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Sympathetic control of nasal blood flow in the rat mediated by α_1-adrenoceptors

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Abstract

Experiments were undertaken, using laser-Doppler flowmetry, to determine the nature of adrenoceptors mediating sympathetic nerve evoked nasal vasoconstrictor responses in anesthetized rats. Presence of sympathetic tone was confirmed by a large (330%) increase of nasal blood flow following section of the ipsilateral preganglionic cervical sympathetic nerve. Electrical nerve stimulation produced reproducible, frequency-related nasal vasoconstrictor responses with near maximal response, observed at less than 10 Hz. Evoked nasal vasoconstrictor responses were largely blocked with intravenous treatment with the non-selective α-adrenoceptor antagonists, phentolamine (5 mg kg^{-1}) and phenoxybenzamine (2 mg kg^{-1}), as well as with the selective α_1-adrenoceptor antagonist, prazosin (300 μg kg^{-1}). α_2-Adrenoceptor antagonism with rauwolscine (500 μg kg^{-1}) potentiated neurally evoked nasal vasoconstriction. Neither atropine (1 mg kg^{-1}) nor propranolol (1 mg kg^{-1}) altered the evoked responses. Rats with intact cervical sympathetic nerves responded to rauwolscine with a modest constriction. Subsequent prazosin administration produced an increase of nasal blood flow of approximately 275%. These results suggest that the nasal vasculature of the rat is under intense sympathetic tone and that the resulting neurogenic vasoconstriction is mediated exclusively by activation of α_1-adrenoceptors.

Keywords: Laser-Doppler flowmetry; α-Adrenoceptor subtype; Sympathetic nerve stimulation; Phentolamine; Phenoxybenzamine; Prazosin; Rauwolscine

1. Introduction

Resistance and capacitance blood vessels of the nasal mucosa are densely innervated by sympathetic adrenergic nerves (Dahlström and Fuxe, 1965). Section of these nerves produces congestion of the nasal mucosa (Stoksted and Thomsen, 1953; Rooker and Jackson, 1969). Electrical stimulation of the cervical sympathetic nerve trunk produces frequency-dependent nasal mucosal vasoconstriction in a variety of species including cats (Franke, 1966; Änggård and Edwall, 1974; Wilson and Yates, 1978), dogs (Rooker and Jackson, 1969; Lacroix et al., 1994a), and pigs (Lacroix, 1989; Lacroix and Lundberg, 1989). In dogs, neurogenic nasal mucosa vasoconstriction appears to be mediated largely by activation of α_1-adrenoceptors (Berridge and Roach, 1986). However, in the pig, both α_1- and α_2-adrenoceptors have been implicated in sympathetic nerve mediated nasal vasoconstrictor responses (Lacroix, 1989; Lacroix and Lundberg, 1989). Comparable studies have not been undertaken in other species.

The present experiments were performed in an attempt to utilize laser-Doppler flowmetry to measure blood flow from the rat nasal mucosa on a continuous basis. The overall aim was to determine the extent to which nasal mucosal blood flow is under sympathetic neuronal control and to define the specific subtype of α-adrenoceptors that may be involved in nasal vasoconstriction in this common experimental animal. Our results suggest that neural release of norepinephrine from cervical sympathetic nerves produces vasoconstriction in the rat nasal mucosa by preferentially activating α_1-adrenoceptors with little, if any, post-synaptic α_2-adrenoceptor involvement.

2. Materials and methods

2.1. General

Male Sprague–Dawley rats weighing 350–460 g were anesthetized with sodium pentobarbital (60 mg kg^{-1}, i.p.),

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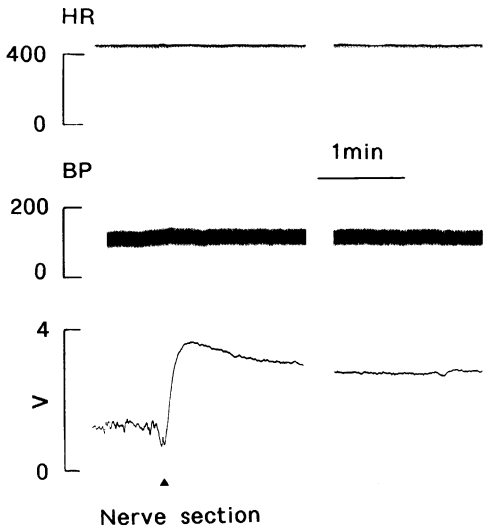

