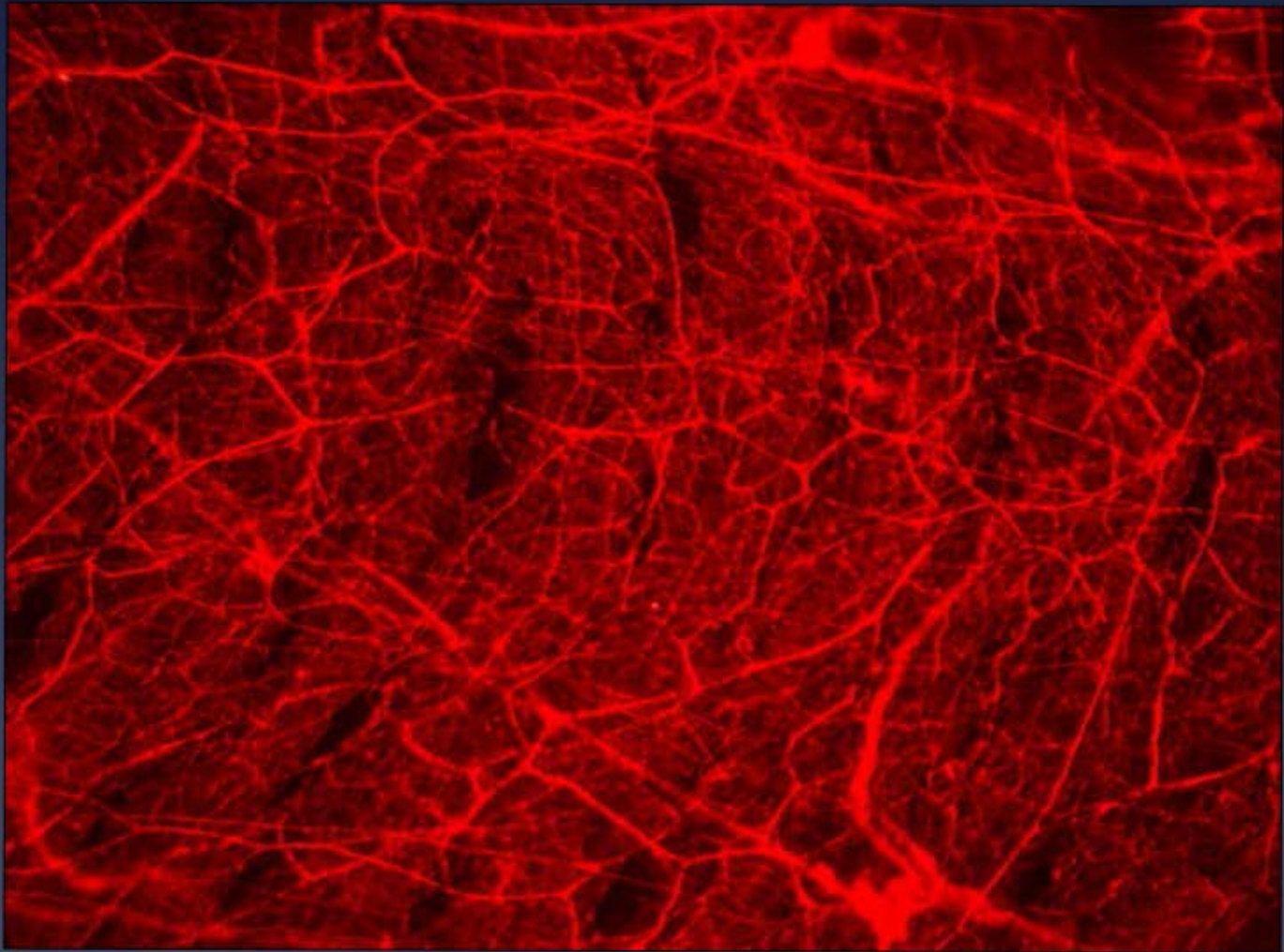


Opportunities for Electrical Neuromodulation of Respiratory Function

Marian Kollarik

The Johns Hopkins University School of Medicine, Baltimore, MD

- * 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

```
graph TD; NERVES[NERVES] --> BRONCHOSPASM[BRONCHOSPASM]; NERVES --> MUCUS_SECRETION[MUCUS SECRETION]; NERVES --> DYSPNEA[DYSPNEA]; NERVES --> COUGH[COUGH];
```

