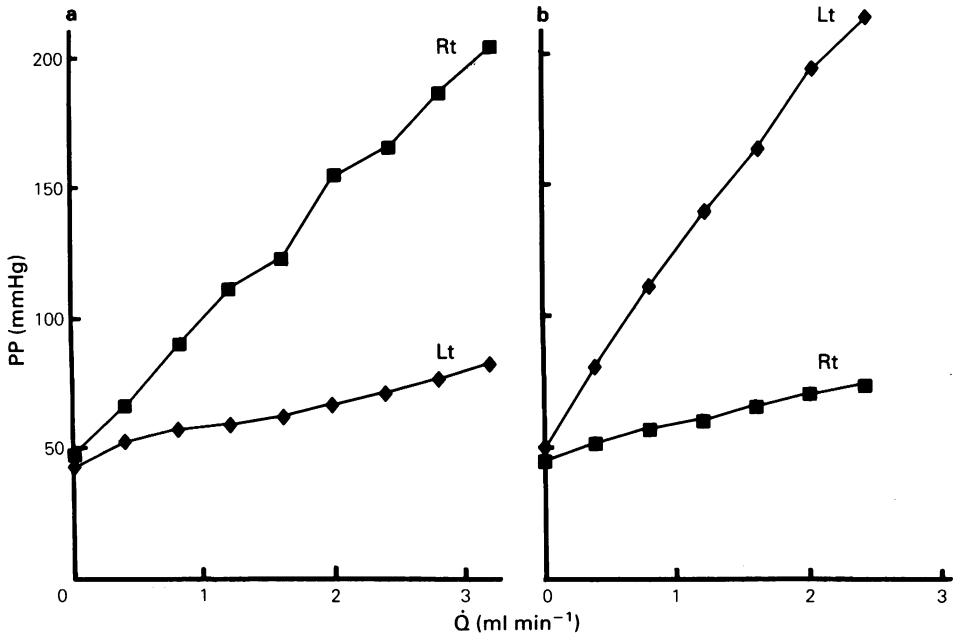

Figure 1 Representative perfusion flow/pressure relationships from one dog for the two sides of the tracheal vascular bed, perfused simultaneously. Ordinates, perfusion pressure (PP); abscissae perfusion flow ($\dot{Q}$). (a) Right perfusion flow was increased in steps while left perfusion flow remained at zero. (b) Left perfusion flow was increased in steps while the right perfusion flow remained at zero. In each instance there was a near-linear flow/pressure relationship for the ipsilateral vascular bed, with the contralateral side showing a smaller change. With zero flows on both sides there was a standing perfusion pressure of just under 50mmHg.

20 s), presumably by distending the segment from which pressure was recorded, followed by small transient (20–40 s) decreases in the perfusion pressure, presumably due to a lowering of blood viscosity. These effects were taken into account by subtracting them from the actions of the drugs if the latter were transient. However, peak changes with drugs usually occurred and were measured at times after the effects of viscosity had elapsed.

For simplicity, only peak changes in perfusion pressure have been analysed, although the latency and timing of some changes are presented in the text and in the Figures. To correlate the potency between different drugs, dose-response curves (dose in mol versus percentage change in vascular resistance) were plotted. Computer analysis of the curves to give threshold, maximum slope and plateau was impractical because the upper responses to drugs were usually not determined; the larger doses often had systemic effects, which might alter the tracheal vascular response by baroreceptor reflexes. Therefore, from the dose-response curves, doses which gave 25% changes in vascular resistance were determined (control resistance being taken as 100%); this 25% response was close to the middle of the maximum responses recorded with most drugs (see Figures). In addition to ipsilateral changes in vascular resistance, contralateral changes were also measured when both sides of the trachea were perfused.

Drugs were injected at intervals of at least 15 min, always after complete recovery from the effects of the previous injection. *n* values apply to the number of injections, never more than four per dog on each side for each drug. Since 186 injections of drugs were tested on the two sides of the tracheal circulation in 14 dogs, an average of less than seven injections per perfused vascular bed was used; in this way it was hoped to minimize tachyphylaxis and drug interaction at the expense of inter-individual variation.

