Neural Control of the Lung

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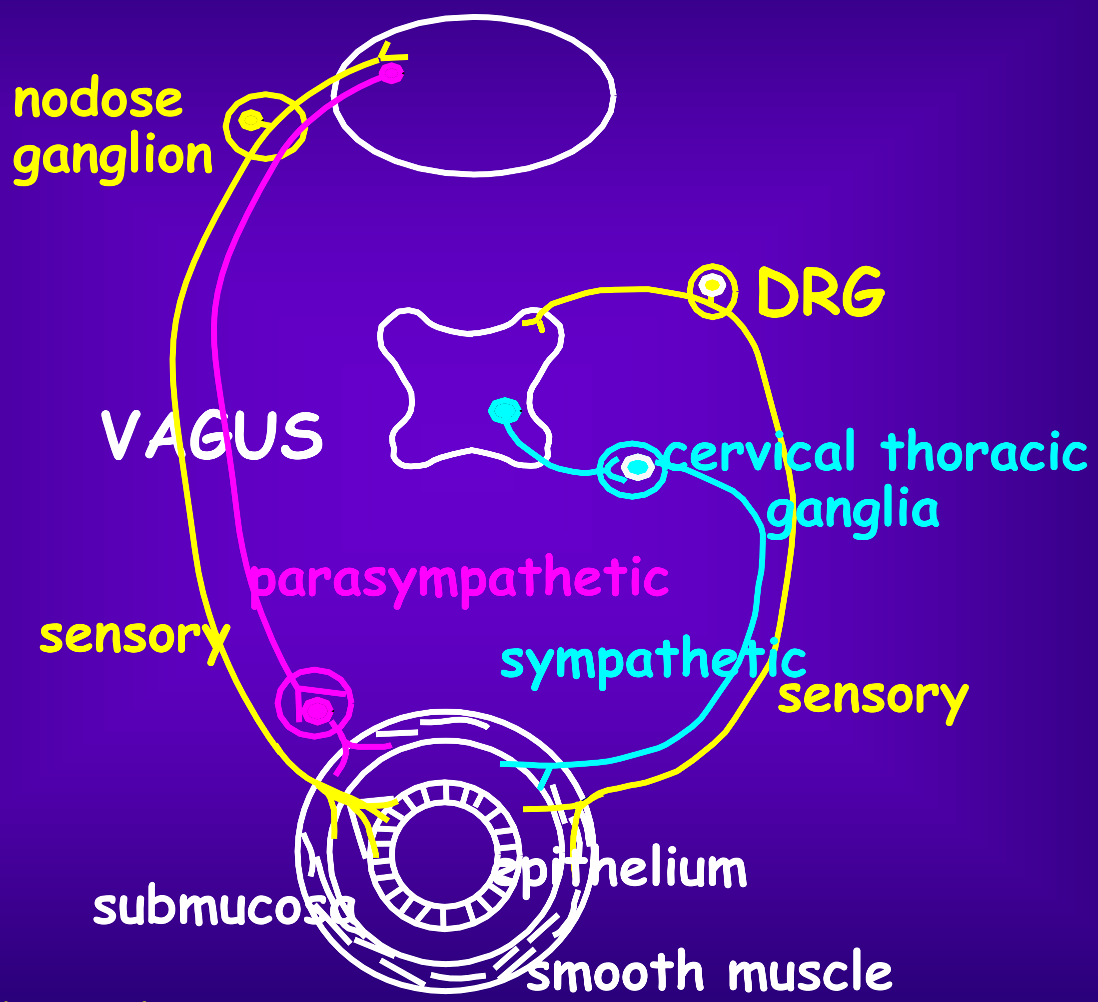
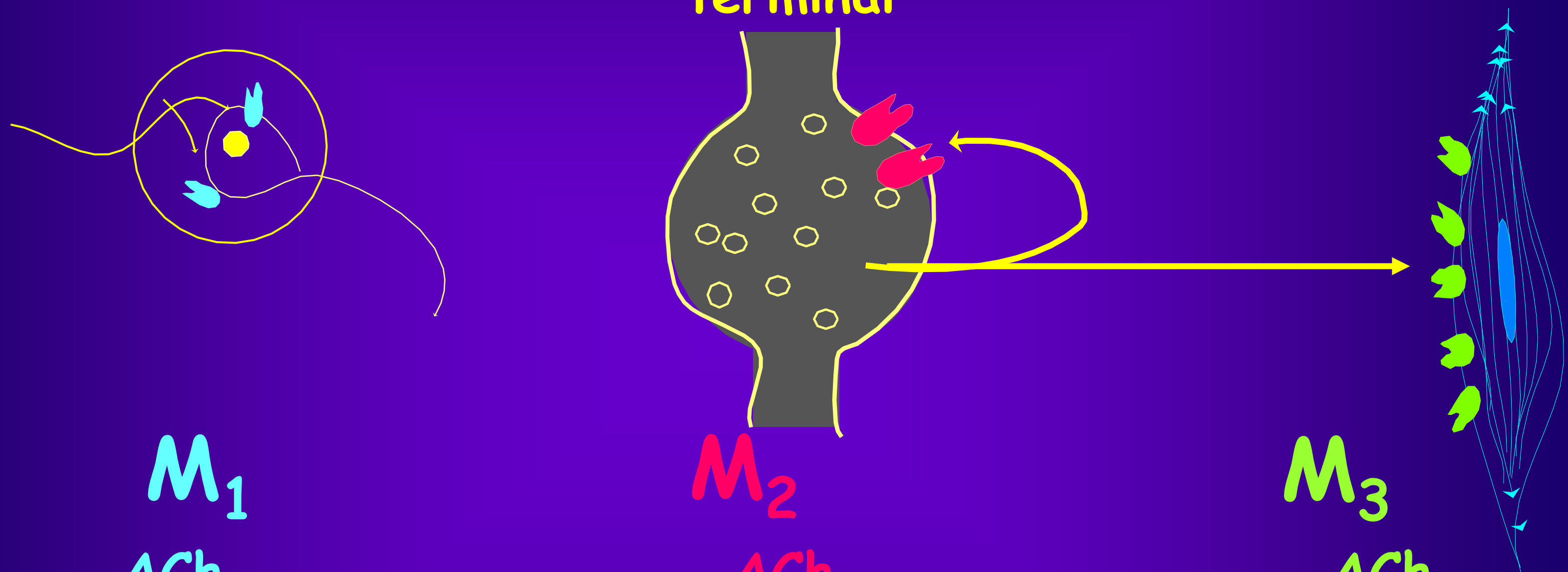
Innervation of the Respiratory Tract



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

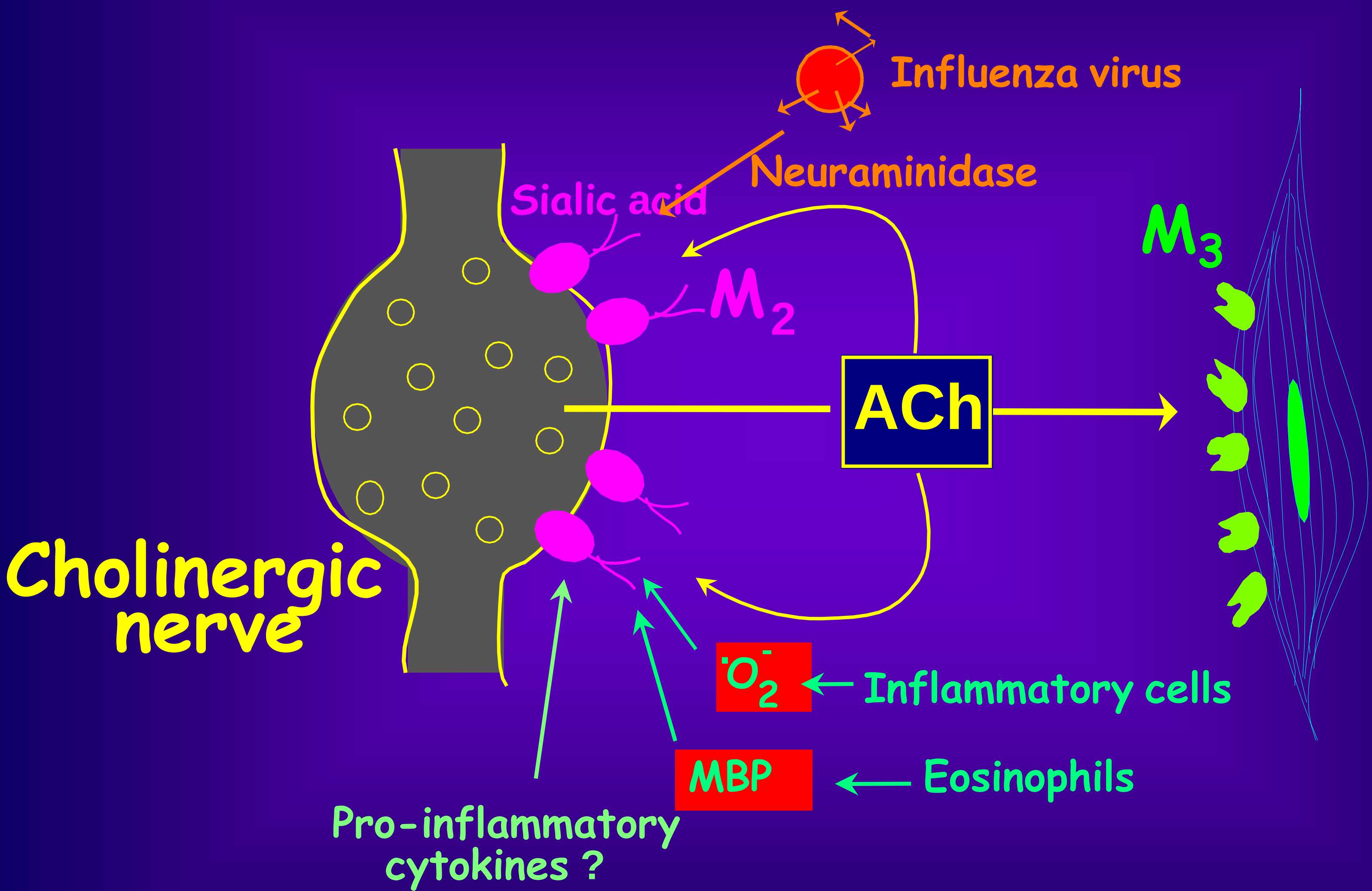
Muscarinic Receptor Subtypes in the Airways

Parasympathetic ganglion	Postgangiolnic cholineric nerve terminal	Airway smooth muscle

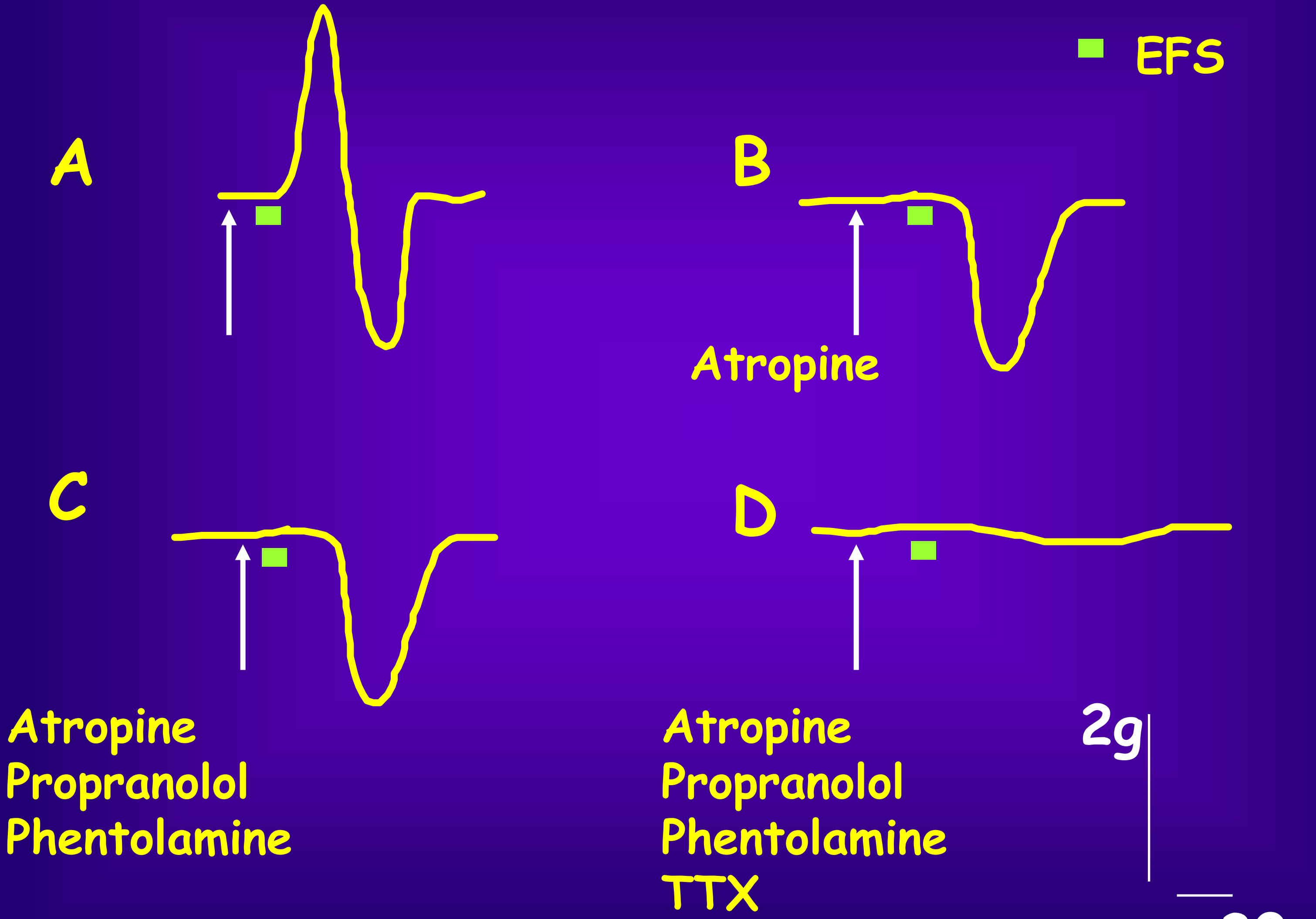


	M_1	M_2	M_3
Agonist	ACh	ACh	ACh
	Oxotremorine	Oxotremorine	Oxotremorine
Antagonist	Ipratropium	Ipratropium	Ipratropium
	Tiotropium		Tiotropium

Muscarinic Autoreceptor Dysfunction in Asthma ?

