Neural Control of the Lung

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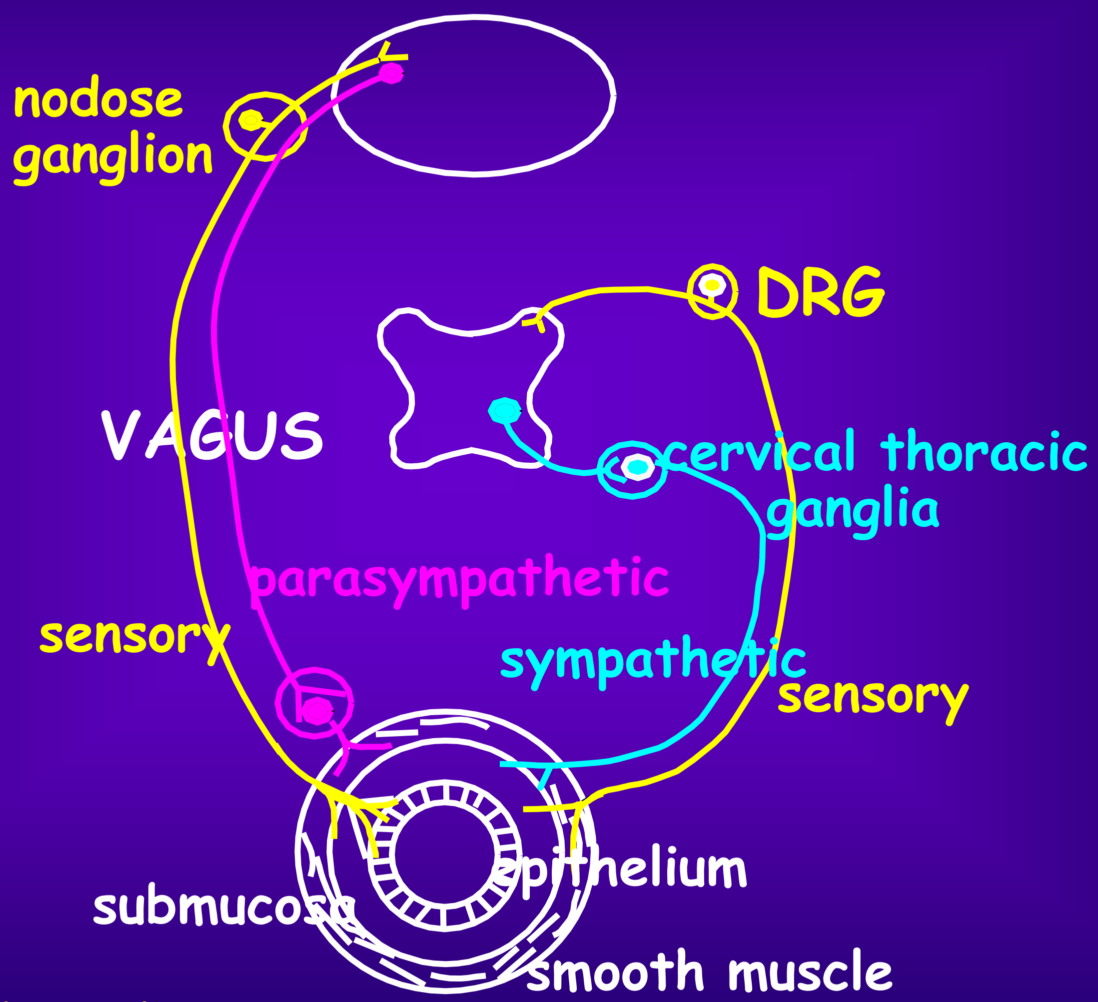
Innervation of the Respiratory Tract



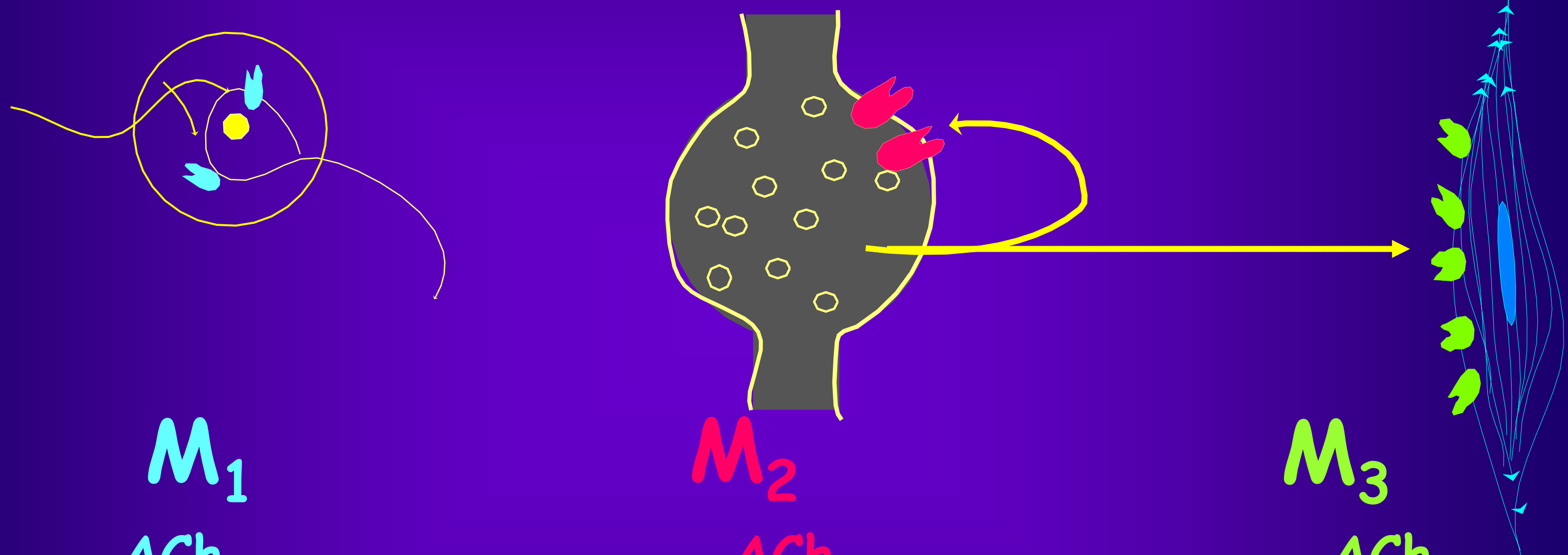
Barnes, Baraniuk, Belvisi, 1991
Am. Rev. Resp. Dis. 144, 1187-1198

Muscarinic Receptor Subtypes in the Airways

Parasympathetic ganglion

Postgangiolnic cholineric nerve terminal

Airway smooth muscle



Agonist ACh ACh ACh

Oxotremorine Oxotremorine

Oxotremorine

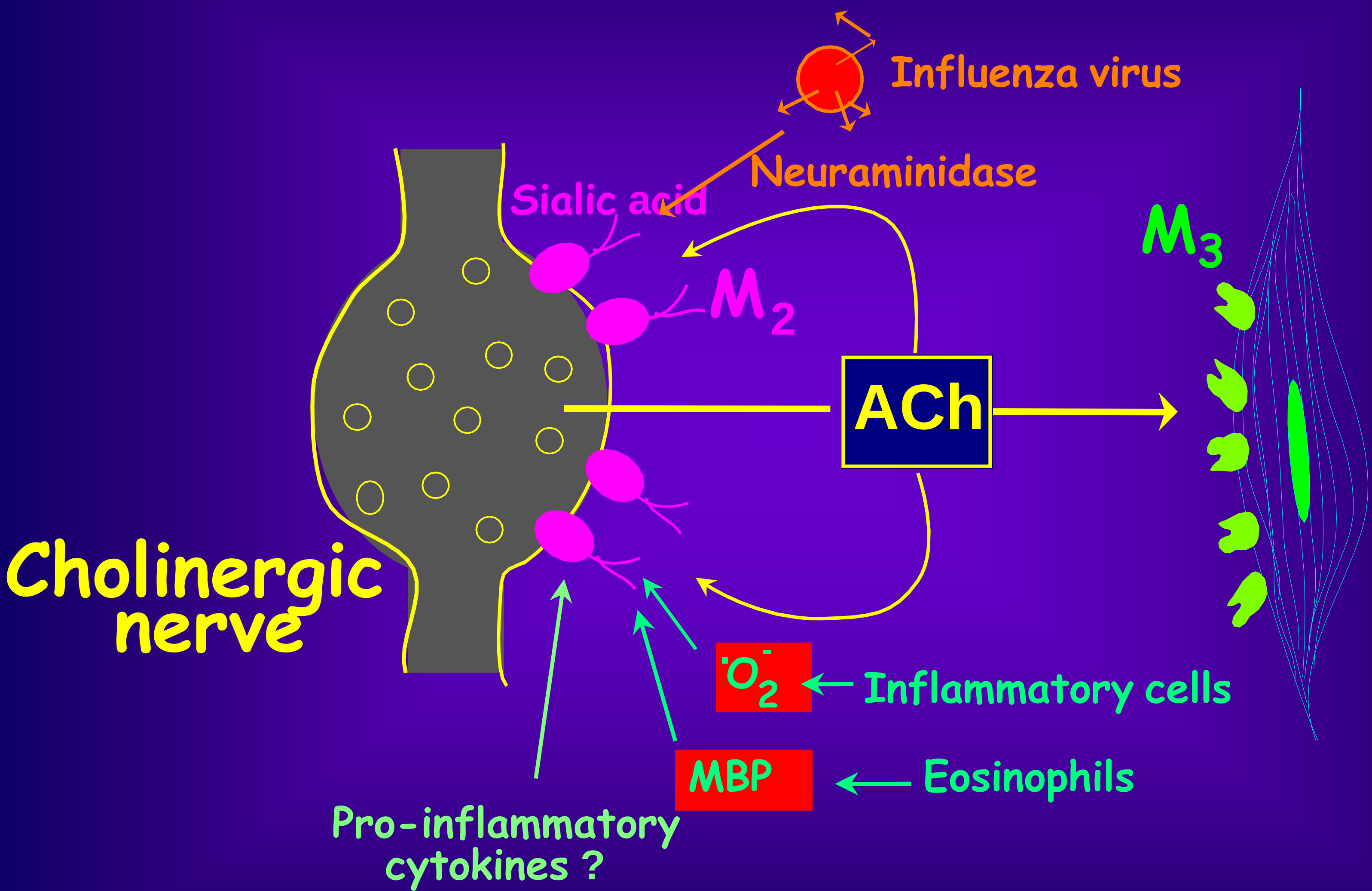
Antagonist Ipratropium Ipratropium

Ipratropium

Tiotropium

Tiotropium

Muscarinic Autoreceptor Dysfunction in Asthma ?



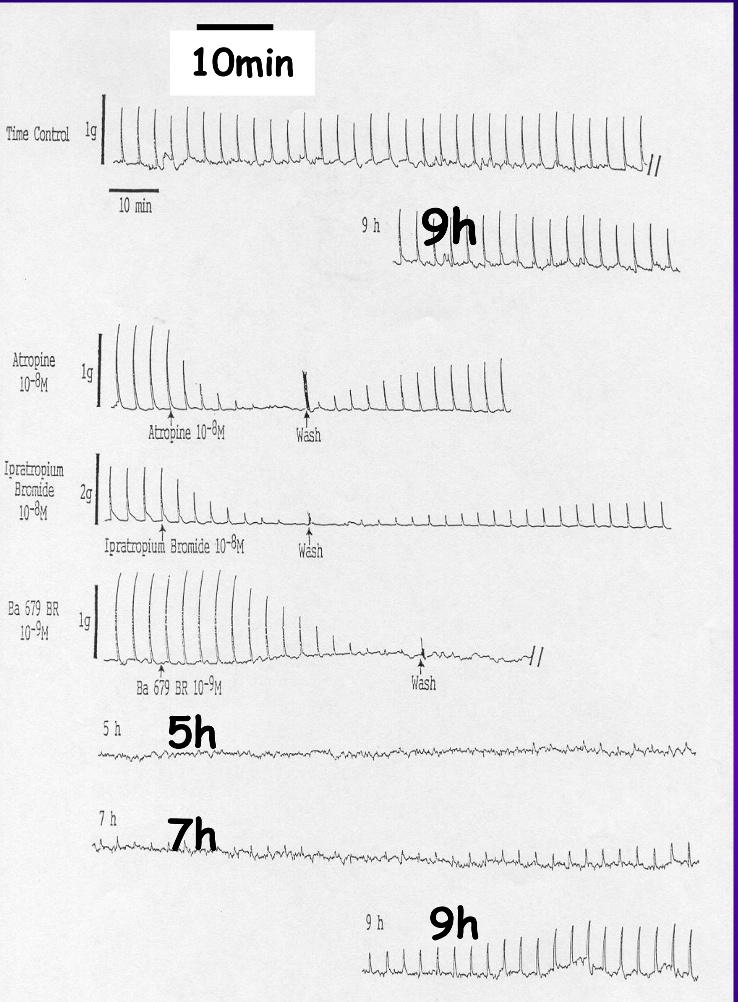
DURATION OF ANTICHOLINERGIC EFFECTS

Control

Atropine

Ipratropium

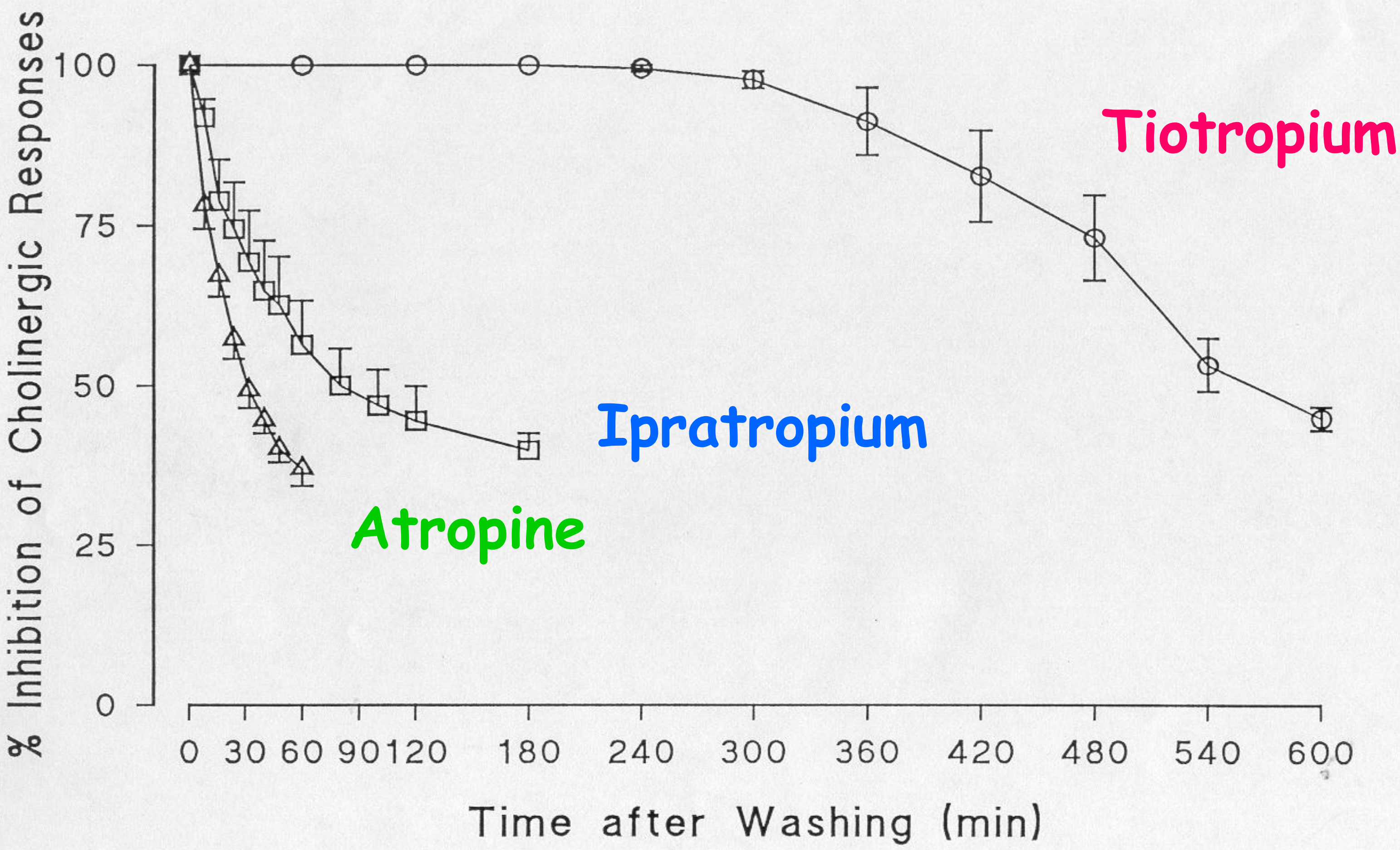
Tiotropium



Guinea-pig trachea
Electrical field simulation

DURATION OF ANTICHOLINERGIC ACTION

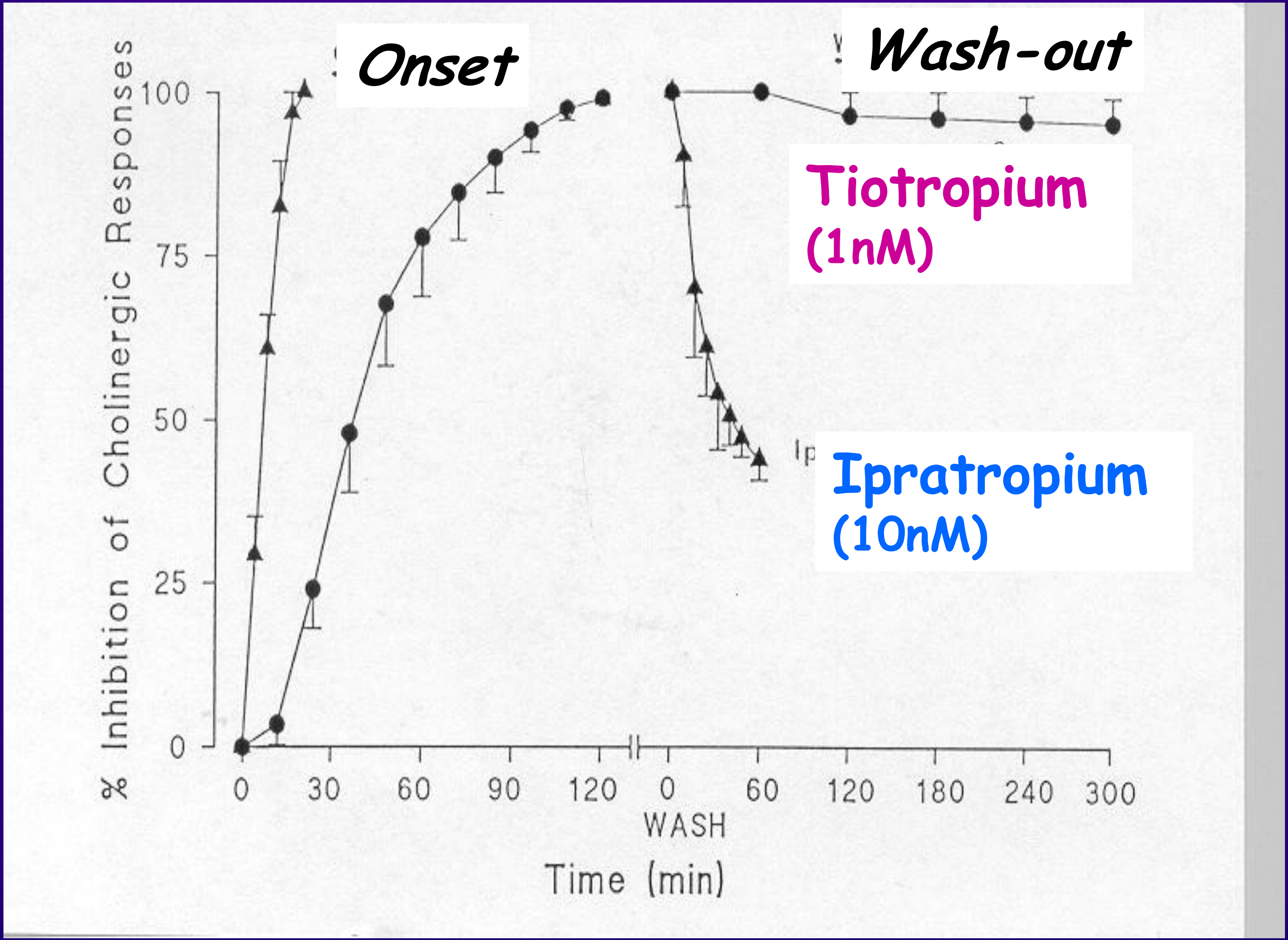
Guinea-pig bronchi *in vitro*: inhibition of cholinergic nerve