Results

All the drugs tested produced dose-related changes in vascular resistance. Table 1 summarizes the results, giving estimations of the doses of drugs that caused 25% change in vascular resistance, and the size of the contralateral responses. Figure 2 gives an example of a

Table 1 Doses (mol) of pharmacological mediators causing 25% changes in tracheal vascular resistance, and their contralateral actions

Drug	*Dose for 25% change* (mol)	*Contralateral action* (%)
PGE_1	7.6×10^{-13} (18)	26.0 ± 1.25 (9)
Bradykinin	1.7×10^{-11} (19)	24.0 ± 2.06 (15)
VIP	4.4×10^{-11} (35)	28.3 ± 3.41 (22)
Substance P	1.5×10^{-10} (12)	24.6 ± 0.67 (6)
PGD_2	9.5×10^{-10} (9)	11.2 ± 1.93 (8)
Methacholine	1.8×10^{-10} (31)	27.1 ± 3.93 (23)
Paf	1.1×10^{-9} (9)	23.0 ± 3.10 (9)
Phenylephrine	1.0×10^{-8} (26)	22.3 ± 4.15 (21)
Histamine	1.6×10^{-8} (15)	17.3 ± 1.03 (10)
Salbutamol	1.7×10^{-8} (6)	30.3 ± 1.02 (6)
$PGF_{2\alpha}$	$> 5.6 \times 10^{-9}$ (19)	30.6 ± 1.45 (8)

Numbers of injections in parentheses. Contralateral responses are mean percentages of ipsilateral effects ± s.e.means. All responses were vasodilatations except for those to phenylephrine which were vasoconstrictions. $PGF_{2\alpha}$ did not decrease resistance 25% or more in the doses tested (up to 5.6×10^{-9} mol).

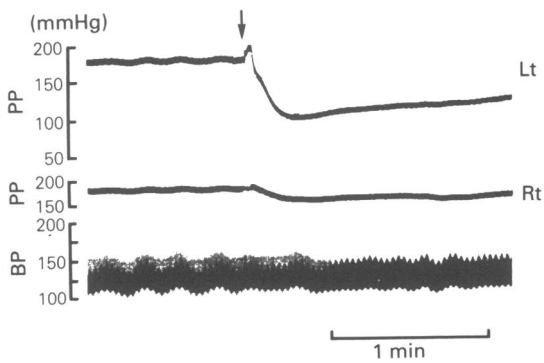

Figure 2 Responses of right and left tracheal vascular beds to close-arterial injection of vasoactive intestinal peptide (6.0×10^{-10} mol, at arrow) on the left side. Traces from above down: left arterial perfusion pressure; right arterial perfusion pressure; systemic arterial blood pressure. The transient rise in left arterial perfusion pressure immediately after the injection is a pressure artefact due to the injection. Subsequently both perfusion pressures fall, with a large effect on the ipsilateral side (43% decrease) and a smaller response on the contralateral side (12% decrease). There are small changes in systemic arterial blood pressure.

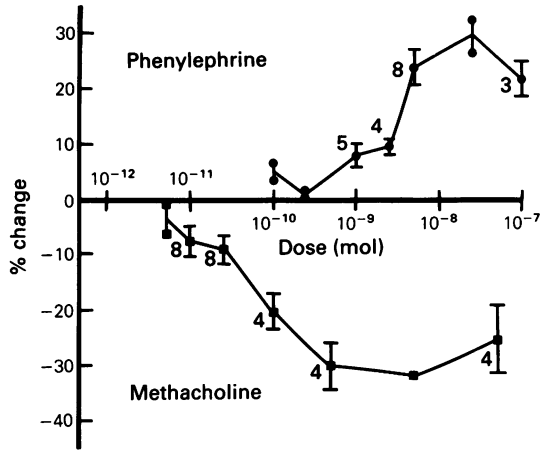

Figure 3 Dose-response curves for methacholine (■) and phenylephrine (●) showing dose in mol (abscissa scale) given by close-arterial injection, against percentage change in tracheal vascular resistance (ordinate scale). Methacholine decreased vascular resistance whereas phenylephrine increased it. In this and subsequent Figures, vasodilatation is downwards. *n* values are shown against mean points, and the vertical lines are s.e.means.

