Rhinology,31, 121-124, 1993

The influence of B-adrenoceptors on nasal mucosal function*

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SUMMARY

The aim of the study was to elucidate the role of]-adrenoceptors in normal human nasal mucosa. In two studies, ft-receptor function was tested by the application of agonists and antagonists. Measurements of nasal secretion and nasal peak expiratory flow were performed at 4-min intervals, during 12 min of rest, pre- and post-treatment, 12 min of exercise and 20 min of recovery. In Study 1, placebo was compared with 100 µg salbutamol and 2 mg propranolol. Neither placebo nor 100 mg salbutamol affected nasal secretion production at rest, but propranolol caused a transient significant increase ($p < 0.05$). Exercise significantly increased secretion production in all three treatment groups ($p < 0.05$). Nasal peak expiratory flow was not altered at rest, but increased significantly ($p < 0.05$) during exercise in the three treatment groups. In Study 2 placebo was compared with 200 mg salbutamol, 80 µg isoprenaline and 2 mg atenolof. Secretion production was not altered at rest by any treatment and increased during exercise in all four ($p < 0.05$). There was no significant difference between weights of secretions produced between any of the treatment groups during exercise. Salbutamol significantly decreased nasal peak expiratory flow at rest compared with placebo ($p < 0.05$). During exercise nasal peak.flow increased in all groups, but peak exercise values were significantly reduced by both salbutamol and isoprenaline ($p < 0.05$). Atenolol appeared to have no effect on nasal peak expiratory flow. It is concluded that j]-adrenoceptors have minimal influence over nasal vascular and glandular function and the ffects seen in this study could be due to a pharmacological action of the drugs used.

INTRODUCTION

There is now good evidence to suggest that B-receptors are to be found in human nasal mucosa. They have been detected pharmacologically using topical isoprenaline (McLean et al., 1976), and fenoterol (Schumacher, 1980; Borum and Mygind, 1980), where the application of both resulted in an increase in nasal resistance. Other studies using other agonists, however, have failed to confirm this (Watase and Okuda, 1986; Svensson et al., 1980). Radioligand- receptor binding has identified a population of 132-receptors in nasal mucosa (Van Megen et al., 1989). This has been confirmed by Woodhead et al. (1991) using autoradiography, which demonstrated 132-receptors in vascular tissue but most pronounced in the glandular tissue, particularly the ducts. Previous studies have shown that parasympathetic stimulation plays a major part in the production of nasal secretions at rest and during exercise (Harris et al., 1992). The anticholinergic drug, ipratropium bromide, did not completely abolish this effect, suggesting other autonomic or neurohumoral mechanisms are involved. It is suggested that 13-receptors have a role in the control of glandular secretion (Watanabe, 1990). This study aims to clarify the role of 13-receptors in nasal secretion production and vascular control.

MATERIALS AND METHODS

Two groups of volunteers performed two studies. Volunteers were healthy males and females, aged 20 to 30 years. They had no history of nasal or respiratory diseases and were free from respiratory infection for 2 weeks. All were non-smokers and not on any medication. Nasal secretions were collected by thorough nose blowing into a