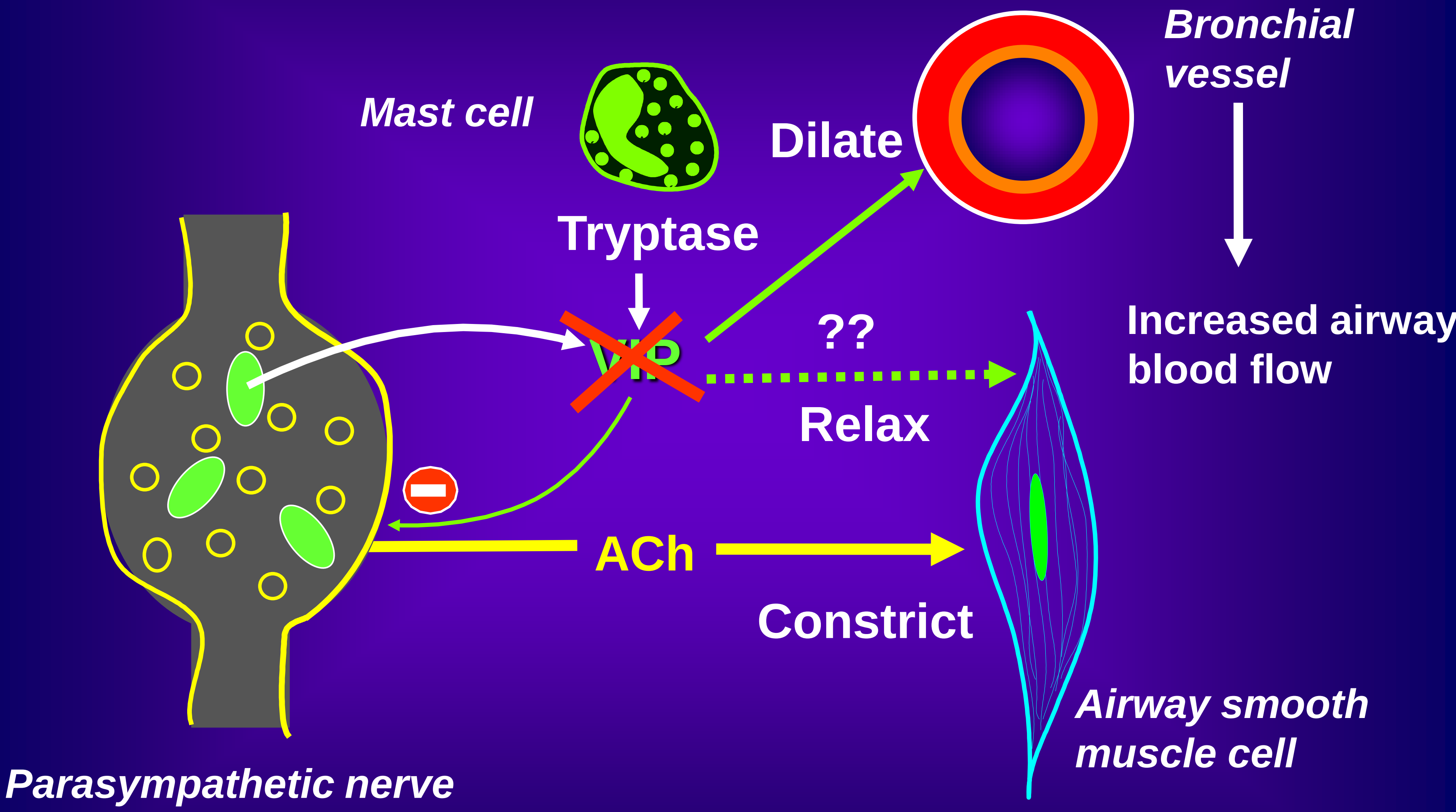


Human Airway Smooth Muscle and the Control of Airway Tone



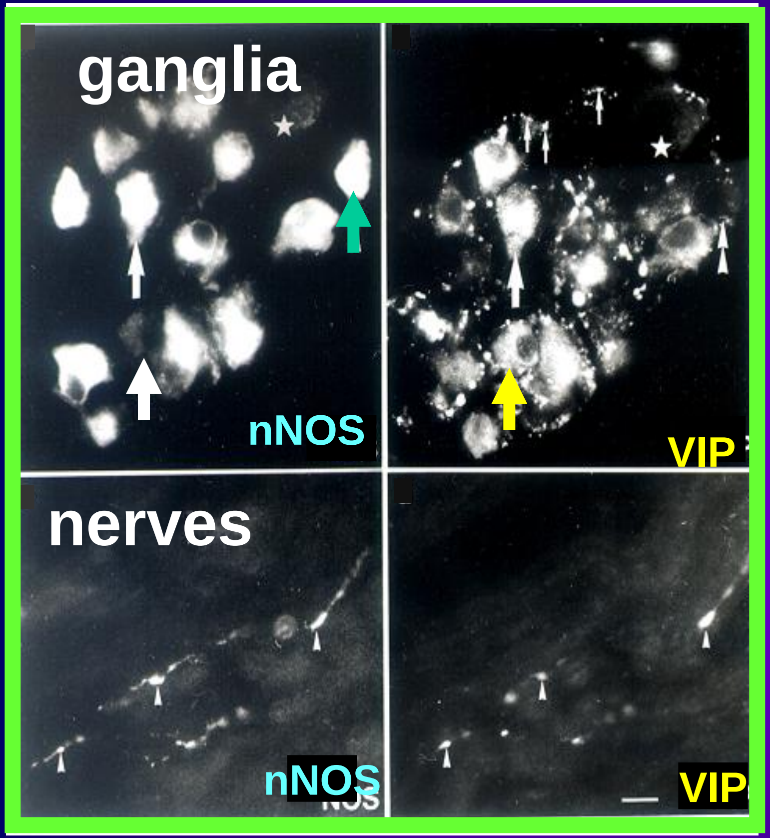
EFS: 40V, 0.5ms, 5Hz for 30s

VIP EFFECTS ON AIRWAYS

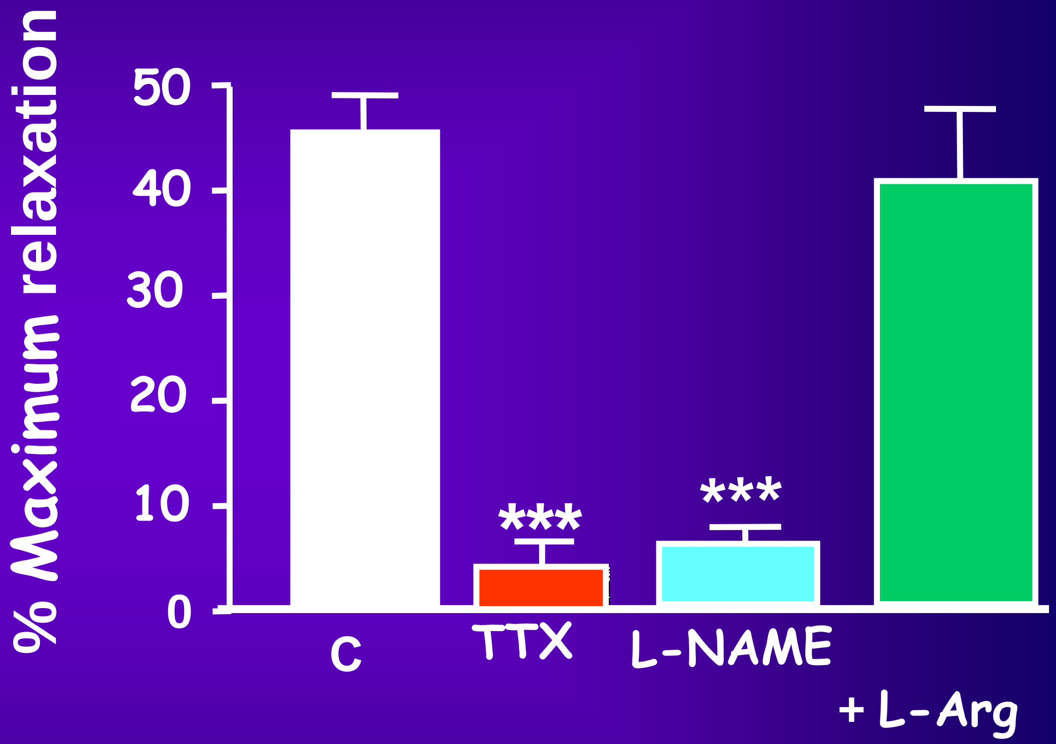


i-NANC Relaxations of Human Trachea: Role for NO

Immunocytochemistry

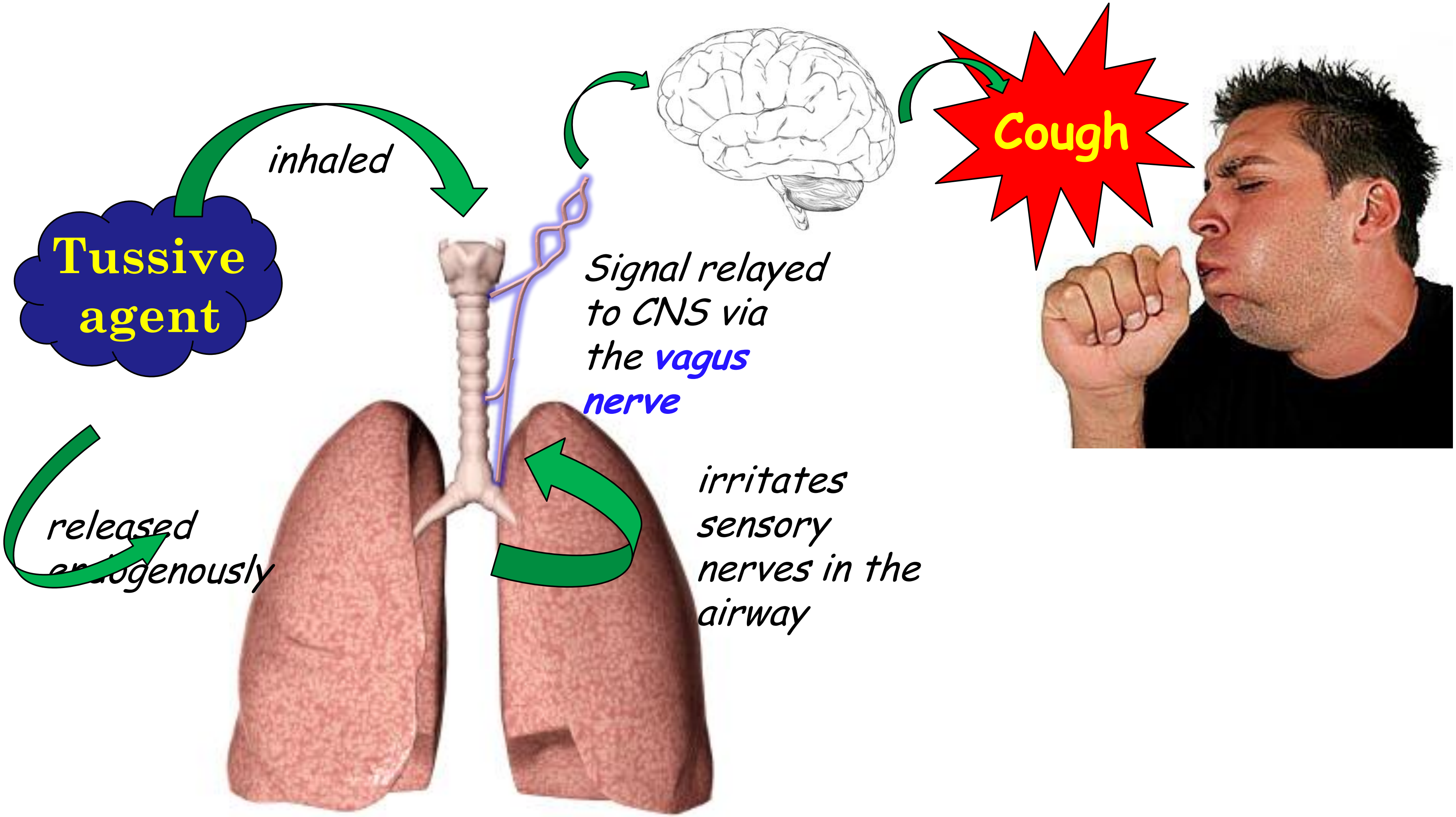


L-NAME: NOS inhibitor



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

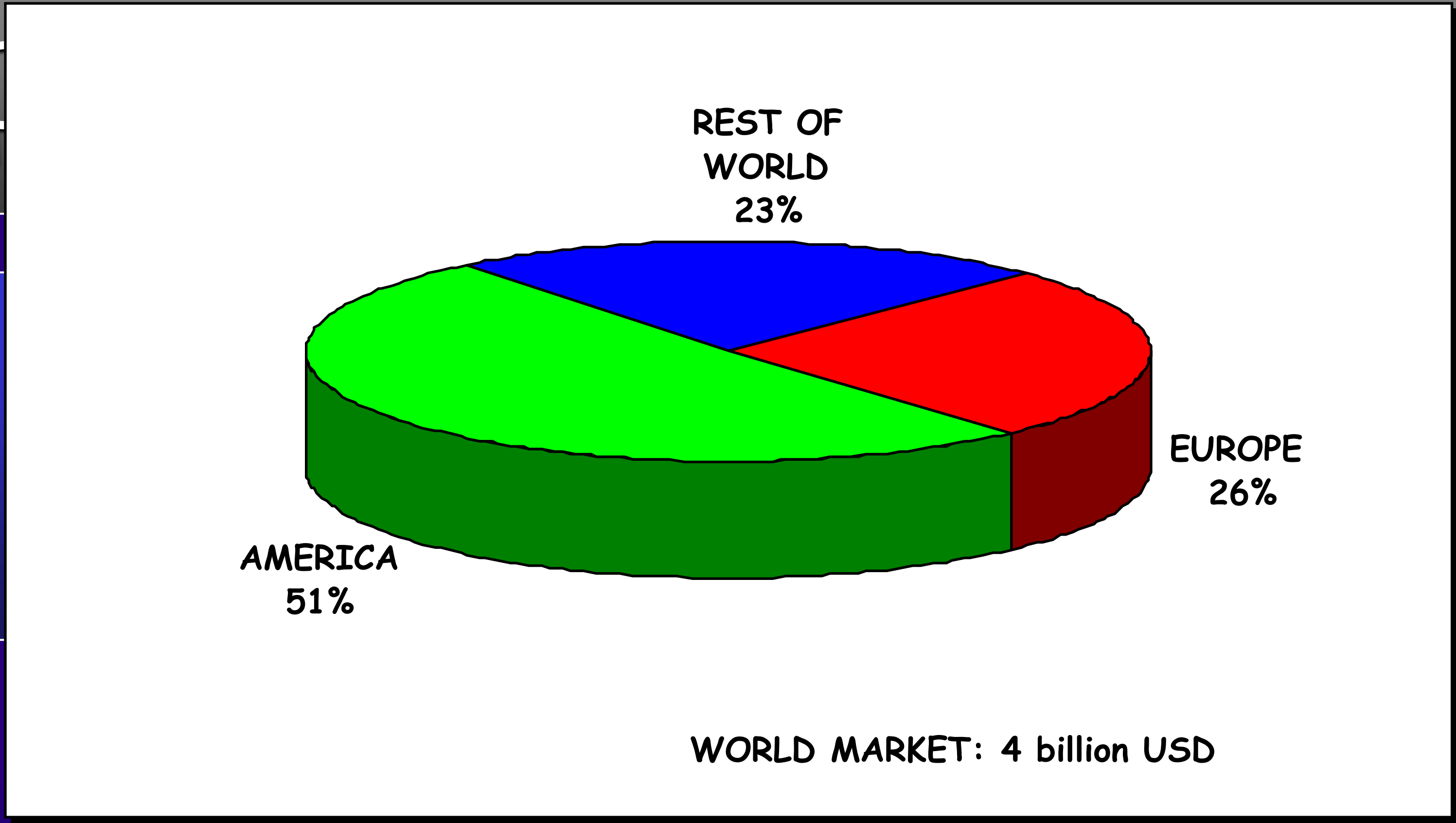
The Cough Reflex



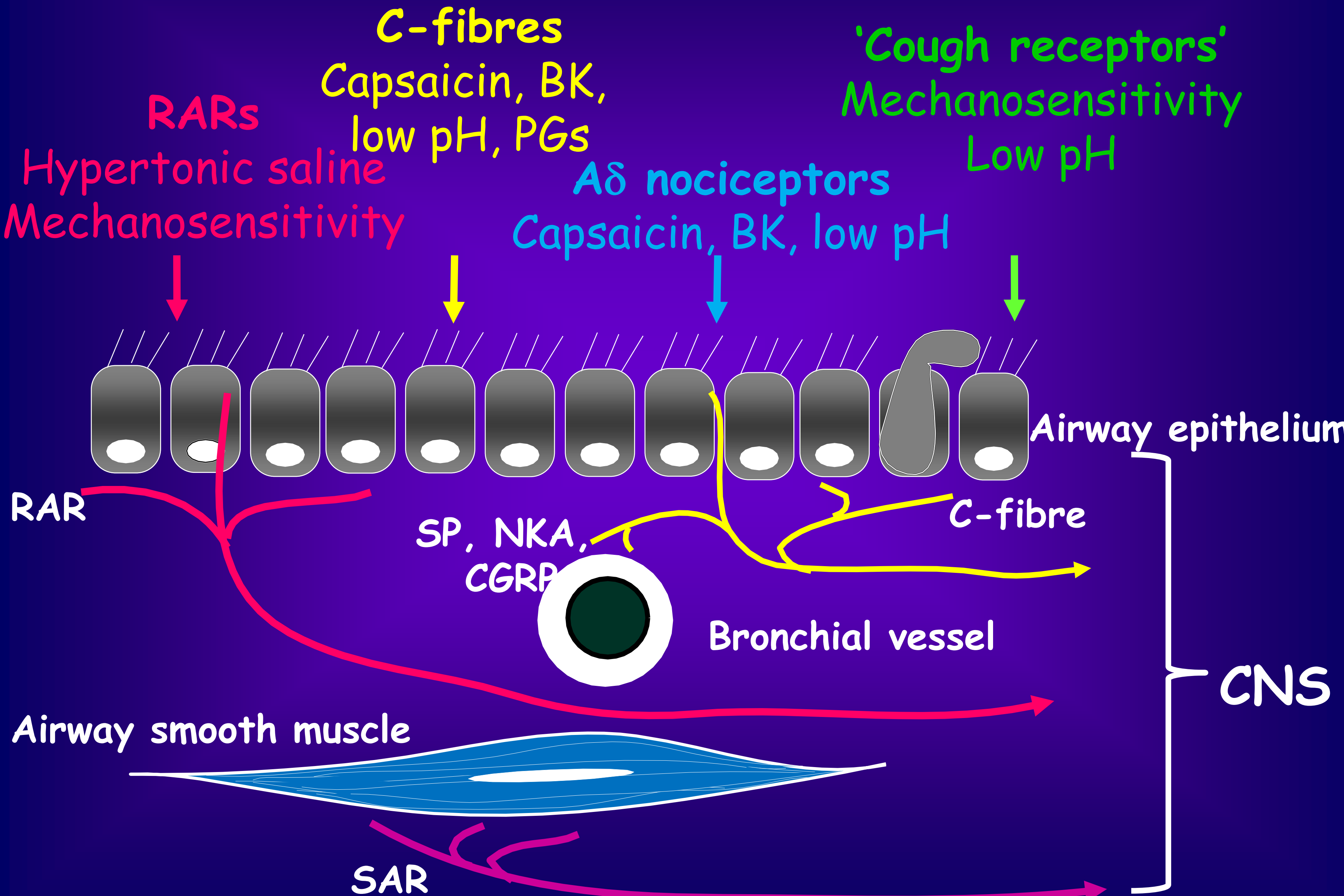
Adapted from Taylor-Clark & Undem 2006

COUGH AS A MAJOR UNMET MEDICAL NEED

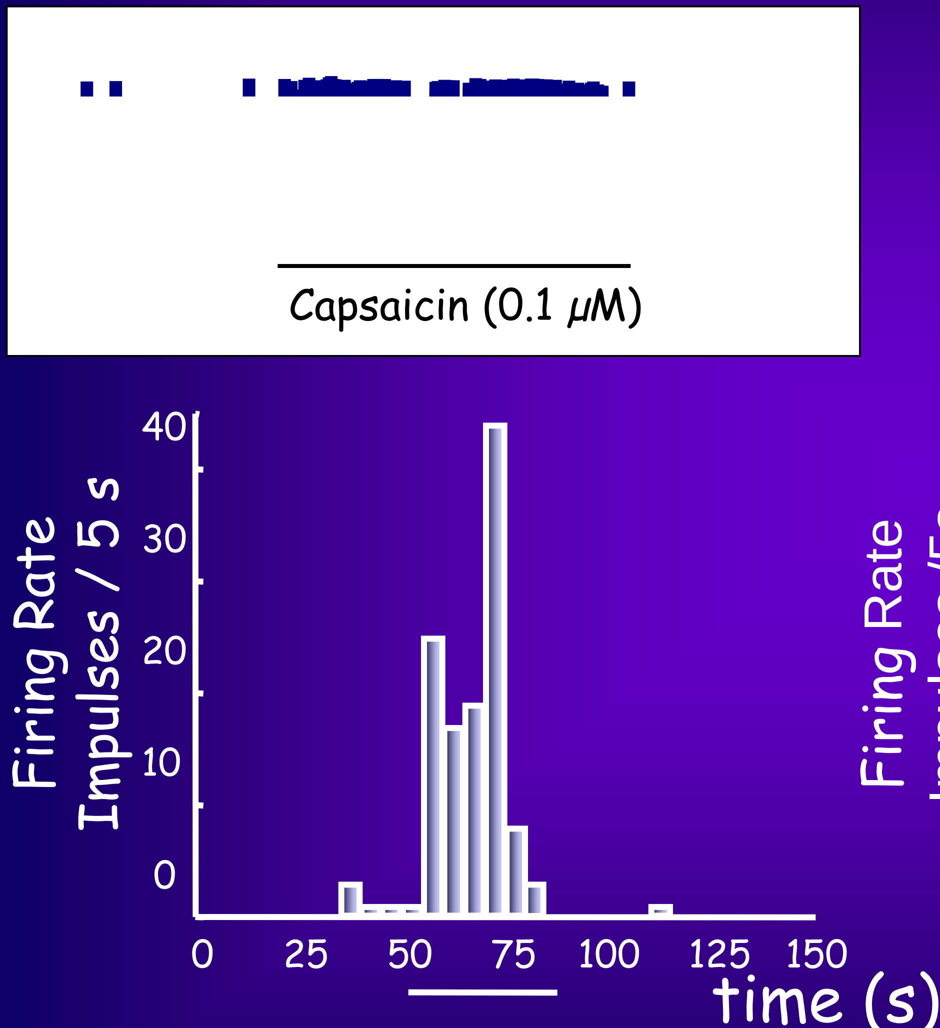
- Commonest symptom for medical consultation
- Chronic cough: 10-38% of pulmonary out-patients
- No effective therapy apart from opiates
- H
- T

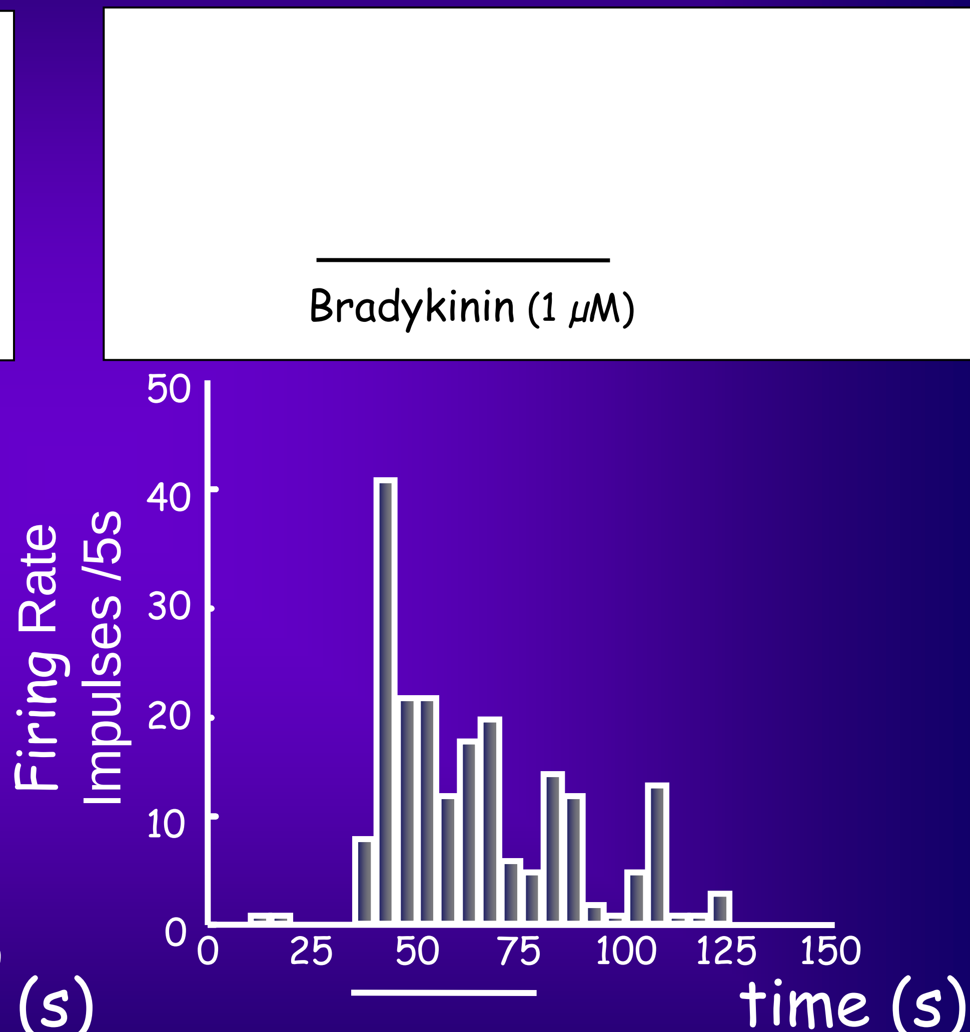


Airway Sensory Nerves



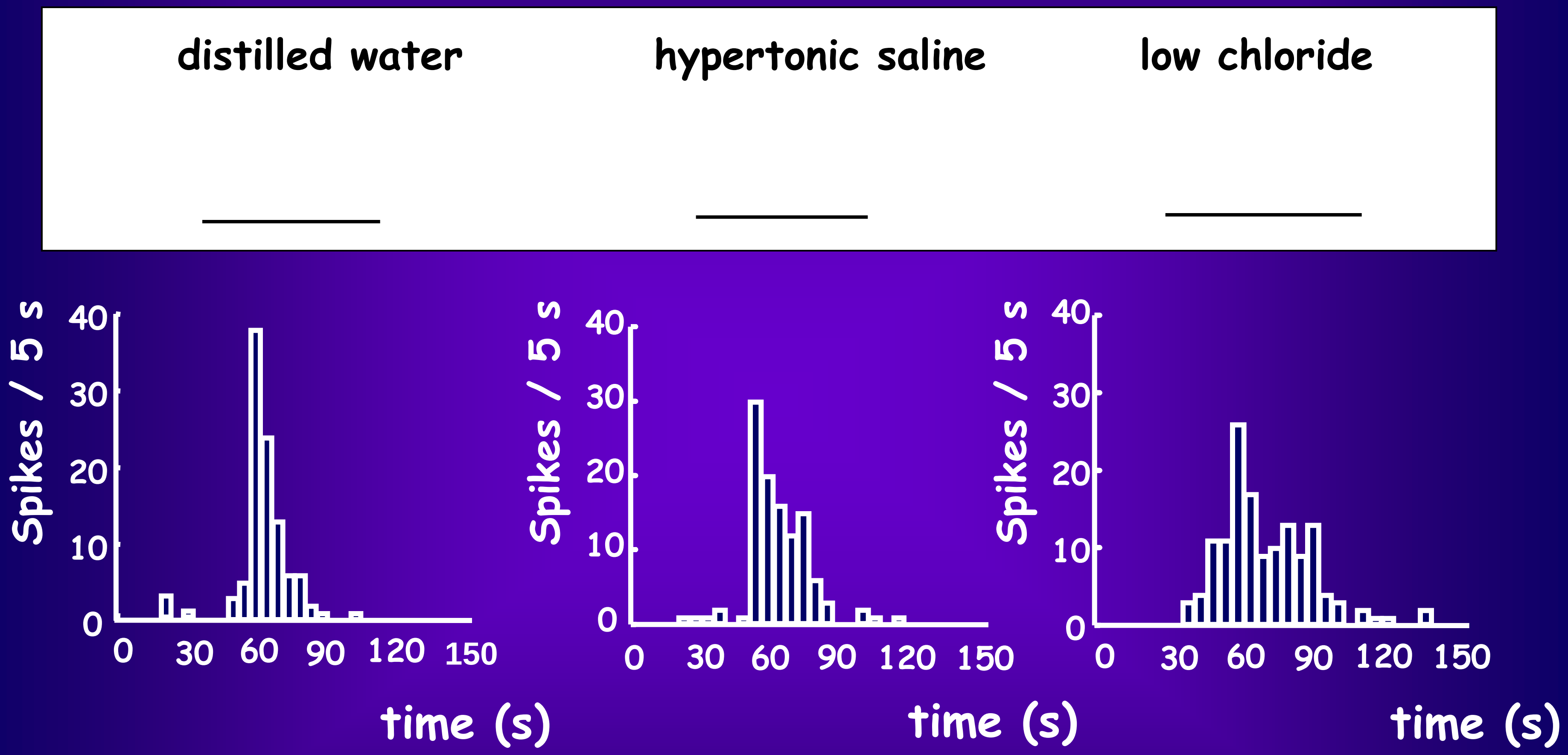
Capsaicin Excitation of C-fibres





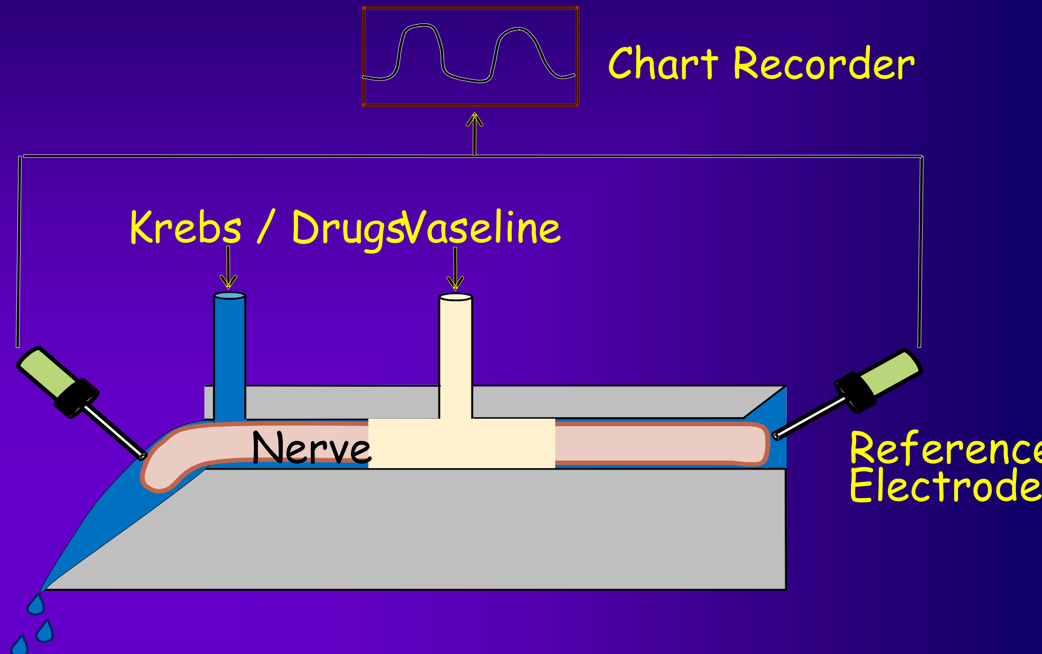
Fox et al 1993. J. Physiol. 460, 21-35

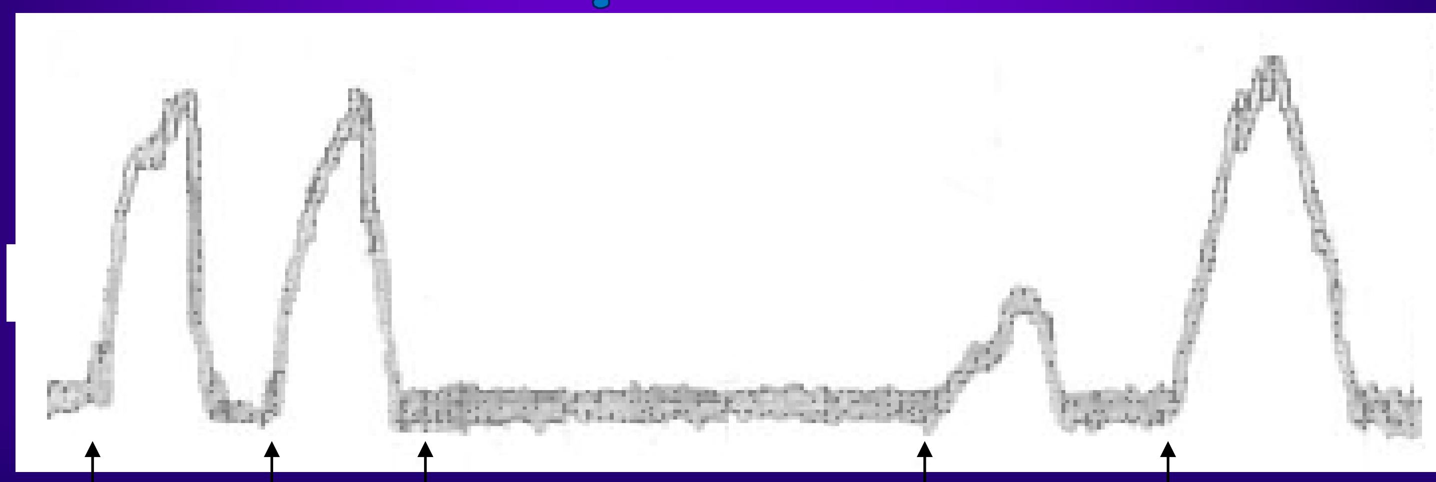
Aδ-fibre Activation



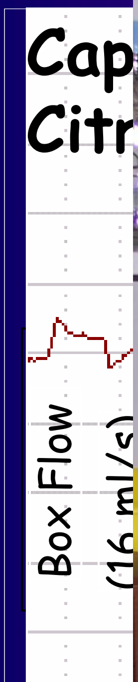
Fox et al 1993. J. Physiol. 482, 179-187

