

Nasal response to substance P and methacholine in subjects with and without allergic rhinitis

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Nasal response of subjects with and without allergic rhinitis to substance P and methacholine. P. Devillier, J.F. Dessanges, F. Rakotosianaka, A. Ghaem, H.A. Boushey, A. Lockhart, J. Marsac.

ABSTRACT: We compared the rise in nasal airway resistance (NAR) provoked by topical application of substance P (SP) and of methacholine (MCH) in seventeen patients suffering from rhinitis and fourteen control subjects. Challenges with SP or MCH were separated by a week or more. NAR was measured by posterior rhinomanometry before and 10 min after intranasal administration of SP (10–40 nmol) or MCH (3–12 µmol). The two groups of subjects had similar baseline levels of NAR and similar small responses to buffered saline. Substance P but not MCH provoked cutaneous flushing in all subjects. Both SP and MCH provoked a significantly greater increase in NAR in patients suffering from rhinitis than in control subjects. The increase in NAR was dose-dependent, and on a molar basis, SP was 375–500-fold more potent than MCH. Pretreatment with 200 µg of a topically active anticholinergic agent, oxytropium bromide, prevented the rise in NAR caused by 12 µmol of MCH but not that caused by 40 nmol of SP in six patients suffering from rhinitis. We conclude that SP is absorbed across the nasal mucosa and causes cutaneous vasodilation, that MCH and SP cause a greater rise in NAR in patients suffering from rhinitis than in control subjects, that SP is about 500-fold more potent than MCH in increasing NAR, and that the rise in NAR caused by SP is not mediated by postganglionic parasympathetic mechanisms.

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Substance P, a neuropeptide found in afferent nerve endings lining the nasal mucosa [1], causes vasodilation, extravasation of plasma proteins, acute airways obstruction in whole animals and contraction of airway smooth muscle on *in vitro* preparations [1–8], but few studies have examined its effects on airway function in humans [9–11]. These effects would be expected to be predominantly vascular, for the nasal airway is not invested with airway smooth muscle but is richly supplied with vessels innervated by efferent parasympathetic fibres from the sphenopalatine ganglia and by afferent fibres of the trigeminal nerves [8, 12]. Substance P may also increase mucus secretion but the dose required appears to be higher than the doses affecting vascular calibre and permeability [7, 8, 13, 14]. The vascular effects of substance P need not be due simply to direct effects on vascular tone, however, for substance P-containing nerve endings are found in the sphenopalatine ganglia [1], where they may modulate ganglionic transmission of parasympathetic activity. It is further possible that substance P may modulate the release of acetylcholine from postganglionic parasympathetic nerve endings or may activate central reflex pathways [3, 8].

The first purpose of this study was, therefore, to examine the effects of intranasal instillation of increasing doses of substance P on nasal airway

resistance, for nasal airway resistance is affected by vascular calibre, mucosal oedema and intraluminal secretion, and to determine whether these effects are blocked by a muscarinic antagonist. Because previous investigators have reported greater nasal responsiveness to methacholine and histamine in subjects with allergic rhinitis than in normal subjects [15–19] and because substance P has been reported to provoke mast cell degranulation [20, 21], we also examined the responses to methacholine and substance P in patients suffering from rhinitis and in control subjects.

Material and methods

Subjects

Seventeen patients suffering from rhinitis with an obvious history of allergic rhinitis and fourteen control subjects without rhinitis (age 23–56 yrs) were studied. The subjects were non-pregnant and non-smoking. The seventeen patients suffering from rhinitis had allergic disease only, *i.e.* rhinitis, asthma, or eczema. They were not receiving medication at the time of the study. Allergy was defined on the basis of a familial or personal history of atopic diseases and one or more positive responses to prick tests with a battery of inhalant allergens (Institut Pasteur, France)

