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## Pulmonary Pharmacology &amp; Therapeutics

journal homepage: [www.elsevier.com/locate/ypupt](http://www.elsevier.com/locate/ypupt)

## Effect of tobacco and electronic cigarette use on cough reflex sensitivity

Peter V. Dicpinigaitis\*

Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY, USA

## ARTICLE INFO

## Article history:

Received 19 August 2016

Accepted 31 January 2017

Available online xxx

## Keywords:

Tobacco

Electronic cigarette

E-cig

Smoking

Vaping

Capsaicin

## ABSTRACT

Multiple previous studies have shown that otherwise healthy tobacco cigarette smokers have suppressed cough reflex sensitivity compared with nonsmokers and furthermore, that smoking cessation, even after years of tobacco use, leads to prompt enhancement of cough reflex sensitivity. Thus, cough reflex sensitivity is demonstrated to be a dynamic phenomenon, responding to the presence or absence of influences such as tobacco smoke. These studies, however, were unable to identify whether it was the influence of nicotine, or one or more of the numerous components of tobacco cigarette smoke, that were responsible for this effect.

More recently, it has been shown that a single exposure to electronic cigarette (e-cig) vapor causes inhibition of cough reflex sensitivity in healthy lifetime nonsmokers. An identical study employing a non-nicotine containing e-cig confirmed an absence of effect on cough reflex sensitivity, thus implicating nicotine as the causative agent of these findings. Recent animal studies demonstrate cough suppression after injection of nicotine into the brains of cats, thus supporting a centrally-mediated antitussive effect of nicotine to explain the results of the aforementioned studies of tobacco smoke and e-cig vapor exposure in humans.

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## 1. Introduction

The health consequences of tobacco smoking, including emphysema, chronic bronchitis, cardiovascular disease and lung cancer, have been well described over the past several decades [1]. More recently, electronic cigarette use has rapidly attained

worldwide popularity [2], yet relatively little scientific data have been generated regarding the respiratory effects of electronic cigarette (e-cig) use, or vaping, thus generating a call for targeted research in this area [2–4].

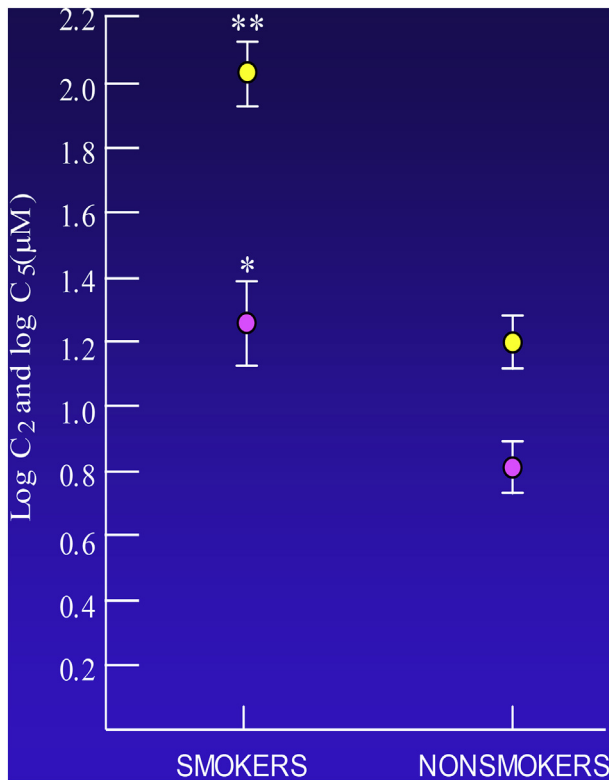
Cough is the most common complaint for which patients in the United States [5] and Europe seek medical attention [6,7]. Yet, cough remains relatively under-researched given its clinical significance. The effects of tobacco cigarette smoking and, more recently, of electronic cigarette vaping, on cough and cough reflex sensitivity have received some attention and those data form the basis of this review.

\* Einstein Division/Montefiore Medical Center, 1825 Eastchester Road, Bronx, NY 10461, USA.

E-mail address: [pdicpin@gmail.com](mailto:pdicpin@gmail.com).

<http://dx.doi.org/10.1016/j.ypupt.2017.01.013>

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**Fig. 1.** Capsaicin cough challenge data in smokers and nonsmokers. Open circles represent mean log C<sub>5</sub>; solid circles represent mean log C<sub>2</sub>. Error bars represent  $\pm$ SEM. \* $p = 0.004$ ; \*\* $p < 0.000001$ . C<sub>5</sub> and C<sub>2</sub> represent the concentration ( $\mu$ M) of capsaicin inducing  $\geq 5$  and  $\geq 2$  coughs, respectively (from ref. [10], with permission).