Takahashi et al: AJRCCM 1995

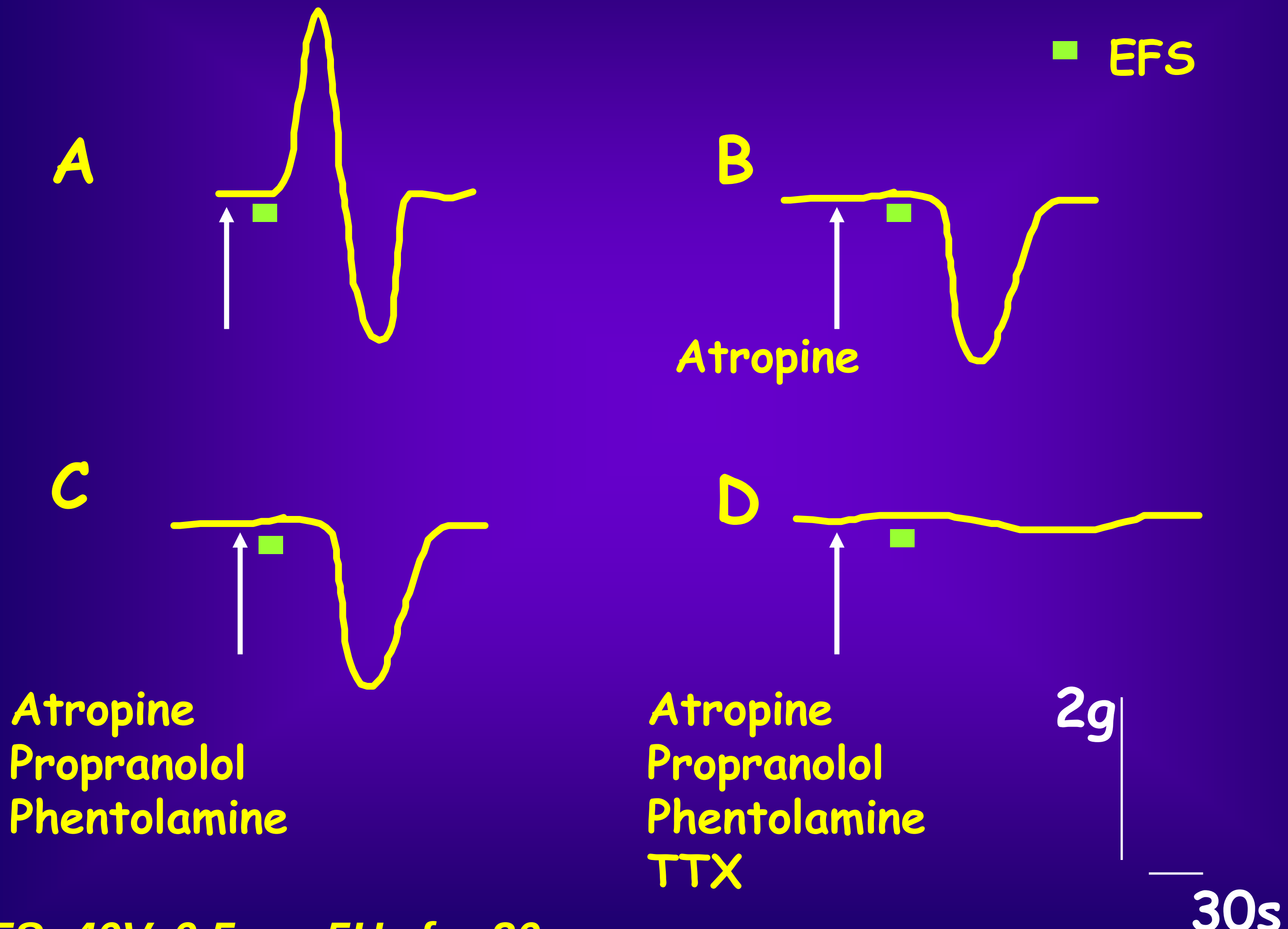
DURATION OF ANTICHOLINERGIC ACTION

Human bronchi *in vitro*: inhibition of cholinergic nerves



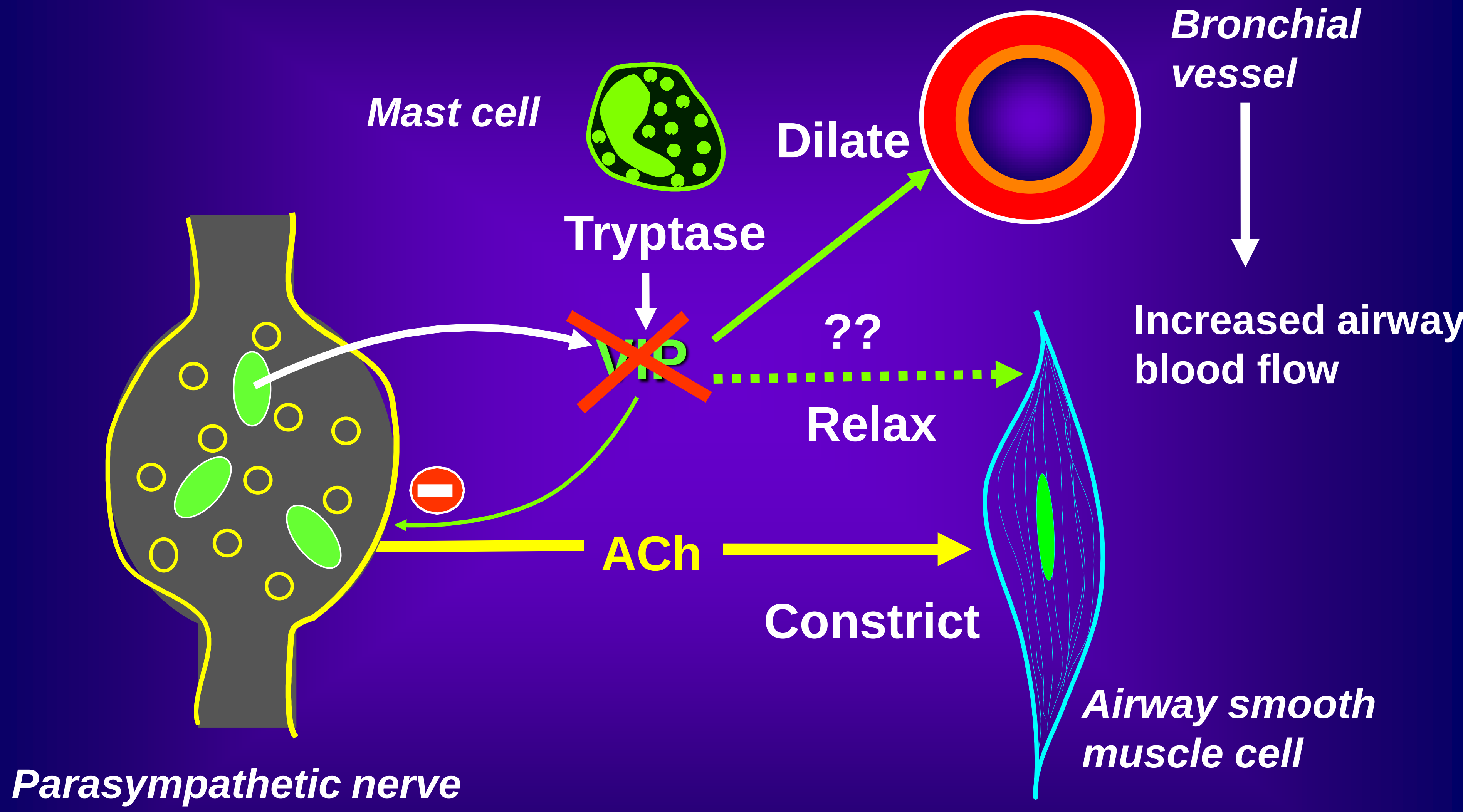
Takahashi et al: AJRCCM 1995

Human Airway Smooth Muscle and the Control of Airway Tone



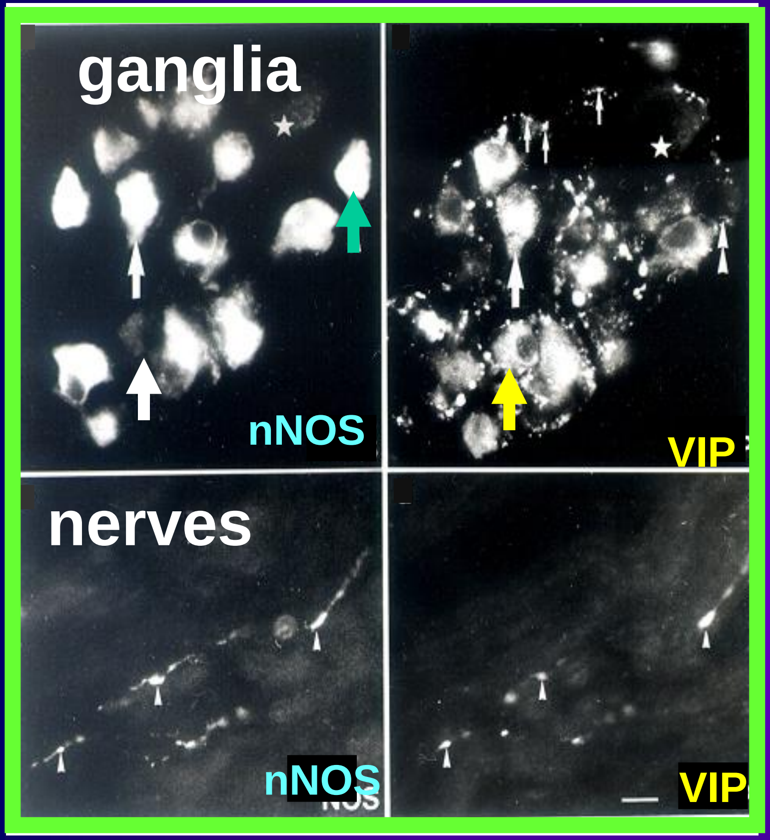
EFS: 40V, 0.5ms, 5Hz for 30s

VIP EFFECTS ON AIRWAYS

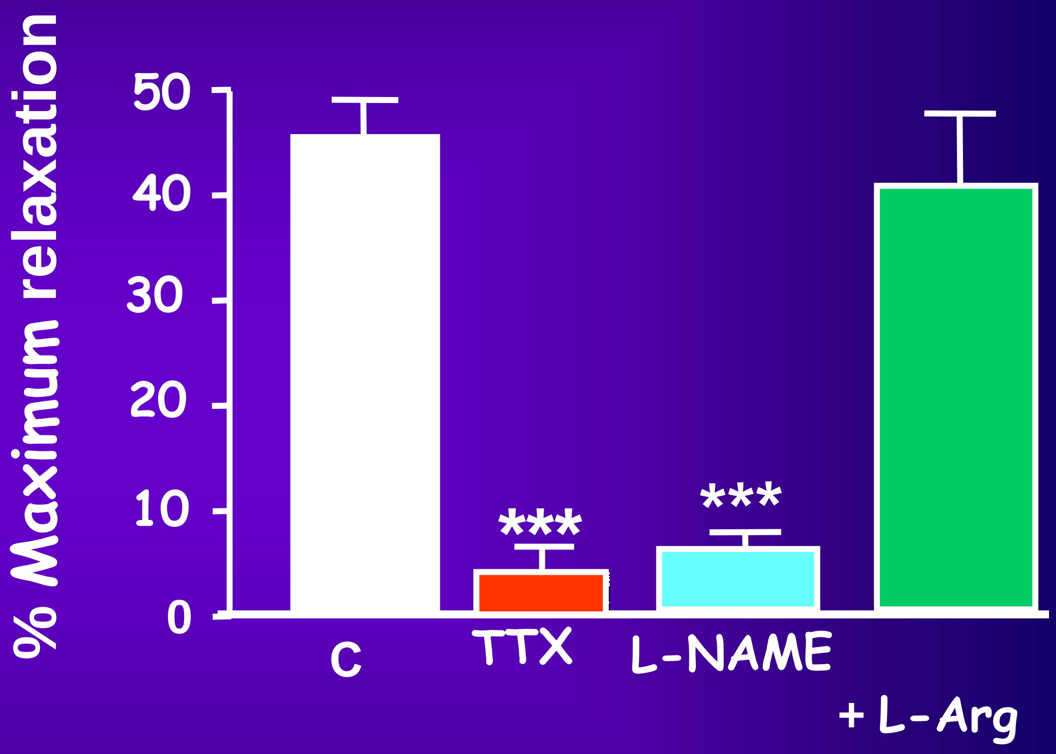


i-NANC Relaxations of Human Trachea: Role for NO

Immunocytochemistry

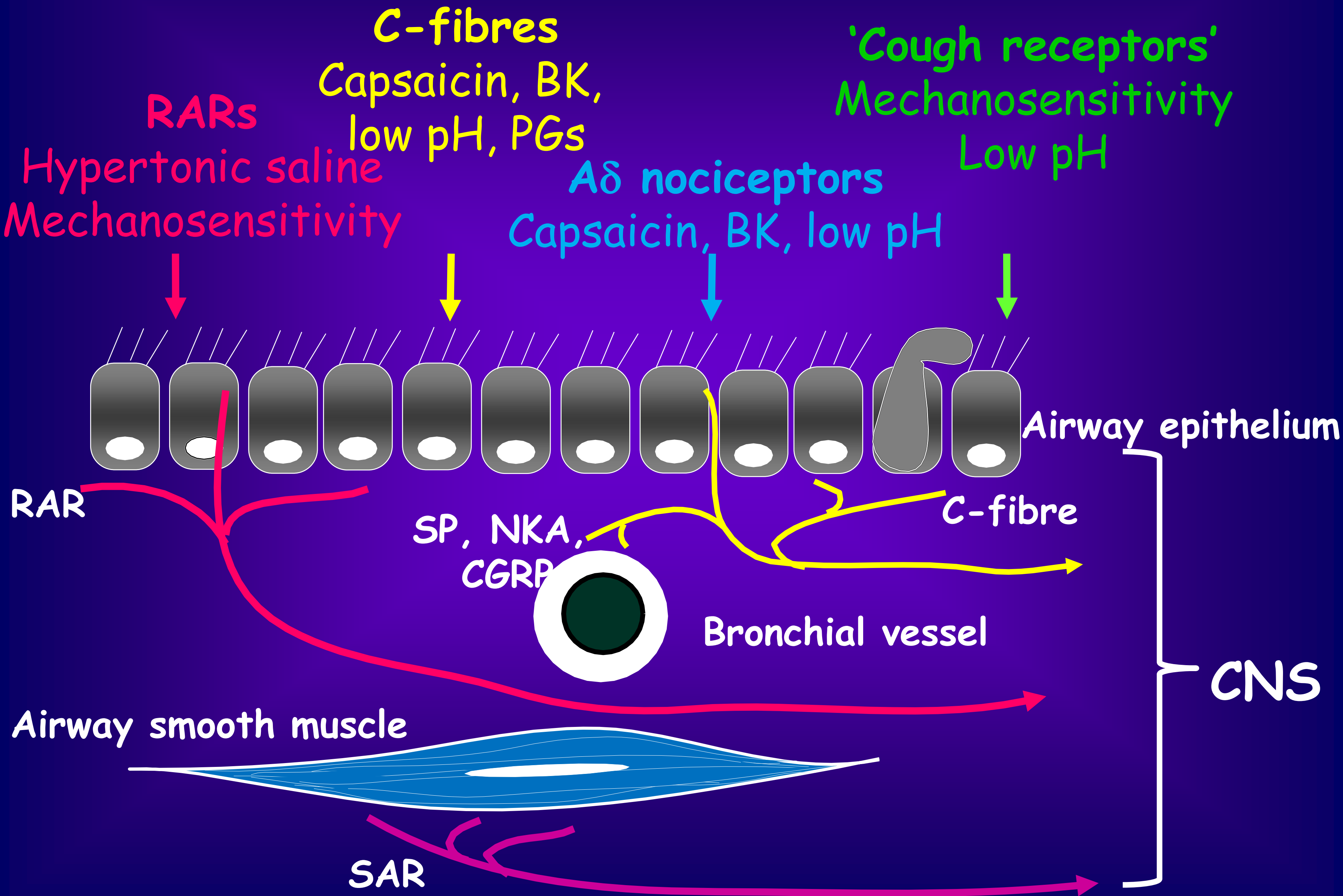


L-NAME: NOS inhibitor

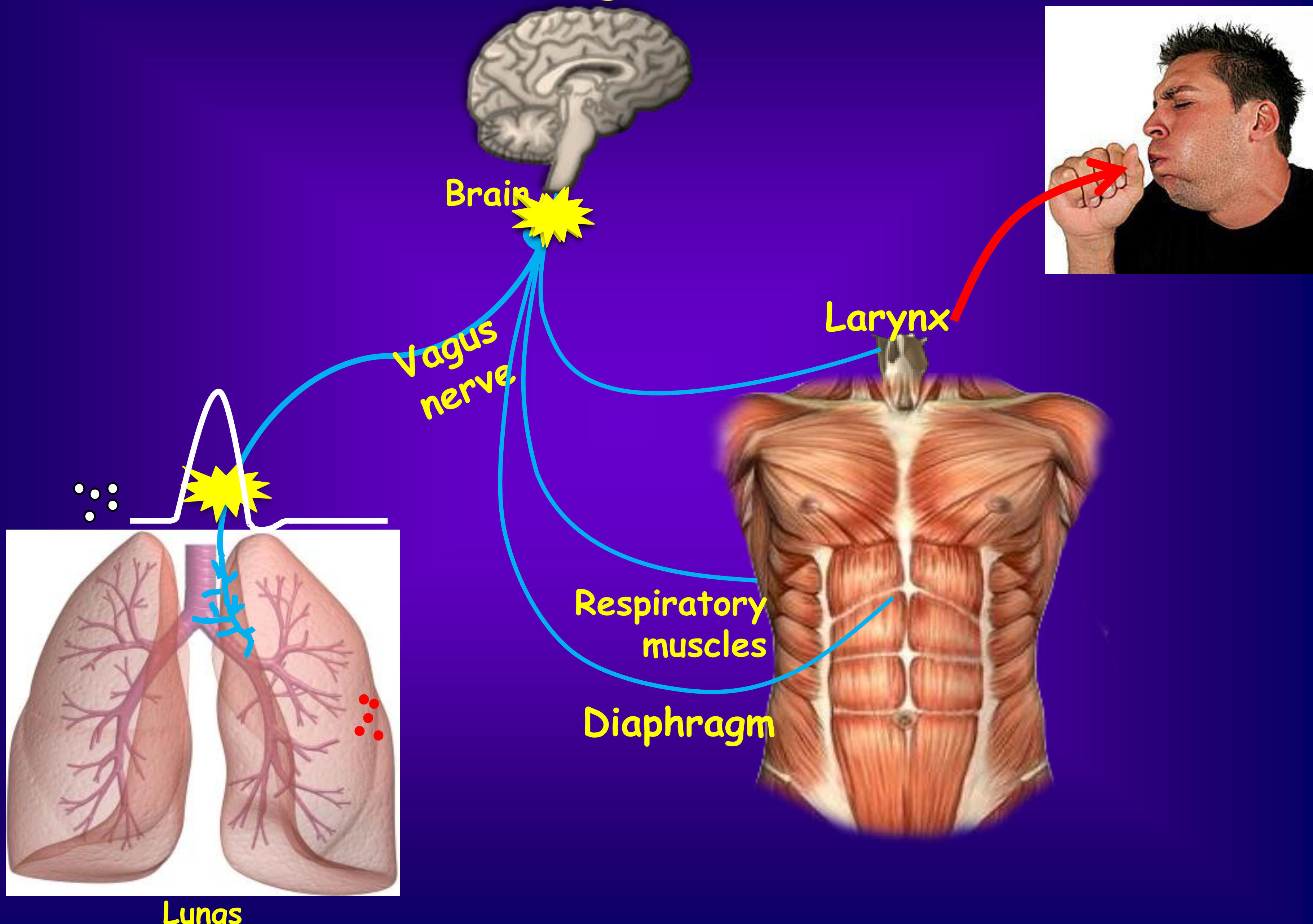


Belvisi M et al: Eur. J. Pharmacol 1992; J Appl Physiol 1992

Airway Sensory Nerves

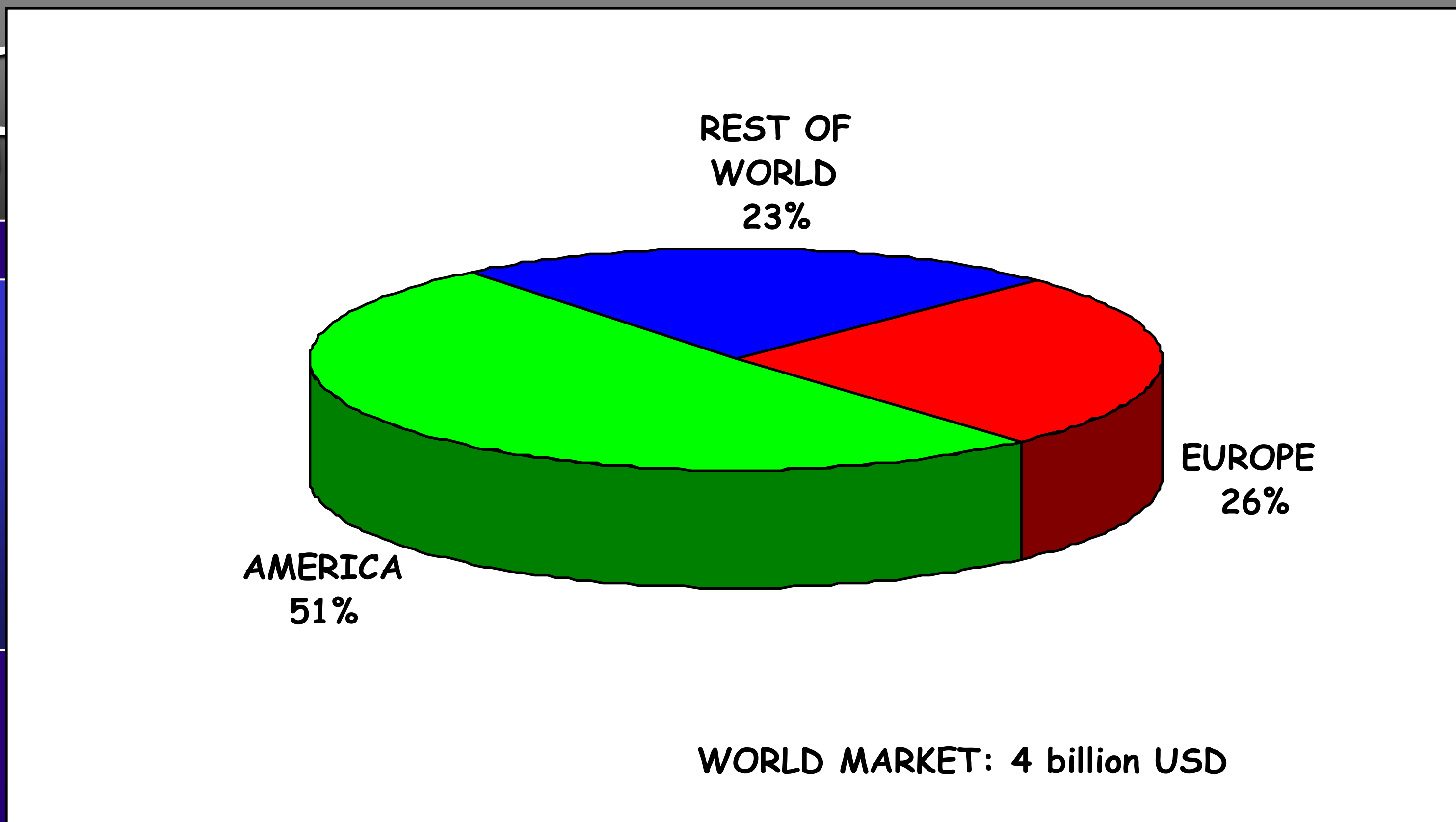


The Cough Reflex



COUGH AS A MAJOR UNMET MEDICAL NEED

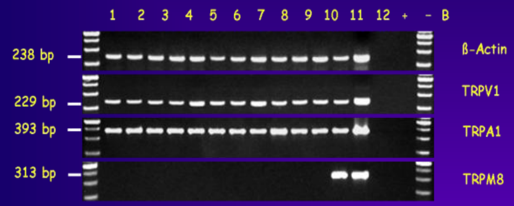
- Commonest symptom for medical consultation
- Chronic cough: 10-38% of pulmonary out-patients
- No effective therapy apart from opiates
- H
- T



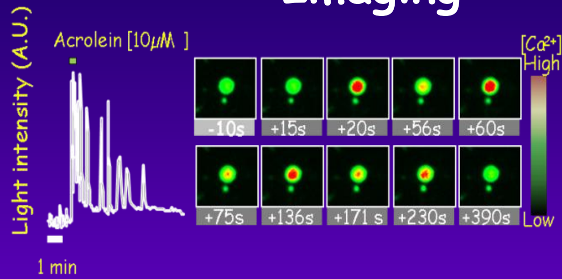
What we do…..

