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Prostaglandin $F_{2\alpha}$ enhancement of capsaicin induced cough in man: modulation by beta$_2$ adrenergic and anticholinergic drugs

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Abstract

The effect of inhaled prostaglandin (PG) $F_{2\alpha}$ on the response to the inhaled tussive agent capsaicin was investigated in normal subjects. Seven subjects inhaled three breaths of four doses of capsaicin (0·3, 0·6, 1·2, and 2·4 nmol) before and immediately after inhaling $PGF_{2\alpha}$ (0·1 μmol) or placebo (0·15M NaCl) on separate days. The numbers of capsaicin induced coughs were greater after $PGF_{2\alpha}$ (mean 42·3 coughs) than after 0·15M sodium chloride (30·1). Visual analogue scores (0–10 on a 10 cm continuous scale) showed that capsaicin was more irritant after $PGF_{2\alpha}$ than after saline. Total respiratory resistance (Rrs), measured by the forced oscillation technique, was unaltered throughout the study. A double blind, placebo controlled study of the effects of inhaled salbutamol (200 μg, 0·6 μmol) and ipratropium bromide (40 μg, 0·1 μmol) on cough induced by capsaicin (2·4 nmol) and by $PGF_{2\alpha}$ (0·1 μmol) and on $PGF_{2\alpha}$ augmented, capsaicin induced coughing was performed in seven subjects. Neither drug had any effect on capsaicin induced coughing. Salbutamol reduced coughing due to $PGF_{2\alpha}$ (mean 7·7 coughs after salbutamol, 9·3 after placebo) but ipratropium bromide did not (mean 6·9 coughs after ipratropium bromide, 6·6 after placebo). Salbutamol also inhibited the augmentation of the capsaicin induced cough that followed inhalation of $PGF_{2\alpha}$ (mean augmentation 1·9 coughs after salbutamol, 4·1 after placebo), whereas ipratropium bromide did not (augmentation 1·7 coughs after ipratropium bromide, 2·7 after placebo). No changes in Rrs were seen after $PGF_{2\alpha}$ or either drug. Thus salbutamol reduces $PGF_{2\alpha}$ induced cough and the augmentation of capsaicin induced cough that follows $PGF_{2\alpha}$.

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Cough frequently accompanies disorders of the airways such as asthma, chronic bronchitis, and upper respiratory viral infections.[1] The precise abnormality in the cough response is not known, but presumably there is an increased sensitivity of laryngeal and airway cough receptors to cough provoking stimuli. For example, a viral upper respiratory infection in normal subjects leads to a reduction in the threshold dose of a tussive agent such as citric acid that produces coughing.[2] Inflammatory mediators released within the airways may increase the sensitivity of cough receptors. One group of mediators, the prostaglandins, has recently been implicated as sulindac, a cyclooxygenase inhibitor, inhibits the cough induced by the angiotensin converting enzyme inhibitor captopril.[3]

To explore the role of inflammatory mediators in cough sensitisation further, we determined whether prostaglandin (PG) $F_{2\alpha}$, a cyclooxygenase product that activates airway sensory nerves, could enhance the cough response in normal subjects. We used inhaled capsaicin, the active ingredient of red pepper, as the tussive agent. Capsaicin stimulates airway sensory nerves, such as non-myelinated C fibres, to induce cough,[4] an effect that is inhibited by the local anaesthetic agent lignocaine.[5] Because cough is a feature of asthma, and because salbutamol, a beta adrenergic agonist, and ipratropium bromide, an anticholinergic agent, are used to treat asthma, we investigated the effects of these agents to see whether they modified any increase in capsaicin induced cough produced by $PGF_{2\alpha}$.

Methods

SUBJECTS

Eleven healthy, non-smoking subjects (mean age 29, range 19–37 years; three female) with no previous history of lung or heart disease gave informed consent for the study, which was approved by the National Heart and Lung Hospital's ethics committee. Subjects were naive and had not previously taken part in studies on cough. They were told the general nature of the study but not its exact purpose. Seven subjects took part in each study, three subjects taking part in both. All subjects had been free of upper respiratory tract infections for at least four weeks and had no spontaneous coughing. None was taking any medication, except for the contraceptive pill.

