Review: Effect of drugs on human cough reflex sensitivity to inhaled capsaicin

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Abstract
Capsaicin, the pungent extract of red peppers, has been used in clinical research for almost three decades. Capsaicin has gained favor as the provocative agent of choice to measure cough reflex sensitivity, as it induces cough in a safe, reproducible, and dose-dependent manner. One of the major uses of capsaicin cough challenge testing has been to evaluate the effect of a pharmacological intervention on the human cough reflex. The current review summarizes the published experience with capsaicin inhalation challenge in the evaluation of drug effects on cough reflex sensitivity. A notable contrast evident between studies demonstrating a drug effect (inhibition of cough reflex sensitivity) and those that do not, is the predominance of healthy volunteers as subjects in the latter. This observation suggests that subjects with pathological cough, rather than normal volunteers, comprise the optimal group in which to evaluate the effect of potential antitussive agents on human cough reflex sensitivity.

Keywords: Cough, Capsaicin, Antitussive, Respiratory tract infection, Asthma

Introduction
Capsaicin, the pungent extract of red pepper (capsicum), has gained widespread use as a research tool among clinical investigators, as it induces cough in humans in a safe [1], dose-dependent, and reproducible manner [2,3]. Capsaicin cough challenge in humans was first described in 1984 [4], and has since been used to evaluate the effect of numerous pharmacological agents on cough reflex sensitivity. Although many drugs have been shown to inhibit induced cough in the laboratory, others have failed to do so, including agents widely regarded as clinically effective antitussives.

Methods
A United States National Library of Medicine (PubMed) search was performed in September, 2012 using the search terms “cough” and “capsaicin” limited to human studies published in English. The abstracts of the 328 articles meeting those search criteria were reviewed and 56 studies were identified in which capsaicin cough challenge was employed to assess the effect of a pharmacological intervention on cough reflex sensitivity. Studies in which a positive drug effect was demonstrated (n = 33) are listed in Table 1 [5-37]; trials in which no effect was noted (n = 30) are summarized in Table 2 [4,10,12,17-19,35,37-59]. In seven of these studies, multiple drugs and/or multiple subject groups were evaluated, resulting in both positive and negative results in terms of assessment of drug activity. As the purpose of this review was to assess drug trials in which a potential therapeutic (antitussive) effect of a drug was being evaluated, studies demonstrating enhancement of cough reflex sensitivity by angiotensin-converting enzyme (ACE) inhibitors or other agents were excluded.

Discussion
This review has identified 33 studies in which a pharmacological intervention was demonstrated to inhibit cough reflex sensitivity to inhaled capsaicin in a variety of subject populations, thus supporting the role of cough challenge as a useful clinical tool in the evaluation of potential antitussives [3]. A striking difference between the studies showing a positive drug effect (Table 1), and those failing to demonstrate a change in cough reflex sensitivity (Table 2) is the predominant subject populations studied. Of the negative studies, 70% involved evaluation of healthy volunteers. Among the trials displaying a positive drug effect, only 27% evaluated healthy...
volunteers, while the majority (73%) investigated various forms of pathological cough. Of note, multiple agents were shown to inhibit cough reflex sensitivity in pathological cough, while having no effect in healthy volunteers, including guaifenesin [10,17] and tiotropium [12] in cough due to acute viral upper respiratory tract infection (URI; common cold). The leukotriene receptor antagonist zafirlukast inhibited capsaicin-induced cough in subjects with cough-variant asthma [21], but not in stable asthmatics without cough and healthy volunteers [44]. Interestingly, gabapentin has recently been shown to improve cough-specific quality of life in patients with refractory chronic cough, without affecting cough reflex sensitivity [38]. This particular study highlights the concept that the optimal approach to the evaluation of a potential antitussive agent should be multifaceted, with cough reflex sensitivity measurement complementing other measures, such as objective cough counting and subjective symptom-based questionnaires.

Conspicuous in their absence from the list of agents having demonstrated the ability to inhibit cough reflex sensitivity to capsaicin during URI are codeine and dextromethorphan, two of the most commonly used agents worldwide for the treatment of cough due to the common cold [60]. The only agents demonstrating the ability to inhibit cough reflex sensitivity to capsaicin in healthy

