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Subject: READ THIS - talk soon

Date: Mon, 10 Sep 2012 18:21:46 +0000

Scan through these articles so we can discuss the experiment. Basically, the way into the autonomic nervous system may be as easy as the nose. The world nose expert (you've met him) is Noam Sobel who is well published in Science and now a prof at Weizmann. He's totally interested and fascinated and can start tomorrow. I could do part time and we would have crazy privacy and tons of bandwidth to do cool stuff. He has all the machines (fMRI, PET, etc – even though I hate those).

The interesting additional thing (kind of tangential) is that this might mean mechanical ventilation is being done all wrong. We bypass the nose with a tube and go straight to the lungs (trachea) which means that you end up with only a stress-response mediated by sympathetic fibers. So that in effect, you are making sick/stressed people more sick by revving up the wrong system. You can see this is true if you read the papers about how noninvasive ventilation (BiPAP etc) lowers heart rate etc. This means we could do some simple experiments to show this an potentially change the way mechanical ventilation is done – you might still put a tube into trachea but you would also need to find a way to mimic more normal autonomic patterns (and not rev up your system) but blowing air past nasal mucosa. Really cool. Also neat about Parkinsons (see below). I've told you and always believed that Parkinson's is an autonomic infectious disease and has nothing to do with degeneration. We can prove this.

ALSO read about the SENSORY INNERVATION OF THE PHARYNX... *VAGUS* which means that everytime you have a sore throat, the afferent fibers of the vagus nerve (meaning from the outside back to the brain) are activated. Essentially, every sore throat could be an entry/passage/sign that infection is entering your vagus (autonomic nervous system).. ANYWAY talk soon. Read below first.

5. Sci Signal. 2011 Jan 11;4(155):pe1.

Autonomic modulation of olfactory signaling.

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The olfactory epithelium is extensively innervated by sympathetic nerve endings, which release norepinephrine, and parasympathetic nerve endings, which release acetylcholine. Because olfactory sensory neurons have adrenergic and muscarinic receptors in addition to odorant receptors, autonomic stimulation can modulate the responses of olfactory sensory neurons to odorants. Recent studies have shed light on the molecular mechanisms that underlie crosstalk between muscarinic and odorant receptor signaling. The emerging view is that the stimulation of odorant receptor signaling by odorants, which is the earliest step in olfaction, can be substantially regulated by the autonomic nervous system.

PMID: 21224443 [PubMed - indexed for MEDLINE]

1. Am J Rhinol Allergy. 2012 Jul;26(4):271-3.

The accessory posterolateral nerve: An immunohistological analysis.

Bleier BS, Feldman R, Sadow PM, Wu A, Ting J, Metson R.

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BACKGROUND: Recent endoscopic dissection studies have redefined the postganglionic pterygopalatine autonomic pathways suggesting that neurovascular rami, termed "accessory posterolateral nerves," project directly through the palatine bone to innervate the posterolateral nasal mucosa rather than traveling with trigeminal arborizations. The goal of this study was to characterize these accessory posterolateral nerves by immunohistochemistry to determine their morphology and composition.

METHODS: This is an Institutional Review Board approved study in seven patients in whom the presence of accessory posterolateral nerves were surgically identified exiting the perpendicular plate of the palatine bone and sampled. The presence of neural tissue was confirmed by hematoxylin and eosin and S-100 protein staining. Nerves were then stained with anti-human choline acetyl-transferase (ChAT; 1:100) and anti-human dopamine beta-hydroxylase (DBH; 1:100) followed by a fluorescein isothiocyanate-labeled secondary antibody to test for the presence of peripheral parasympathetic and sympathetic fibers, respectively. Human cadaveric sensory nerves were used as a negative control.

RESULTS: All seven samples contained neural elements. Two specimens were also associated with arteries. All nerves were comprised of a single fascicle containing an approximately equal distribution of ChAT(+) and DBH(+) fibers.

CONCLUSION: This histological study supports prior descriptions defining a newly recognized neural pathway for innervation of the nasal mucosa. Our data confirm that these accessory posterolateral nerves project directly through the perpendicular plate of the palatine bone and are composed of autonomic fibers. Recognition of this pathway may be exploited in the treatment of sinonasal disease resulting from autonomic dysregulation.

PMID: 22801012 [PubMed - in process]

2. Am J Rhinol Allergy. 2012 Jan-Feb;26(1):49-54.

Cytologic alterations in nasal mucosa after sphenopalatine artery ligation in patients with vasomotor rhinitis.

