Bronchoconstrictor response to inhaled capsaicin in humans

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FULLER, RICHARD W., CAROLINE M. S. DIXON, AND PETER J. BARNES. *Bronchoconstrictor response to inhaled capsaicin in humans.* J. Appl. Physiol. 58(4): 1080–1084, 1985.—The effect of inhaled capsaicin, the irritant extract of pepper, on airway tone has been studied in humans. Inhaled capsaicin (2.4×10^{-10} and 2.4×10^{-9} mol) caused a dose-dependent fall in specific airways conductance (maximum fall 28 ± 19 and 38 ± 19%, respectively; means ± SD, $n = 17$). This was maximal within 20 s of exposure and lasted for < 60 s. There was no difference in the magnitude or duration of bronchoconstriction between normal, smoking, or asthmatic subjects. Capsaicin also caused coughing and retrosternal discomfort. On repeated exposure to capsaicin, there was no evidence for a reduced response (tachyphylaxis). Ipratropium bromide (0.25 mg by inhalation) significantly ($P < 0.05$) reduced the bronchoconstriction (maximum falls 34 ± 14 and 15 ± 9% after saline and ipratropium bromide, respectively; means ± SD $n = 6$), indicating that it was dependent on a cholinergic vagal reflex rather than on local release of substance P from nerves in the airway. Inhaled sodium cromoglycate (10 mg by nebulizer or 40 mg as a dry powder), however, had no significant effect on the bronchoconstrictor response. Capsaicin may be a useful tool for investigating nonmyelinated nerve reflexes in human airways.

asthma; C-fibers; cigarette smoking; reflex bronchoconstriction; substance P

SEVERAL SUBSTANCES which stimulate nonmyelinated fibers in animals, such as sulfur dioxide (21), bradykinin (22), histamine, and prostaglandin $F_{2\alpha}$ (4), cause bronchoconstriction in humans (3, 15, 16, 26), although this may not be their exclusive mode of action. Stimulation of nonmyelinated airway afferent nerves (C-fibers) in animals causes bronchoconstriction (6, 9, 21) and increased secretion of mucus (8) by activation of vagal reflex pathways. Recently, histochemical studies have shown that in animals these nonmyelinated pulmonary nerve fibers contain substance P (18), which can cause bronchial smooth muscle contraction (12) as well as airway mucosal edema (13).

Capsaicin, the hot extract of pepper, stimulates C-fibers in animals (5, 27) and causes the release of substance P from sensory nerve terminals (28). In animal models, capsaicin causes airway smooth muscle contraction both by stimulating a vagal reflex (9, 21) and by the release of substance P (12, 28). The latter response is subjected to tachyphylaxis (12) and is inhibited by a substance P antagonist (14). In isolated human airways, capsaicin causes contraction that is subjected to tachyphylaxis and similar to that caused by substance P (12). A previous study in humans has shown that the inhalation of capsaicin causes a dose-dependent cough, probably due to stimulation of laryngeal nerve endings but no change in forced expiratory volume at 1 s (FEV_1) (7). This contrasts with the capsaicin-induced bronchoconstriction in animals in vivo (9, 26) and contraction of human bronchial smooth muscle in vitro (12). We have now studied the effect of inhaled capsaicin on specific airway conductance (sGaw), a more sensitive measure of airway caliber, in healthy subjects, cigarette smokers, and asthmatic subjects.

MATERIALS AND METHODS

Subjects. Seven normal, five mild asthmatic, and five subjects who smoked cigarettes gave informed consent to take part in the studies, which had the approval of the hospital ethical committee. Subjects were aged 22–48 yr (mean 30), and seven were female (Table 1). Base-line sGaw was within the normal range for all subjects, apart from one asthmatic subject (*subject 11*). No subject was on regular medication, and prior to the study all were asked to refrain from caffeine-containing drinks and cigarettes for 4 h and from bronchodilators for 12 h.

