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CONVERGENCE OF NASAL AND TRACHEAL NEURAL PATHWAYS IN MODULATING THE COUGH RESPONSE IN GUINEA PIGS

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In the present study we investigated the possibility of central convergence of neural pathways coming from distant anatomical regions in modulating the cough response. We addressed this issue by inducing cough from the tracheo-bronchial region on the background of capsaicin-stimulated and mesocain-blocked nasal mucosa in 14 anesthetized guinea pigs. The control group consisted of 6 guinea pigs in which the active agents, capsaicin and mesocain, were substituted for by inert physiological saline. All animals were tracheostomized, and the larynx was disconnected from the proximal part of the trachea with preserved innervations, and all were subjected to the same protocol. Cough, induced by mechanical irritation of the tracheo-bronchial mucosa, was elicited three times: in the control condition, after intranasal capsaicin challenge, and after another capsaicin challenge preceded by intranasal instillation of a local anesthetic, mesocain. The main finding of the study was that the number of cough efforts per bout, assessed from positive deflections on the intrapleural pressure recordings, was significantly enhanced by intranasal capsaicin challenge and this effect was reversed by intranasal pretreatment with the anesthetic mesocain [2.1 ±0.2 (control) *vs*. 3.5 ±0.4 (capsaicin) *vs*. 2.2 ±0.2 (capsaicin after mesocain) (P<0.01)], with no appreciable changes in the magnitude of cough efforts. The cough response in the control group remained unchanged. We conclude that tracheo-bronchial cough may be modified by neural sensory input to the brain coming from nasal mucosa. Therefore, cough reflex is subject to central convergence of peripheral neural pathways originating at distant anatomical locations.

K e y w o r d s: *capsaicin, cough, guinea pigs, neural pathways, nasal mucosa*

INTRODUCTION

Diseases of the nose and sinuses, frequently in combination with other conditions, are the most common cause of chronic cough (1). Chronic cough accompanying various forms of rhinitis and sinusitis is part of a condition previously termed postnasal drip syndrome, currently renamed to the upper airway cough syndrome (UACS) (2). Cough reflex sensitivity, as measured by the lowest dose of a tussigen that evokes cough, is substantially increased in some patients with UACS (3-5). The pathogenesis of chronic cough due to UACS is not completely understood. One proposed mechanism is stimulation of nerve-endings in nasal mucosa by inflammation.

Cough hypersensitivity associated with rhinitis/sinusitis could result from increased sensory output from nasal afferent nerves. However, stimulation of nasal afferents does not directly trigger cough. Consequences of nasal inflammation regarding the cough reflex are several-fold. There could be a direct stimulation of cough reflex due to secretions from the nose or sinuses dripping down to the hypo-pharynx, aspiration of inflammatory secretion from these regions into lower airways, reversible obstruction of extra-thoracic airways (6), or excessive drying of lower airways due to inadequate nasal air conditioning (7).

Afferent inputs from upper airway regions, perhaps even anatomically apart, may interact at the central level with those passing from nasal mucosa to enhance the cough reflex (8).

Previously, we have reported facilitation of the cough response during intranasal capsaicin instillation in anesthetized cats and guinea pigs, in conscious guinea pigs, and in human healthy volunteers (9, 10). The aim of the present study was to examine the role of nasal nerve endings in the facilitation of cough arising from the irritation of the tracheo-bronchial region. We addressed this issue by inducing cough against the background of capsaicin-stimulated and mesocain-blocked nasal mucosa. The study lends support for the notion that the cough response is substantially modified by peripheral sensory inputs distant to the original location of cough-inductive afferents, which, in all likelihood, merge at the central level. Minor aspects of nasal mucosa anesthesia effects on the cough response have previously been published in the conference proceedings (11).

