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Characterization of α-adrenoceptors in the vasculature of the canine nasal mucosa

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1 α-Adrenoceptors present in the vasculature of the nasal mucosa in β-adrenoceptor blocked dogs have been characterized pharmacologically using selective α_1- and α_2-adrenoceptor agonists and antagonists.

2 In pentobarbitone-anaesthetized dogs, intra-arterial (i.a.) administration of the selective α_1-agonists cirazoline and phenylephrine, the selective α_2-agonist UK-14,304 and the mixed α_1/α_2-agonists adrenaline, noradrenaline and oxymetazoline produced dose-related nasal vasoconstrictor responses (as measured by decreases in nasal cavity pressure). The rank order of agonist potency was adrenaline > oxymetazoline = UK-14,304 > noradrenaline > cirazoline > phenylephrine.

3 The nasal response to cirazoline was inhibited by the selective α_1-adrenoceptor antagonist prazosin but not by the new, potent selective α_2-adrenoceptor antagonist RX 811059. In contrast, UK-14,304 was inhibited only by RX 811059. Either prazosin or RX 811059 reduced the effect of the mixed agonist adrenaline.

4 In spinal dogs, the noradrenaline-evoked fall in nasal cavity pressure was reduced by either prazosin or RX 811059. Prazosin attenuated markedly the nasal vasoconstrictor response to electrical stimulation of postganglionic fibres emerging from the superior cervical ganglion (SNS) whereas RX 811059 was ineffective. Administration of the neuronal re-uptake inhibitor cocaine potentiated the effect of i.a. noradrenaline but reduced marginally the maximal response to SNS. After cocaine, RX 811059 enhanced the effect of SNS and attenuated the response to noradrenaline. Prazosin reduced effectively the responses to both SNS and noradrenaline after cocaine. Pretreatment with the α_2-agonist UK-14,304 did not affect the response to noradrenaline in the nasal cavity but evoked a persistent (up to 2 h) reduction in the response to SNS. RX 811059 antagonized the inhibitory effect of UK-14,304.

5 These results demonstrate that both postjunctional α_1- and α_2-adrenoceptors mediating vasoconstriction are present in the canine nasal mucosa. In addition, sympathetic neurones innervating the nasal mucosa are characterized by a very efficient re-uptake process and contain prejunctional α_2-adrenoceptors.

Introduction

α-Adrenoceptors are characterized pharmacologically with the use of selective agonists and antagonists into α_1- or α_2-subgroups regardless of their anatomical location or function (Starke & Langer, 1979). In general, the α-adrenoceptors located prejunctionally on nerve terminals which modulate the exocytotic release of neurotransmitter are of the α_2-subtype. With respect to the α-adrenoceptors located postjunctionally on vascular smooth muscle cells mediating vasoconstriction, a large amount of recent data indicate the presence of both α_1- and α_2-adrenoceptors in the circulatory system of rats (Docherty & McGrath, 1980; Timmermans & Van Zwieten, 1980), dogs (Constantine *et al.*, 1980; Langer *et al.*, 1980) and humans (Elliott & Reid, 1983; Kiowski *et al.*, 1983; Jie *et al.*, 1984). Horn *et al.*, (1982) showed that postjunctional α_1- and α_2-adrenoceptors are not evenly distributed throughout the vascular system of the dog. These workers suggested that in the femoral vascular bed there was a predominance of α_2-adrenoceptors whereas in the renal bed α_1-adrenoceptors predominate. In addition, Shoji *et al.* (1983) found that the distribution and proportions of postjunctional α_1- and α_2-adrenoceptors varied greatly in fifteen isolated veins taken from dogs.

α-Adrenoceptors agonists constrict the microvas-

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culature of the nasal mucosal cavity in rats (Salem, 1972), cats (Malm, 1974), dogs (Hall & Jackson, 1968; Loux, 1970) and humans (Eccles, 1982). α-Adrenoceptor agonists of the phenylethylamine and imidazoline types are used clinically as nasal decongestants (Empey & Medder, 1981). Compounds such as methoxamine and phenylephrine are selective α_1-adrenoceptor agonists whereas the imidazoline derivatives oxymetazoline, naphazoline and tramazoline stimulate both α_1- and α_2-adrenoceptors. However, these latter compounds activate preferentially α_2-adrenoceptors to various degrees (see Starke *et al.*, 1975; Wikberg, 1979; Doxey *et al.*, 1981). In the light of the varying profiles of the α-agonists used as nasal decongestants, it was decided to characterize pharmacologically the α-adrenoceptors in the mucosa of the nasal cavity of the dog.

Methods

All experiments were performed using Beagle dogs of either sex (weight range 8–21 kg) anaesthetized with sodium pentobarbitone (45 mg kg^{-1}, i.v.). The tracheas were intubated and the animals respired artificially with room air (Palmer Ideal Pump, model 16/24; 10 ml kg^{-1} body weight at 20 strokes min^{-1}). The left femoral vein was cannulated through which sodium pentobarbitone was infused continuously throughout the experiment (6 mg kg^{-1} h^{-1} at a rate of 3 ml h^{-1}). Arterial blood pressure was monitored from the cannulated left femoral artery using a pressure transducer (Bell and Howell; type 4-422-0001) connected to a polygraph recorder (Grass model 7D). Bolus injections of drugs were made either intravenously into a brachial vein or intra-arterially (i.a.) into a common carotid artery. The cranial thyroid artery was cannulated retrogradely so that the tip of the cannula reached the bifurcation with the carotid artery.