COUGH CHALLENGE PROCEDURES

Capsaicin (Sigma Chemical Company, Poole) was dissolved in absolute alcohol to make a stock solution of $3·6 \times 10^{-3}$ mol/l, which was stored at −20°C. This solution was diluted with 0·15M sodium chloride solution to make solutions of 45, 90, 180, and 360 μmol/l for inhalation for study 1. Subjects inhaled a single breath of each concentration of capsaicin in random order every minute and the challenge was repeated three times, so that 12 single

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challenges with capsaicin were performed. Each of the three runs was performed in the same order. Aerosols were delivered from a jet nebuliser attached to a breath actuated dosimeter (MEFAR, Brescia, Italy), which was set to trigger for 1·0 second at a pressure of 1·5 kg/cm^2. The output of the nebuliser was 7·7 μl a breath; this produces particles with a mass mean diameter of 3·5 μm. Each breath was taken over five seconds, the subject inhaling from functional residual capacity to total lung capacity. The number of resulting coughs was counted by an independent observer. A visual analogue score was obtained after each inhalation, subjects being asked to evaluate the perceived intensity of the burning retrosternal sensation on a 10 cm straight line, taking 0 as indicating no detectable sensation and 10 the worst imaginable intensity. For study 2 only the highest concentration of capsiacin was used (360 μmol/l), and the capsaicin cough challenge was shortened to consist of four consecutive inhalations at one minute intervals.

$PGF_{2\alpha}$ (Upjohn, Crawley) was nebulised at a concentration of 5 mg/ml (14·9 mmol/l) from the nebuliser-dosimeter system that was used for the capsaicin challenges. Salbutamol (Allen and Hanbury, Greenford) and ipratropium bromide (Boehringer Inngelheim, Bracknell) were delivered from metered dose inhalers.

MEASUREMENT OF RESPIRATORY RESISTANCE (RRS)

Total respiratory resistance was measured by the forced oscillation technique with an Oscillaire (Jones Instruments Company, Chicago) according to the method of Landser *et al.*[6] The seated subject was asked to breathe quietly on a mouthpiece connected to a screen pneumotachograph while supporting his cheeks with the palms of his hands. Oscillations at regular frequencies were generated by a loudspeaker and superimposed during tidal breathing. Two identical differential pressure transducers (Validyne PM5) were used to measure mouth pressure and flow across the pneumotachograph. A Fourier analysis of the pressure and flow signals at the mouth yielded mean Rrs values measured over 16 second periods. The superimposed signal consisted of a frequency spectrum of 4–52 Hz in steps of 2 Hz. As Rrs measured at 6 Hz appeared to be the most sensitive for recording change in airway calibre in normal subjects, only Rrs measured at this frequency is reported. For each measurement of Rrs we used the mean of three consecutive measurements obtained over 4–5 minutes.

PROTOCOL

Study 1

We determined the effect of $PGF_{2\alpha}$ (one breath of 5 mg/ml) on capsaicin induced cough in a randomised, double blind, placebo controlled study. Subjects attended on two days, respiratory resistance (Rrs) being measured by the forced oscillation technique on each day, followed by a capsaicin cough challenge. One minute later subjects inhaled one breath of nebulised $PGF_{2\alpha}$ (5 mg/ml in nebuliser) or 0·15M sodium chloride solution (placebo), followed one minute later by a repeat capsaicin cough challenge. Rrs was measured after the final challenge.