MATERIAL AND METHODS

The study protocol was approved by the Ethics Committee of the Jessenius Faculty of Medicine in Martin, Slovakia. Male TRIK strain guinea pigs were obtained from the Department of Experimental Pharmacology, Slovak Academy of Science (Dobra Voda, Slovakia) and were used after at least 1-week adaptation period. The animals, weighing 530 ±50g, were kept in the institutional Animal House at room temperature of 21-22°C, humidity of 60-70%, at a 12-h light/dark cycle with the lights on

8 a.m. and off 8 p.m. and had free access to water and standard animal chow.

A total of 20 guinea pigs were used for the study. Fourteen of them were used for the experiments aimed at making nasal mucosa to respond and another 6 were used as controls to assess the stability and reproducibility of the tracheo-bronchial cough with time. On the day of the experiment, the animals were anesthetized with urethane (1.1 mg kg^{-1}, i.p., Riedel de Haen AG, Germany) and were placed in the supine position on a heated operating pad. Body temperature was continually monitored and maintained at 37-38°C. The animals were then subjected to surgical instrumentation.

Mechanically-induced cough

Cervical part of the trachea was explored after a midline incision and subsequent preparation of muscles and deeper structures in this region. The larynx was surgically disconnected from the proximal part of the trachea, with attention being paid not to damage the vagal and laryngeal recurrent nerves. A plastic cannula (3 mm of external diameter) allowing spontaneous breathing was introduced into the trachea between the 7-9th tracheal rings. A metal intrapleural cannula was introduced into the right hemithorax *via* the incision of the anterior thoracic wall at the 5th intercostal space and was connected to electromanometer (Electromanometer HSE, Hugo Sachs Electronics, Germany) for recording the intrapleural pressure. Cough was evoked by mechanical stimulation of the tracheo-bronchial region. To stimulate this region, a nylon fiber (diameter 0.3 mm) was introduced through the tracheal cannula with its tip positioned near carina (at a distance of 3-4 cm from the 7th tracheal ring). Repeated caudal advancements (5 movements) of the fiber were performed during 7 s to mechanically stimulate the carina and nearby airways.

Experimental protocol

Capsaicin (15 μl, 50 mol l^{-1}, Sigma Chemicals, St. Louis, MO) was instilled unilaterally into the nostril (in 2 s) using a thin plastic catheter (external diameter 1 mm) with the tip positioned 6-7 mm from the nares. After recording cough responses in capsaicin-treated animals, nasal mucosa was gently washed out of capsaicin remnants by intranasal administration of saline, using analogous plastic catheter. Saline was sucked up from the nasopharynx *via* a thin catheter connected to the suction device introduced through the mouth. Capsaicin challenge was performed twice, before and after mesocain-induced anesthesia of nasal mucosa.

To knock-out sensory nerve endings, nasal mucosa was topically anesthetized with 1% solution of trimecain hydrochloridum (MESOCAIN®, Zentiva, Czech Republic). To preserve innervations of the other parts of airways, mesocain was instilled intranasally *via* a thin catheter introduced into the nasopharynx through a small opening of the lateral and proximal esophageal wall. Nasal cavity was completely filled with the anesthetic during the 5 min interval. The animals were positioned head down to prevent dripping of the solution into the most proximal parts of larynx. After that, the nasal cavity was washed out with saline.

Cough was evoked by mechanical stimulation of the tracheo-bronchial region during three consecutive conditions: (i) basic control - 5 min prior the intranasal capsaicin instillation, (ii) immediately after intranasal capsaicin instillation, and (iii) after a repeated capsaicin challenge that followed mesocain anesthesia of nasal mucosa.

In the control, untreated animals cough was provoked at baseline, after intranasal instillation of 15 μl saline, and finally, after filling nasal cavities with saline for 5 min to emulate the local anesthesia procedure (*Table 1*).

Table 1. Cough response in the control guinea pigs. Cough was provoked mechanically from the tracheo-bronchial region in untreated animals (Control), taken as basic control, after intranasal instillation of 15 μl saline (Saline), and finally after filling nasal cavities with saline for 5 min to emulate the local anesthesia procedure (Sham anesthesia). No statistical differences were evident among the experimental groups concerning each parameter.