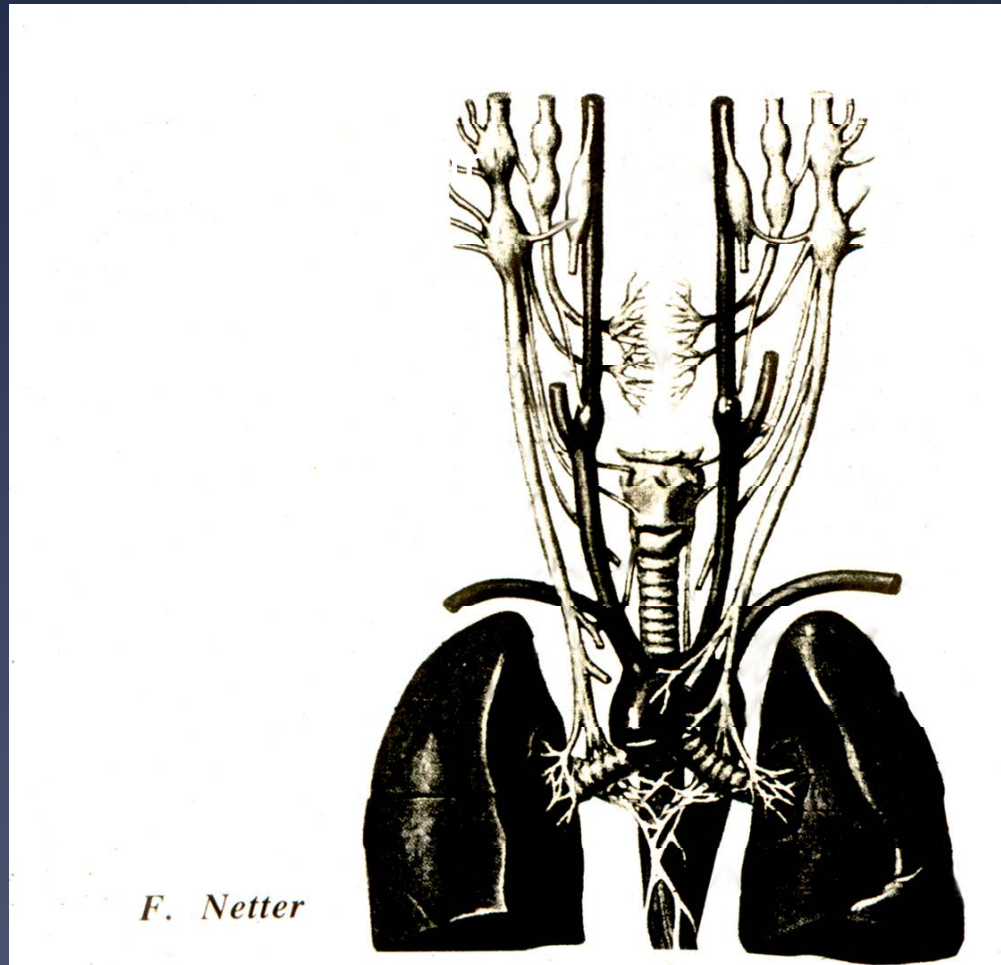
BRONCHOSPASM

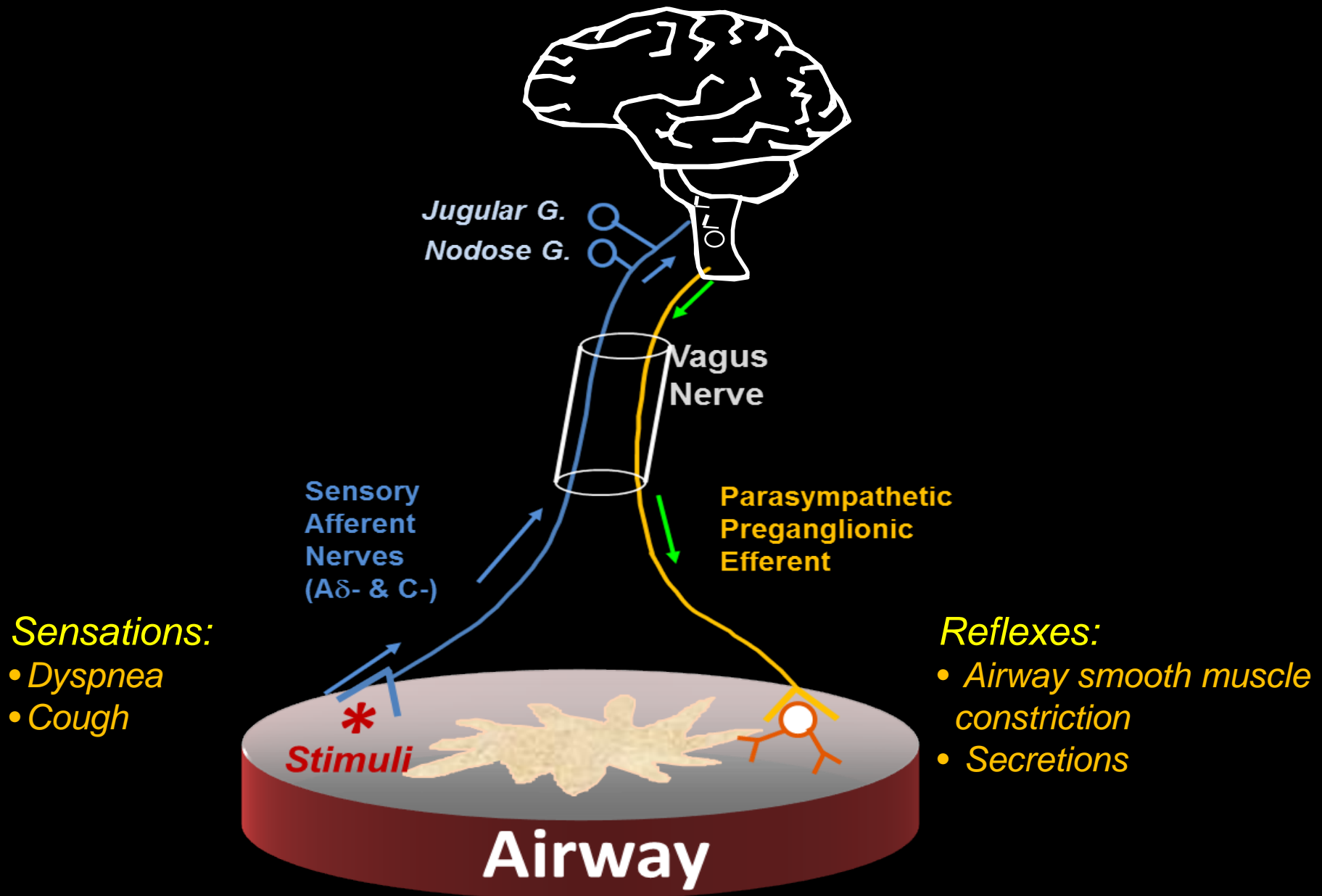
MUCUS SECRETION

DYSPNEA

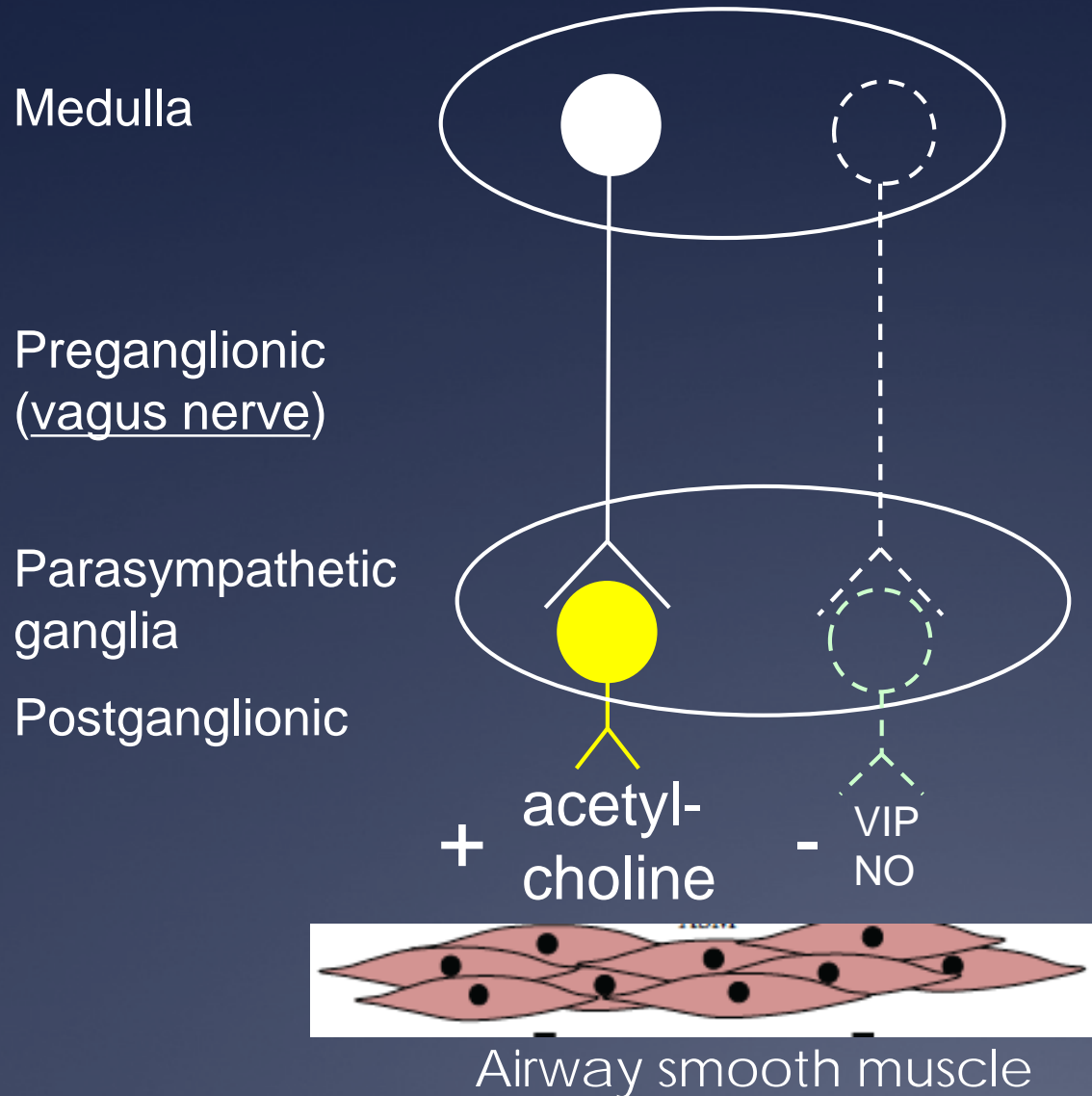
COUGH

Neural regulation of the lung is mediated by vagus nerves





