Cigarette smoke, nicotine and capsaicin aerosol-induced vasodilatation in pig respiratory mucosa

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1 Anaesthetized pigs were used to study vascular responses in the sphenopalatine artery (SPA), superior laryngeal artery (SLA) and bronchial artery (BA) upon exposure to cigarette smoke or aerosol of nicotine and capsaicin. Direct blood flow recordings were made with ultrasonic probes around the vessels.

2 Smoke from one cigarette was administered as inhalation for 2 min with or without a Cambridge filter which removes the particulate matter including nicotine from the smoke. Aerosols of nicotine (2.5 mg) or capsaicin (10 mg) were administered to the nose or the lower airways for 3 min.

3 Cigarette smoke exposure caused a reproducible reduction of the vascular resistance (VR) suggesting vasodilatation in the SPA, SLA, and especially the BA. The vasodilatation was not modified by the Cambridge filter, suggesting that it was caused by vapour phase components rather than nicotine.

4 The smoke effect was not changed after pretreatment with the cyclo-oxygenase inhibitor, diclofenac, or with atropine, guanethidine, H1- or H2-histamine receptor antagonists, nedocromil, or by vagotomy. The smoke-evoked decrease in VR was not modified by the nicotinic receptor antagonist chlorisondamine in the SLA or BA.

5 In pigs pretreated with increasing doses of capsaicin two days earlier, the decrease in VR upon smoke exposure in both the BA and SLA was unaffected while the change in VR was attenuated in the SPA.

6 Nicotine aerosol had no effect on VR in the peripheral airways supplied by the BA while a decrease in VR was observed in the SLA and SPA. The nicotine response was reduced after capsaicin pretreatment in the nasal and upper tracheal circulation.

7 Capsaicin aerosol reduced VR in the vascular beds supplied by the SPA, SLA and BA and this response was markedly reduced after capsaicin pretreatment.

8 The mechanisms underlying vasodilatation upon cigarette smoke exposure in the bronchial mucosa are at the moment unclear while both non-cholinergic parasympathetic and sensory components may be involved in the nose. Capsaicin induced a vasodilatation at all levels via sensory mechanisms, whereas nicotine-evoked vasodilatation is restricted to the upper airway mucosa and is at least partly dependent on parasympathetic reflexes involving capsaicin-sensitive sensory nerves.

Introduction

Inhaled irritants in the upper airway provide triggering responses to defence reflexes that include coughing and sneezing. These effects are potentiated when irritants reach the lower airways (Widdicombe, 1977; Coleridge & Coleridge, 1984). Furthermore, responses to different stimuli vary at diverse levels of the respiratory tract (Sheppard, 1988). Thus, rapid adapting receptors in the larynx and trachea are particularly sensitive to particle irritants such as cigarette smoke rather than to chemicals (Widdicombe, 1986). Intrapulmonary irritant receptors are stimulated by gases such as sulphur dioxide and ozone and also by several inflammatory mediators (Sampson & Vidruk, 1975; Widdicombe, 1988). Stimuli that excite the irritant receptors also cause bronchoconstriction and tracheal mucous secretion (Coleridge & Coleridge, 1986). These effects are mediated by the vagus nerve (Widdicombe, 1988), as well as local endings of C fibre afferents which are present in the respiratory tract (see Lundberg et al., 1988a). The C fibres are sensitive to capsaicin and activated by almost the same group of stimuli as those that affect irritant receptors (Coleridge & Coleridge, 1986). They are also stimulated by inhaled irritants such as the vapour phase of the cigarette smoke in the nasal mucosa (Lundblad & Lundberg, 1984) as well as the rat tracheal mucosa (Lundberg & Saria, 1983). Local nicotine administration also induces protein extravasation in the trachea most likely by the stimulation of nicotinic receptors on sensory nerves (Lundberg et al., 1983, see Saria et al., 1988). Nicotine-evoked sneezing (Lundblad et al., 1984b) or coughing (Forsberg et al., 1988) is not, however, mediated via activation of capsaicin sensitive afferents. Nevertheless, the vascular effects of cigarette smoke exposure in the airways have not yet been directly studied although a classical sign of smoke exposure in the eyes is conjunctival reddening suggesting hyperaemia.

In the present investigation, the nasal, tracheal and bronchial vascular resistance (VR) responses were therefore compared in the pig upon inhalation of cigarette smoke as well as nicotine or capsaicin aerosol.