In some cases, dogs were spinalised at the level of the first cervical vertebra. The spinal cord was exposed after cutting a window (1 cm square) in the vertebra. The cord was transected approximately 10 min after instillation of cinchocaine (6 mg in 0.2 ml saline).

The choanae was sealed with cotton wool moistened with saline. A silicon tube (4 mm external diameter) was passed approximately 1.5–2 cm into each nostril and connected via a Y piece to a Statham (No. 11649) air pressure transducer. Silicone (high vacuum) grease (Dow Corning) was used to seal the tubing into the nostrils and ensure complete isolation of the nasal cavity from the atmosphere. The transducer was calibrated using a water manometer and the pressure within the nasal cavity recorded on a Grass polygraph (Model 7D). Vasoconstriction of the nasal microvasculature causes shrinkage of the mucosa. This is indicated by a negative deflection on the recorder due to the production of a negative pressure within the nasal cavity (see Loux, 1970; Eccles, 1982).

Experiments were carried out to study the effects of sympathetic nerve stimulation on nasal cavity pressure. Spinal dogs were used for these experiments. The sympathetic trunk connecting the vagosympathetic trunk and the cranial cervical ganglion was identified and placed on a bipolar platinum electrode. The nerve distal to the electrode was cut and stimulated using the parameters: 0.5 Hz, 5V, 0.1 ms pulse width for 10 s (SRI Dual Stimulator). Hall & Jackson (1968) observed vasodilatation of the canine nasal mucosa with isoprenaline. For this reason all experiments were performed after pretreatment with propranolol (1 mg kg^{-1}, i.v.).

Series 1: Agonist dose-response relationships

In separate groups of β-adrenoceptor-blocked, pentobarbitone-anaesthetized dogs, the effects of bolus i.a. injections of adrenaline (0.03–3 μg; $n = 5$), noradrenaline (0.1–10 μg; $n = 4$), oxymetazoline (0.1–3 μg; $n = 3$), UK-14,304 (0.05–5 μg; $n = 4$), cirazoline (0.3–10 μg; $n = 5$) and phenylephrine (0.3–30 μg; $n = 5$) on nasal cavity pressure were studied.

Series 2: Effects of α_1- and α_2-adrenoceptor antagonists on the responses to agonists

In separate groups ($n = 4$) of β-adrenoceptor-blocked, pentobarbitone-anaesthetized dogs control nasal vasoconstrictor responses were obtained after i.a. administration of the mixed α_1/α_2-agonist adrenaline (0.3 μg,), the selective α_2-agonist UK-14,304 (0.5 μg; Cambridge, 1981; Van Meel *et al.*, 1981) or the selective α_1-agonist cirazoline (1.0 μg; Cavero *et al.*, 1982; Ruffolo & Waddell, 1982). The animals were then treated with the selective α_1-adrenoceptor antagonist prazosin (0.1 mg kg^{-1}, i.v.), followed 10 min later by the agonists. After termination of the agonist responses, the selective α_2-adrenoceptor antagonist RX 811059 (0.1 mg kg^{-1}, i.v.; Doxey *et al.*, 1984) was then administered followed again 10 min later by the test agonist. It should be noted that RX 811059 was used in place of the selective α_2-antagonist idazoxan since the former compound is devoid of agonist properties (Doxey *et al.*, 1984). Idazoxan increased blood pressure in pithed rats due to a partial agonist action at α_1-adrenoceptors (Paciorek & Shepperson, 1983; Roach *et al.*, 1983a). Control experiments ($n = 3$) were performed by giving the agonists before and 10 min after two separate injections of saline (replacing prazosin and RX 811059).

Series 3: Effects of α_1- and α_2-adrenoceptor antagonists on the nasal response to sympathetic nerve stimulation

Using the same experimental procedure described in Series 2, responses to noradrenaline (1 μg, i.a.) and sympathetic nerve stimulation (SNS) were obtained before and 10 min after first prazosin (0.1 mg kg^{-1}, i.v.) and then RX 811059 (0.1 mg kg^{-1}, i.v.) in spinalised, β-blocked dogs ($n = 5$).

Similar experiments were performed with the exception that the order of administration of the antagonists was reversed ($n = 3$). In a third series of experiments, responses to noradrenaline and SNS were produced before and after inhibition of neuronal re-uptake with cocaine (5 mg kg^{-1}, i.v. infused over 5 min) ($n = 4$). In the same animals the effects of noradrenaline and stimulation were monitored after RX 811059 followed by prazosin.

It was confirmed that the stimulation responses were due to SNS since in three spinal dogs guanethidine (15 mg kg^{-1}, i.v.) abolished completely the effects of SNS but not those of i.a. noradrenaline.