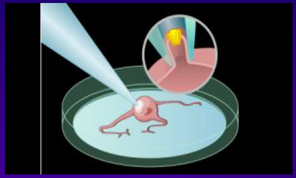
Cough MODEL-Endpoints

Gene expression



Imaging

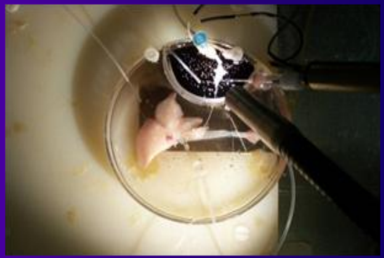




Patch Clamp

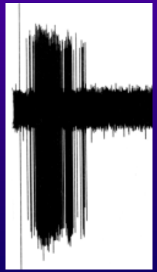
Labelling- airway Specific ganglia

Functional Phenotype



Electrophysiology

Human studies

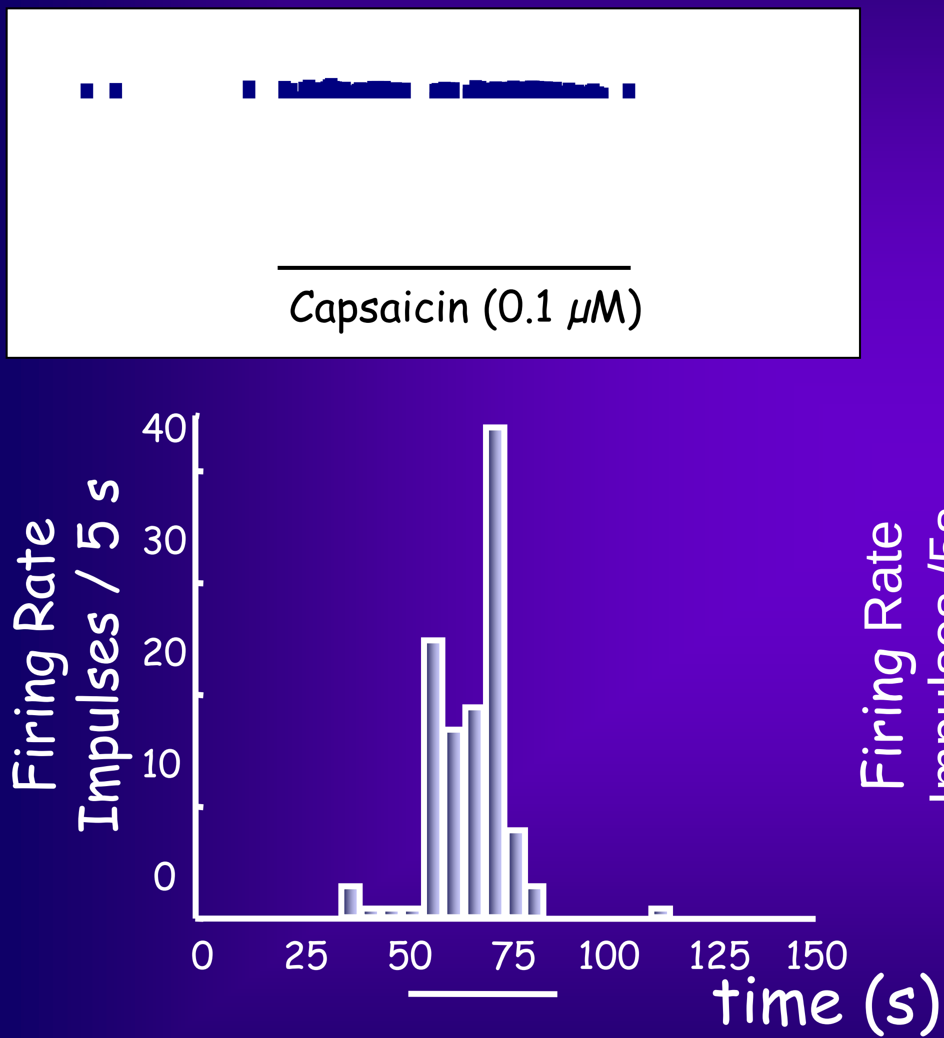


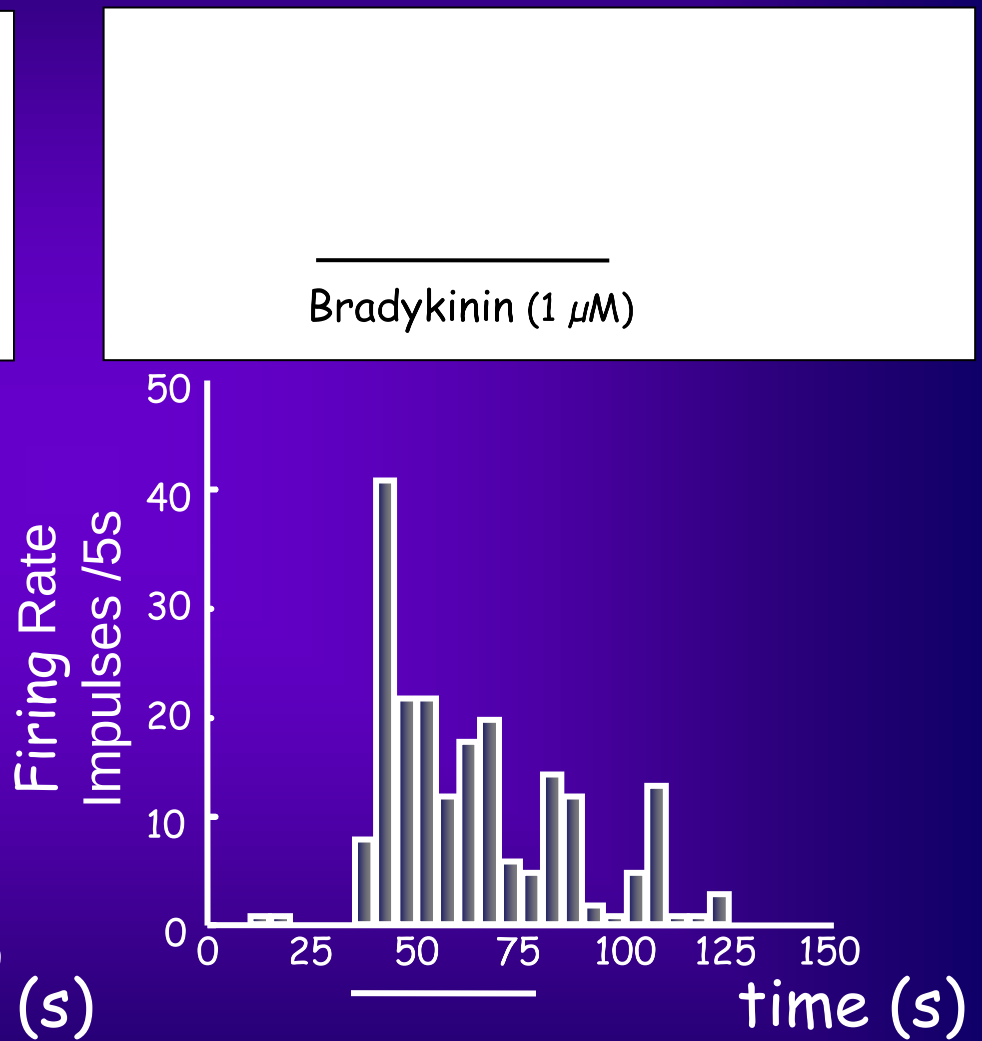
In vivo single Fibre recording studies

Cough

Tissue based bioassay

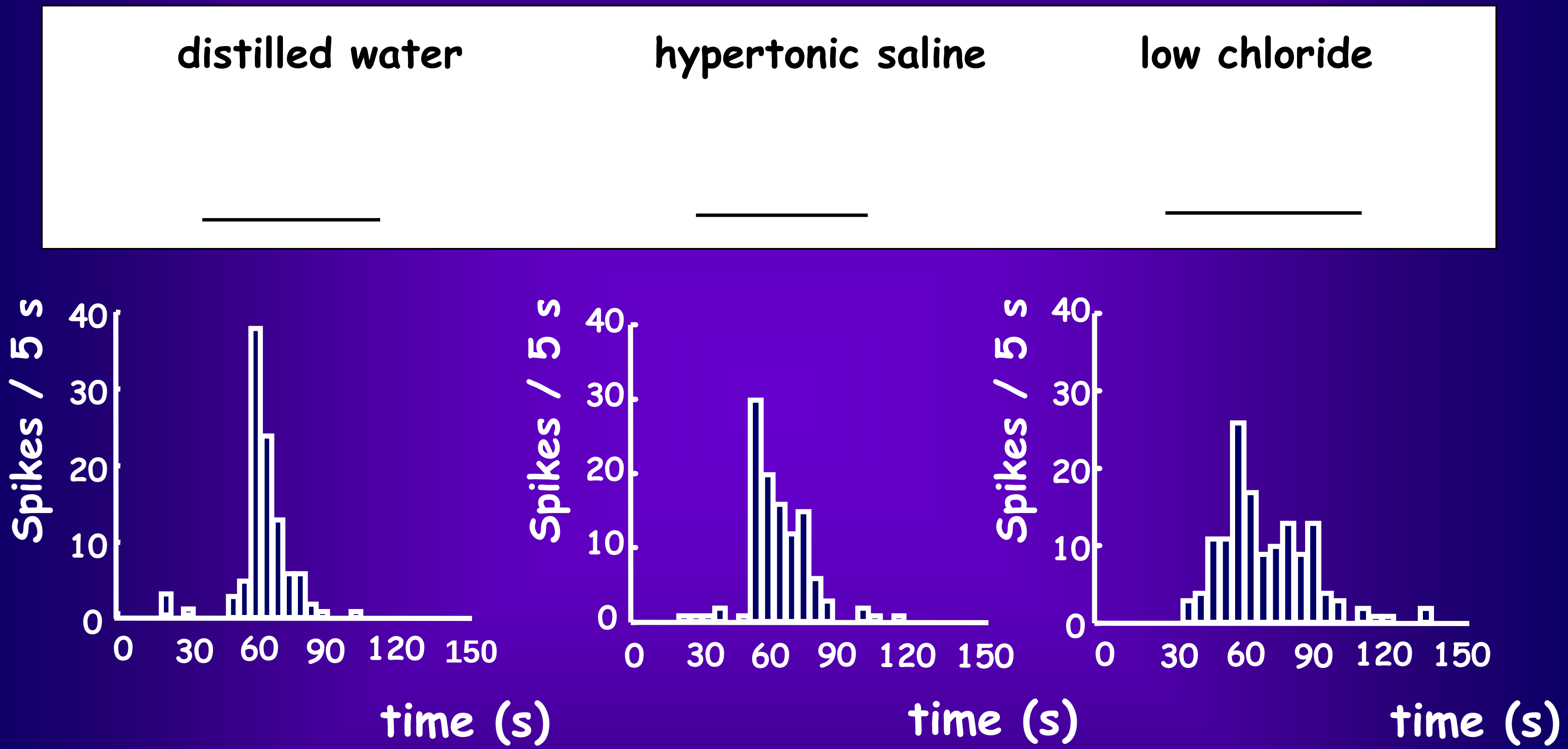
Capsaicin Excitation of C-fibres





Fox et al 1993. J. Physiol. 460, 21-35

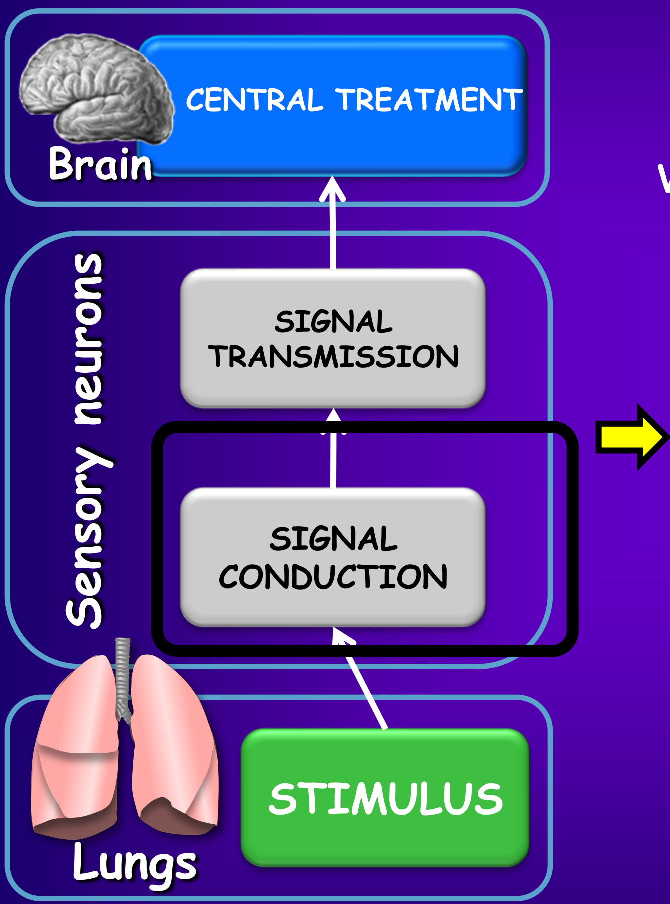
Aδ-fibre Activation

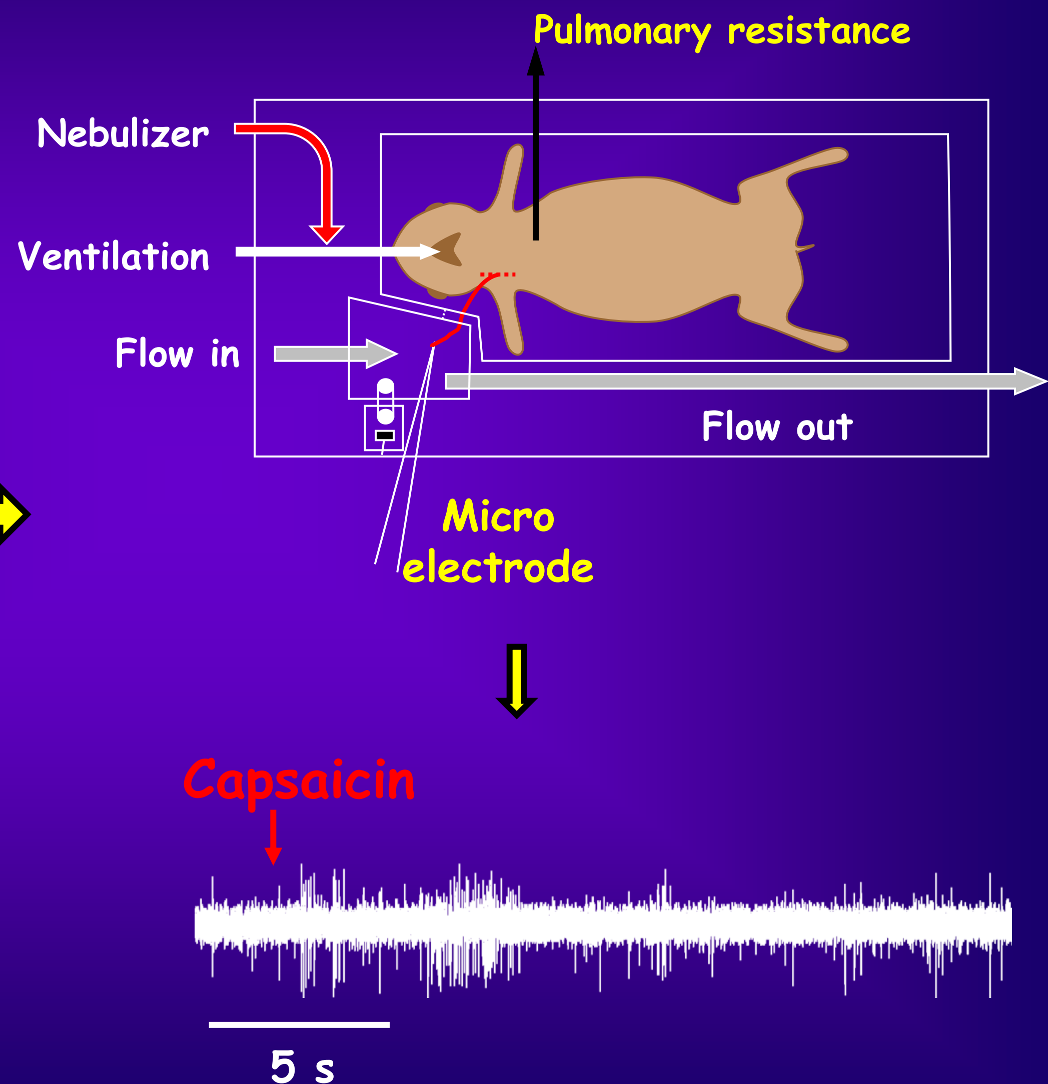


Fox et al 1993. J. Physiol. 482, 179-187

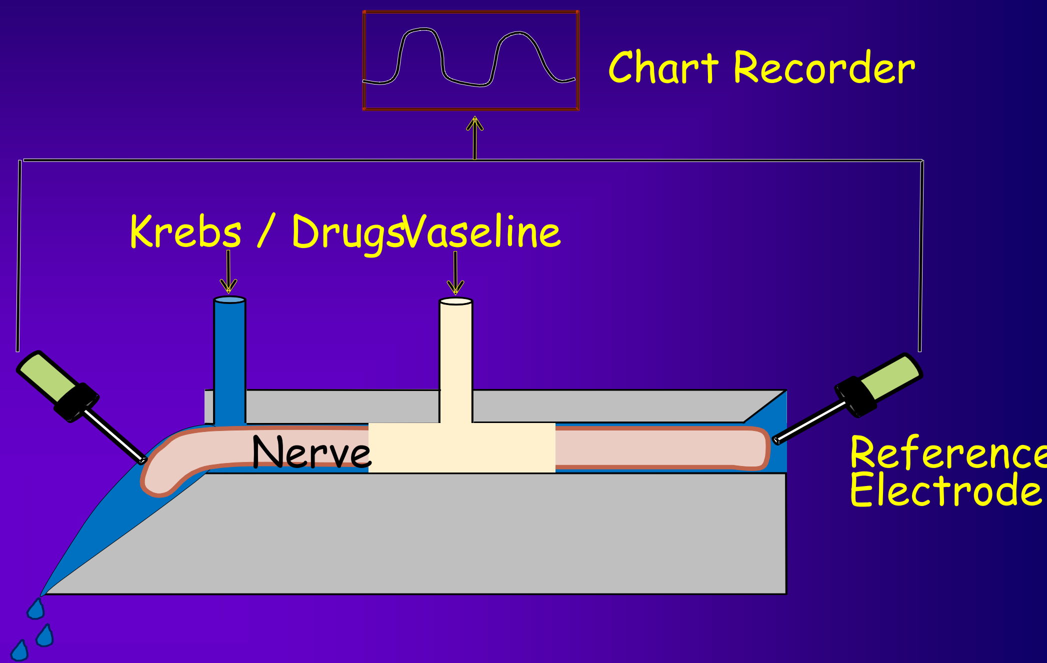
From Airways to Ganglion *in vivo*

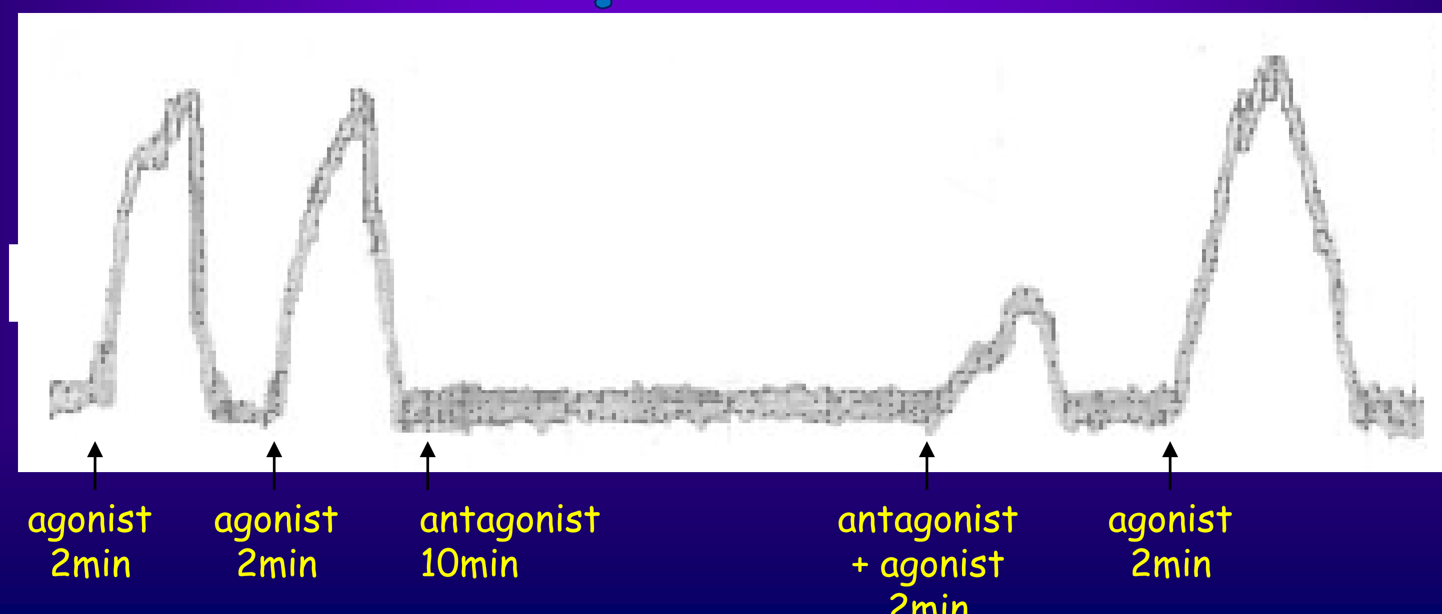
Single fibre recording



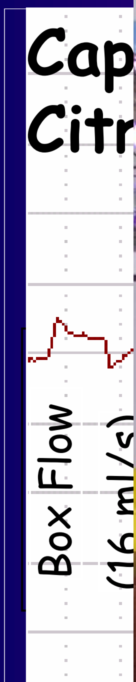


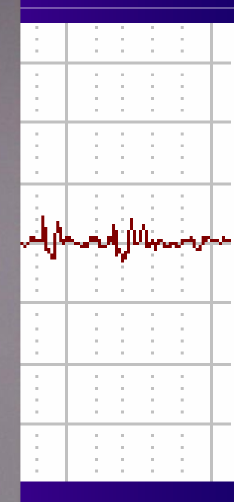
Isolated Vagus Nerve





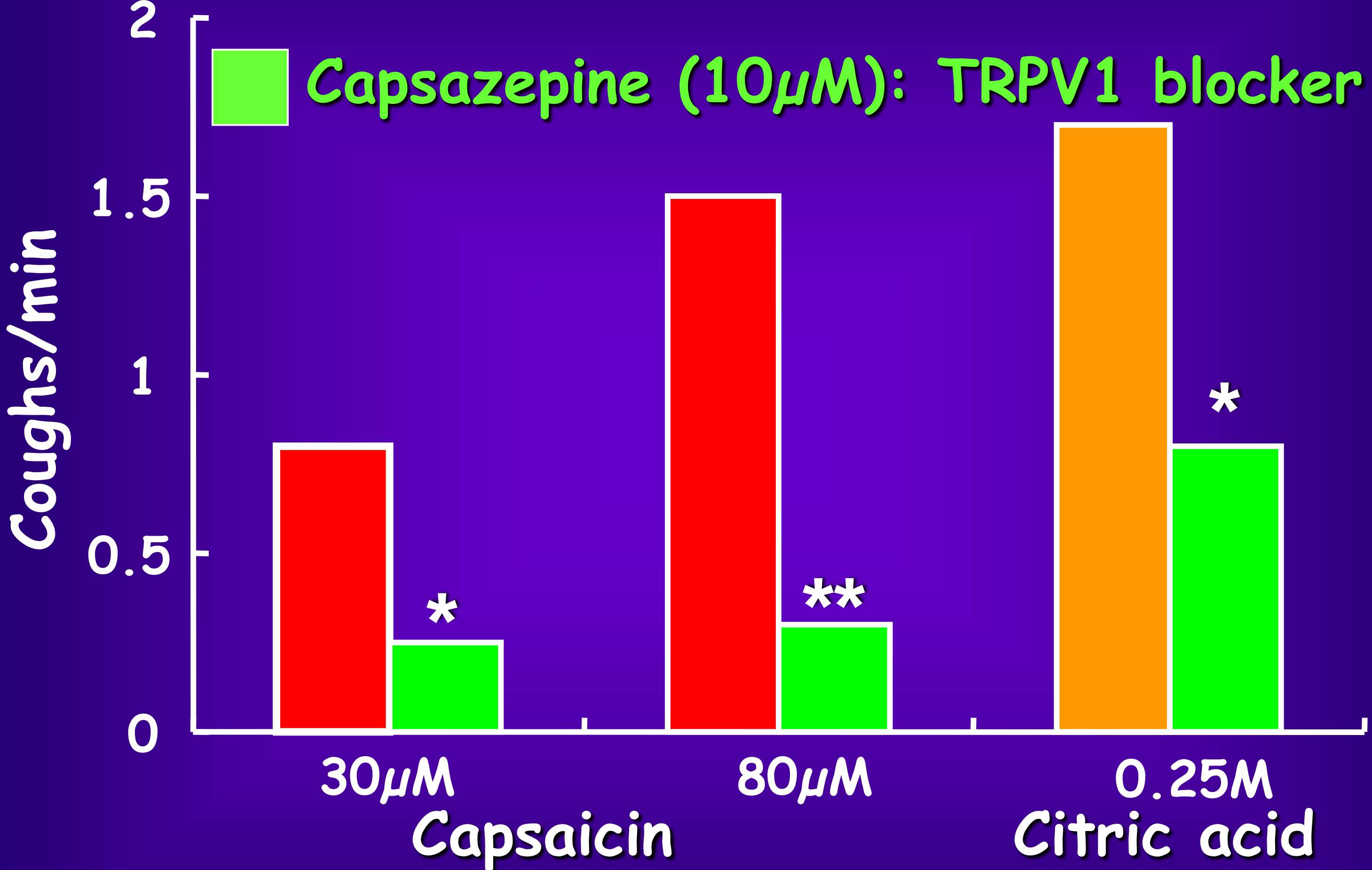
Cough Model





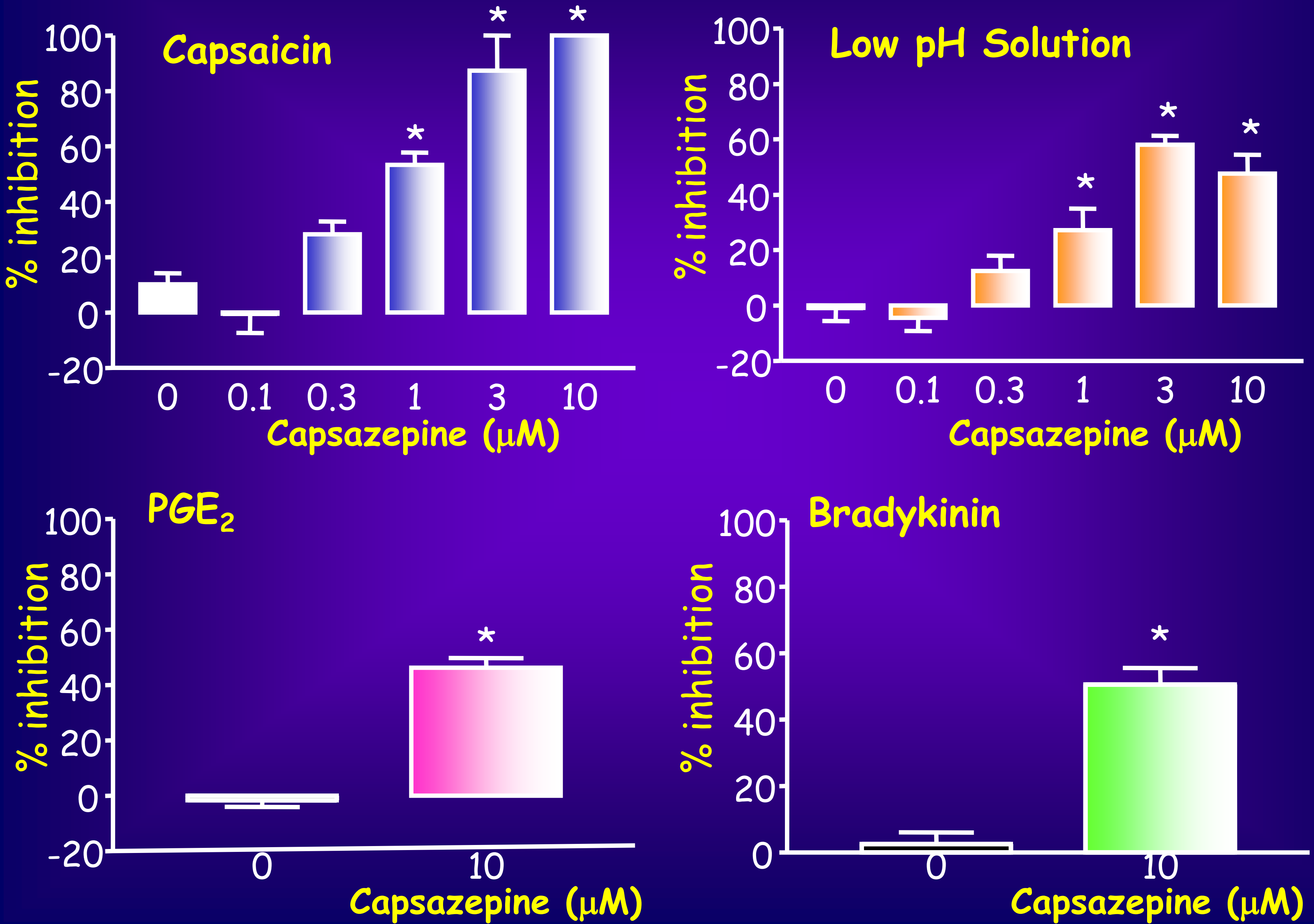
EFFECT OF CAPSAZEPINE ON COUGH