Methods

Surgical procedure

Twenty pigs (25–30 kg body weight) were fasted overnight and premedicated with ketamine hydrochloride (20 mg kg⁻¹, i.m.). Anaesthesia was then induced by pentobarbitone (20 mg kg⁻¹, i.v.) and maintained by a continuous i.v. infusion of pentobarbitone (3 mg kg⁻¹ h⁻¹). After establishment of anaesthesia as revealed by loss of nociceptive reflexes such as evoked by pinching the nipple or ear, a tracheostomy was made and the pigs were intubated and artificially ventilated with a mixture of air and oxygen using an Engström respirator, model 150. For muscle relaxation, pancuronium bromide (0.25 mg kg⁻¹, i.v.) was given intermittently. The body temperature was kept between 38–39°C by use of a heating pad connected to a thermostat. Briefly (for details on the surgical approach see Matran et al., 1989a), the right femoral vessels were cannulated for continuous recordings of mean arterial blood pressure (MAP),
heart rate (HR) and for intravenous administration of Ringer solution and heparin (5000 i.u.). After partial right mandibulectomy, the sphenopalatine artery (SPA) was dissected free, and a probe was placed around the vessel and connected to a T 202S ultrasonic blood flowmeter (Transonic system Inc., NY, U.S.A.). The bronchial (BA) and the right superior laryngeal (SLA) arteries were also exposed and similar flow probes as above were placed around the vessels.

Arterial blood gas partial pressures were regularly monitored with an automatic blood gas analyser (IL 1302, Metric AB, Solna, Sweden). Pulmonary air flow was measured with a heated Fleisch pneumotachograph Model No. 1 connected to a Statham PM15 E pressure transducer and tracheal pressure was measured with a Statham PM131 TC pressure transducer and was used as the transpulmonary pressure due to the thoracotomy. The signals were analysed by an E 80 T pulmonary computer (Processdata AB, Uppsala, Sweden).

Experimental procedure

A Walton Horizontal Smoking Machine (Guerin et al., 1979) was used to expose animals continuously to cigarette smoke during 2 min or intermittently for 2 s every 10 s. In the same animal, smoke exposure was continued for an extended period or intermittently repeated with a Cambridge glass fibre filter, inserted into the smoke stream, which removed the particulate portion of the smoke and therapy >99% of the nicotine content (Wartman et al., 1959; Coggins et al., 1980). Smoke exposure was given with Kenton’s R1 standard cigarettes which deliver smoke with a known composition: tar 42 mg, nicotine 2.5 mg and carbon monoxide 25 mg per cigarette. Smoke was delivered to the nose via a tube inserted into the right nostril or to the lung via the respirator. In some experiments (n = 5), the reproducibility of the vascular response in the same animal was tested by repeating the cigarette smoke exposure with and without filter three times with 10 min intervals. To analyse the mechanism of cigarette smoke-induced vasodilatation the experiments (n = 6) were also done after pretreatment with guanethidine (3 mg kg⁻¹, i.v.) to reveal a possible influence of sympathetic mechanisms, atropine (1 mg kg⁻¹, i.v.) to block the parasympathetic muscarinic cholinergic influence or chlorisondamine (3 mg kg⁻¹, i.v.) to inhibit the nicotinic receptor transmission in autonomic ganglia (Matran et al., 1989a). To block neuronal mechanisms including the stimulating or blocking nicotinic receptors, smoke exposure was also carried out after aerosol application of the local anaesthetic substance lignocaine (40 mg in 2 ml NaCl) (n = 6) or nedocromil (60 mg in 3 ml NaCl) (n = 6) given to the lung for 3–4 min with an ultrasonic nebulizer (Engström Medical). Because stimulation of rapidly adapting receptors causes pulmonary effects by a reflex increase in vagal efferent activity (see Widdicombe, 1988), experiments (n = 5) were also carried out after sectioning of both cervical vagal nerves. Furthermore, six pigs were pretreated with diclofenac (3 mg kg⁻¹, i.v.) to block a possible release of vasodilator prostaglandins or with a combination of the H₂-histamine antagonist, cimetidine (10 mg kg⁻¹) and the H₁-histamine antagonist, terfenadine (2 mg kg⁻¹) (Alving et al., 1989).