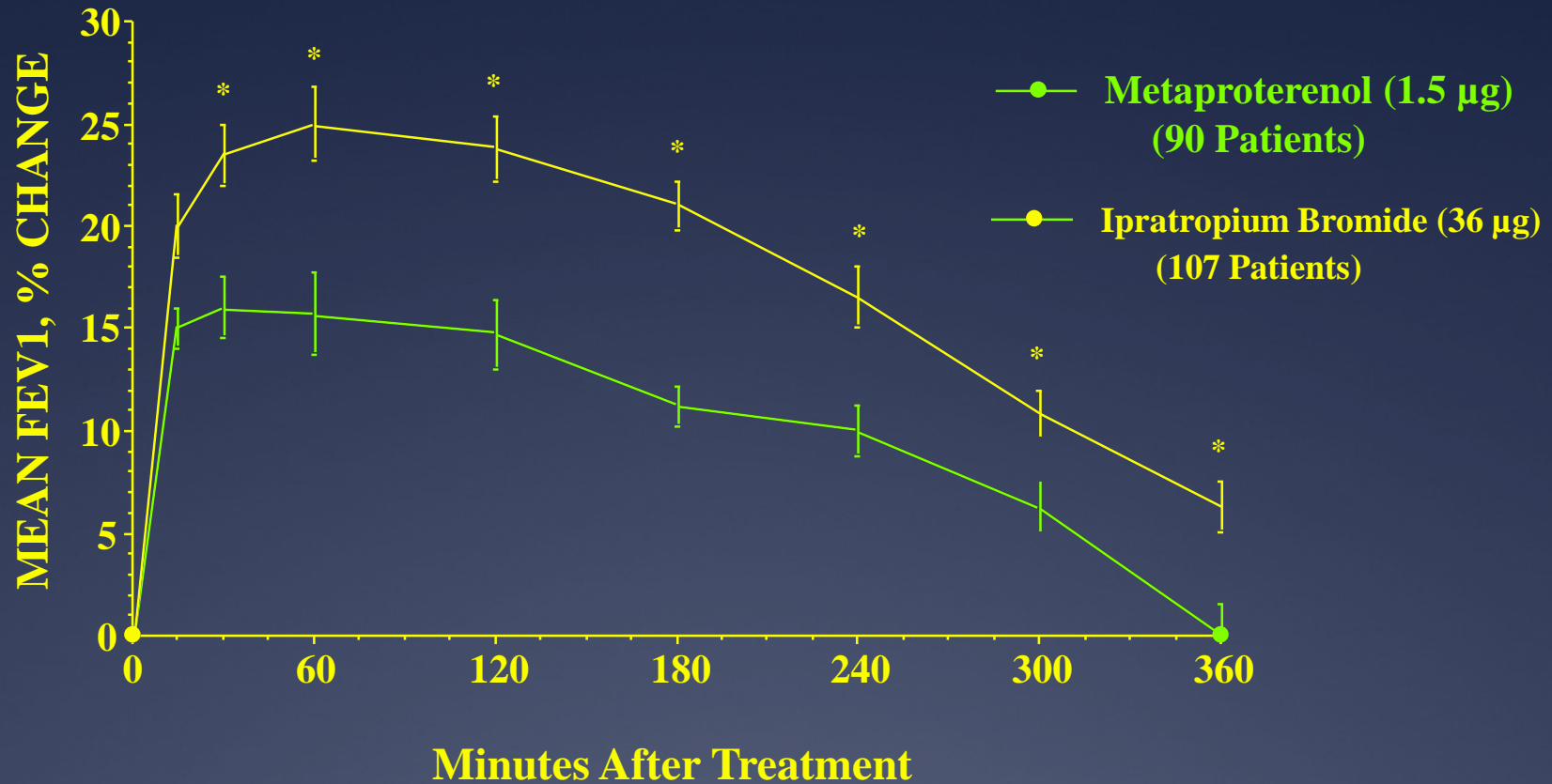
Parasympathetic regulation of airway smooth muscle



Human bronchus



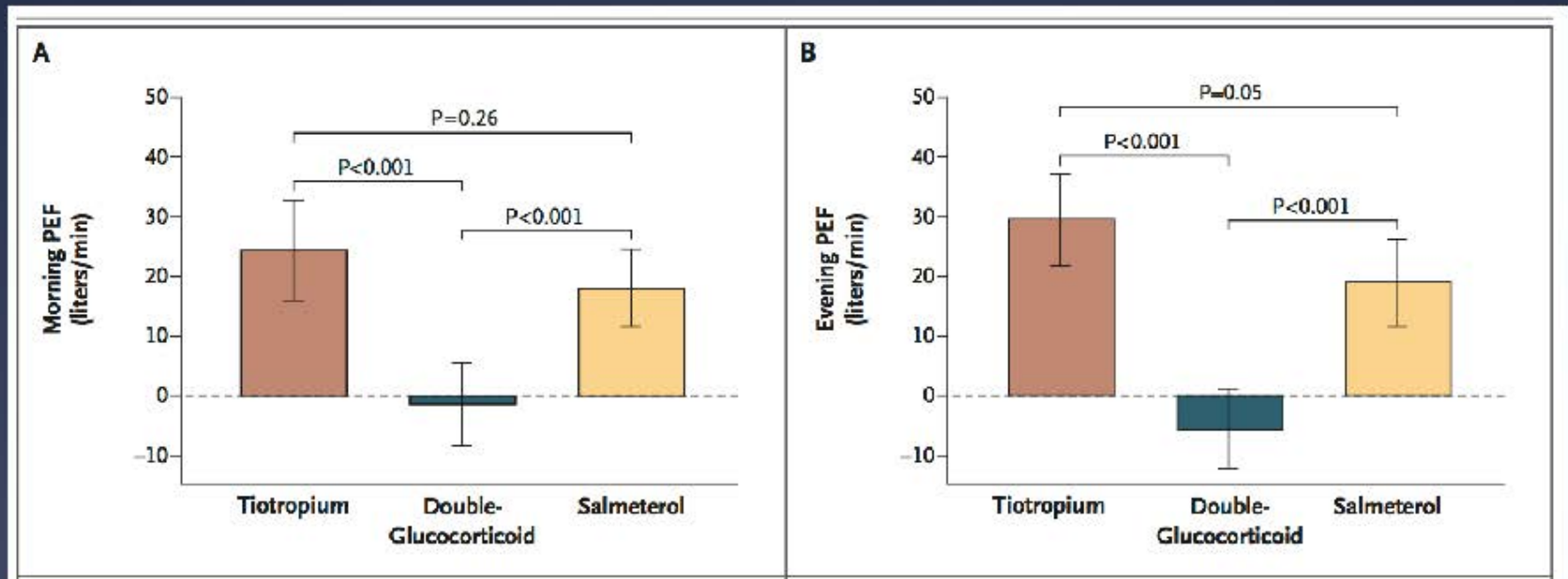
Reversible Airways Obstruction in COPD is Dependent Upon Parasympathetic Cholinergic Nerves

