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Capsaicin inhalation in man and the effects of sodium cromoglycate

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1 The inhalation of capsaicin for 1 min, delivered as an aerosol by nebulising solutions of capsaicin at concentrations of 2–65 μmol l^{-1}, caused dose-dependent coughing in normal volunteers and subjects with mild asthma. Capsaicin did not cause a feeling of breathlessness, and had no effect on forced expiratory volume in 1 s (FEV_1) measured at the 1st, 5th and 9th min after the challenge was completed.

2 Coughing started within seconds of applying the face mask, continued throughout the minute of capsaicin inhalation, and stopped within seconds of the mask being removed. In any one subject the number of coughs was reproducible when repeated on the same day or after an interval of several days.

3 Experiments using local anaesthesia applied to the buccal mucosa or larynx indicated that the cough was caused by the stimulation of capsaicin-sensitive nerve terminals situated in the larynx.

4 Cough response was not altered by the prior inhalation of sodium cromoglycate.

Introduction

When capsaicin, the active ingredient of various species of capsicum, is applied to the skin (Jancso *et al.*, 1968) or buccal mucosa (Szolczanyi, 1977) it causes a sensation of pain and burning followed by a period of local desensitization. Studies in animals suggest that the drug produces its effect by stimulating non-myelinated sensory nerves (Coleridge *et al.*, 1965; Szolczanyi, 1977), and that desensitization probably occurs as these nerves become depleted of substance P (Lembeck & Holzer, 1979). Animal studies also suggest that capsaicin-induced activation of such nerves is attenuated by prior treatment with sodium cromoglycate (SCG) (Dixon *et al.*, 1980). Recent reports indicate that fibres containing substance P are present in human airways (Lundberg, Martling & Saria, 1983) and it has been suggested that these nerves might contribute to the pathophysiology of bronchial asthma (Lundberg & Saria, 1983). If this is so then blockade by SCG might account for some of the effects of SCG in patients with asthma.

In this investigation we have studied the effects of repeated inhalation of capsaicin in man and ascertained whether these effects can be blocked by inhalation of SCG.

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Methods

Studies were performed in healthy volunteers or subjects with mild asthma who had not taken any medicines for at least 24 h. The investigation, for which subjects gave their informed consent, had local ethical committee approval. The study comprised two sections; in the first, experiments were performed to identify the response to inhaled capsaicin; in the second, experiments aimed to assess whether the response could be modified by SCG.

Effect of inhaled capsaicin on cough and FEV_1

Tests of respiratory function were made with the subject seated in a chair. Capsaicin (Sigma; mol. wt. 305), dissolved in dimethyl sulphoxide (DMSO; BDH) and diluted in saline, or DMSO alone in saline, were nebulised using a Minineb nebuliser driven by compressed air at 10 psi. Subjects inhaled the mist (particle size 2–10 μm) for 1 min through the mouth via a face mask. During this period subjects were asked to breath at their normal rate and depth. The concentration of capsaicin in the original solution ranged from 2–65 μmol l^{-1}; the maximum concentration of DMSO was 0.2%. In any one study subjects were challenged with at least two doses of capsaicin and on at least two occasions with vehicle. The order in which capsaicin or DMSO was

presented to the subject was determined by one investigator and neither the subject nor the second investigator (who recorded the responses) knew of the nature or dose of the inhaled material. Challenges were repeated every 10 min. The number of times the subjects coughed during the minute of challenge was counted by the second investigator who also measured the subject's forced expiratory volume in 1 s (FEV_1) 1 min before, and then at 1, 5 and 9 min after the end of the challenge using a dry wedge spirometer (Vitalograph). In four experiments heart rate was also measured before and after challenge. In four subjects the challenges were repeated before and after the subjects sucked a benzocaine lozenge (5 mg) to produce buccal anaesthesia. In two further subjects challenges were repeated before and after the application of lignocaine (4 ml of 4% solution) to the pharynx by spray, and to the vocal cords by applying 2 ml of a 4% solution and 2 ml of a 2% solution under direct vision using a fibreoptic bronchoscope. In three studies selected challenges with capsaicin were inhaled through the nose.