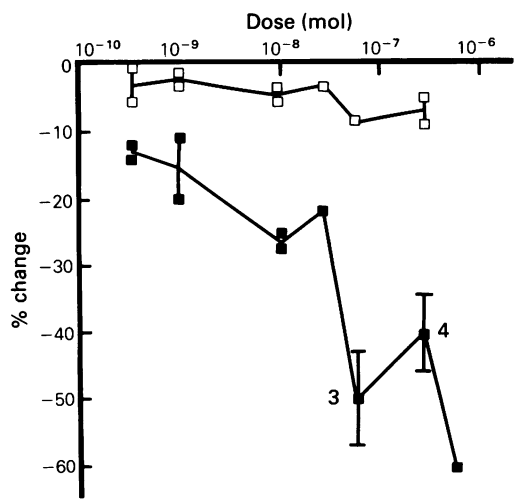

Figure 4 Dose-response curves for histamine showing decreases in vascular resistance (ordinate scale) against dose (abscissa scale): (■) ipsilateral side into which drug was injected; (□) contralateral side. Individual values are given except where vertical lines are shown, which are the s.e.means for the mean values indicated, with *n* values alongside.

response, in this instance to VIP.

The α-adrenoceptor agonist phenylephrine was the only drug tested that always increased vascular resistance (Table 1, Figure 3). Histamine (Figure 4), methacholine (Figure 3) and the β_2-adrenoceptor agonist salbutamol each decreased tracheal vascular resistance.

The peptides bradykinin, substance P and VIP

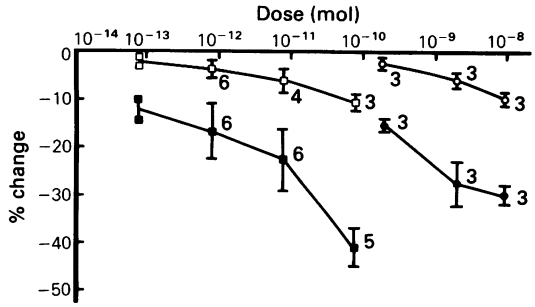

Figure 5 As for Figure 4, but showing the dose-response curves for bradykinin (■, □) and platelet activating factor (Paf) (●, ○).

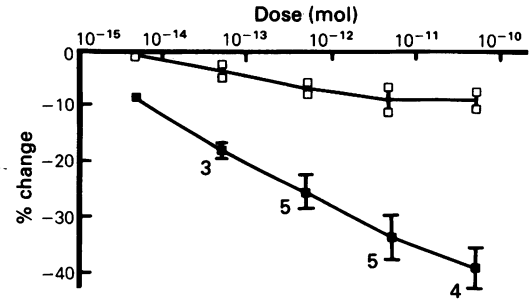

Figure 8 As for Figure 4, but showing the dose-response curves for prostaglandin E_1.

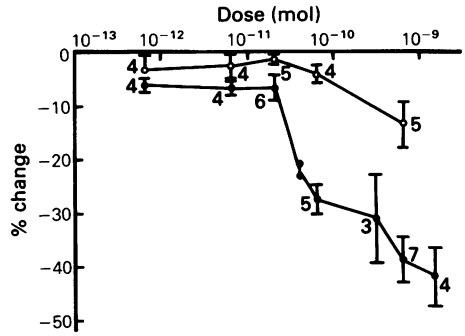

Figure 6 As for Figure 4, but showing the dose-response curves for vasoactive intestinal peptide (VIP).

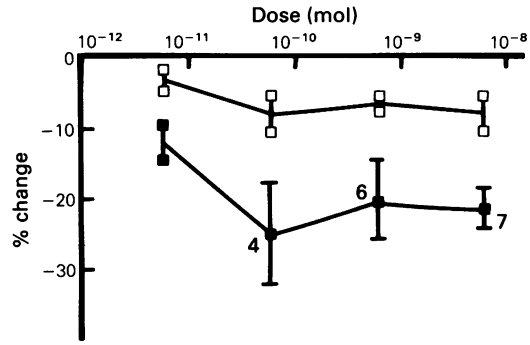

Figure 9 As for Figure 4, but showing the dose-response curves for prostaglandin $F_{2\alpha}$.