	NE (Count)	MEE (kPa)	ICB (kPa)	AEE (kPa)
Basic control	1.8 ±0.3	11.9 ±0.6	19.2 ±2.3	10.9 ±0.8
Saline	1.7 ±0.2	13.1±0.5	19.8 ±3.1	11.5 ±0.7
Shame anesthesia	1.7 ±0.2	12.3 ±0.7	19.6 ±5.1	11.8 ±0.4

NE - number of expiratory efforts during a cough bout, MEE - maximum expiratory effort, ICB- intensity of cough bout, AEE - average expiratory effort. Values are means ±SE.
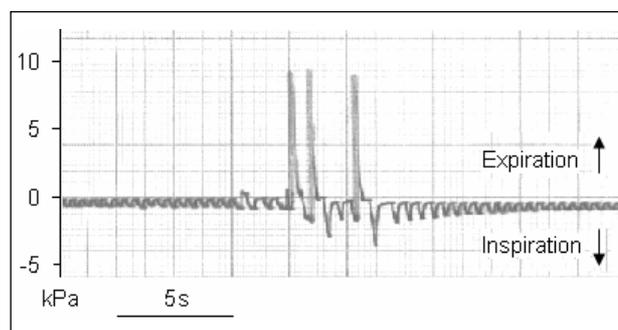

Fig. 1. Original recording of intrapleural pressure deflections during a cough bout in an anesthetized guinea pig.

Assessment of the cough intensity

Cough was detected from the positive deflections of intrapleural pressure (*Fig. 1*) accompanied by a typical cough sound in tracheostomized guinea pigs. The cough response was evaluated using the following quantitative parameters:
- number of cough efforts (NE) = number of expiratory efforts during a cough bout;
- intensity of the cough bout (ICB) = summary amplitude of all positive deflections of intrapleural pressure during all cough efforts in a cough bout;
- maximum expiratory effort (MEE) = maximum positive deflection of intrapleural pressure during a cough attack, measured in kPa;
- average expiratory effort (AEE) = ratio of ICB/NE

Statistical analysis

Data were expressed as means ±SE. Parameters of the cough response among the three experimental provocations were analyzed by one way ANOVA and *post hoc* Tukey´s test. $P<0.05$ was considered to indicate statistical significance. Statistical elaboration was performed with a commercial Systat ver. 11 software package (Systat Software, Richmond, CA).

RESULTS

The intranasal capsaicin challenge significantly enhanced the cough response to mechanical irritation of the trachea. In response to capsaicin challenge, we found significant increases in the number of counted cough efforts [NE: 2.1 ±0.2 (control)
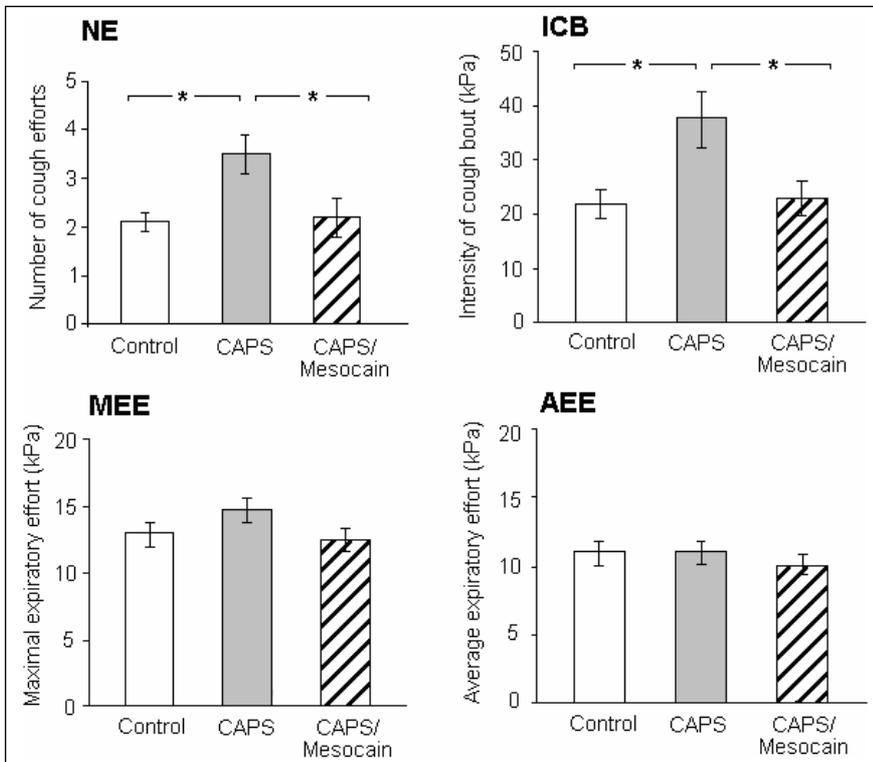
Fig. 2. Parameters of cough response provoked by mechanical stimulation of tracheo-bronchial mucosa in anesthetized guinea pigs in the control condition (Control), intranasal capsaicin challenge (CAPS), and repeated capsaicin challenge following local mesocain anesthesia (CAPS/Mesocain, P<0.01. NE - number of expiratory efforts during a cough bout, ICB- intensity of cough bout, MEE - maximum expiratory effort, AEE - average expiratory effort. Values are means ±SE.