Two days after systemic pretreatment with capsaicin, cigarette smoke exposure was also carried out. After anaesthesia (see above) 10 animals were intubated and artificially ventilated. When they were anaesthetized (see above) increasing doses of capsaicin (total dose 50 mg kg⁻¹) were administered by slow (about 3 ml min⁻¹) injection given subcutaneously (four sites on each side) over 4 h. Then, 2 h after the last injection the animals were allowed to regain spontaneous breathing and the tubes removed. The behaviour was regularly monitored during a further 2 h period. No difference in the behaviour of the pig was noted in the capsaicin pretreated animals when they regained consciousness compared to a vehicle pretreated group (n = 10) used as control. These experiments were approved by the Ethical Committee for animal research at the Karolinska Institute.

Nicotine aerosol (2.5 mg in 2 ml NaCl) and capsaicin aerosol (10 mg in 1 ml 60% ethanol), were given to the nose and the lung by use of an ultrasonic nebulizer in 9 control pigs and after pretreatment with capsaicin. Ethanol (60%) did not induce any vascular reactions. Furthermore, intravenous injection of nicotine (250 μg kg⁻¹) was performed in five controls and five chlorisondamine pretreated animals.

Apart from the pretreatment with capsaicin, the pigs were killed by an overdose of pentobarbitone at the end of the experiment.

Calculations

Change in blood flow in the vascular beds supplied by the SPA, SLA and BA following injections were defined as both peak changes in vascular resistance (VR) and the total integrated changes in ml from basal values. VR was calculated as the MAP divided by the blood flow in the supplying artery (Daly & Hebb, 1966). Data are given as mean ± s.e.mean and statistical differences were estimated by Student's paired t test or Mann Whitney U-test. Differences were considered to be significant when P < 0.05.

Drugs

The following (source in parentheses) were used: ketamine hydrochloride (Ketalar, Parke-Davis, U.S.A.), pentobarbitone (Mebumal) and atropine (ACO, Solna, Sweden), pancuronium bromide (Pavulon, Organon, The Netherlands), guanethidine, chlorisondamine and diclofenac (Ciba-Geigy, AG, Basel, Switzerland), chloridrine and terfenadine (Sigma Co., St Louis, U.S.A.), nicotine bitartrate (Swedish Tobacco Company, Sweden), capsaicin (Fluka Chemie AG, Switzerland), lidocaine (Astra, Södertälje, Sweden) and nedocromil (Fisons, Leicestershire, England).

All the substances except capsaicin and terfenadine were dissolved in saline solution. Capsaicin was initially dissolved in 10% ethanol and 20% Tween 80 for subcutaneous injection or in 60% alcohol for aerosol challenge and subsequently diluted in saline solution. Terfenadine was dissolved in 60% ethanol.

Results

Response to cigarette smoke exposure

Continuous cigarette smoke inhalation for 2 min caused a long lasting increase (5 to 7 min) in blood flow in the vascular beds supplied by sphenopalatine (SPA), superior laryngeal (SLA) and bronchial (BA) arteries (Figures 1a, 2a) with the largest decrease in VR (60%) suggesting vasodilatation in BA (Table 1). There was no significant difference in the total integrated blood flow increase (Figure 3) or the peak decrease in VR (Table 1) upon smoke exposure in the presence of the Cambridge filter in any of the vascular beds. Furthermore, MAP and HR were not changed upon cigarette smoke inhalation with filter while MAP and HR were increased by 82% and 23%, respectively, in 2 pigs out of 10 during the inhalation of smoke without filter. The smoke-evoked peak decrease in VR or the integrated blood flow model increase was not modified by capsaicin pretreatment in SLA and BA (Figures 1b, 2b, 3 and Table 1). In contrast, although the peak VR change was un influenced by capsaicin pretreatment (Table 1), the local integrated blood flow increase was reduced in the SPA both in the presence (P < 0.01) and in the absence (P < 0.05, Mann Whitney U test) of the Cambridge filter (Figures 1b, 3). Cigarette smoke-induced vasodilatation was reproducible at short intervals in BA (Figure 4). Intermittent exposure to cigarette smoke also provoked a clear cut increase in blood flow in BA which was not reduced by capsaicin pretreatment (Figure 5).
Lignocaine or nedocromil aerosol in the lung and bilateral vagotomy had no effect on the smoke induced decrease in VR of BA (Table 2). Intravenous injection of chlorisondamine lowered the basal blood flow in the vascular beds supplied by SLA and BA but this drug also decreased the MAP and consequently the smoke evoked change in VR was not modified (Table 2). On the other hand, chlorisondamine pretreatment increased basal SPA blood flow from 38 ± 9 to 112 ± 23 ml min⁻¹ and decreased MAP from 138 ± 18 to 91 ± 10 mmHg. No decrease in the vasodilator response was

