α-Adrenoreceptor blockade with phenoxybenzamine does not affect the ability of the nose to condition air

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Pinto, Jayant M., Paraya Assanasen, Fuad M. Baroody, Edward Naureckas, and Robert M. Naclerio. α-Adrenoreceptor blockade with phenoxybenzamine does not affect the ability of the nose to condition air. J Appl Physiol 99: 128–133, 2005. First published March 3, 2005; doi:10.1152/japphysiol.00857.2004.—The primary function of the nose is to warm and humidify air. We have previously shown that raising nasal mucosal temperature by immersing feet in warm water increases the amount of water evaporated by the nose as air passes through it (nasal conditioning capacity; Abbott D, Baroody F, Naureckas E, and Naclerio R. Am J Rhinol 15: 41–45, 2001). To investigate further the effect of nasal mucosal temperature on nasal conditioning capacity, we raised the temperature through α-adrenoreceptor blockade by intranasally administering phenoxybenzamine. We hypothesized that blocking α-adrenoreceptors during inhalation of cold, dry air would lead to an increase in nasal blood flow, surface temperature, and nasal conditioning capacity, as measured by the water gradient. After appropriate pilot studies, we performed a double-blind, placebo-controlled, two-way crossover study in nine nontopic, healthy subjects by studying the effect of treatment with intranasal phenoxybenzamine. Nasal mucosal temperature increased significantly after administration of phenoxybenzamine and was associated with a significantly smaller net decrease in nasal mucosal temperature after exposure to cold, dry air (P < 0.05). However, there were no significant differences in nasal conditioning capacity between treatments (P > 0.05). Phenoxybenzamine decreased the symptom of rhinorrhea after exposure to cold, dry air (P < 0.05), but congestion was not different between individuals given phenoxybenzamine and placebo (P > 0.05). Our data demonstrate that phenoxybenzamine, despite raising mucosal temperature and not affecting nasal volume, did not affect the ability of the nose to warm and humidify air.

A MAJOR FUNCTION OF THE NOSE is to warm and humidify air (15). We developed a method in which we used the inhalation of cold, dry air (CDA) to evaluate the ability of the nose to condition air (26).

Hanna and Schere (12) proposed the theory that the two major mechanisms leading to the alteration in nasal conditioning capacity (NCC) are changes in the nasal mucosal temperature (NMT) and the volume of the nasal cavity. Consistent with this theory, our laboratory has previously shown that raising the NMT by immersion of feet in warm water improves the ability of the nose to condition CDA (1, 3). The mechanism underlying the rise in temperature after immersion of feet in water appears to be mediated by a neuroreflex in which there is both a loss of sympathetic tone and an increase in parasympathetic stimulation (4). In this study, we focused on the importance of the loss of sympathetic tone.

During inspiration of CDA, water evaporates from the nasal mucosa to condition inspired air, leading to heat loss and, consequently, a decrease in NMT (7). Our laboratory’s previous work showed that inhalation of CDA [temperature (T) = 0.8°C, 0% relative humidity (RH)] causes a reduction of NMT compared with the effect of inhalation of room air at T = 25°C, 30% RH (3). Local cooling causes vasoconstriction in the skin by α-adrenoreceptor stimulation (11). We speculated that similar effects would be seen in the nose. Thus we hypothesized that blocking α-adrenoreceptors in the nose during inhalation of CDA should lead to increases in nasal blood flow, surface temperature, and NCC.

Phenoxybenzamine (POB), a nonspecific α-adrenergic antagonist, binds irreversibly to α-adrenergic receptors (9). In this study, we examined the ability of the nose to condition CDA in normal subjects after treatment with POB or placebo. We also investigated the parameters that might affect this ability, including NMT and volume of the nasal cavity.

METHODS

Subjects. For both experiments, we recruited healthy volunteers without atopy. In the pilot study group of five subjects, the mean age was 26 yr and ranged from 20 to 32 yr. There were four male and one female subject. The mean age of the crossover study group (9 subjects) was 26 yr and ranged from 19 to 40 yr. There were six women and three men in this group. For all subjects, the allergic status was documented by puncture skin tests to common indoor and outdoor inhalant allergens, including dust mites, cat, tree, timothy grass, ragweed, and mold. None of the above subjects was taking any medications within 2 wk of the evaluation. We excluded subjects who had upper respiratory tract infections within 14 days of the start of the study and those taking intranasal medication during the previous 24 h or oral decongestants during the previous 7 days. In the pilot study, the female subject was taking oral contraceptives; in the crossover study, three female subjects were also on oral contraceptives. All remaining subjects were not taking any medications. The Institutional Review Board of the University of Chicago approved the study, and written, informed consent was obtained before participation in the study.