Fig. 1. Effect of section of ipsilateral preganglionic cervical sympathetic nerve on nasal mucosal blood flow as measured using laser-Doppler flowmetry in an anesthetized rat (V; arbitrary units). Note the elevation of nasal blood flow following sympathetic denervation (lower panel). Also shown are systemic arterial blood pressure (BP) and heart rate (HR) recordings. Break between records represents 10 min.

with supplementary pentobarbital (3–5 mg kg^{-1}, i.v.) given as necessary to maintain stable anesthesia. Animals were paralyzed with gallamine triethiodide (5–10 mg kg^{-1}, i.v.). The trachea was intubated for ventilation with a Harvard respirator using room air at a frequency of 60 strokes min^{-1} and tidal volume of 1 ml per 100 g. A femoral artery and vein were cannulated for recording of systemic arterial blood pressure (Spectramed P23XL) and for the intravenous administration of drugs. Heart rate was derived from the femoral arterial pulse and processed using a cardiotachometer (Sanei 1321, Sanei, Japan). Body temperature was maintained at approximately 37°C with a thermostable chemical heating pad (Deltaphase Isothermal Pad; Braintree Scientific, Braintree, MA, USA). A Sanei model 365 polygraph was used to record all physiological parameters.

2.2. Assessment of blood flow changes in the nasal mucosa

Changes in blood flow in the superficial nasal mucosa of the nasal cavity were measured using a laser-Doppler flowmeter (Omega flow FLO-C1, Omegawave, Japan) fitted with an EG (fine) fiber optic probe. The type EG probe is made from two 250-μm diameter optical fibers consisting of parallel incident and receiving optical fibers separated by a center distance of 250 μm. These optical fibers are very flexible and are laid in parallel to the tissue. The laser-Doppler flowmetry technique involves exposure of a small surface area to coherent light that is reflected from both stationary tissues and blood cells with the moving blood cells producing Doppler beat-frequencies at a photodetector. Computer-processed Doppler beat-frequencies are proportional to the total blood flow within the volume of tissue measured and are dependent upon the relative concentration of blood cells and average cell velocity. The depth of measurement is proportional to the distance between the incident and receiving fibers. We estimate the maximal depth of laser light penetration in our preparations to be about 0.5 mm.

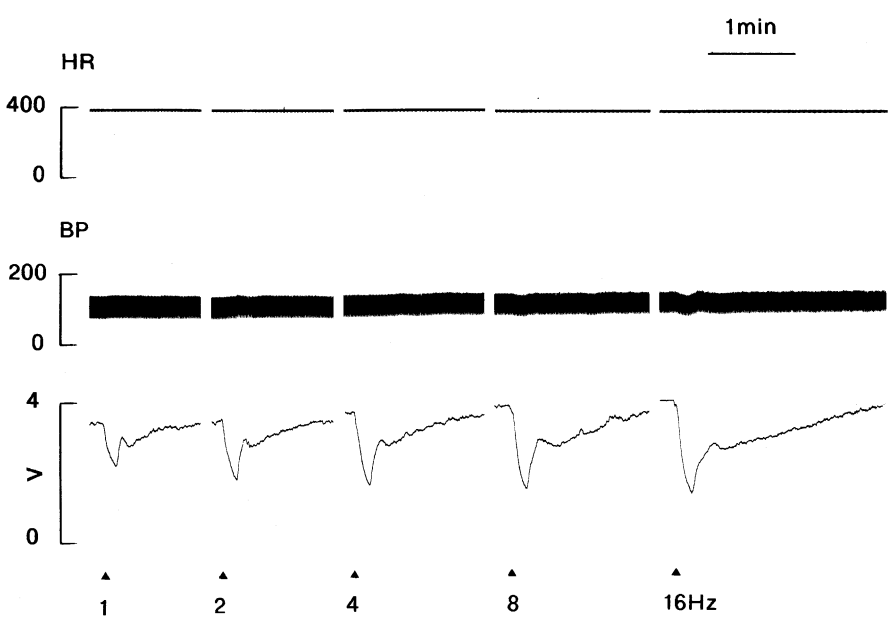

Fig. 2. Effects of increasing frequencies (1–16 Hz) of electrical stimulation of the preganglionic cervical sympathetic nerve on nasal mucosal blood flow (lower panels) measured using laser-Doppler flowmetry in a pentobarbital-anesthetized rat (arbitrary units). Note the graded frequency-related vasoconstrictor responses. Neither systemic arterial blood pressure (BP) nor heart rate (HR) was altered by presentation of these trains of stimuli (4 V; 1 ms; 10-s trains). Breaks represent 3–5 min.

