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Secretion, pain and sneezing induced by the application of capsaicin to the nasal mucosa in man

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1 Topical application of capsaicin to the human nasal mucosa induced a burning sensation and sneezing. A dose-dependent seromucous nasal secretion was also observed. Capsaicin (75 μg) was more potent than methacholine (50 mg) in producing nasal secretion, while topical histamine (200 μg), substance P (135 μg) and calcitonin gene-related peptide (36 μg) did not induce rhinorrhea.

2 Pretreatment with either topical ipratropium bromide, systemic dexchlorpheniramine or indomethacin did not influence the effects induced by capsaicin. Topical pretreatment with lidocaine inhibited the painful sensation but failed to block the rhinorrhea. Desensitization to the effects of capsaicin occurred following 4–5 subsequent applications, and full recovery was observed within 30–40 days.

3 It is proposed that the effects of capsaicin in human nasal mucosa are due to excitation of primary afferent neurones that (a) convey burning and painful sensation, (b) evoke a sneezing reflex and (c) induce nasal secretion by releasing transmitter(s) from their peripheral terminals.

Introduction

Mechanical or chemical irritants, contacting the nasal mucosa, may stimulate protective reflex responses, such as sneezing, increased vascular permeability, secretion and cardiovascular effects (Angell-James & de Burgh Daly, 1969; Lundblad *et al.*, 1984). Mediation of cardiorespiratory reflexes by afferent trigeminal pathways is indicated by the observation that surgical division of trigeminal nerve abolishes these effects (see Eccles, 1982). Increased vascular permeability in the skin around the nose together with nasal secretion were observed in rats, following stimulation of the trigeminal nerve (Jancsó-Gabor & Szolcsányi, 1972). Capsaicin, the pungent ingredient of red peppers, when applied into the nasal mucosa of guinea-pigs and rats, induces violent sneezing, vasodilatation and increases vascular permeability (Lundblad *et al.*, 1983b; 1985). All the effects elicited by acute capsaicin application were abolished by systemic or local pretreatment with the drug (Lundblad *et al.*, 1983b; 1985), thus indicating that they were mediated by capsaicin-sensitive neurones. Further, the number of nose wipings induced by ether inhalation was reduced in guinea-pigs desensitized to capsaicin (Lundblad *et al.*, 1985).

A common experience of those who handle capsaicin when it, by chance, enters the nose, is an intense burning sensation and sneezing accompanied by nasal secretion. However, these phenomena have not been investigated in man. Therefore, it appeared worthwhile to study the effects produced by topical application of capsaicin in the human nasal mucosa. The influence of local anaesthetic, antimuscarinic, antihistamine and cyclo-oxygenase inhibitor drugs on capsaicin-induced actions was also investigated.

Methods

The subjects were 36 healthy volunteers of either sex in the age range of 19–31 years, either medical students or members of the medical staff of our department, from whom informed consent was obtained previously. The study was approved in full by the Supervisory Committee of the Institute of Internal Medicine and Clinical Pharmacology of the University of Florence. All the subjects, prior to drug application, were screened in order to exclude any

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disease of the nose and tracheobronchial tree. Examination of the nasal cavity of all subjects was also performed at the end of the study.

Experimental procedure

Capsaicin was dissolved in saline containing 10% paraffin oil and 10% Tween 80. This medium was chosen in order to avoid local neurotoxic effects of other solvents, such as alcohol (Petsche *et al.*, 1983), which are commonly used for dilution of capsaicin. The subject's head was laid carefully on one side and 25 μl of the appropriate concentration of the capsaicin suspension applied by means of a micropipette into the nostril of the contralateral side, approximately 1.5–2 cm from the external orifice. Then the external surface of the nose was gently massaged for a few seconds. The number of sneezes was recorded. The burning and painful sensation was measured by means of the visual analogue scale method (Scott & Huskisson, 1976). The flow of secretion was collected over a period of 10 min into plastic tubes through a funnel shaped device placed at the external orifice of the nostril. The amount of secretion in 10 min was measured.

Capsaicin desensitization

Desensitization to capsaicin and recovery of capsaicin-induced effects were investigated in 12 subjects by applying 25 μl of 10 mM (75 μg) capsaicin into one nostril, the other receiving 25 μl of the vehicle, once a day for 5 subsequent days. The subjects were then subdivided into 4 groups which were treated with the same dose of capsaicin at either 10, 20, 30 or 40 days from the first drug application. Furthermore, 6 of the 12 subjects desensitized to capsaicin, 2 days after the last drug administration, received an identical dose of capsaicin into the nostril pretreated with the vehicle. When pain sensation was assessed, the subjects were requested to consider the pain experienced during the first drug application as the maximum pain level.