Experimental protocol. To determine the pharmacological effects of POB on nasal temperature, nasal volume, and physiological parameters, as well as to delineate the duration of such effects, we performed a placebo-controlled, two-way crossover pilot study comparing the effect of treatment with POB (Dibenzyline, Smith Kline Beacham, Philadelphia, PA) or placebo (normal saline) on NCC in five subjects. On arrival, subjects waited for 15 min to allow equilibration of the nasal mucosa with the environmental conditions of the laboratory (T = 25°C, 30% RH). Blood pressure [systolic (SBP) and diastolic (DBP)] and heart rate (HR) were measured and recorded as...
a baseline along with NMT and nasal volume [baseline 1 (B1)] (see Fig. 1). The side of the nasal cavity used for drug administration was randomly chosen and maintained for both visits. NMT and the volume of the nasal cavity were measured on both sides at B1 (see below). After baseline measurements, the chosen side was sprayed with either two puffs of 0.2% POB (0.45 mg) (24) or placebo (normal saline). After 10 min, SBP, DBP, HR, NMT, and nasal volume were measured again bilaterally after drug administration. Next we applied three puffs (0.3 ml) of 0.05% oxymetazoline (Nostrilla; Ciba Self-Medication, Woodbridge, NJ) bilaterally. After 5 min, SBP, DBP, HR, NMT, and nasal volume were measured bilaterally after oxymetazoline. At 60 min, we repeated administration of oxymetazoline bilaterally. NMT and nasal volume were measured at 10, 15, 20, 30, 60, 65, 70, and 75 min after oxymetazoline administration. SBP, DBP, and HR were measured again at 30, 60, 65, and 75 min.

Based on the above data, we performed a placebo-controlled, two-way crossover study comparing the effect of treatment with POB or placebo (normal saline) on NCC in nine normal subjects. On arrival, subjects waited for 15 min to allow equilibration of the nasal cavity. After baseline measurements, the nonprobe side was sprayed with either two puffs of 0.2% POB (0.45 mg) or placebo (normal saline). After 5 min, SBP, DBP, HR, NMT, and nasal volume were measured. The mask was then removed, and blood pressure, HR, symptom evaluation, and volume measurement were repeated.

The difference between the water content of air before entry into the nose and that in the nasopharynx is the water gradient (WG) across the nose; it represents the amount of water evaporated by the nose to condition air, a measure of nasal conditioning. The total WG is the sum of the WGs at each flow rate (5, 10, and 20 l/min) and represents NCC.

Symptom scores. Symptoms of runny and stuffy nose were recorded at each time point and graded on a scale as follows: 0 = no

![Diagram](http://jap.physiology.org/)

Fig. 1. Pilot experimental protocol. The different interventions and measurements are indicated by arrows; timing between these is reflected below arrows in the space between them. Measurements included vital signs [blood pressure (BP) and pulse, open arrows] as well as physiological parameters [nasal mucosal temperature (NMT) and nasal volume, solid arrows, performed on both sides]. The protocol is shown on the abscissa and is detailed in the text. B1, baseline; AD, after drug administration [phenoxybenzamine (POB) or placebo].

![Diagram](http://jap.physiology.org/)

Fig. 2. Effect of POB on nasal conditioning capacity: experimental protocol. The different interventions and measurements are indicated by arrows; timing between these is reflected below arrows in the space between them. Measurements included BP, heart rate (HR), symptoms scores (SS), nasal volume (VOL), and NMT. These were performed on the opposite side of the nasal vault containing the probe. The nasopharyngeal probe was inserted into one side of the nose, selected randomly. Cold, dry air (CDA) was delivered by mask at 3 flow rates (5, 10, and 20 l/min) for 12 min each (depicted in the boxed area). The protocol is shown on the abscissa and is detailed in the text.

B2, after probe insertion, B3, before CDA, AC, after CDA.
symptoms, 1 = very mild, 2 = mild, 3 = moderate, 4 = severe, and 5 = very severe symptoms.

Nasal volume measurement. Nasal volume measurement was performed with an Eccovision Acoustic Rhinometry System (Hood Laboratories, Pembroke, MA). The volume was measured at 0–6 cm from the tip of the rhinometry probe. Each measurement was performed in triplicate, and the average values are reported. Because of the instrumentation of the nasal cavity containing the probe, measurements were taken only on the side without the probe; this side received no topical medication other than POB or placebo.