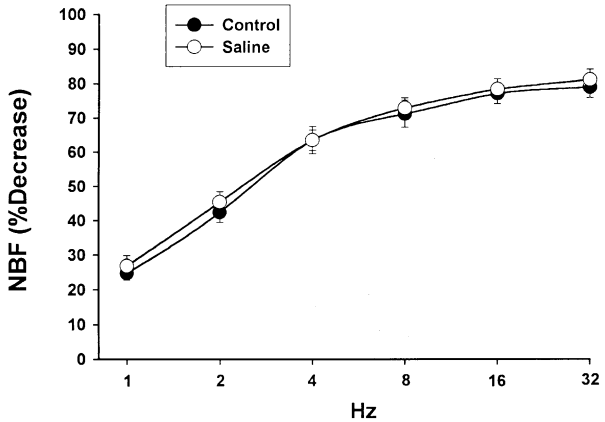

Fig. 3. Composite frequency–response relationships for nasal mucosal vasoconstriction in response to electrical stimulation of the preganglionic cervical sympathetic nerve trunk (1–32 Hz) in 34 pentobarbital anesthetized rats. Nasal blood flow (NBF) values represent percentage decrease from baseline in response to nerve stimulation. Solid circles represent control responses. Open circles represent vasoconstrictor responses 15–20 min after intravenous administration of physiological saline. Note high degree of reproducibility between the two trials. Stimulation parameters: 4 V; 1 ms pulse width; 10-s trains of pulses. Values represent mean response ± S.E.M.

The laser probe was placed, using a micromanipulator, at right angles to the surface of the anterior tip of the inferior turbinate. Care was taken to not record blood flow from the large blood vessels visualized under a stereomicroscope. The time constant was set at 1 s. To avoid influences of blood pressure on the laser-Doppler signal, all the electrical stimulations were performed under conditions of stable blood pressure and when laser-Doppler measurements exhibited a stable baseline.

Because laser-Doppler flowmetry yields only relative flow values, the data were normalized to percentage of the basal flow values. Thus, the change of blood flow (% decrease) was calculated according to the following formula: $(A-B)/A \times 100$, where A represents the blood flow just before electrical stimulation of the sympathetic nerve, and B represents the lowest blood flow level reached in response to stimulation.

Although laser-Doppler flowmetry has many advantages over other techniques, there are also limitations and drawbacks including sensitivity to movement, signal reduction by tissue pigment and restriction of the measurement area. The lack of calibration in units of flow, as well as uncertainty concerning the volume of tissue in which blood flow is measured are additional limitations. As this technique gives only relative flow values, the data are normalized to percentage of the basal flow levels. This is justified in studies of vasoconstrictor mechanisms, as the level of zero blood flow is a known quantity that was determined in each experiment after euthanasia with pentobarbital.

2.3. Sympathetic nerve stimulation

One cervical sympathetic nerve was carefully separated and cut at the mid-cervical level. For electrical stimulation, bipolar silver stimulating electrodes were placed under the distal portion of this preganglionic cervical sympathetic nerve and covered with liquid paraffin. Stimuli were generated by an electronic stimulator and isolation unit (SS-1894S, Nihon Kohden, Japan). Square wave (4 V) trains of 10-s duration were presented. The pulse width was 1 ms with the frequency varied between 1 and 32 Hz. Responses were allowed to recover fully before the next highest frequency of stimulation was tested. The identification of the cervical sympathetic nerve was confirmed by observing concurrent dilation of the pupil during nerve stimula-

Table 1
Effects of autonomic antagonists on nasal blood flow (NBF) expressed as % of initial control vasoconstriction, mean systemic arterial blood pressure (MSAP; mm Hg) and heart rate (HR; beats/min)