Conscious guinea pigs

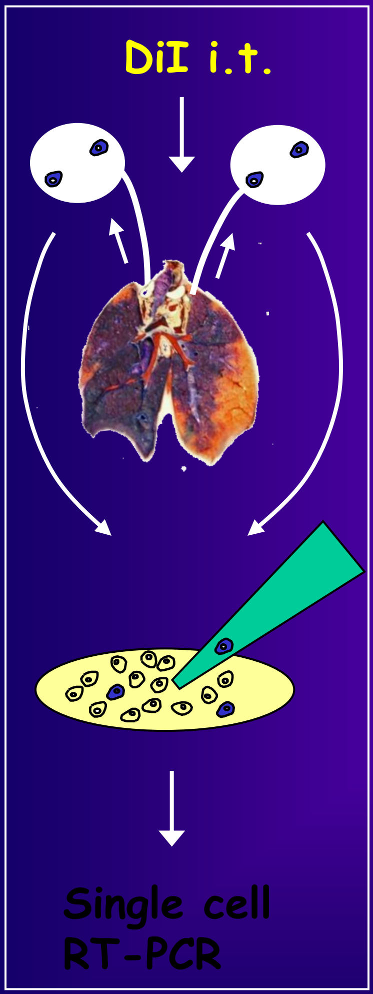


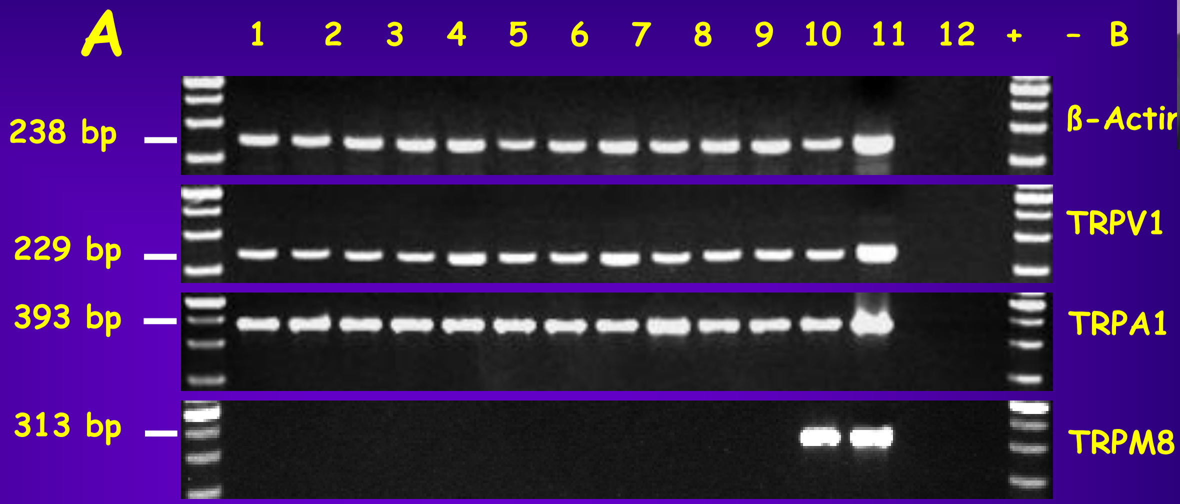
Lalloo, Fox, Belvisi, Chung, Barnes J Appl Physiol 1995, 79(4):1082-7.

Effect of a TRPV1 antagonist on depolarisation of the guinea-pig vagus

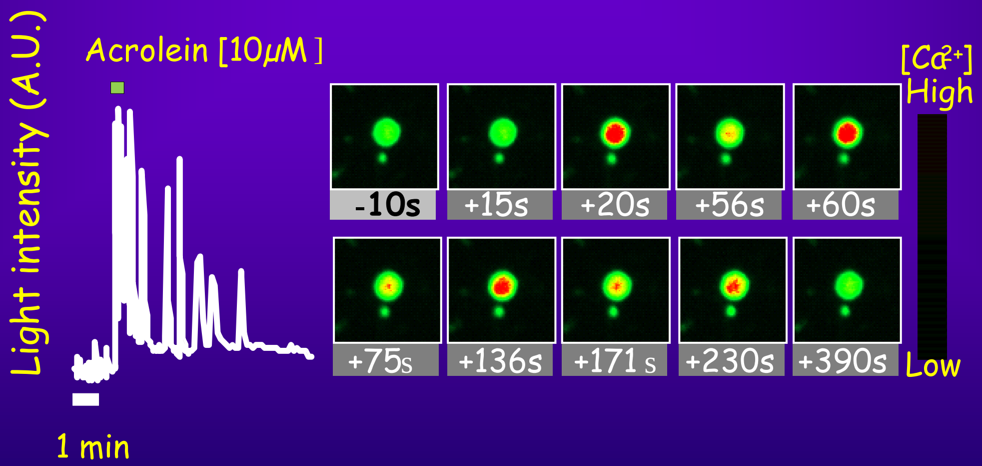


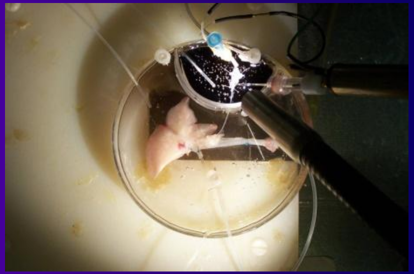
Coexpression of TRP channels in lung-labelled airway neurons



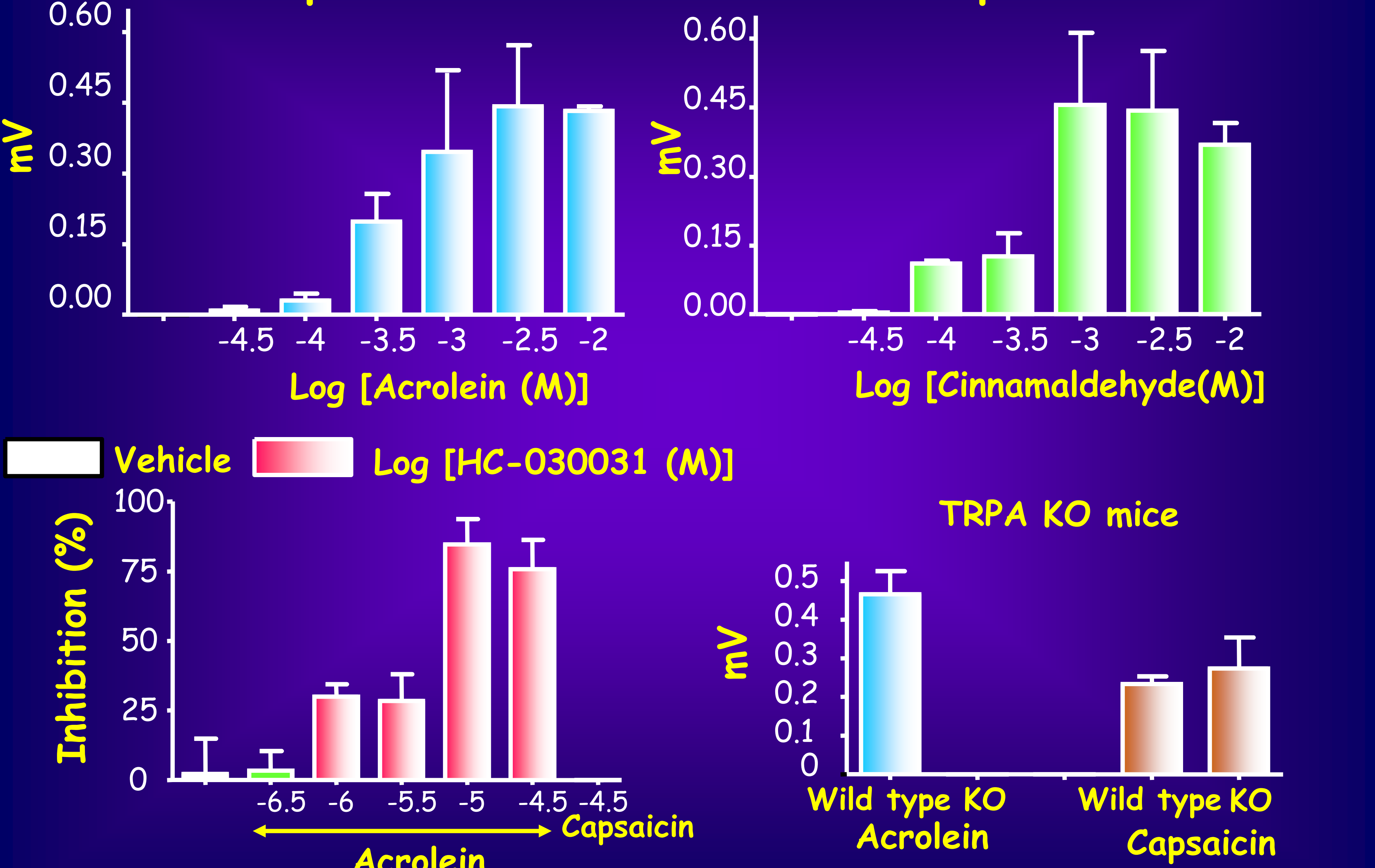


Nassenstein et al., J Physiol 2008



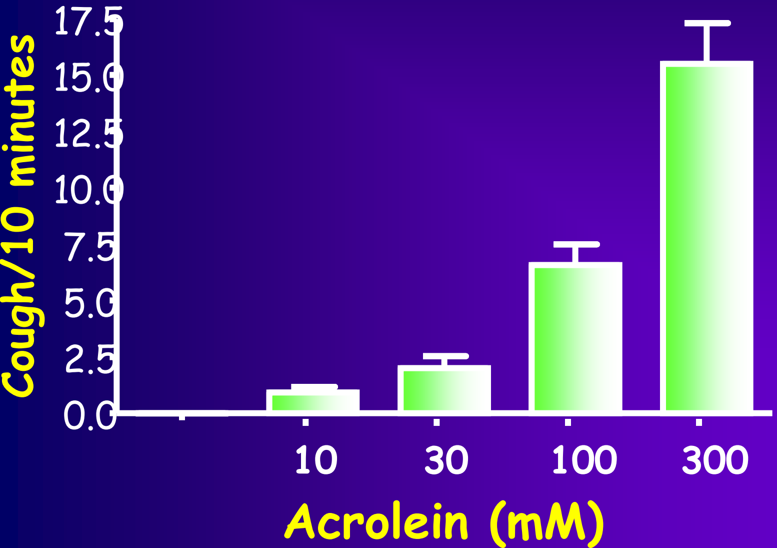


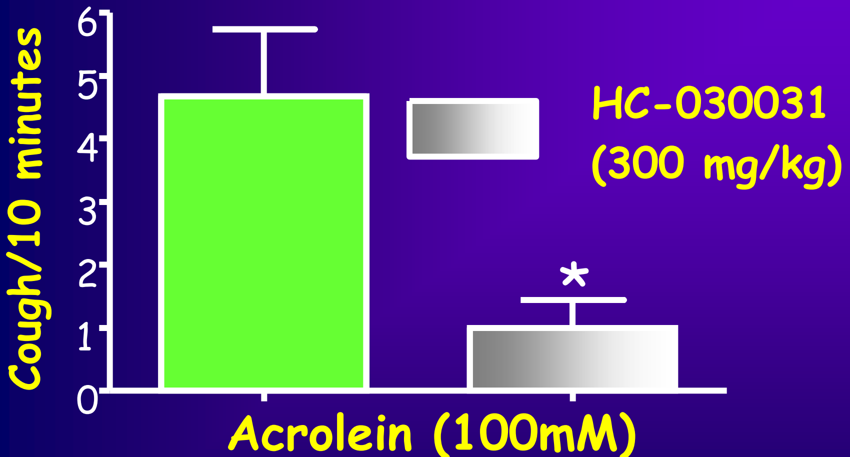
Effect of a TRPA-1 ligands or receptor KO on Depolarisation to acrolein and capsaicin

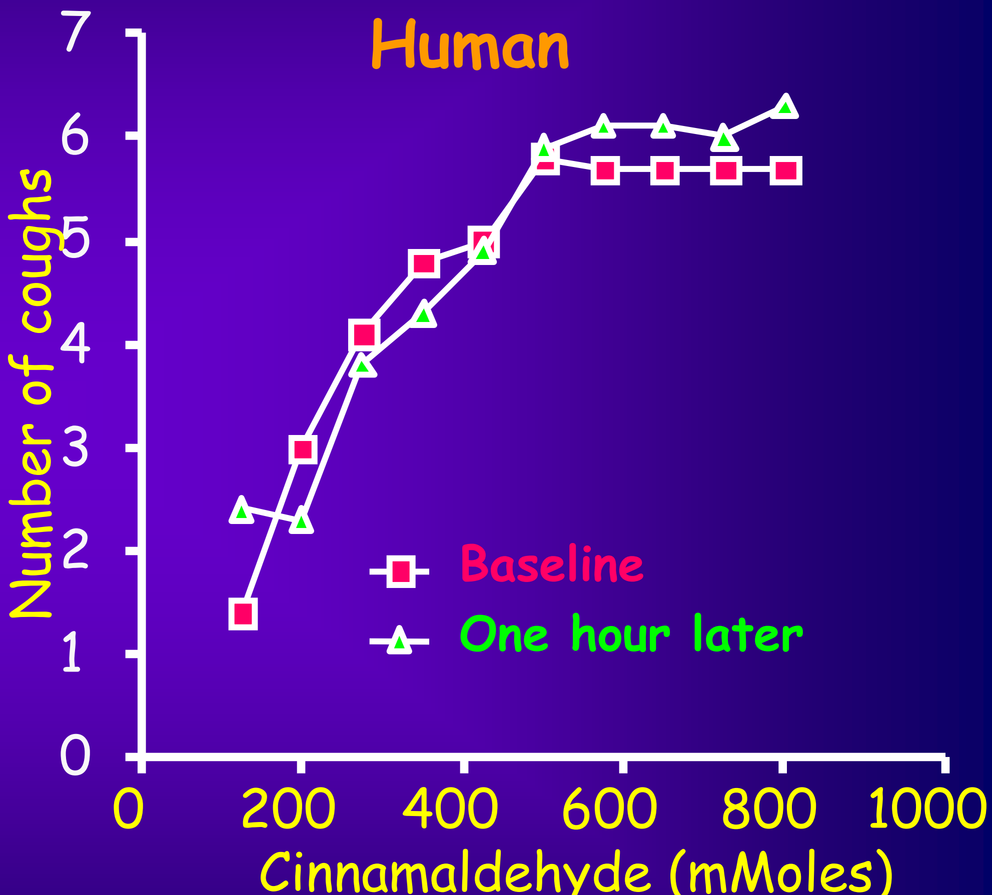


Birrell et al., 2009, Am J Respir Crit Care Med. 180(11):1042-7.

TRPA1 Ligands induce cough in conscious guinea-pig model and in normal volunteers

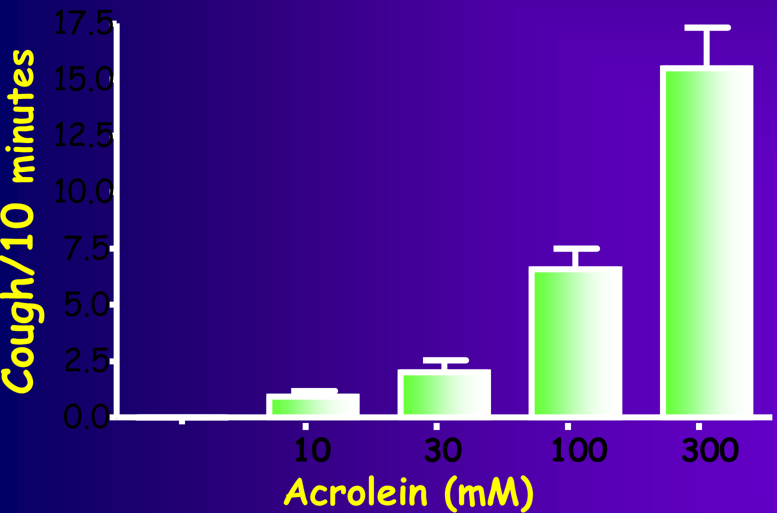


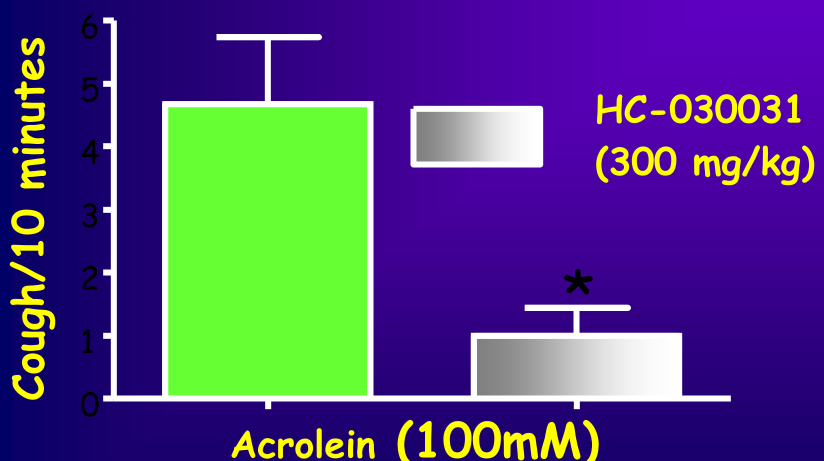


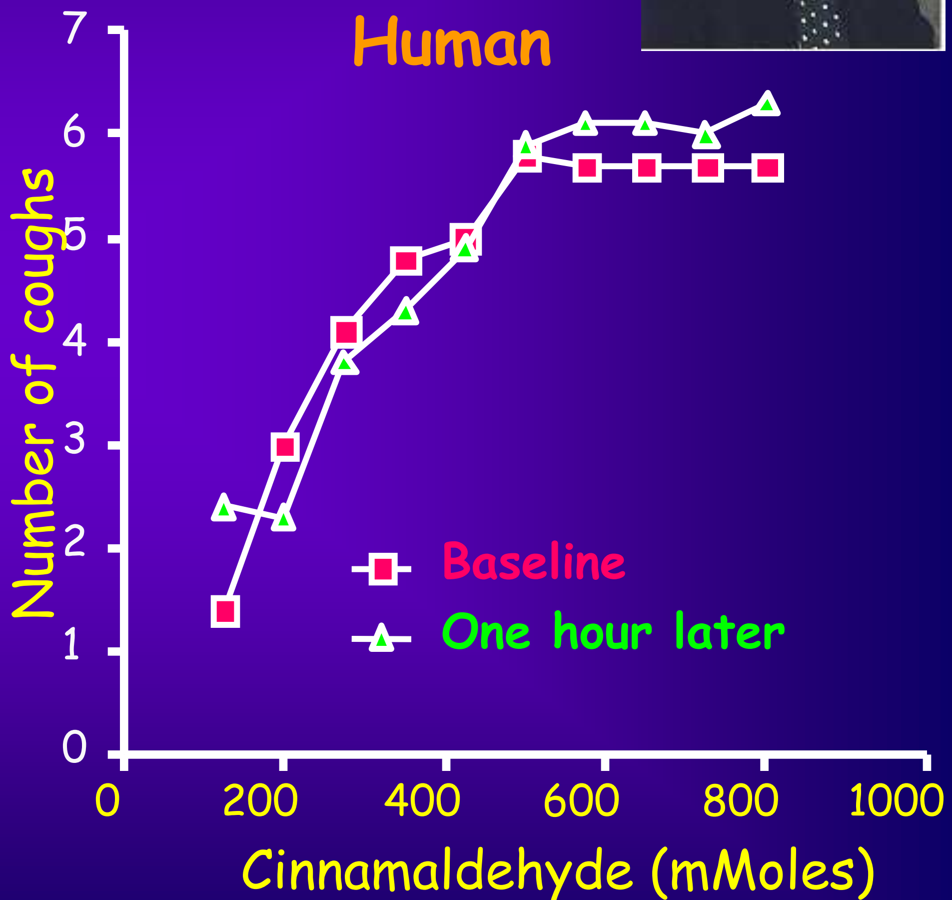


Birrell et al., 2009, Am J Respir Crit Care Med. 180(11):1042-7.
Andre et al., 2009, Br. J. Pharmacol, 158: 1621-1628.

