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COUGH IT UP

PROCEEDINGS

UNIVERSITAS COMENIANA BRATISLAVENSIS
FACULTAS MEDICA JESSENIANA
MCMXIX

Comenius University, Jessenius Faculty of Medicine,

Brainstorming Center and Institute of Medical Biophysics,

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Program and content

<u>Session 1 Chairs – K Morris, J Hanáček</u>

D Bolser - Regulation of airway protection

H Subramanian - Upper airway correlates of PAG induced sound modulation

J Smith - Capsaicin cough responses: beyond the C5

S Gavliaková - The role of nasal TRPM8 and TRPV3 receptors in modulation of cough

M Simera - The role of raphe nuclei in control of cough and sneeze in anaesthetized cats and rabbits

<u>Session 2 Chairs – D Bolser, M Tatár</u>

Z Tomori - Some applications of aspiration, expiration and cough reflexes and their voluntary equivalents

J Martinek - Cough sound analysis

M Veternik - Introduction to computer modeling of breathing (What I have learned at USF)

T Pitts - Repetitive coughing in vivo and computational models

K Morris - Recent advances in simulations of brainstem respiratory networks modeled from multineuron recordings

Introduction by Teresa E Pitts

Warning:

You may not understand the following complex sentences...

There is this thing called cough. You can poke things inside the neck and people / cats / other things will cough. There is a brain attached to the neck, I am sure that it does something. I will test that. So I did some computer thing to see what happened. Cough changed. So, YEAH, that is science.

Comment by Ivan Poliaček:

Thank you Teresa.

Readers, please, do not take it more than 80% seriously. Thank you, readers.

Regulation of airway protection

Donald C Bolser (Department of Physiological Sciences, College of Veterinary Medicine, University of Florida, Gainesville, FL, USA)

Repetitive coughing elicits significant changes in respiratory mechanics, leading to large increases in alveolar ventilation. The purpose of this study was to quantify the effects of repetitive cough on end tidal C02 and the breathing pattern in anesthetized cats. We found that repetitive coughing elicits profound hyperventilation (end tidal C02 less than 20 mm Hg). This level of C02 was considerably less than apneic threshold (approximately 28 mm Hg) in these animals. Following repetitive coughing, the animals had little or no apnea (apnea duration-approximately 3 s). This finding contrasts with apneas produced by mechanical hyperventilation to C02 leves below 20 mm Hg, which produced apneas of approximately 40s. Repetitive coughing also causes reduced blood pressure in these animals, which recovers following cessation of this airway protective behavior. Computational modeling and simulation predicted a reduced apneic threshold following coughing. *In vivo* experiments showed that after mechanical hyperventilation to apnea, coughing elicited an immediate resumption of breathing. Taken together, these results support: a) reduction and elimination of apneic threshold during and immediately (~10 s) after coughing, b) rapid rise of C02 after repetitive coughing, presumably supported by a increased delivery of venous C02 to the pulmonary circulation as blood pressure returns to normotensive levels.

Short summary of the discussion

Did blood pCO2 change during the cough stimulus?

Dr Bolser hypothesized that following hyperventilation, by coughing and analogous hyperventilation, brings an animal below apneic threshold. During hyperventillation apnea occurs, but following a cough stimulus apnea does not. He hypothesized that drive for breathing, followng a repetitive cough trial, may not controlled by chemoreceptors but by mechanoreceptors or other afferents projecting from the larynx or trachea.

There is an old paper by Tomori and co-workers on blood pressure and CO_2 including pCO_2 changes induced by cough.

Does apnea follows also aspiration reflex?

Several deep breaths can result in apnea, however, in aspiration reflex it possibly depends on level of hyperventilation. Single or few aspiration reflexes does not lead to apnea, but multiple frequent aspiration reflexes may cause apnea.

Don has been asked why is he that smart???

Teresa answered: „God loved him more...“

Upper airway correlates of PAG induced sound modulation

Hari Subramanian (*Florey Neurosciences Institute, University of Melbourne, Victoria, Australia 3052*)

Chemical stimulation in the midbrain periaqueductal gray (PAG) produces different types of vocalization, depending on where in the PAG the stimulation takes place. In this presentation we examine the upper-airway muscular correlates of PAG induced sound modulation in cats (mew, howl and hiss) via investigating the recruitment patterns of the posterior cricoarytenoid, cricothyroid and thyroarytenoid muscles. We also investigate how these upper-airway muscles are synchronized with the crural and costal diaphragm, the internal and external abdominal obliques, internal intercostals, the genioglossus (tongue) and the digastric (mouth opening) muscles for producing sound. We propose a functional neuroanatomical framework for sound production and modulation in mammals.