## 2. Effects of tobacco cigarette smoking on cough and cough reflex sensitivity

Animal studies have demonstrated the rapid-onset, cough-inducing effect of cigarette smoke, presumably due to the peripheral stimulation by nicotine of nicotinic acetylcholine receptors expressed on sensory terminals of cough receptors within the airway mucosa [8]. It is interesting therefore, that multiple studies in humans have demonstrated a diminished cough reflex sensitivity to inhaled capsaicin [9,10] and citric acid [11] in otherwise healthy smokers compared with nonsmokers (Fig. 1). One recent study documented diminished capsaicin cough reflex sensitivity in children living with smoking parents compared with children

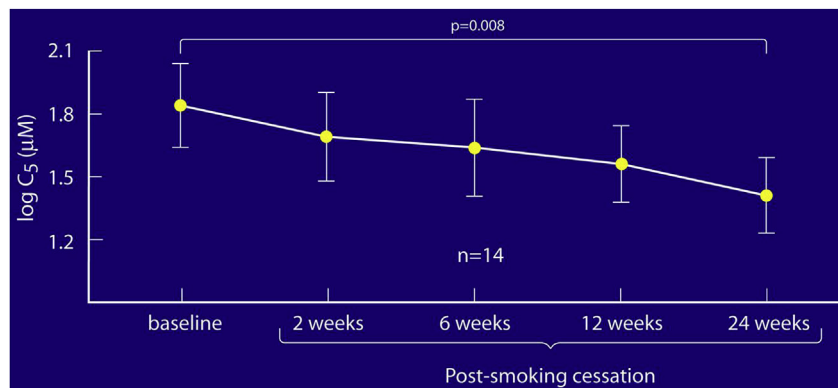
living in smoke-free homes, thus suggesting that exposure to environmental tobacco smoke is sufficient to affect the cough reflex [12].

These observations support the presence of an antitussive agent within cigarette smoke, and furthermore suggest a lack of tachyphylaxis, since suppression of cough reflex sensitivity was demonstrated in chronic smokers. To further explore these findings, a subsequent study evaluated cough reflex sensitivity to capsaicin in chronic cigarette smokers before and after smoking cessation [13]. A significant enhancement of cough reflex sensitivity was documented after 2 weeks of smoking cessation, thus supporting a promptly reversible inhibition of cough reflex suppression even after years of smoking. Further enhancement of cough reflex sensitivity was noted up to 24 weeks after smoking cessation [13,14] (Fig. 2). In those subjects who were unable to remain abstinent from smoking, cough reflex sensitivity was demonstrated to be inhibited back to its previous baseline (pre-smoking cessation) level by 2 weeks after resumption of smoking [15]. In summary, these observations suggest that cough reflex sensitivity is a dynamic phenomenon, able to be suppressed or enhanced based on the presence or absence of stimuli such as cigarette smoke. Whether nicotine or other component(s) of cigarette smoke are responsible for the above observations was unable to be discerned from these investigations.

## 3. Effects of electronic cigarette use (vaping) on cough and cough reflex sensitivity

E-cigs have attained widespread use and popularity so quickly that scientific research on their health consequences lags behind. Indeed, very few studies have evaluated the respiratory effects of e-cig use [16]. A recent study investigated the effects of a single e-cig exposure on healthy adult nonsmokers [16]. The exposure consisted of 30 puffs of a disposable e-cig taken 30 s apart, thus estimating the nicotine exposure of one tobacco cigarette. A significant diminution of cough reflex sensitivity was demonstrated 15 min after the e-cig exposure, and a return to baseline cough reflex sensitivity was documented 24 h after exposure (Fig. 3). A subgroup of subjects with the largest degree of cough reflex suppression was evaluated in a subsequent study of identical protocol in which, unbeknownst to subjects, non-nicotine containing e-cigs, with similar vehicle, were used. No effect on cough reflex sensitivity was observed, thus supporting nicotine as the agent within the e-cig vapor responsible for suppression of cough reflex sensitivity (Fig. 4).

A recent animal study supports the proposed antitussive effect



**Fig. 2.** Enhancement of cough reflex sensitivity after cessation of cigarette smoking. C<sub>5</sub> represents the concentration of capsaicin that induces 5 or more coughs, a standard end point of cough reflex sensitivity measurement (from ref. [14], with permission).

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