consistent with the clinical history. The diagnosis of allergic rhinitis was based upon the occurrence of symptoms immediately after exposure to an identified naturally occurring allergen, i.e. pollen, house dust mite and/or cat dander, and upon positive skin test to the suspected allergen. Four of the patients suffering from allergic rhinitis also suffered from mild asthma but did not need daily use of bronchodilators. In five of the seventeen patients, a nasal challenge with an allergen selected according to the results of the skin test confirmed the diagnosis by the occurrence of sneezing, nasal hypersecretion and nasal obstruction. None of the control subjects had a history of allergic symptoms, and in ten of the fourteen tested, none had positive responses to cutaneous skin testing with five mixes of allergens, common to France, usually used for screening procedures (Institut Pasteur, France: one mix of house dust mites (PA 05), two mixes of weed pollens (H 09 and GF 09), two mixes of tree pollens (AM 04 and AM 06)). We did not study any subject within six weeks of an exacerbation of allergic disease or of a respiratory tract infection. Except for the four patients suffering from rhinitis to cat danders and/or house dust mite, all studies were conducted out of the seasonal allergy period (at least, one month after the end of the season). All subjects belonged to the medical staff of the Department of Pneumology or were medical students and volunteers for the study who had been informed of the protocol and possible side effects.

General outline of the study

Firstly, doubling doses of either SP or MCH were sprayed into the nostrils at 12–15 min intervals and nasal airway resistance was measured by active posterior rhinomanometry after each dose. This was done in both control subjects and patients suffering from rhinitis to establish whether the increase in NAR was dose-dependent and was greater in patients suffering from rhinitis compared to normal subjects.

Since our results suggested that both substance P- and methacholine-induced nasal obstruction was greater in patients suffering from rhinitis, we studied six patients in order to find out whether the dose of a topically administered anticholinergic agent (oxytropium bromide) that was able to block the nasal response to the highest dose of MCH, also antagonized the nasal response to SP.

Technical details

Challenges with SP and MCH were separated by a week or more but were performed at the same time of day for each subject. The challenge solutions were kept at room temperature. As the subject voluntarily suspended respiration, the challenge material was sprayed onto the inferior turbinate area of both nostrils with a plastic hand-activated nebulizer that delivered $100 \pm 10 \mu\text{l}$ of solution (Fisons Laboratories). The nozzle of the nebulizer was held just beyond, but not touching, the nasal vestibule. A total

of 0.2 ml (0.1 ml in each nostril) of solution was used for each challenge. After each spray, the solution was kept in touch with the nasal mucosa for 10 min with a 'nose-clip' that was removed two min before the measurement of nasal resistance.

We used saline solution ($0.15 \text{ mol} \cdot \text{l}^{-1}$ NaCl), methacholine hydrochloride (SIGMA, St Louis, USA) diluted in saline ($30, 60, 120 \mu\text{mol} \cdot \text{ml}^{-1}$), substance P (Novabiochem, Laufelfingen, Switzerland) diluted in saline ($0.1, 0.2, 0.4 \mu\text{mol} \cdot \text{ml}^{-1}$), and oxytropium bromide (Tersigat®, L.F.T. France) in a commercially available nebulizer ($500 \mu\text{g} \cdot \text{ml}^{-1}$).

For measurement of nasal airway resistance, we used active posterior rhinomanometry as described by GHAEM and MARTINEAUD [22], which is preferable to anterior rhinomanometry to assess the patency of nasal airways [22, 23]. Briefly, nasal airflow was measured through a pneumotachograph (Fleisch No. 1) fitted to a diver's face mask closely adjusted around the nose and eyes, and connected to a differential pressure transducer (Validyne Model MP 45-1-871). Posterior oropharyngeal pressure was measured with a catheter placed on the tongue and held between tightly closed lips and connected to a pressure transducer (Validyne MP 45-1-871). The airflow and the transnasal pressure were monitored on-line with an X-Y recorder. A program developed in Dr. A. Ghaem's laboratory for an Apple II microcomputer with an analogue to digital converter card (2 channels and 12 bits: UTC 06-611, Université de Technologie de Compiègne, France) was used for data acquisition, display, storage and analysis. Airflow and transnasal pressure, obtained at 10 msec intervals between the onset of inspiration and maximal inspiratory airflow, were used to establish the pressure-flow curve and compute by interpolation the nasal airway resistance. Because low flows were sometimes achieved after nasal challenge, we only used the values for nasal resistance at a flow of $0.15 \text{ l} \cdot \text{s}^{-1}$ to analyse changes in airway patency. The values of nasal airway resistance reported are the mean of duplicate determinations carried out over a 1 min interval. Duplicate determinations of NAR were obtained 12 min after each nasal spray, 2 min after the nose-clip had been removed and the subject instructed to gently blow his nose.