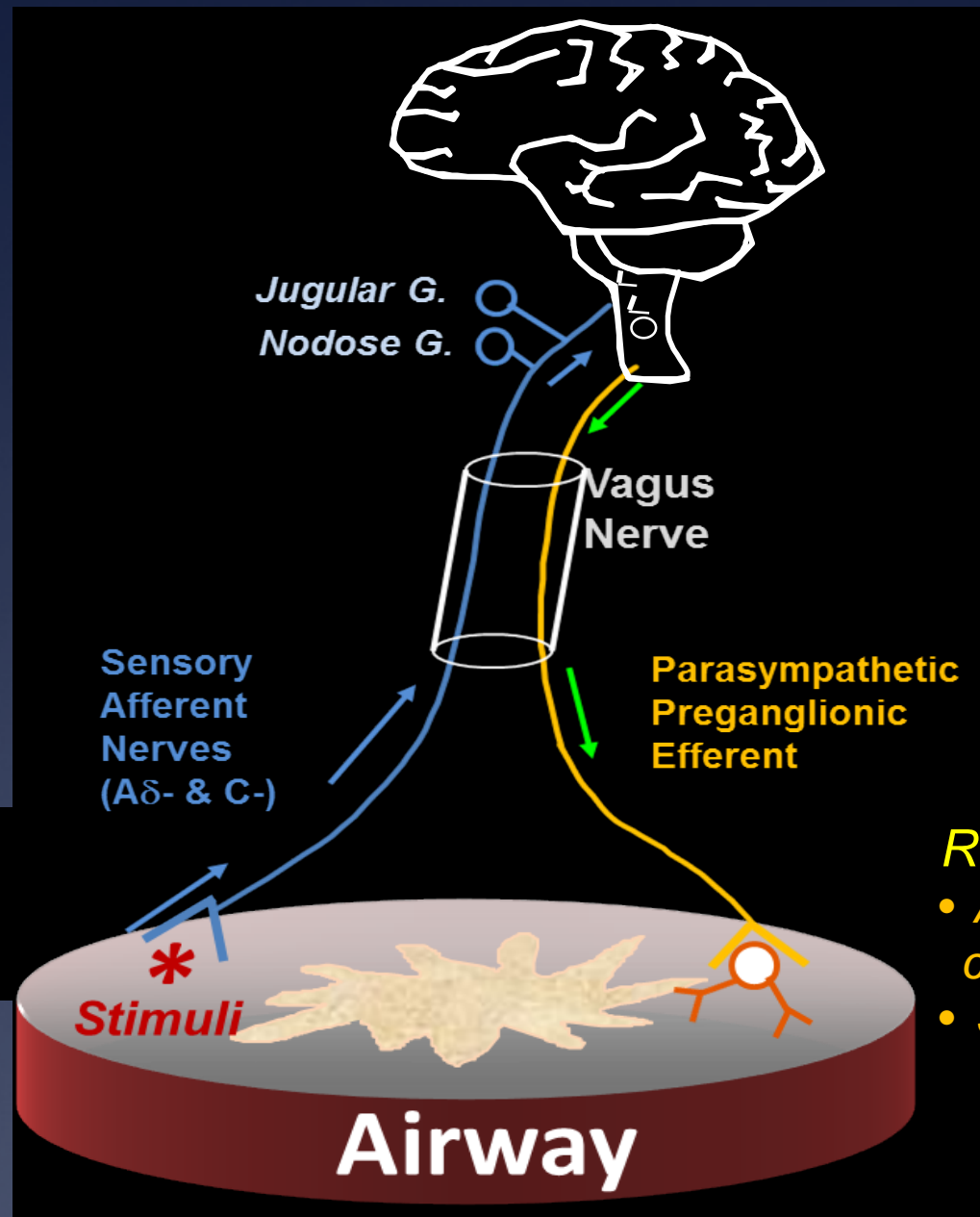


(Modified from Tashkin et al. 1986)

ORIGINAL ARTICLE

Tiotropium Bromide Step-Up Therapy for Adults with Uncontrolled Asthma





Sensations:

- *Dyspnea*
- *Cough*

Reflexes:

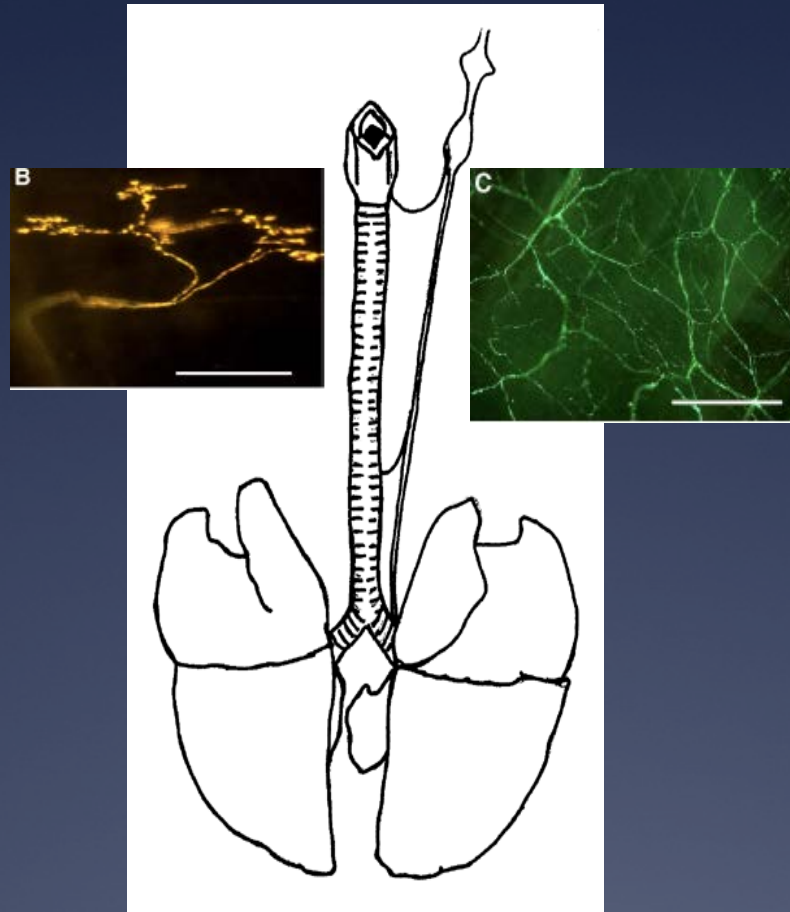
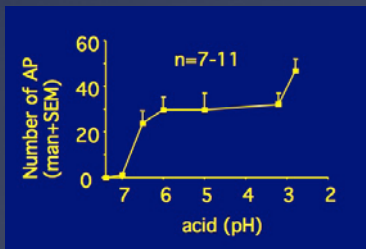
- *Airway smooth muscle constriction*
- *Secretions*