TRPA1 Ligands induce cough

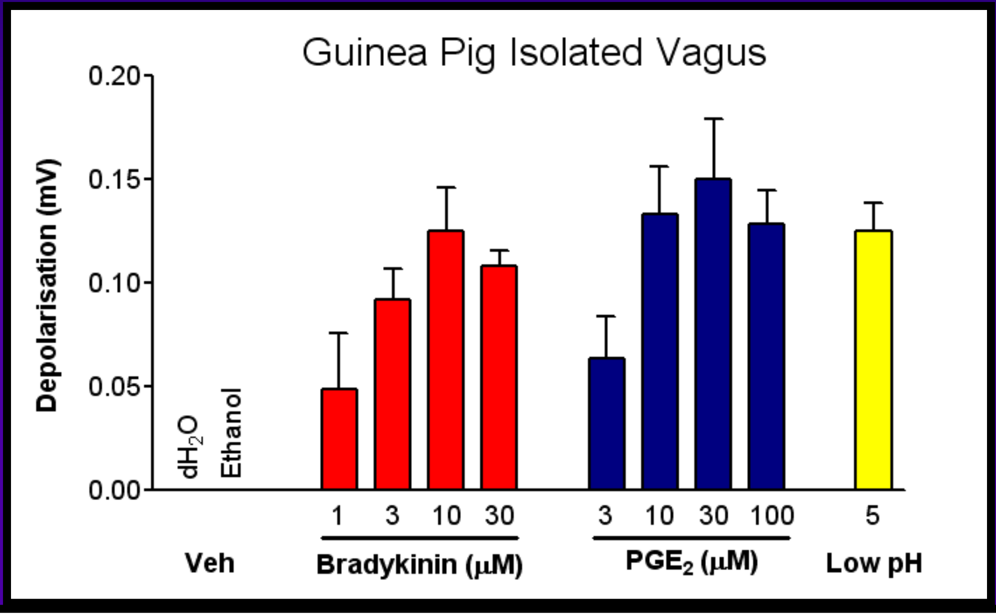


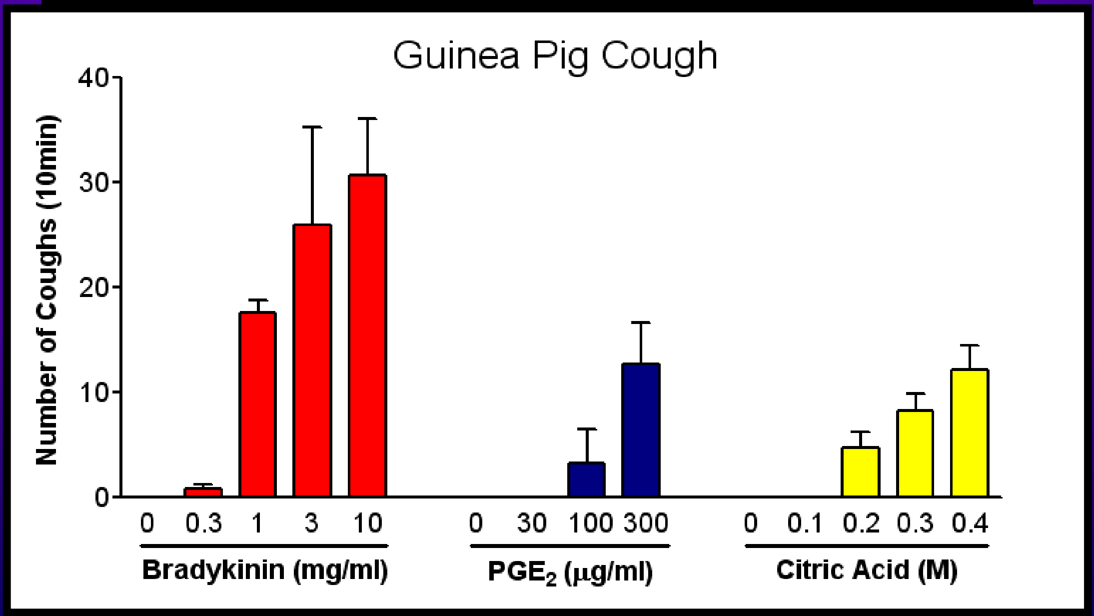




Birrell et al., 2009, Am J Respir Crit Care Med. 180(11):1042-7. Andre et al., 2009, BJP; 159: 98

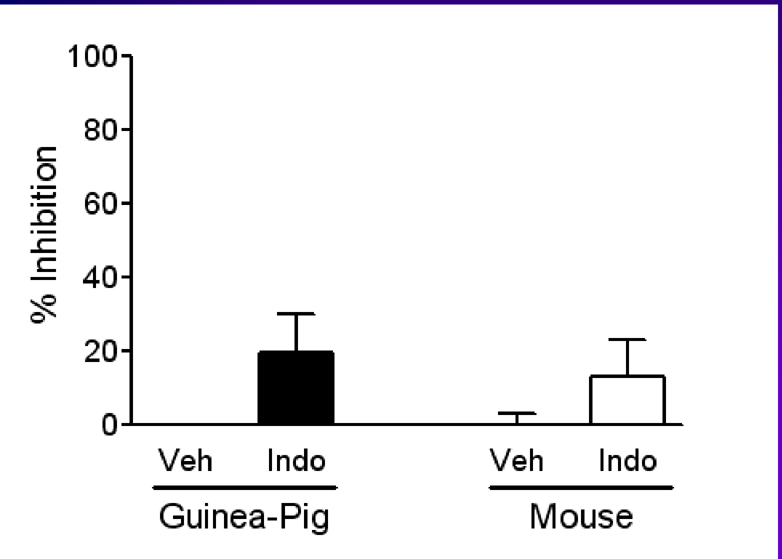
Sensory nerve activation and cough elicited by endogenous tussive agents



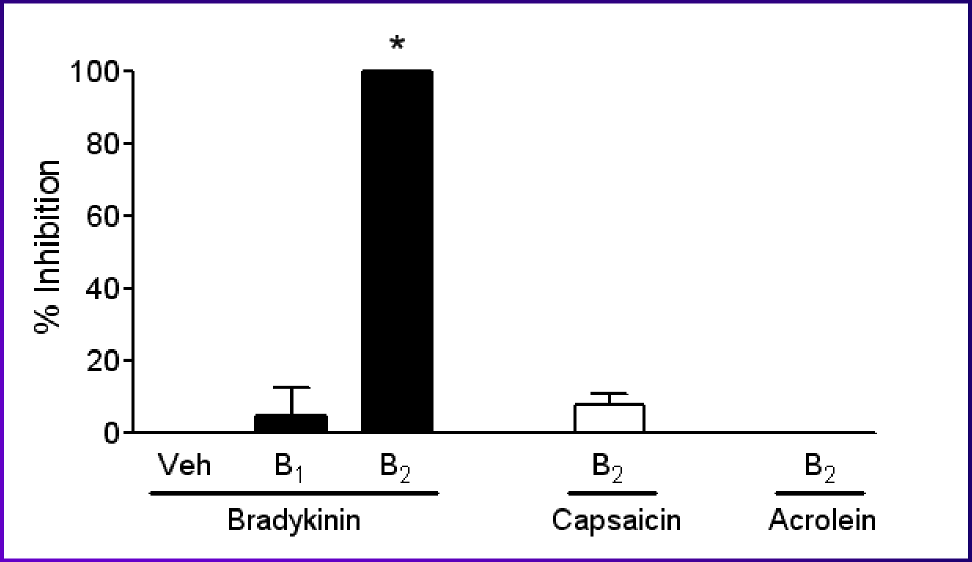


Vagus BK vs Antagonists

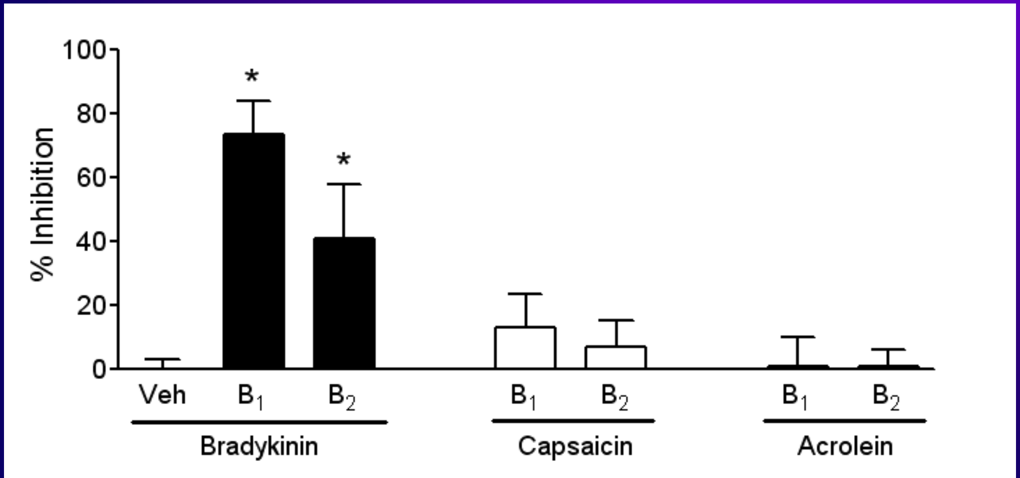
BK vs Indomethacin



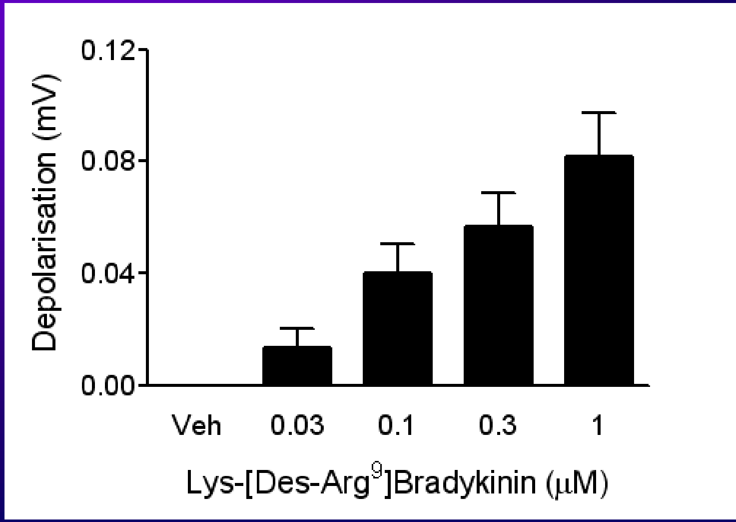
Guinea Pig: BK vs B1 & B2 antagonists



Mouse: BK vs B1 & B2 antagonists



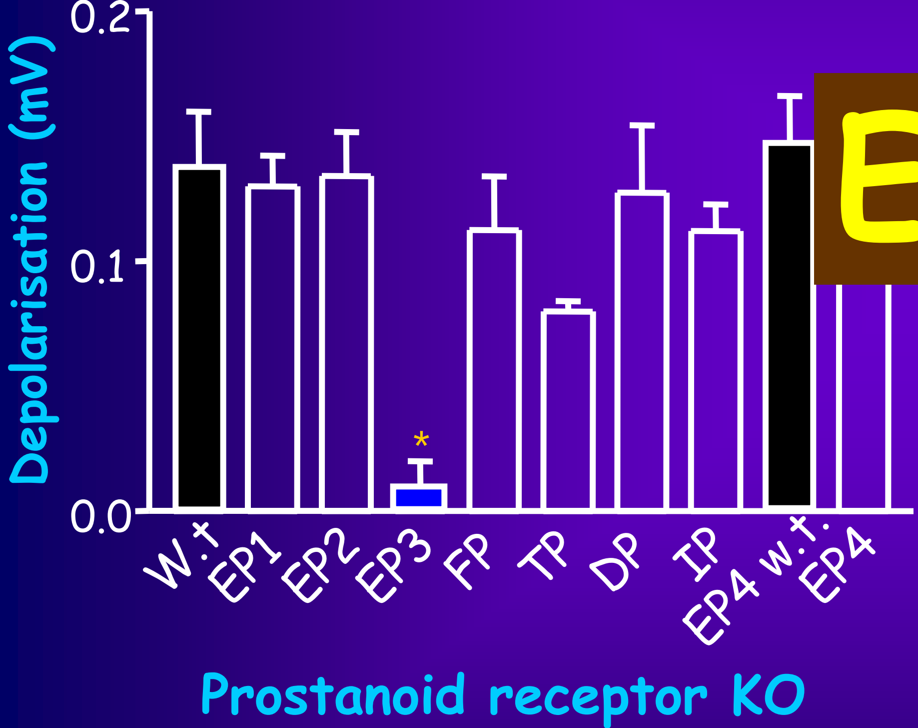
Mouse: B1 agonist



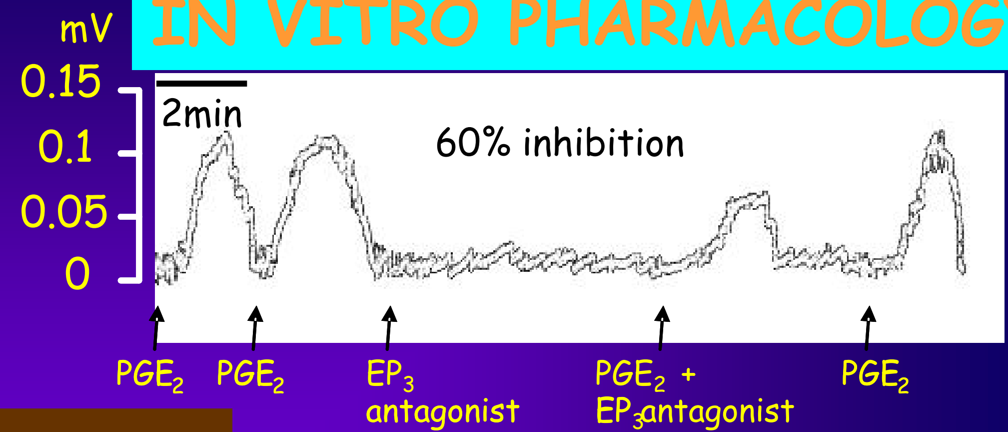
Sensory nerve activation: which prostanoid receptor?

GENE-DELETED MICE

Responses to PGE_2 in KO mice

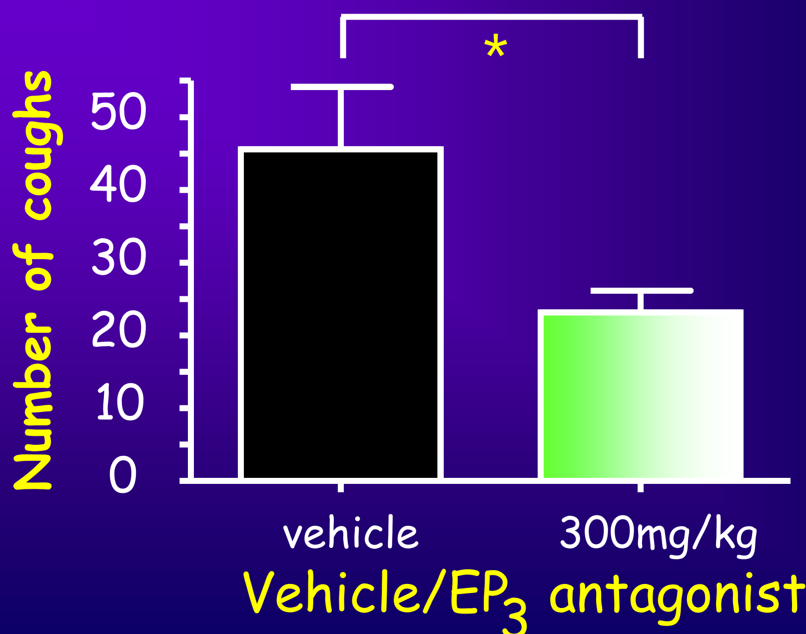


IN VITRO PHARMACOLOGY



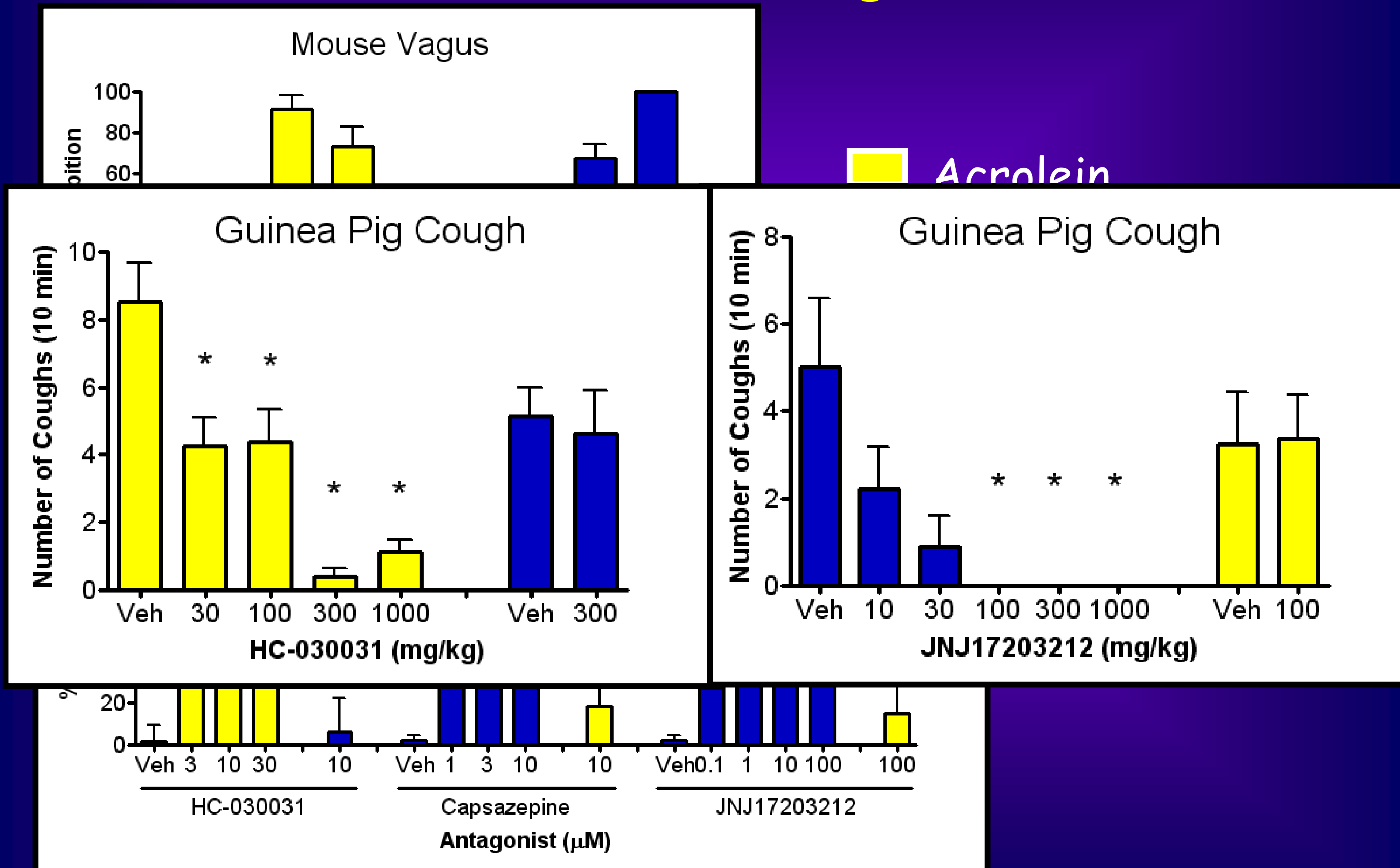
EP_3

IN VIVO PHARMACOLOGY

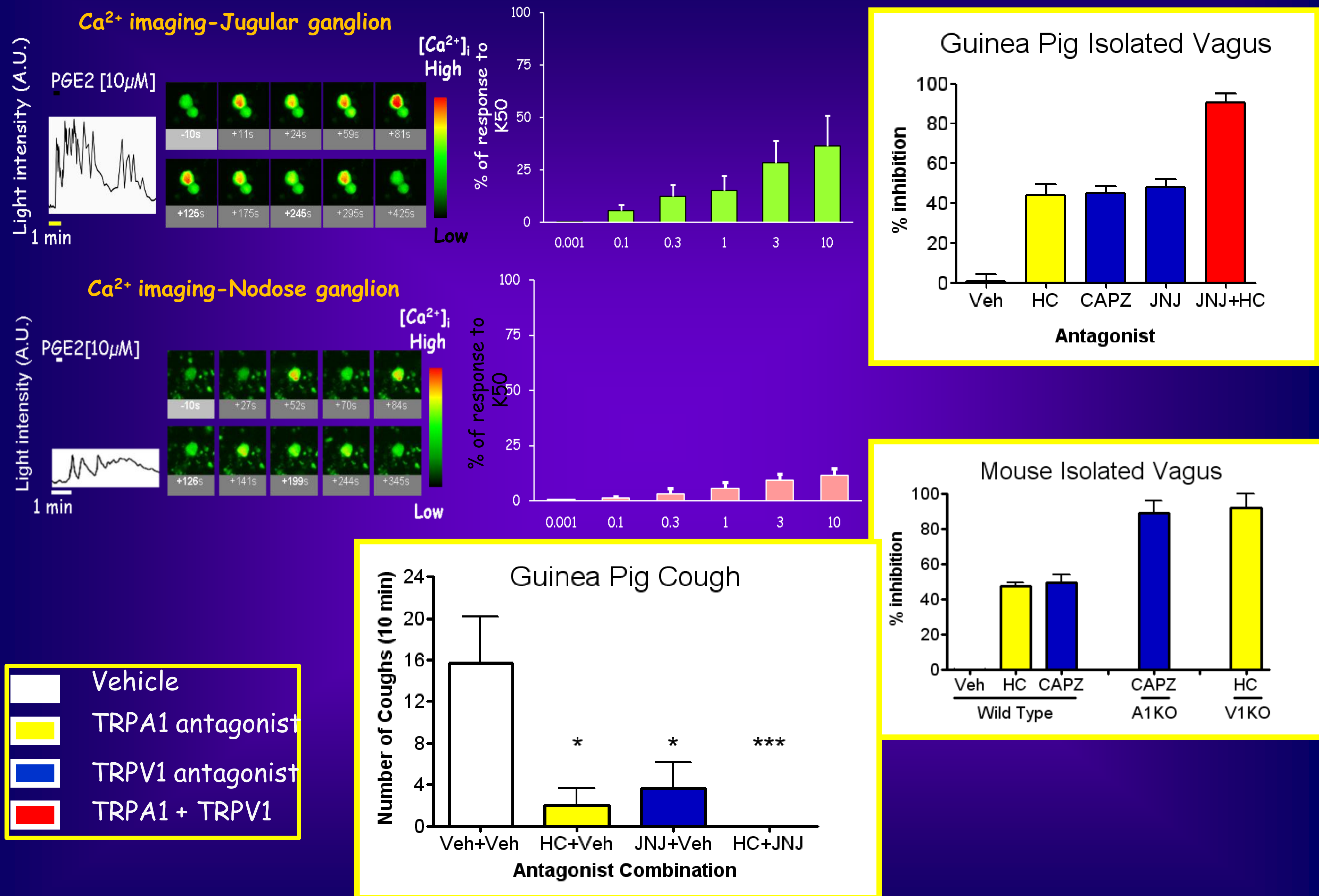


Maher et al., Am. J Respir. Crit. Care Med., 2009; 180: 923-928.

Effect of TRP antagonists on sensory nerve activation/cough

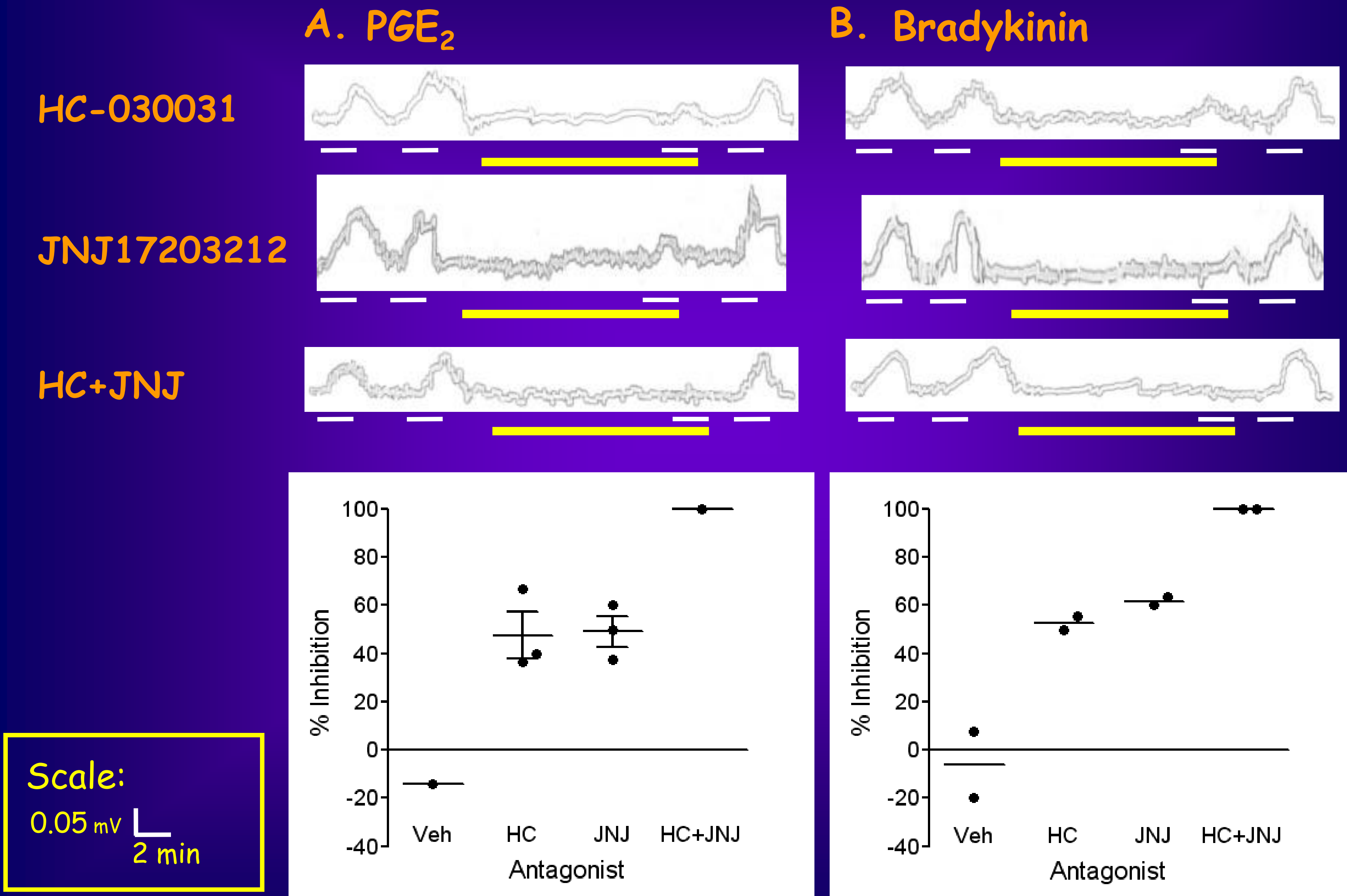


Effect of TRP antagonists on sensory nerve activation/cough elicited by PGE_2



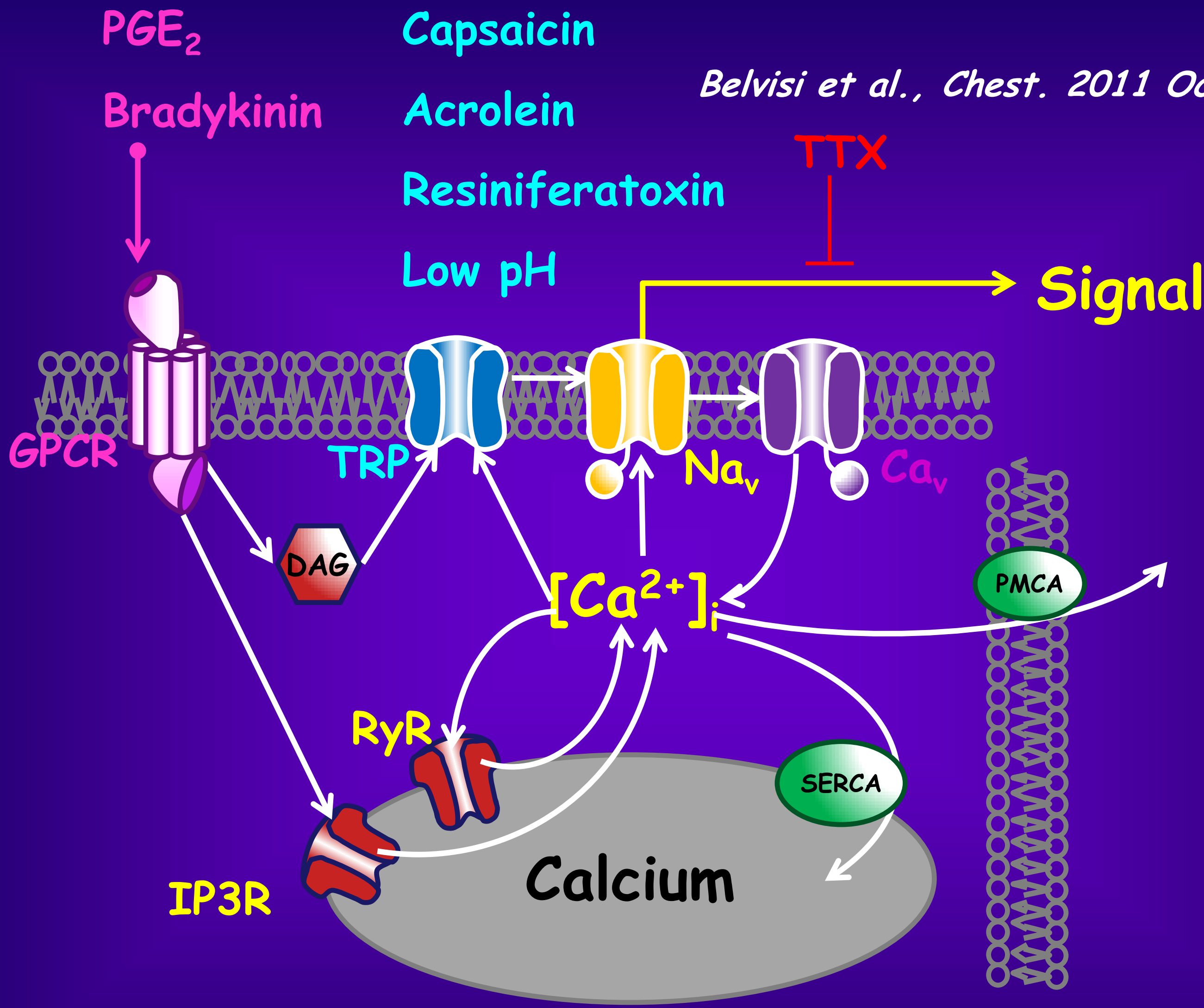
Grace et al., 2012, Thorax, jun 12: Epub