Materials. A stock solution of 10^{-3} M capsaicin (Sigma, Poole, UK) in 100% ethanol was diluted in 0.9% wt/vol saline to the required concentrations of 10^{-4} and 10^{-5} M for inhalation. Ten percent ethanol in 0.9% wt/vol saline was used as the control solution. Sodium cromoglycate (SCG) (10-mg/ml solution and 20-mg capsules) (Fisons, Loughborough, UK), ipratropium bromide (IPB) (0.25 mg/ml) (Boehringer, Bracknell, UK), and placebo solution (0.9% wt/vol saline and lactose capsules) (Fisons) were used in the inhibition studies.

Drug delivery. The drugs were given by a nebulizer controlled by a dosimeter (Mefar, Brescia, Italy). The dosimeter was set to nebulize for 1 s and to deliver 0.024 ml of the solution with each breath. The mass median diameter of the particle size delivered by the nebulizer was 3.5–4.0 μm, measured by a laser beam diffraction technique.

Measurement of sGaw. Subjects sat in a constant-volume body plethysmograph and were asked to pant at a frequency of 2 Hz with a peak-to-peak flow of 2–3 l/s. The signals of box and mouth pressure and airflow were

TABLE 1. *Anthropometric details, base-line sGaw, histamine reactivity, and smoking history for 17 subjects*

Subj	Age	Sex	Base-Line sGaw, $cmH_2O^{-1} \cdot s^{-1}$	PC_{35} histamine*, $mg \cdot ml^{-1}$	Cigarettes, pack years†
1	32	M	0.18	>16	0
2	37	F	0.19	>16	0
3	37	M	0.15	>16	0
4	22	F	0.17	>16	0
5	30	M	0.16	>16	0
6	29	M	0.18	>16	0
7	25	M	0.13	>16	0
8	24	F	0.19	2.0	0
9	30	M	0.12	0.5	0
10	23	F	0.11	0.75	0
11	48	M	0.07	0.25	0
12	25	M	0.13	1.0	0
13	36	F	0.18	>16	2
14	27	F	0.20	>16	30
15	22	M	0.16	>16	3
16	31	M	0.22	>16	10
17	26	M	0.17	>16	10

sGaw, specific airway conductance. * PC_{35} histamine is provocative concentration which causes a 35% fall in sGaw. † Pack years are product of subject's daily cigarette pack consumption and no. of years that subject has smoked.

analyzed by computer (Research machines 380 Z) to give measurements of airways resistance and thoracic gas volume so that sGaw could be determined (2). The mean coefficient of variation for sequential measurements of sGaw in the same subject using this system was 10–15%.

Protocol. The initial part of the study was designed to determine the acute effects of capsaicin inhalation on bronchomotor tone. After recording six base-line measurements of sGaw, the subjects, while remaining seated in the sealed body plethysmograph, inhaled one breath of control solution. Within 10 s of this inhalation sGaw was measured, followed by five further measurements within 60 s. After a rest of 3 min a second series of base-line sGaw measurements was made before the inhalation of 2.4×10^{-10} mol capsaicin (one breath from the dosimeter), followed by a further six measurements of sGaw at 10-s intervals. This procedure was then repeated following inhalation of 2.4×10^{-9} mol capsaicin. In five subjects, sGaw was measured after five further breaths of 2.4×10^{-9} capsaicin inhaled at 1-min intervals to investigate the possibility of tachyphylaxis. The presence or absence of coughing was noted after each inhalation, and the subjects were questioned about symptoms.

In a second study the effect of treatment with inhaled IPB and SCG on the capsaicin response was determined. The study was conducted on three separate days at least 1 wk apart. The treatments were given double-blind, and the order of treatment was randomized. On each day the protocol described above was used, but 1 min after inhalation of 2.4×10^{-9} mol capsaicin, subjects inhaled 1 ml of either saline, SCG (10 mg), or IPB (0.25 mg) from the nebulizer. Thirty minutes later the subjects inhaled first control and then 2.4×10^{-9} mol capsaicin, followed by measurements of sGaw at 10-s intervals.

In a third study the effect of inhaling a higher dose of SCG (40 mg) given as a dry powder on the capsaicin response was determined. This study was conducted on two separate days 1 wk apart. The same protocol was used, except the subjects were treated with either two 20-mg capsules of SCG or two matched placebo (lactose) capsules from a spinhaler. The test drugs were inhaled at an inspiratory flow of between 0.9 and 1.2 l/s to ensure adequate dosing.