vs. 3.5 ±0.4 (capsaicin) *vs.* 2.2 ±0.2 (capsaicin after mesocain)] and in the intensity of cough bouts [ICB: 21.5 ±2.5 kPa (control) *vs.* 36.7 ±5.1 kPa (capsaicin) *vs.* 22.9 ±3.0 kPa (capsaicin after mesocain)]. Characteristically, the increases were abolished by topical anaesthesia of nasal mucosa. The increases in both indices due to capsaicin stimulation differed significantly from both the control and the capsaicin after mesocain anesthesia level (P<0.01). The other two parameters considered, maximum expiratory effort (MEE) and average expiratory effort (AEE), remained unchanged in response to capsaicin challenge (*Fig. 2*). Since the average expiratory effort was taken as the ratio of cough intensity, which was the sum of pressure deflection amplitudes in a bout, to the number of coughs in a bout, and the maximum amplitude of a pressure deflection remained unchanged, it follows that the increase in the intensity actually corresponded to the number of coughs.

None of the above-mentioned parameters describing the tracheo-bronchial cough were appreciably altered during repeated tracheo-bronchial stimulations in the control animals treated with intranasal application of saline, substituted for both the stimulus capsaicin and the anesthetic mesocain (*Table 1*).

DISCUSSION

The major findings of the present study were that intranasal challenge with capsaicin clearly enhanced cough induced by mechanical stimulation of the tracheo-bronchial region and that the enhancement was reversed by topical anesthesia of the nasal mucosa. These effects incriminate afferent sensory neural pathways, originating in nasal mucosa, in the regulation of cough responses. Part of the present study dealing with intranasal capsaicin challenge conforms with previous reports in which stimulation of nasal airway afferents with capsaicin leads to an augmentation of the cough response induced by chemical and mechanical tussigenic stimuli in anesthetised cats and guinea pigs, conscious guinea pigs (9), and in human volunteers (10).

The interaction and mutual functional potentiating of disparate afferent pathways, and also their convergence in the central nervous system, is an intensely studied phenomenon in the somatosensory systems. Such effects have been proposed to be important in the pathogenesis of pain syndromes (12). Recent studies demonstrated a similar 'cooperating' phenomenon in the respiratory system (13). Such mechanisms are liable to be operational in the enhancement of the cough response due to stimulation of nasal mucosa, although there has not yet been clear evidence for that. Reversal of capsaicin-induced enhancement in cough by a local anesthetic instilled into the nostril lends support for neuronal origin of cough.

