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Sympathetic vascular control of the pig nasal mucosa: adrenoceptor mechanisms in blood flow and volume control

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1 The adrenoceptor mechanisms influencing the total blood flow, volume and superficial blood flow in the nasal mucosa of pigs anaesthetized with pentobarbitone have been characterized by use of various agonists and antagonists.

2 Local intra-arterial bolus injection of the selective α_1-agonist phenylephrine, the selective α_2-agonist UK 14.304, the mixed α_1/α_2-agonist oxymetazoline and the mixed α/β-agonists noradrenaline (NA) and adrenaline induced dosed-related reduction of nasal arterial blood flow (BF), nasal mucosal volume (V, reflecting capacitance vessel function) and the laser Doppler flowmetry signal (LDF, reflecting superficial movement of blood cells). The rank order of α-agonist potency regarding BF reduction was UK 14.304 > oxymetazoline > NA > phenylephrine = adrenaline. For the volume response the potency order was UK 14.304 > oxymetazoline = NA = adrenaline > phenylephrine while for the reduction of the LDF signal the potency was UK 14.304 = NA = adrenaline > oxymetazoline > phenylephrine. The selective β_2-agonist terbutaline caused dose-dependent increase of BF whereas only a small augmentation of the V was obtained upon the highest dose (40 nmol) while no modification of the LDF signal was observed.

3 After pretreatment with the selective α_1-antagonist prazosin, the response to phenylephrine was abolished while the selective α_2-antagonist idazoxan attenuated the effect of UK 14.304. After pretreatment with α-antagonists, both NA and adrenaline caused biphasic effects with constriction followed by vasodilatation for BF, but not for V or LDF. This vasodilatation was blocked by the β-antagonist propranolol.

4 The reduction in nasal BF and V upon sympathetic nerve stimulation was attenuated both by prazosin and idazoxan. Propranolol enhanced the remaining reduction of BF but not of V in the presence of α-antagonists.

5 It is concluded that α_2-adrenoceptor mechanisms in the pig nasal mucosa are dominating for the BF, V and LDF responses to exogenous agonists. α_1-Adrenoceptors also seem to be involved in the sympathetic control of BF, V and LDF. Activation of β_2-receptors increases mainly BF and does not influence the LDF signal.

Introduction

The nasal mucosal vascular bed is composed of arteries, arterioles (resistance vessels) and a sub-epithelial capillary network which is drained into collecting veins and large venous sinusoids (capacitance vessels) (Cauna, 1982). Nasal blood vessels receive a very dense sympathetic innervation (Dahlström & Fuxe, 1965) and noradrenaline (NA) is considered as the classical postganglionic transmitter (Salem, 1972; Malm, 1974a; Änggård & Edwall, 1974; Hall & Jackson, 1978; Eccles 1982; Berridge & Roach, 1986). In the pig (Lacroix *et al.*, 1988a, b; 1989) and cat (Lundblad *et al.*, 1987) there is also evidence that non-adrenergic mechanisms are involved in the sympathetic vascular control of the nasal mucosa. The classification of adrenoceptors into α_1- and α_2-subtypes has been a result of the development of various selective agonists and antagonists (see Starke, 1981; 1987). Non-selective α-adrenoceptor agonists acting on both α_1- and/or α_2-receptors are of common clinical use as nasal decongestants (Empey & Medder, 1981). Andersson & Bende (1984) reported that in the human nasal mucosa, α_2-receptors are most important for control of resistance vessels while β-receptor mechanisms

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have minor influence on nasal blood flow (BF) as measured by the ^{133}Xe washout method. However, a detailed characterization of α- as well as β-adrenoceptor mechanisms for exogenous agents and endogenously released NA involved in the control of BF and volume (V, i.e. capacitance vessel function) as well as superficial blood flow as revealed by the laser Doppler flowmeter signal (LDF) remain to be established in the nasal mucosa. By means of a recently developed experimental model which allowed simultaneous recordings of nasal arterial BF, V (Lacroix *et al.*, 1988a) and the LDF signal (Lacroix *et al.*, 1989), we have therefore aimed to characterize adrenoceptor mechanisms in the different compartments of the pig nasal vascular bed.