Treatment	n	NBF %control vasoconstriction				MSAP		HR	
		2 Hz	4 Hz	8 Hz	16 Hz	Before	After	Before	After
Saline	34	109 ± 5	101 ± 4	102 ± 3	100 ± 2	116 ± 4	110 ± 4	415 ± 6	406 ± 6
Phentolamine (5 mg kg^{-1})	8	11 ± 6[a]	11 ± 6[b]	18 ± 5[b]	35 ± 7[b]	112 ± 7	67 ± 3[b]	405 ± 9	383 ± 8
Phenoxybenzamine (2 mg kg^{-1})	8	12 ± 4[b]	17 ± 5[b]	27 ± 6[b]	36 ± 9[b]	116 ± 8	84 ± 6[b]	395 ± 10	391 ± 13
Propranolol (1 mg kg^{-1})	6	107 ± 8	99 ± 6	99 ± 3	101 ± 3	115 ± 8	119 ± 7	411 ± 6	342 ± 11[b]
Atropine (1 mg kg^{-1})	7	105 ± 4	109 ± 6	107 ± 8	99 ± 4	108 ± 5	102 ± 6	382 ± 7	374 ± 9
Prazosin (300 μg kg^{-1})	7	17 ± 6[a]	25 ± 10[a]	29 ± 10[a]	36 ± 10[a]	110 ± 5	74 ± 3[b]	422 ± 11	404 ± 11
Prazosin + rauwolscine (300 μg kg^{-1}) + (500 μg kg^{-1})	7	30 ± 11	34 ± 8	46 ± 8	50 ± 8	74 ± 3	67 ± 2[b]	402 ± 11	398 ± 10
Rauwolscine (500 μg kg^{-1})	8	115 ± 5	111 ± 4[a]	110 ± 4[a]	107 ± 3[a]	107 ± 3	91 ± 2[b]	409 ± 8	402 ± 8
Rauwolscine + prazosin (500 μg kg^{-1}) + (300μg kg^{-1})	8	21 ± 7[b]	27 ± 7[b]	31 ± 7[b]	39 ± 5[b]	91 ± 3	67 ± 4[b]	399 ± 8	379 ± 7

Values represent means ± S.E.M. Measurements taken before and 10–20 min after drug administration. Nasal vasoconstrictor responses were compared to % vasoconstriction of immediately preceding frequency–response curve.

[a] $P < 0.05$.

[b] $P < 0.01$.

tion. After a control period for response stabilization, antagonists were administered intravenously with at least 10–15 min allowed to reach a steady state.

2.4. Drugs and statistical analyses

The following drugs were used: (±)-propranolol hydrochloride, atropine sulfate and gallamine triethiodide (Sigma, St. Louis, MO, USA); prazosin hydrochloride, rauwolscine hydrochloride and phenoxybenzamine hydrochloride (Research Biochemical International, Natick, MA, USA); phentolamine mesylate (Ciba-Geigy, Japan). All drug solutions were prepared in physiological saline with the exception of prazosin [2.5% glucose (w/v):2.5% glycerol (v/v)] and phenoxybenzamine (50% propylene glycol). Drug dosages refer to the respective salts.

Data are reported as means ± S.E.M. Changes of blood pressure, heart rate and nasal blood flow, before and after nerve section and blood pressure and heart rate before and after antagonist administration were analyzed using Student's *t*-test for paired comparisons. Effects of saline and antagonist combinations on frequency-related nasal vasoconstrictor responses were analyzed using the Wilcoxon matched-pairs signed-ranks test. In these instances, the percentage of evoked vasoconstriction was compared, at each frequency, with the immediately preceding frequency–response curve. In all cases, values of $P < 0.5$ were considered statistically significant.

3. Results

3.1. Effect of sympathetic nerve section on basal mucosal nasal blood flow

Nasal mucosal blood flow was measured using laser-Doppler flowmetry before and after section of the ipsilateral preganglionic cervical sympathetic nerve in 18