Detailed protocols

Firstly, NAR was measured in basal conditions, 12 min after saline challenge, and after each of three successive, doubling doses of either MCH or SP. Dose-effect curves to MCH were obtained in fourteen control subjects and fifteen patients suffering from rhinitis. Dose-effect curves to SP were obtained in nine control subjects and nine patients suffering from rhinitis.

Six patients, four of whom had taken part in the first study, took part in the second. On study day 1, NAR was measured under basal conditions and after administration of substance P (40 nmol in each nostril). On study day 2, the same dose of SP was

administered 10 min after pretreatment with oxytropium bromide (200 µg in each nostril). On two other study days, the study was repeated with MCH (12 µmol) instead of SP.

In order to test the reproducibility of posterior rhinomanometry in patients suffering from rhinitis, we carried out two additional studies. Firstly, in four of the fifteen patients suffering from rhinitis, we repeatedly challenged the nose with saline according to the same time-table used in the methacholine and substance P studies. Secondly, in six of these patients, we challenged the nose twice, at a one week interval, with a single dose of methacholine equal to the highest dose (12 µmol) used for the construction of the dose-response curve to methacholine.

Analysis of the results

Resistance at the flow $0.15 \text{ l} \cdot \text{s}^{-1}$ was calculated after a linear regression analysis of the flow-resistance data. Changes in nasal airway resistance values were compared with a two way analysis of variance. Multiple comparisons were made with the Newman-Keuls multiple range test. Results are expressed as mean and standard deviation.

Results

Nasal response to saline challenge

Pre-challenge nasal resistance was similar in the controls and in the patients suffering from rhinitis and was on average the same on the methacholine and substance P days: 0.198 ± 0.03 and $0.208 \pm 0.04 \text{ kPa} \cdot \text{l}^{-1} \cdot \text{s}$ respectively for the controls and 0.256 ± 0.08 and $0.240 \pm 0.06 \text{ kPa} \cdot \text{l}^{-1} \cdot \text{s}$ respectively in patients suffering from rhinitis. Nasal airways resistance was not significantly affected by the saline challenge. For the controls, the post-saline average value of NAR was: $0.201 \pm 0.05 \text{ kPa} \cdot \text{l}^{-1} \cdot \text{s}$ on the methacholine day and $0.202 \pm 0.04 \text{ kPa} \cdot \text{l}^{-1} \cdot \text{s}$ on the substance P day; for the patients suffering from rhinitis the average values were: 0.283 ± 0.09 and $0.277 \pm 0.09 \text{ kPa} \cdot \text{l}^{-1} \cdot \text{s}$ respectively. In the subgroup of four patients suffering from rhinitis challenged repeatedly with saline, there was no significant increase in NAR: $0.245 \pm 0.08 \text{ kPa} \cdot \text{l}^{-1} \cdot \text{s}$ before and $0.284 \pm 0.10 \text{ kPa} \cdot \text{l}^{-1} \cdot \text{s}$ after the fifth challenge. These latter results are in agreement with those already published by MCLEAN [24].