It is known that the population of nasal afferents contains a substantial proportion of capsaicin sensitive nerve endings; about 53% of these afferents respond to capsaicin (14, 15). The retrograde DiI labeling reveals cell bodies of the affected nerve endings in the medial and rostral parts of the ganglion Gasseri, which is the origin of the ophthalmic branch of the trigeminal nerve, and in the lateral field of the ganglion, which is the origin of the maxillary branch of the trigeminal nerve. The nerve endings are activated by intranasal capsaicin receptors, which belong to a family of transient receptor potential vanilloid type 1 (TRPV1) receptors (16). These receptors are liable to be stimulated by vasodilation, plasma exudation, and increase in nasal airway resistance and nasal secretion; all of which leads to nasal obstruction, nasal discharge, and sneezing, all the effects induced by intranasal capsaicin (16-18). Another TRPV1 stimulation may also come from an intensive unpleasant burning sensation, sometimes described by volunteers to be painful, often resulting from capsaicin application into the nose (10).

Despite evidence of capsaicin action in nasal mucosa, postnasal dripping or aspiration of nasal discharge into the more distal parts of the airways cannot be excluded from having an augmentative effect on cough. Such mechanisms should usually be considered, particularly, in conscious animals with intact airways and humans. Inhalation of capsaicin aerosol clearly affects airway afferent endings in such settings, as evidenced by

enhanced cough reflex sensitivity in subjects suffering from seasonal allergic rhinitis, even being out of pollen season (19), or in female adolescents (20),

In the present experiments, the larynx and trachea were surgically disconnected. Therefore, the possibility of the nasal discharge getting into the tracheo-bronchial tree could be excluded. This procedure and a head-down position of animals during challenges also prevented a leakage of both capsaicin and mesocain into the tracheo-bronchial tree. The "tussigenic" areas (larynx and/or tracheo-bronchial tree) could not be affected by intranasal capsaicin and mesocain application either. Thus, these areas could not be a direct trigger of biphasic changes of the cough response observed; an initial increase after intranasal capsaicin and a later return to the pre-capsaicin level after applying local anesthesia to nasal mucosa. Nor could repeated capsaicin stimulation of the laryngeal TRPV1 system cause central cough sensitization, which, from other studies, is known to occur (21). Since the larynx was disconnected in our preparation, capsaicin could reach only the most proximal laryngeal mucosa by the mechanism of mucociliary transportation. It is rather unlikely that this mechanism affected our data, the more so that very small volumes of an intranasal stimulant were applied and only two capsaicin challenges with cough stimulations were performed, all of which taking place during a period far shorter than that required for effective mucociliary transportation (22).

In the present study, the cough response was not altered in control animals in which intranasal saline was used instead of the active agents, capsaicin and local anesthetic. Likewise, exposure to a sequence of three consecutive stimulations alone had no appreciable affect on cough.

We propose that afferent impulses from the nose, carried into the brain *via* trigeminal nerves (23), could synergistically interact with those from the tracheo-bronchial region, carried *via* vagal nerves, at the level of the brainstem neuronal circuits of cough. Synergistic interactions between disparate afferent inputs, such as the carotid sinus and superior laryngeal nerves (24) or extrapulmonary and airway afferents (25), take place at the level of the nucleus tractus solitarii (NTS). In the latter case, the central convergence is implicated in the mediation of bronchial hyperreactivity in the guinea pig; having, therefore, pulmonary consequences of extrapulmonary nociceptive or visceral disturbances (25). The NTS region also seems a central preponderant site of neurotransmitter modulation of the cough reflex originating in the upper airways (26) and of plasticity phenomena engaged in cough modulation (27). The tracheo-bronchial tree is equipped with rapidly adapting receptors whose central projections enter the NTS-cough modulating neuronal network (26). These and other vagal afferents originating in the tracheo-bronchial tree are involved in cough mediation in response to punctuate mechanical stimulation in the anesthetized guinea pig or rabbit (26, 28).