Short summary of the discussion

Is it applicable in speech disorders strategy?

Differences between and plasticity capacity of upper airway muscles and consequently treatment between children and udalts may differ, e.g. motivation. There is a possibility to activate or initiate compensation via different motor pathway.

Are there sound specific not speach specific disorders?

Yes.

Is PAG involved in modulation of cough as a „social“ phenomenon?

Reflex cough is generated at brainstem level, but cough as a „social“ act is not autonomic reflex and PAG is not only respiratory related, but survival related and involved in emotional expression.

Will cat cough with completely damaged PAG?

The literature has demonstrated that humans can not cough with damage to the PAG.

Capsaicin cough responses: beyond the C5

Jacky Smith (University Hospital of South Manchester, Southmoor Road, Wythenshawe, Manchester, Great Britain)

Capsaicin inhalational challenges are widely used in the study of cough and anti-tussive therapies. The standard endpoints (capsaicin concentration evoking 2 and 5 coughs, C2 and C5) are however highly variable between subjects and poorly discriminate between patients with cough and healthy controls.

Pharmacodynamic modelling of full capsaicin dose responses suggests an alternative parameter, the maximal capsaicin cough response (Emax), clearly discriminates health from disease and correlates well with spontaneous cough frequency. Emax therefore also provides important insights into the mechanisms underlying chronic cough.

Short summary of the discussion

Great presentation and data, this moves on the analysis of cough in humans?

C5 did its job.

Did you measure the urge to cough?

Yes, but time here was little short to present these. The data on urge to cough and chronic cough patients are less impressive.

There is the way to look at the data as the ratio of urge to cough and ED50.

Too much cough is uncomfortable, but no cough is dangerous. There are cases in which humans have little to no response to capsaicin inhalation challenge.

Some people do not like C5, because some poeple do not reach C5 at all, but they cough vigorously.

Huge variability is also the case. Emax, maximum response really has advantages as does the ED 50.

Central initiation of cough?

Voluntary modulation of capsaicin challenges is proved phenomenon. Maybe GABA mechanism at some levels participates.

Can people accept the challenges?

Yes, but there are many of them. It is the time to simplify the procedure. Maybe there could be changes to the number of trials presented, whereby shortening the experimental duration.

Will people who can tolerate spicy food, e.g. culters with spicy cooking differ?

Possibly.

Can this differentiate central and peripheral potentiation?

Not with the current protocol.

The role of nasal TRPM8 and TRPV3 receptors in modulation of cough

Silvia Gavliaková (Institute of Pathophysiology, JFM CU, Martin, Slovakia)

Authors: Gavliakova S[1], Biringerova Z[1,2], Buday T[1], Brozmanova M[1], Calkovsky V[3], Poliacek I[4], Plevkova J[1].

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Common cold and seasonal upper airway viral infections are usually accompanied by cough, and it was already documented that cough reflex sensitivity rises during such diseases and goes back to pre-disease values after recovery. Antipyretics, over-the-counter drugs and aromatherapy are commonly used to attenuate upper airway symptoms and coughing. Menthol, eucalypthol, thymol, and other aromatic substances are frequently used in these drugs based on empirical approach. We already documented that nasal administration of menthol drops has antiirritative and cough suppressing effect in humans. Now we focused on thymol. Extract of thyme – phenol with characteristic smell, which has documented antibacterial, antifungal and antioxidative activity. In respiratory system it is known to modulate mucocilliary transport, has indirect effect on airway ß2 receptors and has beneficial effect on cough in children with acute bronchitis. Molecular background for thymol action is TRPV3 channel which is expressed on skin, tongue and afferent somatosensory neurons. We tested hypothesis that intranasal administration of thymol would modulate cough reflex in humans by trigeminal/olfactory pathways.

18 otherwise healthy volunteers, with normal ENT exams and normal lung function tests have been tested after nasal administration of thymol (0.025 ml, 10^{-3}M) into both nostrils and urge-to-cough, cough threshold, cumulative and total count of coughs per provocation were estimated during standardized and validated capsaicin cough challenge.