Study 2

We next determined the effect of inhaled salbutamol and ipratropium bromide respectively on the increase in capsaicin induced cough produced by $PGF_{2\alpha}$ in two randomised, double blind, and placebo controlled studies that were otherwise identical. Each study consisted of two visits at which Rrs was measured, followed by a capsaicin challenge. Rrs was measured again, and followed by inhalation of salbutamol 200 μg (0·6 μmol) or ipratropium 40 μg (0·1 μmol), both administered by metered dose inhaler via a holding chamber (Volumatic), or matched placebo. Fifteen minutes after salbutamol or 45 minutes after ipratropium bromide Rrs was again recorded, followed by a further capsaicin challenge. One minute later a single inhalation of $PGF_{2\alpha}$ (5 mg/ml in nebuliser) was given, followed after a further minute by a third and final capsaicin challenge and Rrs measurement.

DATA ANALYSIS

Study 1

Mean cough counts and visual analogue scale scores for the three inhalations at each dose of capsaicin were calculated and analysed by means of Friedman's two factor analysis of variance by rank to establish the presence of a dose-response relationship for capsaicin. The total number of coughs and the visual analogue scale score for each subject were compared before and after inhalation of placebo and $PGF_{2\alpha}$ by Wilcoxon's paired test. Changes in Rrs were analysed by Student's paired *t* test.

Study 2

Results were analysed on the basis of the total number of coughs produced by each set of four inhalations of capsaicin 360 μmol/l. The number of capsaicin induced coughs before treatment, after treatment, and after $PGF_{2\alpha}$ inhalation were compared by means of Freidman's two way analysis of variance by rank. The increases from the post-$PGF_{2\alpha}$ number of coughs to the post-treatment number of coughs were compared between drug and placebo days by Wilcoxon's paired test. Changes in Rrs were analysed by using analysis of variance for repeated measures.

Results are expressed as means with standard errors in parentheses. A p value of less than 0·05 was considered to be significant.

Results

STUDY 1: EFFECT OF $PGF_{2\alpha}$ ON CAPSAICIN INDUCED COUGH

Capsaicin caused a dose related increase in cough on the two study days before inhalation of placebo or $PGF_{2\alpha}$ (fig 1).

After placebo (0·15M sodium chloride solution) there was a small but significant decrease in the cough response to capsaicin at inter-

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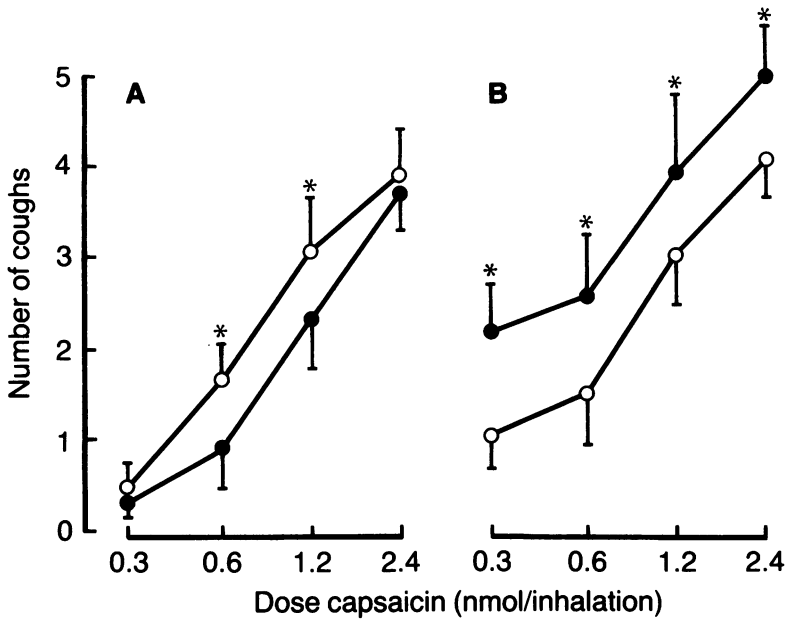

Figure 1 Cough responses to four doses of capsaicin before (○) and after (●) inhaled placebo (panel A) and $PGF_{2\alpha}$ (panel B) in seven normal subjects. The mean (SEM) number of coughs is shown at each dose. Numbers of cough were significantly increased after $PGF_{2\alpha}$ ($p < 0.05$) at all doses.