Effect of sodium cromoglycate on capsaicin-induced cough

Using the same challenge protocol as outlined above, five subjects (one of whom was asthmatic) inhaled either capsaicin or vehicle through the mouth before and after the inhalation of SCG. After obtaining a control dose-response relationship to capsaicin, subjects inhaled the contents of either two SCG capsules (total 40 mg) or two matching placebo capsules. The material was inhaled from a spinhaler attached to a Fleisch Head through which air flow was measured by a mercury NRl flow pressure recorder. The subjects inhaled the powder at an inflow rate of 100 l min^{-1}; a level achieved after training. Five minutes after inhaling the SCG or placebo the subjects received their first rechallenge with either capsaicin or vehicle, and challenges were repeated at 10 min intervals until a second dose-response curve was produced. At 30 and 60 min after the inhalation of SCG (or placebo) 10 ml of blood was taken for estimating the plasma concentration of SCG by means of a radioimmunoassay technique (Fuller & Collier, 1983a). The order of administration of SCG or placebo was randomized and double-blind. Studies were carried out on two separate occasions separated by not less than 48 h.

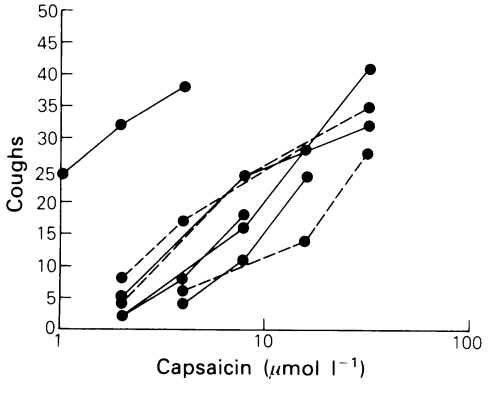

Figure 1 Log dose-response curve relating the number of coughs occurring during the minute of inhalation of capsaicin (vertical scale) with the concentration of capsaicin in the nebulised solution (horizontal scale). The curves from eight subjects are shown; interrupted lines are those from mild asthmatics.

Results

Effect of inhaled capsaicin on cough and FEV_1 and heart rate

A 1 min inhalation of capsaicin derived from solutions containing 4–65 μmol l^{-1} caused coughing in all of 17 subjects (13 non-asthmatic, 4 asthmatic). The number of coughs was dose-dependent (see Figure 1), continued throughout the whole minute of the challenge, and then stopped within seconds of removing the face mask. In any one subject the number of coughs for any given dose was reproducible there being no evidence of desensitization either acutely, (see Figure 3) or when the challenge was repeated after an interval of several days. The cough pattern varied from subject to subject; in some, coughs came singly, in others they came in volleys of 2, 3 or 4. In the group as a whole there was a four fold range in sensitivity to capsaicin (Figure 1) with the sensitivity of the asthmatic subjects falling in the centre of the range. DMSO had no effect in 15 subjects but caused coughing in two, the cough number being equal to that seen with the lowest dose of capsaicin for each subject.

The inhalation of capsaicin caused no change in FEV_1. No subject reported any feeling of shortness of breath, most subjects noticed a warm sensation in the mouth and two reported retrosternal pain.

All three subjects in whom the capsaicin challenge was delivered through the nose developed cough. In two, cough number fell with repeated challenge, and this was associated with rhinorrhoea. In the third, who did not develop rhinorrhoea, cough number was maintained with each challenge. In all three subjects a change to the same dose of capsaicin inhaled through the mouth was associated with an increased cough count. In no subject did FEV_1 alter in response to nasal challenge.

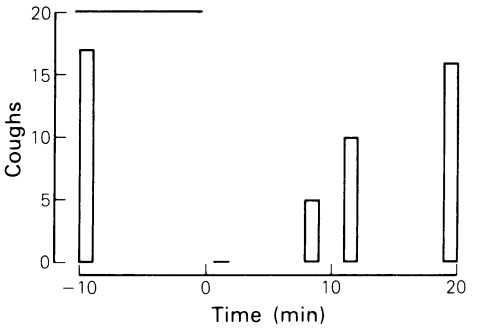

Figure 2 The effect of lignocaine applied to the pharynx and larynx (indicated by horizontal line) on the cough response to repeated inhalations of a fixed dose of capsaicin in one subject. Lignocaine, which was applied under direct vision using a fibroptic bronchoscope, abolished the response to capsaicin challenge at 1 min, but the response had gradually returned after 20 min.

There was no change in the heart rate in response o capsaicin in the four subjects in which it was ·ecorded.

