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α_1-Receptors at pre-capillary resistance vessels of the human nasal mucosa*

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SUMMARY

The aim of the present study was to further characterise the α-adrenoceptors in pre-capillary arteries of the human nasal mucosa. Mucosa was obtained from patients undergoing endonasal surgery. From the isolated conchae small arteries (diameter: 90-220 μm) were dissected, avoiding any direct traumatisation. The arteries were mounted to a Mulvany-Halpern wire myograph allowing isometric registration of the vessel constriction. Receptor subtypes were characterised using the agonists noradrenaline, phenylephrine and oxymetazoline, and the antagonists prazosine and yohimbine. The EC_{50} values of the three agonists were in the micromolar range, whereas the E_{max} values differed. When maximal responses to the agonists were expressed as a percentage of a potassium-induced constriction, values for noradrenaline, phenylephrine and oxymetazoline amounted to 110%, 78% and 21%, respectively. The agonist effects were almost completely blocked by the α_1-receptor antagonist prazosine, whereas yohimbine, the α_2-receptor antagonist, did not affect the agonist responses. From these results it is concluded that the adrenoceptors in pre-capillary arteries of the mucosa in human central concha are of the α-type. Since the decongestive effect of α_2-receptor agonists is beyond any doubt, this subtype of the adrenoceptor must be present on the venous capacitance vessels.

Key words: α_1-adrenoceptor, human nasal mucosa, α-adrenoceptor blockers, catecholamines

INTRODUCTION

Sympathomimetics in the form of nasal decongestants are frequently used to treat diseases of the upper respiratory tract. Phenylethylamines and imidazoline derivatives are commonly used substances. Phenylethylamines, such as phenylephrine, are selective α_1-adrenoreceptor agonists. Imidazoline derivatives, as for example oxymetazoline, primarily act via α_2 adrenoreceptors (Starke et al., 1975; Wickberg, 1979; Bende and Löth, 1986). The effect of these substances on the nasal mucosa vessels has been studied in depth and is well documented. They induce vasoconstriction and, thus, detumescence of the nasal mucosa. The site of action in the nasal vascular bed, however – i.e. the distribution of the different a receptors in the arterial (pre-capillary resistance vessels) and venous (capacity vessels) limbs – has not yet been clarified completely and is still a matter of controversy. Vasoconstriction is thought to be mediated by α_1- and α_2 receptors (Ichimura and Chow, 1988; Berridge and Roach, 1986). *In vivo* studies of human nasal mucosa revealed a predominance of α_2 receptors in the human nasal vessel bed; α_2 receptors were present in both capacity and resistance vessels, while α_1 receptors were found only in capacity vessels (Andersson and Bende, 1984; Bende and Löth, 1986). These findings could not be confirmed by *in vitro* studies of the human nasal mucosa. They even demonstrated a predominance of α_1 receptors (Ichimura and Chow, 1988). Until now, studies on isolated human nasal mucosa vessels focusing on only one part of the vascular bed (arterial or venous), have not been undertaken. Such studies would permit a more precise evaluation of the distribution of receptors in the vascular limb. It is for this reason that studies on isolated pre-capillary resistance vessels (diameter: 90-220 μm) of the human nasal mucosa were performed.

MATERIAL AND METHODS

The material was collected from 15 patients (8 males and 7 females) aged between 29-79 years (mean age: 47 years). Ten patients underwent bilateral endonasal ethmoid and maxillary sinus surgery for chronic bilateral polypous maxillary and ethmoidal sinusitis. Bilateral infundibulotomy because of bilateral infundibulopathy was done in four cases. Dacryorhinocystotomy on the left was performed in one patient with a dacryoste-

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nosis. In all of these operations the caudal part of the central concha was removed as well, either uni- or bilaterally.

Five patients took decongestants over a 5-month period. Four patients, suffering from bronchial asthma, used inhalation sprays containing cortisone on a regular basis.