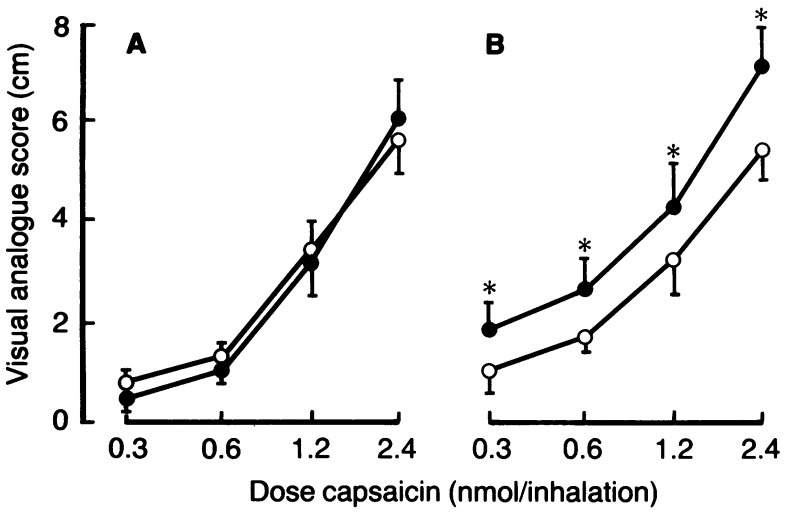

Figure 2 Subjective evaluation of the burning retrosternal sensation induced by inhaled capsaicin as measured on a visual analogue scale (VAS): mean (SEM) responses to four doses of capsaicin before (○) and after (●) inhaled placebo (panel A) and $PGF_{2\alpha}$ (panel B) ($n = 7$). The VAS score was increased after $PGF_{2\alpha}$ ($p < 0.05$) at all doses, whereas placebo had no effect.

Total respiratory resistance (Rrs (mean (SEM)), cm $H_2O.l^{-1}.s$) measured by the forced oscillation technique in seven normal subjects on drug and placebo days for salbutamol and ipratropium bromide studies

Day	*Baseline*	*Before drug*	*After drug*	*After PGF_2*
SALBUTAMOL				
Placebo	2·50 (0·33)	2·63 (0·29)	2·44 (0·23)	2·98 (0·42)
Active	2·56 (0·25)	2·82 (0·45)	2·49 (0·47)	2·78 (0·66)
IPRATROPIUM				
Placebo	2·60 (0·27)	2·72 (0·30)	2·24 (0·14)	2·34 (0·18)
Active	2·31 (0·20)	2·30 (0·18)	2·07 (0·20)	2·16 (0·19)

No significant changes occurred within or between days.

mediate doses. The response was similar on the two study days.

After inhalation of $PGF_{2\alpha}$ all subjects reported a sense of irritation retrosternally, which persisted for up to one hour. Visual analogue scale scores increased significantly on the $PGF_{2\alpha}$ day (mean 4·0 cm after $PGF_{2\alpha}$, 2·8 cm after placebo; $p < 0.05$) but were not reduced when the capsaicin challenge was repeated on the placebo day (fig 2). This was more prolonged and qualitatively different from that caused by capsaicin. The cough response to capsaicin was increased after inhalation of $PGF_{2\alpha}$ by comparison with baseline responses on the same day ($p < 0.05$) or with the response after 0·15M sodium chloride on the placebo day ($p < 0.01$)—see figure 1. $PGF_{2\alpha}$ caused no significant change in Rrs, which was 2·2 (0·3) before and 2·3 (0·2) cm $H_2O.l^{-1}.s$ after $PGF_{2\alpha}$. Inhaling $PGF_{2\alpha}$ produced a mean of 5·9 coughs, compared with 0·1 with 0·15M sodium

