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# Effect of viral upper respiratory tract infection on the urge-to-cough sensation

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Received 5 September 2010; accepted 1 December 2010

Available online 24 December 2010

## KEYWORDS

Cough;  
Urge-to-cough;  
Capsaicin;  
Respiratory tract  
infection;  
Common cold

## Summary

**Background:** Recently, interest has emerged in the sensation of irritation that precedes the motor act of coughing; this phenomenon has been termed the urge-to-cough (UTC). Although one previous study has demonstrated a transient enhancement of cough reflex sensitivity during acute upper respiratory tract infection (URI), the effect of URI on UTC has not previously been investigated.

**Methods:** Employing standard cough challenge methodology, we measured cough reflex sensitivity in 24 otherwise healthy adult nonsmokers during URI and again after recovery (4–8 weeks later) by determining  $C_2$  and  $C_5$ , the concentrations of capsaicin inducing 2 or more and 5 or more coughs, respectively. In addition, we determined the capsaicin concentration at which the UTC sensation first occurred, without an associated motor cough, and termed it  $C_u$ . Furthermore, we determined the difference between concentrations of capsaicin inducing the first motor event of cough ( $C_1$ ) and  $C_u$ , and have termed it  $C_\Delta$ .

**Results:** During URI, cough reflex sensitivity as measured by  $C_1$  ( $p = 0.033$ ) and  $C_5$  ( $p = 0.001$ ), as well as the urge-to-cough threshold,  $C_u$  ( $p = 0.046$ ), were significantly enhanced compared to the post-recovery state. The degree of change in cough reflex sensitivity ( $C_5$ ) was significantly greater than that of the urge-to-cough threshold,  $C_u$  ( $p = 0.044$ ).

**Conclusion:** Our results demonstrate that the UTC sensation is transiently enhanced during URI. We also confirm the results of the lone previous study that demonstrated transient enhancement of cough reflex sensitivity during URI. The UTC threshold may represent an additional relevant end point to measure in future studies evaluating potential antitussive agents.

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## Introduction

Cough is among the most common symptoms associated with acute viral upper respiratory tract infection (URI), or common cold. One previous study has demonstrated that cough reflex sensitivity, as measured by capsaicin cough challenge testing, is transiently enhanced during URI.<sup>1</sup>

Recently, interest has emerged in the perception of irritation that precedes the motor event of coughing, which has been termed the urge-to-cough (UTC). Studies have demonstrated that the UTC sensation precedes the occurrence of cough during inhalation cough challenge, thus suggesting that the cough cognitive sensory process precedes the motor cough event.<sup>2,3</sup> Observations of capsaicin-elicited UTC and behavioral voluntary cough support the concept of a UTC motivation-to-action neural mechanism similar to other visceral urge systems.<sup>3</sup> Whereas the motor act of cough is typically considered a protective brainstem reflex, recent studies employing functional magnetic resonance imaging in healthy volunteers demonstrated that the capsaicin-evoked UTC sensation is associated with activation of a variety of supramedullary brain regions, thus suggesting a cortical neural network in sensing airway irritation and modulating cough.<sup>4</sup>

To our knowledge, the effect of URI on the UTC sensation has not been investigated previously. We hypothesized that URI would transiently enhance the UTC threshold, as has been shown in capsaicin-induced motor cough.<sup>1</sup> Thus, the aim of this study was to evaluate the effect of acute URI on the UTC sensation as well as on cough reflex sensitivity.

## Methods

### Subjects

Otherwise healthy adult nonsmokers developing symptoms consistent with acute viral URI (common cold) were recruited and enrolled within 7 days of symptom onset. An acute URI was defined as an illness of acute onset typical of previous episodes of common cold for that subject, including some but not necessarily all of the standard symptoms of cough, sore throat, rhinorrhea, nasal/sinus congestion, and sneezing. Subjects with history of allergic rhinitis in whom symptoms may not have been attributable to viral URI were excluded. Subjects with symptoms suggestive of possible bacterial infection, such as fever associated with sinus pain and/or purulent nasal discharge were excluded, as were individuals who had taken medication for their illness that could affect cough reflex sensitivity (antihistamines, decongestants, dextromethorphan, codeine, hydrocodone). All subjects provided written informed consent for this study, which was approved by the Institutional Review Board of Montefiore Medical Center, Bronx, NY, USA.

### Capsaicin cough challenge

Upon enrollment (within 7 days of symptom onset) and again after 4–8 weeks (after recovery from URI), subjects underwent capsaicin cough challenge testing as previously described<sup>5,6</sup> but with the additional measurement of the

UTC threshold. Briefly, subjects inhaled single vital-capacity breaths of capsaicin (Formosa Laboratories, Taiwan, ROC) aerosol administered in ascending doubling concentrations (range 0.49  $\mu\text{M}$  up to 1000  $\mu\text{M}$ ) via a compressed air-driven nebulizer controlled by a dosimeter (KoKo DigiDoser, nSpire Health, Louisville, CO, USA), until the concentrations of capsaicin inducing 2 or more ( $C_2$ ) and 5 or more coughs ( $C_5$ ) were determined. Only coughs occurring within 15 s of each inhalation were counted; placebo saline breaths were randomly interspersed to maintain challenge blindness. If no cough occurred 5 s after an inhalation, subjects were shown a modified Borg scale<sup>2,3,7</sup> to which they pointed without speaking, indicating whether a UTC sensation was present, and to what degree (1 = no UTC sensation; 10 = maximal UTC).