Effect of local anaesthesia on cough response

In the three subjects tested, local anaesthesia of the nouth and pharynx had no effect on the cough ·esponse to capsaicin challenge. In all three subjects he anaesthesia was sufficient to prevent the normal ɔuccal sensation of capsaicin.

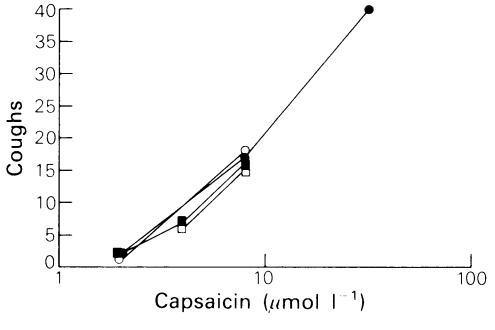

Figure 3 Log dose-response curves in one subject relating the dose of capsaicin (horizontal scale), to the number of coughs (vertical scale) produced over the minute of inhalation during two controlled challenges (■, ●) and then during challenges after placebo (□) or sodium cromoglycate (○). It can be seen that the response to capsaicin is highly reproducible and unaffected by SCG.

In the two subjects in whom local anaesthesia was applied to the pharynx and vocal cords, the response to subsequent challenge by capsaicin was abolished. Neither of these subjects reported dyspnoea. The response returned at different rates for the two subjects, in one it was restored by the 20th min after applying the anaesthesia (Figure 2), while in the second it was still reduced compared to control at the 30th min.

Effect of sodium cromoglycate on capsaicin-induced cough

The inhalation of SCG had no effect on the cough response to capsaicin (see Figures 3 and 4). The results in Figure 3, which come from repeated studies in a single subject, show that the cough response is highly reproducible, both in a single study (before and after placebo) and after an interval of days (the initial inhalation on the two occasions). It also shows clearly the failure of SCG to shift the capsaicin dose-response curve. The results shown in Figure 4 are for the group as a whole and show that for any one dose neither cromoglycate nor placebo significantly altered the response to capsaicin.

The plasma concentration of SCG 30 min after SCG inhalation varied between 5–17 mg ml^{-1}, and 60 min after 1.5–13 mg ml^{-1}. By extrapolation the dose of SCG to reach the airways would have been 0.4–2.7 mg (Fuller & Collier, 1983a).

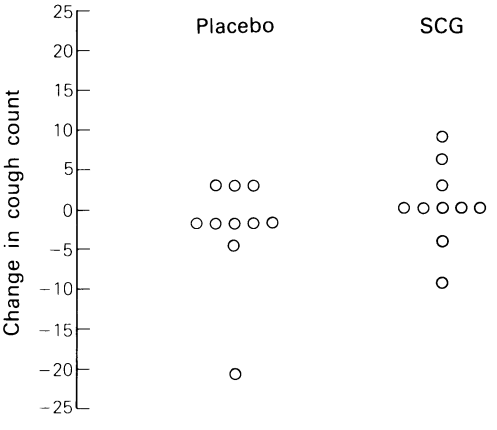

Figure 4 Change in the number of coughs produced by capsaicin when comparing the control responses to those occurring after intervention with either placebo or sodium cromoglycate (SCG). Five subjects were studied, each received 20 control inhalations of capsaicin and 20 post-intervention inhalations (10 after placebo, 10 after SCG).

Discussion

The results of this study show that the inhalation of capsaicin by man causes cough and that in any one subject the number of coughs caused by a particular dose is reproducible. There was no evidence of acute desensitization, nor of densensitization occurring over longer periods as the same response occurred when subjects were challenged at intervals of several days. Coughing, whether it presented as single coughs or as volleys, occurred throughout the minute of inhalation with no evidence of clustering at any one time through the challenge. The cough had always stopped within 10 s of removing the face mask. There was a four fold variation in cough sensitivity to capsaicin for the group as a whole, but the asthmatic subjects showed no evidence of hypersensitivity, their cough response falling almost exactly in the middle of the range (see Figure 1).

The results of the local anaesthetic studies, and the studies in which the subjects breathed through the nose, indicate that the site of stimulation for the cough response is in the region of the vocal cords. The fall in cough number in those subjects challenged via the nose who subsequently developed rhinorrhoea probably results from trapping of the drug in the nasal secretions and not therefore reaching the larynx. The abolition of the cough response by anaesthesia of the vocal cords, and the immediacy of onset and offset of the response, strongly suggest that the effect of capsaicin is mediated through a nervous mechanism. An alternative possibility is that capsaicin-induced cough is secondary to oedema, as has been reported in the rat trachea (Lundberg & Saria, 1983); however, if oedema were the primary cause of cough one might expect a greater latency of the response.