NMT measurement. A nasal probe developed for measurement of mucosal surface temperature (26) was calibrated before each use. The probe was inserted into the anterior part of the nasal cavity by means of a nasal speculum and a headlight. The temperature sensor at the end was placed in contact with the nasal mucosa of the anterior part of the nasal septum just posterior to the mucocutaneous junction, and it sampled the mucosal temperature at a rate of one measurement per second for 30 s. The mean NMT was determined. Measurement of NMT during exposure to CDA was performed by advancing of the temperature sensor attached to a small, straight rod through a small opening in the mask. Because of the instrumentation of the nasal cavity containing the probe, measurements were taken only on the side without the probe; this side received no topical medication other than POB or placebo.

Statistical analysis. For the WG, statistical analysis was performed by use of parametric statistics (10, 26). For the other parameters, nonparametric statistics were used for analysis. Repeated measurements were compared by the appropriate analysis of variance, and post hoc analysis was performed, if indicated (10). P values ≤0.05 were considered significant. Physiological parameters and WG are reported as means ± SE. Symptom scores are reported as median values.

RESULTS

Our pilot experiment demonstrated that POB caused a rise in NMT (Fig. 3). The elevation in NMT occurred in all five subjects and persisted for 75 min, longer than the duration of our subsequent experiments. POB was able to block the drop in NMT caused by oxymetazoline seen on the placebo side, again in all five subjects, indicating an α-adrenergic mechanism for this effect (Fig. 3). Similarly, in all five subjects, POB blocked the increase in nasal volume seen after administration of oxymetazoline (Fig. 3). Again, this difference lasted 75 min. In both cases, administration of oxymetazoline after 60 min did not terminate the effect of POB, confirming its duration of action. There were no differences in SBP, DBP, and HR between POB and placebo (data not shown).

Based on these results, we proceeded with our key experiment in nine subjects. After administration of both POB and placebo, increasing the CDA flow rate progressively increased the WG, as in previous studies (Fig. 4). However, there were no significant differences among WG values at each flow rate (P > 0.05 for each comparison) when we compared treatment with POB and placebo. The total WG was not significantly different between treatments (P > 0.05).

POB caused a significant increase in NMT after administration (B2) compared with the baseline temperature (B1) (B1 vs. B2: 24.40 ± 1.12 vs. 26.97 ± 1.17°C; P < 0.05), whereas placebo showed no significant change from baseline (B1 vs. B2: 25.79 ± 0.91 vs. 26.84 ± 1.18°C; P > 0.05) (Fig. 5). The NMT did not change significantly between treatment applica-

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Fig. 3. Nasal volume and NMT. A: NMT (°C), with time points on the abscissa (minutes). Data are median for 5 subjects. POB or placebo (normal saline solution [NSS]) administration is noted by the open arrow. Oxymetazoline (OXY) administration (bilaterally) is noted by the solid arrow. Circles denote placebo (open, left nasal cavity; solid, right nasal cavity). Bef, before; Aft, after. Triangles denote POB (open, left nasal cavity; solid, right nasal cavity). B: data for nasal volume (ml), with time points on the abscissa (minutes).

Fig. 4. Nasal conditioning capacity. A: water gradient (mg) across the nose at three flow rates (5, 10, 20 l/min). Data are means ± SE for 9 subjects. There was increased conditioning with increasing flow rate. There were no differences between treatments. B: individual data of total water gradient (mg) across the nose. The solid bars represent the mean of individual data points.
tion (B2) and probe insertion with either POB or placebo (B3) \((P > 0.05 \text{ both})\). The NMT after administration of both POB and placebo decreased significantly after CDA \((AC)\) exposure compared with all prior time points \((P < 0.01 \text{ for all})\). Administration of POB was associated with a significantly smaller net decrease in NMT between the two treatments from probe insertion \((B3)\) to AC administration \((-12.39 \pm 0.92 \text{ vs. } -9.27 \pm 1.33^\circ \text{C}; P < 0.05)\) (Fig. 3). There was a significant reduction in nasal volume \((AC)\) exposure in both treatments \((P < 0.05)\), with no difference between treatments \((P > 0.05)\). There were no significant differences in nasal volume at any time point between POB and placebo \((P > 0.05 \text{ for all})\) (Fig. 5).

