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Voluntary suppression of cough induced by inhalation of capsaicin in healthy volunteers

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The aim of the present study was to investigate the voluntary suppression of cough in response to capsaicin inhalation in healthy volunteers, and to determine if the dose–response curve to capsaicin was significantly altered when volunteers were asked to suppress their cough response. The quantification of the degree of voluntary suppression of induced cough could provide a new methodology for screening antitussive agents as antitussives may act by influencing voluntary control of cough.

Cough was induced by inhalation of capsaicin. Two challenges were given 5 min apart, each comprising five ascending concentrations of capsaicin (1×10^{-5} M– 3.33×10^{-4} M). During one of these challenges the volunteer was allowed to cough when required, and during the other they were asked to suppress cough. These two conditions were given in random order. The cough response was recorded by means of a microphone with the integrated sound trace displayed on a chart recorder.

A dose–response relationship was obtained on administration of ascending concentrations of capsaicin. In the non-suppressed challenge 23/24 subjects coughed on inhalation of capsaicin (3.33×10^{-4} M) with a mean number of coughs of 2.92 ± 0.34 , whereas in the suppressed challenge only 3/24 subjects coughed with a mean number of coughs of 0.29 ± 0.18 ($P < 0.001$).

These results demonstrate that cough induced by inhalation of capsaicin can be voluntarily suppressed. The mechanism of voluntary suppression of cough is discussed in relation to capsaicin challenge and the screening of antitussive medications.

Introduction

Cough is a protective reflex response which removes excessive mucus and irritants from the respiratory tract. Unlike other respiratory reflexes such as sneeze, cough can be induced voluntarily and cough due to respiratory tract infection can be voluntarily suppressed, at least for a short period. Although it is generally accepted that cough may be affected by voluntary control (1,2) it is surprising that the degree of this control has not been previously studied and there are several basic questions which need to be addressed. Can cough be totally suppressed by voluntary control or is the control limited to delaying the cough for a few seconds? Is cough suppression possible after inhalation of an irritant such as capsaicin or is suppression restricted to natural cough associated with respiratory tract infection? If cough can be suppressed voluntarily then this may be a complicating and uncontrolled variable in cough studies aimed at testing new antitussives. The mechanism of voluntary suppression of cough is also interesting as it

may be this control mechanism which is influenced by antitussives.

In the present study cough was induced by inhalation of capsaicin as this has been previously shown to give reproducible and dose-related cough responses (3). Capsaicin is less subject to the tachyphylaxis effects often seen with other irritants such as citric acid and distilled water, and more subjects cough in response to capsaicin inhalation than other irritants (4). The aim of the study was to determine if voluntary suppression of cough was possible after inhalation of capsaicin and to quantify the degree of voluntary suppression relative to a dose–response curve for capsaicin-induced cough.

Subjects and Methods

SUBJECTS

Volunteers were selected from the student population of the University of Wales College of Cardiff who presented in response to advertisements for healthy volunteers.

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Twenty-eight volunteers presented for the study, 13 females and 15 males with an average age of 22.79 years.

Volunteers were required to fulfil certain criteria before they were included in the study. Volunteers were excluded if they were not within the age range of 18–60 years, had clinical evidence of an upper respiratory tract infection (URTI) or a history of URTI in the previous 4 weeks, suffered from asthma, were smokers, had clinically significant cardiovascular, urological or neurological disease, had taken a product containing menthol in the previous 6 h, were pregnant or lactating, or had taken any medication (apart from the oral contraceptive pill) in the previous 24 h. Volunteers were also excluded during the trial if they failed to cough at any concentration of capsaicin, or coughed in response to saline (in the non-suppression challenge).

The trial was approved by the Hospital Medical Ethical Committee.

METHODS

The volunteer sat in a comfortable chair and was instructed to carefully watch a monitor screen in front of them and to carry out the instructions as indicated. One of two different instructions was illuminated: 'Please do not cough' or 'Just relax and cough if you wish'.

The study involved inhalation of a single breath of capsaicin in 10% ethyl alcohol in normal sterile saline solution. Varying concentrations (0.0 , 1×10^{-5} , 3.33×10^{-5} , 1×10^{-4} and 3.33×10^{-4} M) of capsaicin were delivered by a compressed-air-driven nebulizer controlled by a breath activated dosimeter (P.K. Morgan, U.K.). The average size of the delivered particles was 2–5 μm . The period of inhalation was set at 1 s. The solutions were made up daily from stock solutions (which were made up weekly) and were stored in a refrigerator at a temperature of between 0 and 6°C. The nebulized solutions were delivered to the subjects at room temperature.

Volunteers were given training and instructions as to the appropriate technique for inhalation of the nebulized solutions and were then given a nebulized saline solution on which to practice the technique.