Influence of various drugs on capsaicin-induced effects

Other experiments were undertaken in order to assess whether or not capsaicin-induced effects were affected by antimuscarinic, antihistamine, local anaesthetic and cyclo-oxygenase inhibitor drugs. For this purpose, all the subjects were first treated with topical capsaicin (75 μg), and the subsequent day, capsaicin application was preceded by the administration of one of the above mentioned compounds. This procedure also required subjects to report pain sensation and treat that experienced during the first drug application as the maximum pain level. Subjects were subdivided as follows: (a) five volunteers (controls) were treated with capsaicin 15 min after the application of 100 μl nasal spray saline; (b) four subjects, 30 min before capsaicin, received 80 μg of the topically active parasympatholytic ipratropium bromide (100 μl, nasal spray); (c) five subjects 15 min before capsaicin were locally pretreated with 16 mg of lidocaine (160 μl, nasal spray); (d) in 4 subjects, capsaicin was applied 20 min after the injection of dexchlorpheniramine maleate (10 mg, i.v.); (e) the last 4 individuals were pretreated, 3 h before capsaicin application with two oral tablets of indomethacin, 100 mg.

Flow of nasal secretion induced by capsaicin and methacholine

The flow of nasal secretion induced by the local application of capsaicin was compared to that produced by methacholine, histamine, substance P (SP) and calcitonin gene-related peptide (CGRP). For this purpose methacholine chloride (dissolved in phosphate buffered saline, pH 7.4), histamine chloride, SP and CGRP (dissolved in saline) were applied as indicated for capsaicin application. Appropriate dilutions of the drugs (100 μl) were administered into one nostril, the other receiving a similar amount of the vehicle. Each drug was used in 5 different subjects.

Drugs

The drugs used in this study were: capsaicin (Sigma); ipratropium bromide (Atem, Chiesi): dexchlorpheniramine maleate (Polaramin, Essex); indomethacin (Metacen, Chiesi); lidocaine (Xylestesina, Espe); histamine chloride (Istamina, Isis); methacholine chloride (Hospital Pharmacy, USL 10/D, Florence); substance P and calcitonin gene-related peptide (Peninsula).

Statistical analysis

All data in the text are mean ± s.e.mean. Statistical analysis was performed by means of Dunnett's test. Statistical evaluation of the effects of capsaicin desensitization and recovery was determined by Student's *t* test for paired data.

Results

The application of capsaicin into the human nasal mucosa was immediately followed by a painful sensation that was described by all the subjects as burning. A variable number of sneezes (from 1 up to 8) also occurred. However, this effect was absent in approximately 50% of the tests performed. After a variable length of time (up to 30–60 s), these two phenomena were accompanied by the production of seromucous

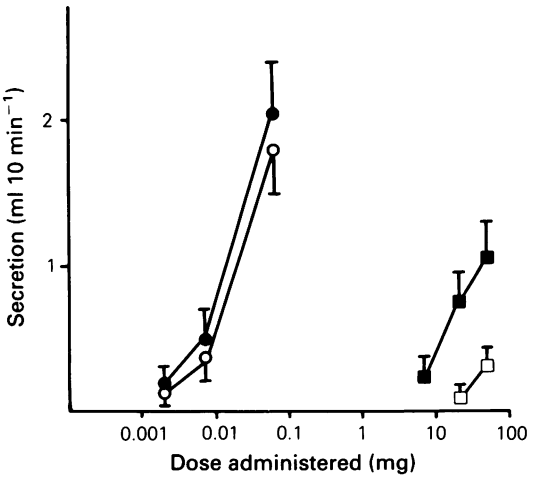

Figure 1 Flow of secretion from the human nasal mucosa induced by the topical application of 25 μl of capsaicin suspension (●) or 100 μl of methacholine solution (■). Capsaicin and methacholine were also administered after pretreatment with 80 μg of nasal spray ipratropium bromide (○ and □, respectively). Each point represents the mean of 5 experiments; vertical lines indicate s.e.mean. Topical application of histamine (200 μg), substance P (135 μg) and calcitonin gene-related peptide (36 μg) did not cause any detectable flow of nasal secretion.