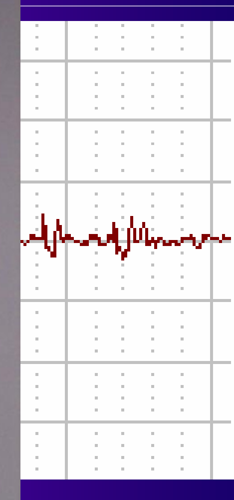
Isolated Vagus Nerve



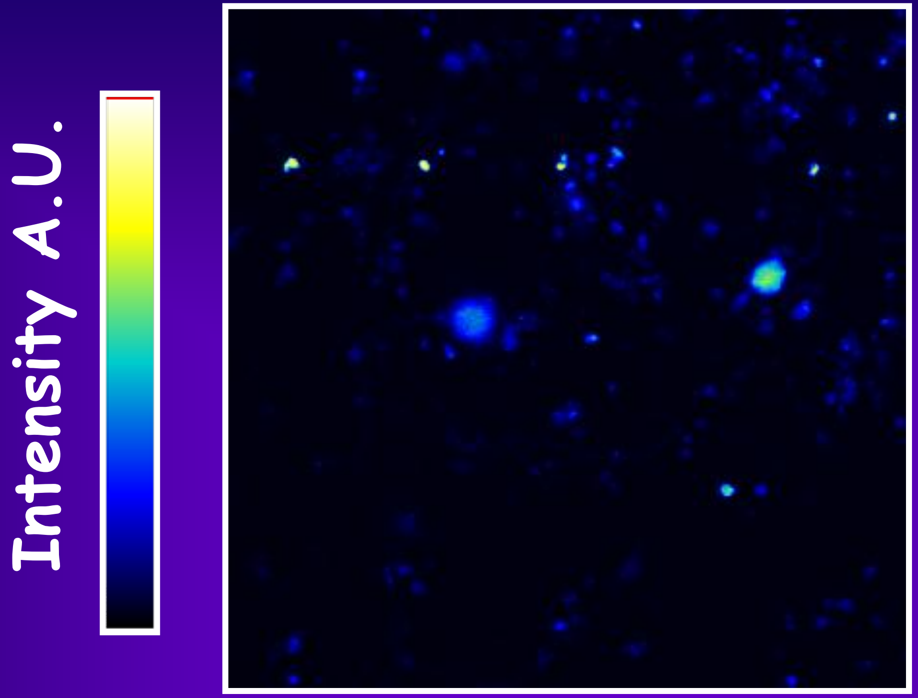


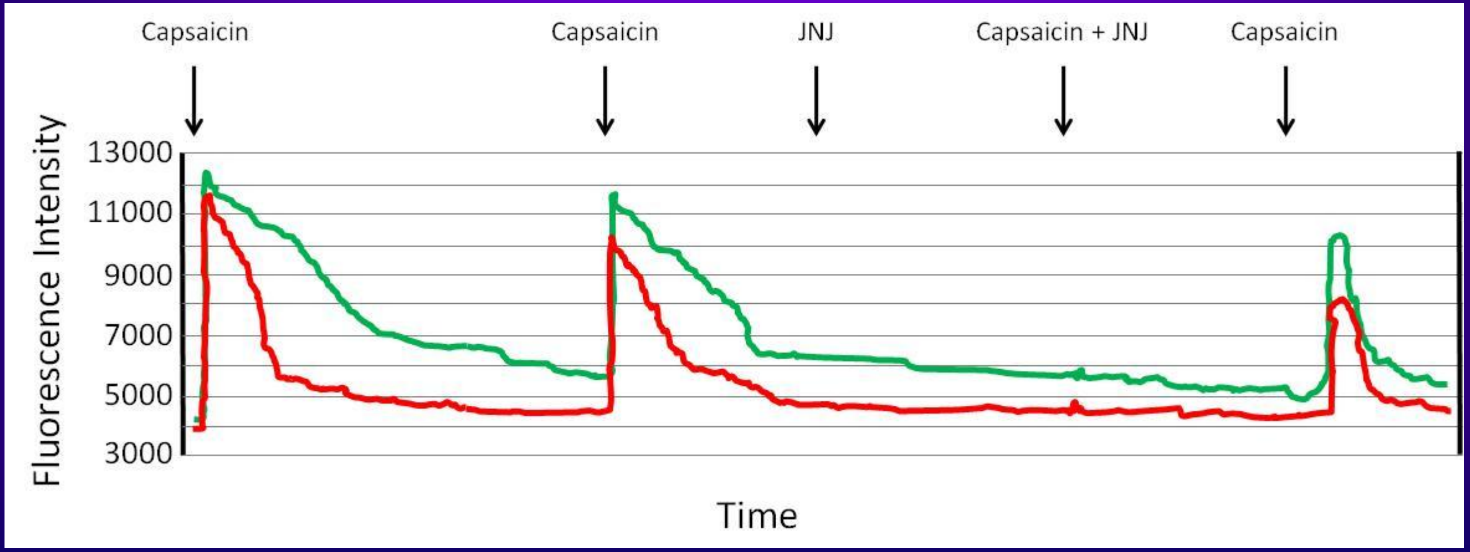
Cough Model





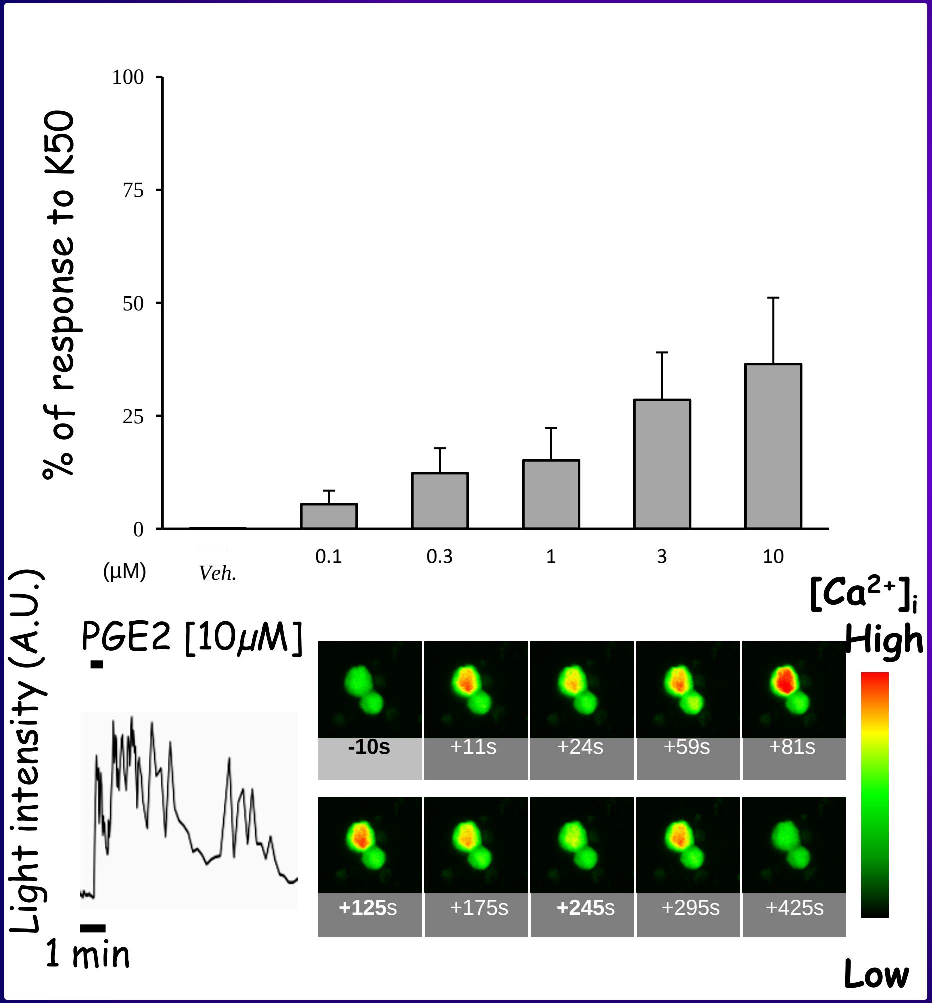
Calcium imaging of vagal sensory neurones



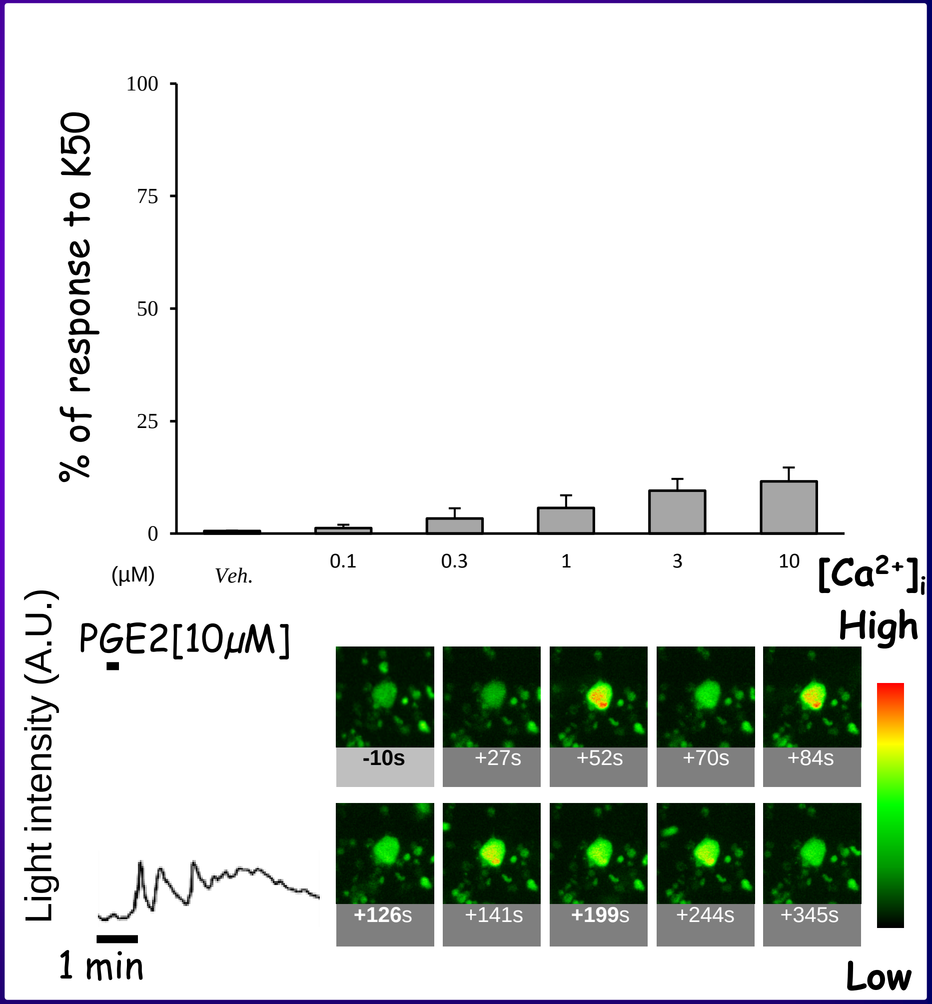


Calcium imaging: Prostaglandin E_2

Jugular ganglion

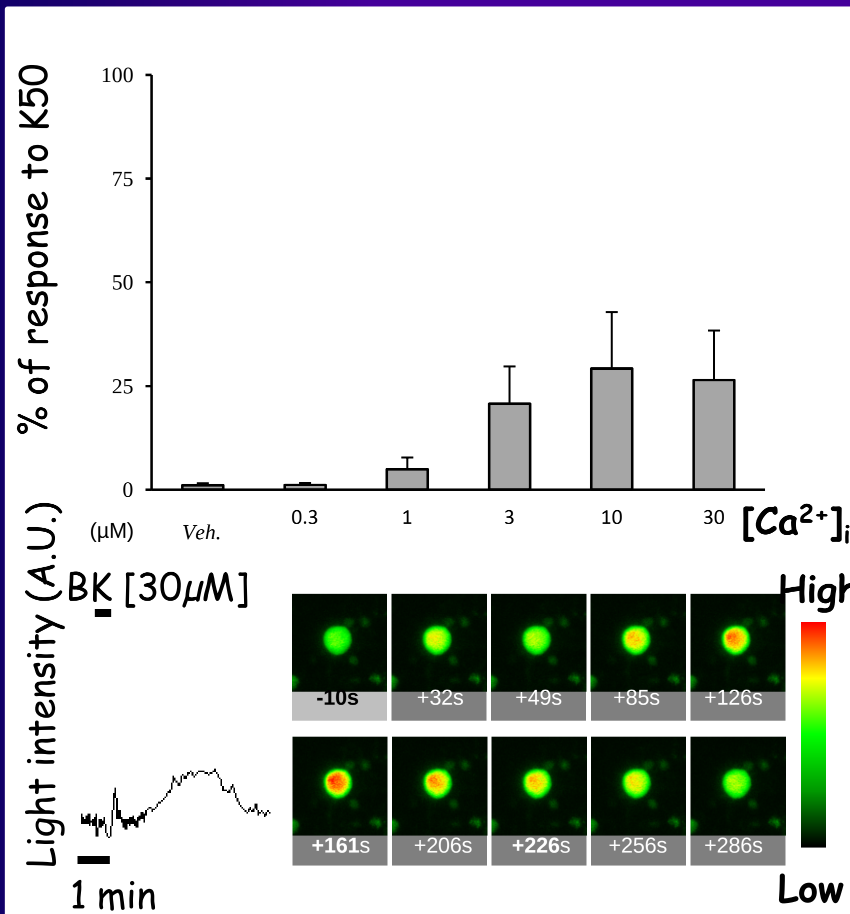


Nodose ganglion

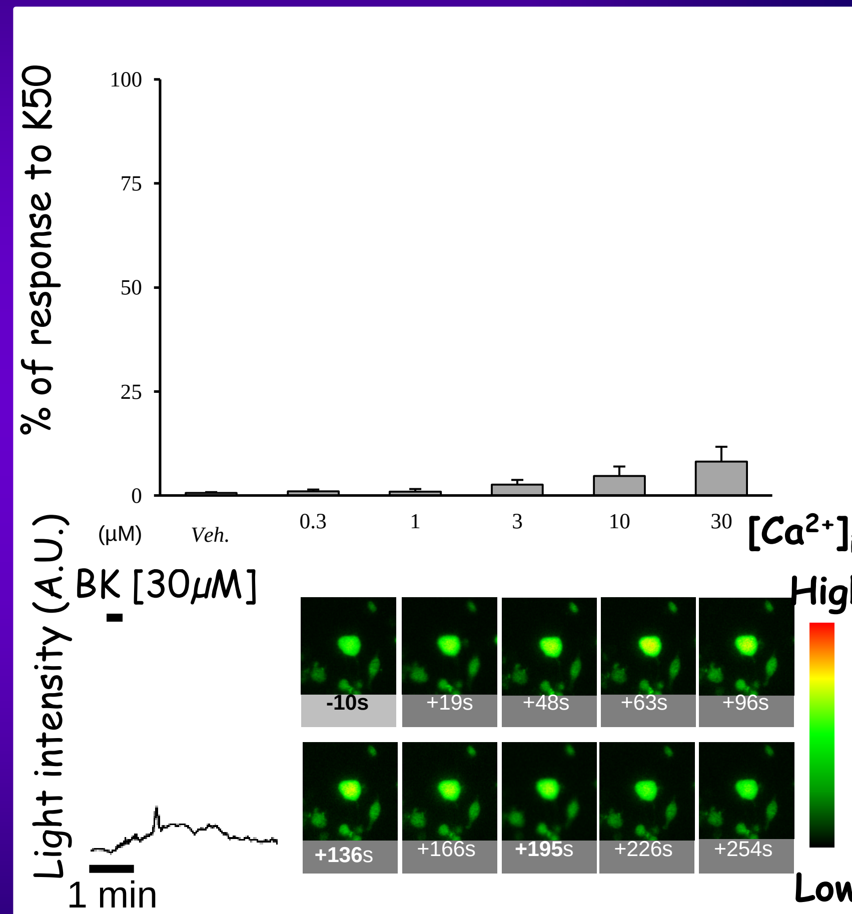


Calcium imaging: Bradykinin

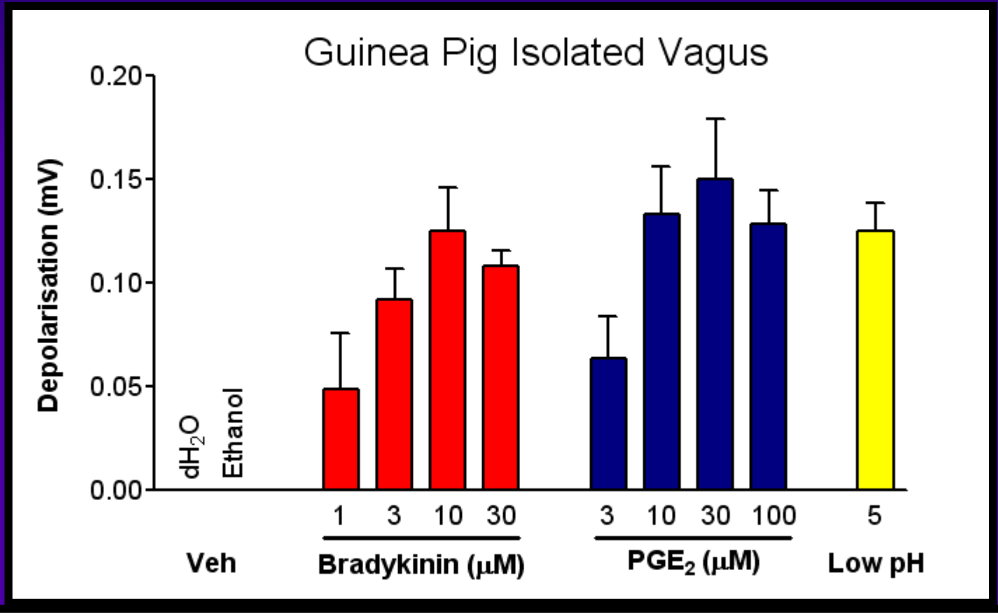
Jugular ganglion

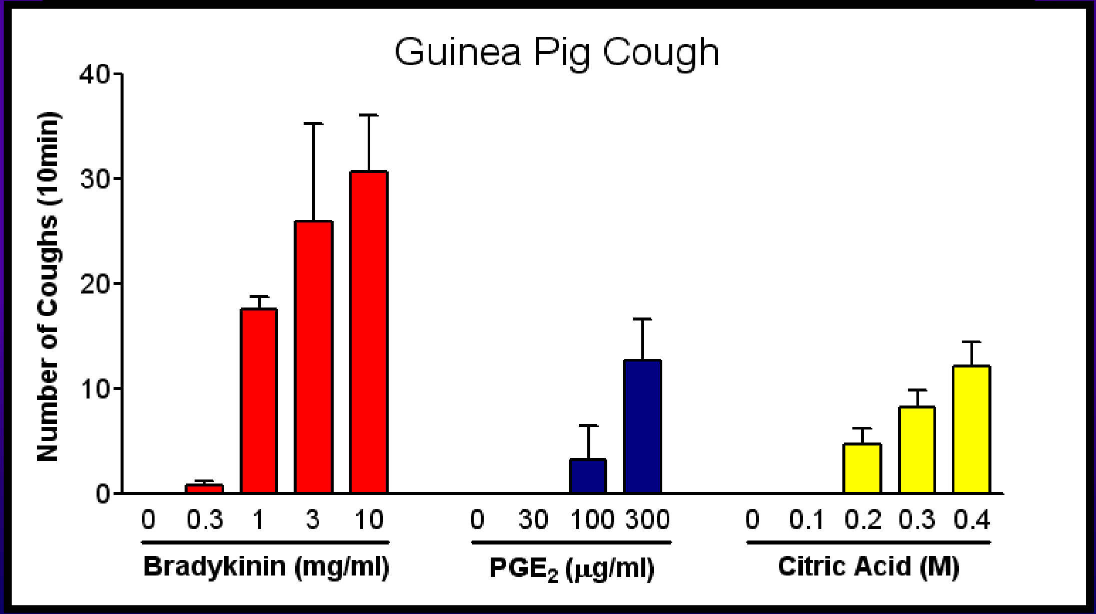


Nodose ganglion



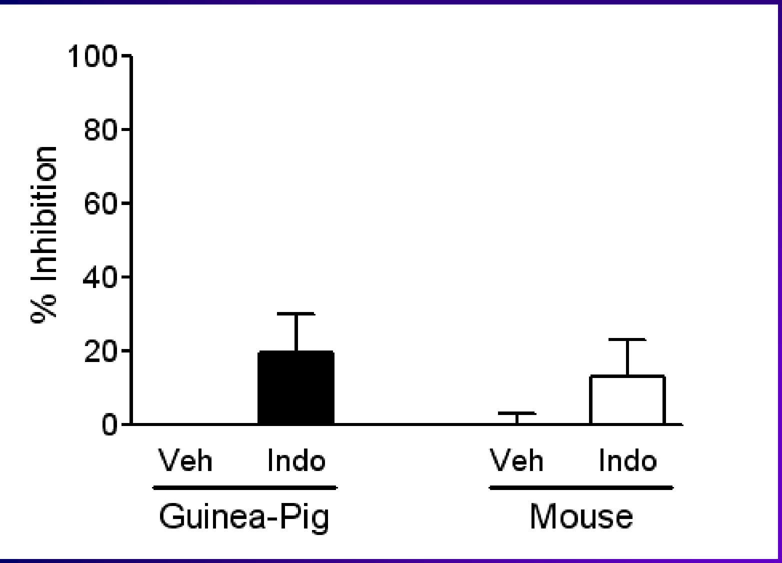
Sensory nerve activation and cough elicited by endogenous tussive agents



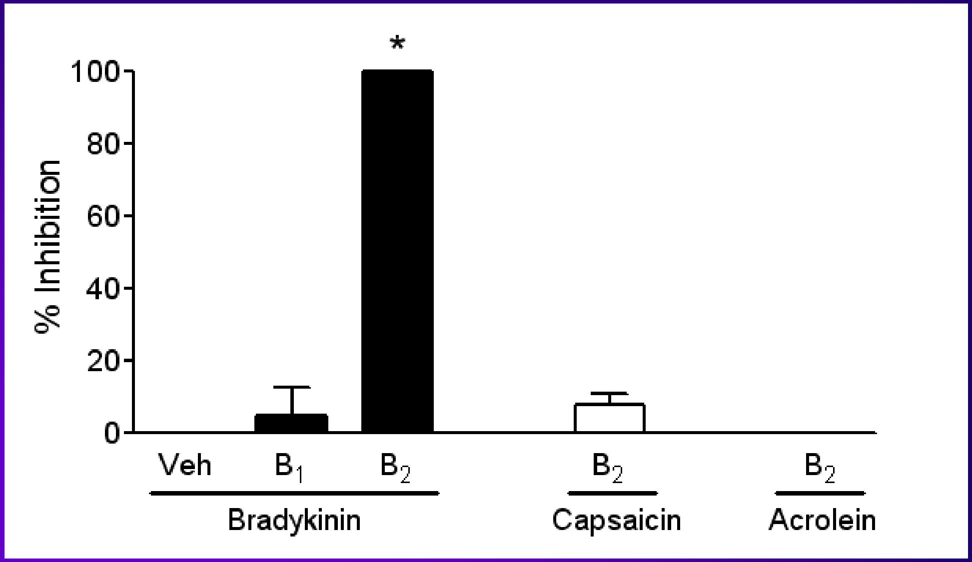


Vagus BK vs Antagonists

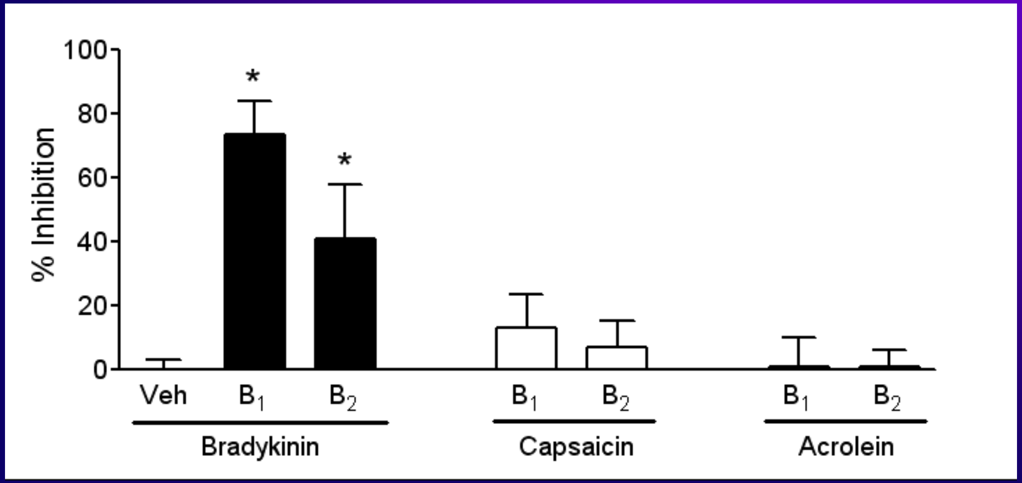
BK vs Indomethacin



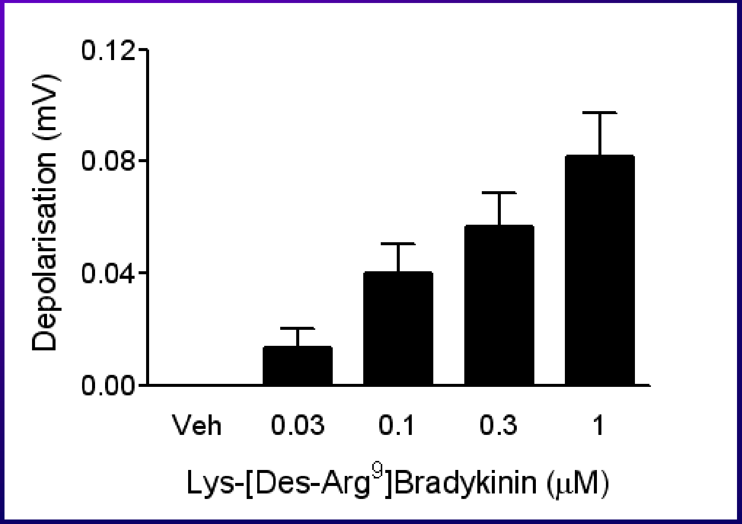
Guinea Pig: BK vs B1 & B2 antagonists



Mouse: BK vs B1 & B2 antagonists



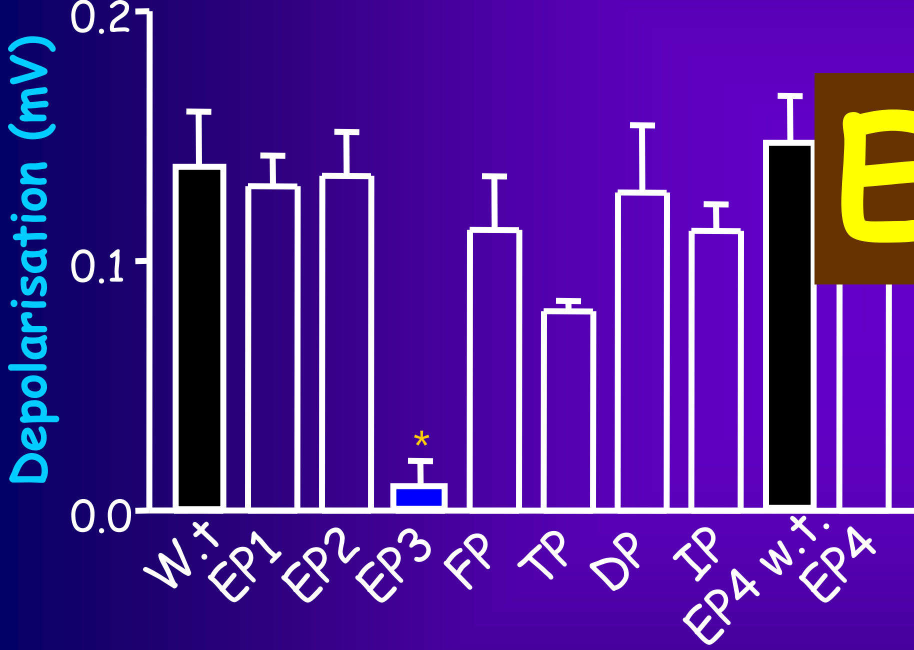
Mouse: B1 agonist



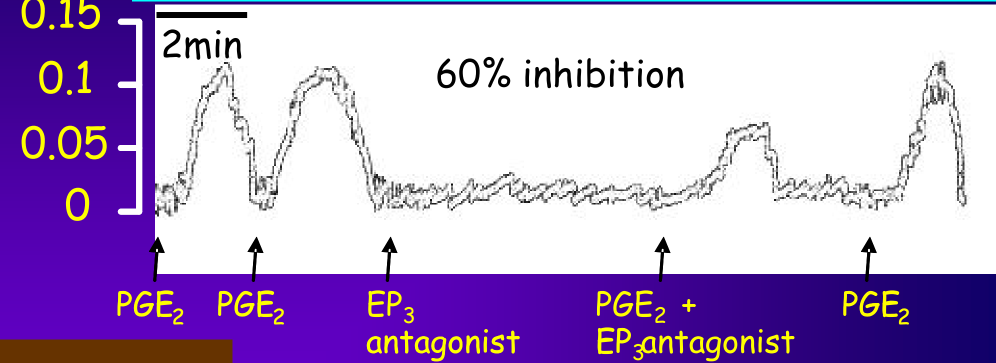
Sensory nerve activation: which prostanoid receptor?

