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Desensitization of the cough reflex during limb muscle contraction in anesthetized rabbits

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ABSTRACT

The 'cough network' exhibits plasticity at the sensor and integration levels leading to modulation of the strength or pattern of the cough reflex. Little is known about the interactions between cough and human activities, especially during exercise. The present study was designed to determine whether exercise, mimicked by electrically induced muscle contractions, can modify the incidence and/or strength of cough following mechanical stimulation of the trachea in anesthetized rabbits.

Thirteen anesthetized, tracheotomized rabbits were studied by a total of 311 tracheal stimulations: 196 at rest and 115 during exercise.

During muscle contractions, the incidence of the cough reflex (CR) decreased and the expiration reflex (ER) increased ($p < 0.0001$). The sensitivity of the CR and ER both decreased during exercise compared to the sensitivity of the CR at rest ($p < 0.02$), while the strength of the expulsive response remained unchanged.

These results indicate that adjustments occurring during muscle contractions likely downregulate tracheal defensive reflexes in anesthetized rabbits.

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1. Introduction

Cough is one of the most common medical afflictions of mankind and has been extensively studied. Unfortunately, current antitussive medicines are not sufficiently effective and are also frequently associated with potentially harmful side effects [1,2]. A better understanding of the underlying mechanisms involved in modulation of the cough reflex could therefore hopefully lead to better antitussive treatments in the future.

Cough can be triggered by mechanical or chemical irritation of the receptor field of the vagus nerve in order to expel inhaled foreign matter from the lungs or to clear the airways of endogenous mucus. The primary role of this defensive reflex is to protect the airways from potentially harmful agents and afferents located in the airway mucosa are most relevant to this physiological function [3]. The 'cough network' can be tuned by various afferent inputs and exhibits significant plasticity in terms of both sensors [4] and integration [5]. This plasticity commonly consists of an increased or decreased strength of the cough reflex or modification of its pattern. 'Tuning' of cough can therefore be due to either interaction of afferent inputs or sensitization (upregulation) or desensitization (downregulation) of brainstem neural pathways [6,7]. Although the factors involved in modulation of the cough reflex have been extensively studied in the clinical setting and in the laboratory, little is known about the modulation of cough with human activities (i.e. behavioral modulation). Although the diurnal and nocturnal variations of cough, especially during sleep, are well documented, little information is available concerning modulation of cough during talking, laughing, singing, eating, drinking or exercising [8]. Based on empirical (sometimes anecdotal) evidence that some athletes experience inhibition of the cough reflex during exercise (contrasting with post-exercise hyperreactivity), physical activity appears to represent an interesting behavioral condition that may be able to modulate cough [8]. As exercise is associated with profound cardiorespiratory adjustments, ranging from changes in the breathing pattern leading to hyperpnea to activation of chest wall, lung, airway receptors and airway water and heat loss

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[9], the consequences of exercise on cough need to be elucidated. In particular, neural and mechanical mechanisms involved in exercise-induced bronchodilation may also influence cough [10].

As only limited information is currently available concerning the impact of exercise on the sensitivity and strength of cough, the present study was designed to determine whether mechanical stimulation of the trachea can effectively trigger cough during exercise elicited by electrically induced muscle contractions in anesthetized rabbits. We hypothesized that cough may be down-regulated during exercise and, more precisely, that the cough reflex may be switched to an expiration reflex response under exercise conditions.

2. Material and methods

Thirteen anesthetized, tracheotomized New Zealand adult rabbits (3.13 ± 0.3 kg) were studied.

2.1. Anesthesia and surgical preparation

Anesthesia was induced with a mixture of urethane (500 mg kg^{-1}), alpha-chloralose (50 mg kg^{-1}) and sodium borate (50 mg kg^{-1}) injected through an ear vein. Supplementary anesthetic doses were administered intravenously as needed. The cervical part of the trachea was explored via a midline incision, paying attention to avoid damage to the vagal nerves. The rabbits were then tracheotomized and intubated with a steel tracheal cannula inserted caudally, while the rostral part of the trachea was ligated. This preparation allowed spontaneous breathing. An arterial catheter (Arrow 5 Fr) was inserted into the femoral artery allowing arterial pH and PCO_2 measurements (ABL 500, Radiometer, Copenhagen, Denmark) by arterial sampling. Rectal temperature was continuously monitored with an electrical thermistor (Physiotemp Instruments, YSI 402 Clifton, NJ, USA) and maintained at 38 °C using a heated operating pad on which rabbits were placed in the supine position. Animal housing and experiments were performed according to Council Directive 86-609 EEC issued by the Council of the European Communities and under license from "Ministère de l'Agriculture et de la Pêche" and the "Ministère de l'Enseignement Supérieur et de la Recherche" (A5418-03409) and supervision by the "Services Vétérinaires Départementaux de Meurthe et Moselle".

