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Changes in vagal afferent drive alter tracheobronchial coughing in anesthetized cats

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ABSTRACT

Unilateral cooling of the vagus nerve (<5 °C, blocking mainly conductivity of myelinated fibers) and unilateral vagotomy were employed to reduce cough afferent drive in order to evaluate the effects of these interventions on the temporal features of the cough reflex. Twenty pentobarbitone anesthetized, spontaneously breathing cats were used. Cough was induced by mechanical stimulation of the tracheobronchial airways. The number of coughs during vagal cooling was significantly decreased ($p < 0.001$). Inspiratory cough efforts were reduced by approximately 30% ($p < 0.001$) and expiratory motor drive by more than 80% ($p < 0.001$). Temporal analysis showed prolonged inspiratory and expiratory phases, the total cycle duration, its active portion, and the interval between maxima of the diaphragm and the abdominal activity during coughing ($p < 0.001$). There was no significant difference in the average effects on the cough reflex between cooling of the left or the right vagus nerve. Compared to control, vagal cooling produced no significant difference in heart rate and mean arterial blood pressure ($p > 0.05$), however, cold block of vagal conduction reduced respiratory rate ($p < 0.001$). Unilateral vagotomy significantly reduced cough number, cough-related diaphragmatic activity, and relative values of maximum expiratory esophageal pressure (all $p < 0.05$). Our results indicate that reduced cough afferent drive (lower responsiveness) markedly attenuates the motor drive to respiratory pump muscles during coughing and alters cough temporal features. Differences in the effects of unilateral vagal cooling and vagotomy on coughing support an inhibitory role of sensory afferents that are relatively unaffected by cooling of the vagus nerve to 5 °C on mechanically induced cough.

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1. Introduction

Vagal afferents play an important role in evoking respiratory reflexes in response to the mechanical and chemical stimulation of the airways (Canning et al., 2006; Korpas and Tomori, 1979; Widdicombe, 1998). Coughing can be partially or completely abolished by vagal cooling or vagotomy (Widdicombe, 1954; Klassen et al., 1951; Adams et al., 1987; Tatar et al., 1994; Canning et al., 2004). Cooling of the vagus nerve simulates a production of the cough reflex with lower excitability, but without direct suppression of cough receptor responsiveness, while vagotomy represents a model of total interruption of vagal afferent feedback. The vagal cooling technique is based upon the fact that the neural conduction of myelinated fibers can be blocked by cooling the nerve trunk to 6–7 °C. Mean blocking temperature of non-myelinated fibers is 2.7 °C (Coleridge and Coleridge, 1984; Franz and Iggo, 1968; Jonzon et al., 1988). However, two subgroups of lung vagal C-fibers were reported by Chen et al. (1999) based upon their different blocking thresholds. A high resistance to capsaicine vagal C-fibers were blocked at 5–3 °C, while low resistance to capsaicine fibers at relatively low temperature from 2 to −2 °C.

Reduced mechanically induced tracheobronchial cough during bilateral vagal cooling to 7–14 °C has been described in cats (Widdicombe, 1954) and rabbits (Sant'Ambrogio et al., 1980). Similar approach in anesthetized dogs (bilateral vagal cooling to 6 °C) eliminated tracheobronchial cough and markedly reduced excitability and intensity of laryngeal cough (Tatar et al., 1994). Cough number was decreased and total cough cycle time was prolonged after unilateral vagotomy in anesthetized rabbits (Hanacek et al., 1984).

Although several animal studies showed the effects of vagal cooling or vagotomy on tracheobronchial cough (Widdicombe, 1954; Klassen et al., 1951; Adams et al., 1987; Tatar et al., 1988; Canning et al., 2004) the influence of graded modulation of vagal

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afferents on cough spatio-temporal parameters has not been systematically studied. There is a vast amount of evidence that the activation of airway C-fibers does not evoke cough in anesthetized animals (Tatar et al., 1988; Widdicombe, 1998; Canning et al., 2004, 2006) and there is some evidence that C-fibers may inhibit cough (Canning et al., 2006; Tatar et al., 1988). These results support a hypothesis that C-fibers have a modulatory effect on mechanically induced cough, even under general anesthesia. Under such conditions, the effects of vagal cooling and vagotomy may slightly differ due to differences in the activity of non-myelinated fibers. Indeed, cough can be induced by stimulation of C-fibers receptors in the lower airways or larynx in the awake state (Collier and Fuller, 1984; Midgren et al., 1986; Paintal, 1986; Forsberg and Karlsson, 1986, 1987; Karlsson, 1987; Fuller et al., 1987).

Our study provides a complete spatio-temporal analysis and correlation analysis of effects of unilateral cold blockade and additionally by hemivagotomy on the mechanically induced tracheobronchial cough in anesthetized cats. The relative contribution of myelinated and non-myelinated fibers in controlling of spatio-temporal parameters of tracheobronchial cough might be derived from comparison of partial (unilateral) cooling of the vagus nerve below 5 °C and the hemivagotomy effects on cough. We hypothesized that in addition to a reduction in the magnitude of respiratory muscle motor drive, significant changes in the temporal characteristics of coughing would be induced during graded changes in vagal afferent feedback. If vagal C-fibers activation is primarily cough inhibitory in anesthetized preparation (Tatar et al., 1988) we expect to see more cough inhibition during cooling than after vagotomy. That would confirm a possible inhibitory role of vagal C-fibers in modulation of cough during partial vagal block.