* Accepted June 15, 1992

previously weighed tissue. The tissue was sealed in a plastic bag. Before collection, the volunteer dried hands and face to remove sweat. The tissue was then replaced in the plastic bag and re-weighed at the completion of the study. Nasal patency was measured by readings of nasal peak expiratory flow (Taylor et al., 1973), using a mini Wright Peak Flowmeter adapted by the addition of a light, plastic anaesthetic mask. An average of three readings for each measurement was used. This method was chosen as it was reproducable and quick to perform, essential for this study. Peak inspiratory flow measurements were not used, as high flow rates as produced by exercise may cause anterior valve collapse and artificially low readings (Gleeson et al., 1986). Nasal secretion collections were performed before nasal peak flow readings. In Study 1, six volunteers were randomly assigned in a double-blind fashion, using Latin square design, to receive the following topical treatments: Placebo (0.24 ml of normal saline per nostril), 2.0 mg propranolol (Bl- and B2-antagonist) in 0.24 ml per nostril, or 100 µg salbutamol *(B2* agonist) per nostril. In Study 2, ten volunteers received in a similar fashion: placebo, as above, 80 µg isoprenaline (Bl- and B2-agonist) in 0.24 ml per nostril, 200 µg salbutamol in 0.24 ml per nostril, or 2 mg atenolol (Bl antagonist) in 0.24 ml per nostril (Table 1). Each treatment was applied by a pump-action atomizer, which delivered 0.12 ml of solution per puff. The volunteer was instructed to place the nozzle of the atomizer past the nasal vestibule, and to sniff on applying the treatment. At the commencement of the study, volunteers were requested to rest 16 min. They then cleared their noses of secretions by thorough blowing. This was discarded. Nasal secretion collections and nasal peak flow readings were then performed at 4-min intervals for 12 min. The treatment was then administered and the subject rested for 16 min. They then blew their nose thoroughly and discarded the tissue. Measurements were then continued at 4-min intervals during 12 min of rest, 12 min of exercise, and 20 min of recovery (Figure 1). Exercise was performed on a cycle ergometer, each subject achieving a pulse rate of 80% maximum predicted for age and sex. The study was approved by the Ethics Committee, Faculty of Medicine, The Queens University of Belfast. Statistical analysis was performed using Student's paired t-test.

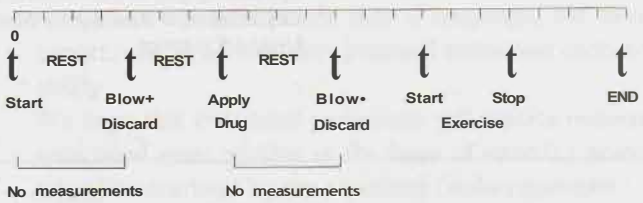
RESULTS

Study 1

The mean nasal secretion production at rest was 22.5 ± 1.3 mg. This value did not change significantly on application of placebo or 100 µg salbutamol (Figure 2). Treatment of the nasal mucosa with propranolol caused an initial increase in secretion production to 93.2±37.0 mg ($p<0.05$), which settled to pre-treatment resting values before exercise. Pain was reported by all volunteers, lasting approximately 20 min. Exercise significantly increased nasal secretion production in all three treatment groups ($p<0.05$). There was no significant difference in peak exercise values between the three. Nasal Peak Expiratory Flow Rate (NPEFR) at rest was

Table 1. The drugs used in Studies 1 and 2, dose in 0.24 ml per nostril, with 13-receptor activity.

Study 1		
propranolol	2 mg	131- and 132-antagonist
salbutamol	100 µg	132 agonist
Study2		
isoprenaline	80 µg	131- and £2-agonist
salbutamol	200 µg	131 agonist
atenolol	2 mg	.Bl antagonist



Time (in 4 min intervals)

Figure 1. Study Protocol

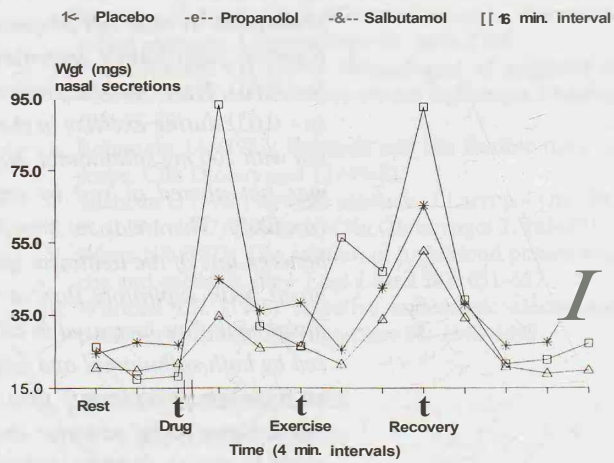


Figure 2. Changes in nasal secretion production on application of placebo, propranolol (131- and 132-antagonist), and salbutamol (132 agonist), at rest and during exercise, in Study 1.