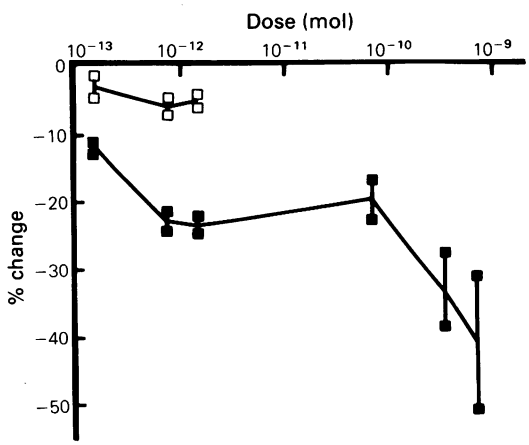

Figure 7 As for Figure 4, but showing the dose-response curves for substance P.

decreased tracheal vascular resistance (Figures 5, 6, 7; Table 1), and were much more powerful than histamine and methacholine (Figures 3, 4; Table 1). Paf was weaker than the peptides (Figure 5; Table 1), and did not decrease vascular resistance by more than 30%; it was unlikely that the Paf was appreciably absorbed on the plastic surfaces used, since the dose-response curve clearly plateaued. Late responses to Paf, possibly due to platelet aggregation, were not studied.

Prostaglandins D_2, E_1 and $F_{2\alpha}$ had wide potency ranges in decreasing tracheal vascular resistance, PGE_1 being very effective even at low doses (Figures 8, 9; Table 1). $PGF_{2\alpha}$ did not decrease vascular resistance by more than 25% in any of the doses used (5.6×10^{-12} to 5.6×10^{-9} mol).

Dose-response curves did not allow accurate determination of the threshold doses of most agents, but the Figures indicate some low doses that gave clear vascular responses.

With regard to contralateral vascular resistance

changes, histamine and PGD_2 had small effects (17.3% and 11.2% respectively) (Table 1). The other drugs more strongly decreased contralateral (compared to ipsilateral) tracheal vascular resistance (23–31%).

Few of the injections of drugs changed pressure in the balloon in the tracheal lumen, although the tracheal muscle contracted in response to electrical stimulation of the superior laryngeal nerve and to asphyxia, and relaxed when the lung inflation reflex was elicited by lung inflation. The exceptions were the higher doses of salbutamol that caused relaxation and the higher doses of histamine that caused contraction.

Discussion

The aim of the present study was to establish dose-related effects of various mediators on the tracheal vascular bed of the dog. This vasculature may be structurally simpler than that of the bronchi, since there is no equivalent to bronchopulmonary anastomoses (Daly & Hebb, 1966). However, the dose-response relationship is still unlikely to be simple because of the anatomy of the airway vascular bed (Laitinen *et al.*, 1986a; 1987a) since any drug may act on arterioles, precapillary sphincters, venules and veins. The dog trachea has no arteriovenous anastomoses (Laitinen *et al.*, 1987a). The existence of tracheal 'capacitance' vessels in the sense of sinusoids is also unclear, although presumably venules can act as capacitance vessels (Laitinen *et al.*, 1987a). The complexity of the airway vascular bed is compounded by the possible connections between the opposite sides of the trachea. Indeed, each drug studied had a contralateral effect (about 10–30%) on vascular resistance.

Constructing a complete dose-response curve was difficult because the highest doses of some drugs sometimes had systemic effects which might change tracheal vascular resistance, for example by baroreceptor reflexes or adrenal medullary secretion. In addition we were concerned about the possibilities of local tissue damage by high doses. Therefore the maximal response was not determined for most drugs although it was reached by some, e.g. methacholine (Figure 3), Paf-acether (Figure 5) and $PGF_{2\alpha}$ (Figure 9). Thus potencies of different drugs were compared by determining the approximate doses which produced 25% changes in vascular resistance (Table 1). The dose-response curves sometimes showed a 'dog-leg' (e.g. VIP, Figure 6) which, with the flatness of some curves (e.g. to bradykinin, substance P and PGE_1; Figures 4, 5, 7), suggests that the curves are composites of actions of the drugs on different parts of the tracheal vasculature with different sensitivities.