Statistical analysis. Results are expressed as means ± SD. Percent change in sGaw from base line refers to the difference between the mean of the base-line measurements of sGaw and the measurements made at 10-s intervals following the inhalation of capsaicin. The data were assessed by two-way analysis of variance, and the significance of any individual differences was determined by Student's *t* test.

RESULTS

Capsaicin caused a dose-dependent fall in sGaw in all subjects, with mean maximum falls of 14 ± 16, 28 ± 19, and 38 ± 19% after control, 2.4×10^{-10} mol, and 2.4×10^{-9} mol of capsaicin, respectively. This bronchoconstrictor response was maximal 10 s after inhalation of capsaicin, and in most subjects sGaw had returned to base-line values within 60 s (Figs. 1 and 2). There was no significant difference between the response to the inhalation of capsaicin in normal subjects, cigarette smokers, or asthmatic subjects (Fig. 3). An apparent reduction in the mean response to the high-dose capsaicin in the smokers is due to the lack of early measurements in one subject, who experienced prolonged coughing and had the largest change at 2.4×10^{-10} mol capsaicin. There

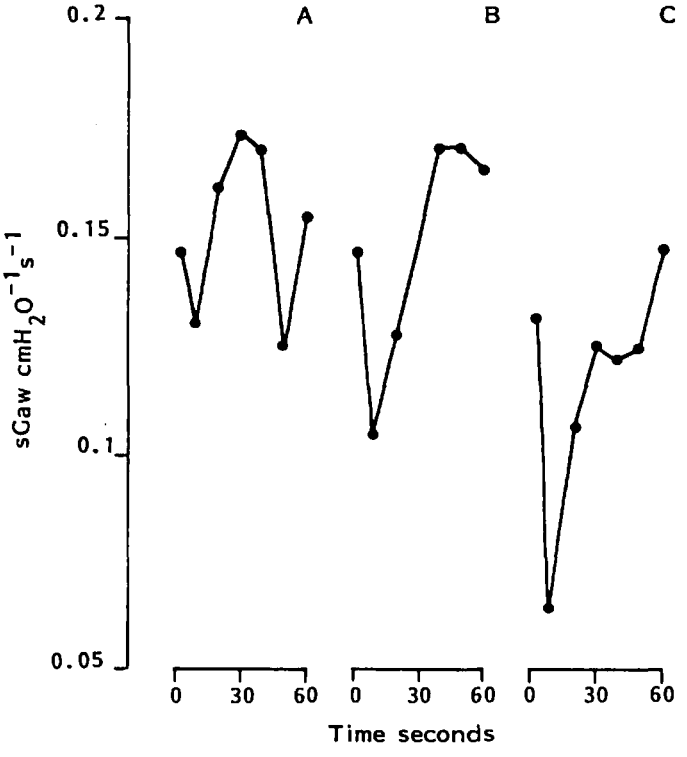

FIG. 1. Specific airway conductance (sGaw) for 1 subject (*no. 9*) after inhaling 0.024 ml of 10% ethanol (control) (*A*), 2.4×10^{-10} mol capsaicin (*B*), or 2.4×10^{-9} mol capsaicin (*C*).