The brainstem mechanisms responsible for the generation and control of the cough reflex remain as yet not fully resolved. Recently, a functional gating mechanism, increasing cough reflex excitability, has been ascribed to the caudal ventral respiratory group, associated with the nucleus retroambigualis and containing mostly premotor expiratory neurons (29). The underlying mechanisms of cough suppression by doing away with the sensory input from nasal mucosa in the present study are unclear. A reduction in the number of coughs might be due to a sudden interruption in the upflow of nasal input, suppression of the cough excitatory gating mechanism, or reshaping of the cough controlling network toward less excitatory output being directed to spinal motoneurons. The exact determinants of suppression of the nasal capsaicin-stimulated cough by anesthesia applied to the nasal mucosa could not be discerned in

our investigation and would require an alternative study design. Nor could it be unequivocally discerned whether the unchanged expiratory effort noted in the present study was due to a peripheral, such as the maximum tracheal stimulation, or central mechanism, such as a differing mode of timing or amplitude patterns of cough efforts. A complex cough gating mechanism with its cross-medullary and downward spinal projections (30) seems to speak in favour of the central effect.

We conclude that activity of the first nasal afferent neuron and, therefore, the afferent outflow from the nose is crucial for the augmentation of mechanically-induced cough from the tracheo-bronchial region in anesthetized spontaneously breathing guinea pigs. Our findings suggest that further explorations are warranted to ascertain the role nasal mucosa in tracheo-bronchial cough control.

Conflicts of interest: The authors declared no conflicts of interest in relation to this article.

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Bronchial breathing is heard normally over the larynx, the trachea in the neck, and at the site of projection of the tracheal bifurcation (anteriorly over manubrium, and posteriorly in the interscapular region at the level of T3 and T4 spinous processes) (Fig. 8). 6. Fig. 8. Trachea and main bronchi projection on the chest. Bronchial breath sounds are inaudible over the lungs because bronchi are covered by air-containing 'pillow' of the pulmonary tissue. If bronchial breathing is heard over the lungs, suspect that air-filled lung has been replaced by fluid-filled or solid lung tissue, which co... In modulating the cough response in guinea pigs. 1Department of Pathophysiology and 3Department of Medical Biophysics, Jessenius Faculty of Medicine, Comenius University, Martin, Slovakia; 2Department of Respiratory Research, Medical Research Center, Polish Academy of Sciences, Warsaw, Poland. In the present study we investigated the possibility of central convergence of neural pathways coming from distant. anatomical regions in modulating the cough response. convergence of peripheral neural pathways originating at distant anatomical locations. Key words: capsaicin, cough, guinea pigs, neural pathways, nasal mucosa. 8 a.m. and off 8 p.m. and had free access to water and standard. animal chow. The response to drugs and the therapeutic response to oxygen can then be monitored easily. Haemoglobin saturation reflects oxygen carriage by the blood and thus the adequacy of tissue oxygenation (if perfusion is satisfactory) and the requirement for oxygen therapy. This can be measured noninvasively by pulse oximetry (Fig.9 &10). Because guinea pigs with dental disease often have concurrent disease processes, a thorough systemic evaluation is indicated before dental treatment is initiated. Dental disease is very commonly identified in guinea pigs presenting with signs of GI stasis. Hepatic lipidosis can occur secondary to anorexia, especially in obese guinea pigs. Clinical signs of GI stasis include decreased/absent fecal material, anorexia, bruxism, gas or fluid-distended stomach, cecum, and bowel loops, pain on abdominal palpation, decreased gastrointestinal sounds, and respiratory or cardiovascular compromise. a Adult CF Centre, Northern General Hospital, Herries Road, Sheffield, S5 7AU, UK b Lund CF Centre, Department of Respiratory Medicine, Lund University Hospital, SE-221 85 Lund, Sweden. c Heart of England NHS Foundation Trust, Birmingham Heartlands Hospital, Birmingham, B9 5SS, UK d Italian CF Research Foundation, Ospedale Maggiore, Piazzale Stefani, 1-37126 Verona, Italy e Consultant Nurse, Royal Brompton Hospital, Sydney Street, London, SW3 6NP, UK. f Adult CF Centre — Lung Transplant Unit, Service de Pneumologie, Hôpital Erasme, 808, Route de Lennik, 1070 Bruxelles, Belgium g Regional Adult...