After having been informed in detail on the purpose of this study on vessels to be obtained from the resected conchae, all patients gave their consent and the ethics commission had no objections concerning the performance of the study.

Immediately after removal, the resected part of the central concha was placed in Tyrode's solution saturated with 95% O_2 and 5% CO_2 at 37°C. At the most, 90 min elapsed between the surgical removal and the final preparation of the periostal arteries. Bones and connective tissue were removed under an operating microscope to expose the arteries. Two parallel wires (diameter: 40 μm) were pushed through the lumen of the arterial segments measuring 2±0.5 mm in length. The specimens were mounted in an organ bath filled with Tyrode's solution. The isometric contractions could be measured by means of a strain gauge to which the wires were attached. After a 1-hour period of equilibration at 37°C and determination of vessel length, a passive diameter-tension curve was constructed as described by Mulvany and Halpern (1977). The vessel was allowed to relax to that tension which occurs at 90% of the diameter corresponding to a transmural pressure of 100 mm Hg. Preliminary studies showed that at this tension the constriction caused by 125 mM KCl was maximal.

At the beginning of every test day a partial depolarisation was done 3 times for 4 min each using Tyrode's solution containing 125 mM KCl (125-mM KCl effect) in order to assess the maximum constriction of the individual vessels. Cumulative-dose response technique was applied after preliminary studies had shown that there is no significant difference ($p>0.05$) between cumulative and single-dose response curves. Once the maximal constriction had been reached and a plateau had set in, the applied drug was removed by changing the incubation medium. The muscles were left to equilibrate for 8 min before stepwise increasing the concentration of the agonist. Once a dose response was established, the muscle was transferred to drug-free medium, an antagonist was added, and after a 30-min period of incubation another dose-response curve for the agonist was established.

Upon completion of the tests, some of the specimens were fixed in 3% glutaraldehyde solution for histological examination of the endothelium. An untreated vessel segment also immersed in 3% glutaraldehyde solution served as a control.

To evaluate the results, the difference between the baseline tone and the maximum action of this substance was measured. Maximum response was calculated by means of the calibration factor α (Mulvany and Halpern, 1977). The response of relaxing substances was expressed as a percentage of the constriction to noradrenaline.

Each experiment ended with a 125-mM KCl effect in order to examine vascular ageing. For a better comparison of the action on the arteries, which varied in lumen, the maximum 125-mM KCl effect of each test day was equated with 100%.

The organ bath contained 20 ml of Tyrode's solution (137 mM NaCl; 2.7 mM KCl; 1.8 mM $CaCl_2$; 1.1 mM $MgCl_2$; 0.21 mM NaH_2PO_4; 12 mM $NaHCO_3$; 5.5 mM glucose; pH 7.4) saturated with 95% O_2 and 5% CO_2. Tyrode's solution used for partial depolarisation consisted of: 14.7 mM NaCl; 125 mM KCl; 1.8 mM $CaCl_2$; 1.1 mM $MgCl_2$; 0.21 mM NaH_2PO_4; 12 mM $NaHCO_3$; and 5.5 mM glucose. Substances used: carbachol hydrochloride (Merck, Darmstadt, Germany), noradrenaline hydrochloride (Hoechst, Frankfurt/Main, Germany), bradykinin (Sigma, Munich, Germany), 1% glyceroltrinitrate (Merck, Darmstadt, Germany), prazosine hydrochloride (Sigma, Munich, Germany), yohimbine hydrochloride (Sigma, Munich, Germany), phenylephrine hydrochloride (Sigma, Munich, Germany), and oxymetazoline hydrochloride (Sigma, Munich, Germany).

Mean values are given as mean±standard deviation (s.d.). A non-linear regression programme was used to estimate the parameters of a logistic function describing the concentration-effect dependency (computer-aided concentration-response curve, inplot, graph PAD software, USA). Statistic comparisons were done with Student's t-test.

