COUGH IT UP

Simulation and modeling in understanding of airway defensive mechanisms

PROGRAM and ABSTRACTS

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Simulation Educational Center
Department of Pathological Physiology
Department of Medical Biophysics

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30 th June - 2 nd July 2014

VENUE & CONTACT

Simulation Educational Center of Jessenius Faculty of Medicine
Novomeskeho St. 7A, MARTIN

Organizing committee

Assoc. prof. **Jana Plevkova** MD, PhD, Assoc. prof. **Ivan Poliacek** Dr, PhD,
Assoc. prof. **Juraj Mokry** MD, PhD, **Martina Antosova** MSc. PhD, MBA,
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„Saving life through simulation technology“

Session chairs

Professor **Jan Jakus,** MD, DSc
Professor **Jan Hanacek,** MD, CsC
Professor **Milos Tatar,** MD, CsC
Professor **Donald C. Bolser** PhD

Monday, JUNE 30th

Round table (organizers and guests): International cooperation. The future of Cough it up meeting.

Tuesday, JULY 1st

Discussion panel (invited professionals): Simulation and modeling of neuronal processes involved in regulation of breathing and airway protective mechanisms.

Wednesday, July 2nd

Session 1: **Modeling as an approach to understanding** (chairs: DC Bolser, M Tatar)

13:00 **TE Pitts**: Stimulation of repetitive cough in humans

13:25 **D Baekey**: Multielectrode recording: Developing the tools to define respiratory network assemblies

13:50 **M Veternik**: Computer modeling of D,L - homocysteic acid microinjection into the Bötzinger complex

14:05 **S Gavliakova**: Graphical tool for 3-D quantitative visualization of neuronal population in the brainstem – aspiration reflex, exspiration reflex and cough – comparison to tidal breathing

14:20 **L Babalova**: Depression of coughing during reduced cough afferent drive in the vagus nerve of cats

14:35-15:00 Coffee break

Session 2: **Cough reflex up-date – novel information from experimental and clinical studies** (chairs: J Hanacek, J Jakus)

15:00 **DC Bolser:** Role of the medial medullary reticular formation in the control of airway protection

15:30 **GA Fontana:** Value of deflation cough in the exclusion of acidic reflux in patients with gastro-oesophageal disorders and chronic cough

16:00 **M Simera**: Cough and sneeze: a separate or a common CPG?

16:15 **B Dobrolubov**: GABA microinjections in the medullary raphe of cat, effects on cough

16:30 **J Mokry**: Phosphodiesterases and cough

16:45 **[a]Sivová Veronika,[a] Flešková Dana, [a]Jureček Ľudovít, [b]Ray Bimalendu, [a]Nosáľová Gabriela**
Cough suppressive activity of herbal polysaccharides. [a]Department of Pharmacology Jessenius Faculty of Medicine in Martin, [b]Department of Chemistry, The University of Burdwan

Our guests:

Teresa Pitts

Teresa´s research has brought to light the co-existence of disordered swallow and cough in Parkinson's disease which puts these patients at risk for significant respiratory complications. Pertinent findings included the viability of using voluntary cough to detect at-risk patients for swallowing disorders, and then treating those at-risk patients with Expiratory Muscle Strength Training which improved cough and swallowing safety scores. She is currently working to develop a model of airway protection including dysphagia (disorder of swallow) and dystussia (disorder of cough) for testing of novel therapies to extend the quality-of-life of persons living with neuromuscular diseases.

Don Bolser

The long-range goal of prof. Bolser´s laboratory is to delineate the how the nervous system produces and regulates cough. They use antitussive drugs as tools to determine how the cough system is controlled. As such, their work also will expand the knowledge of the mechanisms by which these drugs inhibit cough. Our current approach incorporates the use of multiple extracellular electrode array technology to investigate the behavior of spontaneously active and recruited neurons in the brainstem during cough. Determination of the identity and functional relationships between these neurons will allow modeling of the configuration of the brainstem cough network.

David Baekey

David´s research involves the neural control of respiratory and cardiovascular control. Previous work has focused on airway defensive reflexes altering distributed brainstem neural networks involved in respiratory control. Present projects are focused on the coordination between respiration and sympathetic outflow. Unique methods include ensemble recordings (multi-electrode extracellular array) of in vivo and in situ preparations and computer simulations of neural networks inferred from collected data

Giovanni Fontana

Prof. Fontana is a world recognized expert on the physiology and pathophysiology of cough. He is a clinician with huge physiology basis, running specialized cough clinic in Florence, Italy, with attention given to the patients suffering from chronic cough. His research described problems with cough in subjects with Parkinson disease, and he is interested also in so called paradoxical reflexes. Together with his team he described Fontana´s paradoxical reflex, and they are now working on the concept of deflation cough, and its significance in health and disease.