Methods

Surgical procedure

The experiments were performed on 12 pigs of either sex (body weight 25–30 kg). After premedication with ketamine hydrochloride (20 mg kg^{-1}, i.m.) and atropine (0.05 mg kg^{-1}, i.m.), the anaesthesia was induced with sodium pentobarbitone (20 mg kg^{-1}, i.v.) and maintained with continuous i.v. infusion of the same agent (3 mg kg^{-1} h^{-1}). For skeletal muscle relaxation, pancuronium bromide (0.25 mg kg^{-1}, i.v.) was given at regular intervals. The animals were artificially ventilated with a volume regulated ventilator (Engström, model 150, Sweden) and the body temperature was kept between 37–38°C. Catheters were placed in the femoral artery for systemic blood pressure monitoring and sampling for blood gas analysis, and in the femoral vein for drug and fluid administration. Briefly, the external carotid artery and the superficial jugular vein were dissected up to the sphenopalatine fossa. All the arterial branches located down stream to the superficial temporal artery were ligated and cut (for details of the surgical approach see Lacroix *et al.*, 1988a). Nasal arterial blood flow was recorded with a Transonic flow probe (2-4RB143) of 2–4 mm diameter placed around the internal maxillary artery in the portion proximal to the superficial temporal branch. The flow probe was connected to a T202S ultrasonic blood flowmeter (Transonic system Inc, NY, USA). The superficial temporal artery was cannulated with a PE 90 catheter which allowed selective injections of agents into the main nasal arterial blood supply. Volume changes of the nasal cavity (mainly reflecting blood content of the venous sinusoids) were recorded with the latex balloon method (Malm, 1973; Lacroix *et al.*, 1988a). The superficial mucosal blood flow was recorded with a laser Doppler flowmeter probe (Periflux PF 2B, Perimed KB, Sweden) placed on the surface of the anterior tip of the inferior turbinate in a portion which was not in contact with the balloon. Moving blood cells in the capillaries change the frequency of the back-scattered light according to the Doppler principle. The output signal is a function of the product of red cell volume and their mean velocity. The movement of blood cells is measured to a tissue depth determined by the absorption coefficient of the tissue studied as well as by the wavelength used. By means of this LDF method, former studies on the superficial mucosal blood flow, the red light (632.8 nm, He-Ne, 2 mW) from the PF2, has been shown to penetrate the intestinal mucosa to a depth of 2–4 mm (Ahn *et al.*, 1985) and to about 1 mm depth in dark tissue such as the renal cortex (Stern, 1975). The LDF signal was not secondarily influenced by the balloon volume change *per se* as shown by filling or removing 10 ml of saline from the balloon in the presence of the LDF probe within the nasal cavity. Arterial blood flow, volume of the mucosa and the LDF signal were recorded in parallel on a Grass polygraph 7B (Grass Instrument Co., USA). The ipsilateral cervical sympathetic trunk was dissected and cut 2–3 cm below the superior cervical ganglion and the cranial portion of the nerve was placed on a bipolar platinum electrode connected to a Grass S 88 stimulator.

Cervical sympathetic nerve stimulations (15 V, 5 ms) were performed with single impulses or at a continuous frequency of 2 Hz for 2 min (giving a total of 240 impulses).

Experimental procedure

The nasal vascular effects (BF, V and LDF) upon sympathetic nerve stimulation (single pulse and 2 Hz) and local i.a. injection of adrenaline (0.055–55 nmol), NA (0.06–60 nmol), the selective α_2-agonists UK 14.304 (0.05–50 nmol) and oxymetazoline (0.04–40 nmol), the selective α_1-agonist phenylephrine (0.05–50 nmol) and the selective β_2-agonist terbutaline (0.04–40 nmol) were studied by the following procedure:

Group 1 ($n = 4$): Nerve stimulations and local i.a. injections were first performed under control conditions and then repeated 30 min after inhibition of neuronal uptake of monoamines by infusion of desipramine (DMI) (0.5 mg kg^{-1}, i.v.), 10 min after subsequent infusion of the selective α_1-antagonist prazosin (0.1 mg kg^{-1}, i.v.) and 15 min after subsequent administration of the β_1- and β_2-antagonist propranolol (0.5 mg kg^{-1}, i.v.).

Group 2 ($n = 4$): Nerve stimulations and local i.a. injections were performed under control conditions then 30 min after infusion of DMI, 10 min after sub-

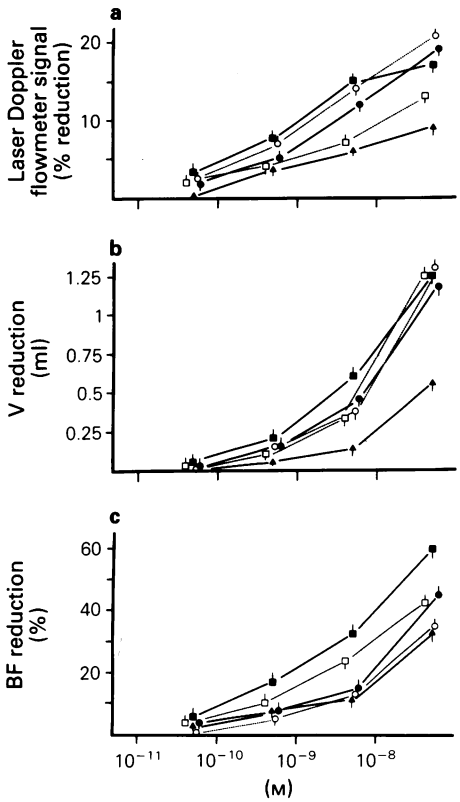

Figure 1 Effects of local i.a. bolus injections of UK 14.304 (■—■), oxymetazoline (□--□), noradrenaline (●—●), adrenaline (○--○) and phenylephrine (▲—▲) on the laser Doppler flowmeter signal (% reduction) the volume (V, in ml) of the nasal mucosa and the nasal arterial blood flow (BF, % reduction). Data are given as mean with s.e.mean shown by vertical lines; $n = 8$.

sequent infusion of the selective α_2- antagonist idazoxan (0.5 mg kg^{-1}, i.v.) and 15 min after propranolol (0.5 mg kg^{-1}, i.v.).