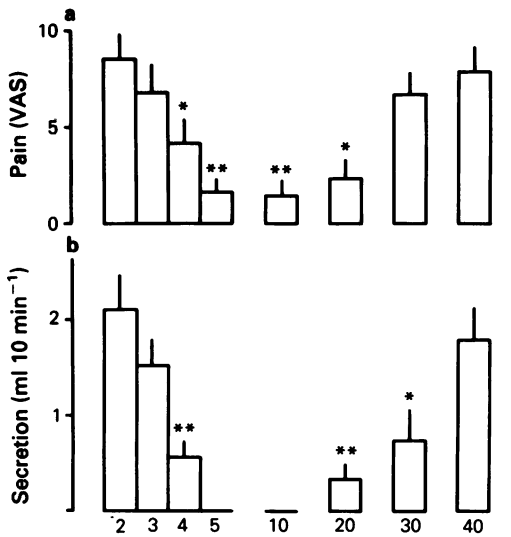

Figure 2 Time course of desensitization and recovery of pain sensation (a) and flow of nasal secretion (b) induced by topical capsaicin (75 μg) to the human nasal mucosa. The number of days from the first capsaicin application are shown below each column. VAS, visual analogue scale. Significantly different from values obtained on day 2, $*P<0.05$, $**P<0.01$.

nasal secretion.

Capsaicin-induced flow of nasal secretion

Capsaicin-induced nasal secretion was dose-dependent (Figure 1). A dose-dependent production of nasal fluid was also observed with methacholine application. However, capsaicin was approximately 200 times more potent than methacholine, and the maximal effect obtained with methacholine (50 mg), which also elicited sweating, facial flushing and palpitations, was half that of capsaicin. In addition, histamine (200 μg), SP (135 μg, a dose that produced moderate facial flushing) and CGRP (36 μg) failed to induce any detectable amount of nasal secretion (Figure 1).

Desensitization to capsaicin and recovery

Desensitization to the burning sensation and the rhinorrhea induced by topical capsaicin developed and these effects were completely abolished after 4–5 applications of the drug (Figure 2). When capsaicin was applied into the contralateral nostril, (treated 4–5 times with the vehicle), it did induce nasal secretion, thus indicating that the procedure induced local desensitization within the treated side. The average number of sneezes recorded per application following the first two capsaicin applications in 8 subjects was 4.1 ± 0.7, while at the fifth consecutive administration it was reduced to 1.3 ± 0.2 ($P<0.01$). Ten days after the first drug administration, capsaicin did not elicit any effect. When 20 days had elapsed, subjects showed little nasal secretion. An almost complete recovery was observed after 40 days from the first application of capsaicin (Figure 2). The time course of the recovery of the burning sensation was almost parallel to that observed for the flow of secretion (Figure 2). Sneezing did not occur in all the subjects when capsaicin was applied 10 to 40 days after desensitization: in view of the few cases analysed, recovery of this parameter was not evaluated.

Effects of various drugs on pain and secretion induced by capsaicin

Capsaicin-induced flow of nasal secretion was not inhibited by any of the compounds tested (Figure 3). Likewise, ipratropium bromide, dexchlorpheniramine and indomethacin failed to inhibit the burning sensation elicited by topical capsaicin, but this was significantly reduced by lidocaine pretreatment (Figure 3). In this set of experiments sneezing was not

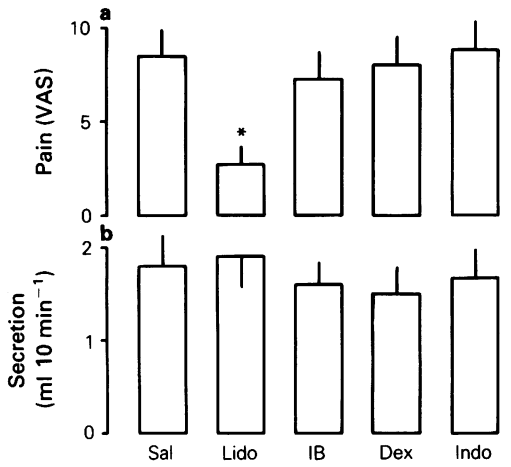

Figure 3 Effect of various drugs on the pain sensation (a) and flow of secretion (b) induced by topical capsaicin (75 μg) to the human nasal mucosa. For further details of the experimental procedure see text. VAS, visual analogue scale. Significantly different from the group pretreated with saline, $*P<0.01$. Abbreviations used; Sal, saline; Lido, lidocaine; IB, ipratropium bromide; Dex, dexchlorpheniramine; Indo, indomethacin.

statistically evaluated since only some subjects had a positive response upon the two capsaicin applications. Examination of the nasal cavity of all the subjects at the end of the experiments did not reveal any gross alteration of the nasal mucosa.

Discussion

In the present study, the application of capsaicin to human nasal mucosa evoked two effects (pain sensation and flow of nasal secretion) which underwent desensitization and time-dependent recovery; sneezing was also induced. Sneezing in response to capsaicin has been demonstrated in other mammals, such as guinea-pig (Jancsó *et al.*, 1961, Lundblad *et al.*, 1985) and rat (Lundblad *et al.*, 1983b). The present experiments indicate that repeated applications of capsaicin reduced significantly the number of sneezes. However, in approximately 50% of challenges sneezing was absent. This prevented analysis of the time course of recovery to sneezing, as well as evaluation of the effect of drugs. Therefore, the reflex nature of the sneezing response to capsaicin cannot be positively demonstrated in this study.