Nasal thymol challenges induced peasant olfactory sensations and in 6/18 subjects also mild cooling sensation, which was transient lasting up to 2 minutes, augmented with every inspiration taken during this interval. This is the first study which objectively documented the effect of nasal thymol drops on selected cough parameters in humans. Cough threshold was not influenced when comparing to intranasal saline and vehicle challenges (11.8 vs 12.7 vs 9.8 μM of capsaicin), but total count of coughs after nasal thymol challenge was significantly lower than that obtained after nasal saline or vehicle challenges (18.7 vs 20.3 vs 14.1 coughs/provocation; $p < 0.05$). The most interesting and important finding was that subjects did not report urge to cough and urge to cough overlaps with C2 concentration, which is quite unique observation. Obtained data are similar to those we get after nasal menthol challenges. The question whether modulation of cough reflex by these herbal extracts (TRPM8 and TRPV3 agonists respectively) is of trigeminal or olfactory origin remains to be elucidated.

Acknowledgements:

Supported by VEGA 1/0031/11.

Short summary of the discussion

There was one challenge with basically no urge to cough, is this fascinating observation true?

I tis true, some subjects did not report any urge to cough, they directly reflexly coughed in response to capsaicin challenge.

Does clonidine duppresses cough, can it be via this mechanism?

Maybe.

Thymol was used as a control and when we noticed the effect we repeated the experiment for conformation.

TRPV3 was not hypothesized to alter cough sensitivity. Is there a integrative neuronal system that underwent modulation via other receptorsto change the excitability and response of the primary neuronal circuit?

There are evidences in cortex and possibly in other areas.

Patients? Right now they were healthy controls.

Smokers non-smokers differences?

Not in this study, but other work has shown no differences. However, they are young students, and have limited smoking durations.

What is the urge to cough under different conditions and in patients?

Patients have varied descriptions of this fascinating phenomenon. The male subjects reported less urge to cough, maybe because of cultural bias.

Paul Davenport has reported a similar effect in a sub-set of boys with asthma. This population are described as “red-zone“ cases in which the boys have limited sensation of airway restriction and are at risk of dying from severe asthma attacks.

The role of raphé nuclei in control of cough and sneeze in anaesthetized cats and rabbits

Michal Šimera (Institute of Medical Biophysics, JFM CU, Martin, Slovakia)

Authors: Šimera M, Poliaček I, Veterník M and Jakuš J.

Our experiments were performed on the 12 cats (3,39 ± 0,26 kg; both sexes) and on the 11 rabbits (6 chinchilla, 5 New Zeeland white; 3.83 ± 0.13 kg). Codeine (3,3 or 16,5 mM) dissolved in aCSF were injected by micropipette with tip thickness of 15 ± 2 µm into the raphe nuclei on the cats. Chemical lesions of the raphe nuclei neurons on the rabbits were induced by microinjections (49±1 nl) of the excitotoxine kainic acid (Sigma, 2.0 mg/ml), dissolved in artificial cerebrospinal fluid (aCSF) (51±1 nl; pH = 7.4). The positions of the micropipette for codeine protocol were 1.6 – 3.1 mm rostral to the obex and 1.2 – 1.6 and 2.8 – 3.1 mm under the brainstem surface and 1.6 - 2.8 mm and 1.4 - 1.6 mm and 2.9 - 3.2 mm for kainic acid protocol.

Microinjection of codeine reduced cough expiratory efforts, expressed as maxima of abdominal muscles electromyogram moving averages, by 18% compared to control coughs ($p<0.05$). The duration between maxima of cough diaphragm and abdominal muscles discharge, cough expiratory phase and periods of relative motor quiescence between coughs were increased (all $p<0.05$). Cough number (related to 10 s stimulation), amplitudes of esophageal pressure during cough, inspiratory and other temporal cough parameters and cardiorespiratory characteristics were not altered significantly.

Microinjections of the excitotoxine kainic acid (0.1 µg; 49±1 nl, range 45-50 nl) reduced cough number and cough „strength“ parameters, amplitudes of sneeze ABD activity and expiratory EP (all $p < 0.05$) and prolonged the cough active expiratory phase from (from 249 ± 38 to 350 ± 51 ms; $p < 0.05$), total active cough phase (from 545 ± 63 to 772 ± 41 ms; $p < 0.05$) No timing changes were detected in sneezing and solitary „expiration reflex-like“ expulsions. The lesions also induced an increase in the systematic blood pressure (from 10.76 ± 0.9 to 12.03 ± 0.8 kPa; $p < 0.01$) and the respiratory rate (from 19.3 ± 2 to 23.9 ± 2 per minute; $p < 0.01$). Our experimental microinjections of the codeine into the raphe nuclei of the cats showed that medullary raphé region rostral to the obex participates in control of cough motor pattern timing by codeine sensitive mechanism however the contribution of this area to codeine (opioid) induced cough suppression seems rather limited.