DEPRESSION OF COUGHING DURING REDUCED COUGH AFFERENT DRIVE IN THE VAGUS NERVE OF CATS

Lucia Babálová, Marcel Veterník, Michal Šimera, Peter Macháč, Nadežda Višňovcová, Boris Dobroľubov, Ján Jakuš, Ivan Poliaček

Comenius University in Bratislava, Jessenius Faculty of Medicine in Martin, Institute of Medical Biophysics, Martin, Slovakia

Tracheobronchial coughing during unilateral cooling of the vagus nerve (<6℃, blocking mainly myelinated fibers) and after unilateral vagotomy was studied on 18 pentobarbitone-anesthetized, spontaneously breathing cats (3.29±0.18 kg).

Cough reflex was induced by mechanical stimulation in the tracheobronchial region. EMGs of the diaphragm and the abdominal muscles, together with blood and esophageal pressures were recorded.

The number of coughs (related to 10s stimulus) during the vagal cooling was 3.1±1.0 vs. control (trials before and after the cooling period) 10.5±2.5 ($p<0.001$). Inspiratory cough efforts were reduced by approximately 1/3 ($p<0.01$) and expiratory ones by more than 80% ($p<0.001$). Inhibition of the coughing by cold block shows no uniform effect. There was no difference between cooling effects of left vs. right vagus, however, the number of coughs and their expiratory strength significantly differed between substantial vs. limited reductions.

Temporal analysis showed prolonged inspiratory, expiratory phase, the total cycle duration, its active portion, and the distance between maxima of the diaphragm and the abdominal activity during cough.

No differences in heart rates and mean arterial blood pressures were seen, however, cold block of vagal conduction reduced respiratory rate.

Control cooling of the sympathetic trunk had no effect on studied parameters.

Unilateral vagotomy produced similar effects to those during unilateral vagal cooling. However, due to variability of effects in individual animals only cough number and cough-related diaphragmatic activity were significantly reduced.

Based on the typical dominance of one vagus nerve and pronounced cough reductions after unilateral elimination of the vagal afferentation we suggest a complex central processing of the afferent signal in order to induce cough response. Reduced cough afferent drive results in modulation of cough central pattern generator and in noticeable prolongation of cough timing.

This work was supported by the Slovak Research and Development Agency under the contract No. APVV-0189-11, by VEGA No. 1/0126/12

ROLE OF THE MEDIAL MEDULLARY RETICULAR FORMATION IN THE CONTROL OF AIRWAY PROTECTION

Bolser DC, Shannon R[1], Morris KF[1], Lindsey BG[1], Davenport PW, Pitts TE, Baekey DM, Rose MJ, Poliacek I[2], Segers LS[1]

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[2]Comenius University in Bratislava, Jessenius Faculty of Medicine in Martin, Institute of Medical Biophysics, Martin, Slovakia

The central neural network for regulation of airway protective behaviors is thought to be made up of neurons primarily located in the ventrolateral brainstem. This network has been extensively studied with regard to its role in breathing, but more recently it has been found to participate in cough, expiration reflex, and swallow. However, current models of function of this ventrolateral network cannot completely account for complex regulation of these behaviors. We have proposed that other brainstem regions participate in the expression of airway protective behaviors. In particular, we are currently investigating the role of the medial medullary reticular formation in these processes. We have approached this problem by recording neurons in this region with extracellular methods in anesthetized or decerebrated cats. Most (>90%) of the neurons in this area are not modulated during breathing. When challenged with tracheobronchial or laryngeal cough, a variety of responses (excitatory, inhibitory, and complex) were observed, with approximately 45% of the neurons responding to either stimulus. Neurons responding to both types of cough represented a minority of the population. Approximately 45% of the neurons in a separate sample responded to swallow. When a subset of medial medullary reticular formation neurons were tested with both tracheobronchial cough and swallow, over 90% of these were affected by one or both of these behaviors. Cross correlation analysis was employed to investigate functional interactions between medial medullary neurons, raphe, and ventrolateral respiratory column neurons. Approximately 8% of pairs involving at least one medial medullary reticular formation neuron showed evidence of functional interaction, including large offset peaks and troughs. The data support: a) almost all of nonbreathing-modulated neurons in the medial medullary reticular formation are involved in the neurogenesis of airway protective behaviors; b) neurons in this region of the medullary functionally interact with ventrolateral respiratory neurons and are part of the respiratory muscle control network.

