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The impact of harmfulness information on citric acid induced cough and urge-to-cough

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ABSTRACT

Purpose: The cough reflex is an automatic protective reflex, which can be modulated by conscious effort or other forms of top-down control. In this experiment, we investigated whether information about harmfulness of a cough-inducing substance would augment cough reflex sensitivity and associated urge-to-cough.

Methods: Healthy participants (N = 39) were randomized to receive information that they were to inhale a harmless substance (natural citric acid), or a potentially harmful substance (a potent agro-chemical acid). Using dosimeter-controlled inhalations, the dose of citric acid eliciting at least three coughs (C3) was determined. Next, participants received 4 blocks of randomized presentations of citric acid at the C3 dose, a sub-threshold dose of citric acid and saline control.

Results: C3 was reached for 27/39 participants, and C3 thresholds were not influenced by harmfulness information. During repeated citric acid presentations, framing the cough-inducing substance as a potentially harmful chemical resulted in a greater urge-to-cough compared to information framing it as natural citric acid ($p < .01$). The experimental manipulation did not influence cough frequencies.

Conclusions: Our findings show that harmfulness information influences urge-to-cough, corroborating the role of cortical mechanisms in modulating the urge-to-cough and suggesting that cognitive manipulations may contribute to cough treatment.

Cough is a protective mechanism that helps to defend the airways against outside threats and helps to clear them of excess mucus [1,2]. Cough reflexes occur in response to mechanical or chemical stimulation of the airways [3]. However, cough reflexes are amenable to volitional control, which can result in augmentation, reduction or suppression of cough responses [4]. Furthermore, cough is usually preceded by urge-to-cough: an unpleasant sensation that is characterized by perceived airway irritation and a motivational drive to cough [5]. Both cough responses as well as the associated sensation of urge-to-cough have been shown sensitive to changes in anxiety, attention, disease context, and placebo antitussive medication [6–9], suggesting regulation of the cough response by cognitive processes (cf. [10] for an extended review).

Apart from a protective mechanism, cough is also an unpleasant physical symptom. It is estimated that 10–12% of the population suffers from chronic cough [1]. Although chronic cough can be a symptom of underlying conditions such as asthma, rhinitis or gastroesophageal reflux, in 7–46% of respiratory clinic patients no underlying pathology is found, and patients are diagnosed with idiopathic or medically unexplained cough [11]. In addition, chronic cough has been characterized by a hypersensitive cough reflex, which has led to the adoption of the term “cough hypersensitivity syndrome” to describe individuals that suffer from chronic cough [12,13].

Cough hypersensitivity shares characteristics with other manifestations of hypersensitivity, such as hyperalgesia (pain in response to lower than normal levels of stimulation) or allodynia (pain in response to stimuli that would normally elicit a qualitatively different response), which are both observed in individuals with chronic pain [14,15]. Furthermore, individuals suffering from environmental hypersensitivity have been shown to have a more sensitive cough response to capsaicin compared to individuals that

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do not report symptoms in response to a variety of environmental stimuli [16,17].

Although clinical manifestations of cough hypersensitivity are a well-established phenomenon, there is no consensus on the processes that contribute to this hypersensitivity, and peripheral (afferent) sensitivity, central (spinal cord) sensitivity, as well as descending (brainstem or cortical) control have been proposed as a source of hypersensitivity and a potential target for treatment [14,15].

The role of descending (cortical) control fits the symptom characteristics of sensitivity syndromes, including reactivity to a variety of environmental stimuli as well as multiple symptom manifestations. For example, individuals with idiopathic environmental intolerance show hypersensitivity to a wide variety of chemicals and aversive odors [18], but this hypersensitivity does not differ from sham challenges during double blind challenge tests [19]. Furthermore, individuals with idiopathic environmental intolerance report greater worries about the harmfulness of environmental exposures of a chemical nature, which has led to the hypotheses about the role of harmfulness beliefs in the symptom presentation of individuals with idiopathic environmental intolerance [20]. These hypotheses are corroborated by studies showing that manipulating the perceived harmfulness of environmental exposures increased self-reported symptom levels when negative information was given about the environmental agents that were used during the challenges [21–23].