Volunteers received all five concentrations of capsaicin. The five inhalations were defined as one challenge unit. The solutions were administered in ascending order of concentration with an interval of 60 s between each inhalation. Two capsaicin challenges were given 5 min apart. On one of these challenges the volunteer was given the instruction 'Just relax and cough if you wish', and was able to cough when necessary, and on the other challenge the

volunteer was given the instruction 'Please do not cough' in which case the volunteer would try and suppress the cough response. Coughs were recorded for a period of 30 s following each inhalation of nebulized solution in the non-suppressed challenge. In the cough suppression challenge coughs were again recorded for a period of 30 s. After the 30-s period of cough suppression the volunteer was given the instruction 'Just relax and cough if you wish' and cough recording continued for a further 30 s following the end of the cough suppression challenge. The order of challenges was randomized between subjects, i.e. some volunteers were asked to suppress cough on the first challenge, and some were asked to suppress cough on the second challenge.

Volunteers were not permitted to eat or drink during each challenge period but were asked to drink a glass of water between each challenge unit.

Cough counting

Coughs were recorded by an independent observer by means of a microphone which was placed on the floor in front of the volunteer. Sound detected by the microphone was integrated with a time constant of 0.02 s and recorded using a Datagraph (U.K.) ink pen recorder.

Coughs were counted on the pen recorder trace following inhalation of capsaicin according to the following method:

- Three voluntary coughs were recorded prior to the challenges in order to set the sensitivity of the pen recorder.
- Three more voluntary coughs were recorded after the sensitivity adjustments. The maximum height from the baseline of each of these three voluntary coughs was used to calculate the mean pen deflection value in mm.
- Induced cough deflections were only counted if they were at least one third mean deflection and arose from or within 2 mm of the baseline. Deflections may have included a number of pen movements but unless they all fell to baseline the height of the deflection was measured from the baseline to the tip of the maximal pen movement in this group.

A Macintosh Statview II package was used to calculate the statistics. Results are expressed as mean \pm standard error, and a non-parametric Wilcoxon signed ranked test was used to compare the mean values for each concentration of capsaicin between the suppressed and non-suppressed challenges. A Mann-Whitney *U*-test was used to determine if there was any significant difference between the frequency of coughs

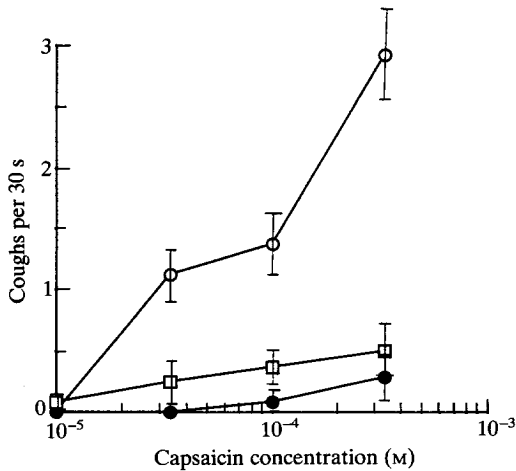


Fig. 1 Mean number of coughs per 30 s (\pm SEM) from 24 subjects produced on inhalation of capsaicin; \circ , non-suppressed challenge; \bullet , suppressed challenge; \square , immediately following 30-s period of cough suppression.

in the non-suppressed challenge with respect to the presenting order of each challenge unit.

Results

From the 28 volunteers entered on the study four were excluded from analysis. Three of these failed to cough at any concentration of capsaicin and one gave an excessive cough response and was considered hypersensitive to capsaicin.

NON SUPPRESSED CAPSAICIN CHALLENGE

A dose-response relationship was obtained on administration of ascending concentrations of capsaicin in response to the instruction 'Just relax and cough if you wish', as illustrated in Fig. 1. None of the 24 subjects coughed in response to inhalation of the lowest concentration of capsaicin (1×10^{-5} M) and 23/24 subjects coughed in response to inhalation of the highest concentration of capsaicin (3.33×10^{-4} M). The mean number of coughs induced by inhalation of capsaicin at the highest concentration (3.33×10^{-4} M) was 2.92 ± 0.34 . At the highest concentration of capsaicin (3.33×10^{-4} M) the mean latency was 1.65 ± 0.18 s ($n=23$) and the mean duration of coughing was 8.07 ± 1.27 s ($n=23$).

SUPPRESSED CAPSAICIN CHALLENGE

Following the instruction 'Please do not cough', the mean number of coughs was significantly reduced from that recorded in the non-suppressed challenge as shown in Fig. 1. Only 3/24 subjects coughed in

response to inhalation of the highest dose of capsaicin (3.33×10^{-4} M) and the mean number of coughs was 0.29 ± 0.18 ($n=3$) which was significantly different from the mean in the non suppressed trial (2.92 ± 0.34 , $n=23$, $P < 0.001$, Wilcoxon signed rank test). In the three subjects who coughed, the mean latency to cough on inhalation of the highest concentration of capsaicin (3.33×10^{-4} M) was 2.16 ± 0.34 s and the mean duration of coughing was 3.6 ± 0.38 s.