2. Material and methods

2.1. Experimental protocol

All procedures were performed in accordance with the laws, rules, and regulations of the Slovak Republic and with the Directive 2010/63/EU of the European Parliament. Protocols were approved by the Ethics Committee of Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava. Experiments were performed on 20 spontaneously breathing cats (16 males; 3.31 ± 0.16 kg) anesthetized with sodium pentobarbital (Biowet, Pulavy, Poland; 40 mg/kg, i.p.). Supplemental doses of the anesthetic agent were administered (1–3 mg/kg, i.v.) as needed, if the withdrawal responses to the paw pinch appeared and/or significant jaw tone and corneal reflex occurred. Atropine (Biotika; 0.15 mg/kg, i.v.) was given at the beginning of the experiment in order to reduce bronchial mucus secretions. The trachea, femoral artery and vein were cannulated. The animals were allowed to breathe spontaneously a gas mixture of 30–60% oxygen. Arterial blood pressure (BP), end-tidal CO_2 concentration ($ETCO_2$), respiratory rate (RR) and body temperature were monitored continuously. Body temperature was maintained at 38.0 ± 0.5 °C. Samples of arterial blood were periodically (before and after the protocol sequence) removed for blood gas and pH analyses. Bipolar fine wire hook electrodes were placed in the sternal diaphragm (DIA), bilaterally in the transversus abdominis and/or the external oblique abdominal muscles (ABD) for electromyogram (EMG) recordings. A soft balloon was inserted into the esophagus for measurement of intrathoracic pressure (esophageal pressure—EP). The cough reflex was induced by mechanical stimulation of the tracheobronchial mucosa with a soft nylon fiber or a soft catheter (with external diameter <1.0 mm). The stimulating fiber/catheter was inserted into the trachea and moved back and forth and rotated approximately once per second during 10 s interval. When the cough response was very high, we employed 5s stimulations in 5 out of 25 cooling protocols. Cough was defined by a large augmenting burst of DIA EMG activity immediately followed (and partially overlapped) by a burst of expiratory ABD EMG activity (Jakus et al., 1987, 2004) and corresponding inspiratory–expiratory (I–E) wave of EP.

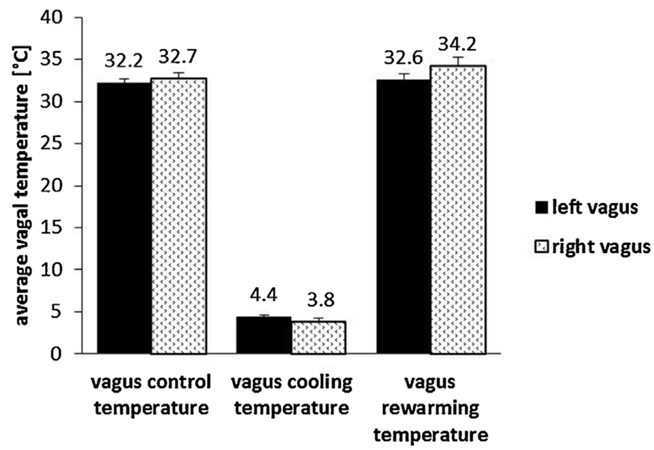

Fig. 1. Average vagal temperatures before, during and after cooling (rewarming).

The vagus nerves were exposed in the mid-cervical region over a length of about 15 mm and bilaterally or unilaterally isolated from their surrounding connective tissues and retained on aluminium cooling plates with a hooked-shaped end (the width of the terminal hook was 12 mm). The thermocouple tip was placed on a nerve surface to monitor the vagal temperature. After the vagus was hooked inside the cooling plate a small piece of cellulose cotton was placed underneath the plate to prevent contact with surrounding tissues and vessels. The vagus on the plate was covered with paraffin jelly to prevent drying. The control temperature as well as temperatures during cooling and rewarming of the right or left vagus nerve are given in Fig. 1. Cooling was performed by the addition and removal of dry ice pieces to the body of cooling plate (the length 12 cm, the width 2 cm) that ended with the hook. Dry ice was never allowed to directly touch the nerve; it was never placed closer than 2 cm from the hook with the nerve. The cough stimulation protocol was performed immediately after the desired temperature of vagus nerve was achieved. In the control studies of unilateral cooling of cervical sympathetic nerve of the vagosympathetic trunk, these nerves were isolated from each other and cervical sympathetic trunk was placed on the cooling hook. The cervical sympathetic trunk was cooled independently to the average temperature of 4.4 ± 0.5 °C, while the temperature of vagus nerve under the cooling plate stayed well above 20 °C. Based on the data obtained when cooling of cervical sympathetic trunk (with no effect on cough; see Section 3) we performed vagal cooling on the whole vagosympathetic trunk in 8 cases (out of 20 cases of vagal cooling).

Our preliminary data showed no significant difference in cough reduction at vagal temperatures approximately 4 °C and 0 °C (*e.g.* reductions in cough number to 47% *vs.* to 40%, in ABD EMG amplitudes to 41% *vs.* to 40%, and in E EP maxima to 39% *vs.* to 42%, all $p > 0.21$, $n = 4$). Thus, instead of an attempt to block non-myelinated fibers by cooling, in 8 animals unilateral vagotomy (by transverse cut of vagus nerve in the mid-cervical region) was performed at the end of experiment and cough was tested immediately after section of the nerve. Five of these cats were earlier included in "vagal cooling" protocols. Other protocols (in the average 2.25 protocols, $n = 8$ cats) on coughing were completed before the vagotomy, as well.

2.2. Data processing and analysis

All EMGs were amplified, filtered (300–3000 Hz; GRASS), digitized (12-bit multi-function plug-in ISA card, Dataq Instruments,

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