Afferent nerve subtypes in the large airways

cough receptor



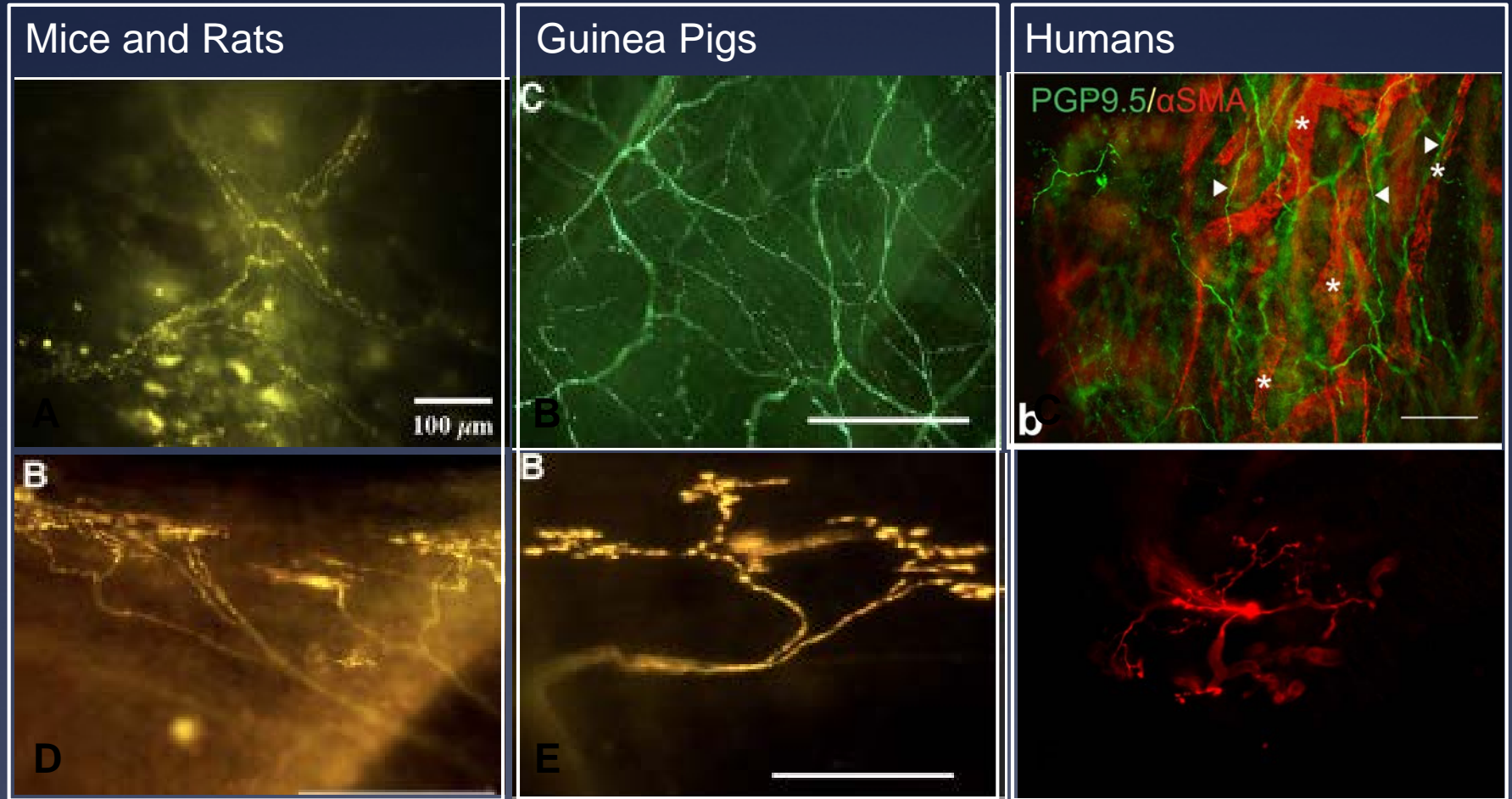
↑ acid pH=6



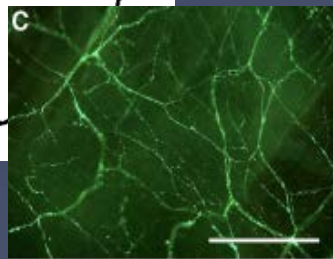
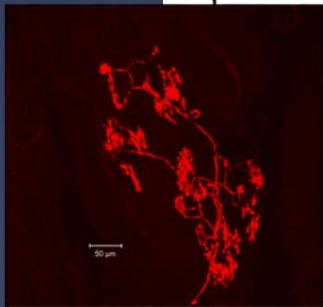
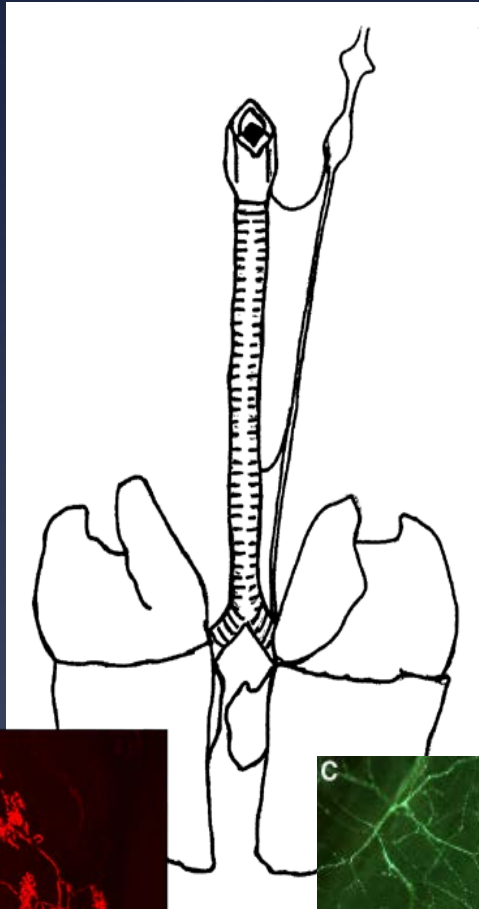
C-fibers

(Kollarik & Undem 2002; Canning, 2004)