Great care was taken to maintain a constant temperature (37±0.5°C) as the recording of the vascular tone proved to be very sensitive to temperature changes.

RESULTS

General observations

The diameter of the vessels lumen was 196±56 μm (n=15). No spontaneous vascular activity was recorded. The response of the vascular preparations to 125 mM KCl and 3 μM noradrenaline was found rather constant during experiments lasting 6-8 h. The results of vessels obtained from patients using decongestants or glucocorticoid-containing remedies and from patients without a history of nasally applied drugs were similar, so there was no evidence that the pre-treatment was of any influence.

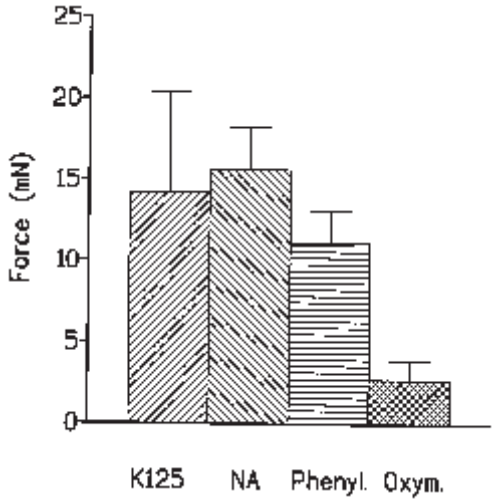

Figure 1. Maximum force generated by vessel constriction after partial depolarization with 125 mM KCl (n=15) and application of noradrenaline (NA; n=15), phenylephrine (Phenyl.; n=9), and oxymetazoline (Oxym.; n=6). The force of constriction generated is expressed in mN. Mean values±standard deviation are presented.

Effect of potassium

Partial depolarisation with 125 mM KCl induced a biphasic contraction in the pre-capillary arteries of the human nasal mucosa. The maximum of the phasic contraction (14.2±6.2 mN; Figure 1) was reached within 2 min, while it took a further 3 min to attain the steady state of the tonic response (74% of maximal phasic contraction).

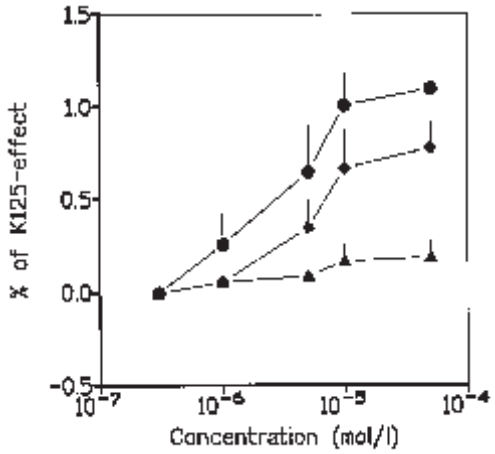

Figure 2. Vasoconstrictive effects of noradrenaline (circles), phenylephrine (squares) and oxymetazoline (triangles) in pre-capillary vessels. The effect is expressed as a percentage of the 125-mM KCl effect. Points represent the mean±standard deviation.

Table 1. Vasoconstrictor effect of the three agonists. The dose-response curves for the vasoconstrictor effects of the adrenoceptor agonists were established. Vasoconstriction is expressed as % of the effect induced by 125 mM KCl. EC_{50} and E_{max} were calculated by nonlinear regression. In case of oxymetazoline only 6 of the 12 specimens could be activated. Values represent means ±s.d..