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BACKGROUND: Vasomotor rhinitis (VR) seems to be related to an imbalance between cholinergic and adrenergic activity in the autonomic nervous system. The nerve fibers of the sympathetic and parasympathetic nervous systems reach the nose through the posterior nasal nerve, which, after crossing the sphenopalatine foramen, distributes to the mucosa following the branches of the sphenopalatine vessels. This study was designed to evaluate the effect of sphenopalatine artery ligation on nasal function and nasal cytology in patients with VR.

METHODS: Thirty patients with VR and bilateral inferior turbinate hypertrophy (ITH) were randomly assigned to receive endoscopic inferior turbinoplasty either with or without sphenopalatine artery ligation. Pre- (baseline) and postsurgical (1-year follow-up) assessment included fiber endoscopy, active anterior rhinomanometry, measurement of mucociliary transport time (MTt), and nasal cytology examination.

RESULTS: At 1-year follow-up there was a statistically significant improvement in nasal resistances in both groups but not on intergroup comparison; MTt significantly decreased in both groups ($p < 0.01$) and was significantly better ($p < 0.05$) in the group that had undergone sphenopalatine artery ligation. Among the patients in this group, significantly fewer were found to have altered ciliated cells ($p < 0.005$) or a hyperchromatic supranuclear stria ($p < 0.005$) on nasal cytology; the differences were statistically significant also on intergroup

comparison ($p < 0.005$ and $p < 0.001$, respectively).

CONCLUSION: In patients with vasomotor rhinopathy and ITH, improvement in symptoms, nasal resistance, ciliated cell trophism, and MTt was observed after sphenopalatine artery ligation.

PMID: 22391083 [PubMed - indexed for MEDLINE]

3. Int J Oral Maxillofac Surg. 2012 Mar;41(3):389-93. Epub 2012 Jan 11.

Determination of trigeminocardiac reflex during rhinoplasty.

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In most rhinoplasty procedures, osteotomies are usually required. The osteotomy areas are innervated by sensory branches of the trigeminal nerve. The trigeminocardiac reflex (TCR) is clinically defined as the sudden onset of parasympathetic activity during stimulation of the trigeminal nerve. When an osteotomy is performed or external pressure is applied over the nasal bone, the infraorbital nerve may send signals via this nerve. The aim of this prospective study is to determine the blood pressure changes and occurrence of TCR during rhinoplasty. one hundred and eight patients were enrolled into the study. Lidocaine and adrenaline combination (LAC) was injected only into the left lateral osteotomy sites. All patients underwent median, right-side, then left-side lateral osteotomies and nasal pyramid infracture. The haemodynamic changes were recorded. A 10% or more decrease in the heart rate from baseline was considered a TCR. TCR was detected in nine patients following lateral osteotomies and nasal pyramid infracture procedures (8.3%). The authors determined that LAC injection prior to osteotomy did not prevent TCR. Manipulation at or near the infraorbital nerve during rhinoplasty may cause TCR, even if local anaesthetic infiltration is used.

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PMID: 22240287 [PubMed - indexed for MEDLINE]

4. Nepal Med Coll J. 2010 Sep;12(3):154-7.

Immediate effect of a slow pace breathing exercise Bhramari pranayama on blood pressure and heart rate.

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The study was carried out to evaluate the immediate effect Bhramari pranayama, a slow breathing exercise for 5 minutes on heart rate and blood pressure. Heart rate and blood pressure of volunteers were recorded. The subject was directed to inhale slowly up to the maximum for about 5 seconds and then to exhale slowly up to the maximum for about 15 sec keeping two thumbs on two external auditory canal, index and middle finger together on two closed eyes and ring finger on the two sides of the nose. During exhalation the subject must chant the word "O-U-Mmmma" with a humming nasal sound mimicking the sound of a humming wasp, so that the laryngeal walls and the inner walls of the nostril mildly vibrate (Bhramari pranayama, respiratory rate 3/min). After 5 minutes of this exercise, the blood pressure and heart rate were recorded again. Both the systolic and diastolic blood pressure were found to be decreased with a slight fall in heart rate. Fall of diastolic pressure and mean pressure were significant. The result indicated that slow pace Bhramari pranayama for 5 minutes, induced

parasympathetic dominance on cardiovascular system.

PMID: 21446363 [PubMed - indexed for MEDLINE]

6. Rhinology. 2010 Jun;48(2):211-5.

Azelastine nasal spray inhibiting parasympathetic function of tracheal smooth muscle.

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BACKGROUND: Azelastine hydrochloride is a histamine receptor-1 (H(1)) antagonist with anti-inflammatory properties that is available in the United States as Astelin Nasal Spray for rhinitis patients who are suffering from sneezing and rhinorrhea. The effect of H(1) antagonists on nasal mucosa in vivo is well known; however, the effect of the drug on tracheal smooth muscle has rarely been explored. During administration via oral intake or inhalation of the H(1) antagonist for nasal symptoms, it might affect the trachea.

