

Effect of viral upper respiratory tract infection on cough reflex sensitivity

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Abstract: Acute viral upper respiratory tract infection (URI; common cold) is among the most common medical conditions affecting man, with cough being a typical feature of the associated syndrome. Studies employing capsaicin inhalation challenge to measure cough reflex sensitivity have demonstrated a transient tussive hyperresponsiveness induced by URI that reverts to normal by 4-8 weeks post infection. Mechanisms proposed to explain the induction of cough by URI include a number of infection-associated airway effects, such as enhanced release of cytokines, neurotransmitters, and leukotrienes; increased neural receptor levels; reduced activity of neutral endopeptidases; transient modulation of afferent neural activity; mucus hypersecretion; and, possibly, effects on cholinergic motor pathways. Recent studies evaluating urge-to-cough (UTC), the sensation of irritation preceding the motor act of coughing, have demonstrated that URI induces a transient enhancement of UTC analogous to the effect observed on cough reflex sensitivity. The recently introduced concept of the Cough Hypersensitivity Syndrome may provide an explanation for the commonly observed clinical phenomenon of acute viral URI triggering what will develop into chronic, refractory cough in a subgroup of patients.

Keywords: Cough; capsaicin; common cold; viral infection; virus

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Introduction

Cough is among the most common reasons for which patients worldwide seek medical attention (1). Most cases of acute and subacute cough are due to acute viral upper respiratory tract infections (URI), otherwise known as the common cold. Given the sheer enormity of the problem of common cold worldwide, the medical and economic implications of cough due to this condition are of tremendous significance. Not only does acute cough due to URI result in tremendous financial expenditure, but the available treatments for acute cough are limited by lack of efficacy or, as in the case of opiates, for example, intolerable side effects at antitussive doses (2,3).

Measurement of cough reflex sensitivity

Measurement of cough reflex sensitivity has allowed insight into the effects of viral URI on human cough reflex

sensitivity. Among the various provocative agents used for induction of cough in the laboratory, capsaicin, the pungent extract of red chili peppers, has gained favor as the tussive agent of choice, given its ability to induce cough in a safe (4), dose-dependent and reproducible manner (5,6). The typical end points of capsaicin inhalation challenge are C₂ and C₅, the concentrations of capsaicin inducing two or more, and five or more coughs, respectively. *Figure 1* illustrates a typical dose-response curve generated during a capsaicin challenge study.

Effect of viral URI on cough reflex sensitivity

Employing capsaicin inhalation challenge to measure cough reflex sensitivity, O'Connell and colleagues initially demonstrated that cough reflex sensitivity is transiently enhanced in otherwise healthy subjects during acute viral URI, compared with the post-recovery state (7).

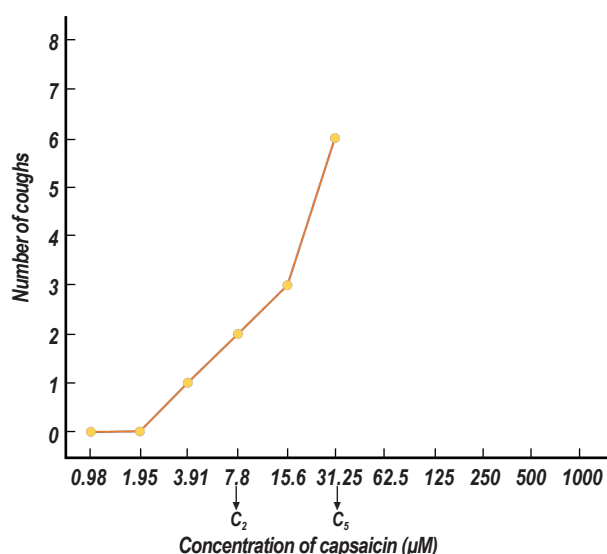


Figure 1 Typical dose-response curve observed during capsaicin inhalation challenge. In this subject, C_2 , the concentration of capsaicin inducing two or more coughs, is 7.8 μM ; C_5 , the concentration of capsaicin inducing five or more coughs, is 31.25 μM .

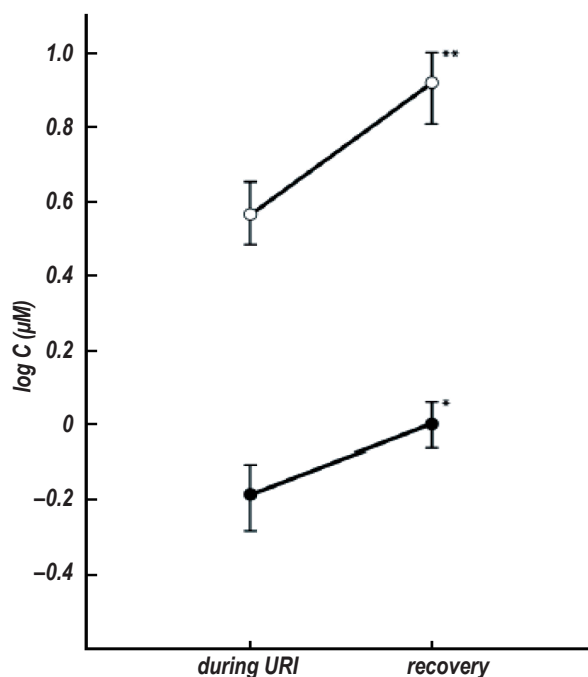


Figure 2 Mean values for log C_5 (open circles) and log C_u (solid circles) during viral upper respiratory tract infection (URI) and after recovery (4-8 weeks after URI). Error bars indicate \pm SEM. Values were significantly lower (i.e., sensitivity enhanced) during URI. * $P=0.046$; ** $P=0.001$. C_5 was affected to a greater degree by URI than was C_u ($P=0.044$). [from Reference (8), with permission].