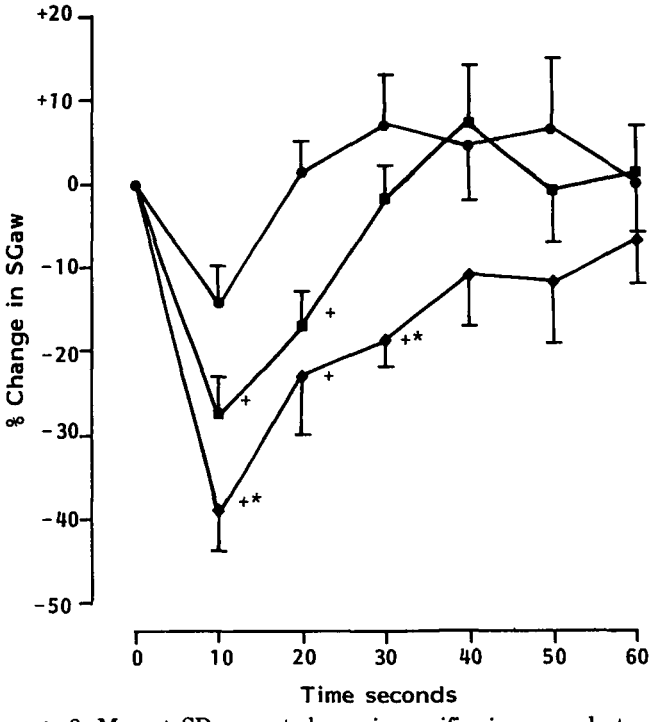

FIG. 2. Mean ± SD percent change in specific airway conductance (sGaw) for 17 subjects after inhaling 0.024 ml of 10% ethanol (control solution) (*filled circles*), 2.4×10^{-10} mol capsaicin (*filled squares*), and 2.4×10^{-9} mol capsaicin (*filled diamonds*). * Values are significantly different from control value ($P < 0.05$). + Values are significantly different from 2.4×10^{-10} mol value ($P < 0.05$).

was no significant reduction in response to 2.4×10^{-9} mol capsaicin after five inhalations (mean fall 45 ± 17 and 48 ± 19% after one breath and five breaths at 1-min intervals of 2.4×10^{-9} mol capsaicin, respectively; $n = 5$), providing no evidence for tachyphylaxis of the acute response.

Cough was reported by 5 out of the 17 subjects with 2.4×10^{-10} mol and 16 out of the 17 subjects with 2.4×10^{-9} mol of capsaicin. The severity of the coughing varied and was not effected by any of the drug treatments. All subjects reported retrosternal discomfort at the higher dose of capsaicin, the magnitude of which was also variable. There was no relationship between the severity of the cough or retrosternal discomfort and the magnitude of the fall in sGaw.

Treatment with 1 ml of nebulized saline or SCG (10 mg) did not alter base-line sGaw in any subject, however, IPB (0.25 mg) caused a mean increase in sGaw of 26%. The fall in sGaw following inhalation of 2.4×10^{-9} mol capsaicin was significantly reduced by IPB, with a mean fall in sGaw 10 s after 2.4×10^{-9} mol capsaicin of 34 ± 14% after saline compared with 15 ± 9% after IPB ($P > 0.05$) (Fig. 4*A*). There was no correlation between the change in base-line sGaw following inhalation of IPB and the reduction of capsaicin-induced bronchoconstriction. SCG (10 mg) treatment did not reduce significantly the change in sGaw caused by inhaling 2.4×10^{-9} mol capsaicin, with mean falls in sGaw of 34 ± 14 and 22 ± 29% after saline and SCG treatments, respectively. A higher dose of SCG (40 mg as dry powder) also failed to reduce significantly the effect of inhaling 2.4×10^{-9} mol capsaicin, with the mean falls in sGaw of 30 ± 18 and 36 ± 23% after lactose and SCG, respectively (Fig. 4*B*).