GRANT SUPPORT: HL R33 89104, HL R33 HL 89071, HL 103415

GABA MICROINJECTIONS IN THE MEDULLARY RAPHE OF CAT, EFFECTS ON COUGH

Boris Dobroľubov, Ivan Poliaček, Michal Šimera, Marcel Veterník, Lucia Babálová, Peter Macháč, Nadežda Višňovcová, Ján Jakuš

Comenius University in Bratislava, Jessenius Faculty of Medicine in Martin, Institute of Medical Biophysics, Martin, Slovakia

GABA microinjections (1 mM in artificial cerebrospinal fluid) in the medullary raphe (2 injections at each of 3 depths: 1.1, 2.2, and 3.3 mm below the dorsal medullary surface; 206±15 nl per all 6 microinjections) were placed at four rostro-caudal positions: 1 mm caudal (number of animals n=5), 1 mm (n=7), 2.5 mm (n=5), and 4 mm (n=7) rostral to the obex. Cough induced mechanically by a soft catheter in the tracheobronchial area has been studied on 14 pentobarbitone anesthetized spontaneously breathing cats. Esophageal pressure (EP) and EMGs of the diaphragm (DIA) and the abdominal muscles (ABD) were recorded and for analysis normalized to their mean amplitudes during control pre-microinjection coughs. ANOVA and paired t-test were employed in statistical analysis.

The number of coughs related to 10s stimulation was reduced only by GABA microinjections 4 mm rostral to the obex (3.17±0.24 coughs vs. pre-injection 4.48±0.30 and 7-60 min post-injection recovery 4.20±0.45; $p<0.01$ for both). GABA injected 4 mm rostral to the obex induced also a prolongation of the cough DIA activity (by 23%; $p<0.05$) and the cough inspiratory phase (by 22%; $p<0.05$) and the attenuation of amplitudes of cough ABD EMG to 50±10% ($p<0.05$; recovery 85±24%) and of cough expiratory EP to 61±9% ($p<0.01$; recovery 83±9%, $p<0.05$). Microinjections of GABA 1 mm rostral to the obex reduced amplitudes of ABD EMG to 49±9% ($p<0.001$; recovery 82±9%, $p<0.01$ vs. post-microinjection value) and of expiratory EP to 64±11% ($p<0.05$; recovery 102±13%, $p<0.01$) during cough with no effect on other parameters of coughing.

No significant changes of heart and respiratory rate and mean blood pressure were found. Similarly, coughing was not changed with other 2 microinjection places.

Active GABA-related inhibition in medullary raphe significantly contributes to generation (and inhibition) of the cough reflex, unlike to the breathing, however, with markedly different efficiency and diversity of effects at the different rostro-caudal raphe positions. Prolongation of some temporal cough characteristics is consistent with interactions of raphe and central pattern generator for breathing and coughing.

This work was supported by the Slovak Research and Development Agency under the contract No. APVV-0189-11 and by VEGA 1/0126/12.

VALUE OF DEFLATION COUGH IN THE EXCLUSION OF ACIDIC REFLUX IN PATIENTS WITH GASTRO-OESOPHAGEAL DISORDERS AND CHRONIC COUGH

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Background: Some subjects exhibit cough-like expiratory efforts ("deflation cough", DC) during slow and/or forced vital capacity maneuver (SVC and FVC, respectively). The cause and motor features of these expulsive efforts are unknown.

Materials and Methods: Of 1720 consecutive patients who underwent lung function measurements, 43 displayed DC during SVC or FVC, and 18 agreed to participate in radiological and clinical examinations and in measurements of the motor pattern of DC. Variables of the intensity and frequency of DC were recorded with a pneumotachograph and the "integrated" surface (Ag-AgCl electrodes) abdominal EMG activity. On different occasions, participants were administered randomly either an antacid or salbutamol and matched placebos. Comparisons between DC variables obtained prior to and after drugs administration were performed by means of the analysis of variance followed by the Dunn's test for multiple comparisons.