GENE-DELETED MICE

Responses to PGE_2 in KO mice

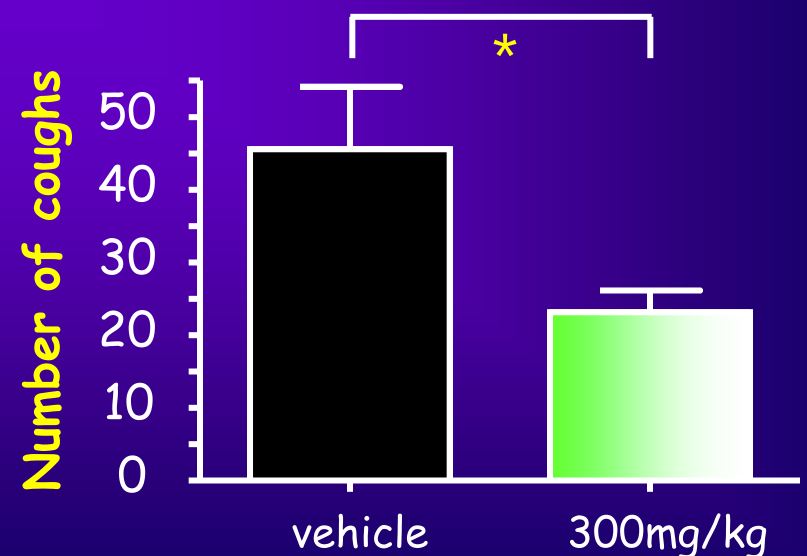


IN VITRO PHARMACOLOGY



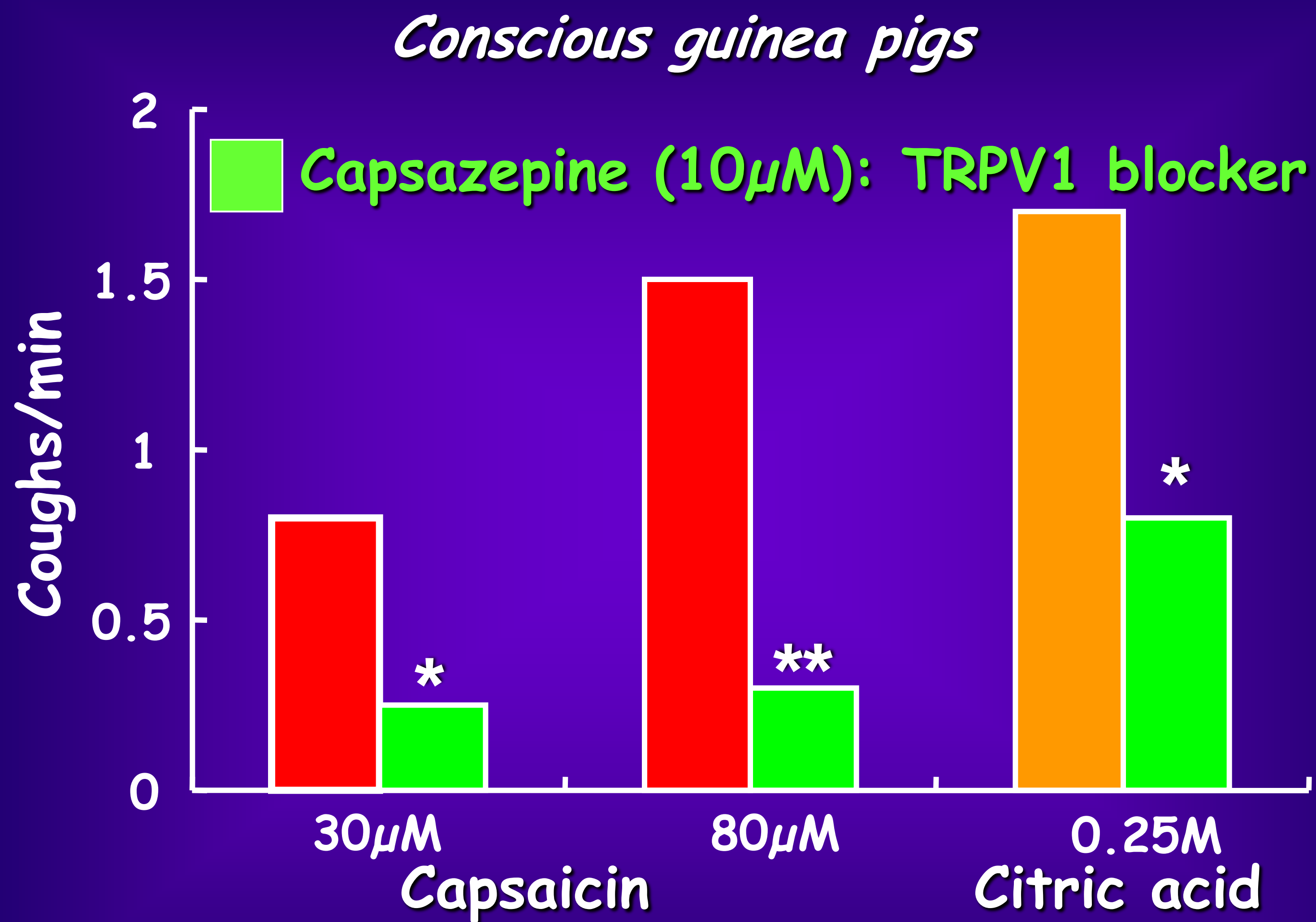
EP_3

IN VIVO PHARMACOLOGY



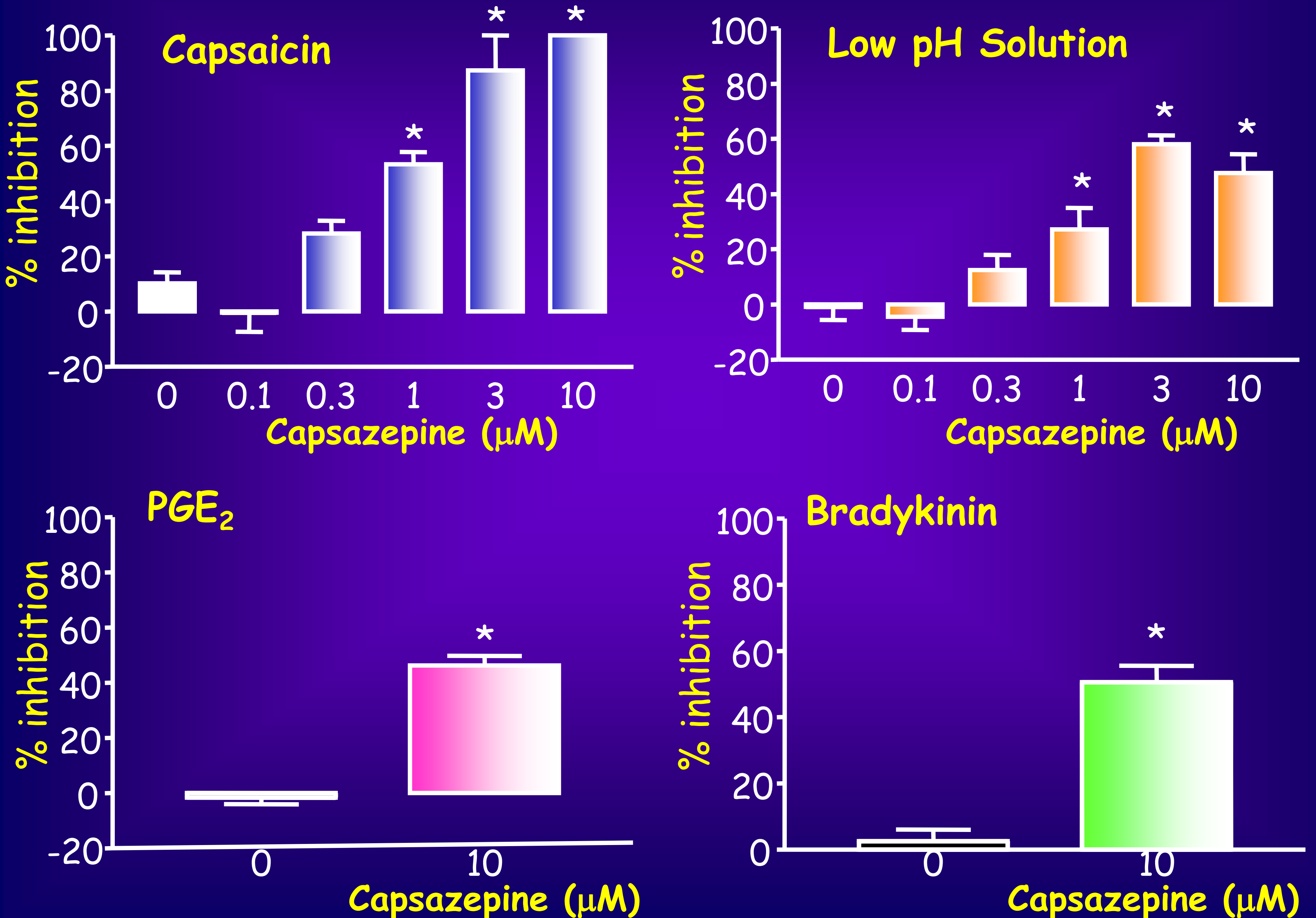
Maher et al., Am. J Respir. Crit. Care Med., 2009; 180: 923-928.

EFFECT OF CAPSAZEPINE ON COUGH

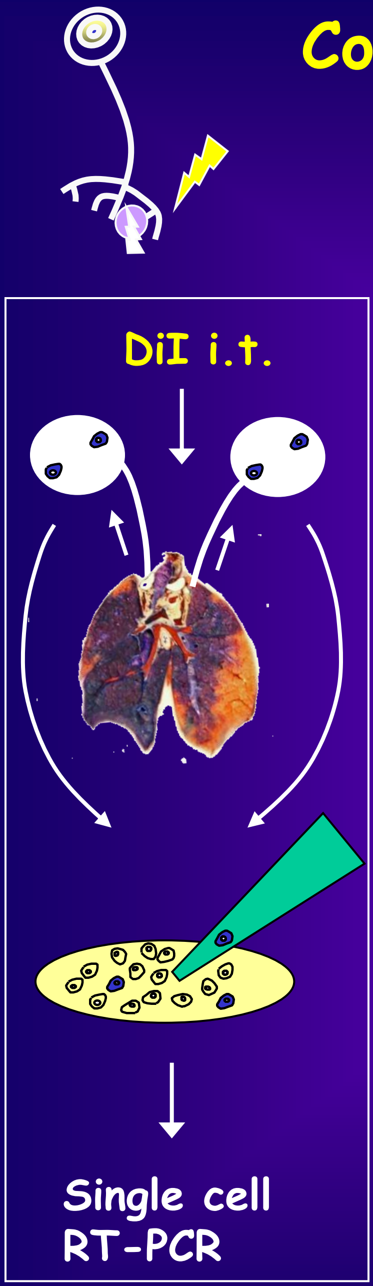


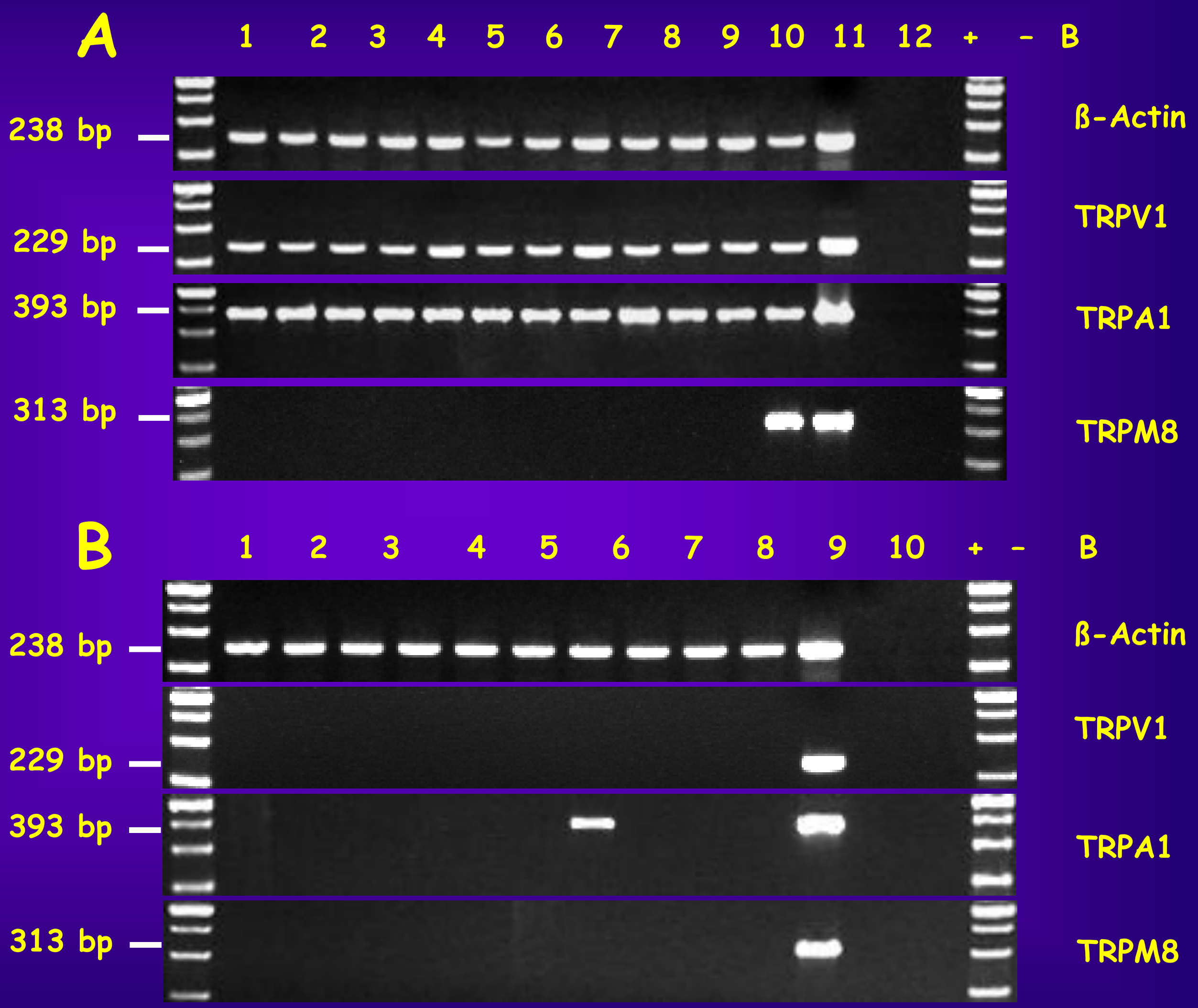
Lalloo, Fox, Belvisi, Chung, Barnes J Appl Physiol 1995, 79(4):1082-7.

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



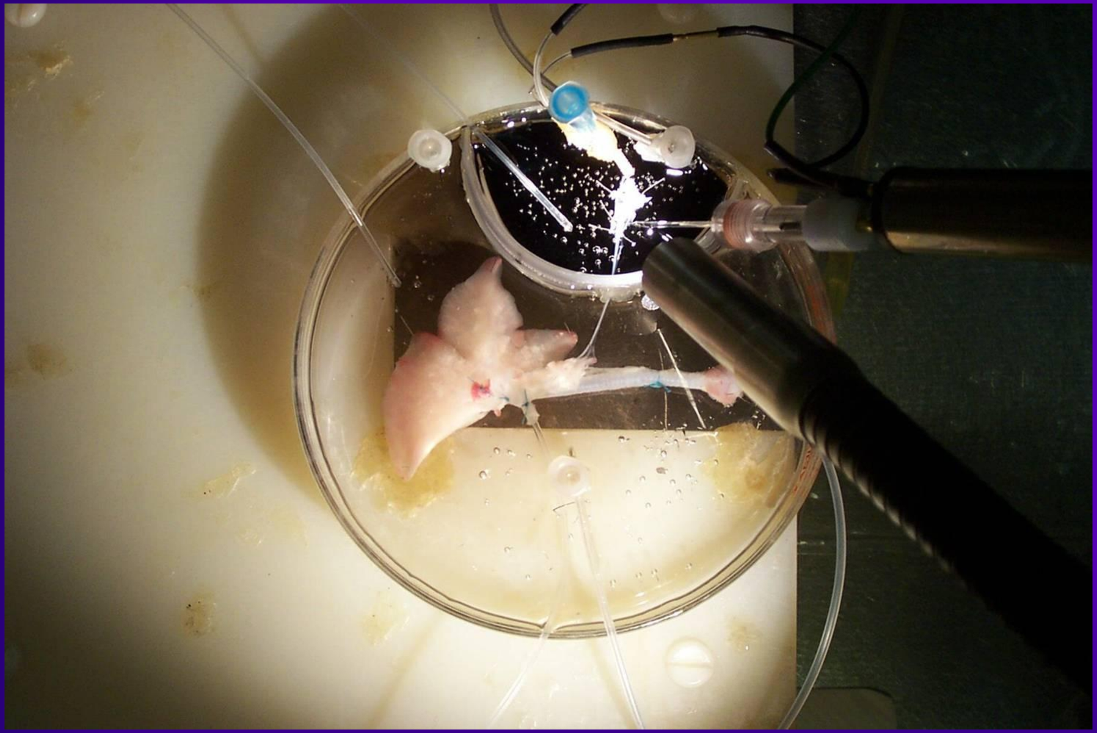
Coexpression of TRP channels in lung-labelled airway neurons

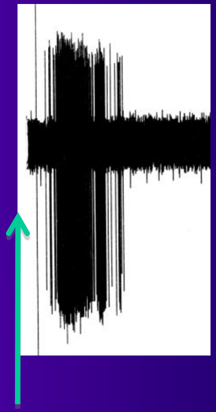




Nassenstein et al., J Physiol 2008

MUSTARD OIL ACTIVATES VAGAL C-FIBERS IN THE GUINEA PIG LUNGS

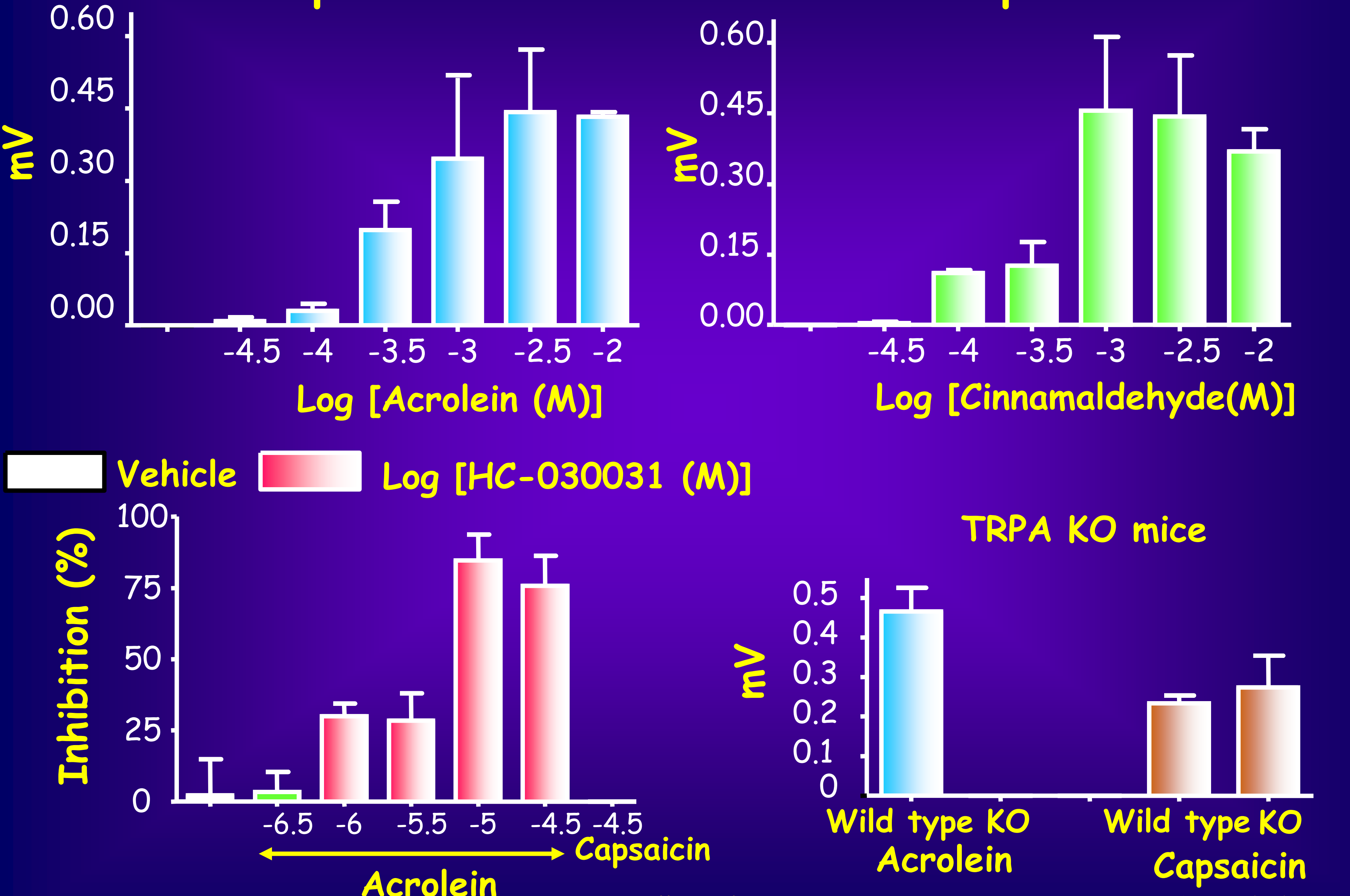




MUSTARD OIL
AITC 30 μM

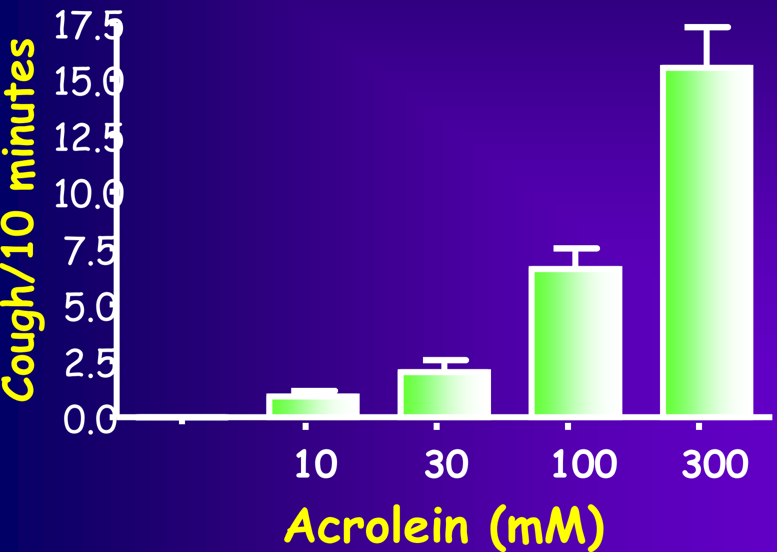
Nassenstein et al., J Physiol 2008

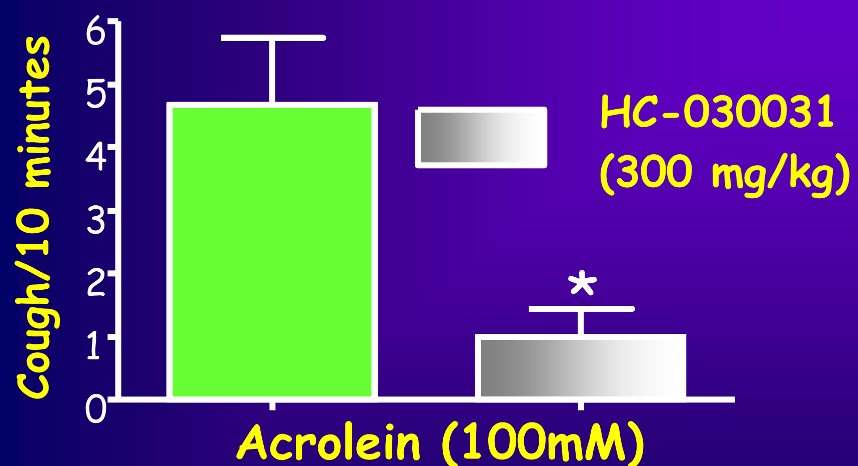
Effect of a TRPA-1 ligands or receptor KO on Depolarisation to acrolein and capsaicin