DISCUSSION

This study demonstrates that inhaled capsaicin causes

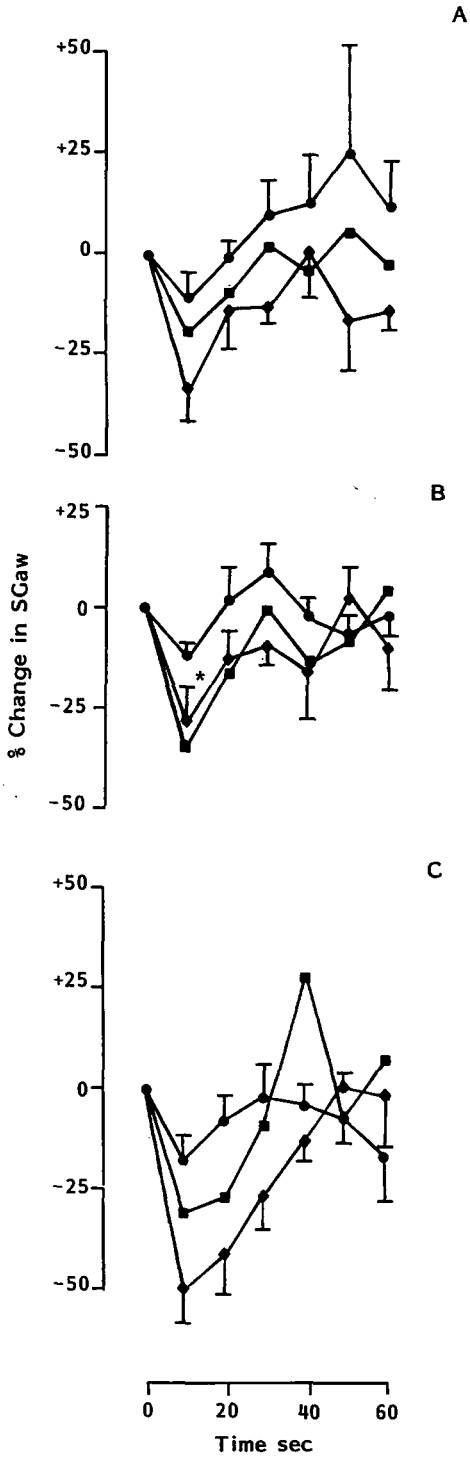

FIG. 3. Percent change in specific airway conductance (sGaw) for 5 normal subjects (*A*), 5 smokers (*B*), and 5 asthmatic subjects (*C*) after inhaling 0.024 ml of 10% ethanol (control solution) (*filled circles*), 2.4×10^{-10} mol capsaicin (*filled squares*), and 2.4×10^{-9} mol capsaicin (*filled diamonds*). * Value is mean of 4 (due to excess coughing in 1 subject).

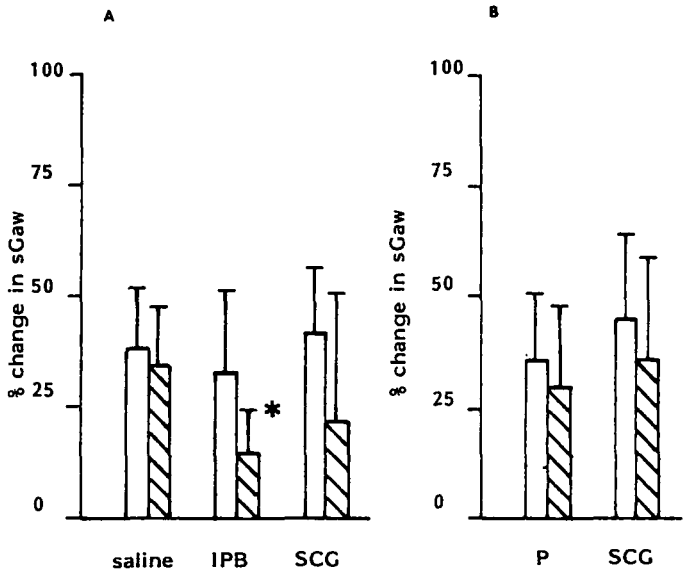

FIG. 4. *A*: means ± SD percent change in specific airway conductance (sGaw) in 6 subjects following inhalation of 2.4×10^{-9} mol capsaicin before (*open*) and after (*hatched*) saline, 0.25 mg ipratroprium bromide (IPB), and 10 mg sodium cromoglycate (SCG). * $P < 0.05$ compared with placebo. *B*: means ± SD percent change in specific airway conductance (sGaw) in 6 subjects following inhalation of 2.4×10^{-9} mol of capsaicin before (*open*) and after (*hatched*) placebo (P) and 40 mg sodium cromoglycate (SCG).

a dose-dependent bronchoconstriction, cough, and retrosternal discomfort in humans. Cigarette smokers and asthmatic subjects had a response which was similar to that of healthy subjects. The bronchoconstriction was demonstrated by a fall in sGaw which was maximal at 10 s after inhalation of capsaicin, rarely lasted for more than 60 s, and did not show tachyphylaxis either acutely or when given at 30-min intervals. This response was reduced by treatment with IPB but not statistically significant by SCG. Previously, inhalation of capsaicin has been shown to cause a dose-dependent cough, probably due to stimulation of laryngeal sensory nerves, but measurements of FEV_1 failed to detect any bronchoconstriction (7). This may have been due to the timing of the measurements, which were performed 1 min after the inhalation of capsaicin, or to the full inspiration needed to perform the measurement, which would tend to reverse the bronchoconstriction (17).