Series 4: Effect of the selective α_2-adrenoceptor agonist UK-14,304 on the responses to noradrenaline and sympathetic nerve stimulation

In 4 spinal, β-adrenoceptor-blocked dogs, consistent nasal vasoconstrictor responses to i.a. noradrenaline and SNS were obtained before and after saline (0.1 ml kg^{-1}, i.v.) followed 10 min later by UK-14,304 (1.5 μg kg^{-1}, i.v. infused over 5 min). UK-14,304 increased systemic arterial blood pressure and decreased nasal cavity pressure; the nasal response returning to baseline values within 7–10 min of the UK-14,304 infusion. Nasal responses to noradrenaline and SNS were then obtained alternately every 6 min for 2 h (responses 10, 60 and 120 min after UK-14,304 being presented in the results). The effects of UK-14,304 given 10 min after RX 811059 (0.1 mg kg^{-1}, i.v.) were studied in a group of 3 dogs. Furthermore, control experiments were performed by replacing both UK-14,304 and RX 811059 with saline ($n = 4$).

Analysis of results

All results are given as means ± s.e.mean. The agonist potency in anaesthetized dogs was assessed by graphically interpolating ED_{-5} values (the i.a. dose (μg) required to reduce nasal cavity pressure by 5 cm H_2O) from individual log dose-response relationships and converting these into mol. Differences in agonist ED_{-5} values (nmol) were compared to those of adrenaline and UK-14,304 using an unpaired t test.

The effect of prazosin, RX 811059 and cocaine on the nasal responses to the agonists and stimulation was assessed by comparing the responses before (pretreatment controls) and after the antagonists using a t test for paired data ($P<0.05$ being significant).

Drugs

The drugs used in the present study were (−)-adrenaline hydrogen tartrate (B.D.H., Poole, Dorset), cinchocaine hydrochloride (Ciba, Horsham, Sussex), cirazoline hydrochloride (Synthélabo, Paris, France), cocaine hydrochloride (MacFarlane-Smith, Edinburgh), guanethidine sulphate (Ciba, Horsham, Sussex), (−)-noradrenaline bitartrate (Koch Light, Haverhill, Suffolk), oxymetazoline hydrochloride (Allen and Hanburys, Ware, Herts), pentobarbitone sodium (Sagatal, May and Baker, Dagenham), (−)-phenylephrine hydrochloride (Koch Light, Haverhill, Suffolk), prazosin hydrochloride (synthesized by Chemistry Department, Reckitt and Colman, Hull), (±)-propranolol hydrochloride (ICI, Macclesfield), RX 811059 (2-(2-(2-ethoxy-1,4-benzodioxanyl)) imidazoline hydrochloride, Reckitt and Colman, Hull), and UK-14,304 (5-bromo-6-(imidazolin-2-yl amino)-quinoxaline tartrate; synthesized by Chemistry Department, Reckitt and Colman, Hull). All doses in the text refer to the salts of the compounds listed above. All solutions were made by dissolving the compounds in sterile 0.9% w/v NaCl solution.

Results

Agonist dose-response relationships on nasal cavity pressure

All six agonists given i.a. caused dose-related vasoconstriction as demonstrated by reductions in nasal cavity pressure of pentobarbitone-anaesthetized dogs (Figure 1). The potencies of the agonists as shown by their ED_{-5} values (i.a. dose reducing nasal cavity pressure by 5 cm H_2O) are listed in Table 1. Adrenaline was the most potent agonist in this experimental model. Surprisingly, the selective α_2-adrenoceptor agonist UK-14,304 was more effective than either noradrenaline or the selective α_1-adrenoceptor agonist cirazoline. Phenylephrine was the weakest agonist tested.

The i.a. administration of the α-adrenoceptor agonists induced small increases in systemic arterial blood pressure. The onset of these responses was delayed and duration was usually shorter than for the nasal responses. The increases in diastolic blood pressure noted with the agonists at i.a. doses approximately equivalent to their ED_{-5} values were 14.8 ± 0.9 mmHg (adrenaline, 0.3 μg), 14.6 ± 2.1 mmHg (UK-14,304, 1.5 μg), 4.7 ± 1.6 mmHg (oxymetazoline, 1 μg), 17.3 ± 0.7 mmHg (noradrenaline, 3 μg), 11.0 ± 1.6 mmHg (cirazoline, 3 μg) and 15.4 ±

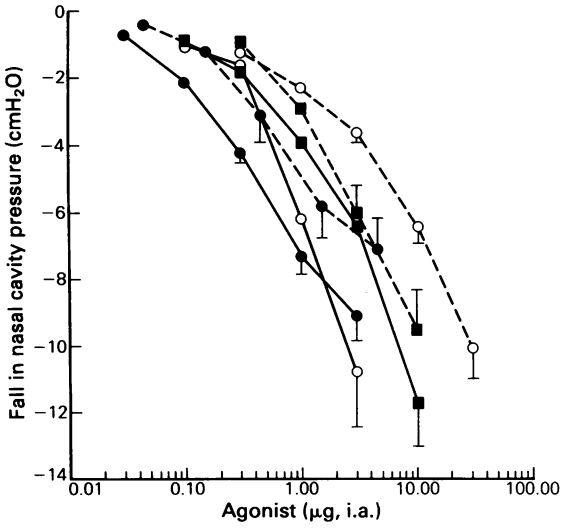

Figure 1 Dose-response curves to adrenaline (●—●), oxymetazoline (○—○), UK-14,304 (●--●), noradrenaline (■—■), cirazoline (■--■) and phenylephrine (○--○) on nasal cavity pressure (cmH_2O) in β-blocked, pentobarbitone-anaesthetized dogs. All agonists were given as bolus injections intra-arterially. Each point is the mean of 4 observations and vertical lines show s.e.means. Data shown in Table 1 are taken from these experiments.