Response to methacholine

Methacholine provoked a significant and dose-dependent increase in NAR in patients suffering from rhinitis and a non-significant increase in the control subjects (fig. 1). In patients suffering from rhinitis, NAR rose significantly ($0.385 \pm 0.17 \text{ kPa} \cdot \text{l}^{-1} \cdot \text{s}$; $p < 0.01$) with the first dose of MCH (3 µmol in each nostril) and reached between 100 and 150% of baseline ($0.562 \pm 0.19 \text{ kPa} \cdot \text{l}^{-1} \cdot \text{s}$; $p < 0.01$) after the highest dose used (12 µmol in each nostril). In the

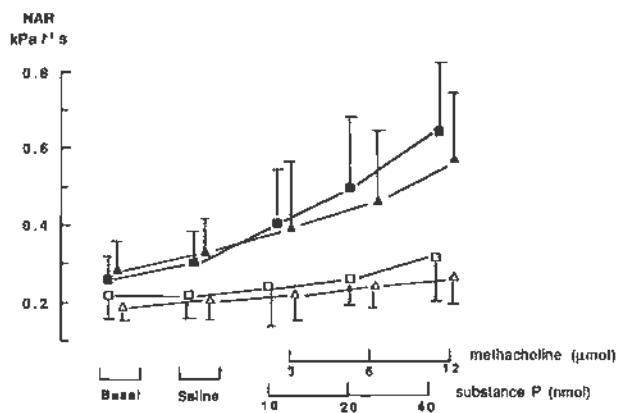


Fig. 1. Nasal airway resistance before challenge (basal) and effects of administration of saline and increasing doses of methacholine (μmol) and substance P (nmol) on the nasal airway resistance (NAR) of control subjects (open symbols) and patients suffering from rhinitis (closed symbols). Substance P challenges (■, □); methacholine challenges (▲, △). Results are shown as mean and standard deviation.

control group, only the highest dose of methacholine induced a borderline increase in NAR ($0.273 \pm 0.07 \text{ kPa} \cdot \text{l}^{-1} \cdot \text{s}$; $0.05 < p < 0.10$). As a result, NAR increased significantly more in patients suffering from rhinitis than in control subjects, a difference which was already present for the lowest dose of methacholine used ($p < 0.01$). That we could obtain reproducible results with methacholine is shown by the similarity in the mean rise in NAR obtained in six patients suffering from rhinitis challenged with 12 µmol of methacholine in each nostril before and after a one week interval (from 0.241 ± 0.049 to $0.418 \pm 0.09 \text{ kPa} \cdot \text{l}^{-1} \cdot \text{s}$ with the first challenge, and from 0.245 ± 0.05 to $0.449 \pm 0.07 \text{ kPa} \cdot \text{l}^{-1} \cdot \text{s}$ with the second). The highest dose of MCH did not cause any systemic reaction except for slight facial flushing.

Response to substance P

Nasal challenge with substance P induced a dose-dependent increase in NAR in patients suffering from rhinitis ($p < 0.01$). The rise in NAR was already significant after administration of 20 nmol of substance P in each nostril (from 0.277 ± 0.09 to $0.478 \pm 0.22 \text{ kPa} \cdot \text{l}^{-1} \cdot \text{s}$; $p < 0.01$) and attained between 150 and 200% of baseline with the highest dose of SP used ($0.656 \pm 0.21 \text{ kPa} \cdot \text{l}^{-1} \cdot \text{s}$; $p < 0.01$). In control subjects, only the highest dose of substance P induced a borderline and non-significant increase in nasal airways resistance (from 0.202 ± 0.043 to $0.336 \pm 0.069 \text{ kPa} \cdot \text{l}^{-1} \cdot \text{s}$; $0.05 < p < 0.10$). The difference between subjects with and without rhinitis was significant with the lowest dose of substance P used ($p < 0.01$; fig. 1). In both control subjects and patients suffering from rhinitis, 40 nmol of substance P induced an intense and transient facial flush, a sensation of heat involving the thorax and bounding of temporal pulse. These effects occurred about 1 min after the topical application of SP and diminished in less than 5 min.