In humans the mechanism of bronchoconstriction following inhalation of capsaicin is uncertain, but possible mechanisms can be inferred from animal studies. First, capsaicin has been shown to release substance P from nerves in vitro (28), and released substance P could cause bronchoconstriction directly by activating specific receptors (12) or alternatively by release of histamine and other mediators (11). Substance P when inhaled can cause bronchoconstriction in human subjects (unpublished observations), but at the doses studied, the capsaicin-induced release of substance P in the lungs may be small. Capsaicin may also cause reflex bronchoconstriction by stimulating C-fibers accessible to both the pulmonary and bronchial circulation (9, 21). Bronchoconstriction following capsaicin inhalation could therefore be secondary either to release of substance P or to a vagal reflex. The time course of the capsaicin-induced bronchoconstriction and the 60% reduction by treatment with IPB indicate that it is, at least in part, due to a vagally mediated cholinergic reflex. However, the remaining decrease in sGaw could be due either to laryngeal constriction or to the action of released substance P. The inhibitory effect of IPB was not simply the result of bronchodilatation as there was no relationship between the bronchodilator response and the reduction in the capsaicin-induced bronchoconstriction. The bronchoconstrictor effect of capsaicin is similar in its time course to the reflex bronchoconstriction seen after stimulation of airway C-fibers in animals by parenteral capsaicin and topical bradykinin (21, 22).

It is unlikely for two reasons that capsaicin-induced coughing caused a reflex fall in sGaw. First, there is a disparity between the cough and bronchoconstriction, since there was a fall in some subjects in sGaw without cough. Second, coughing itself tends to lead to bronchodilatation (20), perhaps because of the inspiratory maneuver made before coughing (17). The site and nature of the capsaicin-sensitive receptors are not known. In a study of capsaicin-induced cough the evidence favored laryngeal receptors, as lignocaine applied to the larynx inhibited the cough. Animal studies, however, have demonstrated reflex bronchoconstriction from stimulation of C-fibers accessible to the pulmonary and bronchial circulations. Nerve fiber recordings in animals (4, 26) after capsaicin administration have demonstrated C-fiber activation, but it is uncertain whether capsaicin can also stimulate the nonmyelinated endings of myelinated fibers (25). If capsaicin were to stimulate both fiber types, then the bronchoconstriction may be expected to be more like that induced by sulfur dioxide, which stimulates both myelinated and nonmyelinated fibers of the larynx and bronchi (1, 21, 29). The time course of the bronchoconstrictor effect of inhaled capsaicin is similar to that seen after smoking a cigarette (19), which stimulates myelinated fibers in dogs (24). The effect of inhaling capsaicin was studied in regular smokers, who have a reduced bronchoconstrictor response to cigarette smoke (19), but the response to capsaicin was not reduced, indicating no loss of this reflex in smokers.

In dogs, SCG reduces the number of C-fiber impulses after stimulation by intravenous capsaicin (10), but SCG does not reduce either capsaicin-induced cough (7) or statistically significantly the bronchoconstrictor response reported in this study. This may reflect either a species difference between C-fibers or a difference in the population of fibers stimulated by capsaicin inhalation. In any case, these results suggest that inhibition of capsaicin-sensitive nerves is unlikely to be the only or primary mechanism of action of SCG in the prevention of asthma.

This study confirms that a bronchoconstrictor reflex following capsaicin stimulation reported in animals is also present in humans, although its mechanism has still to be determined. This reflex and the cough also stimulated by capsaicin may be part of a protective mechanism for the airways. The similarity between the responses in asthmatic and normal subjects means that an enhanced

capsaicin-sensitive reflex is unlikely to underlie bronchial hyperreactivity. Inhaled capsaicin in low doses may be a means of examining airway reflexes in humans; however, the associated cough and retrosternal discomfort make it unlikely that a sufficently high dose can be given to study the release of substance P in vivo.

M. Clay (Dept. of Thoracic Medicine, Royal Free Hospital, London) measured the particle size of the nebulizer output by a laser beam diffraction technique.

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