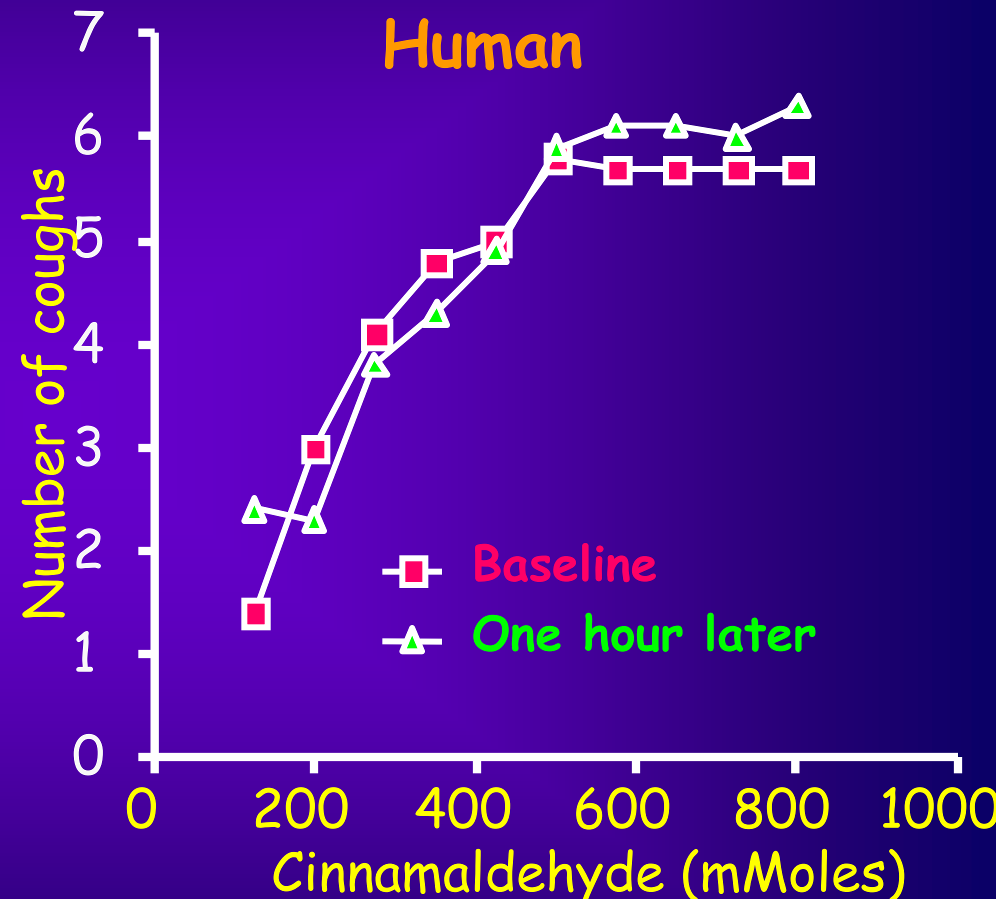


Birrell et al., 2009, Am J Respir Crit Care Med. 180(11):1042-7.

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

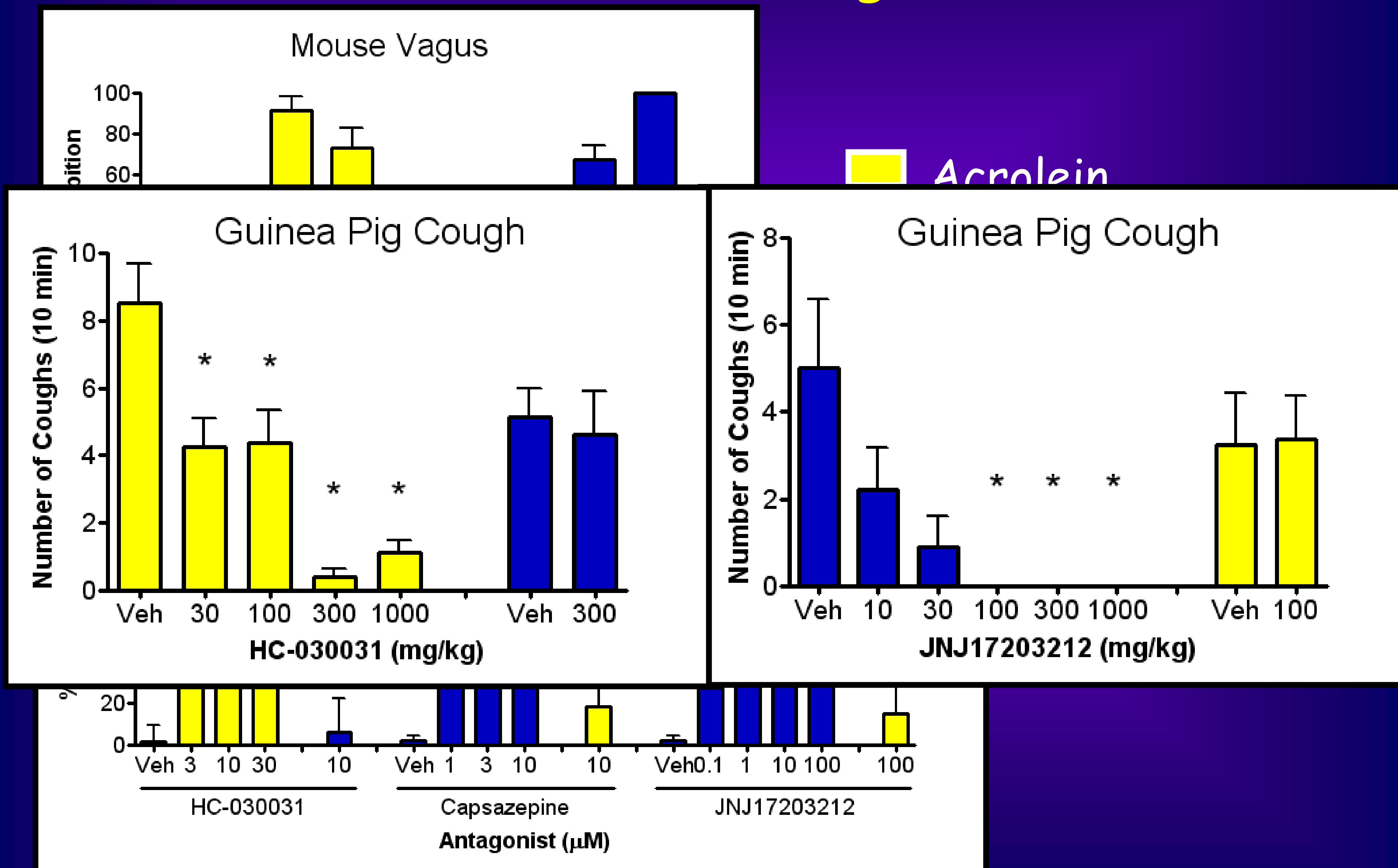




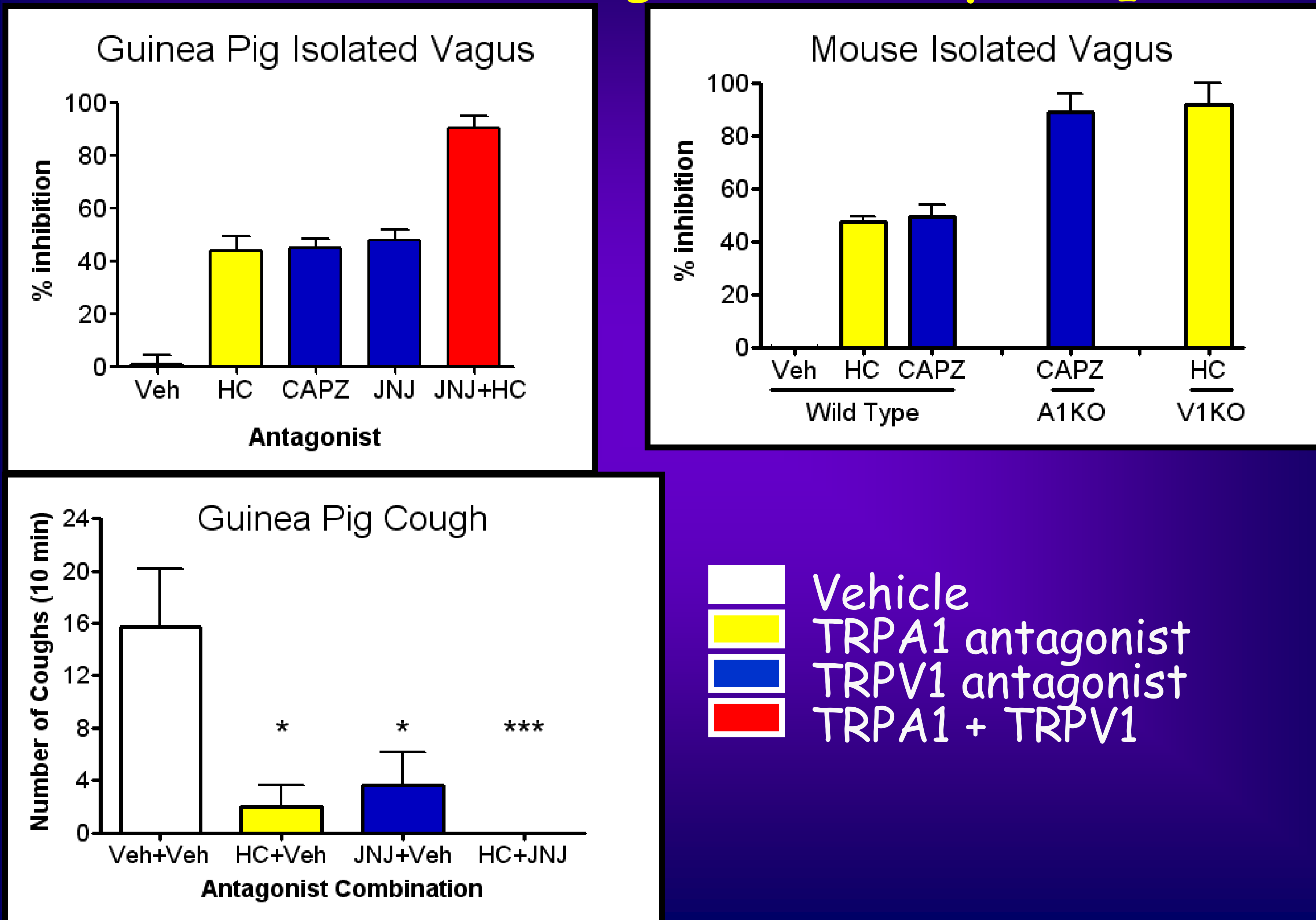


Birrell et al., 2009, Am J Respir Crit Care Med. 180(11):1042-7.
Andre et al., 2009, Br. J. Pharmacol, 158: 1621-1628.

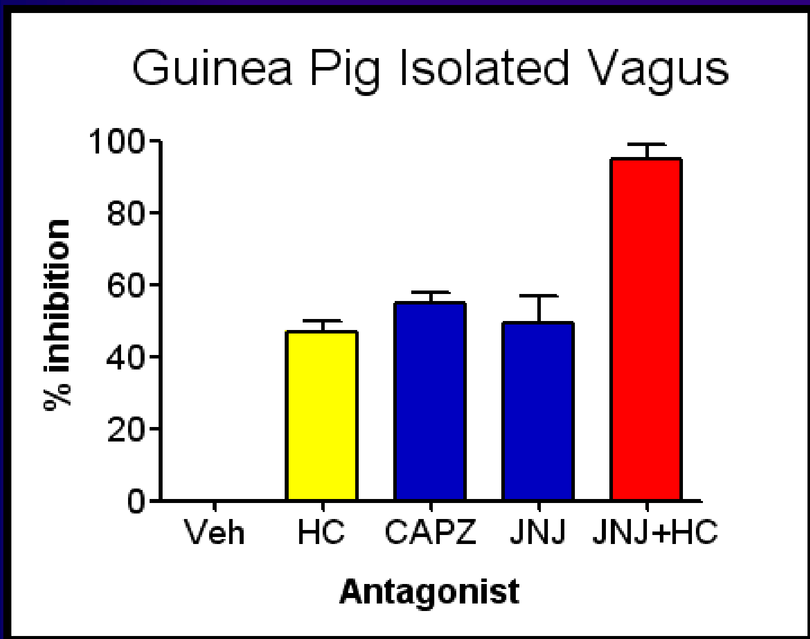
Effect of TRP antagonists on sensory nerve activation/cough

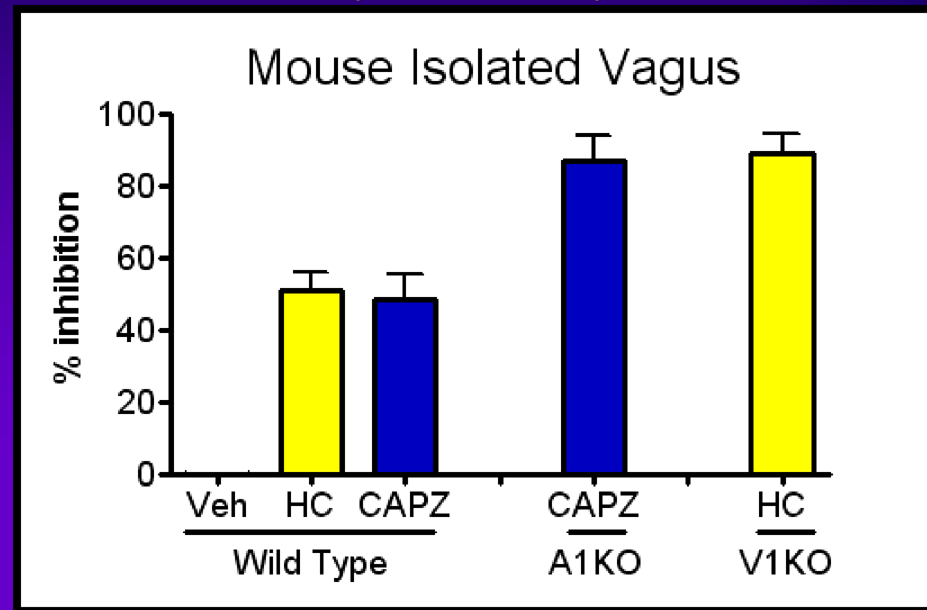


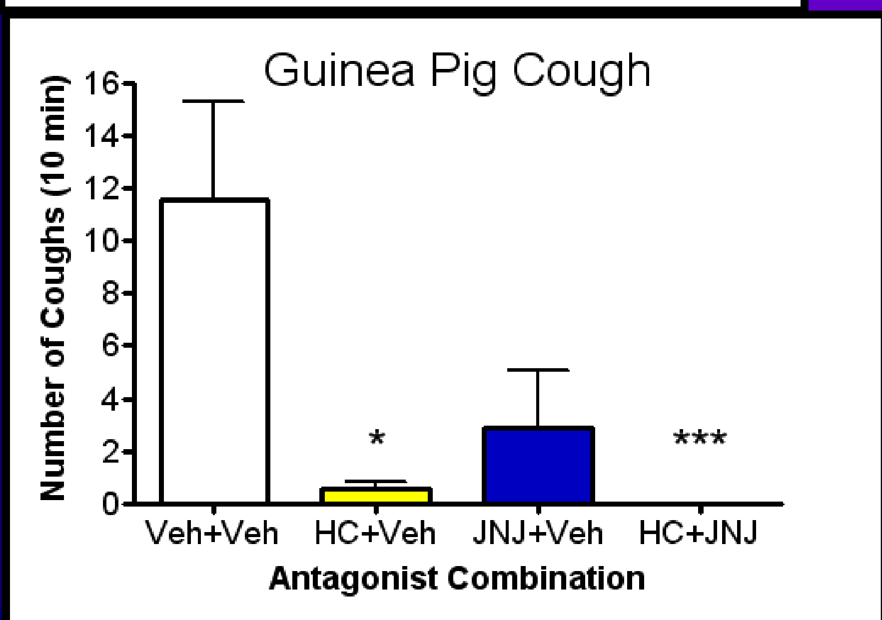
Effect of TRP antagonists on sensory nerve activation/cough elicited by PGE_2



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

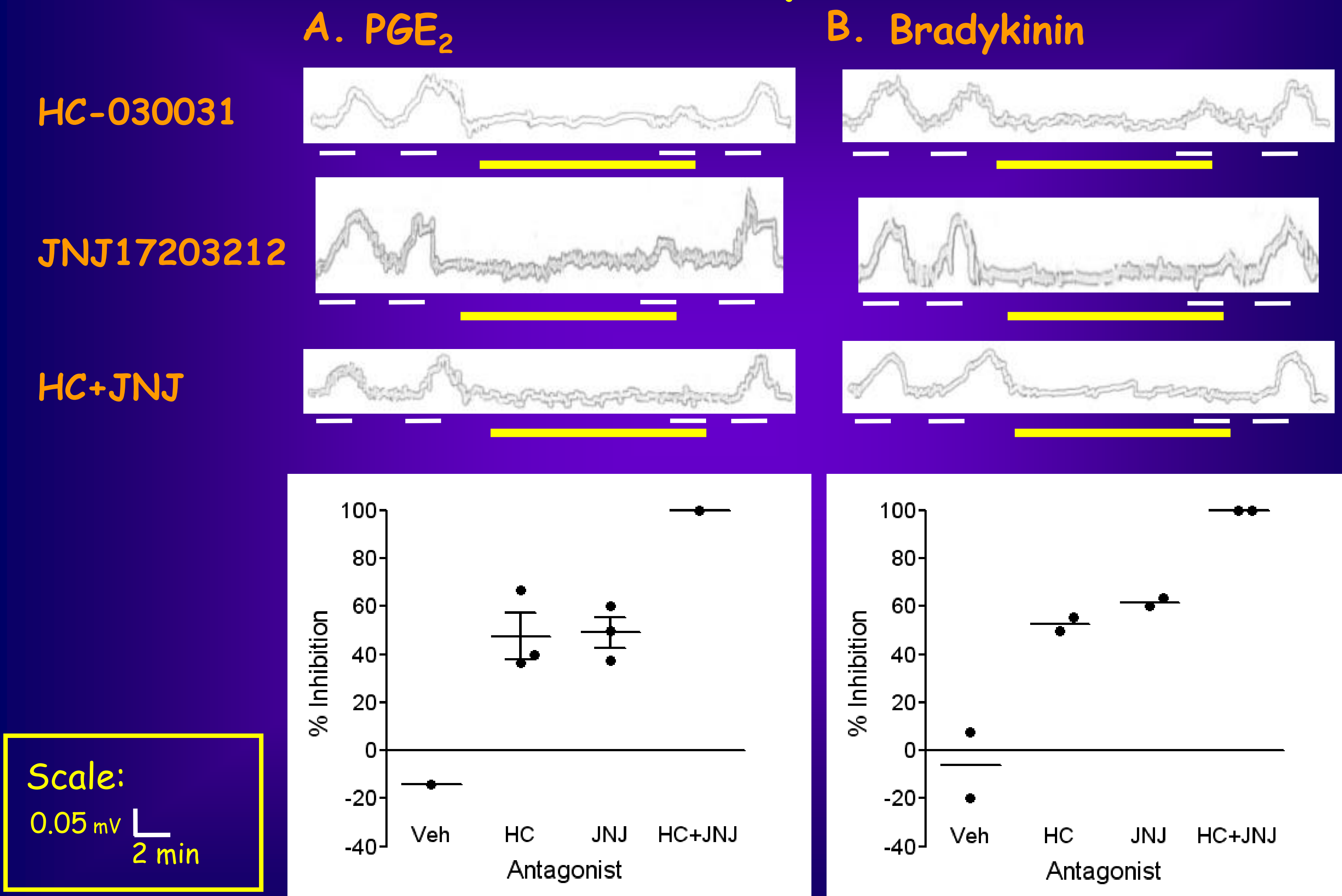




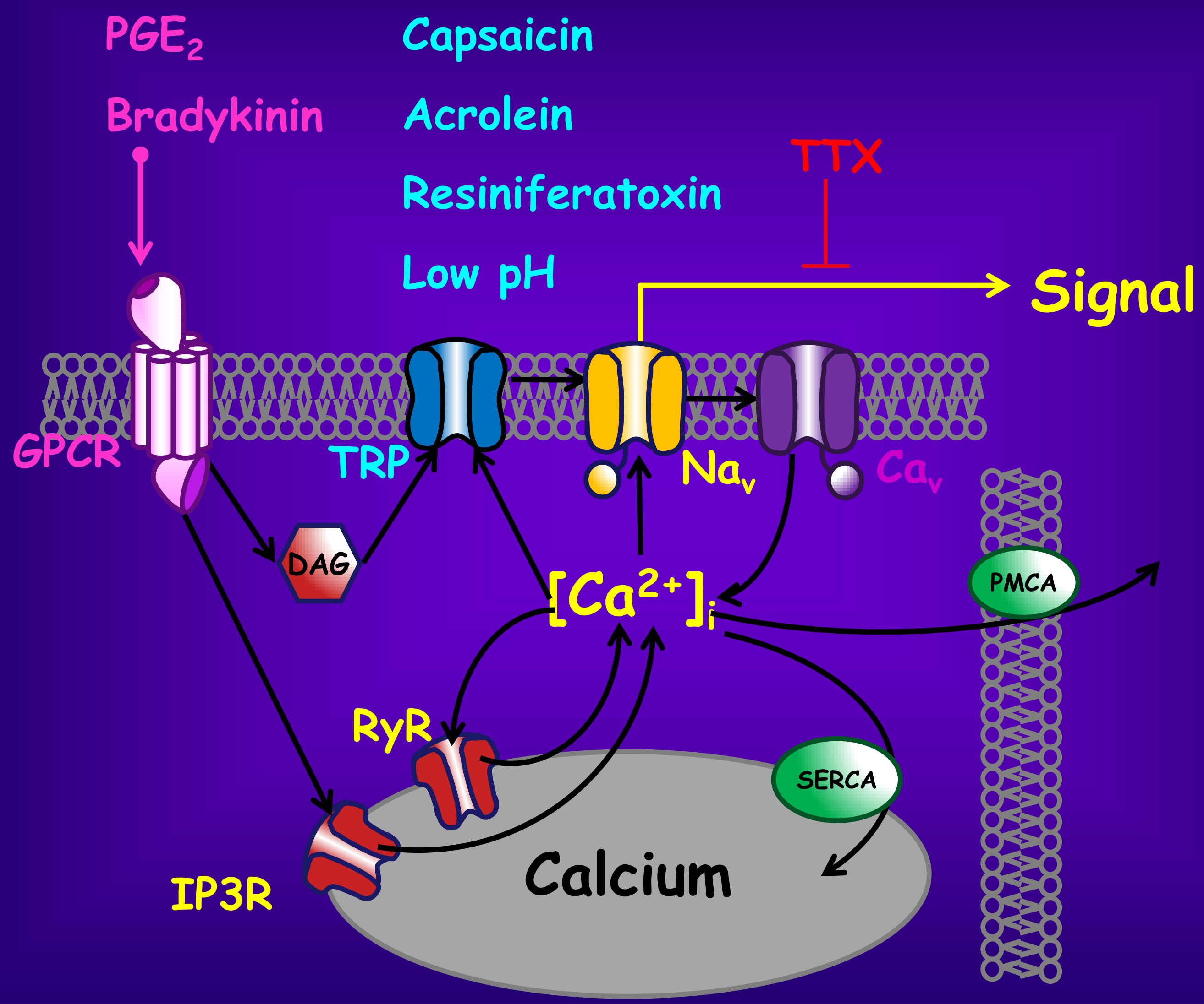


Vehicle
TRPA1 antagonist
TRPV1 antagonist
TRPA1 + TRPV1

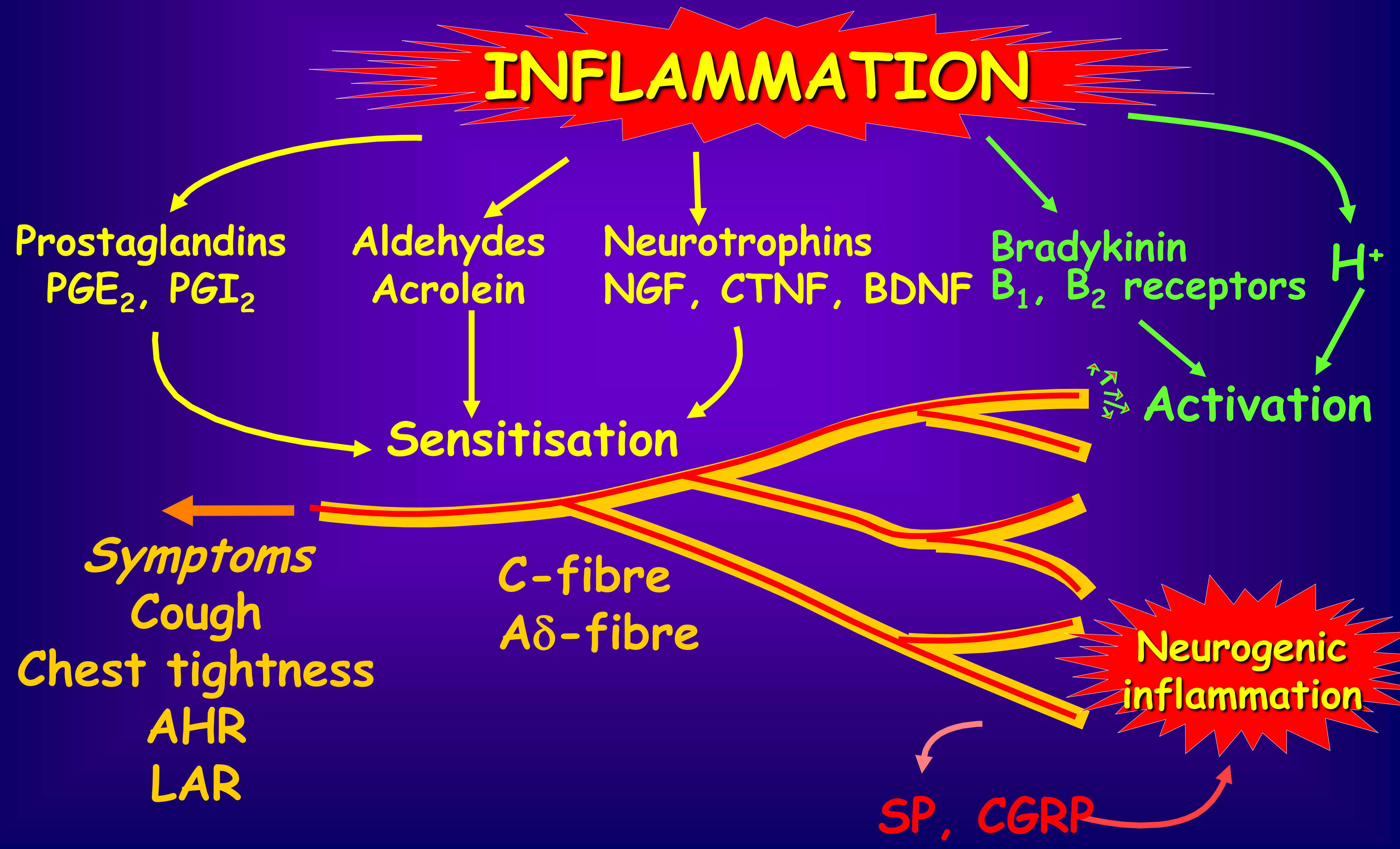
Effect of TRP antagonists on human sensory nerve activation elicited by PGE_2 and BK