If changes in perceived threat and harmfulness have an impact on urge-to-cough and cough reflex sensitivity, this would increase the plausibility of threat perception as a contributing factor to cough hypersensitivity. In this experiment, we therefore investigated the impact of harmfulness information on urge-to-cough and cough reflex sensitivity during citric-acid induced cough challenges. We hypothesized that when participants receive the information that an inhaled substance is potentially harmful, this would increase cough frequency and urge-to-cough ratings compared to when participants were told that the substance was harmless.

1. Methods

1.1. Participants

Participants were 45 undergraduate (29 female, 16 male) students who volunteered and received €7 for participation. Exclusion criteria were a diagnosis of asthma, allergies or hay fever, lung disease, poor lung function (<80% predicted FEV1), gastroesophageal reflux, heart disease, epilepsy, other medical conditions, clinical depression, anxiety disorder or another psychiatric disorder, the presence of an electronic implant, or a common cold. Exclusion criteria were listed in the recruitment materials, and checked at the start of the experimental session using self-report. Lung function was assessed using spirometry. Three participants met exclusion criteria. Furthermore, three participants were excluded due to technical difficulties with the dosimeter, resulting in a sample of 39 participants (26 female, 13 male).

1.2. Cough induction

Cough was induced by a 2-sec single breath inhalation of citric acid, using a compressed air-driven dosimeter (Jaeger APS, Hoechberg, Germany). Participants were instructed to take a series of deep breaths through the dosimeter. This was followed by a training trial using an isotonic saline solution.

1.3. Determining cough thresholds

For each individual, five challenges were presented in random order: saline, 30 mM or 5.8 mg/ml citric acid, 100 mM or 19.2 mg/ml citric acid, 300 mM or 58 mg/ml citric acid and 1000 mM or 192 mg/ml citric acid. All inter-trial intervals were 90 s, during which the participant was required to take a sip of water. Reflex cough in response to the challenges was measured in order to define the lowest concentration at which 3 or more coughs occurred (C3 criterion). Although guidelines recommend the use of both C2 and C5 criteria [24], the C3 criterion was chosen as a good balance between reproducibility and clinical validity of the criterion, a choice which has been made previously when using repeated tailored cough challenges to study the impact of psychological variables on cough [7].

1.4. Assessment of cough frequency

Cough sounds were recorded with a microphone connected to a laptop equipped with Adobe Audition, sampling the sound at 44.1 kHz. The microphone was fixed with a clip to the participant's clothes, as close as possible to the mouth. A researcher who was blinded to the group assignment processed cough recordings. During a 30 s epoch following dosimeter activation, every cough-like expulsive event was scored as a single cough, regardless of inspiratory efforts in between.

1.5. Assessment of lung function

Lung function was measured using a spirometer (Jaerger Masterscope, Hoechberg, Germany), in accordance with ERS/ATS guidelines [25], and Forced Expiratory Volume in 1s (FEV1) was extracted as a variable of interest.

1.6. Self-reported urge-to-cough

Perceived urge-to-cough was measured after each cough challenge using a modified vertical Borg scale. Participants indicated their urge-to-cough on a 1-10 scale labeled from “not at all” to “extremely strong”.

1.7. Procedure

The study was approved by the Internal Review Board of University Hospitals Leuven (study number S55169). Participants responded to an advert, which described the study as an investigation of cough reflex sensitivity in response to different airborne substances. Test sessions were conducted in the evening (5–11 pm) in order to reduce diurnal variability in cough reflex sensitivity [26].

Participants were randomly assigned to either low or high threat/harmfulness information. Information about threat/harmfulness was provided to participants as a section in the participant information and consent form. In the low threat/harmfulness condition, participants were informed that they would receive different concentrations of citric acid. The natural origin this substance was emphasized by referring to the fact that citric acid is the main component of lemon juice and that it is produced without any addition of chemical additives. In the high threat/harmfulness condition, participants were informed that they would receive different concentrations of an acid with irritant properties. The chemical origin of this substance was emphasized by framing the substance as a chemical byproduct of the agro-industry and that due to its novelty, there was so far no sufficient research to make a final judgment about the long-term harmfulness of the substance.