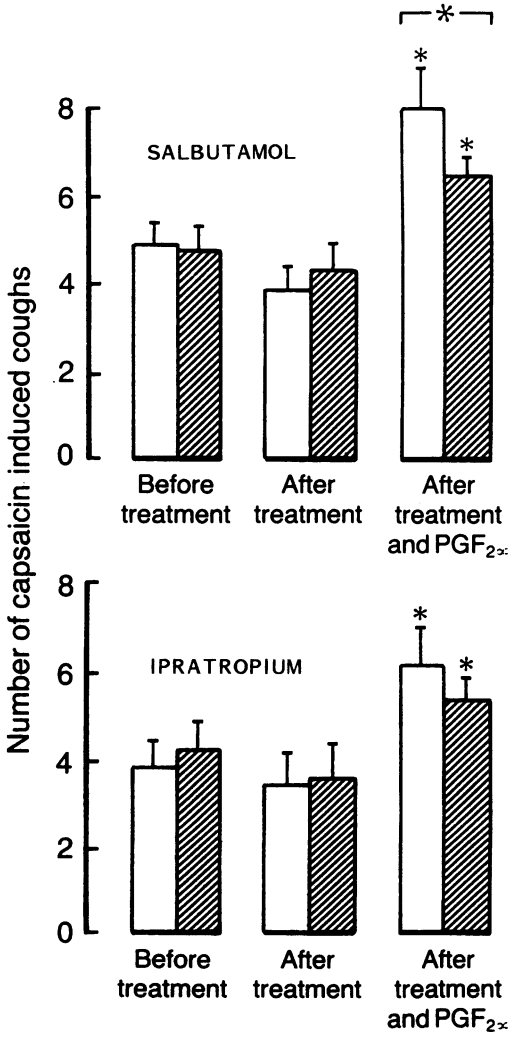

*Figure 3 Effect of salbutamol (upper panel) and ipratropium (lower panel) on capsaicin induced cough. The open bars indicate measurements on the placebo day and hatched bars on the treatment day (salbutamol or ipratropium). *$p < 0.05$ by comparison with before and after treatment. Salbutamol but not ipratropium caused a significant inhibition of $PGF_{2\alpha}$ augmentation of capsaicin induced cough.*

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chloride; the coughs occurred within the first 30 seconds of inhalation.

STUDY 2: EFFECT OF TREATMENT

Salbutamol

Salbutamol did not inhibit capsaicin induced cough. There was a reduction in cough due to $PGF_{2\alpha}$ following salbutamol compared with placebo (7·7 and 9·3 respectively; $p < 0·05$). $PGF_{2\alpha}$ potentiated capsaicin induced cough, the mean number of coughs increasing from 3·9 to 8·0 ($p < 0·01$) on the placebo day. Salbutamol caused a partial inhibition of this increase ($p < 0·05$)—figure 3. The mean increase in coughs after $PGF_{2\alpha}$ was 2·18 (95% confidence interval 0·26 to 4·1) more on the placebo day than on the salbutamol day. There was no significant change in Rrs after $PGF_{2\alpha}$, salbutamol, or capsaicin (table).

Ipratropium bromide

Ipratropium bromide did not inhibit cough induced by capsaicin or $PGF_{2\alpha}$; it caused some decrease in the $PGF_{2\alpha}$ induced augmentation of capsaicin induced cough, but this was not significant (fig 3). The augmentation of cough on the placebo day was 0·75 (95% confidence interval −0·23 to 1·25) coughs more than on the ipratropium day. There was no significant change in Rrs after $PGF_{2\alpha}$, ipratropium, or capsaicin (table). The $PGF_{2\alpha}$ augmentation of capsaicin induced coughing was less on the salbutamol day than on the ipratropium day by 1·43 (95% confidence interval 0·12 to 2·27).

On the basis of changes in Rrs observed on the placebo days the study had an 80% power to detect a change in Rrs of 0·5 cm $H_2O.l^{-1}s^{-1}$ at the 5% level of significance.