Group 3 ($n = 4$): Thirty min after infusion of DMI, nerve stimulations and local i.a. injections were performed 10 min after combined i.v. pretreatment with idazoxan (0.5 mg kg^{-1}) and prazosin (0.1 mg kg^{-1}), and 15 min after subsequent addition of propranolol (0.5 mg kg^{-1}, i.v.).

Calculations

Blood flow reduction is expressed as the percentage decrease compared to zero flow (100% reduction) obtained by clamping the external maxillary artery upstream to the flow probe. Calibration of the nasal cavity volume changes was achieved by removal of 1 ml from the reservoir directly connected to the latex balloon placed in the nasal cavity (see Lacroix *et al.*, 1988a). Under control conditions, the balloon contained 5 ± 1.5 ml. The LDF signal is expressed as a percentage of the maximal internal calibration signal (100%). The duration of the vascular responses is given in seconds and calculated as the time for recovery of basal values from the end of the sympathetic stimulation or, for local i.a. injections of exogenous α- and β-agonists, from the beginning of the vascular effects until return to former baseline. Data are given as means ± s.e.mean and statistical differences were estimated with Student's paired t test or Kruskal-Wallis analysis of variance with multiple comparisons (Theodorsson-Norheim, 1986).

Drugs

The following drugs (source) were used: ketamine hydrochloride (Ketalar, Parke-Davis, U.S.A.), sodium pentobarbitone (Mebumal), atropine (ACO, Sweden), pancuronium bromide (Pavulon, Organon, Netherlands), noradrenaline hydrochloride ((±)-arterenol), adrenaline hydrochloride ((±)-adrenaline) and phenylephrine hydrochloride (Sigma Chemical Company, USA), desipramine hydrochloride (DMI) and propranolol (Inderal, Ciba, Basel, Switzerland), oxymetazoline hydrochloride, terbutaline (Draco, Sweden). UK 14.304 (5-bromo-6-(imidazoline-2-yl amino-quinoxaline tartrate), prazosin hydrochloride (Pfizer, Sandwich), idazoxan (RX 781094, Reckitt & Colman, Hull). All solutions except prazosin (which was initially dissolved in ethanol) were freshly prepared before each experiment by dissolving the compounds in sterile 0.9% w/v NaCl solution.

Results

The local i.a. administration of the adrenoceptor agonists or the sympathetic nerve stimulations did not significantly affect the heart rate (HR) or the mean systemic arterial blood pressure (MAP). The HR was, however, increased by 22 ± 4% after i.v. infusion of idazoxan and by 16 ± 2% after prazosin. Prazosin induced a MAP reduction of 10 ± 2%. However, the basal value of BF (75 ± 10 ml min^{-1}), the V and LDF signal (50 ± 10%) were not significantly affected by the administration of prazosin, idazoxan or propranolol.

Control effects of adrenoceptor agonists

Local i.a. injections of the five α-adrenoceptor agonists studied gave dose-related reductions of BF, V and LDF (Figure 1). The relative potency of the

Table 1 Local i.a. bolus doses required of various adrenoceptor agonists to reduce, under control conditions, the nasal arterial blood flow by 25% (BF 25), the nasal mucosal volume by 0.5 ml (V 0.5) and the laser Doppler flowmeter signal by 10% (LDF 10) in pigs anaesthetized with pentobarbitone

	Blood flow (25%) (nmol)	*Mucosal vol.* (0.5 ml) (nmol)	*LDF* (10%) (nmol)
Agonist			
UK 14.304	1.6 ± 0.3*	3.2 ± 0.4*	1.1 ± 0.2**
Oxymetazoline	5.1 ± 0.5*	5.7 ± 0.5	12.0 ± 1.5
Noradrenaline	8.7 ± 0.7*	7.0 ± 0.6***	3.1 ± 0.5***
Phenylephrine	18.0 ± 3.0	39.0 ± 5.0	50.0 ± 6.0
Adrenaline	20.0 ± 4.0	7.5 ± 0.6	1.5 ± 0.4

* $P < 0.05$; ** $P < 0.001$, *** $P < 0.001$ (Student's paired t test) when compared to the following agent. Data are given as mean ± s.e.mean, $n = 8$.

agonists under control conditions were somewhat different for each vascular parameter studied, as shown in Table 1. The rank order potency regarding BF reduction was UK 14.304 > oxymetazoline > NA > phenylephrine = adrenaline. For the V response the order was UK 14.304 > oxymetazoline = NA = adrenaline > phenylephrine while for the reduction of the LDF signal the potency order was UK 14.304 = NA = adrenaline > oxymetazoline > phenylephrine. Local i.a. administration of terbutaline caused a dose-dependent increase of BF whereas a small augmentation of V was obtained only upon the highest dose (40 nmol) (Figure 2). The LDF signal was not affected by terbutaline (not shown).