Table 1  Peak decrease in vascular resistance in control and systemically capsaicin-pretreated pigs exposed to cigarette smoke without (-) or with (+) Cambridge filter or aerosol of nicotine (2.5 mg) and capsaicin (10 mg)

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<thead>
<tr>
<th></th>
<th>Cambridge smoke</th>
<th>Nicotine aerosol</th>
<th>Capsaicin aerosol</th>
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<tr>
<td></td>
<td>Control</td>
<td>Capsaicin pretreatment</td>
<td>Control</td>
</tr>
<tr>
<td>Sphenopalatine artery</td>
<td>+ 35.7 ± 3.5</td>
<td>29.2 ± 3.0</td>
<td>17.5 ± 3.6</td>
</tr>
<tr>
<td>Superior laryngeal artery</td>
<td>- 42.6 ± 4.1</td>
<td>35.8 ± 2.6</td>
<td>42.8 ± 7.4</td>
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<tr>
<td>Bronchial artery</td>
<td>+ 51.0 ± 5.4</td>
<td>38.0 ± 5.3</td>
<td>60.4 ± 4.5</td>
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Data are given as mean ± s.e.mean and expressed as percent change compared to control conditions. n = 6–10, **P < 0.01, ***P < 0.001 by Mann Whitney U test. ND = not determined.
observed upon smoke exposure in SPA after chlorisondamine pretreatment (Table 2). Moreover, pretreatment with diclofenac or antihistamines did not change the smoke response in any of the three vascular beds (Table 2).

Smoke exposure without filter in the lung provoked a bronchodilatation as revealed by reduction of pulmonary resistance by 24.4 ± 5.3% (P < 0.001) and increase in dynamic compliance by 15 ± 1.6% (P < 0.001 Student’s t test, n = 8). Although it was absent upon insertion of the Cambridge filter, this bronchomotor response was not modified by pretreatment with capsaicin, chlorisondamine, diclofenac or antihistamines; their respective values were 26 ± 5.3%, 27 ± 9.4%, 21 ± 6.1% and 26 ± 4.0%.

**Response to capsaicin**

Capsaicin aerosol caused a slowly developing, long lasting increase in blood flow with a peak decrease in VR of 25–30% (Table 1) in SPA, SLA and BA (Figures 1, 2). In the capsaicin pretreated pigs, capsaicin aerosol-evoked vasodilatation was markedly reduced in BA and SPA (P < 0.01 and P < 0.001, respectively, Mann Whitney U test) while it was lowered in the SLA (P < 0.05) (Figure 6, Table 1). Capsaicin aerosol had no effect on MAP or HR in both control and capsaicin pretreated animals. Furthermore, the basal VR in SPA, SLA and BA was not altered by the pretreatment with capsaicin. Pulmonary resistance or dynamic compliance was not changed by capsaicin aerosol.

<table>
<thead>
<tr>
<th>Table 2 Peak decrease in vascular resistance in control and systemically pretreated-pigs with chlorisondamine, diclofenac, antihistamines, nedocromil aerosol, lidocaine aerosol and after bilateral vagotomy (for details see Methods) on the vasodilator effect of cigarette smoke exposure in the presence of Cambridge filter</th>
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<tbody>
<tr>
<td><strong>Sphenopalatine artery</strong></td>
</tr>
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<td><strong>Control</strong></td>
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<tr>
<td>Chlorisondamine</td>
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<td>Diclofenac</td>
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<td>Antihistamines</td>
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<td>Nedocromil</td>
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<td>Lignocaine</td>
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<td>Bilateral vagotomy</td>
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</tbody>
</table>

Data are given as mean ± s.e.mean and expressed as percent change compared to control conditions. n = 5–6. No significant difference by Mann Whitney U test between control and pretreatment.
Response to nicotine

In control pigs, nicotine aerosol also induced a decrease in VR in the nasal and upper tracheal circulation while it had no effect on the peripheral airways supplied by BA (Figure 6, Table 1). In capsaicin pretreated pigs, both the area under the curve of blood flow and the change in VR evoked by nicotine were reduced in SPA (P < 0.001) and SLA (P < 0.01, Mann Whitney U test) (Figure 6, Table 1). Nicotine aerosol did not influence MAP, HR or the pulmonary calibre. Intravenous injection of nicotine provoked an increase in blood flow in the SPA, SLA and BA (not shown). Since nicotine also increased the MAP, the VR in the airway mucosa as well as pulmonary calibre were not modified by the systemic injection. Pretreatment with chlorisondamine completely blocked the vascular effects of i.v. nicotine (not shown).