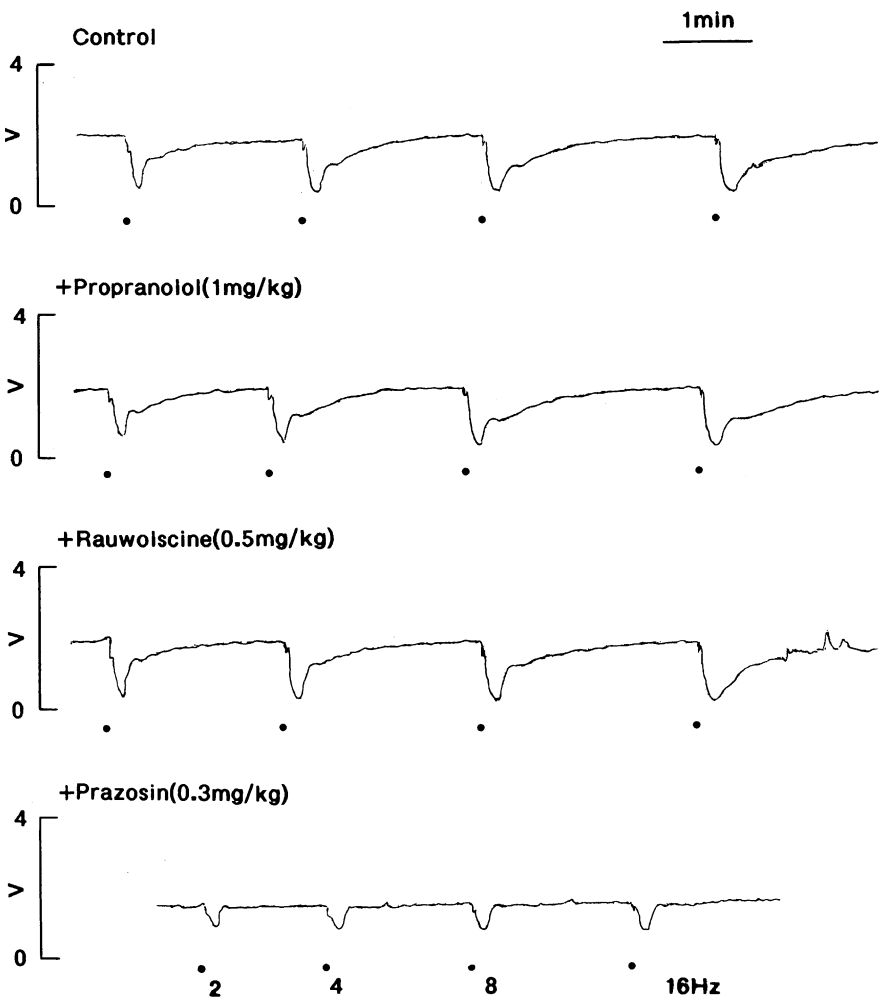

Fig. 4. Effects of increasing frequency (2–16 Hz) of electrical stimulation of the preganglionic cervical sympathetic nerve on nasal mucosal blood flow as measured using laser-Doppler flowmetry in a pentobarbital anesthetized rat (arbitrary units). Upper panel represents frequency-related vasoconstrictor responses measured from the nasal mucosa under control conditions (4 V; 1 ms; 10-s trains). Second panel represents responses repeated after intravenous administration of propranolol (1 mg kg^{-1}). Third and fourth panels represent responses after subsequent intravenous administration of rauwolscine (500 μg kg^{-1}) followed by prazosin (300 μg kg^{-1}).

anesthetized rats. This procedure produced a brief vasoconstriction followed by a dramatic increase of nasal blood flow (Fig. 1). This highly significant ($P < 0.001$) vasodilation peaked at 351% of control after 1 min and remained elevated (328% of control at 5–10 min after nerve section). Neither systemic arterial blood pressure nor heart rate was significantly altered by cervical sympathetic nerve section.

3.2. Responses to sympathetic nerve stimulation

Electrical stimulation of the preganglionic cervical sympathetic nerve produced frequency-dependent nasal vasoconstrictor responses that approached their maximal effect at frequencies above 4 Hz (Figs. 2 and 3). Ten to 20 min after intravenous administration of saline, the frequency-related vasoconstrictor responses were virtually identical in amplitude (Fig. 3).

3.3. Effects of autonomic antagonists

In order to determine the nature of the adrenoceptors mediating these vasoconstrictor responses, both non-selective and selective antagonists were employed. For non-selective α-adrenoceptor antagonism, we chose phentolamine and phenoxybenzamine; propranolol and atropine were chosen for β-adrenoceptor and muscarinic acetylcholine receptor antagonism. The data in Table 1 illustrate the effects of these receptor antagonists, on nasal vasoconstriction produced at 2, 4, 8, and 16 Hz. In each case, the percentage vasoconstriction was compared with that of the immediately preceding frequency–response curve. As shown in Table 1, both of the non-selective α-adrenoceptor antagonists caused significant depression of neurally evoked nasal vasoconstriction at all stimulation frequencies. Neither propranolol (1 mg kg^{-1}) nor atropine (1 mg kg^{-1}) had any effect on the evoked responses. Cardiovascular responses to each antagonist, before and after antagonist administration also are shown in Table 1.