Effect of muscarinic antagonist on response to substance P

Intranasal administration of oxytropium bromide (OB) or saline did not cause any significant modification of nasal airway resistance in the six patients suffering from rhinitis. Oxytropium bromide effectively blocked the methacholine (12 pmol)-induced increase in nasal airway resistance (0.460 ± 0.096 without OB vs 0.273 ± 0.047 kPa·l⁻¹·s with OB; $p < 0.01$) but did not affect that induced by 40 nmol of SP (0.450 ± 0.069 without OB vs 0.418 ± 0.086 kPa·l⁻¹·s with OB) (fig. 2).

Discussion

In our subjects, both methacholine and substance P provoked a greater rise in NAR in patients suffering from allergic rhinitis than in control subjects. On a molar basis, substance P appeared 375 500-fold more potent than MCH in causing this effect. Substance P did not appear to act via postganglionic parasympathetic pathways, because its effects were unaltered by pretreatment with a dose of a muscarinic antagonist sufficient to entirely block the response to the highest dose of MCH administered. SP also appeared to be absorbed across the nasal mucosa, because intense facial flushing was observed in all subjects after instillation of 40 nmol of SP.

We cannot be certain that the rise in NAR caused by either agent was due to vascular engorgement.

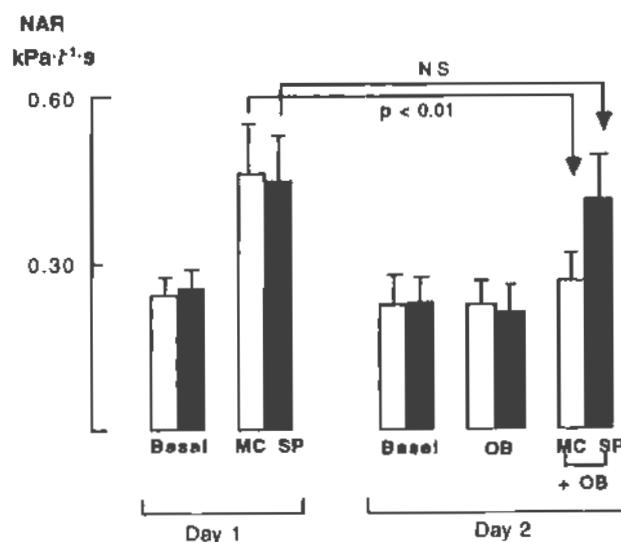


Fig. 2. Effect of 200 µg oxytropium bromide (OB) on the increase in NAR induced by 12 pmol of methacholine or 40 nmol of substance P in six patients suffering from rhinitis. On day 1, nasal airway resistances were determined before challenges (basal) and either after a single dose of methacholine (MC, open columns) or substance P (SP, closed columns). On day 2, nasal airway resistances were determined before challenges (basal), after administration of oxytropium bromide (OB) and then, after a single dose of methacholine (MC + OB) or substance P (SP + OB) administered 10 min after oxytropium bromide. Results are shown as mean and standard deviation. NS: non-significant; $p < 0.01$; significant at the 1% level.

Indeed, local intra-arterial infusion of acetylcholine causes dose-dependent vasodilation in cats and dogs and an increase in nasal resistance in dogs [8, 25]. However, nasal submucosal glands are densely innervated by cholinergic fibres [25] and previous studies have shown that MCH can provoke an increase in the volume and protein concentration of nasal secretions [12, 16, 17, 19, 26, 27] and that SP may also increase secretions [11, 13, 14]. Our results may, therefore, partly reflect greater secretory responsiveness of our patients suffering from rhinitis, although higher doses of SP are required to stimulate mucus secretion than are needed to cause vasodilation. We minimized the influence of nasal secretion by having our subjects gently blow their nose just before each measurement of NAR. Furthermore, we used doses of MCH smaller than those previously shown to cause a marked increase in secretion [15, 16].