Table 1 Agonist doses (i.a.) required to reduce the nasal cavity pressure by 5 cmH_2O (ED_{-5}) in β-blocked, pentobarbitone-anaesthetized dogs

Agonist	ED_{-5} μg	ED_{-5} *n mol*
Adrenaline	0.4 ± 0.1	1.2 ± 0.3 (1.0)
Oxymetazoline	0.9 ± 0.2	3.0 ± 0.7 (0.40)
UK-14,304	1.3 ± 0.3	2.9 ± 0.7 (0.41)
Noradrenaline	1.7 ± 0.5	5.3 ± 1.6 (0.23)
Cirazoline	2.5 ± 0.4	9.9 ± 1.6 (0.12)
Phenylephrine	6.3 ± 1.3	30.9 ± 6.4 (0.04)

Values in parentheseis indicate the relative potencies of the agonists compared to adrenaline. All compounds with the exception of UK-14,304 and oxymetazoline were significantly weaker than adrenaline ($P<0.05$; unpaired t test). UK-14,304 was significantly more potent than cirazoline and phenylephrine ($P<0.05$; unpaired t test).

1.2 mmHg (phenylephrine, 10 μg).

Effects of α_1- and α_2-adrenoceptor antagonists on agonist responses

In control dogs ($n = 3$), i.a. adrenaline (0.3 μg), UK-14,304 (0.5 μg) and cirazoline (1 μg) produced falls in nasal cavity pressure of -4.8 ± 0.8, -4.0 ± 0.5 and -6.4 ± 0.9 mmHg, respectively. Subsequent responses to these agonists were not significantly altered by two administrations of saline (0.2 ml kg^{-1}, i.v.); the two responses to adrenaline were -5.2 ± 0.7 and -5.2 ± 1.0 mmHg, to UK-14,304 -3.8 ± 0.4 and -4.2 ± 0.4 mmHg and to cirazoline -6.4 ± 0.7 and -6.2 ± 0.8 mmHg.

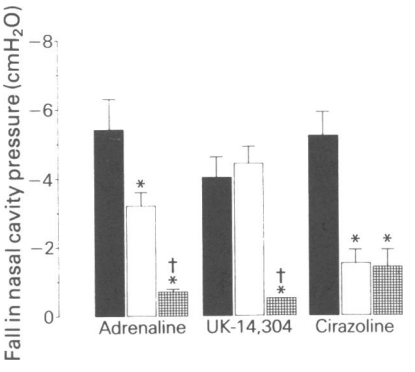

Figure 2 Effects of adrenaline (0.3 μg, i.a.), UK-14,304 (0.5 μg, i.a.) and cirazoline (1 μg, i.a.) on nasal cavity pressure (cmH_2O) in β-blocked, pentobarbitone-anaesthetized dogs before (control; solid columns) and 10 min after prazosin (0.1 mg kg^{-1}, i.v.; open columns) and then 10 min after RX 811059 (0.1 mg kg^{-1}, i.v.; stippled columns). Values represent mean of 4 observations and vertical lines denote s.e.means. * Indicates a significant difference ($P<0.05$) from pretreatment control responses and † shows that the response after RX 811059 was significantly different from the post-prazosin response ($P<0.05$; paired t test).

Relatively similar control nasal vasoconstrictor responses were obtained to i.a. adrenaline (0.3 μg), UK-14,304 (0.5 μg) and cirazoline (1 μg) (Figure 2). Prazosin (0.1 mg kg^{-1}, i.v.) did not alter significantly the response to the α_2-agonist UK-14,304 but reduced significantly ($P<0.05$, paired t test) the responses to adrenaline and cirazoline (41 and 71% inhibition, respectively; Figure 2). Subsequent blockade of α_2-adrenoceptors with RX 811059 (0.1 mg kg^{-1}, i.v.) attenuated markedly the effect of UK-14,304 (88% inhibition) whereas the response to adrenaline was further reduced and that to cirazoline was unaffected (87 and 73% inhibition after both antagonists for adrenaline and cirazoline, respectively).

In these pentobarbitone-anaesthetized dogs ($n = 4$), prazosin (0.1 mg kg^{-1}, i.v.) produced a sustained fall in diastolic blood pressure (control DBP 72.3 ± 6.0 mmHg; $\Delta -16.0 \pm 2.5$ mmHg) and an increase in nasal cavity pressure ($\Delta 2.5 \pm 0.3$ cmH_20). Heart rate was unaffected by prazosin. RX 811059

(0.1 mg kg^{-1}, i.v.) produced a transient (5 min) fall in diastolic blood pressure (control DBP 54.0 ± 2.6 mmHg; Δ −20.5 ± 1.9 mmHg) and increased pressure in the nasal cavity (Δ 1.9 ± 0.5). RX 811059 evoked a tachycardia (control heart rate 114 ± 4 beats min^{-1}; Δ 36 ± 9 beats min^{-1}) which persisted longer than its effects on DBP and nasal cavity pressure.