Microinjections of kainic acid into the raphé nuclei of rabbits showed a diverse role of raphé neurons in central control of different motor responses from the airways (cough vs. sneeze) the contribution of raphé neurons to the cough expression as well as to the generation of cough motor pattern.

Acknowledgements:
This study was co-financed form VEGA 1/0038/09 and EC sources - European Regional Development Fund (CECR).

Short summary of the discussion

Raphé is compartmentalized and could be influenced by different volume differently. So, what was the total volume injected?

The injections were 2 doses each below 50 nl. Histological analysis was done to examine the site of the injections and the distribution of the dye from the injection site.
The Raphé has broad effects on different functions, but is not a discrete nuclues. Due to this anatomical limitation single injections are not adequate to effect enough neurons to alter its overall activity patterns.

When kainic acid, an excitatory neurotoxin, kills the neruons does it then release a high amount of serotonin into the surrounding tissue?

Within 30 minutes the cells are eliminated. What actual amount of serotonin is released we do not know.

Serotonin can have long lasting effect.

Stable recording after more than 30 min was done. Codeine has some simmilar effects on cough as kainic acid. Respiratory rate and Blood Pressure went down in cat, up in rabbit with kainic acid in raphé.
The microinjection technique we use has been developed to effect a compact and spherical area of tissue. The reticullar formation presents similar problems and this multiple injection technique is necessary to induce an effect.

Raphé is „better pons", based on collaboration wuth Ted Dick – Pons Dick, we would like you to try similar injections in this area as well.

Some applications of aspiration, expiration and cough reflexes and their voluntary equivalents

Zoltán Tomori (Department of Physiology, University of P J Safarik, Košice, Slovakia)

Conclusions:

1) In addition to **the cough reflex** characterized by deep inspiration followed by powerful expiration there are 2 special distinct reflexes mediated by brainstem generators for inspiration and expiration with reciprocal inhibition.

2) Stimulation of the nasopharynx strongly activates the generator for inspiration and evokes a rapid and spasmodic **sniff- and gasp-like "aspiration reflex" (AspR)** without successive active expiration. In cats it can be elicited even in agonal stage, **resembling gasping (auto)-resuscitation.**

3) Stimulation of the larynx in animals and humans activates the expiratory generator and evokes the **expiration reflex (ExpR)**, characterized by prompt and strong expiration without preceding inspiration.

4) Sniffs and **prompt expirations** are **voluntary counterparts** of AspR and ExpR , which activate the brainstem generators for inspiration and expiration. Such **sudden and strong voluntary inspiratory and-or expiratory efforts** may change a variety of hypo- and hyper-functional disorders. Some of these applications are currently tested by us using special methods.

5) The revitalization and resuscitation effects of these special airway reflexes and their voluntary counterparts may have extraordinary importance, particularly in emergency and catastrophic situations.

Short summary of the discussion

Cats, during tracheal occlusion, produce a specific behavior, possible asphyxic response, characterized by forcefull and short ballistic-like expirations Have you see this in your rat experiments, and how do you describe it?

Rat, similar to cat, does have aspiration reflex. The behavior described is possible but such inspirations should be followed by an expiration.

Is there any knowledge and studies about heart rate variability and cough? Sympathetic outflow influenced by cough was described in presentation.

There is a relationship, cough causes post-tussive hypotension and can lead to alterations of heart rate along with airway collapse and syncope. Powerful cough can be a problem in patient populations.

Can repetitive cough improve cardiovascular function in cardiac patients?

There is a possibility, because cough and aspiration reflex activate an inspiratory neuronal pool in the preBOT.

Blood flow might be improved by coughing.

Deeper inspiration and following forceful expiration may improve diastolic heart volume and ejection and consequently blood flow.