The contribution made by activation of selective α-adrenoceptor subtypes was evaluated by the use of prazosin and rauwolscine (given both alone and in combination) on neurally evoked nasal vasoconstrictor responses. A typical example of these experiments is shown in Fig. 4. As shown in Fig. 5A, the α_1-adrenoceptor antagonist, prazosin (300 μg kg^{-1}), produced a dramatic depression of neurally elicited vasoconstriction at all stimulation frequencies which was partially reversed by subsequent intravenous administration of rauwolscine (500 μg kg^{-1}). However, this rauwolscine reversal effect was not statistically significant.

Fig. 5B shows the effects of rauwolscine followed by administration of prazosin. Note that rauwolscine, given initially, facilitated nasal vasoconstriction at 4–16 Hz ($P < 0.05$). Subsequent prazosin administration produced a

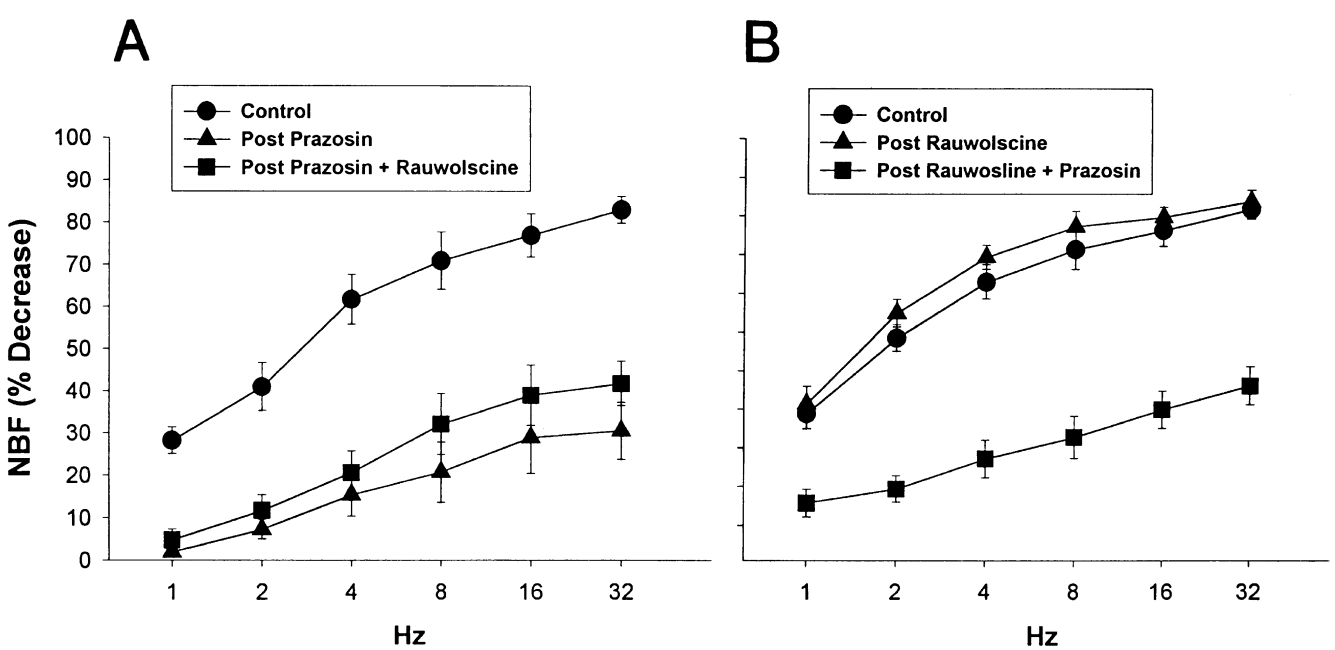

Fig. 5. Composite frequency–response curves representing electrically evoked nasal mucosal vasoconstriction produced by stimulation of the ipsilateral cervical sympathetic nerve of pentobarbital-anesthetized rats. Nasal mucosal blood flow (NBF) expressed as percentage decrease from baseline levels. (A) Solid circles represent control responses. Triangles represent responses after intravenous prazosin (300 μg kg^{-1}). Squares represent responses after subsequent administration of rauwolscine (500 μg kg^{-1}). (B) Circles represent control responses. Triangles represent responses after intravenous rauwolscine (500 μg kg^{-1}) and squares represent responses after subsequent administration of prazosin (300 μg kg^{-1}). Values represent means ± S.E.M. for seven animals in (A) and eight animals in (B). Note potentiation of vasoconstriction produced by rauwolscine (α_2-adrenoceptor antagonism) and depression of responses by prazosin (α_1-adrenoceptor antagonism).

dramatic attenuation of these responses to the same level as prazosin given alone. Basal cardiovascular responses to these selective α-adrenoceptor antagonists also are shown in Table 1.