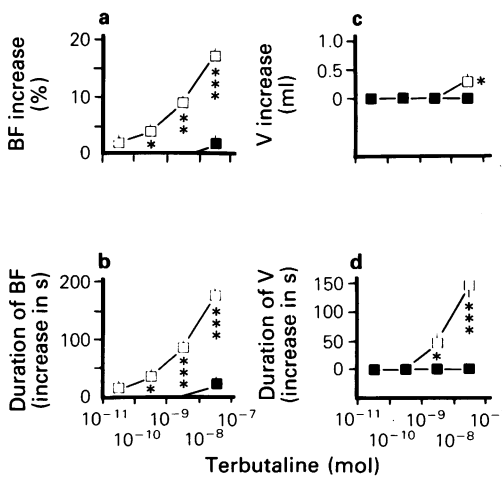

Figure 2 Effects of local i.a. bolus injections of the β_2-agonist terbutaline before (□—□) and after (■—■) pretreatment with propranolol (0.5 mg kg^{-1}, i.v.). (a) Nasal arterial blood flow (BF) % increase, (b) duration (in s) of the BF increase, (c) nasal mucosal volume (V, in ml) increase and (d) duration (in s) of the V increase. Mean (with s.e.mean shown by vertical lines) are given, $n = 8$. * $P < 0.05$, ** $P < 0.01$; *** $P < 0.001$ (Student's paired t test).

Effects of desipramine and adrenoceptor antagonists

Under control conditions, a parallel reduction of the LDF signal, BF and V of 19 ± 4%, 44 ± 3.5% and 1.17 ± 0.13 ml, respectively, was observed upon local i.a. injection of NA (60 nmol) (Figures 1, 3, Table 2). The peak LDF, BF and V responses to NA were enhanced by 18 ± 3.5% (NS), 38 ± 6% ($P < 0.05$) and 27 ± 5% ($P < 0.05$) after DMI pretreatment (Table 2, BF and V not shown). The BF and V responses to NA and adrenaline were significantly prolonged after DMI (not shown) while DMI did not influence the reduction of LDF signal, BF and V induced by UK 14.304, oxymetazoline or phenylephrine (not shown).

Compared to control, the LDF signal, BF and V responses to NA (60 nmol) were reduced by 70 ± 10%, 60 ± 7% and 60 ± 9%, respectively, after pretreatment with prazosin (Figure 3a–b). The remaining BF response to NA after prazosin was biphasic (Figure 3b) and the reduction of BF (by 16 ± 2%) was followed by a 8 ± 1.5% increase. After idazoxan pretreatment the LDF, BF and V responses evoked by NA were reduced by 40 ± 5%, 11 ± 2% and 60 ± 7.5%, respectively, compared to control (Table 2, Figure 3c). A short lasting BF reduction was then followed by a 22 ± 3% increase which lasted for 120 ± 15 s (Figure 3c). When prazosin and idazoxan were combined, the LDF and V responses to NA were reduced by 80 ± 15% and 87 ± 17% whereas a 13 ± 2% increase of BF occurred (Table 2, Figure 3d). Following concomitant pretreatment with propranolol, the increase of the BF response observed to NA (60 nmol) after α-antagonists was absent (Figure 3e, Table 2).

The three nasal vascular parameters studied upon local i.a. injection of adrenaline were, in principle,