We determined the initial concentration of capsaicin that induced the UTC sensation without provoking an associated motor cough event, and have termed it  $C_u$ . To evaluate the relationship of the UTC threshold to the motor cough threshold, we also determined  $C_1$ , the concentration of capsaicin inducing 1 or more coughs, and considered that the cough threshold. We termed the difference between the cough threshold and UTC threshold  $C_\Delta$ :

$$C_\Delta = C_1 - C_u$$

### Statistical analysis

Descriptive summaries, i.e., mean (SD), are employed to summarize results. A paired *t*-test was carried out to compare cough challenge data during URI and post-recovery. In addition, a non-parametric, Wilcoxon signed rank sum test, was applied to assess the robustness of the results. In this comparison, each individual subject acts as his or her own control. A linear regression analysis was employed to assess whether change is influenced by gender, age or both, by considering change, i.e., post-recovery – during URI, as a response variable in a model that includes gender, age and an interaction term simultaneously. Age was dichotomized as  $\leq 30.5 / > 30.5$  (median of the empirical distribution of age).

## Results

Twenty-four subjects (12 female; mean age 35.2 (SD = 7.3) years) underwent capsaicin cough challenge during the acute phase of URI (within 7 days of symptom onset; mean duration of symptoms at study enrollment: 4.4 (SD = 2.0) days) and after 4–8 weeks (post-recovery). The end point of induction of 5 or more coughs was achieved in all subjects. In 7 subjects, however, the UTC threshold,  $C_u$ , was unable to be determined because a motor cough event occurred after the previous concentration of capsaicin had not induced a UTC sensation or a motor cough event. In 4 subjects tested during URI, the UTC sensation was induced by inhalation of physiologic saline. This did not occur in any subject tested after recovery from URI.

During URI, cough reflex sensitivity, as measured by  $C_1$  and  $C_5$  was significantly enhanced compared to the post-recovery state (Table 1). Notably,  $C_2$  was not altered to

**Table 1** Capsaicin cough challenge data.

	n	During URI	Post-recovery	95% CI <sup>a</sup>	<i>p</i> <sup>b</sup>
log $C_u$ <sup>c</sup>	17	-0.176(0.353) <sup>d</sup>	0(0.260)	(0.017,0.034)	0.046
log $C_1$	24	0.225(0.487)	0.450(0.460)	(0.030,0.420)	0.033
log $C_\Delta$	17	0.459(0.215)	0.582(0.403)	(-0.066,0.313)	0.219
log $C_2$	24	0.375(0.453)	0.500(0.490)	(-0.055,0.305)	0.187
log $C_5$	24	0.563(0.436)	0.913(0.438)	(0.167,0.533)	0.001

$C_u$ , concentration of capsaicin inducing urge-to-cough sensation without associated motor cough;  $C_1$ ,  $C_2$ ,  $C_5$ , concentrations of capsaicin inducing 1, 2 and 5 coughs, respectively;  $C_\Delta = C_1 - C_u$ .

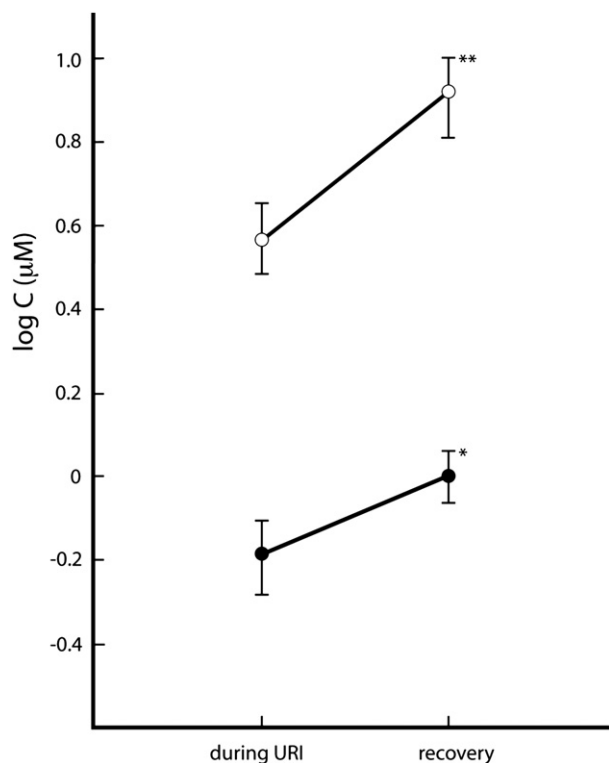
<sup>a</sup> confidence interval.