Effects of α_1- and α_2-adrenoceptor antagonists on nasal responses to endogenous and exogenous noradrenaline in spinal dogs

In spinalized, β-blocked dogs ($n = 5$), noradrenaline (1 μg, i.a.) and SNS reduced nasal cavity pressure by −4.4 ± 0.4 and −7.0 ± 0.7 cmH_2O respectively (Figure 3). Pretreatment with prazosin (0.1 mg kg^{-1}, i.v.) attenuated significantly ($P<0.05$, paired t test) the responses to i.a. noradrenaline (59% inhibition) and to SNS (79% inhibition) (Figure 3). Additional α_2-adrenoceptor blockade with RX 811059 almost abolished the noradrenaline response and produced a further small, but non-significant, inhibition of the effect of SNS. Prazosin (0.1 mg kg^{-1}, i.v.) evoked a small increase in nasal cavity pressure (Δ 1.3 ± 0.5 cmH_2O) and decrease in diastolic blood pressure (control DBP 59.0 ± 3.3 mmHg; Δ −8.2 ± 2.7 mmHg); both effects lasting approximately 5 min. In contrast, RX 811059 (0.1 mg kg^{-1}, i.v.) was virtually without effect on the nasal cavity pressure (Δ 0.3 ± 0.2 cmH_2O) and diastolic blood pressure (control DBP 55.4 ± 3.2 mmHg; Δ −1.4 ± 0.6 mmHg) in spinal dogs. Neither antagonist altered baseline heart rate.

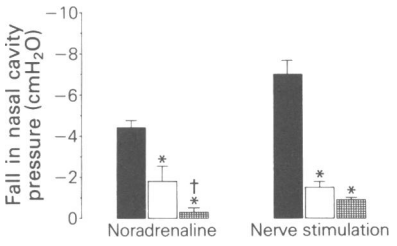

Figure 3 Effects of noradrenaline (1 μg, i.a.) and sympathetic nerve stimulation (0.5 Hz, 5V, 0.1 ms pulse width for 10s) on nasal cavity pressure (cmH_2O) in β-blocked, spinalised dogs before (control; solid columns) and 10 min after prazosin (0.1 mg kg^{-1}, i.v.; open columns) and then 10 min after RX 811059 (0.1 mg kg^{-1}, i.v.; stippled columns). Values represent mean of 5 experiments and vertical lines denote s.e.means. * Indicates a significant difference from pretreatment control responses and † shows that the response after RX 811059 was significantly different from the post-prazosin response ($P<0.05$; paired t test).

Results from experiments in which the α_2-adrenoceptor antagonist RX 811059 was given before prazosin showed that RX 811059 significantly reduced

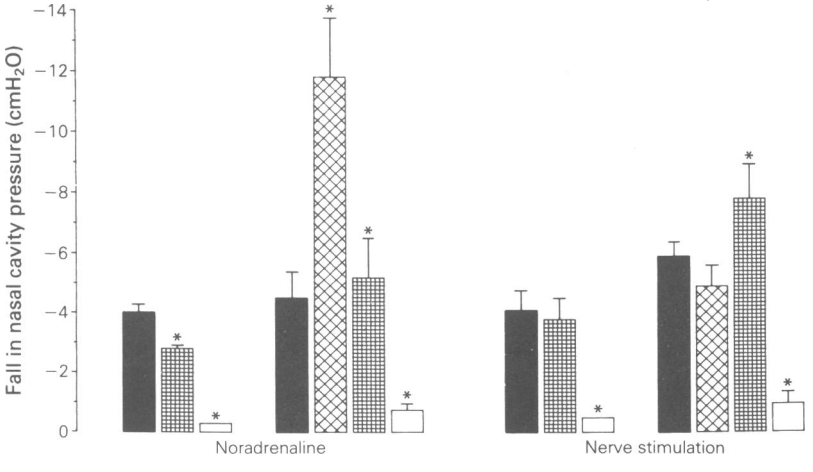

Figure 4 Effects of noradrenaline (1 μg, i.a.) and sympathetic nerve stimulation (0.5 Hz, 5V, 0.1 ms pulse width for 10s) on nasal cavity pressure (cmH_2O) in β-blocked, spinalised dogs either in the presence ($n = 3$) or absence ($n = 4$) of a functional neuronal re-uptake process. Responses before (control; solid columns) and 10 min after cocaine (5 mg kg^{-1}, i.v.; cross-hatched columns), RX 811059 (0.1 mg kg^{-1}, i.v.; stippled columns) and prazosin (0.1 mg kg^{-1}, i.v.; open columns) are shown. The vertical lines denote s.e.means. * Indicates a significant difference from the preceding response ($P<0.05$; paired t test).

(−30%) the response to the mixed α_1/α_2-agonist noradrenaline but did not affect the SNS response (Figure 4). Further administration of prazosin almost abolished the effects of i.a. noradrenaline and of SNS (Figure 4).