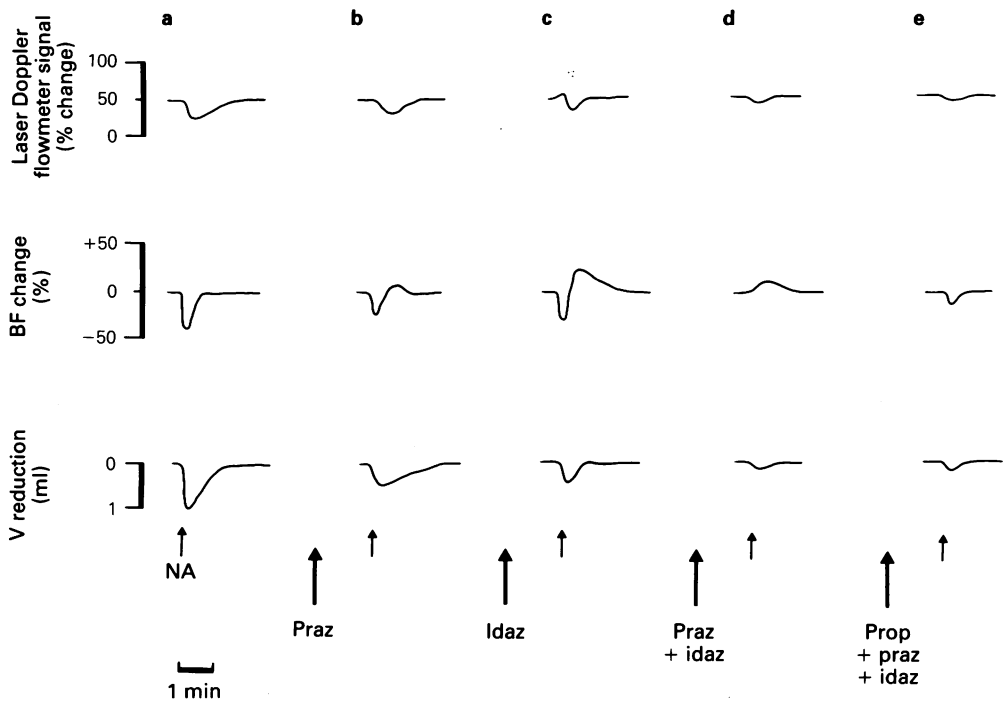

Figure 3 Original pen-trace recordings of the laser Doppler flowmeter (LDF) signal (% change), the blood flow (BF) change (%) and the nasal mucosal volume (V) reduction (in ml) to local i.a. bolus injection of NA (60 nmol). (a) under control conditions, (b) after pretreatment with prazosin (Praz, 0.1 mg kg^{-1}, i.v.), (c) after pretreatment with idazoxan (Idaz, 0.5 mg kg^{-1}, i.v.), (d) after simultaneous pretreatment with idazoxan and prazosin, and (e) after simultaneous pretreatment with idazoxan, prazosin and propranolol (Prop, 0.5 mg kg^{-1}, i.v.).

Table 2 Variations of the laser Doppler flowmeter (LDF) signal upon preganglionic stimulation (5 ms, 15 V) of the superior cervical sympathetic trunk with single impulses or at 2 Hz for 2 min as well as changes to local intra-arterial injections of noradrenaline, adrenaline, UK 14.304, phenylephrine or oxymetazoline

	Laser Doppler flowmeter (Peak change %)					
	Control	*+DMI*	*+Idazoxan*	*+Prazosin*	*Prazosin +idazoxan*	*Prazosin +idazoxan +propranolol*
Single pulse	+4.6 ± 1***	−13.5 ± 1.5***	+4 ± 1	+7 ± 2*	+2.7 ± 0.5	+4 ± 1
2 Hz	−25 ± 5	−33 ± 6**	−15.4 ± 4	−12.6 ± 2.5	−8.7 ± 2	−8.7 ± 2
Noradrenaline	−19 ± 4	−23 ± 3*	−11.4 ± 3*	−5.6 ± 1.5	−4 ± 1.5	−5 ± 1.5
Adrenaline	−21 ± 4	−15 ± 2	−13 ± 3	−7.6 ± 2	−6 ± 0.5	−5.3 ± 1
UK 14.304	−17 ± 3	−18.5 ± 4*	−8.3 ± 2	−5.5 ± 1	−3 ± 0.5	−5 ± 1.5
Phenylephrine	−10 ± 2	−8.5 ± 2	−5 ± 1.5*	0	0	0
Oxymetazoline	−13 ± 2.5	−10 ± 2.5	−8 ± 2	−6 ± 1.5	−4.5 ± 0.5	−6 ± 1.5

The LDF signal responses under control conditions have been compared to those 30 min after pretreatment with the monoamine uptake inhibitor desipramine (0.5 mg kg^{-1}, i.v.), the competitive α_2-antagonist idazoxan (0.5 mg kg^{-1}, i.v.), the competitive α_1-antagonist prazosin (0.1 mg kg^{-1}, i.v.), simultaneous pretreatment with idazoxan and prazosin, and simultaneous pretreatment with idazoxan, prazosin and the β-antagonist propranolol (0.5 mg kg^{-1}, i.v.). Values are mean ± s.e.mean; n = 4–8.
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ (Kruskal-Wallis analysis of variance with multiple comparisons).