Afferent nerve subtypes in the large airways

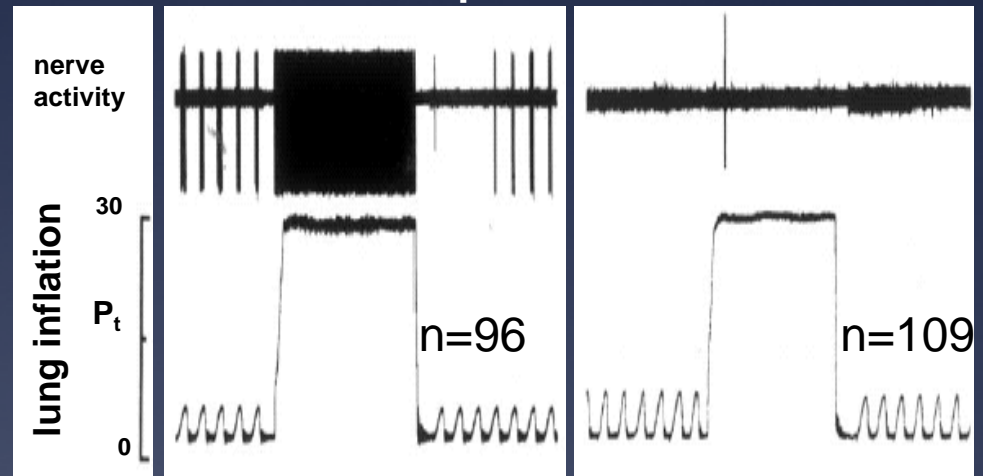


Afferent innervation of the lung



A-fiber stretch
mechanoreceptors

Bronchopulmonar
y C-fibers



RAR

SAR

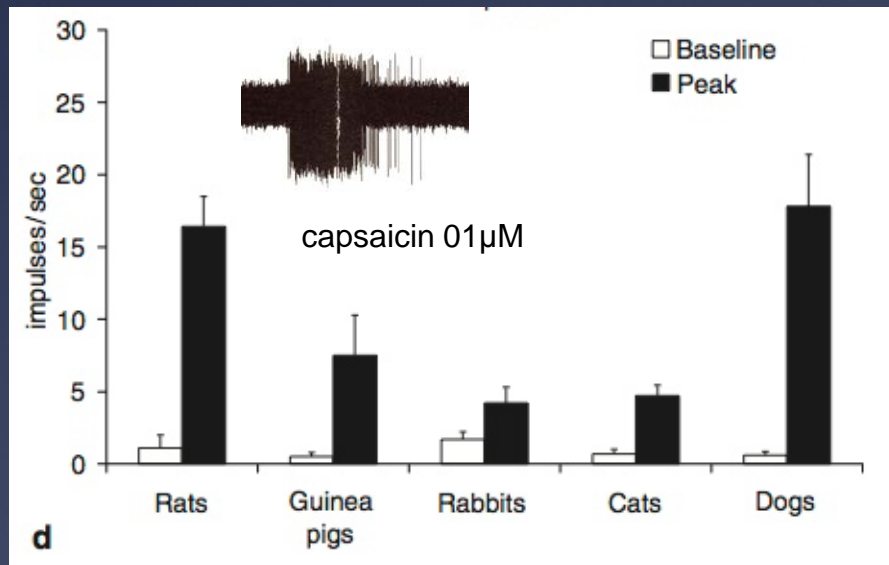
nodose
C-fibers

jugular
C-fibers

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

Bronchopulmonary C-fibers

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

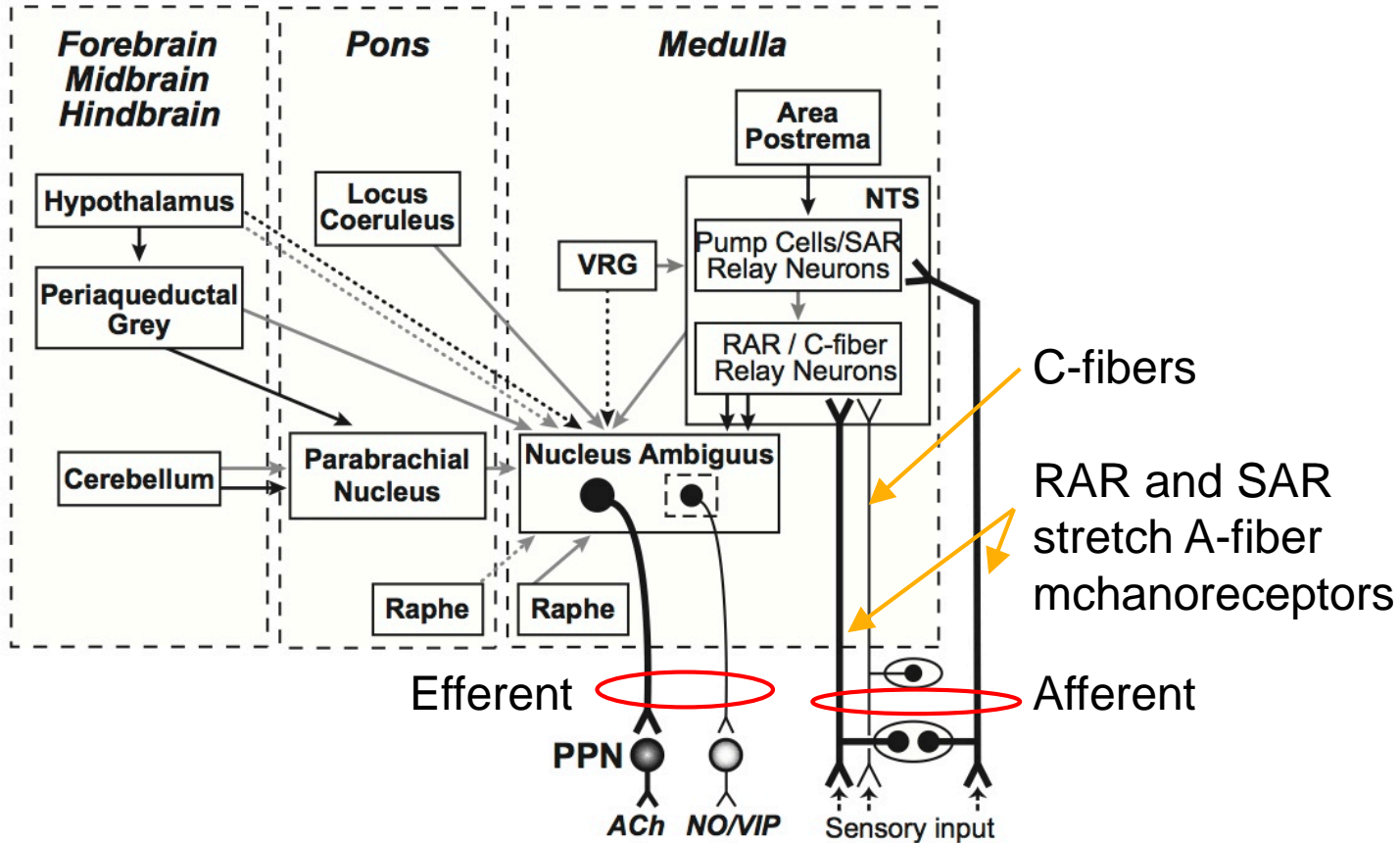


C-fiber activators initiate cough in humans and animal models

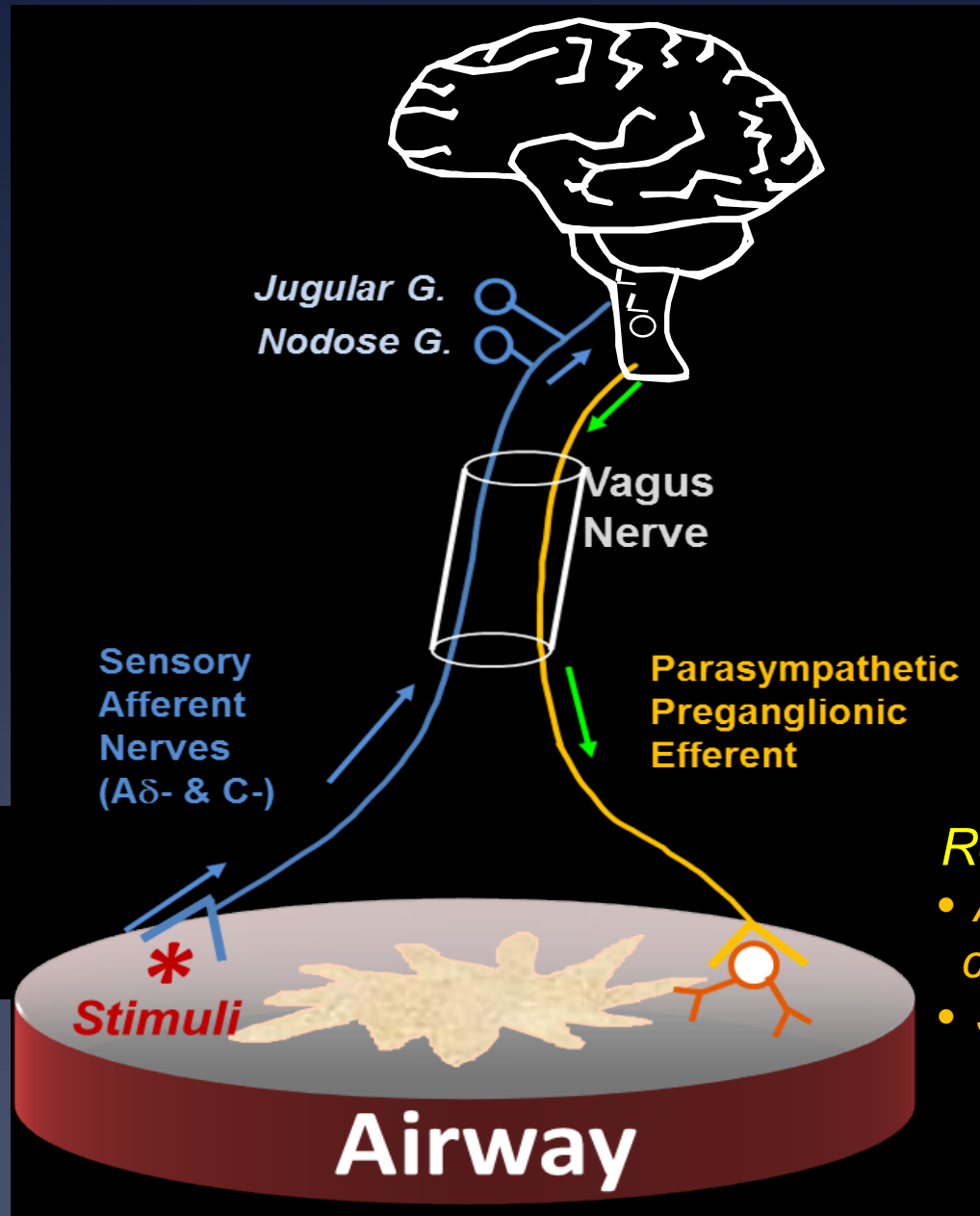
- Capsaicin (TRPV1)
- Cinnamaldehyde (TRPA1)
- Citric Acid (TRPV1/ASIC)
- Bradykinin (B2)
- Water (?)