Cough sound analysis

Jozef Martinek (Institute of Pathophysiology, JFM CU, Martin, Slovakia)

Authors: Martinek J, Klco P, Vrabec M, Zatko T, Tatar M, Javorka M

Cough is the commonest symptom of many respiratory diseases. Our aim was to prepare the algorithm based on cough sound analysis, which will be useful for objective cough sound monitoring. The first step of preparation of the algorithm was to find parameters, which will characterize and differentiate the cough sound. We used the linear and nonlinear analysis in time and frequency domain to find these parameters. Obtained (recorded) sound events were classified using classification tree and artificial neural networks (ANN). Better results (cough classification) were reached using ANN compared to classification tree. Reached values of sensitivity and specificity encourage us to find next parameters in order to increase the classification.

Short summary of the discussion

There was developed neuronal network to differentiate behaviors.
Awake humans can produce a variety of expiratory behaviors including cough, and throat clear which are difficult to categorize.

What was sampling frequency in this study?
34 kHz

Do you see high frequency sounds?
Jacky's comment : people did this. Frequency concept did not work, e.g. ten experiments went well and the eleventh one is messing up all data.

How does it look like „Voluntary snoring"? (one type of analyzed sound)
Don said: „It is what my wife does when I start talking".

Can help differentiate cough sounds and other cough parameters?
Jacky Smith did this with limited success.

There are cough sounds, speech, different sounds in upper airways etc. Number of these events is not similar, there is too many non-cough sounds resulting in high variability, instability and irregularity. Many sounds are very similar to cough sound. Algorithm worked well for similar sample size with voluntary coughing.

Capsaicin can induce long, short, weak, strong coughs in humans (experiment done by Wheeler-Hegland and Davenport). Very high variability, voluntary changes in cough sound, which may explain real world variability.

Introduction to computer modeling of breathing (What I have learned at USF)

Marcel Veterník (Institute of Medical Biophysics, JFM CU, Martin, Slovakia)

Authors: Veterník M, Šimera M, Jakuš J, Poliaček I

We know several types of models of breathing. Probably as a first there were constructed mechanical models like parallelogram or Hering's model of the breathing and many others. Later with improving mathematics there were developed mathematical models and later with coming computers it is possible to find many computer models of breathing. Some of these models are interested in ventilation parameters like tidal volume, reserve volumes, vital capacity, etc. The next area of computer modeling is neural modeling of breathing. In this area, we can say that probably the most important part of models are neurons. Scientists developed several types of computer neurons, less or more complicated. A biological neuron model (also known as spiking neuron model) is a mathematical description of the properties of nerve cells, or neurons, which is designed to accurately describe and predict biological processes. As the knowledge in the neuronal area was wider and wider, also other new neural theories were developed [1].

Programs for creating neural models and neural networks are called neural simulators. Very successful simulator was developed at the University of South Florida. It is based on MacGregor's simulator published in his book Neural and Brain Modeling in 1987. Simulator is composed of two main parts: NEWSNED and SNEDSKOP. Newsned makes it possible to create a model by placing cell and fiber populations on a graphical display, drawing connections between them, and entering parameters in dialog boxes. Snedskop is a waveform display program, by which it is possible to display waveforms of simulations. USF simulator offers to set many parameters of the model. There are 6 main groups of parameters which can be inserted to this simulator in two ways: as a text file, which is a result of entering of values to the graphical windows or as answers to questions that the simulator asks on the command line. Output is a text file, which is transformed by the Snedskop to graphical waveforms. USF model is probably the only so complex and working neural model of breathing in the whole scientist community and it is promising way how to improve knowledge about neural principles of breathing.

[1] Biological neuron model [online] [cit. 2012-08-15]. Accessible on internet: <http://en.wikipedia.org/wiki/Biological_neuron_model>.

[2] Lindsey, B.G. USF Neural Simulator. 2011, 1 – 48.

Short summary of the discussion

Feldman stated that synaptic inhibition is not required for generation of rhythm. Comment.
Marcel successfully modeled a simple oscillating system.
Kendall’s comment: Our actual model was developed by 20 people for 10 years.

Can we model synaptic properties and regional effects?
There are general parameters modifying this in the model.

The model represents neuronal network, populations of neurons and one of them has internal property.