The vehicle pretreated group was used as control to establish whether vehicle injection modified vasodilator responses to cigarette smoke, nicotine or capsaicin aerosol. Capsaicin-evoked vasodilatation was not changed in vehicle pretreated pigs compared to non-pretreated pigs. The vasodilator effects of cigarette smoke exposure and nicotine aerosol were not changed compared to control pigs (non-pretreated pigs). It was clear that vehicle pretreatment did not modify the effects obtained with different irritant substances.

Discussion

The present findings show a clear cut vasodilatation as revealed by decreased VR upon cigarette smoke exposure in the vascular beds supplied by BA and SLA. Cigarette smoke can be subdivided into a particulate portion, with tar and nicotine, and a vapour phase containing a variety of gases and irritant chemicals (see Stedman, 1967). It is likely that cigarette smoke-induced vasodilatation is mainly due to components in the vapour phase rather than tar or nicotine considering the inefficiency of the Cambridge filter in modifying the response. Furthermore, nicotine aerosol had no effect on the BA where the smoke-induced vasodilatation was greatest. The effect of nicotine aerosol in the larynx and bronchi is in accordance with results from vagal nerve stimulation in the pig (Matran et al., 1989a) where vasodilator neuronal mechanisms were found to be purely sensory in the bronchi while parasympathetic non-cholinergic and cholinergic mechanisms involving receptor transmission dominated in the larynx. Many foreign irritants such as dust, ammonia vapour, ether and cigarette smoke evoke irritant reflexes from the respiratory tract (Coleridge & Coleridge, 1984). Tracheal insufflation of powdered talc in cats (Widdicombe, 1954) and of carbon dust in rabbits (Sellick & Widdicombe, 1971) stimulate irritant receptors while the effect of inhaled chemical irritants are less consistent. Furthermore, these irritant substances also cause laryngeal constriction, bronchoconstriction and mucus secretion (Widdicombe, 1964). In our model, cigarette smoke exposure was associated with macroscopical signs of nasal and tracheobronchial secretion as revealed by visual inspection. Unexpectedly, cigarette smoke exposure without filter provoked bronchodilatation in the lung. Since smoke with filter did not evoke any bronchial response, either smoke particles or nicotine may be involved in the smoke-induced bronchodilatation. Vagal activation may not only induce bronchoconstriction but also bronchodilatation (see Diamond et al., 1983) presumably via non-adrenergic, non-cholinergic (NANC) mechanisms which are dependent on nicotinic receptor transmission in local airway ganglia. Alternatively nicotine may activate the sympathetic-adrenal system and release catecholamines which have bronchodilator actions. Such an effect is also supported by the slight tachycardia and increase in MAP in a few animals upon smoke exposure without, but not with, the filter; however, this sympathetic-adrenal response should have been abolished by chlorisondamine. Furthermore, the bronchodilatation induced by cigarette smoke was not abolished by capsaicin pretreatment, suggesting that sensory C-fibres were not involved. Since cigarette smoke in man is generally assumed to provoke bronchoconstriction dependent on smoke particles activating a vagal cholinergic reflex (Sterling, 1967), the present data from anaesthetized pigs, where cigarette smoke-evoked bronchodilatation may have resulted from the vagal reflexes being attenuated by anaesthesia while the local effect was still intact. Since nicotine aerosol did not change bronchial calibre, other components of the smoke may be of relevance.

The cigarette smoke-induced vasodilatation in BA was not abolished by the local anaesthetic lignocaine, by bilateral vagotomy or atropine and chlorisondamine, suggesting that irritant receptors via an afferent vagal pathway are less likely to be involved.

Since the C-fibres are activated by almost the same group of stimuli as those that affect myelinated irritant receptors (Coleridge & Coleridge, 1986), the atropine-resistant vasodilatation in the airway mucosa upon cigarette smoke exposure might be mediated via a capsaicin-sensitive mechanism. In a recent study, we have shown that local blood flow in the upper trachea (SLA) is regulated by both cholinergic and non cholinergic parasympathetic, as well as capsaicin-sensitive sensory components, whereas the vagal control of the bronchial circulation (BA) seem to be involved exclusively in capsaicin-sensitive sensitive sensory nerves (Matran et al., 1989a). Activation of C-fibre afferents by irritant chemicals including nicotine induces a release of multiple tachykinins (Saria et al., 1988) and calcitonin gene-related peptide (CGRP) (Martling et al., 1988) from the lung. These peptides are potent vasodilator agents (see Lundberg & Saria, 1987) and both substance P (SP) and CGRP mimic the reduction in the tracheobronchial circulation of the pig (Matran et al., 1989b). However, in capsaicin-pretreated pigs, the vasodilatation induced by cigarette smoke was not modified in BA and SLA in spite of the fact that the capsaicin aerosol-induced vasodilatation was strongly reduced, suggesting that sensory nerves were not involved in the smoke response.