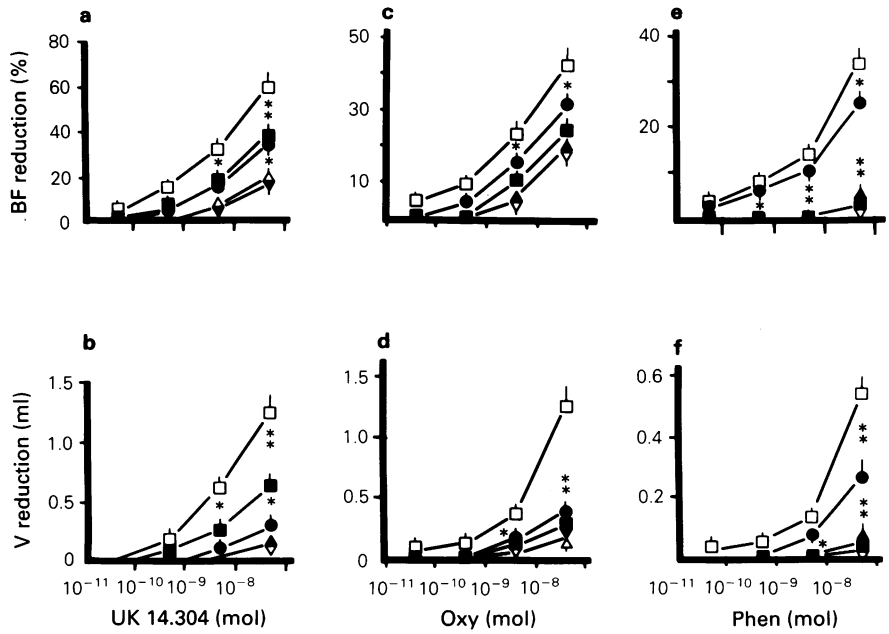

Figure 4 Dose-response curves to local i.a. bolus injections of UK 14.304 (a, b), oxymetazoline (Oxy, c, d), phenylephrine (Phen, e, f) on the nasal arterial blood flow (BF, in %) and on the nasal mucosal volume (V, in ml). (□—□) under control conditions, (■—■) after pretreatment with prazosin (0.1 mg kg^{-1}, i.a.), (●—●) after pretreatment with idazoxan (0.5 mg kg^{-1}, i.v.), (△—△) after simultaneous pretreatment with idazoxan and prazosin, and (▲—▲) after simultaneous pretreatment with idazoxan, prazosin and propranolol (0.5 mg kg^{-1}, i.v.). Means (with s.e.mean shown by vertical lines) are given, $n = 4$–8. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ using Kruskal-Wallis analysis of variance with multiple comparisons.

not significantly different compared to NA and an 18 ± 3% increase of the nasal BF was observed after concomitant prazosin and idazoxan pretreatment. This BF increase was abolished when propranolol was added to the α-adrenoceptor antagonists (not shown).

The reduction of BF and LDF by UK 14.304 (55 nmol) was attenuated to about the same extent after separate pretreatment with either prazosin or idazoxan (Figure 4a, Table 2). When these antagonists were given in combination, both the BF and LDF responses were further attenuated. The V reduction induced by UK 14.304 was more sensitive to idazoxan pretreatment than to prazosin ($P < 0.01$, Figure 4b).

Prazosin and idazoxan were equally effective in attenuating the LDF, BF and V responses to oxymetazoline (Figure 4c and 4d). Simultaneous administration of these antagonists did not further reduce the responses to oxymetazoline (Figure 4c–d, Table 2).

After idazoxan pretreatment the effects on BF and V observed upon phenylephrine administration were only marginally influenced and significantly reduced only at the highest dose (50 nmol) whereas after prazosin less than 10 ± 3% of these responses to phenylephrine remained (Figure 4e and f). Phenylephrine induced no modification of the LDF signal after prazosin (Table 2).

The LDF, BF and V responses to phenylephrine, UK 14.304 and oxymetazoline were not further modified after addition of propranolol (Figure 4a–f, Table 2).

Effects of adrenoceptor antagonists on the responses to sympathetic nerve stimulation

Single impulse stimulation of the superior cervical sympathetic trunk caused a BF and V reduction by 47 ± 5% and 0.41 ± 0.08 ml, respectively (Figure 5a, b), whereas a 4.6 ± 1% increase of the LDF signal occurred (Table 2). Following DMI pretreatment the BF response was prolonged more than 5 fold whereas the increase of the peak BF reduction was not significant. On the other hand, after DMI, the V

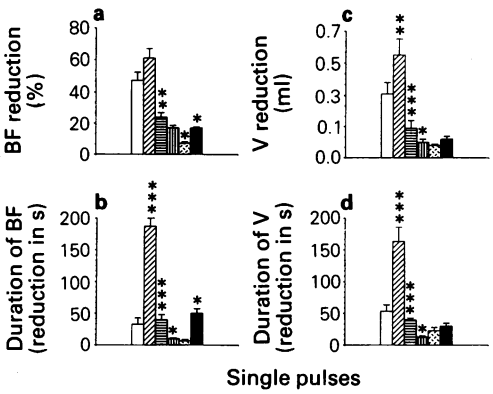

Figure 5 Effects of superior cervical sympathetic trunk stimulation (5 ms, 15 V) with single shocks on (a) the blood flow (BF, in %) reduction, (b) the duration of the BF response (in s), (c) the mucosal volume (V, in ml) reduction and (d) the duration of the V reduction (in s). Under control conditions (open columns), 30 min after pretreatment with desipramine (0.5 mg kg^{-1}, i.v., hatched columns), after pretreatment with prazosin (0.5 mg kg^{-1}, i.v., horizontally lined columns), after pretreatment with idazoxan (0.1 mg kg^{-1}, i.a., vertically lined columns), following simultaneous pretreatment with idazoxan and prazosin (stippled columns), and simultaneous pretreatment with idazoxan, prazosin and propranolol (0.5 mg kg^{-1}, i.v., solid columns). Values represent mean of 4–8 experiments and vertical bars denote s.e.mean * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ when compared to the preceding stimulation by Kruskal-Wallis analysis of variance with multiple comparisons.

response upon single impulse was significantly enhanced by 38 ± 8% ($P < 0.01$) (Figure 4c) and the LDF signal then showed a reduction by 13.5 ± 1.5% ($P < 0.001$) (Table 2). After prazosin pretreatment 48 ± 5% and 46 ± 6% respectively of the BF and V responses observed to a single impulse in control animals remained (Figure 5a, b). Idazoxan also reduced the BF response and was a more effective blocking agent than prazosin regarding the V response to a single impulse. A cumulative effect of these adrenoceptor antagonists was seen on the BF response to single pulse but not on the V. An enhancement of the reduction in the remaining vascular responses was observed only for BF when propranolol was added (Figure 5). Prazosin and idazoxan attenuated the reduction of the LDF response to single impulse stimulation after DMI (Table 2). Thus, the negative LDF response observed after DMI pretreatment was then changed to an increase of the LDF signal (Table 2).