Pretreatment with the neuronal re-uptake inhibitor cocaine caused a very marked potentiation of the nasal vasoconstrictor response to noradrenaline both in terms of the maximal response (+157% potentiation; Figure 4) and duration. Cocaine induced a small, non-significant reduction (−16%) of the maximal response to SNS (Figure 4) although the duration of the effect was extended by the re-uptake inhibitor. RX 811059, given after cocaine, reduced the effect of noradrenaline (−56%; $P<0.05$ cf. response after cocaine) and augmented the response to SNS (+59%; $P<0.05$ cf. response after cocaine) (Figure 4). Further blockade of α_1-adrenoceptors with prazosin produced inhibition of both responses (Figure 4).

Effect of UK-14,304 on nasal responses to endogenous and exogenous noradrenaline

Reductions in nasal cavity pressure evoked by i.a. noradrenaline (1 μg) and SNS did not change significantly throughout the experimental duration, as shown in Figure 5. Administration of UK-14,304 (1.5 μg kg^{-1}, i.v.) itself produced a transient (7–10 min) fall in nasal cavity pressure ($\Delta -12.4 \pm 1.3$ cmH_2O) and increased resting diastolic blood pressure (control DBP 57.5 ± 3.8 mmHg; Δ 50.5 ± 6.1 mmHg). The nasal response to noradrenaline was unaffected by UK-14,304 throughout the duration of the 2 h experiment. However, the SNS response was reduced significantly (63, 39 and 30% inhibition at 10, 60 and 120 min respectively after UK-14,304) by the selective α_2-adrenoceptor agonist (Figure 5). Pretreatment with the α_2-antagonist RX 811059 abolished the inhibitory effects of UK-14,304 on the SNS responses (Figure 5).

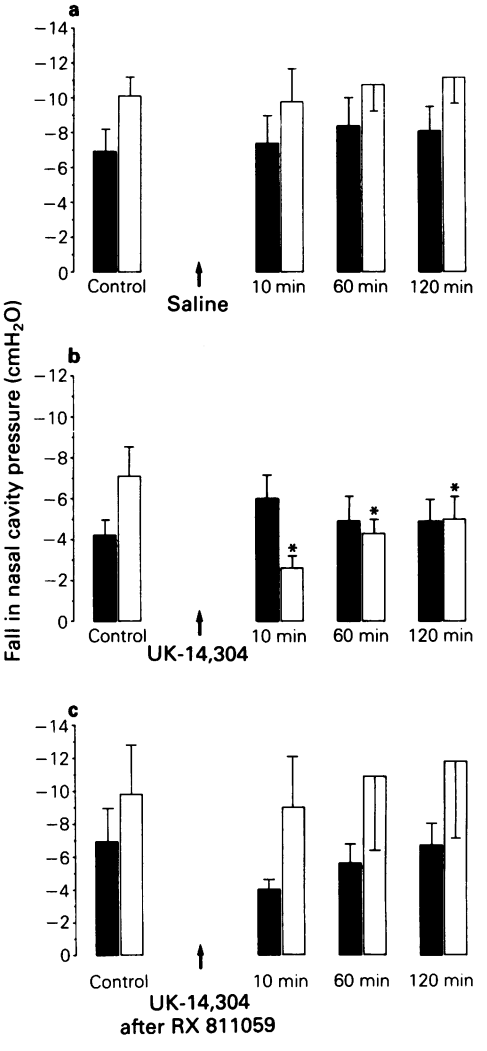

Figure 5 Effects of noradrenaline (1 μg, i.a.; solid columns) and sympathetic nerve stimulation (SNS; 0.5 Hz, 5V, 0.1 ms pulse width for 10s; open columns) on nasal cavity pressure (cmH_2O) in β-blocked, spinalised dogs before and 10, 60 and 120 min after either saline (2 × 0.1 mg kg^{-1}, i.v.) (a), saline and UK-14,304 (1.5 μg kg^{-1}, i.v.) (b) RX 811059 (0.1 mg kg^{-1}, i.v.) and UK-14,304 (1.5 μg kg^{-1}, i.v.) (c). Values are the means of 4, 4 and 3 animals respectively and vertical lines denote s.e. means. *Indicates a significant difference from the control pretreatment response ($P<0.05$; paired t test).

Discussion

Systemic arterial blood pressure of dogs, like that of pithed rats, can be elevated via stimulation of α_1- and α_2-adrenoceptors (Constantine *et al.*, 1980; Langer *et al.*, 1981). Attempts have been made using both *in vitro* and *in vivo* experiments to characterize their distribution. It has been relatively difficult to demonstrate postjunctional α_2-adrenoceptors in isolated arterial smooth muscle preparations although more success has been achieved with venous tissues (De Mey & Vanhoutte, 1980; 1981; Shoji *et al.*, 1983; Langer & Hicks, 1984). Using intact dog preparations, postjunctional α_1- and α_2-adrenoceptors have been identified in the forelimb (Cavero & Lefèvre-Borg, 1981) and hindlimb (Langer *et al.*, 1980; Gardiner & Peters, 1982; Horn *et al.*, 1982) vascular beds as well as the mesenteric (Shepperson *et al.*, 1982) and coronary (Holtz *et al.*, 1982) circulations.