The main motor control of the airway vasculature is presumably sympathetic and adrenergic (Daly & Hebb, 1986). α-Adrenoceptor agonists constrict the bronchial (Bruner & Schmidt, 1947; Lung *et al.*, 1976) and tracheal vasculature (this paper), and also decrease tracheal mucosal thickness (Laitinen *et al.*, 1987b). Isoprenaline dilates the bronchial vessels (Lung *et al.*, 1976; Yamatake & Yanaura, 1978) and salbutamol decreases tracheal vascular resistance (this paper). Salbutamol also decreases the permeability of bronchial venules (Persson *et al.*, 1982). Catecholamines given by aerosol may have actions on the airway vasculature as well as on the smooth muscle.

Our finding that methacholine decreases tracheal vascular resistance is consistent with parasympathetic nerve stimulation results (Widdicombe *et al.*, 1986; Laitinin *et al.*, 1987c) which showed a vasodilatation partly blocked by atropine. Thus there may be a cholinergic dilator motor supply to the vasculature.

Inflammatory mediators such as histamine, bradykinin and most prostaglandins increase bronchial blood flow in sheep (Long *et al.*, 1985; Parsons *et al.*, 1985). Our results show that all these agents tested dilate the dog tracheal vasculature, and may partake in the mucosal inflammatory response.

The neuropeptides substance P and VIP decreased vascular resistance, and were far more powerful than histamine and methacholine. VIP-immunoreactive nerve fibres occur around bronchial arteries in dogs, cats and man (Dey *et al.*, 1981; L.A. Laitinen, A. Laitinen and J.G. Widdicombe, unpublished observations). Electrical stimulation of parasympathetic (superior laryngeal) nerves to the dog trachea dilates tracheal vasculature by a mechanism only partly blocked by atropine and partly blocked by hexamethonium (Widdicombe *et al.*, 1986; Laitinen *et al.*, 1987c). Thus VIP may be a vasodilator neuropeptide released from motor nerves in the airways.

Substance P-like immunoreactive afferent nerves occur in the lower respiratory tract of guinea-pig, rat, mouse, cat, man, rabbit (Wharton *et al.*, 1979; Laitinen *et al.*, 1983; Lundberg *et al.*, 1984) and dog (L.A. Laitinen, A. Laitinen and J.G. Widdicombe, unpublished observations). Our results are consistent with a role for substance P as a vasodilator neuropeptide released from afferent nerve fibres in the airways (Lundberg & Saria, 1982), a view consistent with results of nerve stimultion experiments (Laitinen *et al.*, 1987c).

In conclusion, several mediators, irrespective of which chemical class they belong to, have definite, dose-related effects on the canine tracheal vascular bed. Thus the drugs may act on the airway vasculature when given systemically or into the airway lumen by aerosol. Although many of the agents tested had no or small effects on tracheal smooth muscle tone compared with vascular resistance, it is impossible to relate the results to the actions of endogenous mediators

without knowing the sites and concentrations of these mediators released naturally.

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References

BAIER, H., LONG, W.M. & WANNER, A. (1985). Bronchial circulation in asthma. *Respiration*, **48**, 199–205.

BRUNER, H.D. & SCHMIDT, C.F. (1947). Blood flow in the bronchial artery of the anaesthetized dog. *Am. J. Physiol.*, **148**, 648–666.

DALY M. de B. & HEBB, C. (1966). *Pulmonary and Bronchial Vascular Systems*. London: Edward Arnold.

DEY, R.D., SHANNON, JR., W.A. & SAID, S.I. (1981). Localization of VIP-immunoreactive nerves in airways and pulmonary vessels of dogs, cats and human subjects. *Cell Tiss. Res.*, **220**, 231–238.