Another reason for our belief that the increase in NAR caused by substance P was due to acute vasodilation is that it was associated with transient, intense cutaneous flushing in all subjects. No subjects reported an increase in nasal secretions as already described by PETERSSON *et al.* [11]. Local intra-arterial infusion of substance P in animals causes dose-dependent vasodilation in the nasal mucosa [8, 25], with the vasodilator effect of substance P being 10–50 times more potent than those of VIP or acetylcholine. The appearance of cutaneous flush is not only indirect evidence that substance P probably causes vasodilation in the nasal mucosa, but is also evidence that substance P crosses the nasal epithelium and is absorbed into the circulation.

Whatever the underlying mechanisms of the rise in NAR, they appear to be exaggerated in our patients suffering from rhinitis, because all doses of both MCH and substance P provoked a significantly greater rise in NAR in patients suffering from rhinitis than in controls. Greater nasal responsiveness to MCH in allergic patients has previously been found by some, but not all, investigators who have examined changes in nasal resistance as the end point [16, 18, 28, 29] and has been found by others who have examined changes in the volume or protein content of nasal secretions [16, 17, 19, 27]. A systemic increase in vascular responsiveness to alpha-agonists has also been reported in allergic patients [30]. Our findings are thus consistent with previous work and again suggest that nasal reactivity to methacholine is increased in people with allergic rhinitis just as bronchial reactivity is in people with asthma [28, 31–33]. Our findings with substance P are similar. The greater responsiveness to SP may reflect the increased number of basophils and mast cells in and on the nasal epithelium of subjects suffering from allergic rhinitis [34, 35], because substance P has been reported to provoke histamine release from murine peritoneal mast cells and human cutaneous mast cells [20, 21, 36]. However, it has been reported that human lung mast cells and blood basophils are not responsive to substance P [20]. Whatever the underly-

ing mechanism, our finding that SP provokes nasal congestion suggests that release of this neuropeptide from afferent nerves in the nasal mucosa may be important in mediating nasal responses to inhaled materials.

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RÉSUMÉ: Nous avons comparé l'augmentation des résistances des voies aériennes nasales provoquée par l'application topique de substance P et de méthacholine (MCH) chez 17 patients souffrant de rhinite et chez 14 sujets-contrôle. Les provocations avec la substance P ou la méthacholine furent séparées d'une semaine ou davantage. La résistance des voies aériennes nasales a été mesurée par rhinomanométrie postérieure à la fois avant et 10 minutes après l'administration intranasale de substance P (10 à 40 nmol) ou de méthacholine (3 à 12 µmol). Les deux groupes de sujets ont des valeurs de base similaires en ce qui concerne la résistance des voies aériennes nasales, et de petites réponses similaires à la provocation au moyen de solution saline tamponnée. La substance P a provoqué un flush cutané chez tous les sujets, mais non la méthacholine. La substance P et la méthacholine ont provoqué une augmentation significativement plus marquée de la résistance des

voies aériennes nasales chez les sujets souffrant de rhinite que chez les sujets-contrôle. L'augmentation de la résistance des voies aériennes nasales est apparue dose dépendante et, sur une base molaire, la substance P est 375 à 500 fois plus puissante que la méthacholine. Un traitement préalable au moyen de 200 µg d'un agent anticholinergique à action topique, le bromide d'oxytropium, a prévenu l'augmentation de résistance des voies aériennes nasales causée par les 12 pmol de méthacholine, mais non celle causée par 40 nmol de substance P chez 6 patients atteints de rhinite. Nous

concluons que la substance P est absorbée par la muqueuse nasale et provoque une vasodilation cutanée, que la méthacholine et la substance P provoquent une augmentation plus marquée des résistances des voies aériennes nasales chez les sujets contrôles, que la substance P est environ 500 fois plus puissante que la méthacholine en ce qui concerne l'augmentation des résistances des voies aériennes nasales, et que l'augmentation des résistances des voies aériennes nasales causée par la substance P n'est pas médierée par des mécanismes parasympathiques post-ganglionnaires.