| 1st author | Ref. # | Year | Drug | Subject population |
|------------|--------|------|------|-------------------|
| Wise P     | [5]    | 2012 | menthol | healthy volunteers     |
| Takemura M | [6]    | 2012 | montelukast | cough-variant asthma |
| Eklostrand Y | [7]    | 2011 | inhaled steroids | asthma |
| Ishiura Y  | [8]    | 2010 | etodolac | sinobronchial syndrome |
| Ishiura Y  | [9]    | 2009 | etodolac | asthma |
| Dicpinigaitis P | [10] | 2009 | guaifenesin | viral URI |
| Davenport P | [11]  | 2009 | nicotine | healthy smokers     |
| Dicpinigaitis P | [12] | 2008 | tiotropium | viral URI |
| Ishiura Y  | [13]   | 2008 | suplatast | atopic cough |
| Ferrari M  | [14]   | 2007 | omeprazole | asthma + GERD |
| Usmani O   | [15]   | 2005 | theobromine | healthy volunteers |
| Shioya T   | [16]   | 2004 | epinastine | atopic cough |
| Dicpinigaitis P | [17] | 2003 | guaifenesin | viral URI |
| Ishiura Y  | [18]   | 2003 | carbocysteine | asthma |
| Ishiura Y  | [19]   | 2003 | seratrodast | chronic bronchitis |
| Shioya T   | [20]   | 2002 | suplatast | cough-variant asthma |
| Dicpinigaitis P | [21] | 2002 | zafirlukast | cough-variant asthma |
| Ceyhan B   | [22]   | 2002 | oxolamine | COPD |
| Dicpinigaitis P | [23] | 2000 | baclofen | cervical SCI |
| Brightling C | [24] | 2000 | budesonide | eosinophilic bronchitis |
| Dicpinigaitis P | [25] | 1998 | baclofen | healthy volunteers |
| Shioya T   | [26]   | 1998 | azelastine | asthma |
| Dicpinigaitis P | [27] | 1997 | baclofen | healthy volunteers |
| Shioya T   | [28]   | 1996 | azelastine | cough-variant asthma |
| Fujimura M | [29]   | 1995 | indomethacin | asthma, chronic bronchitis |
| Hargreaves M | [30] | 1995 | sodium cromoglycate | ACE-inhibitor cough |
| Hansson L  | [31]   | 1994 | lignocaine | healthy volunteers |
| Van Wyck M | [32]   | 1994 | glycopyrrolate | ACE-inhibitor cough |
| Cazzola M  | [33]   | 1993 | theophylline | ACE-inhibitor cough |
| Foster G   | [34]   | 1991 | sulindac | healthy volunteers |
| McEwan J   | [35]   | 1990 | sulindac | ACE-inhibitor cough |
| Choudry N  | [36]   | 1990 | lignocaine | healthy volunteers |
| Fuller R   | [37]   | 1988 | codeine, morphine | healthy volunteers |

Abbreviations: URI-acute upper respiratory tract infection; GERD-gastroesophageal reflux disease; SCI-spinal cord injury; ACE-angiotensin-converting enzyme.
volunteers were theobromine [15], baclofen [25,27], inhaled lignocaine [31,36], sulindac [34], systemic opi-
ates [37], menthol [5] and, in healthy smokers, nicotine [11]. Interestingly, this list includes drugs thought to be
centrally acting antitussives, as well as agents whose cough-inhibiting properties are presumed to occur
through a peripheral mechanism.

Limiting the evaluation of a potential modulator of cough reflex sensitivity to a study group of healthy
volunteers, whose cough reflex is not hyperresponsive, may not allow the drug to demonstrate its inhibitory
effect. Thus, subjects with pathological cough appear to comprise the optimal study population when evaluating
the effects of a potential antitussive agent on cough reflex sensitivity. The particular type of pathological cough best
suited for evaluation of a novel antitussive may depend on the specific pharmacological action of the drug, and
currently remains a question under vigorous debate.

Competing interests
The author declares that he has no competing interest.

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Table 2 Drugs shown not to inhibit cough reflex sensitivity to capsaicin

| 1st author | Ref. # | Year | Drug | Subject population |
|------------|--------|------|------|--------------------|
| Ryan M     | [38]   | 2012 | gabapentin | chronic cough       |
| Yousaf N   | [39]   | 2010 | erythromycin | chronic cough       |
| Dicpinigaitis P | [10]  | 2009 | benzonatate | viral URI           |
| Dicpinigaitis P | [12]  | 2008 | tiotropium | healthy volunteers  |
| Davenport P | [40]   | 2007 | codeine | healthy volunteers  |
| Dicpinigaitis P | [41]  | 2003 | fexofenadine | healthy volunteers |
| Dicpinigaitis P | [17]  | 2003 | guaifenesin | healthy volunteers  |
| Ishiura Y   | [18]   | 2003 | ambroxol | asthma              |
| Ishiura Y   | [19]   | 2003 | pranlukast | chronic bronchitis  |
| Dicpinigaitis P | [42]  | 2001 | celecoxib | asthma              |
| Fujimura M  | [43]   | 2000 | mexiteline | healthy volunteers  |
| Dicpinigaitis P | [44]  | 1999 | zafirlukast | asthma without cough|
| Capon D     | [45]   | 1996 | dextromethorphan | healthy volunteers |
| Hansson L   | [46]   | 1994 | nicotine | healthy nonsmokers  |
| Hutchings H | [47]   | 1994 | codeine | healthy volunteers  |
| O’Connell F | [48]   | 1994 | clonidine | healthy volunteers  |
| Fujimura M  | [49]   | 1993 | procaterol | asthma, chronic bronchitis |
| Choudry N   | [50]   | 1993 | MAO inhibitors | healthy volunteers |
| Stone R     | [51]   | 1993 | 5-HT (serotonin) | healthy volunteers |
| Fujimura M  | [52]   | 1992 | procaterol | healthy volunteers  |
| Ventresca P | [53]   | 1992 | furosemide | healthy volunteers  |
| Karlsson J  | [54]   | 1992 | furosemide, HCTZ | healthy volunteers |
| Studham J   | [55]   | 1992 | terfenadine | healthy volunteers  |
| Choudry N   | [56]   | 1991 | inhaled mu opioid agonist | healthy volunteers |
| Smith C     | [57]   | 1991 | salbutamol, ipratropium | healthy volunteers |
| Choudry N   | [58]   | 1991 | granisteron (5-HT3) | healthy volunteers |
| Mcewan J    | [55]   | 1990 | sulindac | idiopathic cough    |
| Hansson L   | [59]   | 1988 | nedocromil | healthy volunteers  |
| Fuller R    | [37]   | 1988 | inhaled opiates | healthy volunteers |
| Collier J   | [4]    | 1984 | sodium cromoglycate | healthy volunteers |

Abbreviations: URI-acute upper respiratory tract infection; MAO-monoamine oxidase; HCTZ-hydrochlorothiazide.
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