Immediately after the application of capsaicin, all subjects experienced a painful sensation, described as burning and pungent. This effect underwent a clear-cut desensitization upon repeated application of the drug and a time-dependent recovery thereafter. Pretreatment with lidocaine but not with ipratropium bromide, dexchlorpheniramine and indomethacin, effectively reduced the painful sensation. These findings suggest that the pungent sensation is dependent upon stimulation of capsaicin-sensitive trigeminal afferents in the nasal mucosa.

Another striking effect induced by the topical application of capsaicin was the copious flow of nasal secretion. Capsaicin was approximately 200 times more potent than methacholine in producing rhinorrhea (Figure 3). Methacholine, at the higher dose used, also elicited systemic effects, but the maximal response to this drug did not exceed 50% of that produced by capsaicin. However, a parasympathetic mechanism seems not to participate in capsaicin-induced nasal secretion, since this was not reduced by ipratropium bromide; this agent inhibited methacholine-induced rhinorrhea (Figure 2) (Borum, 1979). The albumin content of capsaicin-induced nasal secretion was not measured. Therefore, it cannot be established whether nasal fluid originates, at least in part, from the transudation of plasma, due to increased vascular permeability.

We cannot exclude a direct effect of capsaicin on seromucous glands. However, the observation that capsaicin-induced rhinorrhea exhibits desensitization favours the interpretation of a specific action of capsaicin on sensory nerves. Desensitization of the response to capsaicin seems a useful functional marker distinguishing specific (on sensory nerves) from non-specific actions of this substance (Maggi *et al.*, 1987a). Following induction of desensitization, a time-related recovery of both sensory (pain) and effector responses (rhinorrhea) to topical capsaicin was observed. This finding parallels previous observations in animals indicating that, in adult rats, both sensory and efferent functions mediated by these sensory neurones exhibit a time-related recovery (Maggi *et al.*, 1987b).

In dogs, histamine (i.a.) was found to induce a small flow of secretion from the nasal gland (Wells & Widdicombe, 1986). Contrary to our findings, Konno *et al.* (1983) demonstrated that histamine applied to the human nasal mucosa evoked a flow of secretion. Methodological differences in the fluid collection and drug application may account for this discrepancy. Irrespective of this point, histamine seems not to participate in the capsaicin-induced nasal secretion, since dexchlorpheniramine did not reduce this effect.

Primary afferent sensory neurones have been regarded as possessing two functions: (a) the 'afferent' function by which information is conveyed to the central nervous system and, (b) an 'efferent' function producing various effects in peripheral organs (Szolcsányi, 1984; Maggi & Meli, 1986). SP immunoreactive nerve fibres have been found within human nasal mucosa, and in several rodent species, close to blood

vessels and within the respiratory epithelium, but not contacting the seromucous glands (Lundblad *et al.*, 1983a). SP seems not to be responsible for capsaicin-induced nasal secretion in man. In agreement with Malm & Petersson (1985) we have not observed any effect of topical SP at a dose capable of inducing facial flushing. Nerve fibres, containing CGRP, have recently been shown in the human airways (Palmer *et al.*, 1987). Functional evidence has been presented indicating that CGRP may be responsible for many acute responses to capsaicin which cannot be ascribed to SP (Franco-Cereceda & Lundberg, 1985; Maggi *et al.*, 1986; Hua & Lundberg, 1986). We have not observed any effect of CGRP applied topically to the human nasal mucosa. However, the use of a dose of the peptide that does not induce any systemic effect may raise doubts about its absorption and/or dosage, and therefore prevents any definitive conclusion on CGRP action in human nasal mucosa.

Capsaicin causes respiratory effects. Inhalation of a low dose (100 mM) induces, in man, an increase of ventilatory drive (Maxwell *et al.*, 1987), while a higher dose causes bronchoconstriction and coughing (Collier & Fuller, 1984; Fuller *et al.*, 1985). Stimulation of capsaicin-sensitive fibres may be involved in all these effects. In this study, capsaicin was revealed as a potent agent in inducing secretion from glands of the human nasal mucosa. This observation adds support for a role for capsaicin-sensitive sensory neurones, which innervate the nasal mucosa and contain a peptide transmitter, in protective actions (dilution and removal of noxious agents), and possibly in the pathogenesis of diseases characterized by abnormal secretion, such as allergic and vasomotor rhinitis (Noruma & Matsuura, 1972; Konno & Togawa, 1979).

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