Rhinorrhea and congestion are the major symptoms after exposure to CDA. Treatment with POB did not cause significant changes in rhinorrhea and congestion scores \((AC)\) exposure, although, with placebo, significant changes were seen \((P < 0.01)\) (Fig. 6). Symptoms of rhinorrhea were decreased with POB compared with placebo \((0.2; P < 0.05)\), and the net change in rhinorrhea symptoms from probe insertion \((B3)\) to AC was also higher with POB treatment \((0.1; P < 0.05)\). Symptoms of congestion were decreased with AC with POB compared with placebo \((0.1; P < 0.01)\); however, the net change in congestion symptoms from probe insertion \((B3)\) to AC was not significantly different between treatments.

No adverse effects of the administration of POB were reported or seen by the investigators. HR and blood pressure varied slightly during the experiments, but there was no difference between treatments (data not shown).

**DISCUSSION**

The goal of our study was to gain a better understanding of the effect of surface temperature, which is linked to blood flow, on nasal air conditioning. The nasal vasculature consists of resistance vessels (arteries and arterioles), exchange vessels (subepithelial and preglandular capillaries), shunts (arteriovenous connections), and capacitance vessels (collecting veins and venous sinusoids) (20). Sympathetic pathways cause vasoconstriction through the \(\alpha\)-agonists, primarily epinephrine and norepinephrine (22), that work through \(\alpha_1\)- and \(\alpha_2\)-subtypes of adrenoceptors. The precise location and distribution of adrenoceptors in the nasal vascular bed are controversial (18). However, the \(\alpha_2\)-receptors tend to be concentrated on precapillary arterioles, whereas the \(\alpha_1\)-receptors populate the postcapillary venules (19). Vasoconstriction caused by \(\alpha_2\)-receptors causes diminished blood flow, reducing congestion and rhinorrhea. Similar effects are seen after stimulation of \(\alpha_1\)-receptors, which decrease both the volume of blood in the mucosa and the mucosal volume. Using a radiolabeled tracer washout technique that examines resistance vessels, Andersson and Bende (2) were able to distinguish decreased blood flow in vivo with application of topical \(\alpha_2\)-adrenergic agonist, but not with \(\alpha_1\)-adrenergic agonist, and suggested that \(\alpha_1\)-receptors are of lesser importance in the nose. This distinction, however, may not be clinically relevant because both \(\alpha_1\)- and \(\alpha_2\)-agonists are used in the treatment of nasal congestion. Additionally, an in vitro study of human nasal mucosal biopsies was able to demonstrate contractile responses with both \(\alpha_1\)- and \(\alpha_2\)-agonists (14). Further elucidations of these issues in the human nose are warranted, especially in light of the use of \(\alpha\)-antagonists, including POB, in the treatment of prostate hypertrophy (13).

We investigated whether treatment with POB, a nonspecific \(\alpha\)-adrenergic antagonist that blocks both \(\alpha_1\)- and \(\alpha_2\)-receptors, would affect NCC by its effects on nasal blood flow. We predicted increased blood flow to the nasal cavity \((AC)\) by...
blocking of α-adrenergic-mediated vasoconstriction. An increase in blood flow would be predicted to increase the NMT and reduce the fall in surface temperature after exposure to CDA. We have previously shown that elevation of NMT by warming the feet increases the ability of the nose to condition air (1). This was thought to occur through a neural reflex, which involved both parasympathetic stimulation and a loss of sympathetic tone. α-Adrenergoreceptor blockade, however, might also cause a decrease in nasal volume because of engorgement capacitance vessels. Prior studies showed that reduction in nasal volume through supine positioning decreases nasal conditioning (5, 8, 26). Thus our prediction was that POB would increase NCC through favorable effects on NMT and that the effect on nasal volume would be minimal.

POB caused an increase in NMT after administration to the nose compared with baseline, indicating its effects on the nasal vasculature. Additionally, the net change in NMT AC was significantly less with POB than with placebo, indicating that POB did mitigate the known CDA-induced decrease in NMT. POB had no measurable effect on nasal volume or congestion. Despite achieving our predicted outcome from the administration of POB, our study demonstrates no significant difference in NCC with POB or placebo treatment, contrary to the prediction of Hanna and Schere (12).

In our laboratory’s prior study involving raising the mucosal temperature by warming the feet, a ~1°C change in NMT was obtained (1). Because POB did not cause a rise in NMT AC of this magnitude, it is possible that the effect of POB on nasal blood flow was not large enough to affect the NCC. A larger dose of POB might have led to a greater effect on mucosal temperature. Alternatively, the suggestion that warming the feet also initiated parasympathetic activation might explain the difference in outcomes.