	EC_{50}±s.d. (μM)	E_{max}±s.d.(mN)	E_{max}in % of 125mM KCl	n
noradrenaline	3.3±0.13	15.6±2.6	110±18	15
phenylephrine	5.3±0.3	11.1±2.7	78±21	9
oxymetazoline	4.1±0.32	2.7±1.2	21±9	6(12)

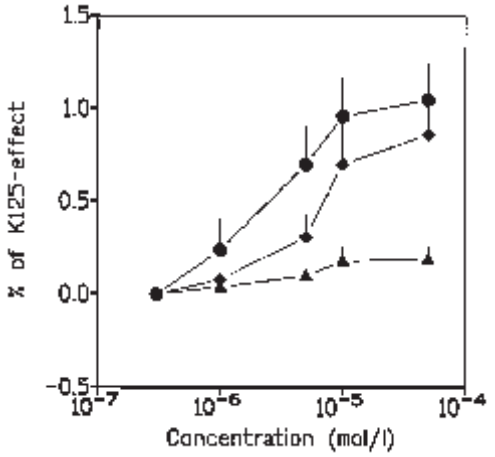

Figure 3. Vasoconstrictive effects of noradrenaline (circles), phenylephrine (squares) and oxymetazoline (triangles) after 30-min pre-treatment of the pre-capillary vessels with 50 μM yohimbine ($p<0.05$). The effect is expressed as a percentage of the 125-mM KCl effect. Points represent the mean±standard deviation.

Agonists

The kinetics of the response to the sympathomimetic agonists were quite comparable to that of 125 mM KCl. The concentration-response curves for three sympathomimetics – noradrenaline, phenylephrine, and oxymetazoline – were established and are depicted in Figure 2. The parameters of the logistic function used to describe the concentration response curves (E_{max} and EC_{50}) are given in Table 1. Out of 12 specimens investigated with oxymetazoline only 6 could be activated by this agonist. There was no difference between the responding and the non-responding vessels with respect to activation by 125 mM KCl and noradrenaline.

Table 2. Vasoconstrictor effect of the three agonists after pre-treatment with yohimbine. After pre-treatment of the vessels with yohimbine (0.5 μM to 50 μM), no significant inhibition could be registered ($p<0.05$). Vasoconstriction is expressed as % of the effect induced by 125 mM KCl. EC_{50} and E_{max} were calculated by nonlinear regression. Values represent means ±s.d..

	EC_{50} ±s.d. (μM)	E_{max} ±s.d. (mN)	E_{max} in % of 125 mM KCl±s.d.	n
noradrenaline	2.8±0.8	14.2±2.4	100±15	6
phenylephrine	6±0.4	12.2±2.4	85±15	6
oxymetazoline	3.8±0.17	2.1±0.9	16±7	6

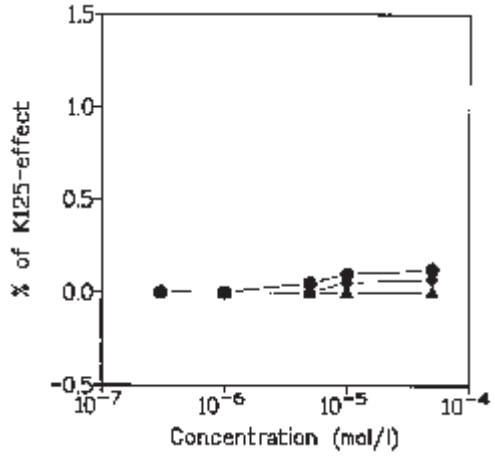

Figure 4. Vasoconstrictive effects of noradrenaline (circles), phenylephrine (squares) and oxymetazoline (triangles) after 30-min pre-treatment of the pre-capillary vessels with 5 μM prazosine. The effect is expressed as a percentage of the 125-mM KCl effect. Points represent the mean±standard deviation.