Effect of TRP antagonists on human sensory nerve activation elicited by PGE_2 and BK



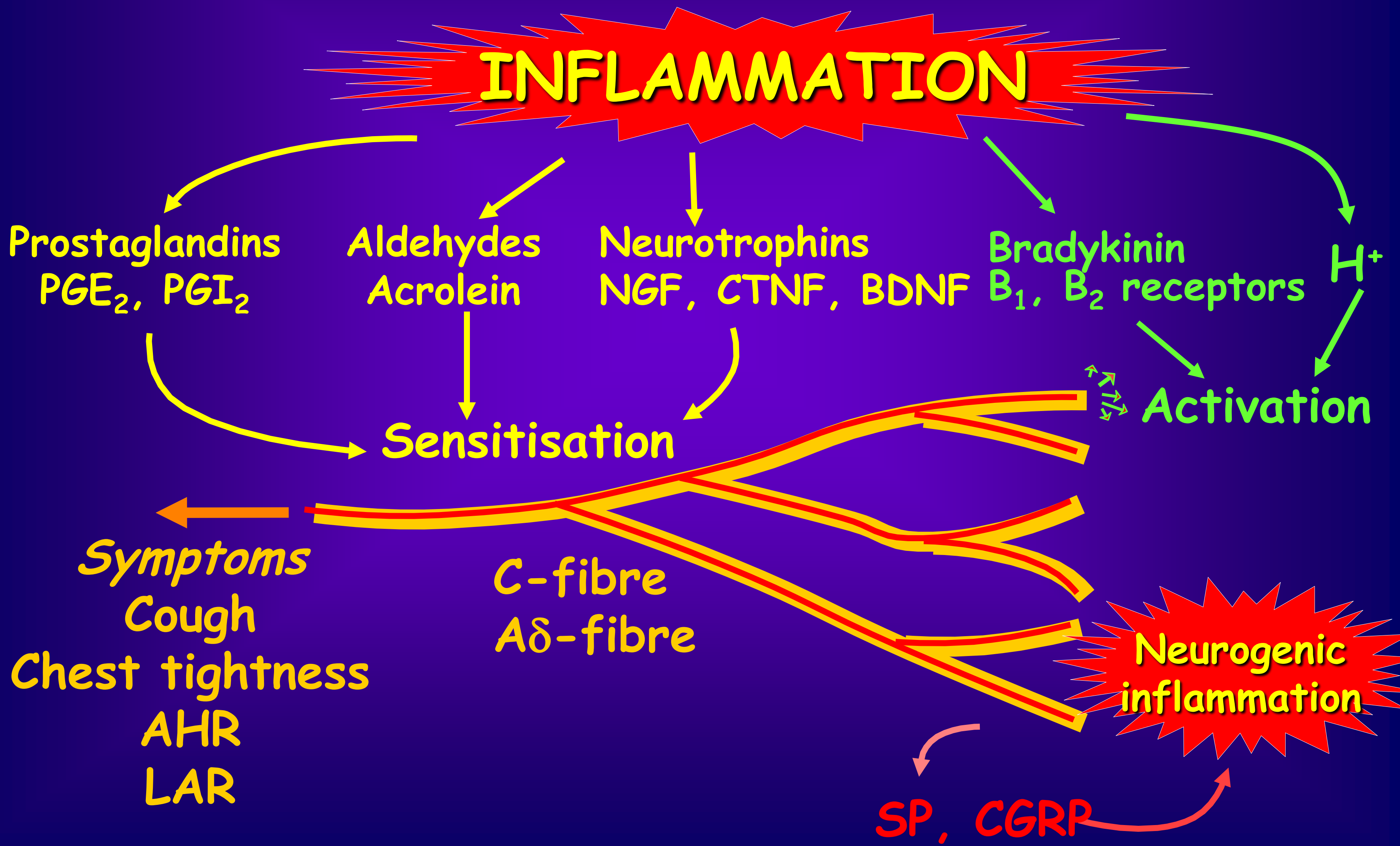
Tussive agents, sensory nerves and signalling pathways

Belvisi et al., Chest. 2011 Oct;140(4):1040-7.

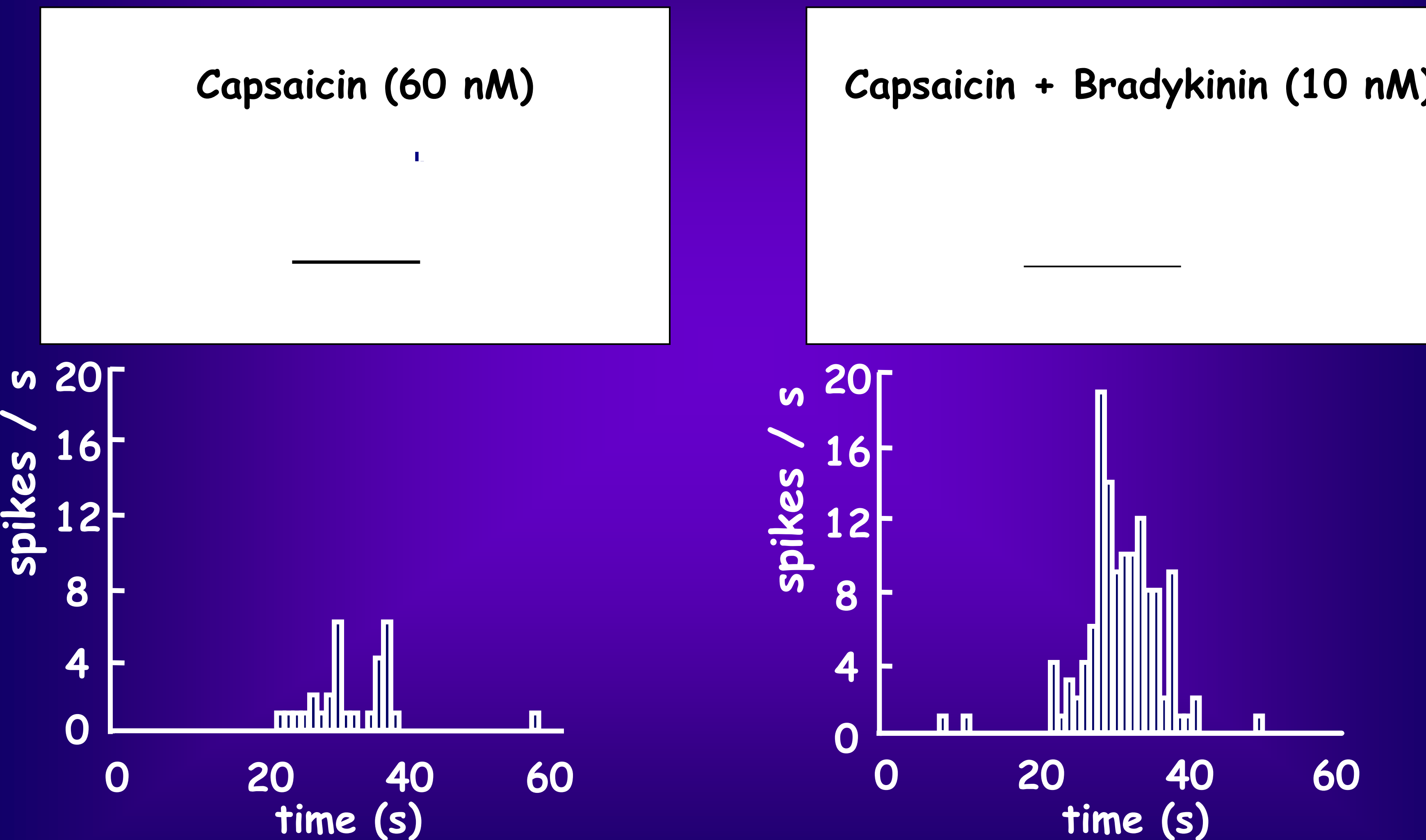


Cantero-Recasens G, Loss of function of TRPV1 genetic variant associated with lower risk of active childhood asthma. J Biol Chem. 2010 Sep 3;285(36):27532-5.
Smit et al., TRP genes smoking occupational exposures and cough. Respir Res 2012, 13:26.

Sensitisation and activation of airway sensory nerves



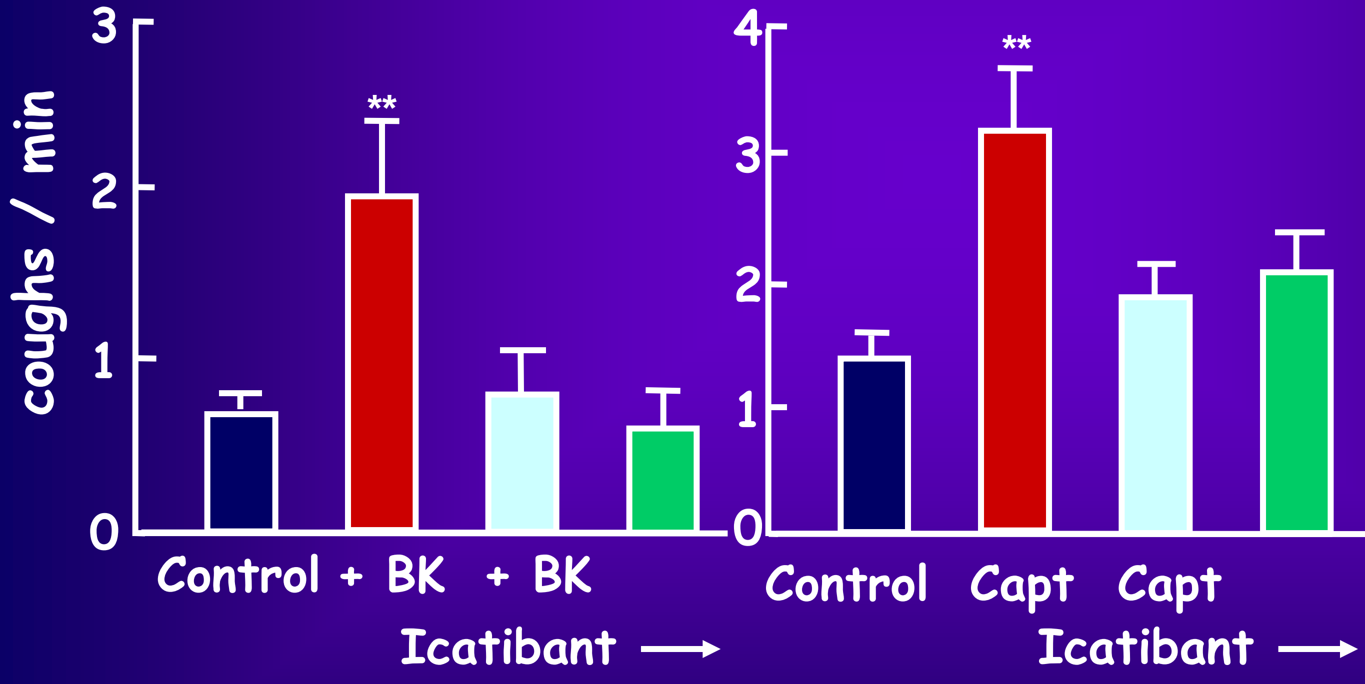
C-fibre Sensitisation by Bradykinin

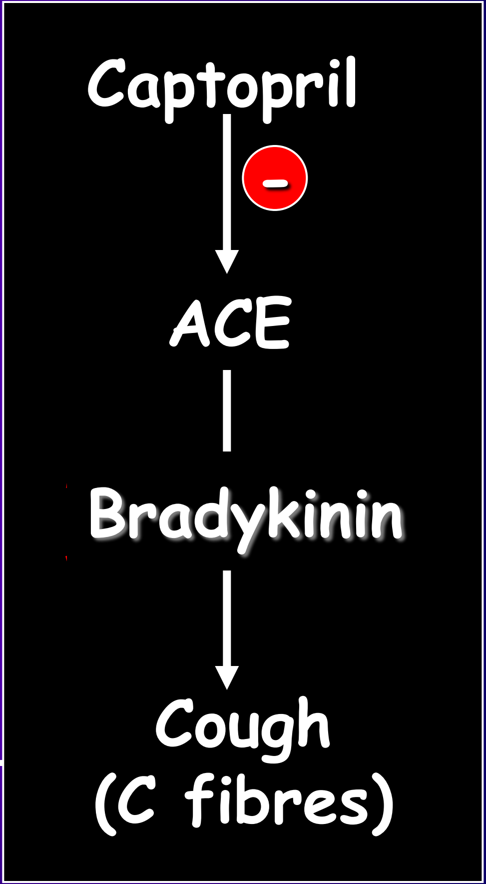


Fox et al 1996. Nature Med. 2, 814-817

Bradykinin Sensitises the Cough Reflex

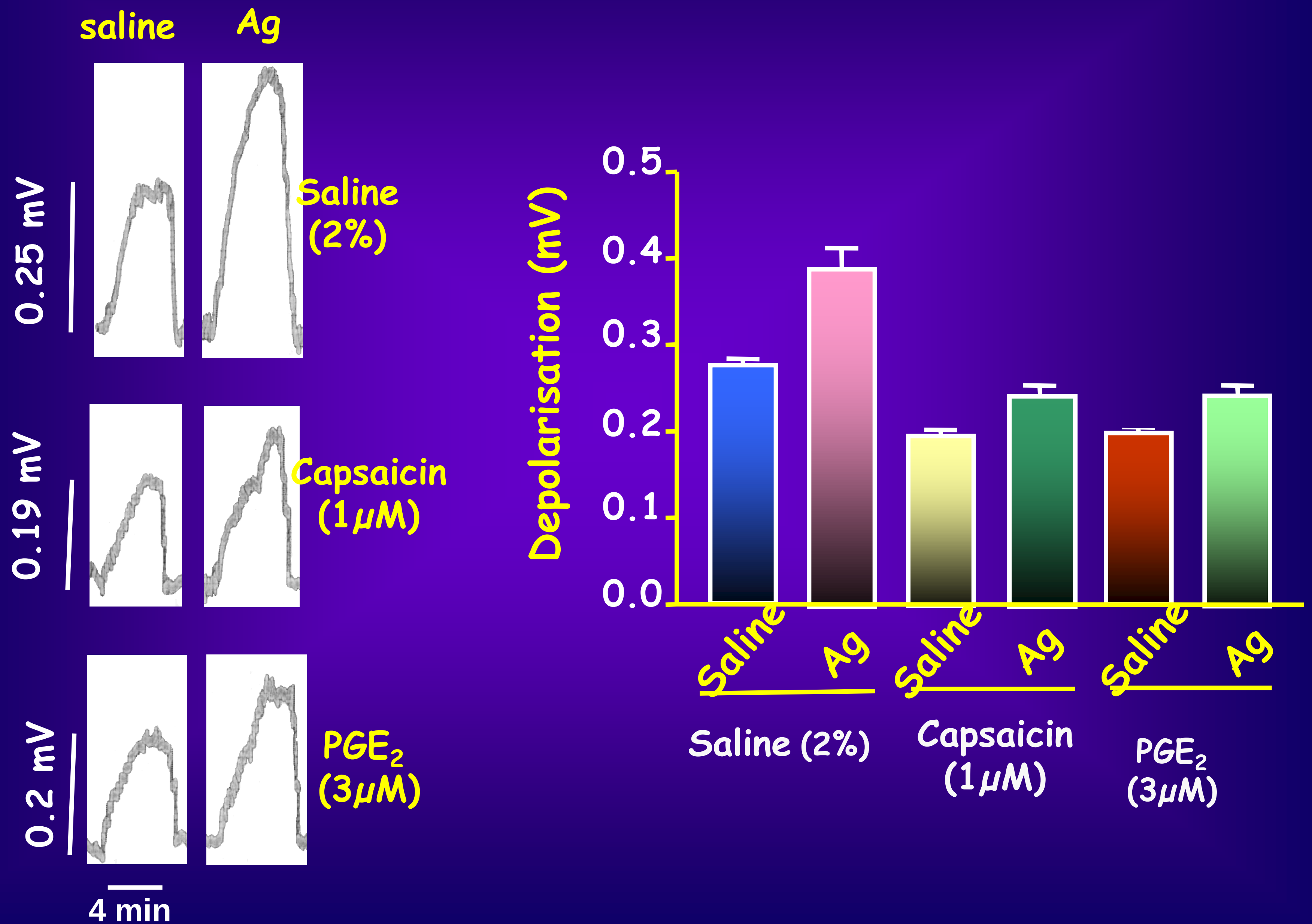
Guinea-pigs challenged with citric acid (0.25 M, 10 min)



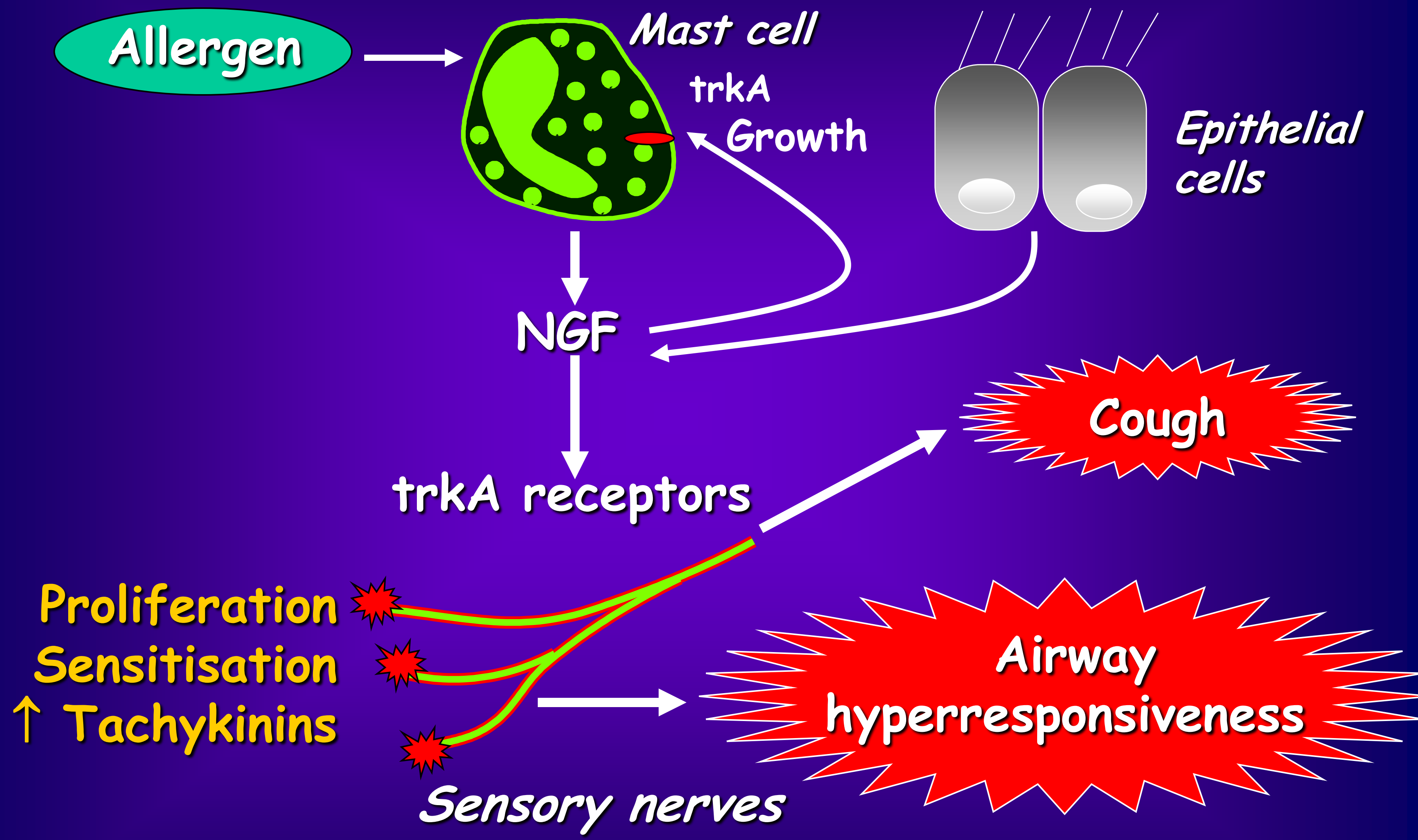


Fox et al 1996. Nature Med. 2, 814-817

Effect of sensory nerve stimulants on isolated vagus nerve from allergen sensitised and challenged mice