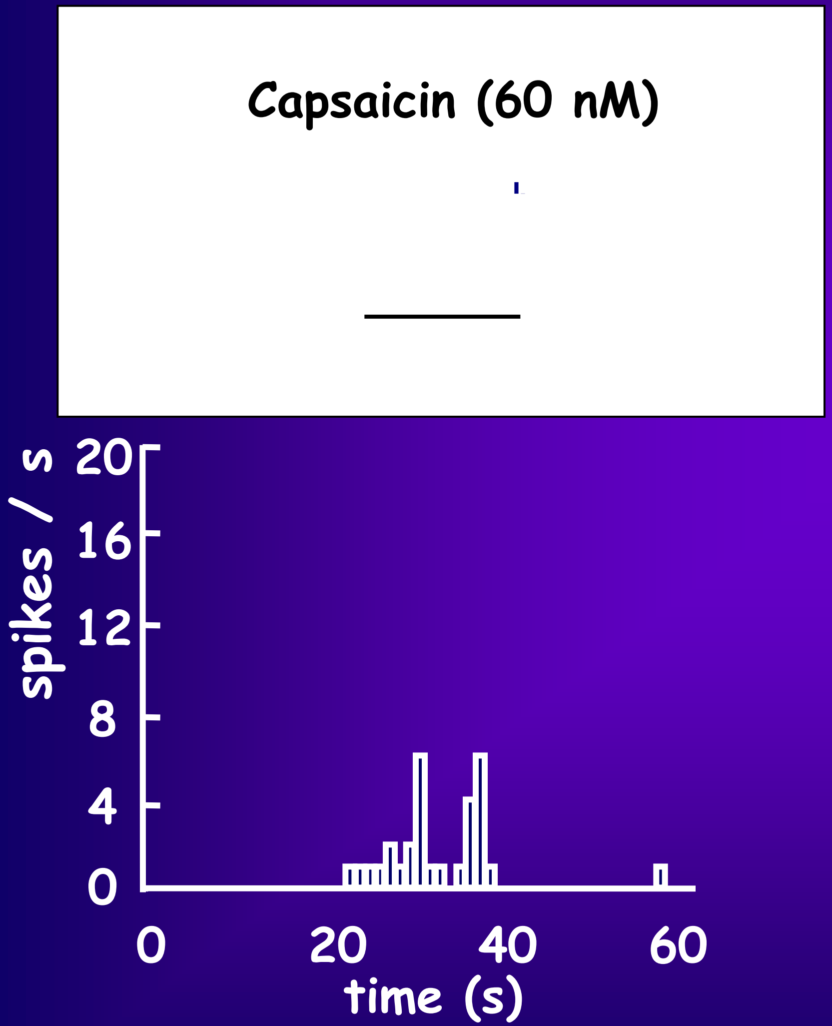
Tussive agents, sensory nerves and signalling pathways

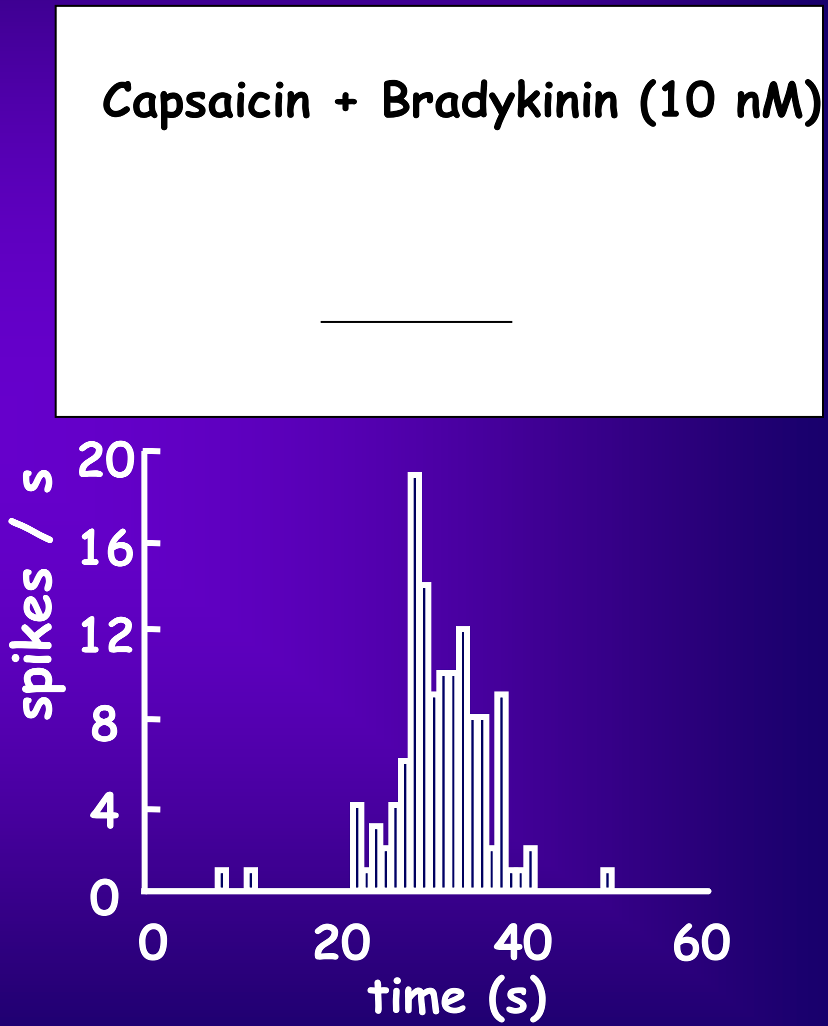


Sensitisation and activation of airway sensory nerves



C-fibre Sensitisation by Bradykinin

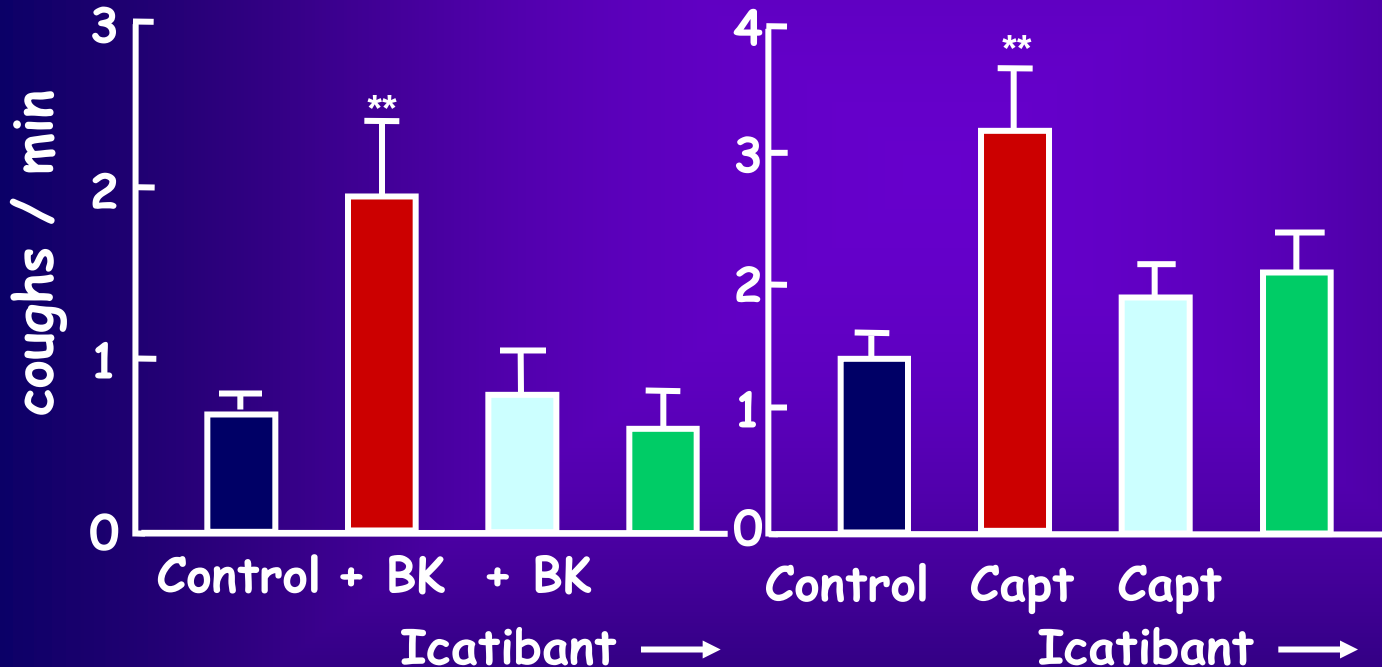


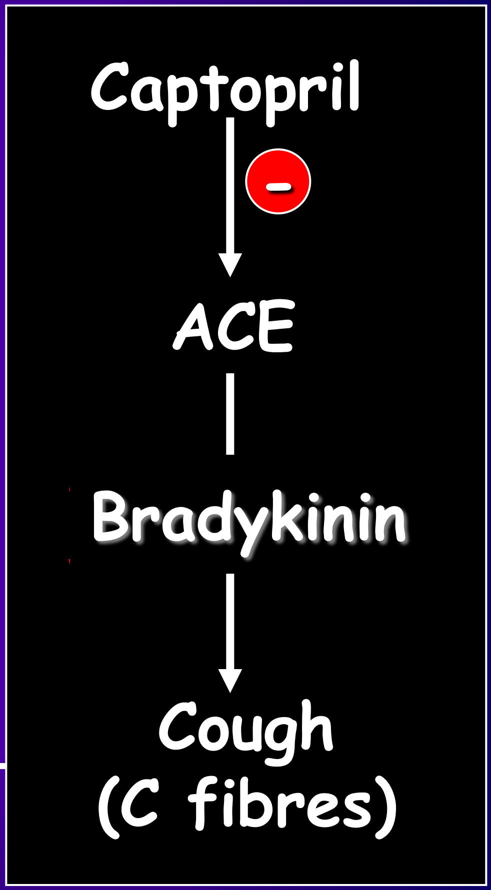


Fox et al 1996. Nature Med. 2, 814-8

Bradykinin Sensitises the Cough Reflex

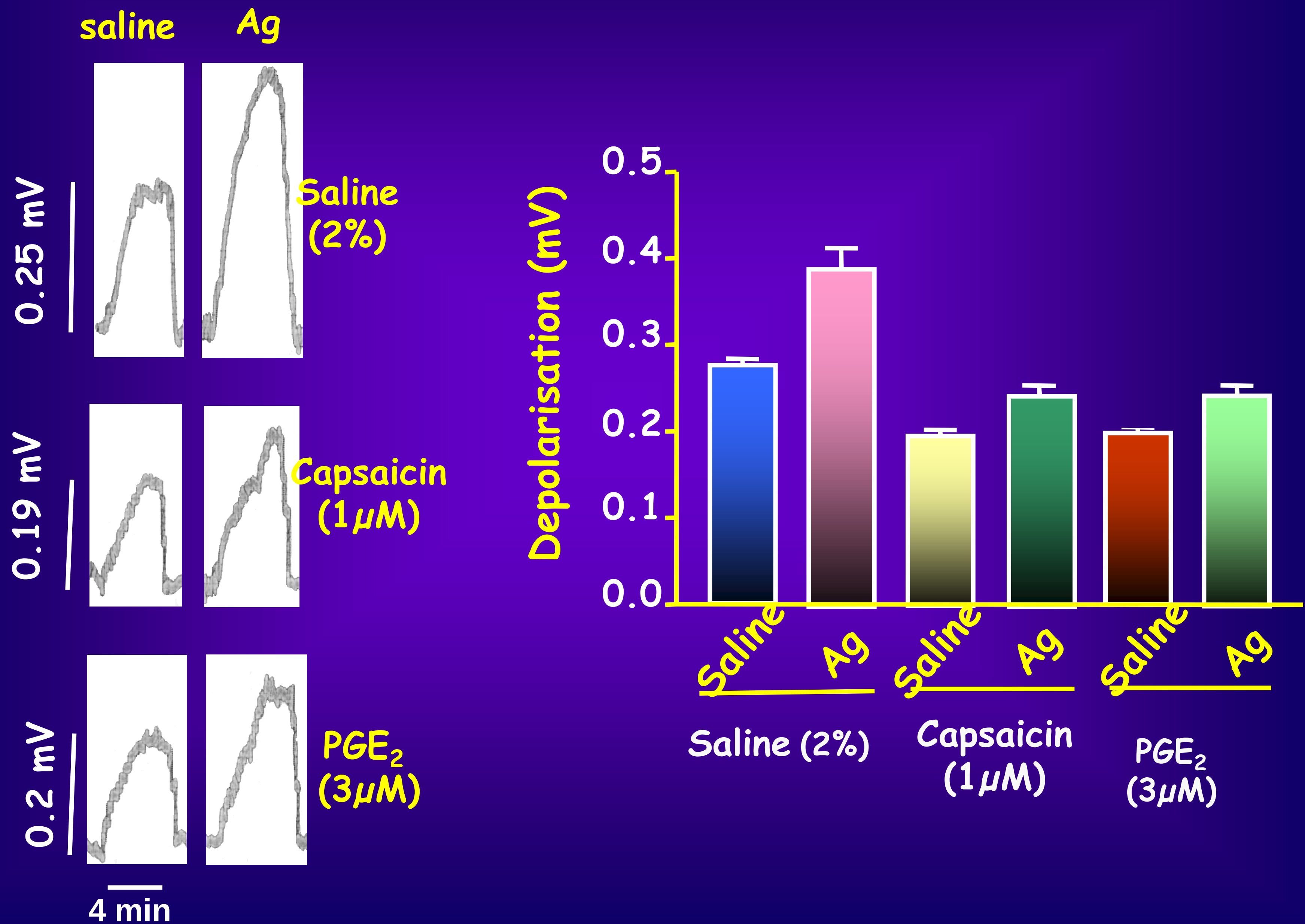
Guinea-pigs challenged with citric acid (0.25 M, 10 min)



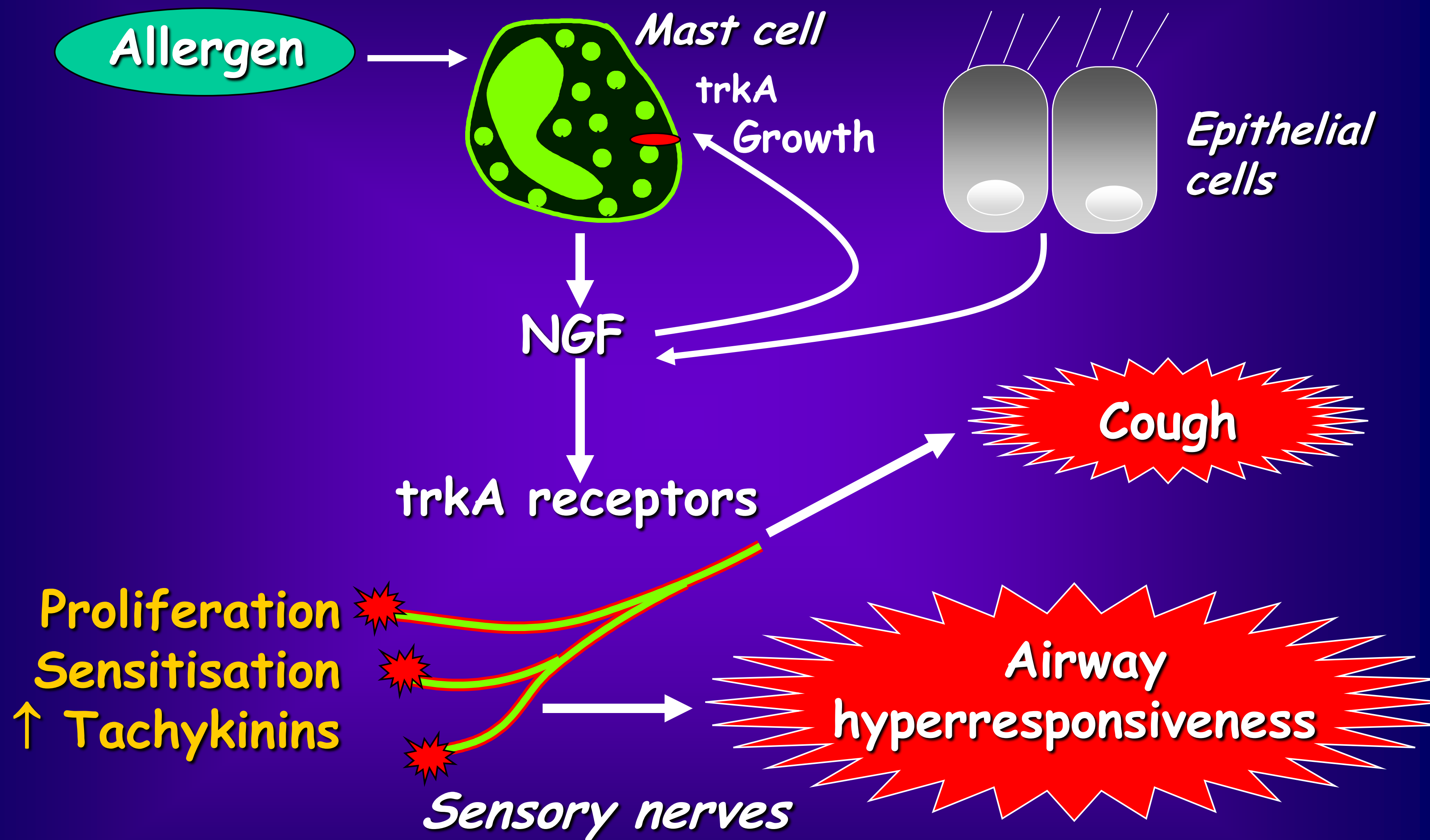


Fox et al 1996. Nature Med. 2, 814-8

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



MAST CELLS AND NERVE GROWTH FACTOR

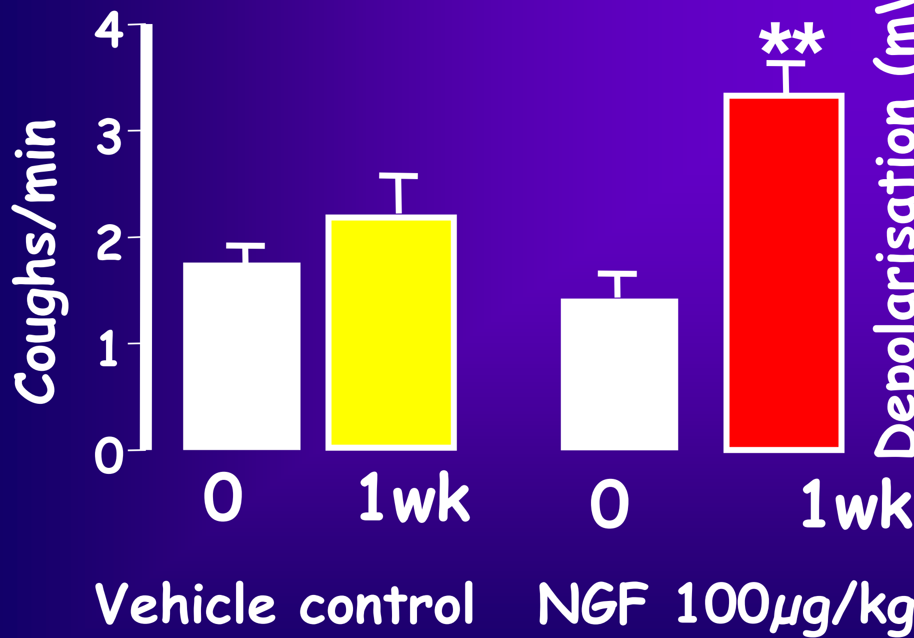


EFFECT OF NGF ON COUGH

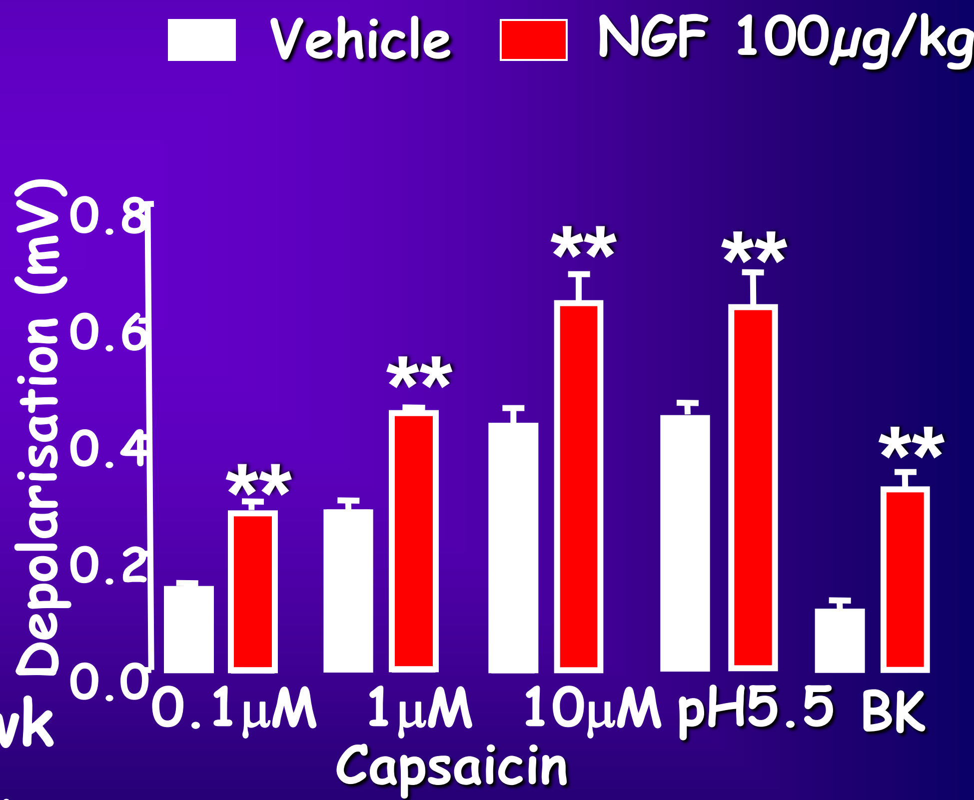
Conscious guinea pigs (n=6)