Results: Fourteen patients (77.8%) turned out to be affected by a respiratory disease and all of them also reported typical and/or atypical symptom(s) of gastro-esophageal reflux (GER). In control conditions, maximal lung emptying was consistently accompanied by the appearance of DC. Administration of salbutamol or matching placebo had no effect. Antacid abolished DC in 11 patients, reduced its frequency in 4 and was ineffective in 3. Matched placebo was significantly less effective ($p<0.01$).

C**onclusions:** All patients with DC present symptoms of GER; acidic reflux possibly evoked by the efforts of lung emptying may be the causative factor. A role by receptors sensitive to lung collapse also mediating cough cannot be excluded when antacid administration fails.

GRAPHICAL TOOL FOR 3-D QUANTITATIVE VISUALISATION OF NEURONAL POPULATION IN THE BRAINSTEM – ASPIRATION REFLEX, EXPIRATION REFLEX AND COUGH – COMPARISON TO TIDAL BREATHING

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Respiratory neuronal network located in the brainstem is multifunctional, it undergoes appropriate reorganization and reconfiguration. Distinct spatial distribution of all the respiratory neurons is often difficult to comprehend. Most of the respiratory centre neurons are located in the nucleus tractus solitarius, ventro-lateral medulla and dorso-lateral pons.

Therefore we designed a graphical tool using Matlab® to visualize and summarize the distribution and quantification of brainstem respiratory neurons in a three-dimensional view. The aim of our work was to compare spatial distribution of regions involved in 3 different respiratory reflexes and spontaneous breathing.

In the database we included data on feline brainstem studies from relevant literature sources. Actual database consists of 44 entries for spontaneous inspiration, 39 for spontaneous expiration, 37 for aspiration reflex, 57 for expiration reflex, and 57 for cough reflex. Each entry contains data on number, spontaneous or reflex character, and type of neurons assigned to respective anatomic region and the literature reference.

Visualized data locations differ in marker type, size and colour, allowing easier orientation for the user. The visual display demonstrates that there are more regions and more neurons involved in the generation of cough, expiration, and aspiration reflexes than those in tidal breathing.

This graphical tool was designed for students and researchers to improve their spatial orientation of distinct brainstem respiratory areas involved in different functions e.g. reflexes. The database designed in Microsoft Excel® is simple and flexible so users can apply their own entries, resulting from variable procedures, anytime.

This study was supported by VEGA 1/0031/11 & VEGA 1/00107/14.

PHOSPHODIESTERASES AND COUGH

Mokrý J, Nosáľová G, Medveďová I, Fulmeková A, Mokrá D*

*Department of Pharmacology, *Department of Physiology, Jessenius Faculty of Medicine, Comenius University, Martin, Slovakia*

It is widely known that methylxanthines possess bronchodilating and anti-inflammatory activity, dependent on their plasmatic concentration. The major mechanisms involved in these actions include non-selective phosphodiesterase (PDE) inhibition, antagonism of adenosine receptors, activation of histone-deacetylase, influencing different ion channels etc. In several previous studies (both experimental and clinical) their antitussive effect was confirmed. However, the mechanisms involved in their antitussive actions are not completely elucidated. In our previous experiments we have proved the antitussive effects of theophylline and theobromine in conscius cats (mechanically induced cough) and in conscious healthy and ovalbumin-sensitized guinea pigs (citric acid induced cough). This effect was accompanied with significant bronchodilating effect. However, the dose used in these experiments was relatively low (10 mg/kg b.w.), as demonstrated by plasma levels measurements using HPLC methods (2.5 mg/l). Dubuis et al. (2014) demonstrated in their recent study involvement of opening small and intermediate-conductance calcium-activated potassium channels in antitussive effect of theophylline. As we supposed involvement of PDE inhibition, we decided to check several PDE isoforms in healthy and ovalbumin-sensitized guinea pigs for their antitussive action (aerosol of citric acid at concentration of 0.3 mol/l, 2 minutes during and 2 minutes after nebulization). Vinpocetin (PDE1 inhibitor), olprinone (PDE3 inhibitor), citalopram (PDE4 inhibitor), and zaprinast (PDE5 inhibitor) have shown antitussive effects, especially in ovalbumin-sensitized guinea pigs. Some other selective PDE3 (cilostazol) and PDE4 inhibitors (rolipram, YM976) have not demonstrated their antitussive effects in our experiments.