<sup>b</sup> *p*-value based on paired *t*-test.

<sup>c</sup> 7 subjects did not have demonstrable  $C_u$  (see text).

<sup>d</sup> S.D.

a significant degree. The UTC threshold,  $C_u$ , was also enhanced to a significant degree due to the presence of URI.  $C_\Delta$ , reflecting the difference between motor cough threshold ( $C_1$ ) and UTC threshold ( $C_u$ ), remained stable. The degree of change in cough reflex sensitivity, as measured by  $C_5$ , was significantly greater than the degree of change induced by presence of URI in  $C_u$  ( $p = 0.044$ ; Fig. 1). A non-parametric analysis also provided similar results. In addition, an exploratory multivariable analysis did not suggest modification of the post-recovery versus during-URI change by gender and age, i.e., the regression coefficients for the



**Figure 1** Mean values for  $C_5$  (open circles) and  $C_u$  (solid circles) during viral upper respiratory tract infection (URI) and after recovery (4–8 weeks after URI). Error bars indicate  $\pm$ SEM. Values were significantly lower (i.e., sensitivity enhanced) during URI. \* $p = 0.046$ ; \*\* $p = 0.001$ .  $C_5$  was affected to a greater degree by URI than was  $C_u$  ( $p = 0.044$ ).

corresponding terms did not reach statistical significance (results not shown).

## Discussion

We have demonstrated that the presence of URI transiently enhances the urge-to-cough sensation. In addition to this initial observation, we have also shown that cough reflex sensitivity to capsaicin is transiently increased during URI. To our knowledge, this is the first study to confirm the cough reflex sensitivity results of O'Connell et al., in 1996.<sup>1</sup> Although we have demonstrated that the urge-to-cough (UTC) sensation can be readily measured in the laboratory, some subjects, in our case 7 of 24, did not have a demonstrable UTC threshold ( $C_u$ ) since they progressed from absence of UTC to a motor cough event when exposed to successive doubling concentrations of capsaicin during inhalation challenge. This observation should be kept in mind when planning sample size for future studies in which UTC determination will be required.

Our results suggest that the presence of URI affects cough reflex sensitivity to a greater degree than the UTC sensation. The enhancement of  $C_5$  during URI was significantly greater than that of  $C_u$  in this study. However,  $C_\Delta$ , a measure of the difference between cough threshold ( $C_1$ ) and the UTC threshold ( $C_u$ ), remained stable, as both  $C_1$  and  $C_u$  were significantly enhanced during URI. Furthermore, 4 of our subjects, during URI, experienced UTC after administration of physiological saline. This phenomenon has not been reported in other studies of induced UTC.<sup>4,7,8</sup>

The mechanism by which URI affects the UTC sensation remains speculative. Since it is believed that activation of cough afferents elicits the cognitive sensations representing urge-to-cough,<sup>2,3</sup> it may be that the peripheral inflammation induced by the URI enhances central stimulus perception. Interestingly, our observation of a differing degree of influence of URI on cough reflex sensitivity and the UTC sensation supports the concept that these phenomena are distinctly controlled, as is suggested by Mazzone and colleagues, who demonstrated in a brain imaging study that some, but not all, cortical regions that were activated during capsaicin-induced cough had signal intensities that were correlated with UTC.<sup>4</sup> Indeed, these findings suggest the presence of urge-specific and urge-independent elements in the suprapontine control of coughing.<sup>9</sup>

Notably,  $C_2$ , one of the standard end points of cough challenge testing, did not demonstrate a significant change during URI, whereas  $C_5$  was affected to a greater degree than any other parameter measured. This observation supports the opinion of the authors and others that  $C_5$  is the optimal end point in cough challenge testing when serial studies are performed to evaluate the effect of a pharmacological or other intervention on cough reflex sensitivity.<sup>5</sup> Although mean  $C_2$  was indeed lower during URI than post-recovery (0.375 vs. 0.5), this difference did not reach statistical significance. As has been described,  $C_2$  measurements are susceptible to technical issues not affecting the determination of  $C_5$ .<sup>5</sup> These factors, in addition to the relatively small subject population, likely contributed to the inability of the  $C_2$  value to achieve statistical significance.

Our results demonstrate not only that UTC can be readily measured in the laboratory, but that changes in the UTC threshold induced by environmental factors such as URI can be perceived. Our experience complements the results of a recent study in which the UTC sensation in adult smokers was demonstrably modulated by withdrawal and administration of nicotine.<sup>8</sup> Another study, however, was unable to detect an effect of codeine on the UTC sensation in healthy volunteers.<sup>7</sup>

Since the UTC sensation can be effectively measured, and as it has been shown to be responsive to certain environmental factors such as URI and the presence or absence of nicotine, it would appear that the UTC threshold may be an additional relevant end point to monitor in future studies evaluating potential antitussive agents.

## Conflict of interest

None.

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