None of the subjects in the present study developed feelings of breathlessness during inhalation of capsaicin. It was not practical to measure FEV_1, during exposure to capsaicin at a time when the subjects were coughing, but measurements 1, 5 and 9 min after the challenge was completed showed no evidence of bronchoconstriction. It would have been difficult to detect bronchoconstriction limited to the period of inhalation. However, such a brief response would be very unusual since in our hands falls in FEV_1 in response to the inhalation of agents such as sulphur dioxide, histamine, mist, and antigen are detectable at least a minute after the challenge has been removed. If the effects of capsaicin result from direct stimulation of afferent nerves these results suggest that there must be a dissociation between the nerves that subserve cough, and those that control the airways calibre. Previously it has been assumed that the two reflexes were more closely associated. We have also reported a dissociation of the two effects in response to inhalation of distilled water (Fuller & Collier, 1983b).

In animal studies demonstration of a response to capsaicin has been used to indicate the presence of C-fibres. Such fibres have been found in human airways by some workers (Lundberg & Saria, 1983) but not by others (Laitinen *et al.*, 1983); this study strongly suggests that such nerves are present in the larynx. C-fibres have also been found in the larynx of the cat (Boushey *et al.*, 1974). The present study suggests that in man, C-fibre stimulation leads to cough. Animal studies however have not revealed this response but this could be because in all instances the animals were anaesthetized and in some the animals were given morphine and/or intubated via the trachea. In animals C-fibre stimulation leads to bronchoconstriction (Russell & Lai-Fook, 1979; Delpierre *et al.*, 1981; Coleridge *et al.*, 1982). This does not appear to be the response in man. It might be that to cause bronchoconstriction C-fibres sited lower in the airways need to be stimulated and that in the present study these were protected from exposure by the laryngeal 'guard'. The experimental design of the animal studies (Delpierre *et al.*, 1981; Coleridge *et al.*, 1982; 1983) would have tended to direct the capsaicin to sites in the lower airways.

The reproducibility of the cough response to capsaicin is of interest as it is at variance with the reports of tachyphylaxis seen when the drug is applied to the skin (Jancso *et al.*, 1968), or buccal mucosa (Szolczanyi, 1968) of man, or the tracheal surface in rat (Lundberg & Saria, 1983). It may be that tachyphylaxis is not a property of pulmonary 'C'-fibres as it was not reported to occur in the pulmonary fibres in dog (Coleridge *et al.*,1964). Alternatively it may be that the doses of capsaicin reaching the larynx in the present study were below the threshold concentration to produce such an effect. In general, tachyphylaxis is a dose-dependent phenomenon and in the present study the total dose to reach the airways would have been only 0.14–2.6 mmol as derived from calculations based on the results of pharmacokinetic studies of agents nebulised in the same way as in this study (Fuller & Collier, 1983b).

Assuming C-fibres to be present, animal investigations would suggest that their stimulation by capsaicin could be blocked by SCG (Dixon *et al.*, 1980). However, the present investigation failed to show such blockade. Care was taken to deliver the SCG to the upper airways by causing the subjects to inhale the drug at a relatively slow flow rate of $100\,l\,min^{-1}$, and from measurements of the concentration of SCG in the blood it would certainly appear this was achieved since the blood levels in this study were lower than those that occur when the drug is inhaled at $150\,l\,min^{-1}$ (Fuller & Collier, 1983a). At the slower rate the powder would be deposited preferen-

tially in the upper airways and larynx from which absorption into the blood is likely to be poor. It might be argued that the failure to reveal SCG-blockade of capsaicin was because we used these lower flow rates which result in less SCG reaching the airways. However, from earlier studies these local levels are certainly sufficient to block the response to inhaled mist (Fuller & Collier, 1983b), it might therefore be that the C-fibres of the human larynx are relatively insensitive to the blocking action of SCG.

The results of this study clearly raise important issues concerning the distribution, sensitivity and clinical role of C-fibres in human airways. In addition capsaicin provides a means by which some of these variables can be studied in more detail.

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