Based on observed results we can conclude that non-selective PDE inhibitors (e.g. methylxanthines) have potent antitussive effects; however, the role of PDE inhibition in this effect is questionable. PDE3 and PDE4 inhibitors are potentially effective in modulation of cough, mostly via indirect mechanisms. Nevertheless, other selective PDE inhibitors present in airways (e.g. 2nd generation PDE4 and PDE5 inhibitors) or brain (PDE2, PDE9, PDE10 inhibitors) and dual PDE3/4, and PDE4/5 inhibitors need to be tested for their antitussive effects in future.

Supported by *grants APVV-0305-12, MZ 2012/35-UKMA-12, VEGA 1/0030/11, VEGA 1/0260/14, and project BioMed (ITMS 26220220187)*

Dubuis E, Wortley MA, Grace MS, Maher SA, Adcock JJ, Birrell MA, Belvisi MG. Theophylline inhibits the cough reflex through a novel mechanism of action. J Allergy Clin Immunol. 2014 Jun;133(6):1588-98.

STIMULATION OF REPETITIVE COUGH IN HUMANS

Pitts TE

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Cough creates high expiratory airflows necessary to aerosolize and remove material from the lungs. Humans are able to cough with one inspiration followed by a series of compression and expiratory phases, termed a cough epoch. With a single voluntary cough, our lab has demonstrated the viability of cough airflow for detection of penetration/aspiration in Parkinson's disease (PD). However, the single voluntary cough challenge may have a ceiling effect making it difficult to measure small cough change. To increase task difficulty 36 male participants (72+5.1 years) diagnosed with PD (Hoehn Yahr 3+0.96) and healthy controls (60.4+16.2 years) performed three cough epochs. All healthy controls completed the task with one inspiration and at least three subsequent compression and expiratory phases. The first expiratory effort had the largest expiratory peak flow and each subsequent peak flow decreased. There were no changes in compression phase duration across the cough epoch. In contrast, PD participants employed three broad strategies. The first group performed similarly to the healthy controls. A second strategy consisted of one clear inspiration followed by low-flow expiratory efforts with short compression phases. A third strategy was to produce a series of coughs with separate inspirations for each compression and expiratory phase. Challenging PD patients with a cough epoch task demonstrated different motor programs not previously described. The pattern's functional significance is not fully understood. It is possible that the divergent patterns represent compensatory mechanisms in response to impairment in respiratory muscle coordination and/or central excitatory drive to respiratory muscle motoneurons.

COUGH SUPPRESSIVE ACTIVITY OF HERBAL POLYSACCHARIDES

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[a]Department of Chemistry, The University of Burdwan, India

Herbal polysaccharides (PSs) exhibit various biological activities, including antitussive activity. Herein we isolated arabinogalactan polysaccharides from leaves of *Solanum xanthocarpum* and *Adhatoda vasica,* roots of *Withania somnifera* and *Glycyrrhiza glabra* and examined their antitussive activity in guinea pigs test system. Moreover we followed structures that are connected with cough suppressive activity of herbal polysaccharides in the central and peripheral level. Therefore we used pretreatment of antagonists of opioid receptors and 5-hydroxytryptamine receptors as well as agonist of $GABA_B$ receptors.

Materials and Methods: We carried out our experiments on adult healthy TRIK strain male guinea pigs. Polysaccharides as well as both control agents were tested on individual groups of animals consisting of 8 guinea pigs. PSs were administered per orally in a dose 50 $mg.kg^{-1}$. A "negative" control, water for injection (dose 1 $ml.kg^{-1}$) and "positive" control, codeine phosphate (dose 10 $mg.kg^{-1}$) were also administered per orally. In other individual groups of animals we administered before PSs following agents: naloxone hydrochloride (dose 3 $mg.kg^{-1}$ i.p.), naloxone methiodide (dose 10 $mg.kg^{-1}$ i.p.), baclofen (dose 3 $mg.kg^{-1}$ s.c.) and ketanserin (dose 1 $mg.kg^{-1}$ i.p.). For control purpose we administered these agents alone. The cough reflex was evoked by inhalation of citric acid in concentration 0.3 mol/L for 3 min in bodyplethysmograph box. During this time the number of cough efforts was counted and subsequently values of specific airway resistance (sRaw) were measured.