2.2. Breathing pattern and respiratory resistance

Airflow was measured at the tracheal cannula using a heated Fleisch # 0 pneumotachograph (Metabo, Hepalinges, Switz erland) and airway pressure was measured at a side port of the cannula. The flow signal was digitized at 200 Hz, fed to a computer and integrated to volume. Tidal volume (V_T) and flow were displayed breath by breath throughout acquisition and were stored on disk for subsequent analysis. Respiratory resistance (Rrs) was measured by an adaptation of the forced oscillation technique, as described previously [11,12]. The airway opening was attached to a 3-way connector. A loudspeaker (ZR4009A, Bouyer, Montauban, France) connected to one end of the 3-way connector oscillated the transrespiratory pressure at a frequency of 20 Hz. The animal breathed spontaneously through a high-inertance tubing connected to the second connector, while a constant flow source flushed the breathing circuit with fresh air through the third connector to prevent CO_2 accumulation. Rrs was computed from the real part of the complex airway pressure-flow ratio at 20 Hz.

2.3. Tracheal stimulation

The apparatus developed to elicit discrete stimulation of the trachea has been described in detail and validated in previous reports [13–15]. Briefly, a semi-rigid rotating silastic catheter (0.7 mm OD) introduced through the tracheotomy toward the caudal end of the trachea is driven by a small electrical motor (low voltage DC motor 719RE280, MFA/Comodrills, UK) that spins the catheter and rubs the catheter tip on the airway mucosa for a short period of time. The duration of probing can be as brief as 50 ms, corresponding to almost a single probe rotation. The electrical signal from the motor was fed to a computer together with the respiratory signals to allow precise identification of the time-course of the stimulus.

2.4. Rhythmic electrically induced muscle contractions (EMC)

A validated technique was used to induce contraction of hindlimb muscles, previously performed in anesthetized sheep [16] and modified to be as close as possible to the approach used by Cross et al. [17]. Muscle contractions were generated using a timed stimulation frequency applied for 2 s every 4 s. Current intensity was set to between 10 and 30 mA with a rise and fall time of 0.5 s. The hindlimbs were shaved and fitted with stimulating surface electrodes (Dura-Stick Premium, REF 42205, DJO, USA) taped over the skin covering the gastrocnemius lateralis and connected to an electrical stimulator (Neuro Trac Rehab, Verity Medical LTD, UK). Stimulation was maintained for 3–4 min, during which the stimulus intensity was progressively increased from 10 to 30 mA, if needed, in order to at least double resting minute ventilation.

2.5. Arterial blood sampling

Arterial blood samples were drawn from 4 rabbits for pH and PCO_2 measurements at different time-points of the sequence: at rest and during electrically induced muscle contractions (at 1 min, 2 min and 4 min after the beginning of muscle contractions, respectively).

2.6. Protocol

One data acquisition sequence included recording of resting conditions followed by electrically induced muscle contractions (EMC). After a first sequence without tracheal stimulation allowing Rrs measurement, each rabbit was submitted to 2 to 3 sequences (separated by intervals of at least 10 min without stimulation) including tracheal stimulation. Mechanical stimulation of the trachea was performed at rest, while the animal had been breathing quietly for at least 1 min. Stimulations for various durations (50 ms, 150 ms, 300 ms, 600 ms and 1000 ms) were applied in random order. Stimulation times ranging from 50 ms to 300 ms were sufficiently brief to allow triggering of stimulation exclusively during inspiration, whereas stimulation lasting 600 ms and 1000 ms started during inspiration, but ended during expiration (i.e. longer stimulation time than the rabbit's inspiratory time). During EMC and after almost 1 min following onset of muscle contractions, 3 to 4 stimulations were applied at intervals of 1 min. Stimulations were also applied in random order and always during active muscle contraction.

2.7. Data analysis

A reference breath was characterized (at rest and during exercise) by averaging the following parameters on 3 reproducible breathing cycles prior to tracheal stimulation: V_T, peak expiratory

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