Citric acid-induced cough

(citric acid 0.35M x 10 min)



Guinea pig vagus nerve in vitro

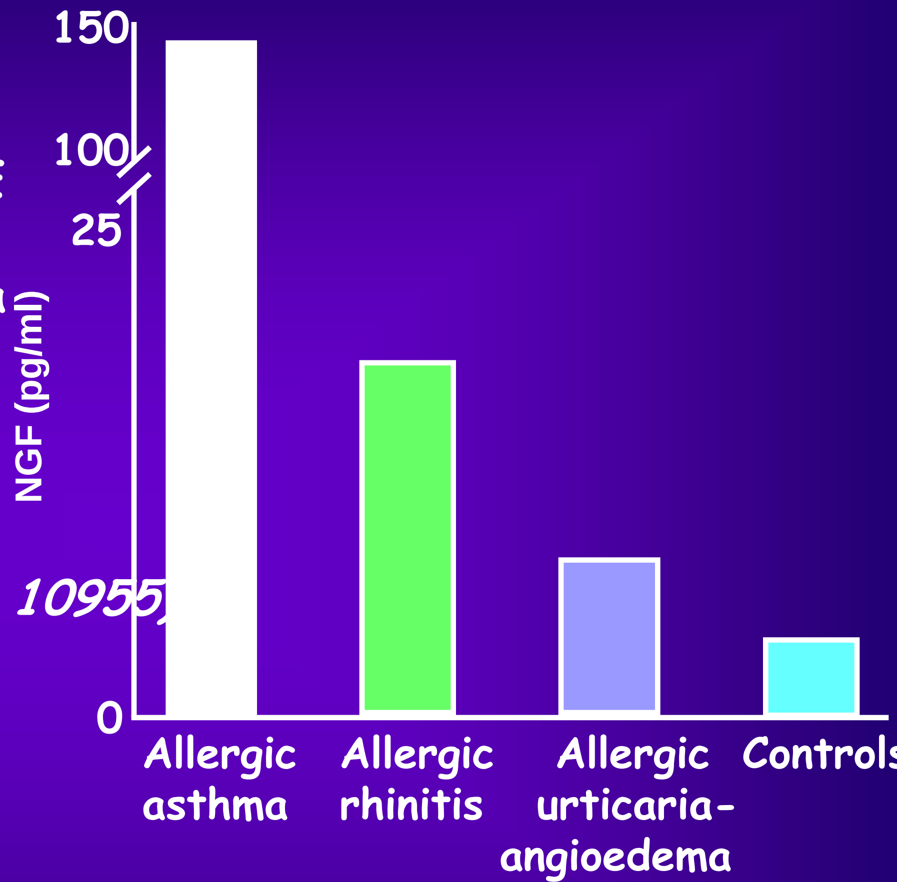


Neurotrophins, humans, allergy and asthma

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)

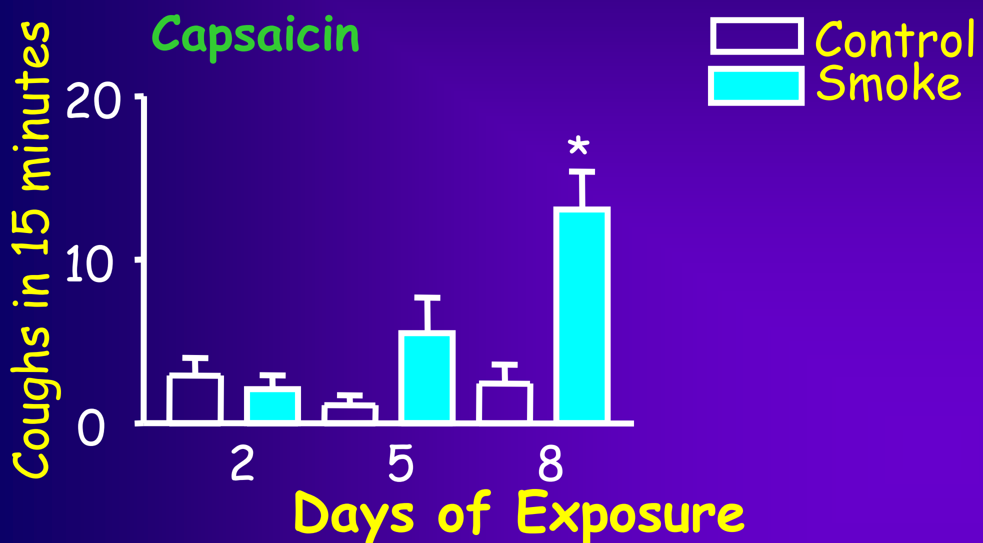


Segmental allergen challenge —18h→ BALF ↑: NGF, BDNF and NT-3

(Christian et al 1998 Am J Respir Crit Care Med 158, 2002)

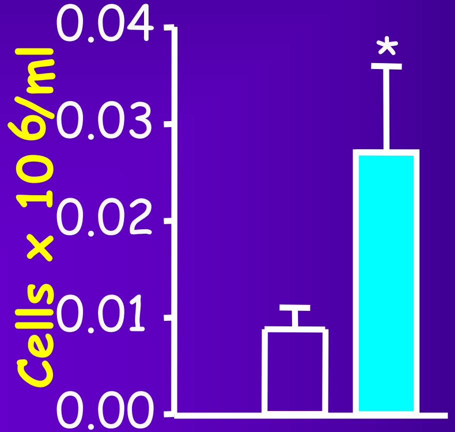
Models of enhanced cough

In Vivo Cough

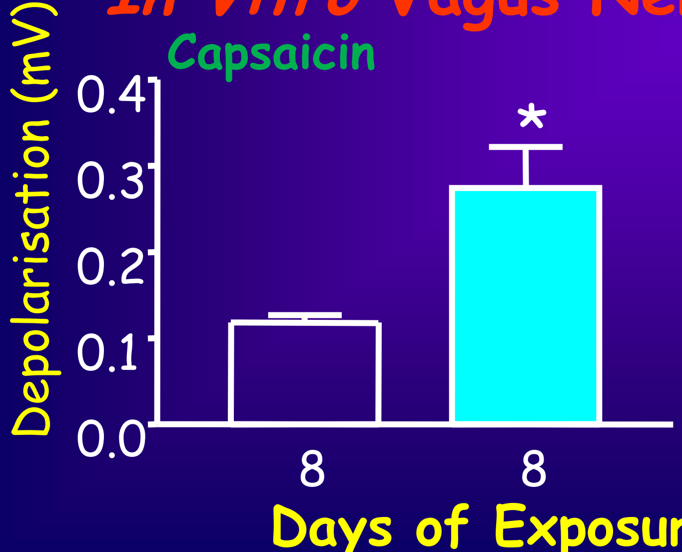


Inflammation

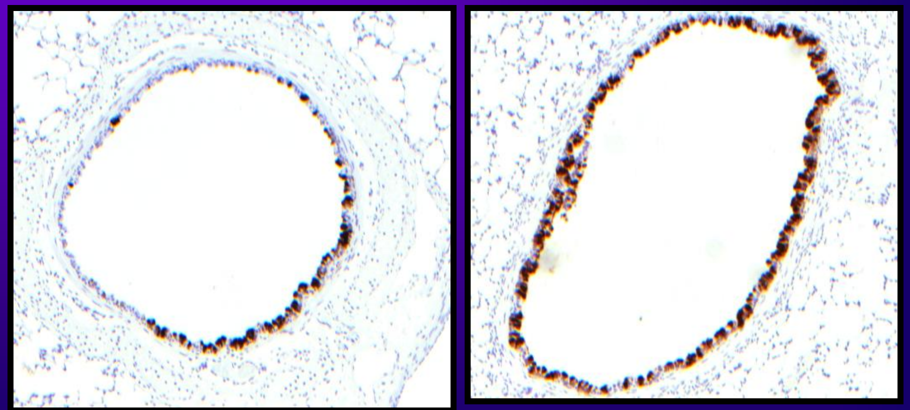
Neutrophils at Eight Days



In Vitro Vagus Nerve

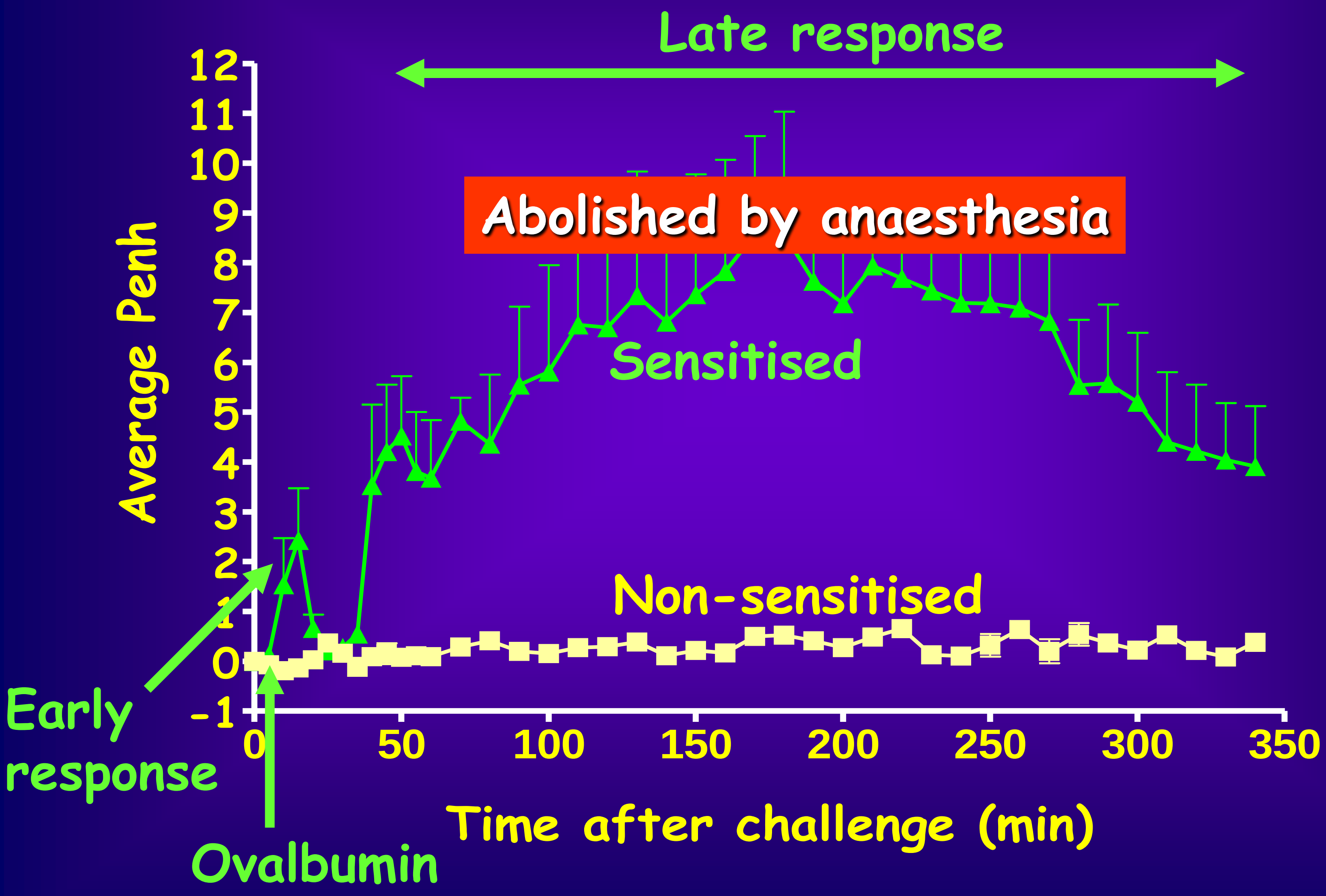


Mucus



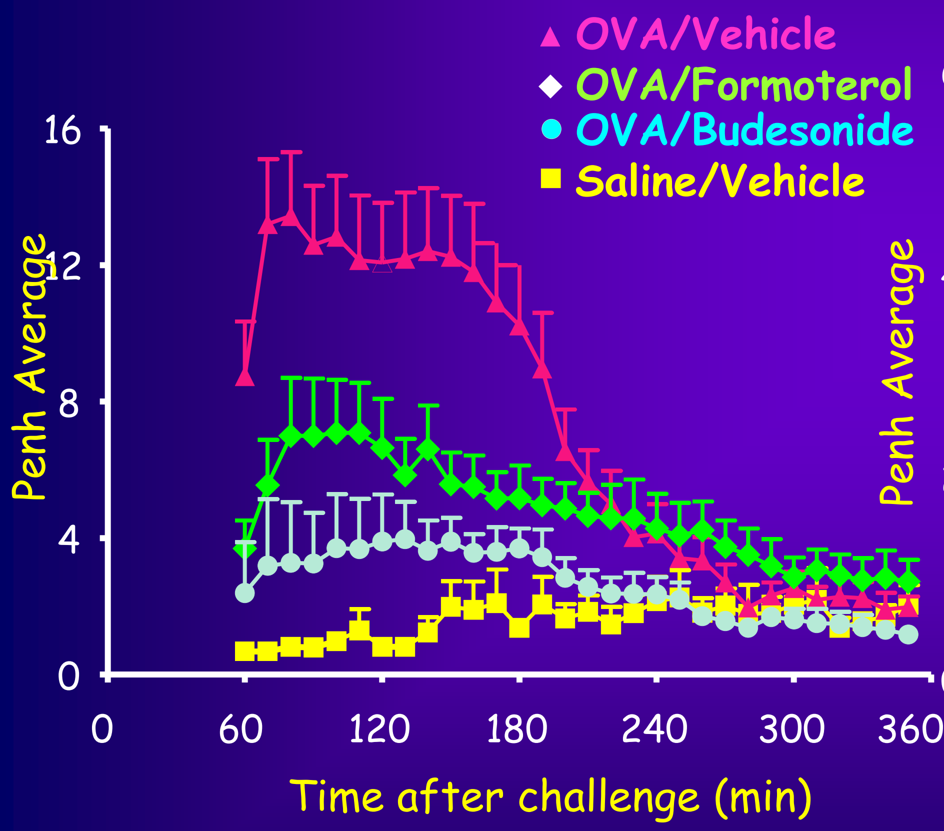
Control (8 days) Smoke (8 days)

OVA inhalation induces EAR and LAR in sensitised Brown Norway rat

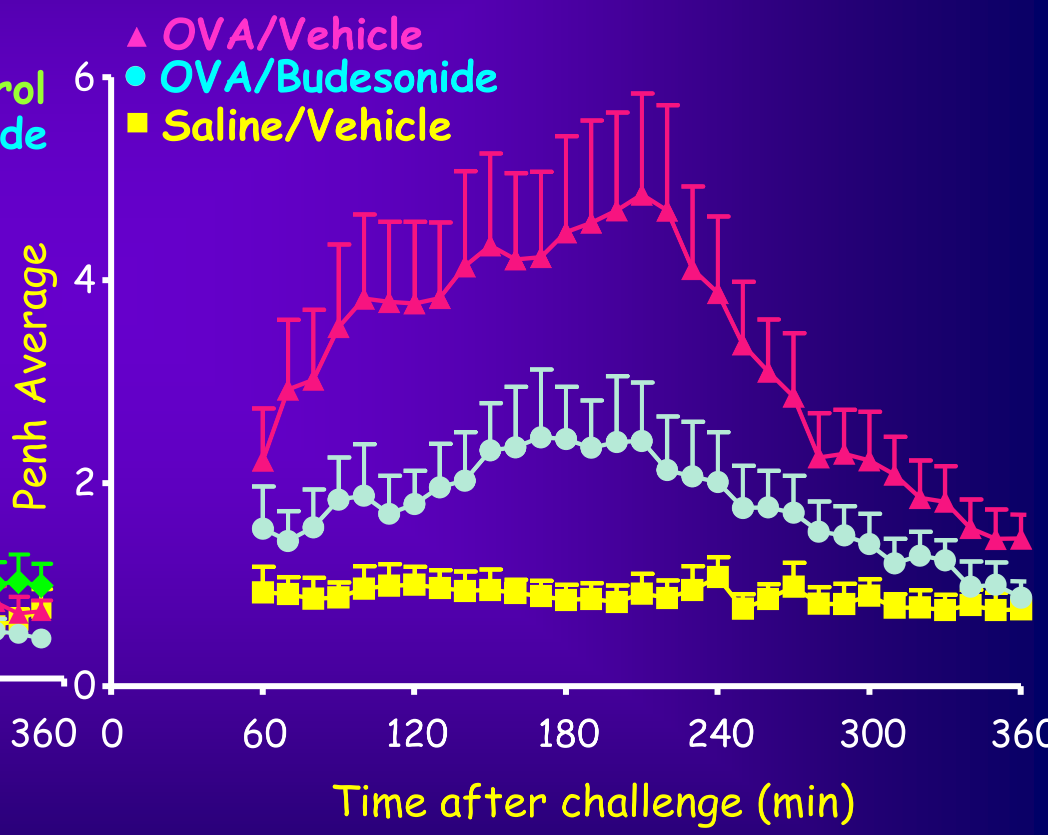


OVA inhalation induces LAR in sensitised rodents: Effect clinically relevant compounds

Brown Norway Rat



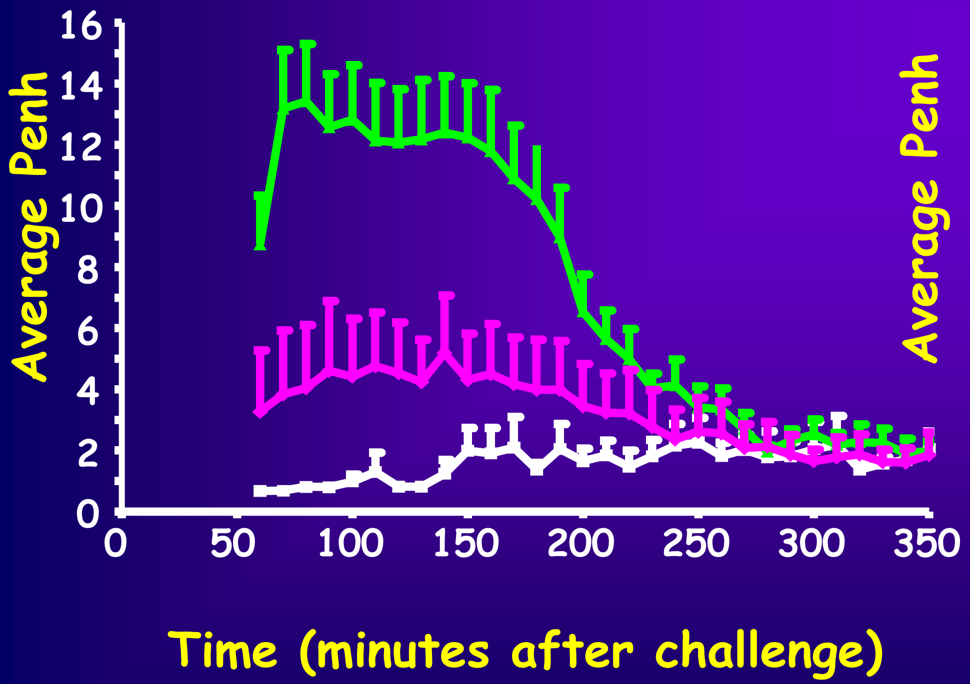
C57 BL/6J mice



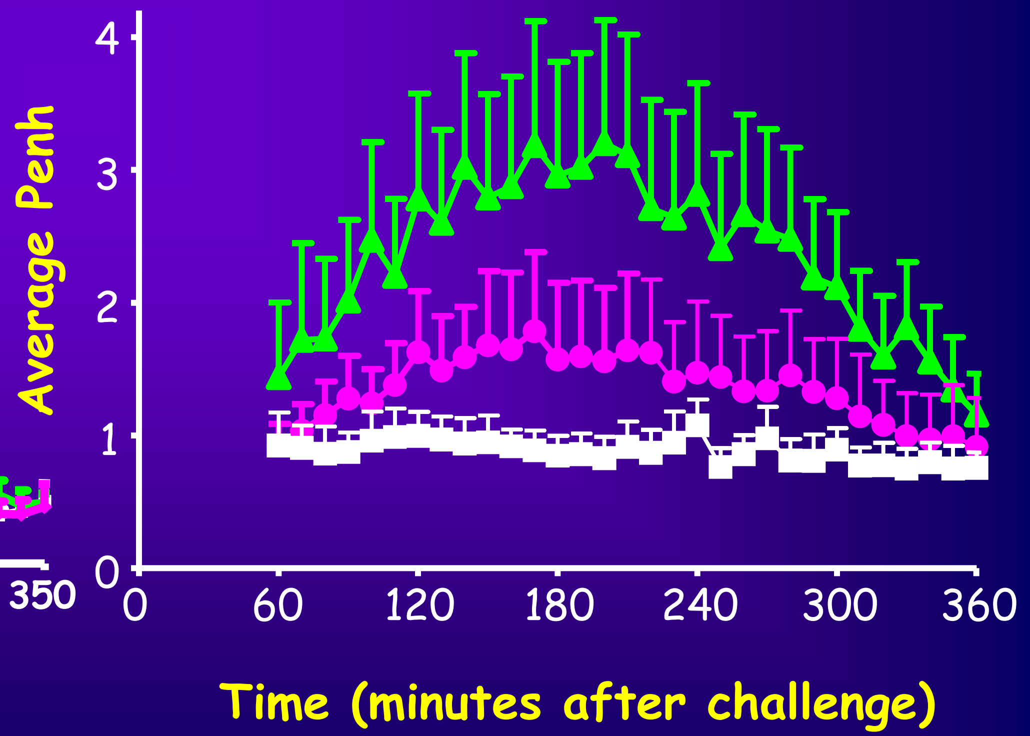
LAR is attenuated by a non-specific sensory nerve blocker (ruthenium red)

Brown Norway Rat

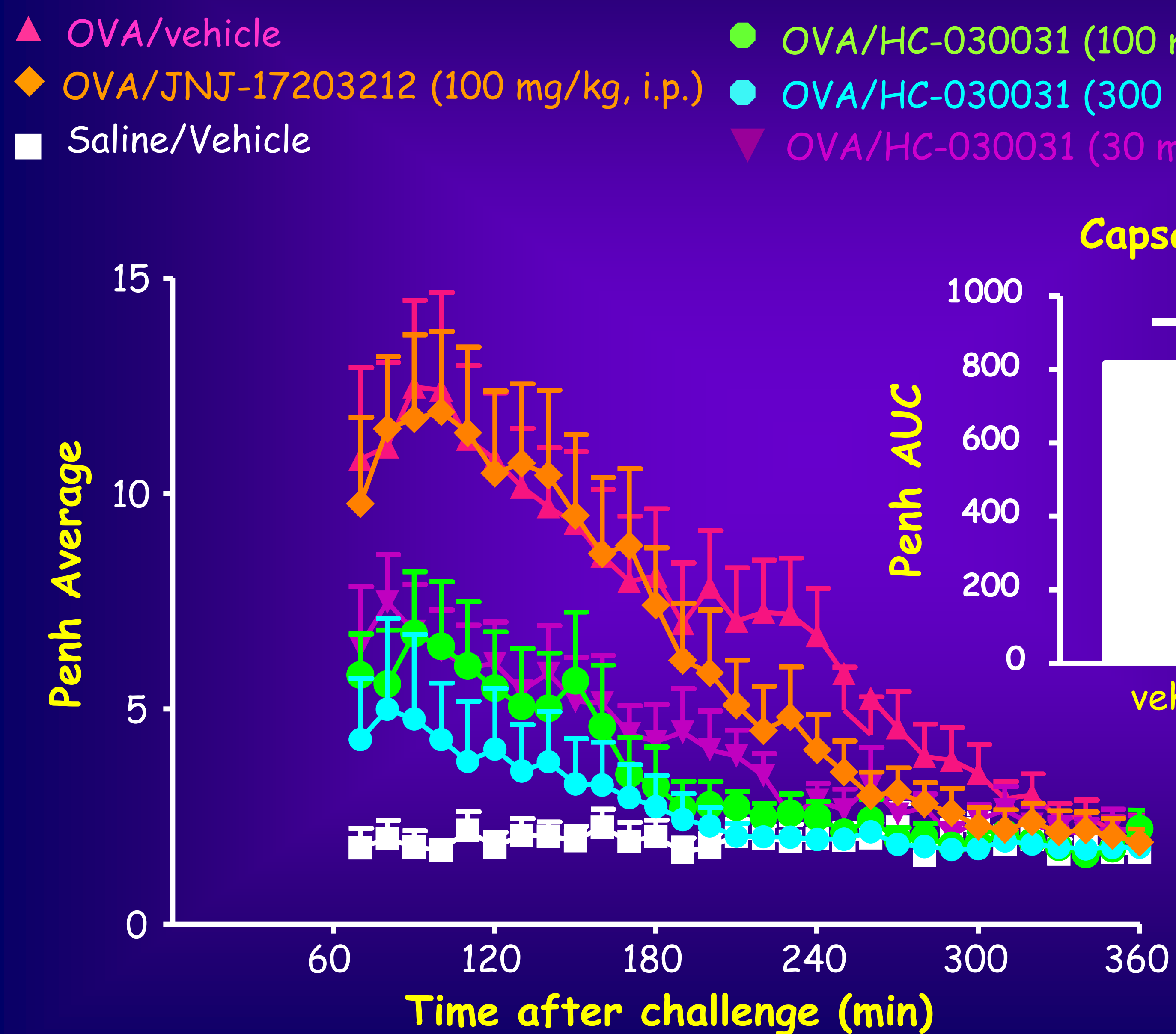
- OVA/Vehicle
- OVA/Ruthenium red (2 mg/kg, i.p.)
- Saline/Vehicle