METHODS: We examined the effectiveness of azelastine on isolated rat tracheal smooth muscle by testing: 1) the effect on tracheal smooth muscle resting tension; 2) the effect on contraction caused by 10^{-6} M methacholine as a parasympathetic mimetic; and 3) the effect on electrically induced tracheal smooth muscle contractions.

RESULTS: The results indicated that addition of methacholine to the incubation medium caused the trachea to contract in a dose-dependent manner. Addition of azelastine at doses of 10^{-5} M or above elicited a significant relaxation response to 10^{-6} M methacholine-induced contraction. Azelastine could inhibit electrical field stimulation-induced spike contraction. It alone had a minimal effect on the basal tension of trachea as the concentration increased.

CONCLUSIONS: This study indicated that high concentrations of azelastine might actually inhibit parasympathetic function of the trachea. Azelastine might reduce asthma attacks in rhinitis patients because it could inhibit parasympathetic function and reduce methacholine-induced contraction of tracheal smooth muscle.

PMID: 20502763 [PubMed - indexed for MEDLINE]

7. Rhinology. 2010 Mar 2;48(1):7-10.

Gustatory rhinitis.

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Gustatory rhinitis is characterized by watery, uni- or bilateral rhinorrhea occurring after ingestion of solid or liquid foods, most often hot and spicy. It usually begins within a few minutes of ingestion of the implicated food, and is not associated with pruritus, sneezing, nasal congestion or facial pain. It is considered to be a non-immunological reaction. Immunohistological and pharmacological observations suggest that this disease is most likely caused by stimulation of trigeminal sensory nerve endings located at the upper aerodigestive track. Recent evidence suggests that sensory nerve stimulations could be associated with a parasympathetic reflex and activation of cholinergic muscarinic receptors, sensitive to atropine. There are various types of gustatory rhinitis, including age-related, posttraumatic, postsurgical and associated with cranial nerve neuropathy. Avoidance of the implicated foods, is the first treatment option, but it is rarely sufficient. The intranasal topical administration of anticholinergic agents such as atropine, either

prophylactically or therapeutically has been shown effective. Surgical therapy in the form of posterior nasal nerve resection or vidian nerve neurectomy is not recommended because of its short lasting result and frequent unpleasant side effects.

PMID: 20502728 [PubMed - indexed for MEDLINE]

11. Tohoku J Exp Med. 2009 Nov;219(3):187-91.

Cardiac autonomic imbalance in children with allergic rhinitis.

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The involvement of autonomic imbalance has been reported in the pathogenesis of hypersensitivity reactions. Allergic diseases are more frequent in children and some of predisposing factors may be changed according to the increasing age, but the involvement of autonomic imbalance has not been investigated in pediatric population. In this cross-sectional, case-control study, we evaluated the autonomic system by measuring heart rate variability (HRV) in pediatric patients with allergic rhinitis. Thirty-five pediatric patients with allergic rhinitis and 36 healthy children (mean age 11 +/- 2.7, and 12 +/- 3 years, respectively) were enrolled in the study. Age and gender were not different between the groups. The diagnosis of allergic rhinitis was based on the history, symptoms, and skin prick tests. Participants with acute infection, nasal polyposis, bronchial asthma, and any other medical problems, assessed by history, physical examination and routine laboratory tests, were excluded. Twenty-four hour ambulatory electrocardiographic recordings were obtained, and the time domain and frequency domain indices of HRV were analyzed. We found significant increase in calculated HRV variables in children with allergic rhinitis compared to controls, which reflect parasympathetic tones, such as number of R-R intervals exceeding 50 ms, root mean square of successive differences between normal sinus R-R intervals, the percentage of difference between adjacent normal R-R intervals, and high frequency. These results indicate that HRV is increased, which implies sympathetic withdrawal and parasympathetic predominance. We propose that autonomic imbalance may be involved in the pathophysiology of allergic rhinitis in pediatric patients.

PMID: 19851046 [PubMed - indexed for MEDLINE]

12. Ann N Y Acad Sci. 2009 Jul;1170:615-22.

Parkinson's disease: the dual hit theory revisited.