Sympathetic stimulation at 2 Hz caused a BF and LDF reduction of 87 ± 12 and 25 ± 4%, respectively, whereas a 2.37 ± 0.26 ml decrease of the V was observed (Figure 6, Table 2). No significant enhancement of the LDF signal, BF and V peak values upon 2 Hz stimulation occurred after DMI pretreatment but all these parameters were markedly prolonged ($P < 0.001$) (Figure 6). In the presence of prazosin the vascular responses upon 2 Hz stimulation were attenuated by 30–40% ($P < 0.01$). The BF and LDF reduction at 2 Hz were not affected by pretreatment with idazoxan when compared to the effects observed after DMI, whereas the V response was significantly reduced (Figure 6, Table 2). Simultaneous pretreatment with idazoxan and prazosin had no cumulative effect on the attenuation of the vascular responses at 2 Hz when compared to prazosin given alone (Figure 6, Table 2). However, when propranolol was added after these agents, a significant increase ($P < 0.05$) of the BF and V responses occurred while the LDF recordings remained unchanged (Table 2).

Discussion

The present study gives a detailed description of the adrenoceptor mechanisms for endogenously released transmitter and exogenous agonists in three different compartments of the nasal mucosal vascular bed of the pig. The duration of the vascular responses to nerve stimulation, both regarding BF and V, were enhanced after neuronal reuptake inhibition by DMI (see also Eccles & MacLean, 1977). This suggests that noradrenergic mechanisms play an important role in the sympathetic vascular control especially at low frequency stimulation (Lacroix *et al.*, 1988b; 1989). Although both the agonists and antagonists studied have relative α_1-, α_2- and β-receptor selectivity, some comparative conclusions can be drawn regarding the occurrence of adrenoceptor subtypes in the different vascular compartments studied. For the resistance vessels it is likely that both α_1- and α_2-adrenoceptor mechanisms are present. Thus, the BF response to single impulse stimulation, when the 'non-adrenergic component' is relatively small (see Lacroix *et al.*, 1988b), was reduced to a similar extent by both prazosin and idazoxan. It is generally assumed that α_1-receptors are located close to the neuronal release sites for NA while α_2-receptors are mainly activated by circulating catecholamines (Docherty & McGrath, 1980; Langer *et al.*, 1980; Yamaguchi & Kopin, 1980; Langer & Shepperson, 1982). In the present study where DMI pretreatment was used, the released NA may have diffused away from the release sites, escaping neuronal reuptake to activate also α_2-receptors. A second argument for the presence of α_1-receptors in the resistance vessels was

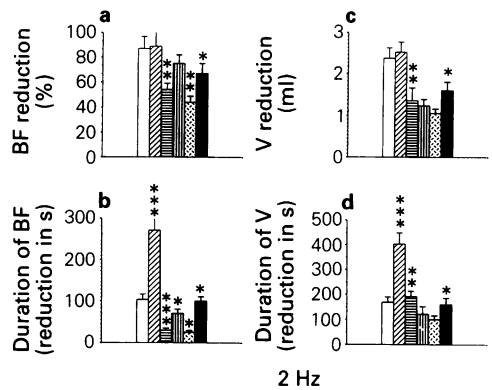

Figure 6 Effects of superior cervical sympathetic trunk stimulation (5 ms, 15 V) at 2 Hz on (a) the blood flow (BF, in %) reduction, (b) the duration of the BF response (in s), (c) the volume (V, in ml) reduction and (d) the duration of the V reduction (in s). Under control conditions (open columns), 30 min after pretreatment with desipramine (0.5 mg kg^{-1}, i.v., obliquely hatched columns), after pretreatment with prazosin (0.1 mg kg^{-1}, i.v., horizontally lined columns), after pretreatment with idazoxan (0.5 mg kg^{-1}, i.v., vertically lined columns), following simultaneous pretreatment with idazoxan and prazosin (stippled columns), and simultaneous pretreatment with idazoxan, prazosin and propranolol (0.5 mg kg^{-1}, i.v., solid columns). Values represent mean of 4–8 experiments and vertical bars denote s.e.mean. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ when compared to the preceding stimulation using Kruskal-Wallis analysis of variance with multiple comparisons.

the finding that the BF response to low doses of the preferential α_1-agonist phenylephrine was markedly reduced by prazosin but only to a small extent by idazoxan. The similar reduction of the BF response to the selective α_2-agonist UK 14.304 by both prazosin and idazoxan may be related to the prazosin dose used, which was at the upper limit of α_1-selectivity.