Repetitive coughing in vivo and computational models

Teresa E Pitts (Department of Physiological Sciences, College of Veterinary Medicine, University of Florida, Gainesville, FL, USA)

Paroxysmal coughing occurs in patients with chronic obstructive pulmonary disease and is responsible for significant morbidity. Anesthetized cats produces bouts of coughing that are similar to paroxysmal coughing. However, the spatiotemporal features of repetitive coughing are unknown. We speculated motor drive during successive coughs within a repetitive bout would be dynamic. Further, we hypothesized successive coughs could be modeled by manipulation of second order interneuronal elements in a model of the unified cough/breathing network. *In vivo*, cough esophageal pressures (Pes) and expiratory muscle electromyogram (EMG) magnitudes increased during successive coughs to peak and declined thereafter. First cough had the lowest magnitude (Pes=25.06 ± 3.9 cmH_20) and increased with successive coughs until reaching maximum at the 8^{th} cough (Pes=51 ± 5.6 cmH_20). A model of the brainstem cough/respiratory network previously incorporated a single population of second order cough interneurons to transmit airway sensory information to the rest of the network. A second cough interneuron population was added which interacted with the original group through inhibition at stimulus onset. Simulations of this modified model produced abdominal motor drive during repetitive coughing that mimicked patterns observed *in vivo*. We conclude that significant dynamic features of *in vivo* repetitive coughing can be modeled by incorporating a feed-forward inhibitory system into the extant model of the cough/respiratory network. These data suggest more than a simple "relay" of cough related afferent information to the CNS and support a model with cascading interactions that sequentially promote and limit reflex effects.

Support: NIH HL 89104; HL 103415.

Short summary of the discussion

Can you turn expiratory drive on later to solve problem of E2 phase timing

Some model alterations have deleterious effects, such as absent lumbar drive during eupnea.

How much modeling and simulation match real neuronal wiring?

This model is based on real neuronal recordings in the cat, and also real behaviors parameters from experiments.

Can be expiration reflex modeled?

It does depend on phase where stimulus was delivered.

There is a model of expiration reflex based on David Baekey work. There are different ways how to make pattern corresponding to this response.

Sorting signal from different areas of airway possibly within NTS may be involved.

Volume timing relation known for respiration is not present in anesthetized cats (data by Bolser and Davenport). We are not sure if this is expressed in model, but expiration reflex is volume dependent as Jan Hanacek and coworkers have shown.

Repetitive coughing, some species do not have it.

Some animals keep coughing after the stimulus ceased. There are differences how cough is typically induced in guinea pig (inhalation of irritants vs. mechanical continuous stimulus).

Capsaicin in cat can induce repetitive coughing.

Recent advances in simulations of brainstem respiratory networks modeled from multineuron recordings

Kendall F Morris (University of South Florida, Tampa, FL, USA)
Authors: K Morris, R O'Connor, T Pitts, D Bolser, L Segers, S Nuding, I Poliacek, B Lindsey

The long range goal of our research is to delineate brainstem mechanisms for the production and regulation of breathing and airway protective reflexes, such as cough. Our central hypothesis is that the core respiratory network is controlled by neuronal assemblies dynamically organized into regulatory elements required for breathing and the expression of airway defensive behaviors. These behavioral control assemblies are composed of neurons that operate in transiently-configured circuits to process and store information related to the regulation of a given behavior. Our overall approach is to expand and test models for known regulatory features of breathing and the cough reflex, as well as to predict features via simulation. Using arrays of individually-adjustable microelectrodes, we record the extracellular activities of many distinct brainstem neurons together with electromyograms and whole nerve activity in decerebrated or spontaneously breathing, anesthetized cats. Spike train analysis methods are used to identify correlations among the neurons. We iteratively incorporate the inferred functional interactions among the brainstem neuronal populations into computational models. Recent progress includes identification of the spatiotemporal determinants of the cough motor pattern and the effects of baroreceptor input. We have also produced simulations of feed-forward oscillatory networks based on cross-correlation evidence from *in vivo* experiments involving modulation of afferent input. We hypothesize that such feed-forward oscillatory brainstem neural networks act as filters and are involved in both behavior selection and appropriate timing of behaviors in coordination with breathing.

Support: HL89104, NS019814 & HL89071.

Short summary of the discussion

We would like to do some microinjection modeling.

Miloš (Tatár) visited the lab some time ago and he said that Roger (Shannon) always needed more electrodes.

Bruce (Lindsey) always needs more electrodes as well.

There are similarity between cough and pain regulation.

Behavior filtering system e.g. serotonin neurons may be involved in frequency modulation of behavior occurrence with proposed efferent copy of pattern sent back to e.g. NTS.

Are there differences in expiration reflex from larynx and expiration reflex – like response from trachea.

Possibly. There is paper about motor patterns by Poliacek et al.