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Accumulating evidence suggests that sporadic Parkinson's disease (sPD) has a long prodromal period during which several nonmotor features develop; in particular, impairment of olfaction, vagal dysfunction, and sleep disorder. Early sites of Lewy pathology are the olfactory bulb and enteric plexuses of the foregut. We propose that a neurotropic pathogen, probably viral, enters the brain via two routes: (a) nasal, with anterograde progression into the temporal lobe; and (b) gastric, secondary to swallowing of nasal secretions in saliva. These secretions might contain a neurotropic pathogen that, after penetration of the epithelial lining, could enter axons of the Meissner's plexus and via transsynaptic transmission reach the preganglionic parasympathetic motor neurons of the vagus nerve. This would allow retrograde transport into the medulla and from here into

the pons and midbrain until the substantia nigra is reached and typical aspects of disease commence. Evidence for this theory from the perspective of olfactory and autonomic dysfunction is reviewed and the possible routes of pathogenic invasion are considered. It is concluded that the most parsimonious explanation for the initial events of SPD is pathogenic access to the brain through the foregut and nose-hence the term "dual hit."

PMID: 19686202 [PubMed - indexed for MEDLINE]

13. Ann N Y Acad Sci. 2009 Jul;1170:604-9.

Neuroregulation of human nasal mucosa.

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Multiple subsets of nociceptive, parasympathetic, and sympathetic nerves innervate human nasal mucosa. These play carefully coordinated roles in regulating glandular, vascular, and other processes. These functions are vital for cleaning and humidifying ambient air before it is inhaled into the lungs. The recent identification of distinct classes of nociceptive nerves with unique patterns of transient receptor potential sensory receptor ion channel proteins may account for the polymodal, chemo- and mechanosensitivity of many trigeminal neurons. Modulation of these families of proteins, excitatory and inhibitory autoreceptors, and combinations of neurotransmitters introduces a new level of complexity and subtlety to nasal innervation. These findings may provide a rational basis for responses to air-temperature changes, culinary and botanical odorants ("aromatherapy"), and inhaled irritants in conditions as diverse as allergic and nonallergic rhinitis, occupational rhinitis, hyposmia, and multiple chemical sensitivity.

PMID: 19686200 [PubMed - indexed for MEDLINE]

14. Eur Arch Otorhinolaryngol. 2010 Jan;267(1):73-6.

Parasympathetic overactivity in patients with nasal septum deformities.

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Nasal septum deformities (NSD) are one of the most frequent reasons for nasal obstruction presented with a reduction in nasal airflow and chronic mucosal irritation. Nasocardiac reflex which includes afferent stimulus with maxillary division of the trigeminal nerve and the efferent pathway of the heart via the vagus nerve is not a well-known part of autonomic nervous system (ANS). Heart rate variability (HRV) is a parameter reflecting the ANS activity on heart. The purpose of this study is to evaluate ANS functions in patients with NSD by HRV analysis. Twenty-nine patients with NSD and 26 control subjects were included in the study. The diagnosis of NSD was made with history, symptoms, anterior rhinoscopy, and nasal endoscopic examination. 24-h ambulatory electrocardiographic recording was performed by a 3-channel recorder. HRV parameters were obtained by analyzing these parameters. Baseline features were similar in patients and controls (mean age: 31 ± 8 in the patients, 32 ± 9 in control subjects; $P = \text{NS}$). Night-RMSSD (the square root of square of mean square differences of successive NN intervals) (47 ± 21 , 34 ± 13 ; $P = 0.008$), night-PNN50 (the number of interval differences of successive NN intervals greater than 50 ms) (24 ± 16 , 14 ± 10 ; $P = 0.007$), 24-h-RMSSD (39 ± 18 , 27 ± 12 ; $P = 0.004$), and 24-h-PNN50 (16 ± 12 , 9 ± 7 ; $P = 0.016$) were significantly higher

in patients than controls. Other HRV parameters were not significantly different between two groups. Changes in these parameters demonstrated an increased parasympathetic tone and discordance in sympatho-vagal activity in NSD.

PMID: 19629510 [PubMed - indexed for MEDLINE]

15. Acta Clin Croat. 2009 Mar;48(1):65-73.

New concepts of neural regulation in human nasal mucosa.

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Nasal mucosa is innervated by multiple subsets of nociceptive, parasympathetic and sympathetic nerves. These play carefully coordinated roles in regulating glandular, vascular and other processes. These functions are vital for cleaning and humidifying ambient air before it is inhaled into the lungs. The recent recognition of distinct classes of nociceptive nerves with unique patterns of sensory receptors that include seven transmembrane G-protein coupled receptors, new families of transient receptor potential and voltage and calcium gated ion channels, and combinations of neurotransmitters that can be modulated during inflammation by neurotrophic factors has revolutionized our understanding of the complexity and subtlety of nasal innervation. These findings may provide a rational basis for responses to air temperature changes, culinary and botanical odorants ("aromatherapy"), and inhaled irritants in conditions as diverse as idiopathic nonallergic rhinitis, occupational rhinitis, hyposmia, and multiple chemical sensitivity.

PMID: 19623876 [PubMed - indexed for MEDLINE]