The BF response to nerve stimulation (both single impulse and 2 Hz) after α-adrenoceptor blockade was enhanced by addition of propranolol, suggesting that neuronally released NA activated β-receptors on resistance vessels. Furthermore, both exogenous NA and adrenaline caused biphasic BF effects after prazosin or idazoxan with an initial decrease followed by an increase. When combined pretreatment of these α-blocking agents with propranolol were done, both the NA and adrenaline induced increase of BF was attenuated. Finally, the selective β_2-agonist terbutaline caused a dose-dependent increase of BF. The presence of β_2-adrenoceptors in resistance vessels of the pig nasal mucosa therefore seems to be well documented. β_2-Adrenoceptors may also be present in resistance vessels of the nasal mucosa of cat (Malm, 1974b).

Regarding capacitance vessels function, α_2-receptors seem to dominate over α_1-mechanisms (see Berridge & Roach, 1986) since the V responses to (1) single impulse stimulation, (2) exogenous NA and (3) UK 14.304 were more attenuated by idazoxan than prazosin. Only a minor contribution by β-adrenoceptors seemed to be present for the capacitance function since the V response to single impulse nerve stimulation was not influenced by propranolol. Furthermore, adrenaline, which has potent β-stimulating actions, was a relatively more potent agent in reducing V than the BF. Moreover, terbutaline caused only a minor increase of the nasal mucosa V (see also Malm, 1974b). This last observation also suggests that 20% increase in BF via dilatation of the resistance vessels only marginally influenced the capacitance vessels of the nasal mucosa.

Andersson & Bende (1984), postulated that α_1-adrenoceptors are functionally more important for capacitance function than for control of BF, based on experiments with local applications of phenylephrine and α_2-agonists in the human nasal mucosa. However, the present data suggest that α_2-mechanisms clearly dominate in the pig nasal mucosa. Thus, the ratio between α_1- and α_2-receptor mechanisms (as revealed by phenylephrine and UK 14.304 effects, respectively) was about 1:10 both regarding BF (BF 25) and V (V 0.5) control (see Table 1). In our study, the α-agonists were given i.a. which may give a different access to receptor sites compared to when the agents are applied locally to the nasal epithelium. Furthermore, Andersson & Bende (1984), observed only systemic effects of the β_2-agonist terbutaline but no influence on local nasal blood flow. In addition, the ^{133}Xe washout method used may mainly reflect superficial nasal BF and the LDF signal was also not influenced by terbutaline in the pig nasal mucosa. β-Adrenoceptor mechanisms seemed to be of minor importance for the LDF signal since in addition: (1) propranolol did not change the nerve stimulation evoked response, and (2) adrenaline caused only a strong reduction of the LDF signal. The absence of a β-adrenoceptor mediated response therefore separates the LDF signal from the BF recording. Both α_1- and α_2-receptor mechanisms influenced the LDF signal, however, since the response to single impulse nerve stimulation was reduced to a similar extent by either prazosin or idazoxan. It is notable that the LDF signal was increased upon single impulse stimulation under control conditions in spite of a parallel BF reduction. Whether this apparent contradiction between the total BF recording and the LDF signal

is related to shunting of blood flow from deeper to more superficial layers of the nasal mucosa or some other mechanism such as increased velocity of blood cells in contracting vessels remains to be established.

Regarding the vascular response that remains to nerve stimulation in the pig nasal mucosa after the competitive adrenoceptor blocking agents used in this study, this is also observed after local i.a. infusion of a very high dose of the irreversible α-adrenoceptor antagonist phenoxybenzamine (Lacroix *et al.*, 1988a, b). Relatively similar responses to single impulse stimulations (almost 20% of BF and V) remain after the combination of prazosin and idazoxan compared to phenoxybenzamine (Lacroix *et al.*, 1988b). Furthermore, the response to exogenous NA was blocked to a similar extent by the present combination of competitive adrenoceptor antagonists and phenoxybenzamine (see Lacroix *et al.*, 1988a). Due to interference by idazoxan with the α_2-mediated feedback inhibition of mediator release upon nerve stimulation at 2 Hz (but probably not to single impulse) the increase in NA release (see Berridge & Roach, 1986; Lacroix *et al.*, 1989) may reduce the postjunctional antagonist effects of this drug. The BF and V reduction to sympathetic nerve stimulations, however, persist especially at 2 Hz and higher frequency and also after depletion of NA induced by reserpine pretreatment (Lacroix *et al.*, 1988b). These remaining vascular responses could be due to the release of another vascoconstrictor agent from sympathetic nerves namely neuropeptide Y (NPY) (see Lacroix *et al.*, 1988b; 1989). NPY release, however, is also likely to increase in the presence of α_2-adrenoceptor blockade (see Lacroix *et al.*, 1989; Lundberg *et al.*, 1989).

In conclusion, the occurrence of adrenoceptor mechanisms in the nasal mucosa of the pig varies between different vascular compartments. Thus, whereas both α_1- and α_2-receptor-mediated actions seem to be involved in the sympathetic control of BF, V and the LDF signal, the α_2-effects dominate for exogenous agonists. On the other hand β-receptor-mediated vasodilatation is mainly present in resistance vessels.

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