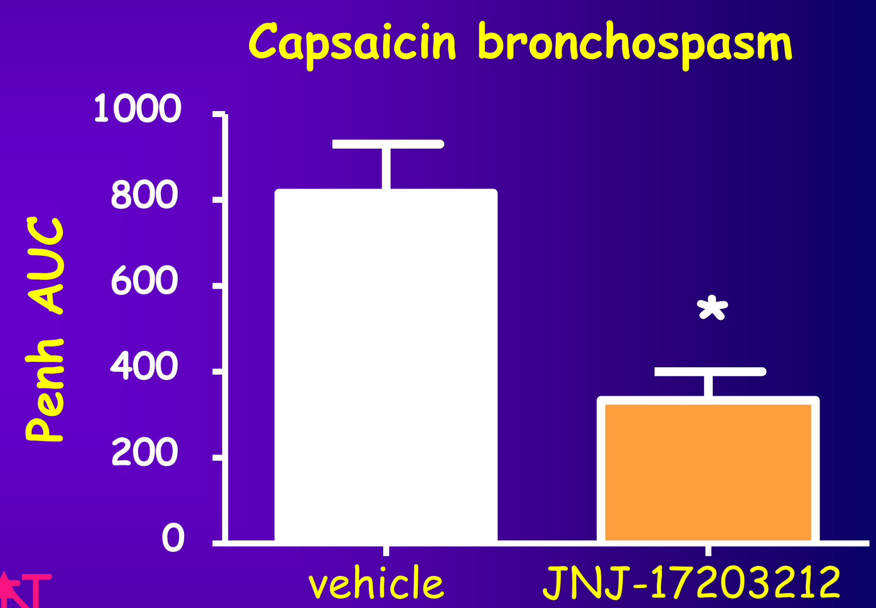


C57 BL/6J mice

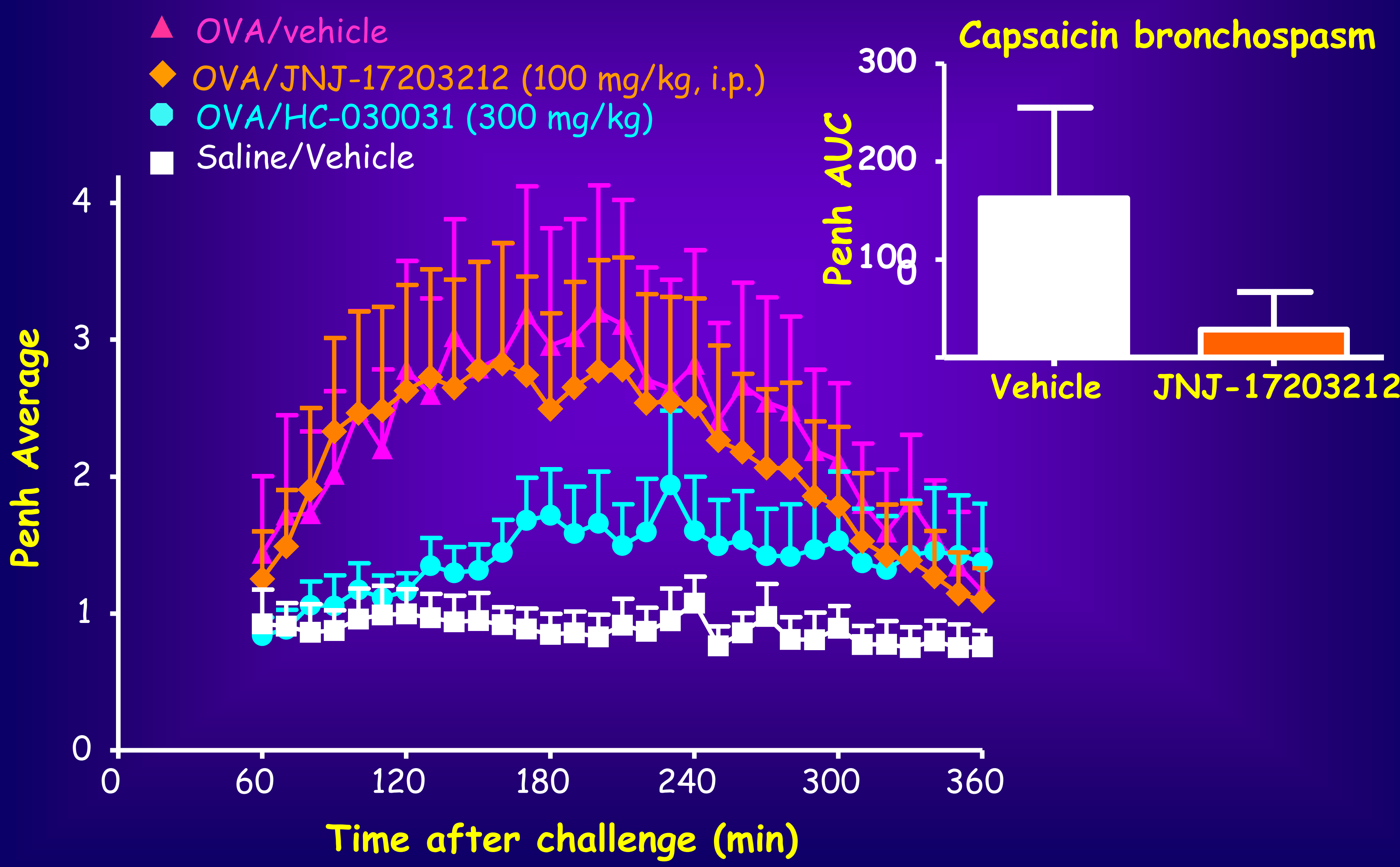


LAR is attenuated by TRPA1 inhibitor (HC-030031) but not TRPV1 inhibitor (JNJ-17203212) in the BN rat

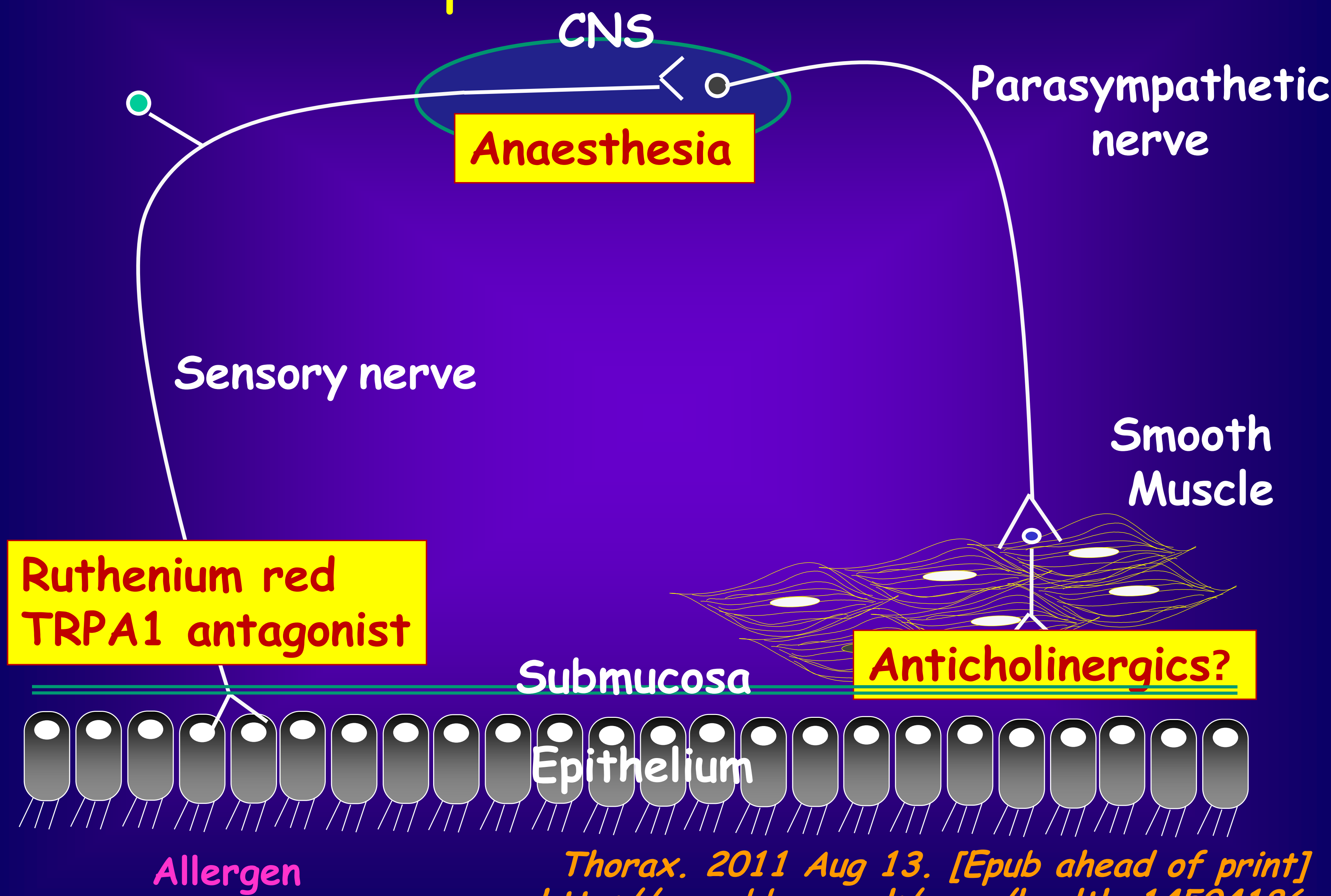




LAR is attenuated by TRPA1 inhibitor (HC-030031) but not TRPV1 inhibitor (JNJ-17203212) in C57 BL/6J mice

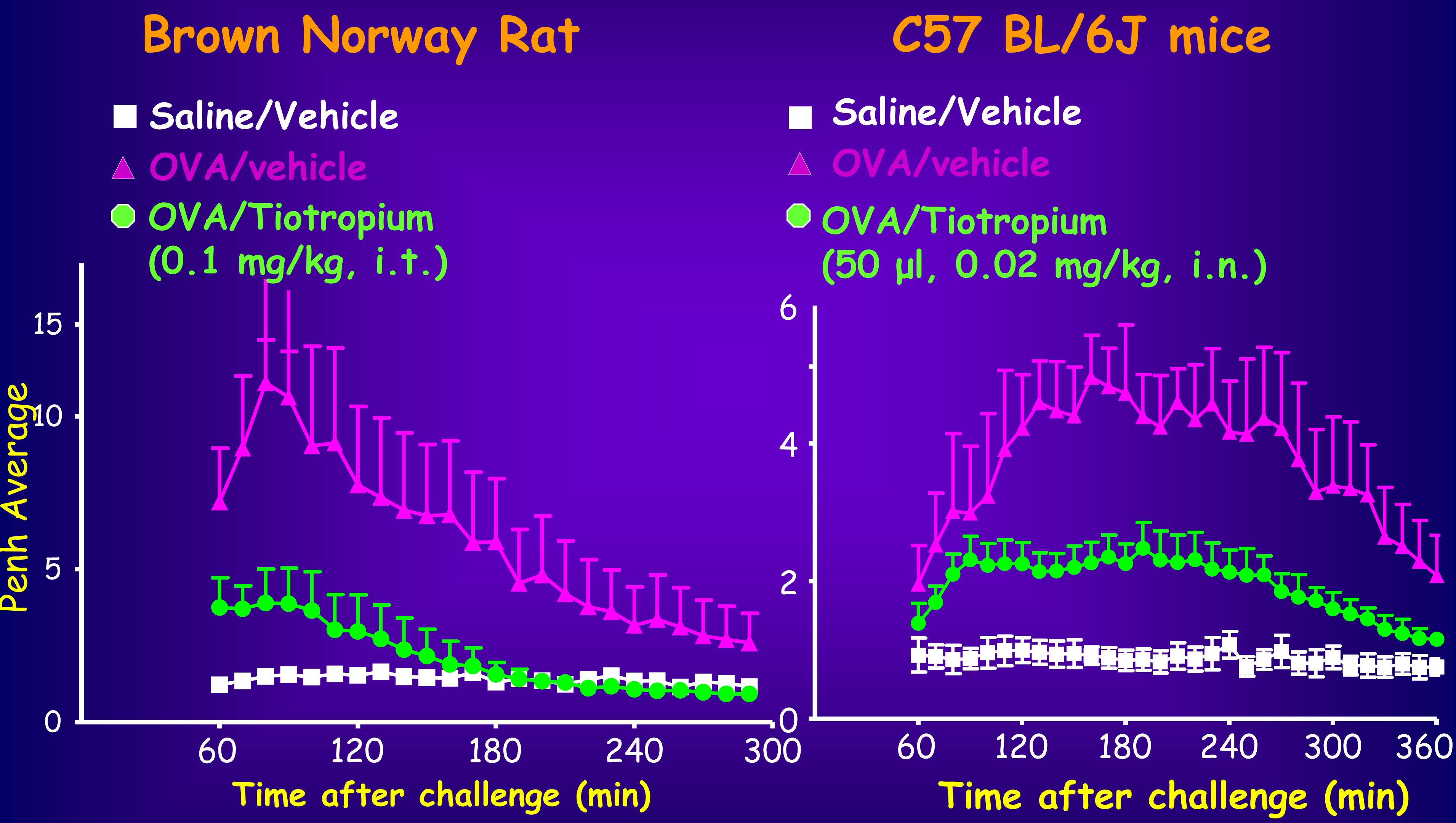


Proposed mechanism

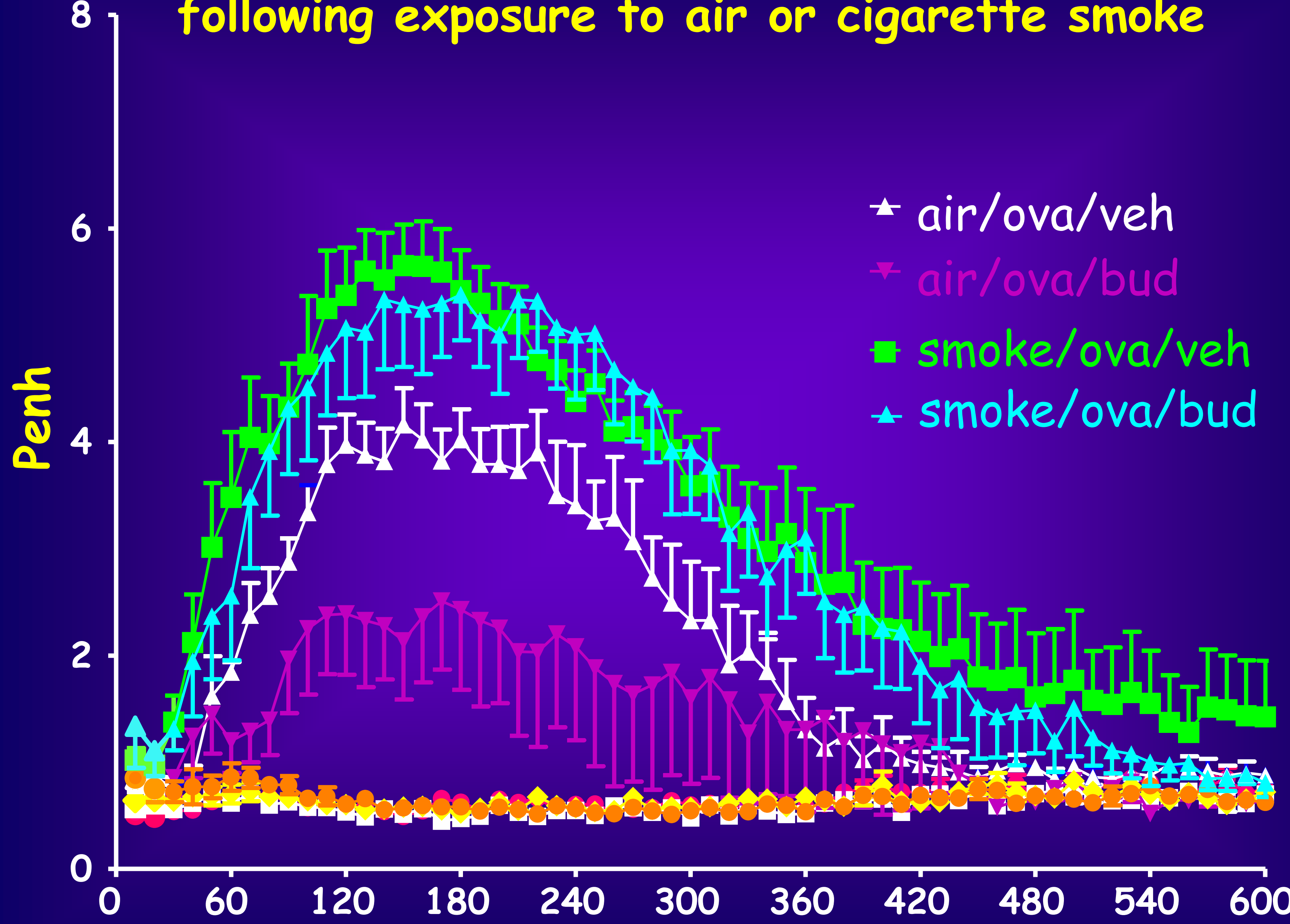


Thorax. 2011 Aug 13. [Epub ahead of print]
http://www.bbc.co.uk/news/health-14504186

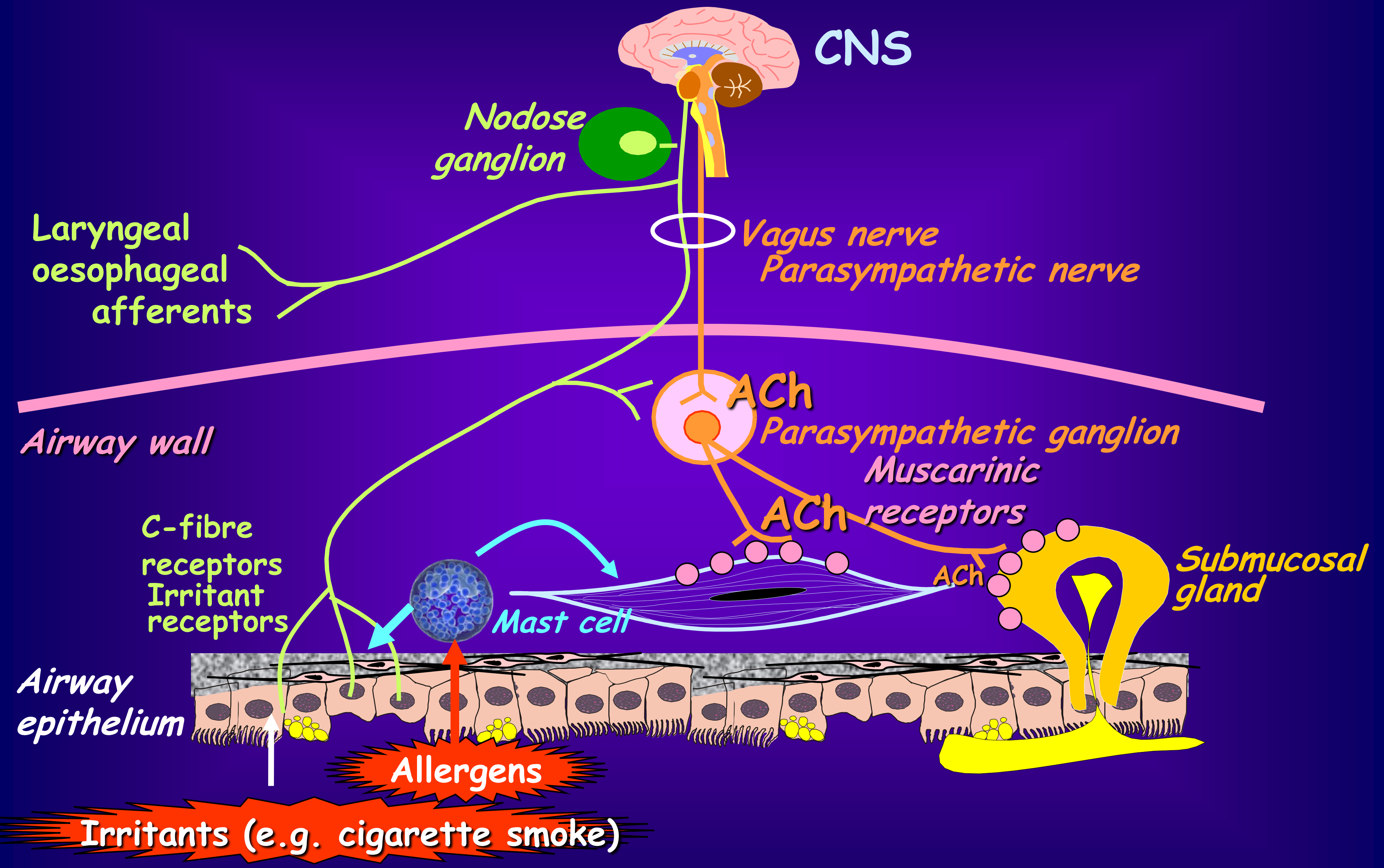
LAR is attenuated by tiotropium bromide in Brown Norway rats and C57 BL/6J mice



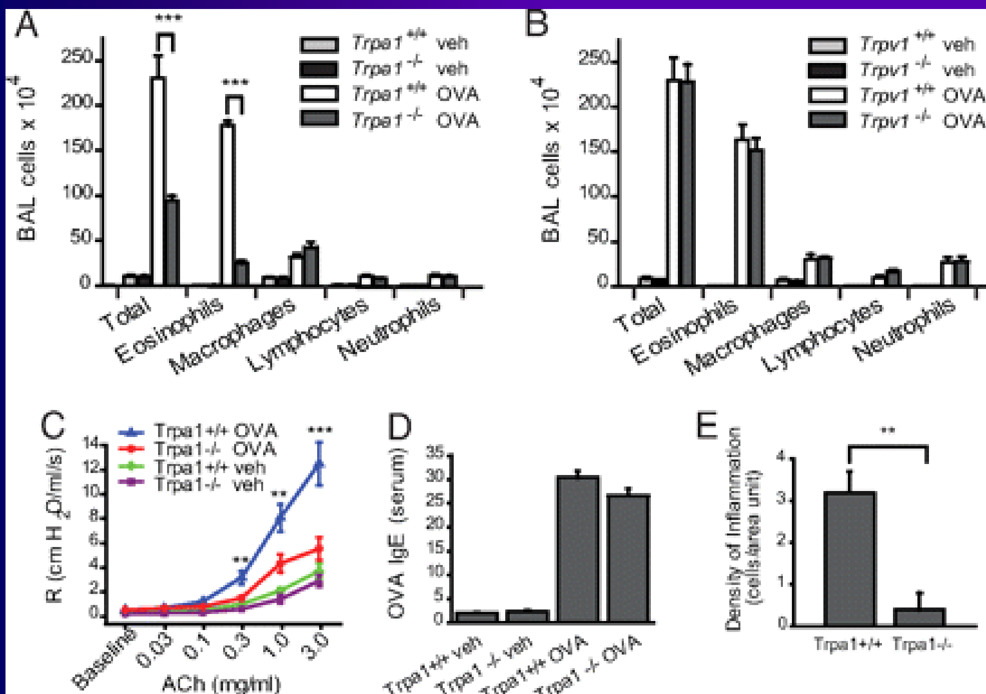
Effect of budesonide on LAR in mice following exposure to air or cigarette smoke

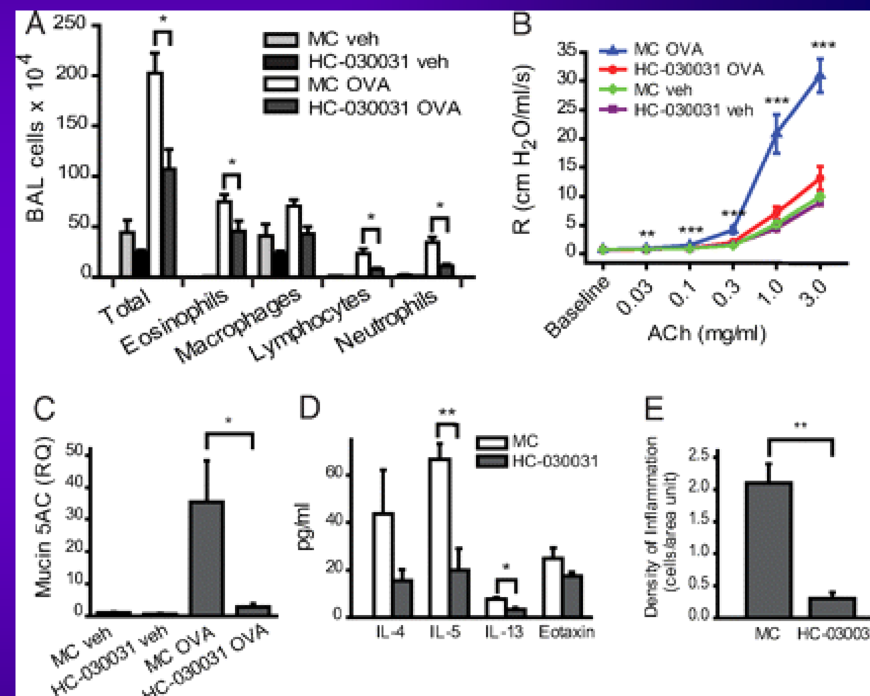


CHOLINERGIC CONTROL OF AIRWAYS



TRPA1 and inflammation





Caceres et al., 2009, PNAS 106: 9099-9104