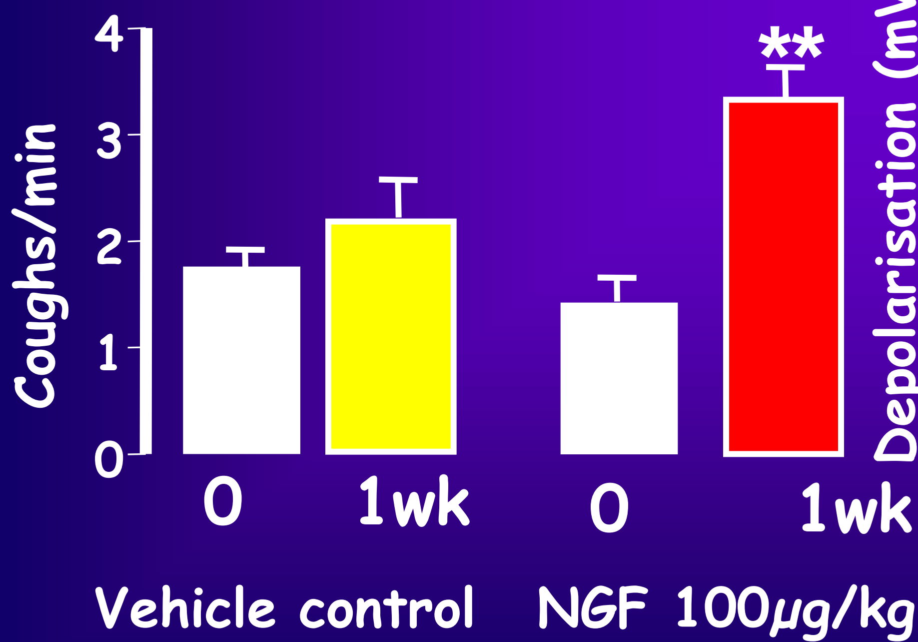
MAST CELLS AND NERVE GROWTH FACTOR

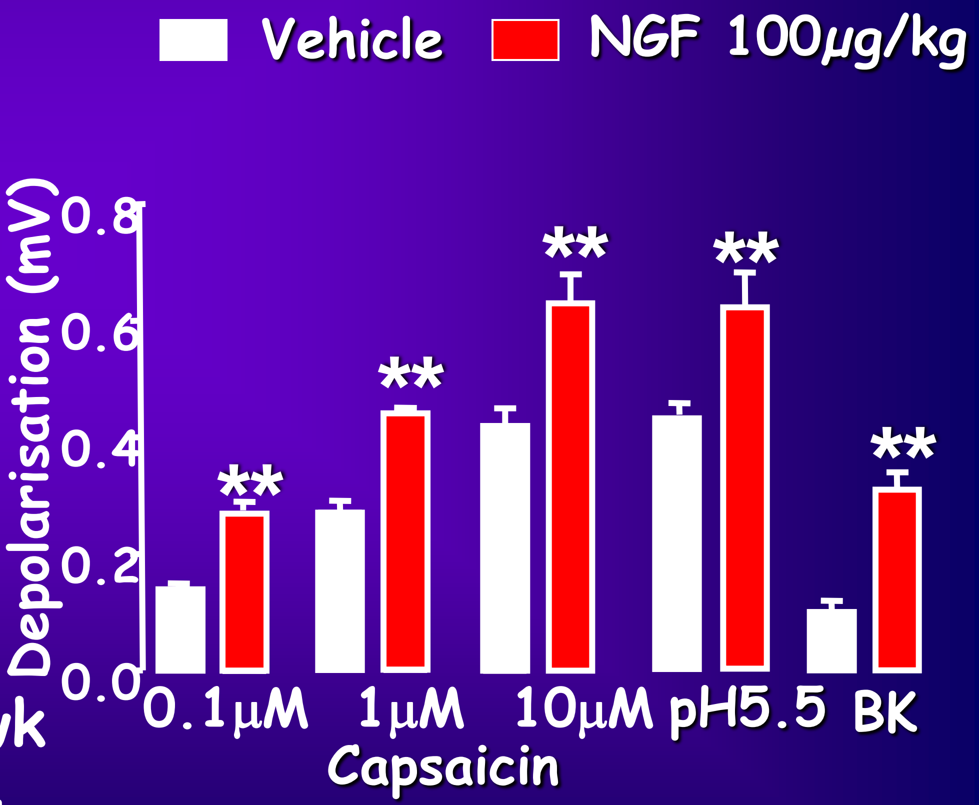


EFFECT OF NGF ON COUGH

Conscious guinea pigs (n=6)
Citric acid-induced cough
(citric acid 0.35M x 10 min)

Guinea pig vagus nerve in vitro



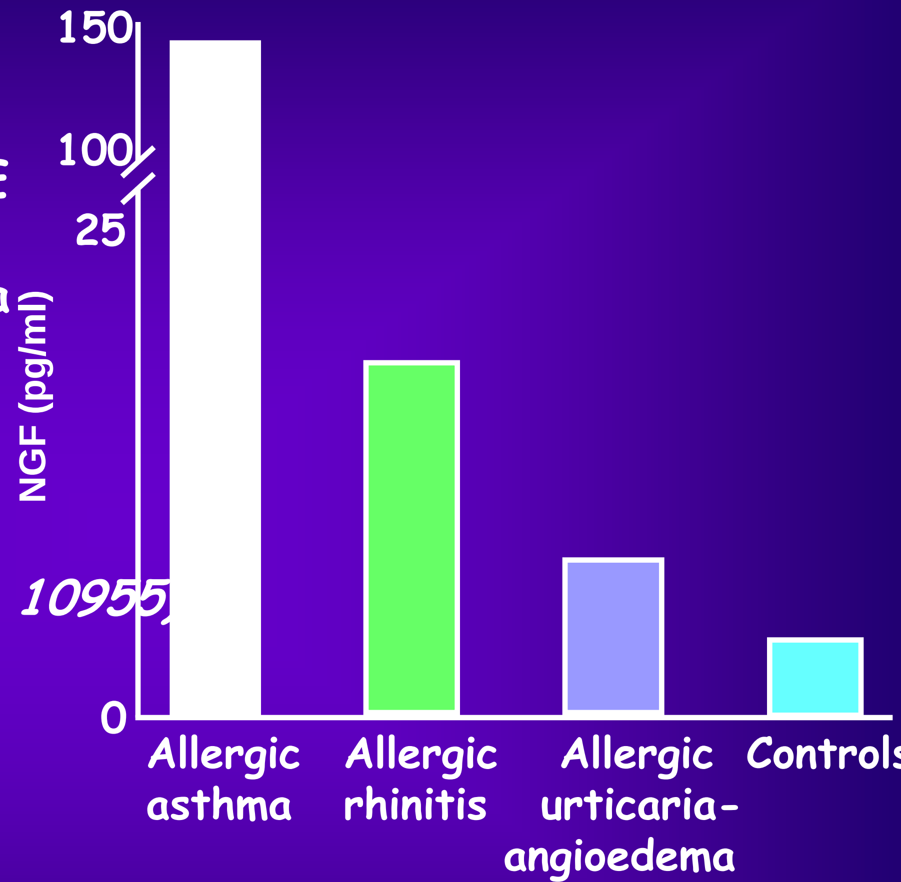


Neurotrophins, humans, allergy and asthma

NGF serum levels:

- correlation with serum IgE
- highest NGF:
    - severe allergic asthma
    - high BHR
    - high serum IgE
    - high serum ECP

(Bonini et al 1996 PNAS-USA 93, 10955)

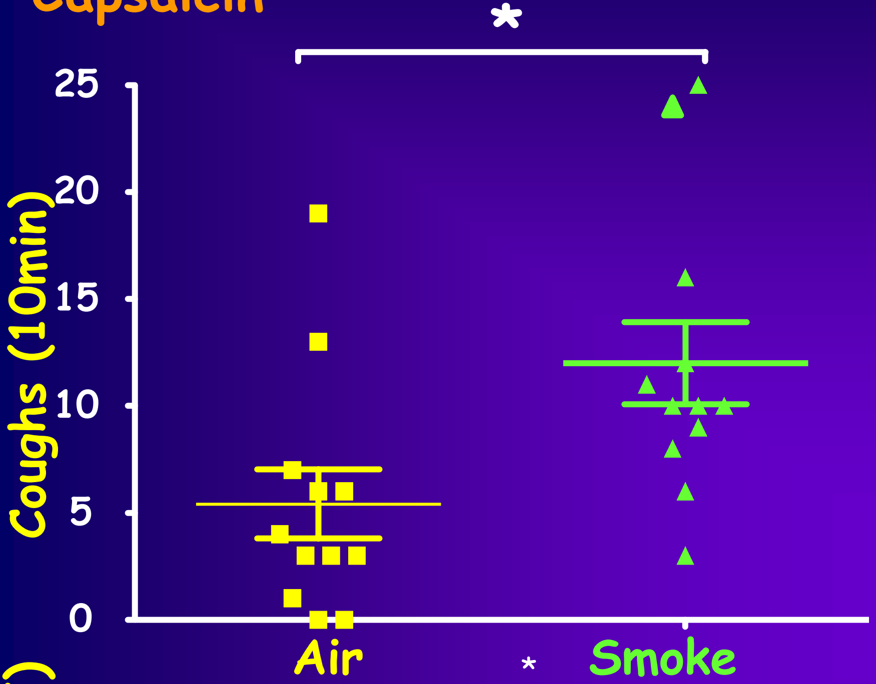


Segmental allergen challenge —18h→ BALF ↑: NGF, BDNF and NT-3

(Virchow, Am J Respir Crit Care Med 158, 2002)

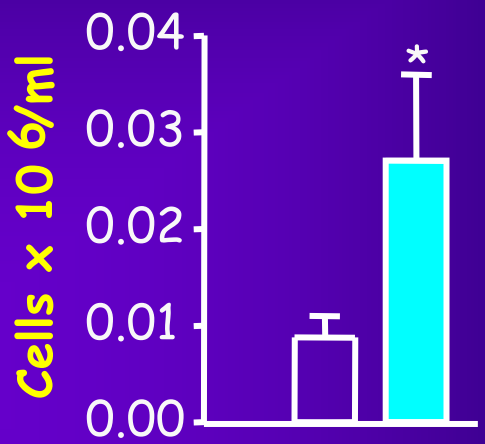
Models of enhanced cough

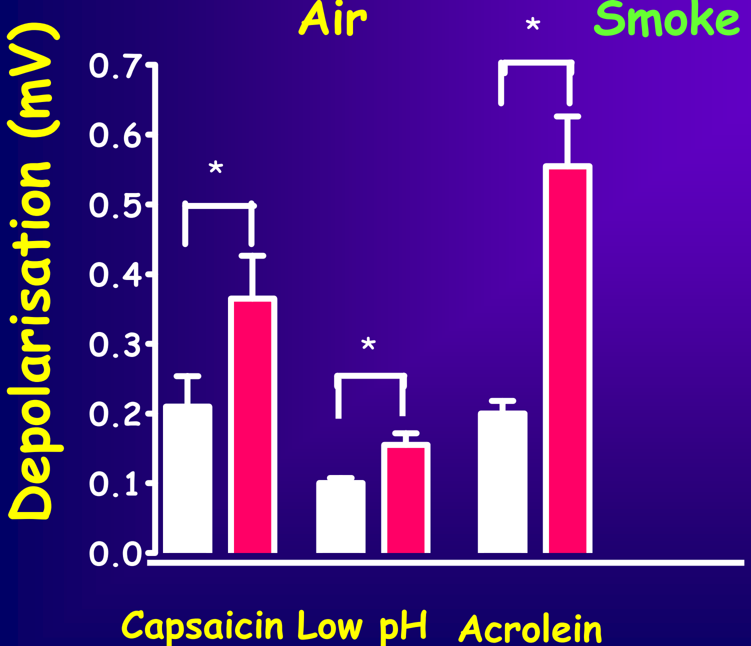
Capsaicin



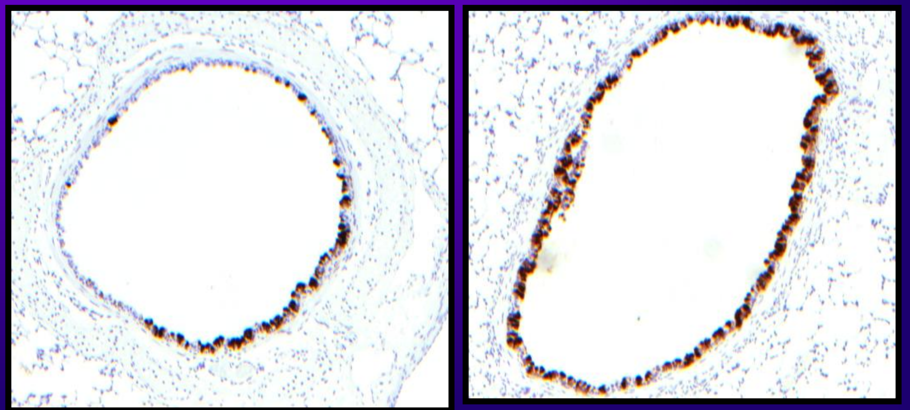
Inflammation

Neutrophils at Eight Days





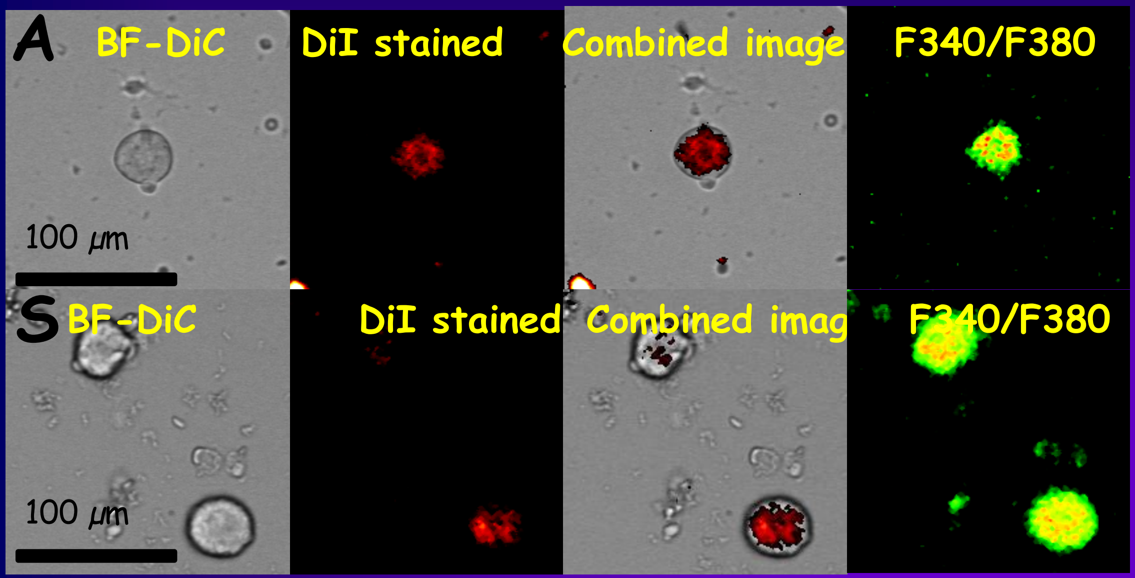
Mucus



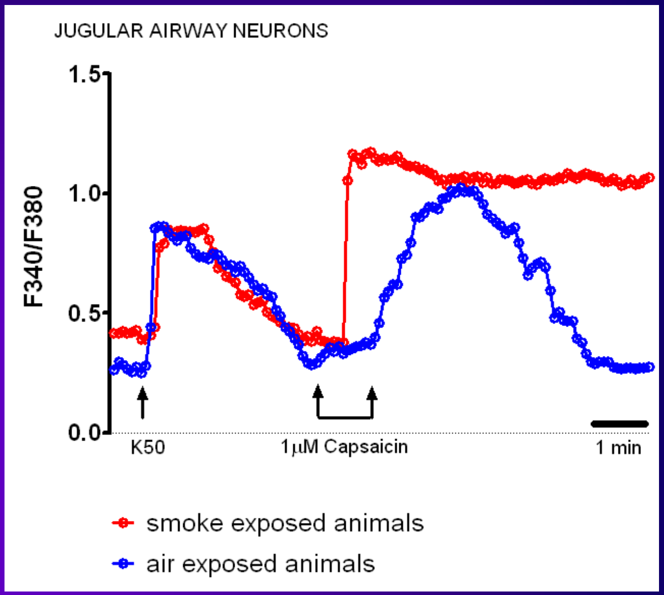
Control (8 days)

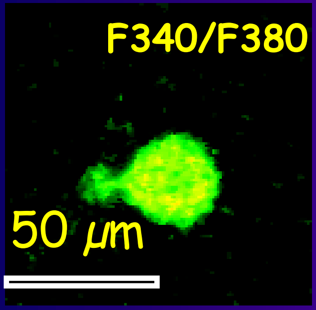
Smoke (8 days)

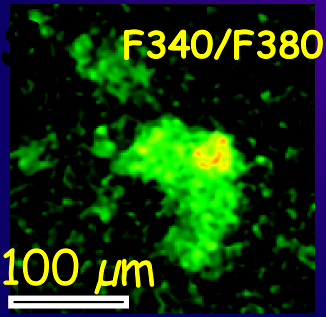
Calcium imaging in jugular ganglia following CS exposure



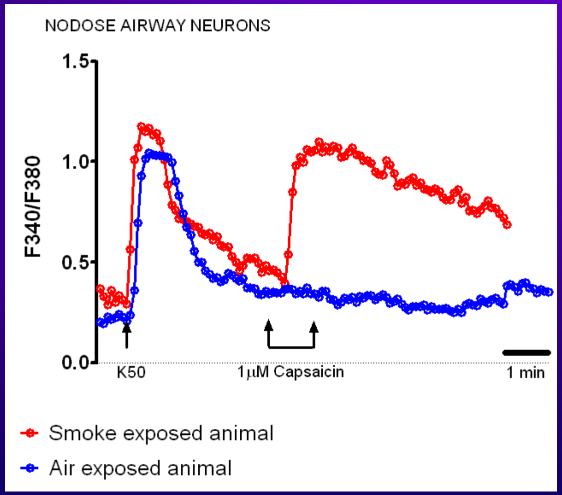
Jugular Ganglia



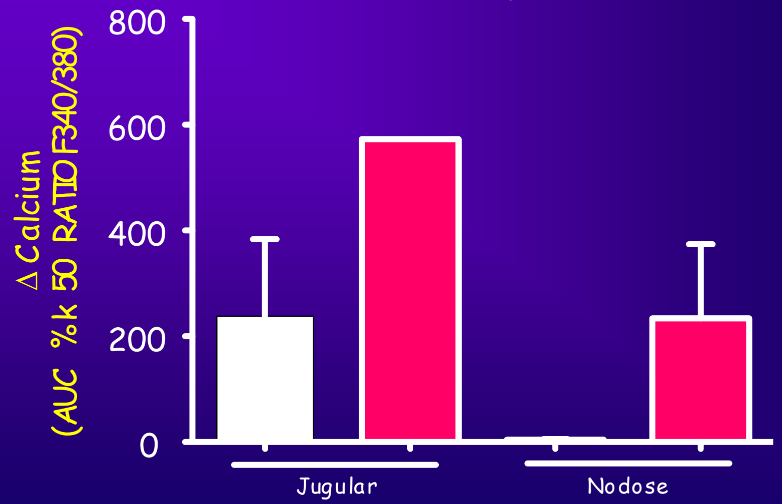




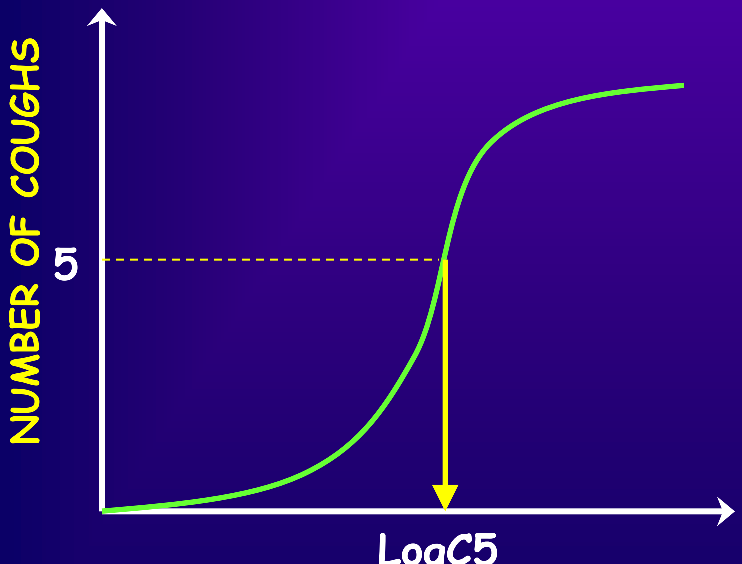
Nodose Ganglia

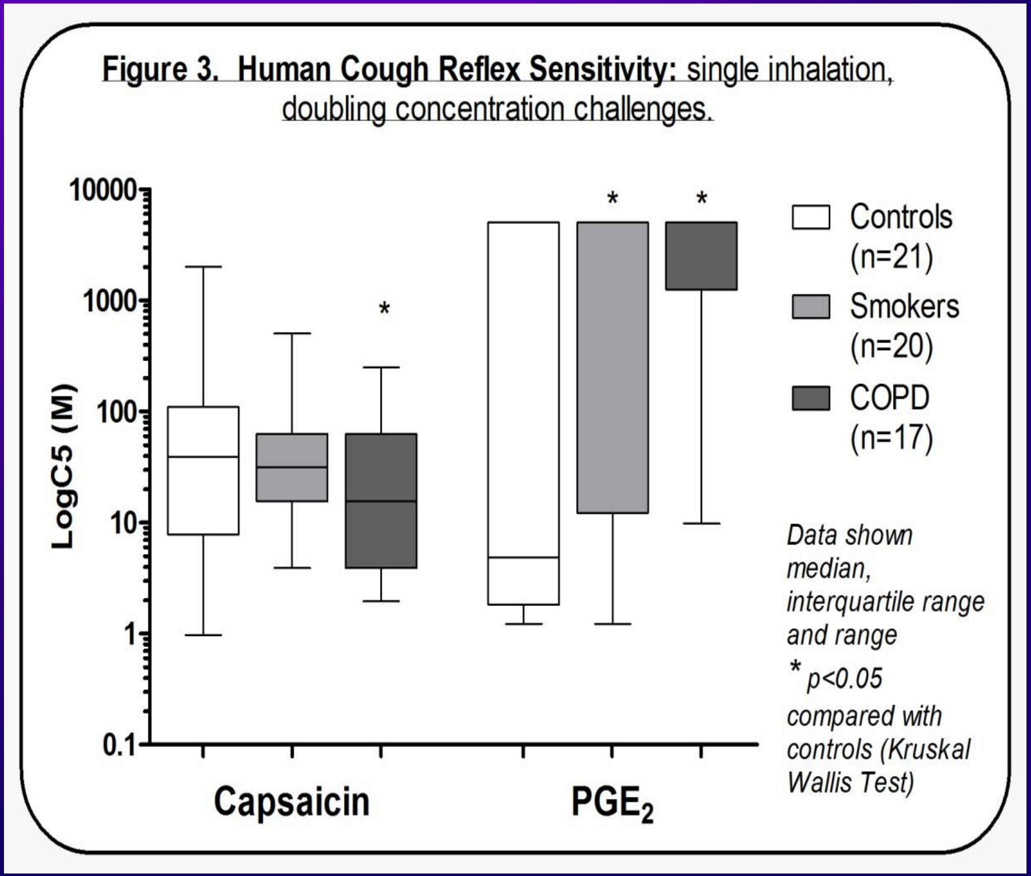


Calcium



Standard Cough Challenge

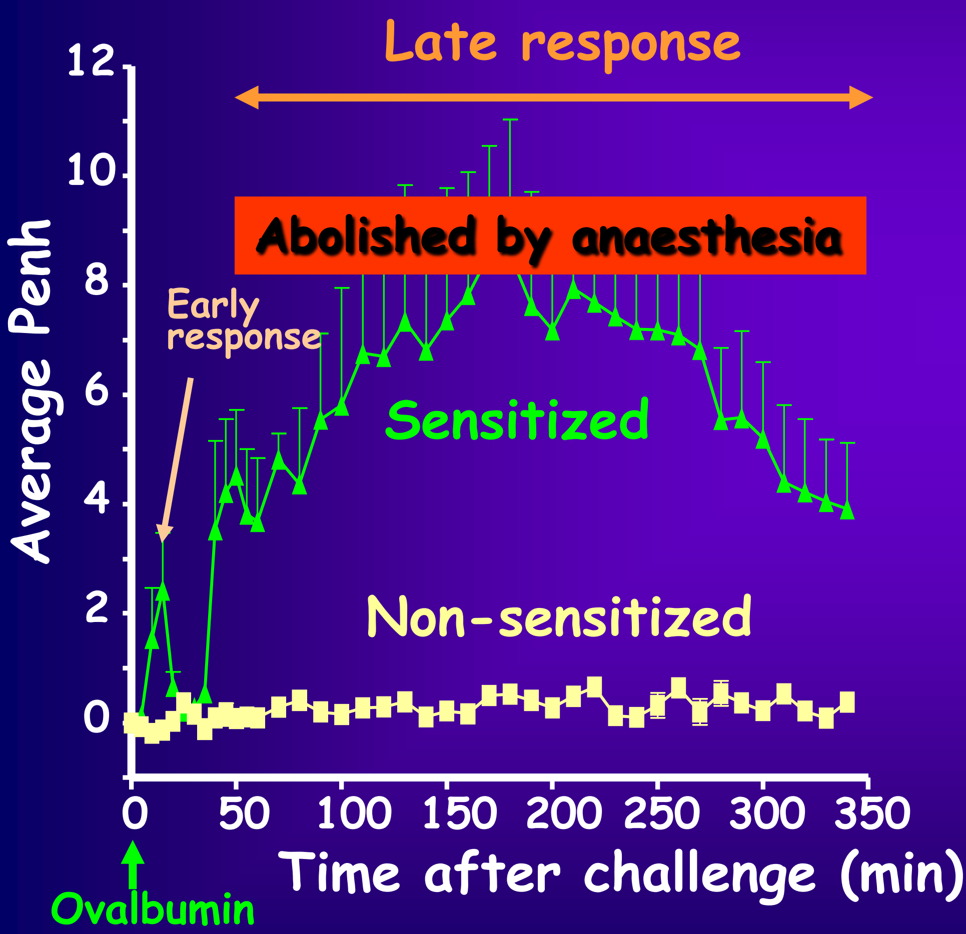




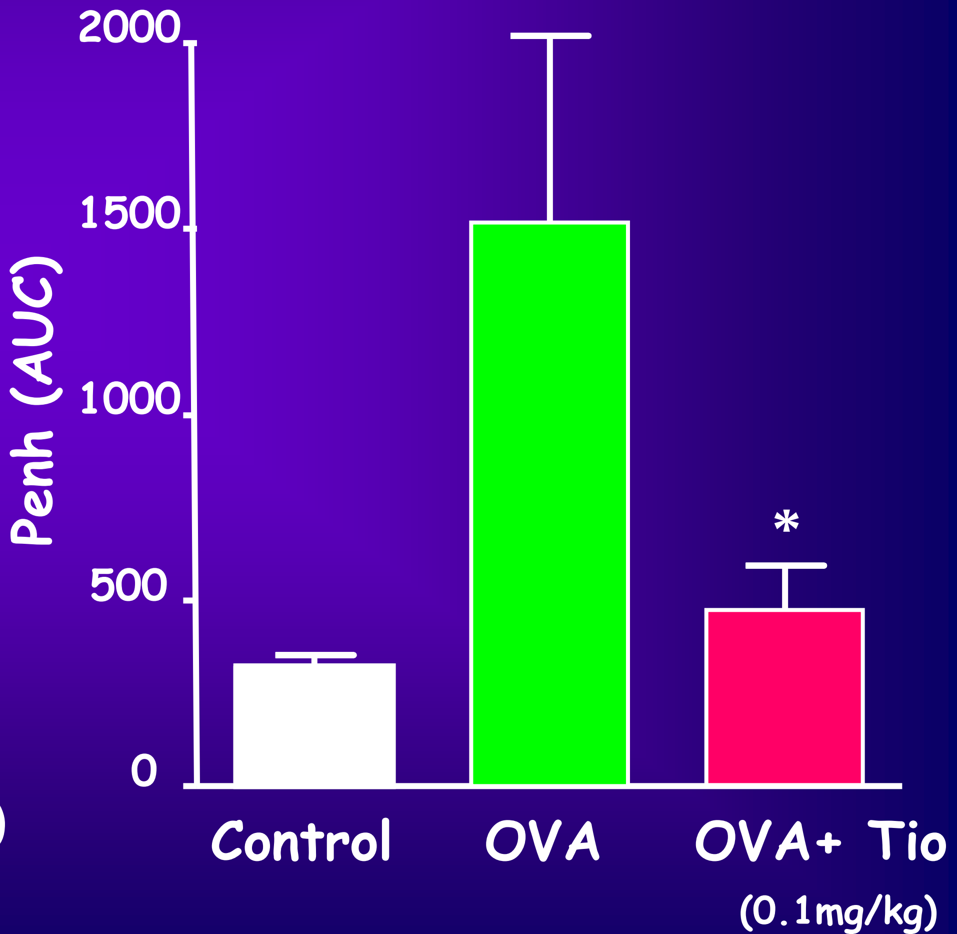
TIOTROPIUM BLOCKS LATE RESPONSE TO ALLERGEN