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



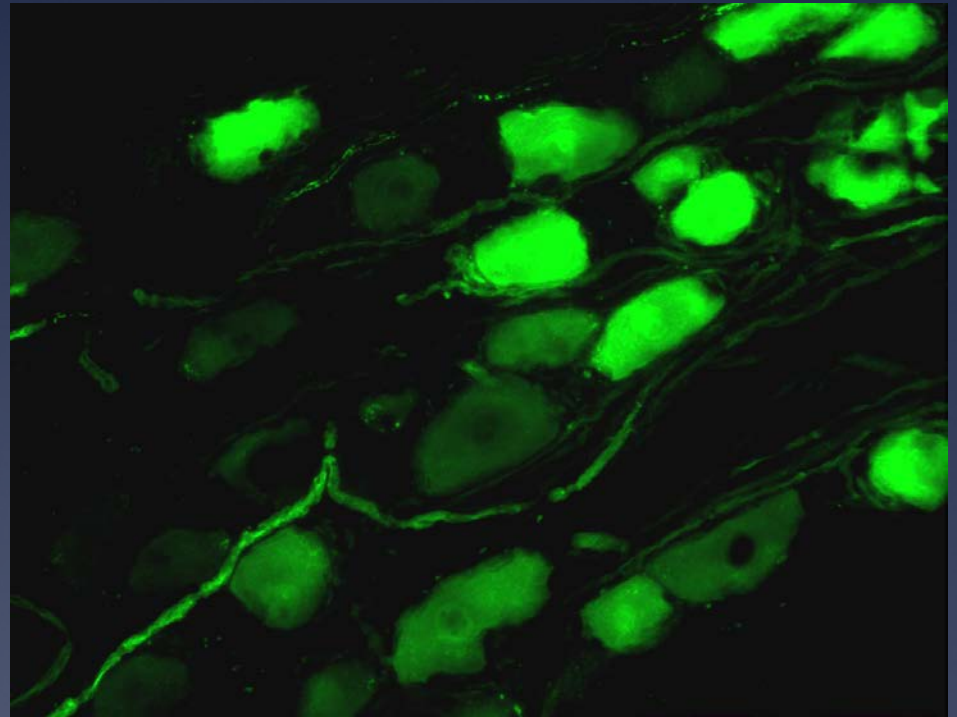
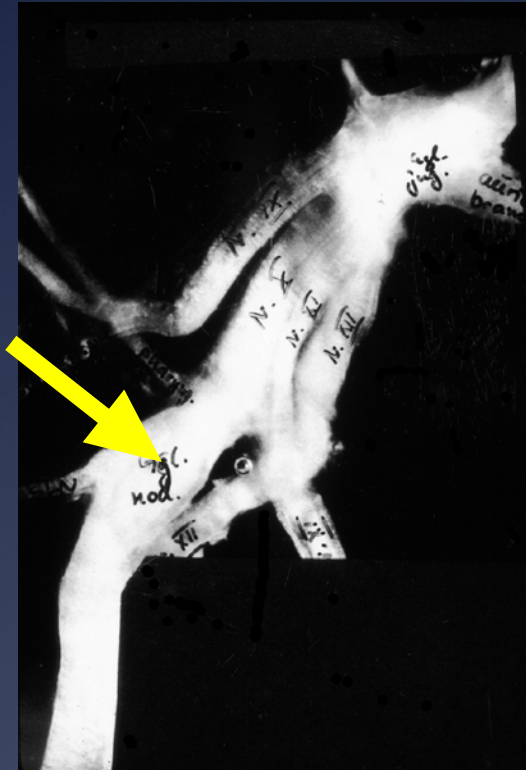
Sensations:

- *Dyspnea*
- *Cough*

Reflexes:

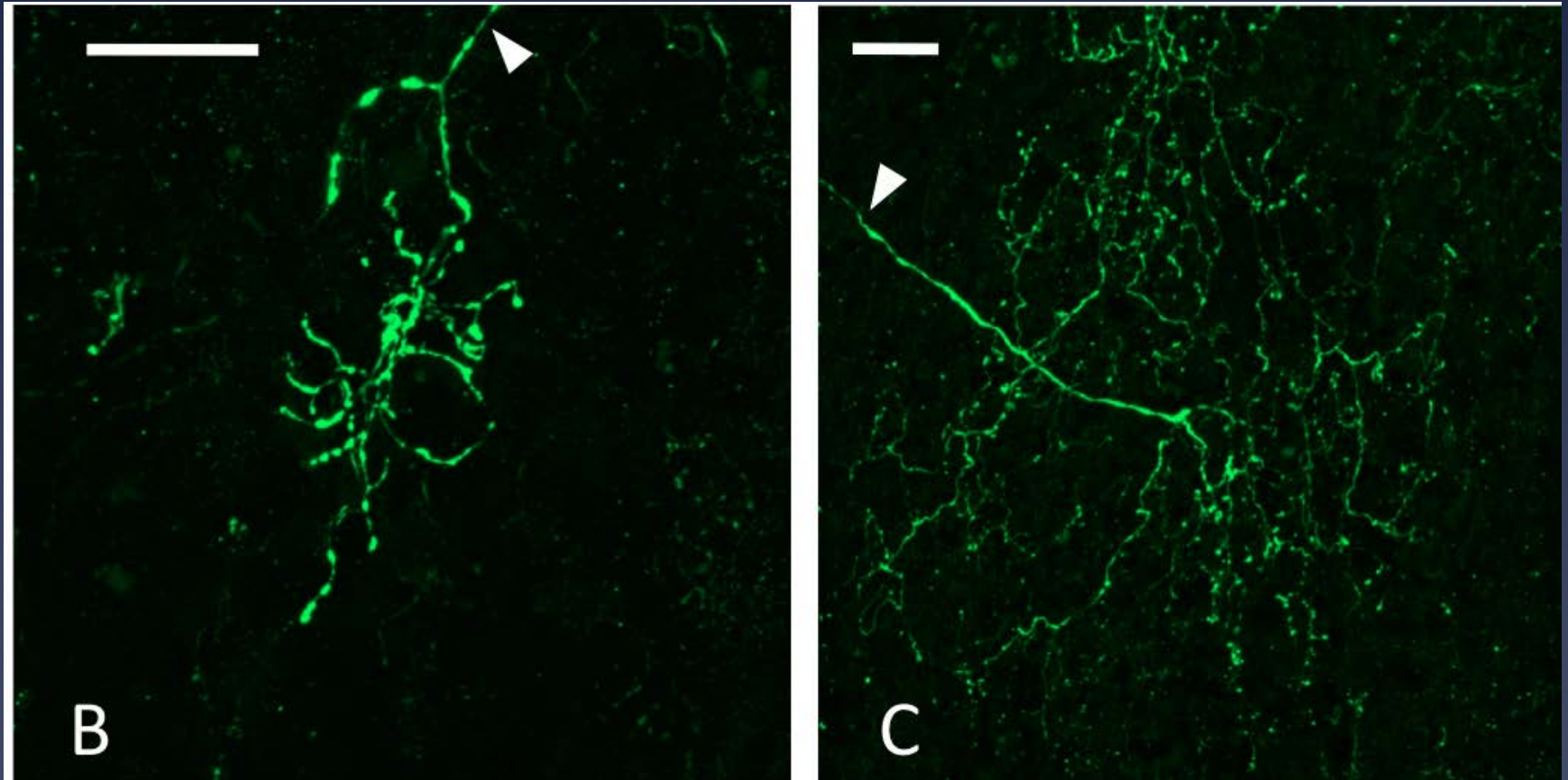
- *Airway smooth muscle constriction*
- *Secretions*