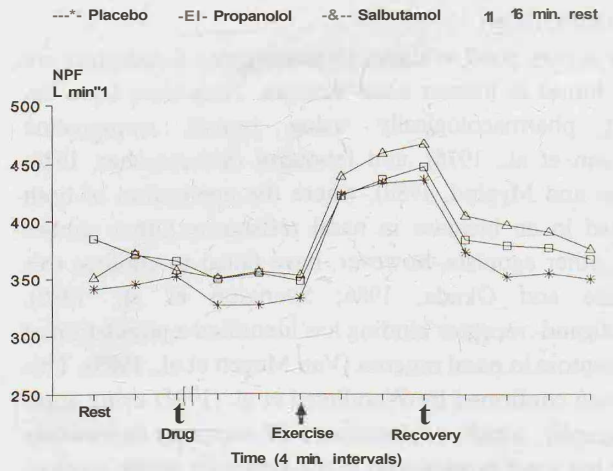


Figure 3. Alteration in nasal peak expiratory flow rate (NPEFR) on application of placebo, propranolol (131- and 132-antagonist), and salbutamol (132 agonist), at rest and during exercise, in Study 1.

360±5 1/min. The application of placebo, propranolol or 100 μg salbutamol did not significantly change this value ($p>0.05$; Figure 3). Each treatment group shows an increase in NPEFR during exercise ($p<0.05$).

Study 2

The mean nasal secretion production at rest was 15.9± 1.7 mg. The treatment of the nasal mucosa with placebo, isoprenaline, 200 μg salbutamol or atenolol did not significantly ($p>0.05$) alter nasal secretion production at rest (Figure 4). All treatment groups show an increase of secretion production during exercise ($p<0.05$). There is no significant difference ($p>0.05$) in the weights of secretion produced during exercise between the four treatment groups.

The mean NPEFR at rest was 274±21/min. The application of atenolol did not significantly alter ($p>0.05$) NPEFR at rest (Figure 5). The application of placebo reduces NPEFR at rest ($p<0.05$), but there is no significant difference between placebo values and that achieved with atenolol. Isoprenaline reduces NPEFR to 253 ± 4 1/min, but this is not significantly different than that seen with placebo ($p>0.05$). Salbutamol reduces NPERF to 237±2 1/min, which is significantly less than placebo values ($p<0.05$). During exercise there is an increase in NPEFR in all treatment groups ($p<0.05$). Peak exercise values are significantly less than placebo with both salbutamol and isoprenaline ($p<0.05$). Post-exercise values are also reduced by salbutamol ($p<0.05$).

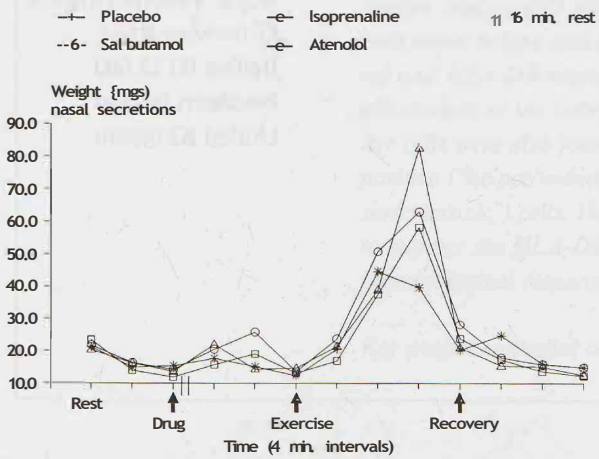


Figure 4. Changes in nasal secretion production on application of placebo, salbutarnol (132 agonist), isoprenaline (131- and 132-agonist), and atenolol (131 antagonist), at rest and during exercise in Study 2.