Conscious Brown Norway rats

Allergen Challenge



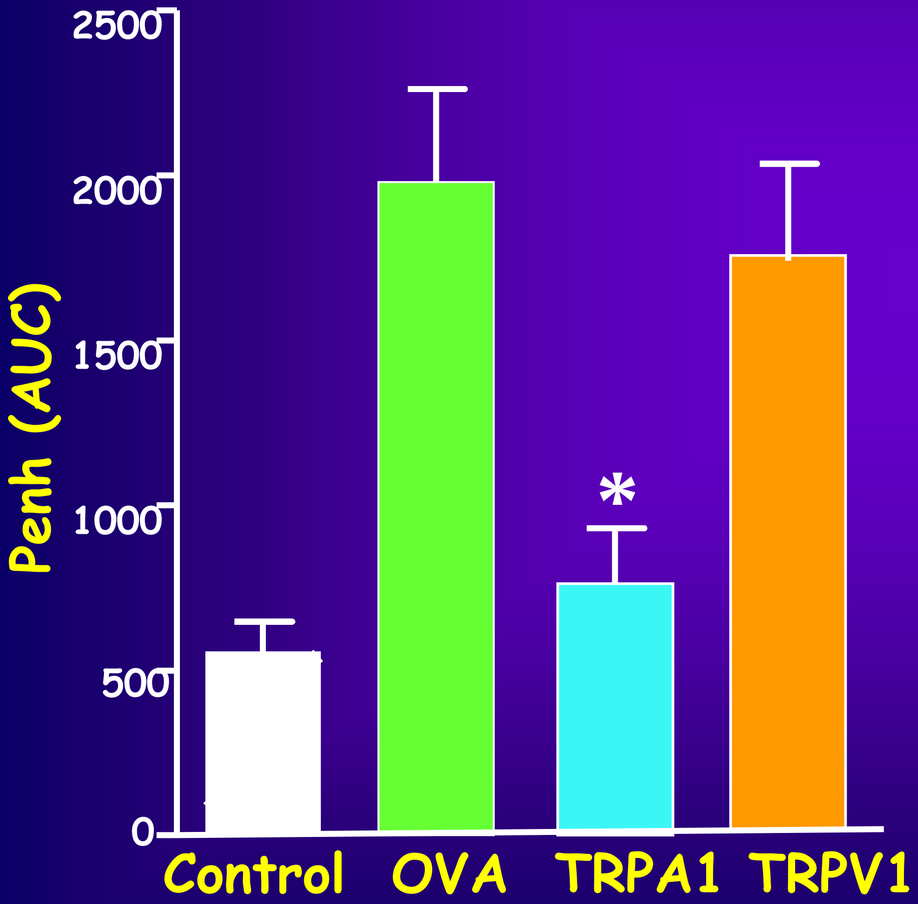
Effect of tiotropium

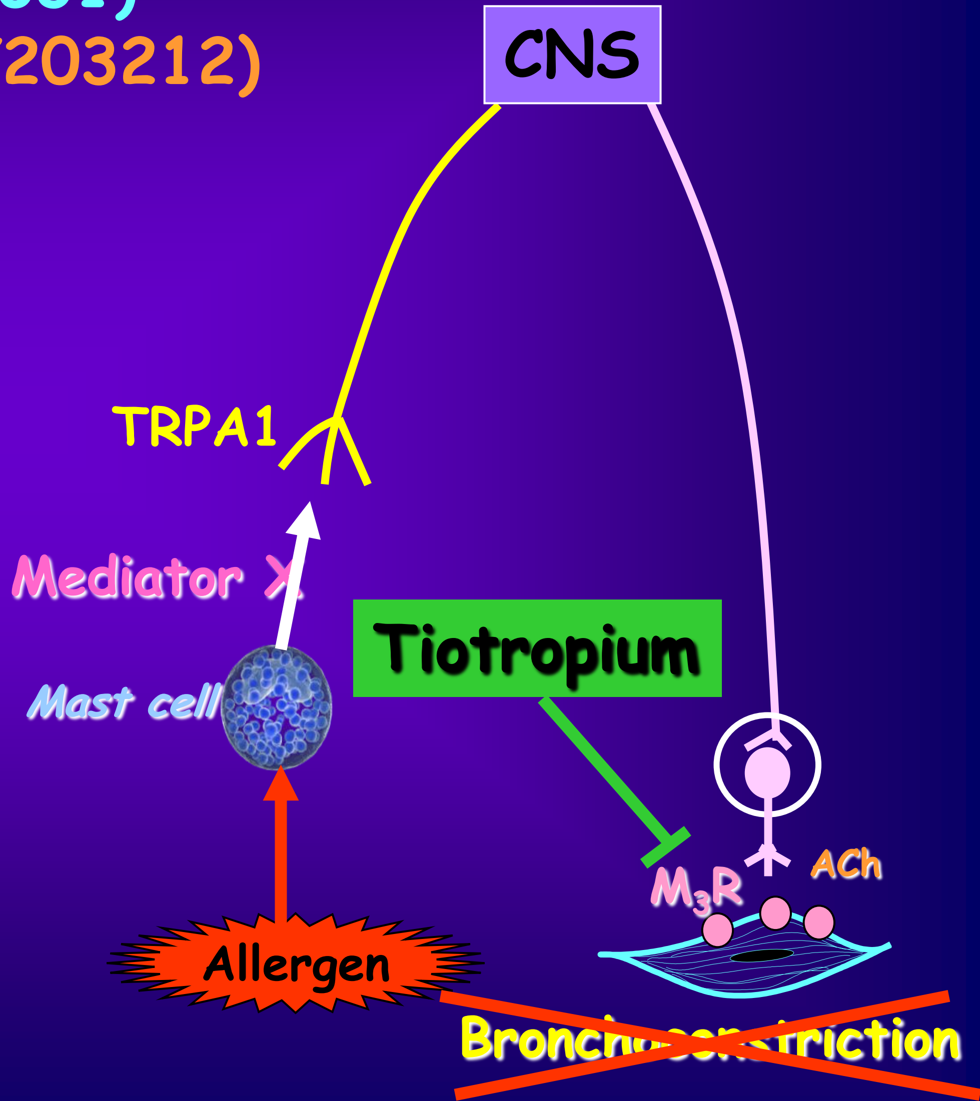


Raemdonck K et al: Thorax 2011

TRPA1 INHIBITOR BLOCKS LATE RESPONSE TO ALLERGEN

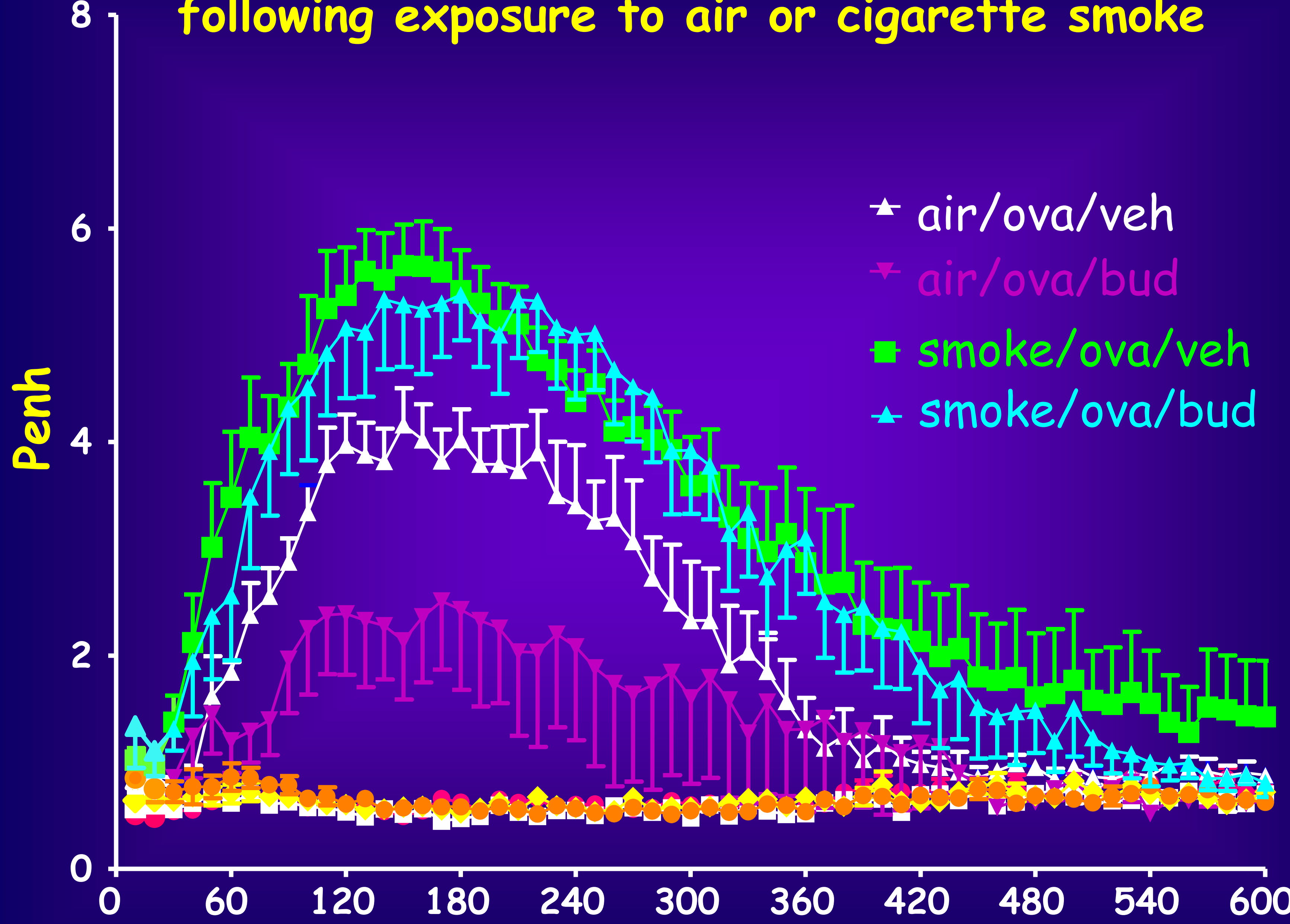
TRPA1 inhibitor (HC-030031)
TRPV1 inhibitor (JNJ-17203212)



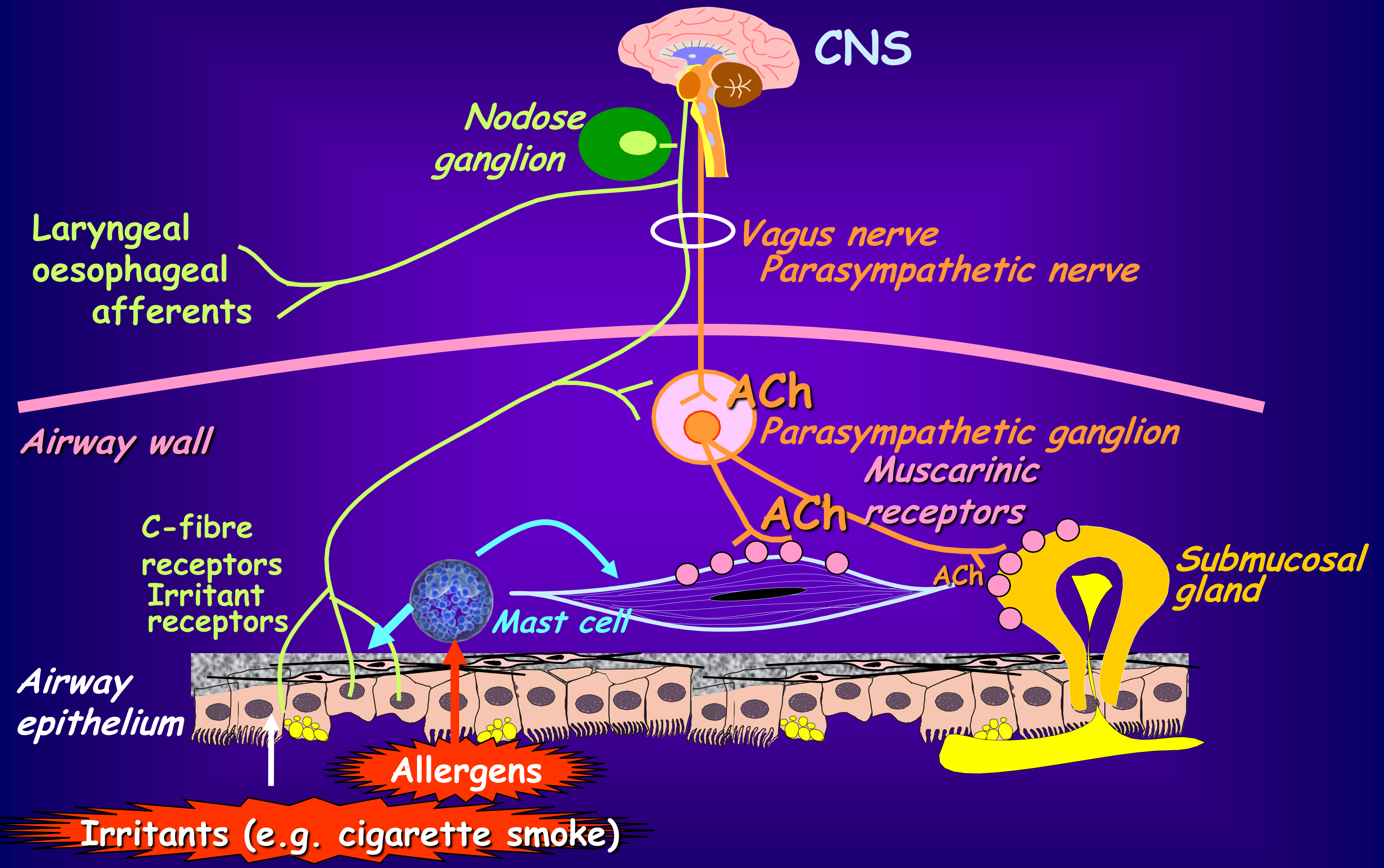


Raemdonck K et al: Thorax 2011

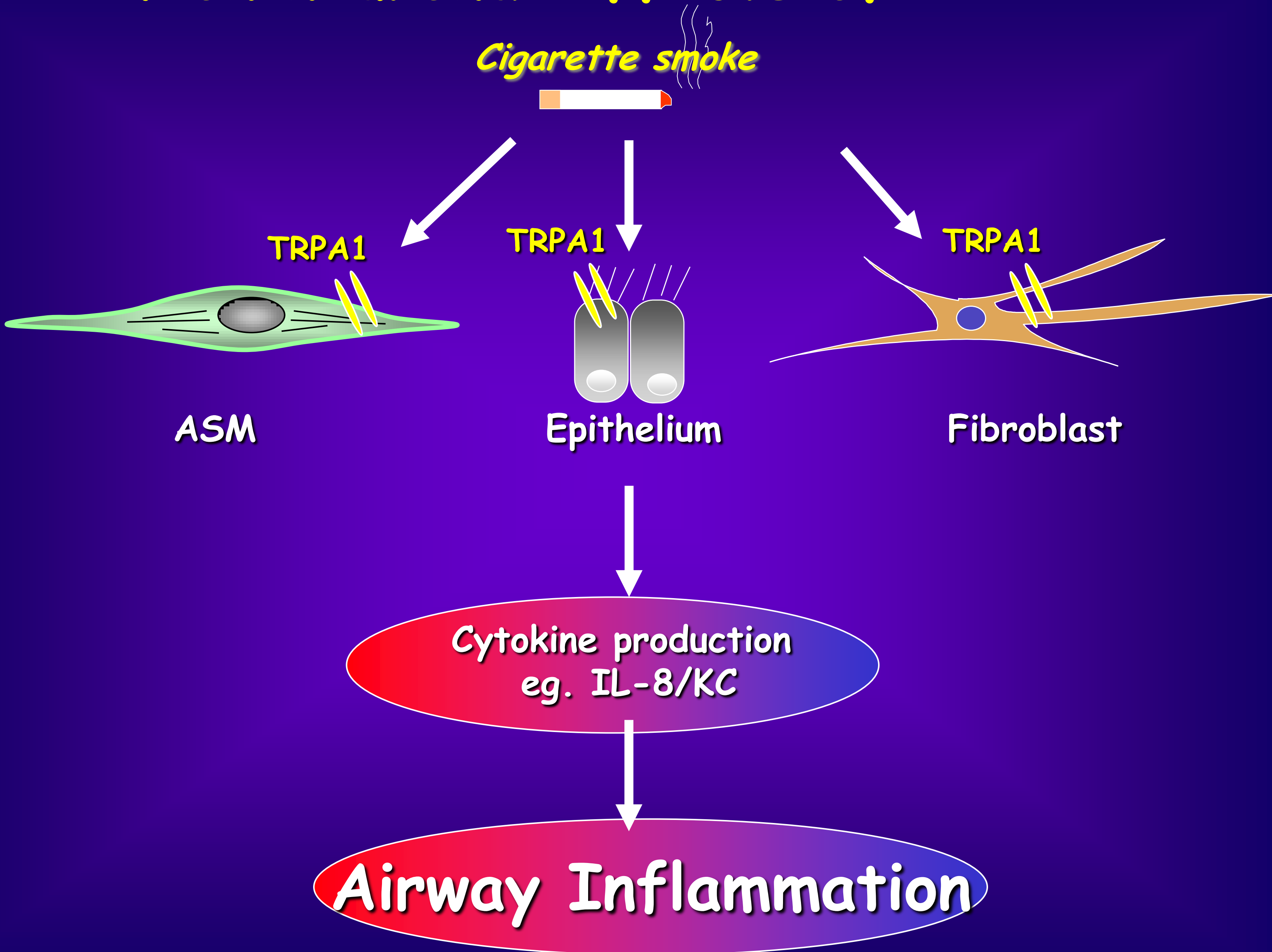
Effect of budesonide on LAR in mice following exposure to air or cigarette smoke



CHOLINERGIC CONTROL OF AIRWAYS

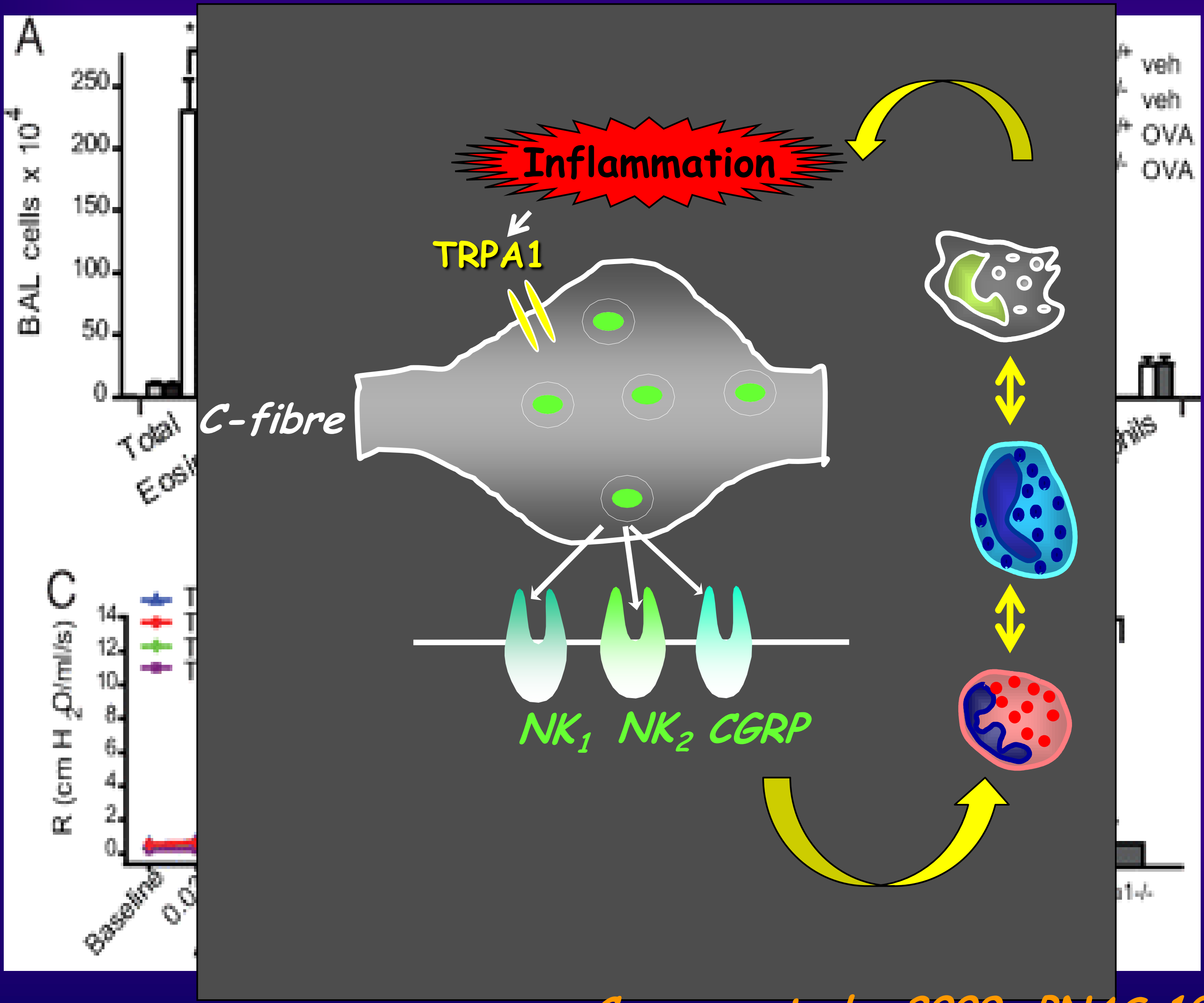


Non neuronal effects of TRPA1



Nassini et al., 2012; PLOS 1; 7: e4245

TRPA1 in Asthma



Caceres et al., 2009, PNAS 106: 9099-910