We have now characterized pharmacologically α-adrenoceptors which mediate vasconstriction in the canine nasal mucosa. The data obtained clearly demonstrate the presence of both postjunctional α_1- and α_2-adrenoceptors in this highly vascularised region of the dog. In pentobarbitone-anaesthetized dogs pretreated with propranolol to block dilator β-adrenoceptors (Hall & Jackson, 1968), the selective α_1-adrenoceptor agonists cirazoline and phenylephrine and the selective α_2-adrenoceptor agonist UK-14,304 induced dose-related vasoconstriction in the nasal mucosa as measured by falls in nasal cavity pressure. The effect of cirazoline was sensitive to blockade by prazosin (α_1-antagonist) and resistant to the new potent selective α_2-adrenoceptor antagonist RX 811059 (Doxey *et al.*, 1984). In contrast, the response to UK-14,304 was inhibited by RX 811059 and unaffected by prazosin. Adrenaline and noradrenaline decreased nasal cavity pressure and, as expected, their responses were reduced by both prazosin and RX 811059, thus confirming that these agonists stimulate both α_1- and α_2-adrenoceptors in the nasal vasculature.

It is not possible to determine the exact location of the relative populations of postjunctional α_1- and α_2-adrenoceptors in the nasal vasculature from the present experiments. However, since we have measured changes in pressure of the sealed nasal cavity, falls in pressure most probably reflect shrinkage of the nasal capacitance vessels, due to constriction of the venous erectile tissue in the nose (Eccles, 1982), rather than changes in blood flow of the arterial resistance vessels. Therefore, postjunctional α_1- and α_2-adrenoceptors are most probably present in the venous system of the dog nasal mucosa. The fact that UK-14,304 was more potent than the α_1-agonists cirazoline and phenylephrine may indicate a predominance of α_2-adrenoceptors in the nasal mucosal vasculature. Ichimura & Jackson (1984) using an *in vitro* preparation of the vascular smooth muscle of the canine nasal mucosa identified the presence of both postjunctional α_1- and α_2-adrenoceptors. However, they concluded that the former receptor subtype was the dominant receptor in this preparation which is in contrast to our results *in vivo*. The differences may be explained by the fact that Ichimura & Jackson (1984) used clonidine as their selective α_2-agonist which is a partial agonist (see Roach *et al.*, 1983b) and has a modest selectivity compared to UK-14,304 (Doxey *et al.*, 1981).

Andersson & Bende (1984) have recently measured blood flow in the human nasal mucosa in order to determine the α-adrenoceptor subtypes responsible for controlling the tone of the nasal resistance vessels. They found that topical application of agonists which stimulate α_2-adrenoceptors, such as oxymetazoline and clonidine, reduced nasal mucosal blood flow whereas the α_1-agonist phenylephrine was ineffective. All three compounds are effective nasal decongestants. Andersson & Bende (1984) concluded, therefore, that both α_1- and α_2-adrenoceptors are present in capacitance vessels (since both preferential α_1- and α_2-agonists cause nasal decongestion) whereas only α_2-adrenoceptors are found in human nasal resistance vessels.

It has been proposed that vascular postjunctional α_1-adrenoceptors are situated within the neuro-effector junction and are stimulated by neuronally released noradrenaline, whereas α_2-adrenoceptors are located mainly extrajunctionally and are activated by circulating catecholamines (Docherty & McGrath, 1980; Langer *et al.*, 1980; 1981; Yamaguchi & Kopin, 1980; Langer & Shepperson, 1982; Wilfert *et al.*, 1982). This suggestion was derived mainly from data obtained from *in vivo* experiments. Recently, Flavahan *et al.*, (1984) found that noradrenaline released from sympathetic nerves can stimulate both postjunctional α_1- and α_2-adrenoceptors in the canine isolated saphenous vein. Since nasal mucosal blood vessels receive a dense sympathetic innervation (Dahlstrom & Fuxe, 1965; Nomura & Matsuura, 1972; Proctor & Adams, 1976) it was decided to compare the effects of prazosin and RX 811059 on the responses to exogenous (i.a. administration) and endogenous (sympathetic nerve stimulation) noradrenaline. Electrical stimulation of the postganglionic sympathetic nerve fibres from the superior cervical ganglia to the nasal vasculature produced a pronounced fall in nasal cavity pressure in spinal dogs. Unlike the response to exogenous noradrenaline which was only partially blocked by prazosin, the effect of nerve stimulation was inhibited almost totally by this selective α_1-antagonist. On the other hand, the selective α_2-adrenoceptor antagonist RX 811059 reduced significantly the response to i.a. noradrenaline but did not alter the effect of sympathetic nerve stimulation in normal spinal dogs. The contribution particularly of postjunctional α_2-adrenoceptors in mediating neuronal responses in this preparation is impossible to assess from the experiments using RX 811059. If prejunctional α_2-adrenoceptor mediated feedback inhibition occurs in these sympathetic nerves (see discussion below), then blockade of these receptors by RX 811059 would increase noradrenaline release which in turn could counteract the postjunctional α_2-adrenoceptor antagonism produced by RX 811059. However, results with prazosin indicate that the majority of the nerve-mediated response is produced by activation of α_1-adrenoceptors. Therefore, these latter data are consistent with the concept that noradrenaline released endogenously from postganglionic sympathetic neurones supplying the nasal vasculature in dogs stimulates intrajunctional α_1-adrenoceptors, whereas vascular α_2-adrenoceptors are located primarily ex-

trajunctionally and are activated by exogenous noradrenaline.