Antagonists

Yohimbine (0.5 μM to 50 μM) by itself had no effect on the vascular tone, neither under control condition nor in vessels pre-contracted by 40 mM KCl. Concentration response curves for the three agonists were not affected when pre-treating the vessels by yohimbine (50 μM) for 30 min ($p<0.05$; Figure 3). The EC_{50} values in presence of yohimbine are listed in Table 2 and are not different from control values. The vasoconstrictor action of noradrenaline, phenylephrine and oxymetazoline was almost

completely blocked by 5 μM prazosine. The EC_{50} values amounted to $5.6\times10^{-5}\pm3.7\times10^{-5}$ M (n=6; Figure 4) for NA and $2.9\times10^{-5}\pm2.8\times10^{-5}$ M (n=6) for phenylephrine. The maximum effect of NA was at 12±1.1% of the 125 mM KCl control stimulus and at 7±0.6% for phenylephrine. Prazosine showed no vasoconstrictive effect on the non-stimulated and partially depolarized muscle.

Endothelial function

A direct cholinomimetic, carbachol, was applied in order to check the integrity of the endothelium. In eight out of 15 cases 5×10^{-7} M carbachol initiated a weak vasodilation of the pre-capillary vessels, which had been activated by 10^{-5} M noradrenaline. Seven preparations showed no vascular reaction. The maximum dilative effect (E_{max}) was reached at 21.5±11% (n=8) No effect was produced by bradykinin, neither on the non-stimulated nor on the pre-contracted vessels (n=10). After preliminary arterial contraction with 10^{-5} M noradrenaline, a maximum dilation of 90.8±17% (n=8) was achieved with glyceroltrinitrate at a concentration of 10^{-7} M.

Histological evaluation of the vessels studied showed the vascular endothelium to be almost intact. Impressions on the vessel walls and compressions of the vessel media could be detected in those areas of direct contact to the wire.

DISCUSSION

Information about the distribution of adrenergic receptors in the vasculature of the nasal mucosa stems mostly from *in vivo* observations. To quantify vascular effects of adrenergic receptor activation or blockade changes of mucosal blood flow were measured. *In vivo* investigation of vascular reactivity combines the advantage of a physiological surrounding with that of a small risk of traumatisation. However, the observations do not necessarily reflect changes of the vascular region under investigation, but can be more or less determined by reactions initiated elsewhere in the body. Experiments in isolated small arteries of the nasal mucosa are not available up to now. In the present paper the pattern of vascular responses to adrenergic stimuli was investigated in isolated pre-capillary arteries in order to obtain information on the distribution of adrenergic receptors in this type of vessel.

Periostal arteries were used since these vessels are of importance for the blood supply and thereby for the volume of the capacity vessels in the nasal mucosa (Zuckerkandl, 1885; Rosatti, 1953). Noradrenaline, the α_1-selective agonist phenylephrine, the α_2-selective oxymetazoline, the α_1-selective antagonist prazosine and the α_2-selective yohimbine were used as pharmacological tools to identify the predominant receptor subtype of the adrenergic family. The high constrictor activity seen with noradrenaline and phenylephrine and the complete blockade by prazosine as well as the poor activity of oxymetazoline and yohimbine indicate that an α_1-type adrenergic receptor mediates the constrictor response in pre-capillary arteries of the nasal mucosa. At a first glance, these results are in contrast with the opinion that constriction of the pre-capillary arteries is mediated by α_2-type receptors and α_1-receptors are responsible for activating both capacity and resistance vessels. This opinion is based on *in vivo* experiments in humans and rabbits, where phenylephrine caused decongestion and oxymetazoline caused decongestion and a decrease of blood flow in the nasal mucosa (Andersson and Bende, 1984; Bende and Löth, 1986; Berridge and Roach, 1986). Ichimura and Chow (1988) measured the shrinkage of intact, isolated human mucosa under the influence of noradrenaline as well as of oxymetazoline and concluded that both receptor subtypes are involved, but α_1 receptors are predominant. According to our results constriction of arteries of the human nasal mucosa is almost exclusively mediated by α_1 receptors, and this provides indirect evidence for the speculation that α_2 receptors are responsible for a constriction of the capacity vessels. Oxymetazoline possesses a high but not an absolute selectivity for α_2 receptors (Gerold and Haesler, 1983; Lacroix, 1989) and therefore the small contraction seen with high concentrations of oxymetazoline in arteries of the nasal mucosa does not necessitate to assume a separate α_2-receptor population.