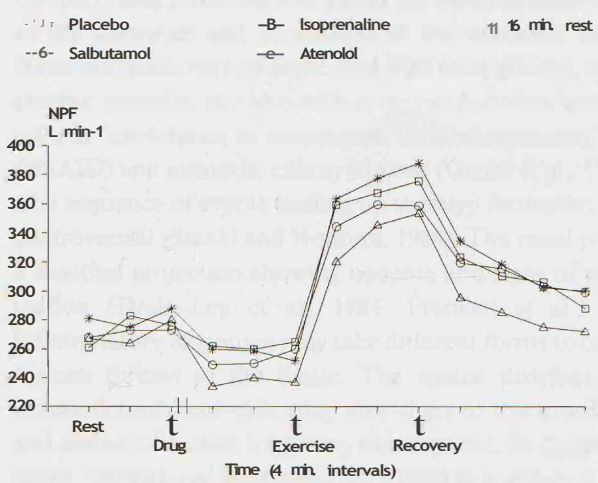


Figure 5. Alteration in nasal peak expiratory flow rate (NPEFR) on application of placebo, salbutarnol (132 agonist), isoprenaline (131- and 132-agonist), and atenolol (131 antagonist), at rest and during exercise, in Study 2.

DISCUSSION

In Study 1 the application of propranolol, a B1- and B2- antagonist, transiently increased secretion production at rest. This was not reported by Watase and Okuda (1986), but the dose used here is greater. Malm (1981) reported propranolol as a cause of watery nasal secretion, but not atenolol, in those taking the drug for treatment of hypertension. Propranolol has been reported to cause histamine liberation from rats (Nosal et al., 1988). The application of atenolol, a B1 antagonist, in Study 2 does not cause an increase in secretion production. Propranolol caused pain on application lasting approximately 20 min. The Vth nerve was therefore stimulated, possibly accounting for the increase in secretion. Salbutamol, a predominantly B2 agonist, in either 100 μg or 200 μg per nostril doses did not alter the amounts of secretions produced by the nasal mucosa at rest or during exercise. Atenolol, a predominantly B1 antagonist, also did not have an effect on secretion production. Beta-receptor function appears to have no influence on the ammount of secretions produced at rest or during exercise. It has been demonstrated that intranasal application of methacholine causes increased nasal secretion in normal subjects (Borum, 1979). The anticholinergic drug ipratropium bromide reduces nasal secretion production at rest and during exercise, but does not completely block the effect (Harris et al., 1992). This suggests the parasympathetic nervous system has a major role to play in the production of nasal secretions, but other autonomic or neurohumoral mechanisms are involved. The results of this study implies this is not a 13-receptor effect, but does not rule out fl-receptor influence in the content of secretions as suggested by Watanabe (1990). Nasal Peak Expiratory Flow Rate (NPEFR) was reduced by placebo in Study 2. McLean et al. (1976) also demonstrated an increase in nasal airway resistance after application of phosphate-buffered saline. There was also a reduction in NPFER with atenolol, although this is not satistically significant. Salbutamol, in the 200-μg dose per nostril, causes a significant reduction in NPEFR at rest compared with placebo, suggesting a B2-receptor-mediated response in nasal vascular tissue. Both isoprenaline and salbutamol reduce the nasal vasculature reponse to exercise. The failure of propranolol to cause a reciprocal increase in NPEFR demonstrates an absence of fl-effector resting tone in nasal vasculature. The high doses required to achieve this response may imply a pharmacological action rather than a

direct 13-receptor effect. Woodside et al. (1991) using autoradiography, has detected 132-receptors on both blood vessels, mainly arterioles, and glandular tissue, predominantly ducts. The results of our study imply that these receptors do not have a major role in the maintanance of nasal vasculature control or secretion production rate and further investigation is required as to their function.

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