On the other hand, cigarette smoke-induced vasodilatation was lowered in the BA in capsaicin-treated animals. These data are in agreement with earlier work on guinea-pigs which demonstrated that smoke-induced irritation is primarily due to activation of capsaicin-sensitive sensory nerves in the nasal mucosa by vapour phase components (Lundberg & Lundberg, 1984). It may therefore be postulated that axon reflex activation by cigarette smoke can evoke local release of neuropeptides such as SP and CGRP in the tracheobronchial circulation of the pig (Matran et al., 1989b). However, our data, which show that systemic pretreatment with capsaicin did not induce a total loss of response to irritant substances in the nasal mucosa, suggest the possibility that cigarette smoke not only activates capsaicin sensitive C-fibres but may also stimulate other types of chemoafferent sensibility. Since the decrease in nasal VR upon exposure to smoke was not influenced by the Cambridge filter, however, it is likely that vapour phase components rather than nicotine activate afferent nerves with subsequent parasympathetic reflexes and decrease in nasal VR. Since atropine did not influence the smoke response, parasympathetic, non-cholinergic nasal vasodilator mechanisms (see Lundberg, 1981) may be activated by smoke.

Irritant substances such as cigarette smoke may also result in release of histamine and various prostanoids, which are known to provoke vasodilatation. However, cyclo-oxigenase inhibition with diclofenac, antihistamines, such as cimetidine and terfenadine, or mast cell stabilization by nedocromil did not influence the acute response induced by cigarette exposure. Since diclofenac does not inhibit release of other mediators such as lipoxin A4 which also causes vasodilatation (Dahlen et al., 1987), this issue has to be studied further.

The nicotine aerosol-induced vasodilatation in the SPA and SLA was strongly reduced after capsaicin pretreatment, suggesting a mechanism that is dependent on capsaicin-sensitive
neuroines in accordance with earlier works on protein extravasation (Lundberg & Saria, 1983; Lundberg et al., 1988b). Nicotine as well as capsaicin aerosol did not induce a nasal hypertensive reflex in the anaesthetized control pigs while intravenous injection of nicotine provoked an increase in MAP and HR. This nasal cardiovascular reflex following chemical irritation is mediated via capsaicin-sensitive fibres in anaesthetized guinea-pigs (Lundblad et al., 1984a), whereas the sneezing response to nicotine is not affected by capsaicin pretreatment in conscious animals (Lundblad et al., 1984b). Thus nicotine should activate both irritant receptors on myelinated nerves and C fibre afferents in the nasal mucosa. However, the absence of hypertensive response may be explained by the anaesthesia with pentobarbitone which blocked the central nervous system transmission of the nasal reflex.

The absence of nicotine-evoked changes in BA may be explained either by differences in the nervous vascular control between the bronchial mucosa on one hand and the upper tracheal and nasal mucosa (see Matran et al., 1989a) or alternatively that much higher local concentrations of nicotine are required to elicit vasodilatation. The nicotine dose used should, however, be comparable with the composition of the standard cigarette (2.5 mg). Nevertheless, the nicotine component in the smoke does not seem to be of importance for the vasodilatation upon cigarette smoke exposure either in the lung or the nose. This finding is in contrast to the pulmonary reflexes elicited by cigarette smoke inhalation in dogs where the nicotine component is essential (Lee & Morton, 1986). The protective cough reflex upon nicotine inhalation in the guineapig is not, however, mediated via capsaicin-sensitive sensory nerves (Forberg et al., 1988).

In conclusion, cigarette smoke exposure provokes marked vasodilatation in the pig airway mucosa. Our results show that the local blood flow increase in the nose produced by cigarette smoke is mediated at least partially by parasympathetic and sensory components. However, in the peripheral airways supplied by BA the mechanisms underlying the vasodilatation upon cigarette exposure are unclear. Other mechanisms including direct actions of vapour phase components in the smoke (Stedman, 1967) should therefore be investigated.

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