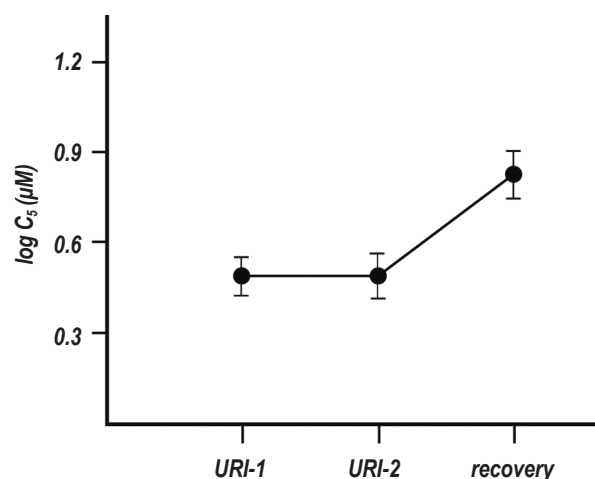


Figure 3 Mean log C_5 values for subjects ($n=42$) measured on consecutive days during the first 8 days of acute viral upper respiratory tract infection (URI-1 and URI-2), and 4-8 weeks after URI (recovery). Error bars indicate \pm SEM.

These findings were subsequently confirmed in a similar population (8), as shown in Figure 2, with C_5 significantly decreased (cough reflex sensitivity enhanced) during URI compared with repeated measurement after recovery (4-8 weeks post-URI).

A recent study was the first to perform multiple cough reflex sensitivity measurements during the acute phase of viral URI in otherwise healthy subjects (9). Capsaicin cough challenge, performed twice during the first eight days of acute URI, demonstrated stability of cough reflex sensitivity during acute URI, with subsequent diminution (increased C_5) post-recovery (Figure 3). This observation is of significance to future investigators evaluating the effect of a pharmacological intervention on acute cough, as changes in cough reflex sensitivity can be assumed to reflect the effect of the study drug, rather than significant, naturally occurring fluctuations in cough reflex sensitivity occurring during the early stages of acute URI.

Relatively few studies have evaluated the effect of a drug on cough reflex sensitivity during URI. The widely used expectorant, guaifenesin, has been shown in two clinical trials to inhibit cough reflex sensitivity in subjects with acute viral URI, but not in healthy volunteers (10,11). Similarly, the anticholinergic bronchodilator, tiotropium, has been shown to suppress cough reflex sensitivity in otherwise healthy nonsmokers with acute URI, but not in healthy controls (12). Interestingly, the antitussive effect of tiotropium occurred without demonstrable bronchodilation, thus highlighting the concept that tiotropium may

Table 1 Proposed mechanisms of virus-induced cough*

Effects on airway epithelium - inflammation and cytokine release (IL-1, TNF- α , IL-6, IL-8, GRO- α , IL-11, RANTES, GM-CSF, eotaxin)
Increased airway neurotransmitter levels - Substance P;
Reduced activity of neutral endopeptidases in airway;
Increased neural receptor levels (NK-1);
Modulation of afferent neural activity (transient).
Effect on cholinergic motor pathways (bronchoconstriction, airway hyperresponsiveness)
Increased leukotriene production;
Mucus hypersecretion.

*Adapted from Reference (15).

have pharmacological effects beyond that of reversal of pathological airway obstruction (13). Notably, both of these agents inhibited capsaicin sensitivity in subjects with URI, whose cough reflex sensitivity was transiently enhanced, whereas the drugs had no effect in healthy volunteers, whose cough reflex was at its baseline. These observations raise the concept that subjects with pathologically enhanced cough reflex sensitivity, rather than healthy volunteers, comprise the optimal study population for clinical trials evaluating potential antitussive agents (14).

Mechanisms of enhanced cough reflex sensitivity during viral URI

Numerous mechanisms have been proposed to explain the transient cough and enhancement of cough reflex sensitivity associated with acute viral URI (15). Direct effects of the viral infection on airway epithelium include inflammation and cytokine release. Other airway effects of URI include increase in neurotransmitter levels, such as Substance P; reduced activity of neutral endopeptidases; increased neural receptor levels (NK-1); and, transient modulation of airway neural activity. Increased leukotriene production and mucus hypersecretion are likely additional contributors to cough induction. Viral infections induce bronchoconstriction and airway hyperresponsiveness through their influence on cholinergic pathways, but the significance of these effects on cough and cough reflex sensitivity remains to be elucidated (*Table 1*).

It is of interest, and likely quite significant, that many patients presenting with chronic cough relate the onset of their longstanding condition to an episode of URI. The newly emerging concept of the Cough Hypersensitivity Syndrome (16-19) suggests that an underlying hypersensitivity of the cough reflex potentiates the effect of an exogenous stimulus

such as acute viral URI, resulting in refractory, chronic cough in a particular subgroup of individuals whereas the same stimulus causes a merely transient cough in the great majority of the population.

Effect of viral URI on the urge-to-cough (UTC) sensation

Recently, increasing interest has focused on the sensation of irritation that precedes the motor act of coughing; this phenomenon has been termed the UTC (20-23). Studies employing functional magnetic resonance imaging in subjects administered inhaled capsaicin have demonstrated that the UTC sensation is associated with activations in a variety of cortical brain regions (24,25). As is the case with the motor cough reflex, acute viral URI has been demonstrated to induce a transient enhancement of the UTC sensation (8). As shown in *Figure 2*, UTC, as measured by C_{50} , the lowest concentration of capsaicin inducing the UTC sensation without an associated motor cough (23), is significantly enhanced during URI compared to the post-recovery state.

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