We were unable to detect an effect of POB on nasal volume. There were no differences between POB and placebo at any time point, nor was the net change in nasal volume AC significantly different. In both treatments, CDA was associated with a decrease in nasal volume, an effect seen in prior studies. Our results show no effect of POB on nasal volume, suggesting that a change in nasal volume is not a mechanism for any effect of POB on NCC. The lack of effect of POB on nasal volume is interesting, given that systemic use of POB is known to cause symptoms of nasal congestion (9); this may indicate a difference between topical and systemic administration of the drug. Hence, our lack of an effect may reflect the known, multifactorial control of vascular tone in the nose, which can be affected by other pathways (sensory, parasympathetic) (6) and by substances, including neurokinins, neuropeptide Y, substance P, chemotaxins, serotonin, prostaglandins, and others (22), limiting the effect of one agent on this parameter. We also cannot exclude a compensatory, nonadrenergic-mediated mechanism, nor can we exclude competing forces (CDA causing a decrease in nasal volume, and blockade of α-receptors causing an increase in nasal volume) that canceled to result in no net effect.

Treatment with POB was associated with decreased symptoms of rhinorrhea AC. The decrease in rhinorrhea that we observed AC supports a role for α-adrenergic receptors in nasal secretion. This is supported by an in vivo study in which phenylephrine stimulated lysozyme release, suggesting that α-agonists have some stimulatory effects on glandular secretion (23). An increase in glandular secretion caused by POB could mitigate any decreased water transport caused by other

Fig. 6. Subject symptoms. A: rhinorrhea scores, with time points on the abscissa. Medians are shown in 9 subjects. C: individual data for net change in rhinorrhea scores from before CDA to AC, with treatment on the abscissa. The solid bars with the number above represent the means of individual data points. B: congestion scores, with time point on the abscissa. Medians are shown in 9 subjects. D: individual data for net change in congestion scores from before CDA to AC, with treatment on the abscissa. The solid bars represent the medians of individual data points.
mechanisms, preventing us from detecting an overall effect on conditioning. The symptom of congestion was minimal and did not differ significantly between treatments.

On the molecular level, POB could affect ion transport by affecting the channel function of the nasal epithelium. Aside from glandular secretion, α-agonists have been implicated in vitro in Na-Cl cotransport; sodium and water transport may be affected by such agents and explain this effect (21). α1-Adrenergic stimulation of chloride transport has been shown in the human airway epithelium in vitro, with the suggestion that this process occurs at the basolateral membrane (21). Therefore, the secretory state of the nasal epithelium could be affected by POB, with blockage of this process decreasing conditioning by decreasing ion and water transport across the epithelium. Again, the direction of the effect may be the opposite of that for other mechanisms, preventing our detection of a net change in condition. In contrast, however, in vitro studies of cultured human nasal epithelial cells showed no significant effects of oxymetazoline on sodium or chloride transport when an Ussing chamber system was used (17). Unfortunately, we did not measure secretion weights or the ionic composition of secretions in our study. Further study of the effect of intranasal medications, including decongestants, on ion transport is necessary.

Because the probe occupies one nasal cavity, we made our measurements and topical application of POB or placebo on the nonprobe side. The side with the probe was occluded before the administration of CDA so that all air was forced through the patent nasal cavity. All physiological measurements were made on that side. Thus our calculations of WG was only of the nonprobe side. Although the nonprobe nasal cavity was unmanipulated, nasonasal reflexes caused by probe insertion could have affected our results. In this study, contralateral nasal airway resistance was unchanged, a finding that supports the use of unilateral measurements that were required by experimental design and monitoring equipment.

Last, because this was a small study, we estimate sample size based on the objective measures of previous studies (16, 25). It is possible that use of a larger sample would have made it easier to detect an effect of POB on symptom scores. Because our data demonstrate that we were able to perturb NMT, we believe that the sample size was adequate.

In conclusion, our data demonstrate that POB, although blocking the effects of oxymetazoline, does not affect the ability of the nose to warm and humidify air. POB mitigated the effects of CDA on nasal surface temperature and reduced symptoms of rhinorhoea AC, but had no effects on nasal volume. Hence, although we were able to manipulate physiological parameters affecting NCC and show effects on symptoms through the use of α-adrenergic blockade, we could detect no change in NCC. This indicates a high degree of complexity of nasal physiology and its responses to pharmacological intervention. Further study is necessary for identifying and characterizing the parameters that contribute to the process of nasal humidification.

REFERENCES


GRANTS

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