LAITINEN, A., LAITINEN, L.A., MOSS, R. & WIDDICOMBE, J.G. (1986a). The structure of the lower airway blood vessels in dog. *Clin. Respir. Physiol.* **22** (Suppl. B), 235.

LAITINEN, A., LAITINEN, L.A., MOSS, R. & WIDDICOMBE, J.G. (1987c). The organisation and structure of tracheal and bronchial blood vessels in the dog. *J. Physiol.*, **382**, 10P.

LAITINEN, L.A., LAITINEN, A., PANULA, P.A., PARTANEN, M., TERVO, K. & TERVO, T. (1983). Immunohistochemical demonstration of substance P in the lower respiratory tract of the rabbit and not of man. *Thorax*, **38**, 531–536.

LAITINEN, L.A., LAITINEN, A. & WIDDICOMBE, J.G. (1987b). Effects of inflammatory and other mediators on airway vascular beds. *Am. Rev. Respir. Dis.*, **135**, S67–S70.

LAITINEN, L.A., LAITINEN, A. & WIDDICOMBE, J.G. (1987c). Parasympathetic nervous control of tracheal vascular resistance in the dog. *J. Physiol.*, **385**, 135–146.

LAITINEN, L.A., ROBINSON, N.P., LAITINEN, A. & WIDDICOMBE, J.G. (1986b). Relationship between tracheal mucosal thickness and vascular resistance in dogs. *J. Appl. Physiol.*, **61**, 2186–2193.

LAKSHMINARAYANAN, S., JINDAL, S.K., KIRK, W. & BUTLER, J. (1985). Increases in bronchial blood flow following bronchoconstriction with methacholine and prostaglandin $F_{2\alpha}$ in dogs. *Chest*, **87**, 183S–184S.

LINDSEY, D.C., CHI-HSIUNG, W., CROSS, C.E. & KRAMER, G.C. (1986). Distribution of bronchial blood flow during histamine infusion in anaesthetised sheep. *Thorax*, **41**, 245–246.

LONG, W.M., SPRUNG, C.L., EL FAWAL, H., YERGER, L.D., EYRE, P., ABRAHAM, W.M. & WANNER, A. (1985). Effects of histamine on bronchial artery blood flow and bronchomotor tone. *J. Appl. Physiol.*, **59**, 254–261.

LUNDBERG, J.M., HOKFELT, T., MARTLING, C.-R., SARIA, A. & CUELLO, C. (1984). Substance P-immunoreactive sensory nerves in the lower respiratory tract of various mammals including man. *Cell Tiss. Res.*, **235**, 251–261.

LUNDBERG, J.M. & SARIA, A. (1982). Capsaicin-sensitive vagal neurons involved in control of vascular permeability in rat trachea. *Acta Physiol. Scand.*, **115**, 521–523.

PARSONS, G.H., KRAMER, G.C., LINK, D.P., LANTZ, B.M.T., GUNTHER, R.A., GREEN, J.F. & CROSE, C.E. (1985). Studies of reactivity and distribution of bronchial blood flow in sheep. *Chest*, **87**, 180S–182S.

PERSSON, C.G.A., ERJEFALT, I., GREGA, G.J. & SVENSJO, E. (1982). The role of β-receptor agonists in the inhibition of pulmonary edema. In *Mechanisms of Lung Microvascular Injury*. ed. Malik, A.B. & Staub, N.C. pp. 544–556. New York: Ann NY Acad Sci.

WHARTON, J., POLAK, J.M., BLOOM, S.R., WILL, J.A., BROWN, M.R. & PEARSE, A.G.E. (1979). Substance P-like immuno-reactive nerves in mammalian lung. *Invest. Cell. Pathol.*, **2**, 3–10.

WIDDICOMBE, J.G., LAITINEN, A. & LAITINEN, L.A. (1986). Parasympathetic nervous control of tracheal vascular resistance in the dog. *Fed. Proc.*, **45**, 558.

YAMATAKE, Y. & YANAURA, S. (1978). New method for evaluating bronchomotor and bronchosecretory activities; effects of prostaglandins and antigen. *Jap. J. Pharmacol.*, **28**, 391–402.

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