In vivo transfection of sensory nerves with AAV virus vectors

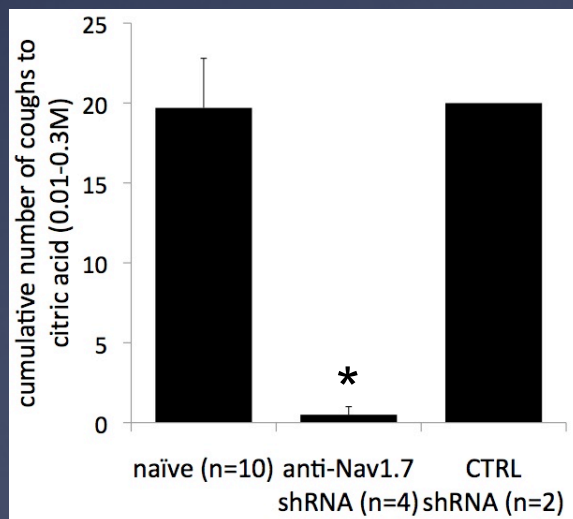
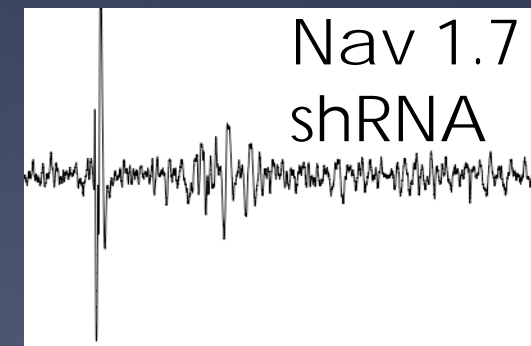
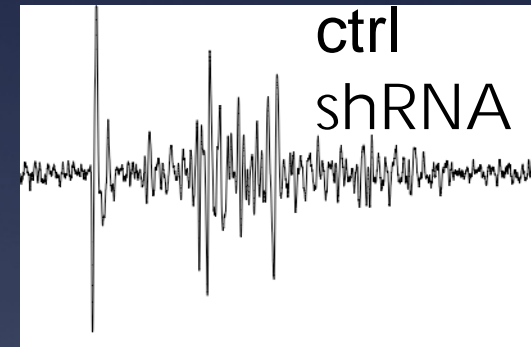
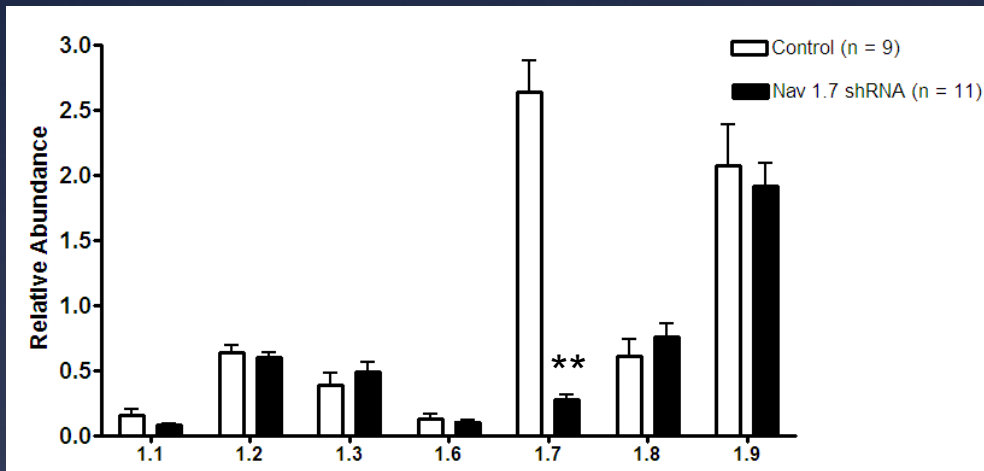


In injection into sensory ganglia

Vagal afferent nerve terminals in the trachea



Knockdown of Nav 1.7 expression and function by AAV-delivered shRNA



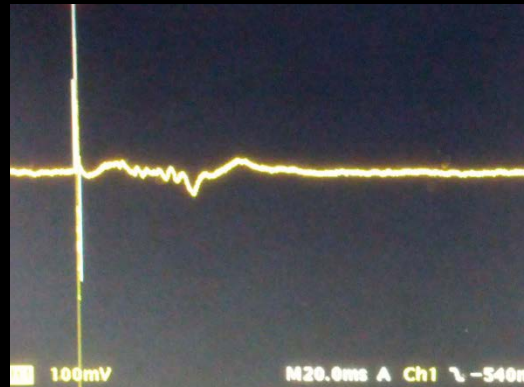
Muroi Y, Ru F, Kollarik M, Canning BJ, Hughes SA, Walsh S, Sigg M, Carr MJ, Undem BJ. *J Physiol.* 2011

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

C-wave



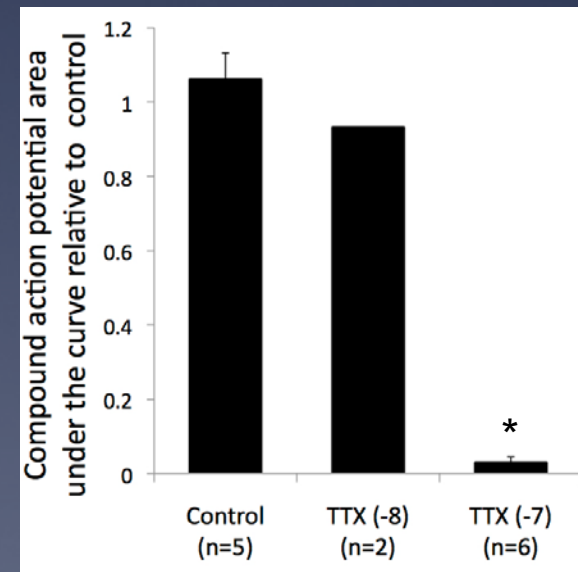
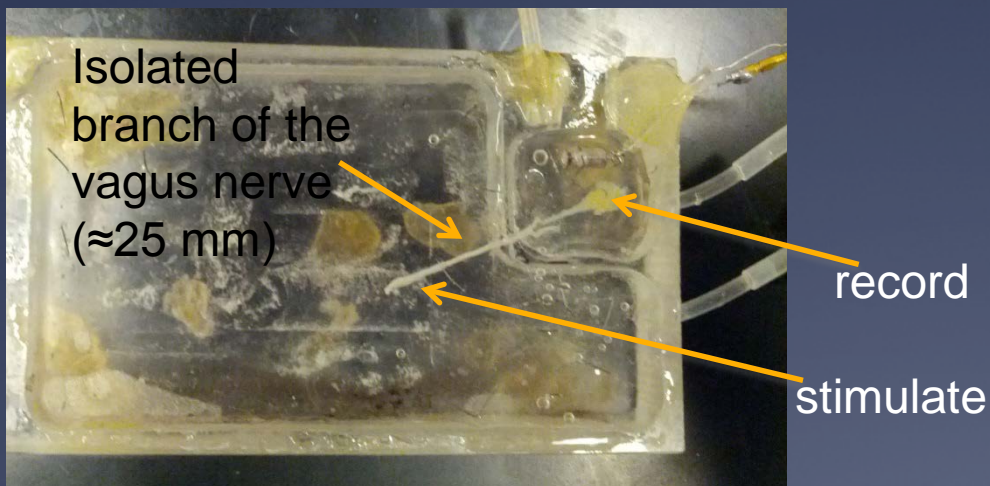
CTRL



Cmpd X (Nav1.7 blocker)
1 μ M



WASH (>3h)



Kollarik, unpublished.

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- * The lung is a very feasible target for peripheral neuromodulation.
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