3.4. Changes in basal nasal blood flow in response to selective α-adrenoceptor antagonism

The final series of experiments were undertaken to explore the effects of selective α-adrenoceptor subtype antagonists on basal nasal blood flow in animals with intact sympathetic innervation. In six animals with intact sympathetic tone, systemic administration of rauwolscine (500 $\mu g\ kg^{-1}$) caused a decrease of nasal blood flow to $90 \pm 6\%$. However, this was not statistically significant. Thirty minutes after subsequent prazosin administration (300 $\mu g\ kg^{-1}$), there was a significant elevation of nasal blood flow of $272 \pm 23\%$ ($P < 0.01$). This increase of blood flow was not statistically different from the increase seen after preganglionic cervical sympathetic nerve section (see above).

4. Discussion

In the present study, removal of sympathetic neuronal tone resulted in a large increase of mucosal blood flow. These results on rats are qualitatively similar to those from studies using other species, although the magnitude of increased blood flow (300 + %) is greater than that observed in other species. In cats and dogs, sympathetic nerve section increased blood flow in the internal maxillary artery by 51% and 43%, respectively (Lacroix et al., 1994a). However, in a separate study, these investigators found acute sympathectomy to produce only 14% increase of nasal blood flow in dogs (Lacroix et al., 1994b). It appears that the rat is under more intense sympathetic tone to nasal blood vessels than are cats or dogs. This may be due to differences in ventilatory pathways between these species or due to different methods used to measure nasal blood flow.

Sympathetic nerve stimulation produces frequency-related vasoconstrictor responses in the nasal mucosa of both dogs and cats (Franke, 1966; Rooker and Jackson, 1969; Malm, 1974). As in the present study, near maximal responses are observed at relatively low frequencies of nerve stimulation. Sympathetic vasoconstriction in all species studied is antagonized by pretreatment with non-selective α-adrenoceptor antagonists (Lung and Wang, 1989; Lacroix and Lundberg, 1989; Lacroix, 1989; Lacroix et al., 1994a,b).

The present study is the first concerning characterization of innervated adrenoceptor subtypes of the vasculature of the rat nasal mucosa. Clearly, sympathetic nerve stimulation produced vasoconstriction exclusively by activation of α_1-adrenoceptors. This is similar to what we reported previously regarding ocular choroidal vasoconstrictor mechanisms in rats (Kawarai and Koss, 1998). We found no evidence for α_2-adrenoceptor induced vasoconstriction although neurally activated prejunctional activation was apparent. Similar prejunctional effects have been demonstrated in dogs (Berridge and Roach, 1986) and in experiments using an in vitro canine nasal mucosal preparation (Ichimura and Jackson, 1984).

Postjunctional α_1- and α_2-adrenoceptors coexist in the systemic vasculature and both receptor subtypes appear to mediate vasoconstriction (Drew and Whiting, 1979). It was originally hypothesized that α_1-adrenoceptors are preferentially innervated and that α_2-adrenoceptors are only "extrasynaptic", responding mainly to circulating catecholamines (Langer et al., 1981; Timmermans and Van Zwieten, 1981). More recently, however, neuronally mediated activation of both α_1- and α_2-adrenoceptors has been reported in many in vivo systems (see Koss et al., 1991). The present observations of lack of innervated α_2-adrenoceptors in the rat nasal mucosa are in agreement with results of others showing that postjunctional α_1- and α_2-adrenoceptors are not evenly distributed throughout the vascular system (Horn et al., 1982).

There are only a few other studies attempting to delineate α-adrenoceptor subtypes involved in sympathetic neural control of nasal blood flow. In pigs, prazosin and idazoxan pretreatment were both effective in the reduction of nasal blood flow in response to low frequency cervical sympathetic nerve stimulation (Lacroix, 1989; Lacroix and Lundberg, 1989). Their results suggest that both α_1- and α_2-adrenoceptors mediate nasal vasoconstriction in this species. In contrast, in the dog, sympathetic nerve mediated vasoconstriction appears to be primarily due to α_1-adrenoceptor activation (Berridge and Roach, 1986). This latter conclusion is supported by in vitro studies using electrical field stimulation of vascular smooth muscle preparations of the dog nasal mucosa where α_1-adrenoceptors also predominate (Ichimura and Jackson, 1984).