It is accepted that prejunctional α_2-adrenoceptors are present on sympathetic nerve terminals where they modulate neurotransmitter release (see reviews Starke, 1977; Gillespie, 1980; Langer, 1980). Experiments were performed in spinalised dogs in order to determine their presence on sympathetic neurones supplying the nasal cavity vasculature. Results from experiments using UK-14,304 and RX 811059, either given separately or in combination against stimulation responses, indicate that α_2-adrenoceptors are situated prejunctionally on the sympathetic neurones innervating the canine nasal mucosa. After producing a transient vasoconstrictor response, the selective α_2-agonist UK-14,304 caused a prolonged reduction in the response to nerve stimulation. This inhibitory effect of UK-14,304 was not due to a reduced postjunctional receptor sensitivity since the response to i.a. noradrenaline remained unaffected. Therefore, it is reasonable to assume that UK-14,304 inhibits nerve stimulation responses by activating prejunctional α-adrenoceptors to reduce the amount of transmitter released. These receptors are of the α_2-type since they were stimulated by a low dose of UK-14,304 and this effect was antagonized by the selective α_2-antagonist RX 811059. Furthermore, phenylephrine has little effect on the nasal responses to sympathetic nerve stimulation in spinal dogs (unpublished observations). Our present *in vivo* results compliment those of Ichimura & Jackson (1984); they observed that clonidine reduced and yohimbine potentiated the electrically-evoked contractions of the isolated strip of canine nasal mucosa and suggested the presence of prejunctional α_2-adrenoceptors in this preparation.

It is difficult to assess the physiological relevance of the prejunctional α_2-adrenoceptors from the present results. However, it appears likely that these receptors are activated, and negative feedback occurs, only when the concentration of agonist (either endogenous noradrenaline or exogenous UK-14,304 in these experiments) in the biophase is high (see Heepe & Starke, 1985). This is consistent with the finding that after blockade of neuronal re-uptake with cocaine (i.e. elevated levels of noradrenaline in the biophase), RX 811059 significantly potentiated the response to stimulation whereas under normal conditions the α_2-antagonist was ineffective. The sympathetic neurones of the canine nasal mucosa appear to have a marked neuronal re-uptake process since cocaine potentiated greatly the response to exogenous noradrenaline. However, cocaine was without effect on the peak responses to nerve stimulation, indicating that a marked stimulation of the feedback mechanism probably counteracted the possibility of an enhanced end organ response.

The possibility that functional negative feedback occurs in normal dogs (i.e. in the absence of cocaine) cannot be totally dismissed. If this were the case then, as discussed above, the increased release of noradrenaline that results after blockade of prejunctional α_2-adrenoceptors with RX 811059 may be sufficient to stimulate postjunctional α_2-adrenoceptors, which are also blocked by RX 811059. Thus, in this situation it may be possible for both the pre- and postjunctional effects of RX 811059 to cancel each other out thereby leaving the stimulation response relatively unaffected.

A point which merits discussion, with possible clinical implications for nasal decongestants, is the finding that UK-14,304 inhibited sympathetic nerve responses (via stimulation of prejunctional α_2-adrenoceptors) for a much longer time period than its vasoconstrictor response due to activation of postjunctional α_2-adrenoceptors. A similar difference in duration of action has been found for clonidine at cardiac prejunctional α_2-adrenoceptors and vascular postjunctional α-adrenoceptors in pithed rats and guinea-pigs, as well as spinal dogs and cats (Cavero *et al.*, 1978a; Roach *et al.*, 1978). The agonist-induced pressor response is very transient compared to the duration of inhibition of a sympathetic nerve-induced tachycardia. Oxymetazoline and tramazoline (two clinically effective nasal decongestants) had similar profiles to clonidine at these receptors in pithed rats (Cavero *et al.*, 1978b).

It is conceivable that nasal decongestants, which possess α_2-adrenoceptor agonist activity, could reduce sympathetic tone to the nasal vasculature after termination of their beneficial postjunctional vasoconstrictor actions, thus resulting in a delayed dilator effect. This mechanism may, at least in part, be responsible for the rebound phenomenon which is common after cessation of treatment with nasal decongestants, particularly of the imidazoline type (Empey & Meddar, 1981). Therefore, a nasal decongestant selective for α_1-adrenoceptors should be preferable to an agonist which also stimulates prejunctional α_2-adrenoceptors, since at present there are no compounds which selectively activate postjunctional α_2-adrenoceptors over prejunctional α_2-adrenoceptors.

In conclusion, results have been obtained which demonstrate that postjunctional α_1- and α_2-adrenoceptors are present in the dog nasal mucosa. Stimulation of both receptor types induced vasoconstriction as indicated by a fall in pressure of the sealed nasal cavity. In addition, the sympathetic neurones which densely innervate the nasal mucosa have a marked re-uptake process for noradrenaline and contain prejunctional α_2-adrenoceptors.

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