After the 30-s period of cough suppression subjects were instructed to 'Just relax and cough if you wish' and 11/24 subjects coughed in the 30-s period following the period of cough suppression. The mean number of coughs occurring during this post suppression period was related to the concentration of capsaicin inhaled as illustrated in Fig. 1.

The number of coughs induced by capsaicin inhalation was not influenced by the presenting order of the capsaicin challenges and there was no significant difference between the mean coughs at any concentration of capsaicin with respect to the presenting order of the challenges ($P > 0.22$ for all concentrations, Mann-Whitney *U*-test).

In the cough suppression challenge some subjects coughed and others were able to completely suppress cough but there does not appear to be any difference between these groups when comparing the mean coughs elicited during the non-suppressed capsaicin challenge. In the non-suppressed challenge the mean coughs induced with capsaicin (3.33×10^{-4} M) in those subjects who coughed during the period of cough suppression or immediately afterwards was 3.4 ± 0.5 ($n=10$) which was not significantly different from the mean of 2.57 ± 0.45 ($n=14$) in those subjects who did not cough at all ($P=0.47$ Mann-Whitney *U*-test).

Discussion

It is common knowledge that cough can be initiated voluntarily and this has some clinical importance since patients with brainstem damage who lack a cough reflex can still voluntarily induce coughing to help clear their airways (1). Cough associated with upper respiratory tract infection can be voluntarily suppressed as when it is inconvenient to cough 'the moment of expiratory thrust may at least be postponed for a few seconds' (2). The degree of control as far as voluntary suppression of cough is concerned has not been previously investigated, but Bucher in 1958 (2) suggested that the mechanism of voluntary control may serve as a point of attack for antitussives.

It is believed that capsaicin causes reflex coughing by stimulation of sensory nerves at the level of the larynx (5,6). On inhalation of capsaicin the glottis

immediately closes to protect the lower airways and coughing rapidly follows closure of the airway.

In the present study coughing occurred within seconds after inhalation of capsaicin and the period of coughing did not last longer than 10 s. This short time course of induced cough agrees with the previous findings of Collier and Fuller (5). A possible explanation for the rapid onset and short duration of the cough response to inhaled capsaicin is that capsaicin triggers coughing as soon as it comes into contact with the larynx and that cough removes capsaicin containing mucus from the larynx and expels any capsaicin still suspended as nebulized particles in the dead space air. This indicates that cough is effective in clearing the capsaicin from the airway. Capsaicin is not readily absorbed or metabolized and orally ingested capsaicin is not digested and is passed in faeces (8). It is therefore unlikely that coughing was terminated by breakdown or absorption of capsaicin in the respiratory tract.

Desensitization to the effects of capsaicin can occur due to depletion of substance P from sensory nerve endings (9) but this type of desensitization does not explain the present findings. If coughing stopped after application of capsaicin due to peptide depletion in the sensory nerves then one would not expect a subsequent inhalation of capsaicin 1 min later to induce cough as was observed in the present study. The results of the present study clearly demonstrate that almost all of the subjects (21/24) were able to completely suppress cough induced by capsaicin for a period of 30 s. During the period of voluntary cough suppression capsaicin was present in the airway and presumably would have stimulated sensory nerves in the same way as during the non-suppressed challenge. The drive to cough following inhalation of capsaicin appears to have persisted for more than 30 s as some subjects (11/24) coughed after the 30-s period of cough hold was complete when they were instructed to 'Just relax and cough if you wish'. The drive to cough during the period of cough suppression and immediately after suppression may be related to continuing sensory input from airway receptors stimulated by capsaicin or a central cough memory related to a peripheral input. The post cough hold number of coughs was related to the concentration of capsaicin inhaled and therefore does not appear to be an artefact of the study design. The majority of subjects (13/24) did not cough even during the post cough hold period when they were instructed to cough if they wished. In these subjects the suppression of cough was complete and presumably

the capsaicin was removed from the airway by swallowing during the cough hold period as no coughing occurred following the cough hold period.

The presenting order of the challenges did not influence the number of coughs induced on inhalation of capsaicin and this shows that the non-suppressed challenge was repeatable even after subjects had learned that they could completely suppress cough voluntarily. This indicates that although subjects can suppress cough and they may be aware of the degree of voluntary control this does not appear to influence the number of coughs produced during the non-suppressed challenge when subjects coughed freely. Therefore voluntary suppression of cough does not appear to be a complicating factor in induced cough studies.

The present study provides some basic information about voluntary suppression of induced cough which has not been previously available. The mechanism of voluntary suppression is at present unknown. Suppression could occur at the level of the brainstem or at the spinal outflow to expiratory muscles. The finding that voluntary suppression can be quantified in a dose-response relationship provides a starting point for further studies on the voluntary control of cough.

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