Neither propranolol nor atropine altered evoked nasal mucosal vasoconstrictor responses suggesting that neither β-adrenoceptors nor cholinergic muscarinic mechanisms are involved. This conclusion is in agreement with those of others in cats and dogs (Änggård and Edwall, 1974; Lung and Wang, 1989). In contrast, propranolol enhanced sympathetic vasoconstrictor responses in anesthetized pigs, indicating that neuronally released norepinephrine can also activate postjunctional, vasodilatory β-adrenoceptors in that species (Lacroix, 1989; Lacroix and Lundberg, 1989).

Studies with adrenergic agonist administration are more common. As with neuronal activation, non-selective α-adrenoceptor agonists clearly block vasoconstrictor effects produced by adrenergic agonists in dogs, cats and pigs (Rooker and Jackson, 1969; Änggård and Edwall, 1974; Lacroix, 1989; Lung and Wang, 1989) as well as in rats (Kristiansen et al., 1993) and in isolated human mucosal tissues (Ichimura and Chow, 1988).

Attempts to define α-adrenoceptor subtypes involved in agonist-induced nasal vasoconstriction have been undertaken using a variety of species. However, studies using selective adrenoceptor agonists and antagonists are equivocal. For example, in humans, Andersson and Bende (1984) suggest that α_2-adrenoceptors are totally responsible for adrenergic-induced reduction of nasal mucosal blood flow. In contrast, Druce et al. (1984) found both α_1- and α_2-adrenoceptor activation to be involved. Still others present evidence that α_1-adrenoceptors predominate in man (Ichimura and Chow, 1988).

In pigs, α_2-adrenoceptor agonists were 10-fold more potent than were α_1-adrenoceptor agonists in decreasing nasal blood flow (Lacroix, 1989; Lacroix and Lundberg, 1989). Rabbits and dogs respond with nasal mucosal vasoconstriction when exposed to either α_1- or α_2-adrenoceptor agonists (Ichimura and Jackson, 1984; Berridge and Roach, 1986; Ichimura and Chow, 1988; Akerlund et al., 1993). In dogs, one group suggests that α_2-adrenoceptor mechanisms predominate with regard to adrenergic drug-induced nasal mucosal vasoconstrictor responses (Berridge and Roach, 1986). Other investigators claim that the dog nasal mucosal vessels are mainly responsive to drugs stimulating α_1-adrenoceptors (Ichimura and Jackson, 1984). There is one study using rats concerning nasal decongestant effects of adrenergic agents where only α_1-adrenoceptor stimulation produced significant nasal vasoconstrictor responses (Kristiansen et al., 1993). In contrast, others demonstrate nasal vasoconstrictor responses in rats in response to both phenylephrine (α_1) and oxymetazoline (mainly α_2) administration (Salem and Clemente, 1972).

Systemic administration of rauwolscine produced a modest nasal mucosal vasoconstriction and subsequent administration of prazosin caused a large vasodilator effect in rats with intact sympathetic innervation. Similar responses, of lesser magnitude, have been observed in response to phenoxybenzamine given to dogs (Hall and Jackson, 1968; Rooker and Jackson, 1969). Our results in rats with antagonists given to animals with intact sympathetic tone confirm the previously observed high level of sympathetic tone to the nasal mucosa seen after the sympathetic nerve section in this species. Results from these latter experiments also support our conclusions regarding the existence of functional prejunctional α_2-adrenoceptors and of the predominance of postsynaptic α_1-adrenoceptors in producing nasal mucosal vasoconstriction.

In conclusion, nasal mucosal blood flow can be measured on a continuous basis using laser-Doppler flowmetry techniques in anesthetized rats. Section of the ipsilateral cervical sympathetic nerve produced a large increase of nasal mucosal blood flow indicating a high degree of sympathetic neuronal tone to this vascular bed in the rat. Prazosin administration mimicked the effect of nerve section. Sympathetic nerve stimulation caused frequency-dependent vasoconstrictor responses mediated exclusively by norepinephrine acting on postjunctional α_1-adrenoceptors. Involvement of α_2-adrenoceptors appears to be only prejunctional or "extrasynaptic" in this vascular bed in rats.

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