Discussion

We have shown that $PGF_{2\alpha}$ augments the number of coughs induced by capsaicin in normal subjects and the subjective irritation that accompanies capsaicin inhalation. This increase in cough and irritation was not accompanied by detectable bronchoconstriction as measured by the forced oscillation technique. Salbutamol and to a lesser extent ipratropium bromide reduced both the number of coughs and the potentiation of capsaicin cough induced by $PGF_{2\alpha}$. Neither salbutamol nor ipratropium bromide affected capsaicin induced cough nor caused significant changes in airway calibre. In the first study, the mean dose-response curve for capsaicin was similar on the two days; when the challenge was repeated within 12–15 minutes, however, the response showed some degree of tachyphylaxis with the middle doses. At the highest dose of 360 μmol/l tachyphylaxis was minimal, and this dose was therefore chosen for the second study.

Capsaicin induced cough is presumed to occur through the stimulation of a neural reflex by airway sensory nerves because it is inhibited by topically administered lignocaine.[5] Inhaled capsaicin probably acts mainly on the larynx, trachea, and major bronchi, which are areas of greatest sensitivity for provocation of cough.[7,8] Although the larynx may be the initial site of cough stimulation, the sublaryngeal airways may also contribute to the response; patients who have had a laryngectomy cough when they inhale capsaicin aerosol through their tracheostomy tubes.[9] Animal studies suggest that capsaicin stimulates non-myelinated C fibre endings.[4,10]

The mechanisms by which prostaglandin $F_{2\alpha}$ aguments the cough induced by capsaicin remain speculative. PGE_2, a prostaglandin with tissue activity similar to that of $PGF_{2\alpha}$,[11] which also activates afferent C fibres,[12] can also potentiate capsaicin induced cough.[13] The augmenting effect of $PGF_{2\alpha}$ is unlikely to be secondary to bronchoconstriction because of the lack of significant changes in respiratory resistance in our study. An interesting parallel to our observation is the capacity for prostaglandins to increase pain sensitivity to other chemical mediators, such as bradykinin and histamine in the skin,[14,15] which suggests that $PGF_{2\alpha}$ may be directly sensitising capsaicin sensitive C fibres. This is supported by the increase in capsaicin induced discomfort observed after $PGF_{2\alpha}$ inhalation.

Augmentation of the cough reflex occurs in various clinical contexts. It was therefore of particular interest to study at doses used clinically the effect of salbutamol and ipratropium bromide on the augmentation of the cough response. Although neither salbutamol nor ipratropium bromide was effective in inhibiting capsaicin induced cough, salbutamol partially but significantly reduced the enhanced cough response seen after $PGF_{2\alpha}$. Ipratropium caused a small but non-significant effect. This apparent difference between the two agents must be qualified in the light of the small differences found and the fact that single doses only were used; the use of higher doses may yield more effective inhibition. No changes in airway tone were detectable by our measurements of respiratory resistance. Possibly we have missed a bronchodilator effect, but only small falls in resistance have been previously recorded after isoprenaline and atropine in normal subjects by the forced oscillation technique.[16] We cannot exclude the possibility that a small decrease in airway tone caused by salbutamol could have contributed to its antitussive effect. Whether the inhibition of $PGF_{2\alpha}$ induced cough and of $PGF_{2\alpha}$ augmentation of cough by salbutamol are mediated through the same mechanism is not known. Another possibility is that beta agonists, by raising intracellular cyclic AMP, reduce the access of $PGF_{2\alpha}$ to epithelial paracellular spaces, where cough receptors are situated.[17] Other effects may be mediated through epithelial transport systems and on secretory processes in the glands and epithelium.[18,19] Salbutamol may therefore be more effective than ipratropium in reducing the augmented cough state in the airways. Our results are compatible with the effectiveness of beta adrenergic agonists in inhibiting the increased cough response after upper respiratory tract infections,[2] during fibreoptic bronchoscopy,[20] and during exacerbations of allergic asthma.[21]

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