Results: We observed a significant inhibition of citric acid-induced cough reflex in guinea pigs after per oral administration of followed PSs. Antitussive activity of PSs from leaves of *Adhatoda vasica* and from roots of *Withania somnifera* showed the same cough suppressive activity (63%; 62%) as codeine phosphate (62%). Arabinogalactan from leaves of *Solanum xanthocarpum* exceeded it slightly (69%) and PS extracted from roots of *Glycyrrhiza glabra* was much more effective (81%) in suppression cough than codeine. Our additional results showed involvement of central and peripheral opioid and GABA receptors in the cough suppressive activity of polysaccharide from *Withania somnifera.* We showed that $5HT_2$ receptors are not involved in this activity. PSs did not change the values of sRaw, therefore we suppose bronchodilation does not play role in their antitussive activity. We did not register any serious adverse reactions after administration of PSs except hypersalivation.

Conclusion: Our results lead to discover ability of arabinogalactan polysaccharides to modulate chemically-induced cough reflex without significant changes of specific airway resistance. This study also revealed the participation of opioid and GABA receptors in cough suppressive activity of herbal polysaccharides, but not 5-HT_2 receptors.

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COUGH AND SNEEZE: A SEPARATE OR A COMMON CPG?

Michal Simera, Ivan Poliacek, Boris Dobrolubov, Marcel Veternik, Jana Plevkova*, Jan Jakus

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Mutual interactions of cough and sneeze were studied on 12 spontaneously breathing pentobarbitone anesthetized cats. Reflexes were induced by mechanical stimulation of the tracheobronchial and nasal airways, respectively. The amplitude of the styloglossus muscle EMG moving average during the sneeze expulsion was 16-fold higher than that during cough ($p<0.01$). Larger inspiratory efforts occurred during coughing ($p<0.01$) vs. those in sneeze. The number of reflexes during simultaneous mechanical stimulation of the nasal and tracheal airways was not altered significantly compared to controls ($p>0.05$) and there was no modulation in temporal characteristics of the behaviors. When both reflexes occurred during simultaneous stimuli the responses were classified as either sneeze or cough (no hybrid responses occurred). During simultaneous stimulation of both airway sites, peak diaphragm EMG and inspiratory esophageal pressures during sneezes were significantly increased. The expiratory maxima of esophageal pressure and amplitudes of abdominal EMGs were increased in coughs and sneezes during simultaneous mechanical stimulation trials compared to control reflexes.

Our correlation data strongly support selection of coughs and sneezes in the dual stimuli trials. The TI as well as the amplitudes of ABD were strongly correlated between control cough and coughs observed to occur during the simultaneous trials.

There were strong linear correlations between TI and TE1 for control and combined sneeze

No association of the ABD amplitudes between cough and sneeze (either control or combined responses) occurred and some correlation of ABD and SG amplitudes for sneeze (almost none for cough) was seen

We propose that either there are two different CPGs for cough and for sneeze and just one of them at a time generates the related motor pattern, or alternatively there is a common CPG that reconfigures for generation of either cough or sneeze.

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COMPUTER MODELING OF D, L – HOMOCYSTEIC ACID MICROINJECTION INTO THE BÖTZINGER COMPLEX AREA

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Computer modeling has achieved noticeable progress in last years. It is employed in many areas including medicine. The opportunity to discover and better understand mechanisms and functions of studied processes makes the computer modeling basic research method. In the paper we tested hypothesis that neuronal activation within the Bötzinger complex area can modify the spatiotemporal characteristics of the cough reflex in the computer model. Employing the functional model of breathing and coughing we performed simulations of neural excitation, which was executed on animals by D, L – homocysteic acid (DLH) microinjections into the area of Bötzinger complex located in the rostral ventrolateral part of medulla oblongata. The excitation represented by fiber population had 2 levels, DLH1 (more synaptic connections with lower synaptic strength) and DLH2 (less synaptic connections with higher synaptic strength). DLH excitations had synaptic connections into E-AUG early (expiratory augmenting), E-AUG late and E-AUG cough neural populations in the model. Our simulations manifested high level of analogy with cough reflex changes observed in experiments. Principal manifestations of simulated neural excitations were 1) the attenuation of the cough reflex represented by decrease of cough number (control: 16, DLH1: 6, DLH2: 1); 2) the compression of cough phrenic activity (in control, DLH1 and DLH2) compared to quiet breathing. Although shortening of cough phrenic activity was not observed in experiments on cats our simulations demonstrated the ability of computer model to simulate functional behaviors in neural populations and their connectivity.

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