Opportunities for Electrical Neuromodulation of Respiratory Function

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Nerves play a major role in pathophysiology of respiratory diseases (asthma, COPD).

The lung is a very feasible target for peripheral neuromodulation.

Additional functional and anatomical mapping will enable more refined neuromodulation strategies.
RESPIRATORY SYSTEM

NERVES

- BRONCHOSPASM
- COUGH
- MUCUS SECRETION
- DYSPNEA
Neural regulation of the lung is mediated by vagus nerves
**Reflexes:**
- Airway smooth muscle constriction
- Secretions

**Sensations:**
- Dyspnea
- Cough

Diagram:
- Sensory Afferent Nerves (Aδ- & C-)
- Vagus Nerve
- Parasympathetic Preganglionic Efferent
- Jugular G., Nodose G.
Parasympathetic regulation of airway smooth muscle

- Medulla
- Preganglionic (vagus nerve)
- Parasympathetic ganglia
- Postganglionic

+ acetylcholine

- VIP
- NO

Airway smooth muscle

Human bronchus
Reversible Airways Obstruction in COPD is Dependent Upon Parasympathetic Cholinergic Nerves

(Modified from Tashkin et al. 1986)
Tiotropium Bromide Step-Up Therapy for Adults with Uncontrolled Asthma

A

Morning PEF (liters/min)

- Tiotropium
- Double-Glucocorticoid
- Salmeterol

P = 0.26
P < 0.001
P < 0.001

B

Evening PEF (liters/min)

- Tiotropium
- Double-Glucocorticoid
- Salmeterol

P < 0.001
P < 0.001
P = 0.05
Reflexes:
- Airway smooth muscle constriction
- Secretions

Sensations:
- Dyspnea
- Cough

Stimuli

Airway

Sensory Afferent Nerves (Aδ- & C-)

Jugular G. Nodose G.

Vagus Nerve

Parasympathetic Preganglionic Efferent
Afferent nerve subtypes in the large airways

(Kollarik & Undem 2002; Canning, 2004)
Afferent nerve subtypes in the large airways

- **Mice and Rats**
- **Guinea Pigs**
- **Humans**

**Images**:
- **A**: Image of nerves in Mice and Rats
- **B**: Image of nerves in Guinea Pigs
- **C**: Image of PGP9.5/αSMA in Humans

**Legend**:
- Scale bar: 100 μm
Afferent innervation of the lung

Rat, In vivo, adapted from (Lee et al. 2003)

A-fiber stretch mechanoreceptors

Bronchopulmonary C-fibers

nerve activity

lung inflation

RAR

SAR

nodose C-fibers

jugular C-fibers

mice, rats, guinea pigs, rabbits, cats, dogs

Rat, In vivo, adapted from (Lee et al. 2003)
Bronchopulmonary C-fibers

- relatively quiescent in normal tissue
- readily stimulated by noxious chemicals, inflammatory mediators or excessive physical stimuli

C-fiber activators initiate cough in humans and animal models

- Capsaicin (TRPV1)
- Cinnamaldehyde (TRPA1)
- Citric Acid (TRPV1/ASIC)
- Bradykinin (B2)
- Water (?)

Reviewed in (Coleridge et al., 1984; Lee et al., 2001; Canning 2009).
Central neural circuitry regulating the parasympathetic innervation of the airways
Inflammation-induced neuroplasticity

Reflexes:
- Airway smooth muscle constriction
- Secretions

Sensations:
- Dyspnea
- Cough

Stimuli:

Vagus Nerve

Jugular G.
Nodose G.

Sensory Afferent Nerves
(Aδ- & C-)

Parasympathetic Preganglionic Efferent

Airway
In vivo transfection of sensory nerves with AAV virus vectors

*In* injection into sensory ganglia

Kollarilk et al., J Physiol 2010
Vagal afferent nerve terminals in the trachea
Knockdown of Nav 1.7 expression and function by AAV-delivered shRNA

Recording from human vagal pulmonary branches – ex vivo optimization of stimulation parameters

Kollarik, unpublished.
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