The biphasic nature of the contraction also points to an α_1-receptor-mediated effect on the resistance vessels. The phasic constituent is said to be caused by the release of calcium from intracellular storage (Somlyo, 1985), while the tonic component can be attributed to an influx of calcium into the cells (Hinke et al., 1964). An α_2-receptor-mediated vascular reaction can be blocked completely by calcium-channel-blocking agents, and it thus depends solely on extracellular calcium (Van Meel, 1981). It is the α_1 receptor that activates the different (intra- and extracellular) calcium sources (Wilson et al., 1987; Nielsen and Mulvany, 1990). The binding of noradrenaline to the receptor enhances phospholipase activity, whose site of action is located on the cytoplasmic side of the cell membrane. The activated enzyme cleaves phospatidylinositol-4,5-biphosphate (PiP_2) into 1,2-diacylglycerol (DG) and inositol-1,4,5-triphosphate (IP_3) (for a review, see Chuang, 1989). Both act as intracellular second messengers. IP_3 induces the release of calcium from the endoplasmic reticulum into the cytosol (Berridge and Irvine, 1984; Hashimoto et al., 1986). DG remaining in the membrane activates membrane-bound kinase C, which is probably linked to the influx of calcium into the cell (Exton, 1985; Nishizuka, 1988). It is therefore possible that the IP_3-induced intracellular release of calcium is connected to the phasic constituent, while the activation of protein kinase C by DG is connected to the tonic component of the contraction (Abdel-Latif, 1986).

The α-sympathomimetic decongestion of the human nasal mucosa can therefore be induced by vasoconstriction of the pre-capillary arterioles, which is primarily mediated through α_1-receptors. A second possibility would be a vasoconstriction of the dense highly-muscularised venous plexus, which – being the cavernous body of the nasal mucosa – can alter the lumen of the meatuses considerably (Zuckerkandl, 1885). Alpha-2 receptors seem to be highly significant in this context.

One can only speculate about the slight effect of the cholinomimetic agent carbachol. It is an effect mediated through muscarine receptors, which Furchgott and Zawadzki (1980) already demonstrated in studies on the rabbit aorta using acetylcholine. They observed that there was no acetylcholine action at all after

mechanical or enzymatic removal of the endothelium. As a mediator of the endothelium-dependent effect they suggested an "endothelium-derived relaxing factor" (EDRF). These findings were substantiated by experiments on different vessels of several species (Vanhoutte and Miller, 1985; Komori and Suzuki, 1987; Van Bibber et al., 1995). In the meantime, EDRF was identified as nitric oxide (Ignarro et al., 1987). Nitric oxide activates protein kinases via cyclic guanosine monophosphate (cGMP), decreasing the free calcium concentration in the cytosol and thus vessel tone (Geiger et al., 1992). Nitric oxide induced an almost complete relaxation of the preliminary tension in the vessels of the nasal mucosa studied. The slight effect of carbachol on the resistance vessels must therefore be receptor-related, since nitric oxide is very effective and the vascular endothelium is not damaged by vessel preparation and therefore be able to produce nitric oxide.

Evidence of endothelium-dependent relaxation was found for many other substances in different species and areas of blood flow (for a review, see Furchgott, 1990). The relaxing effect of bradykinin, for example, was demonstrated in studies on rabbit heart and lung vessels (Chand and Altura, 1981; Cherry et al., 1982). Bradykinin does not seem to have an effect on pre-capillary vessels of the human nasal mucosa.

Summarizing the vasoconstrictive action of adrenergic substances in pre-capillary vessels of the mucosa of human central concha is almost exclusively mediated through α_1 receptors. Alpha-2 receptors are of minor importance in this context. The distribution of adrenergic receptors in the capacity vessels has not been completely clarified, although α_2 receptors seem to be very important.

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