

# TONSSE CRONICA:

## Aspetti di neurofisiopatologia

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# **DEFINIZIONE TOSSE SECCA**

**TOSSE ACUTA:** durata < 3 settimane in genere per infezioni alte vie aeree.

**TOSSE SUBACUTA:** durata > 3 e < 8 settimane

**TOSSE CRONICA:** durata > 8 settimane.

ERJ 2007; 29: 1256 e 2019; DOI:[10.1183/13993003.0136-2019](https://doi.org/10.1183/13993003.0136-2019)

Med J Aust 2010; 192: 265

CHEST 2006; 129: 1S e successivo aggiornamento  
<https://doi.org/10.1016/j.chest.2017.10.016>)

Chin Med J 2011; 124: 3207

# TONSILLE CRONICA

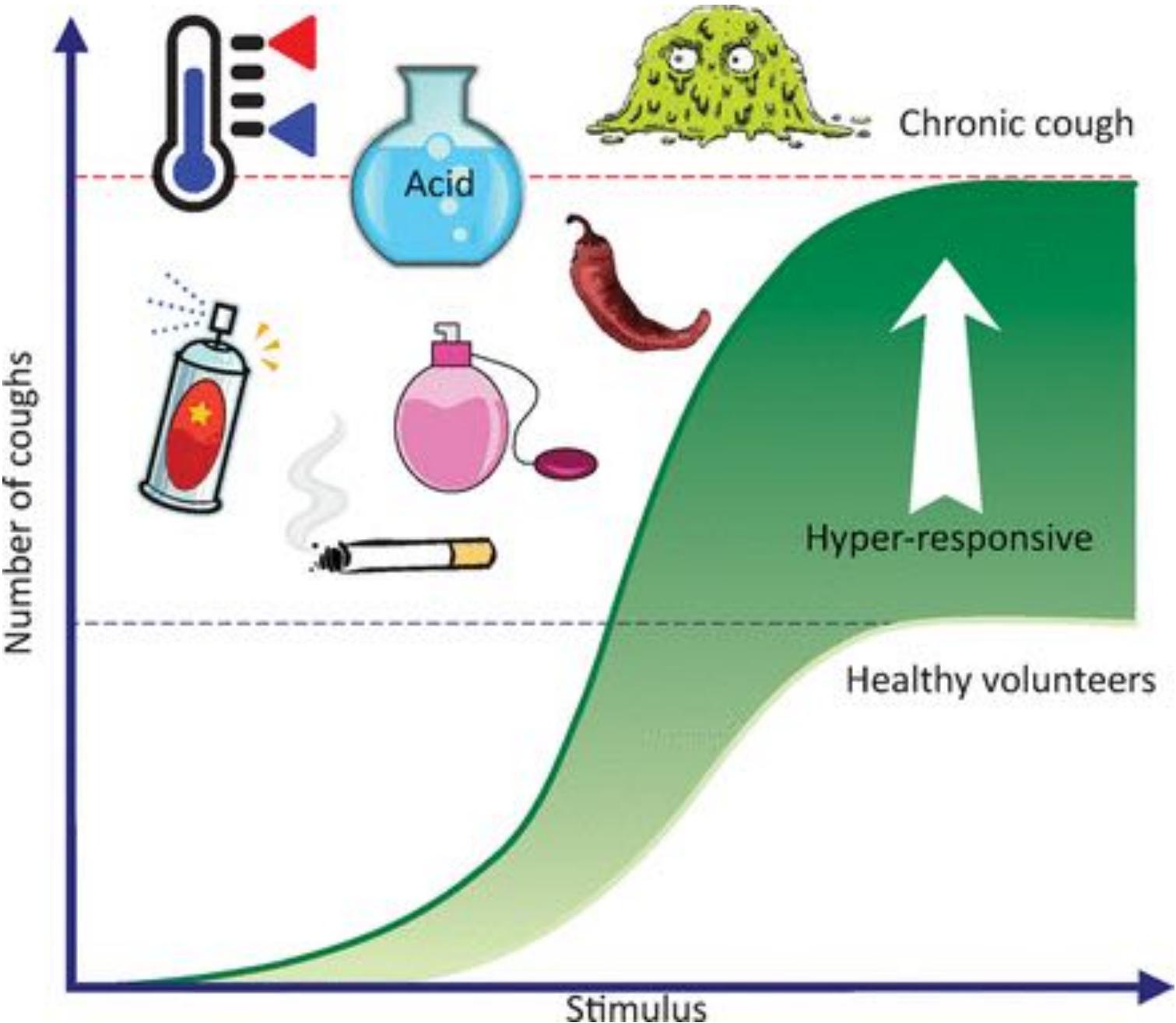
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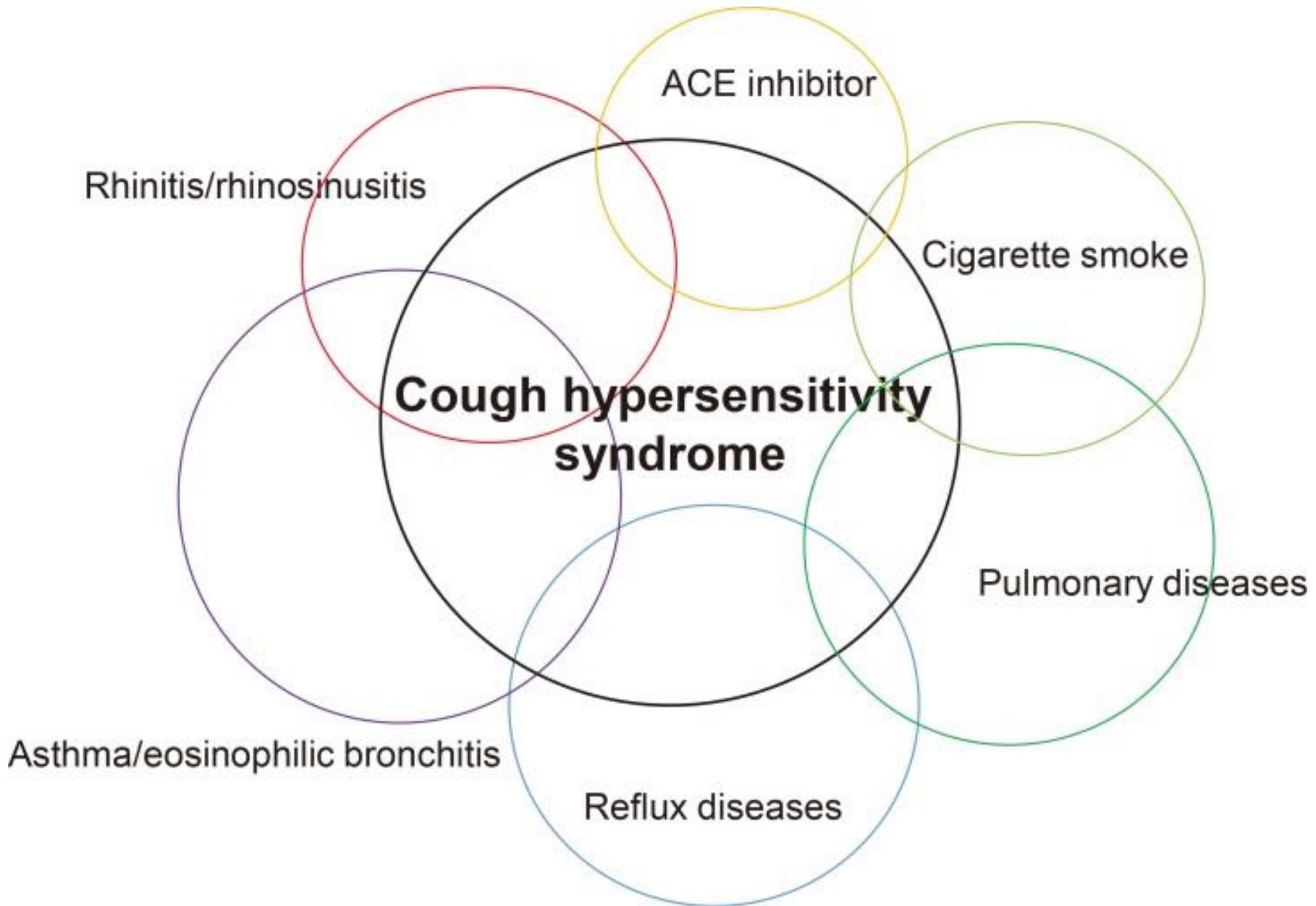
1977: Sintomo della TRIADE:

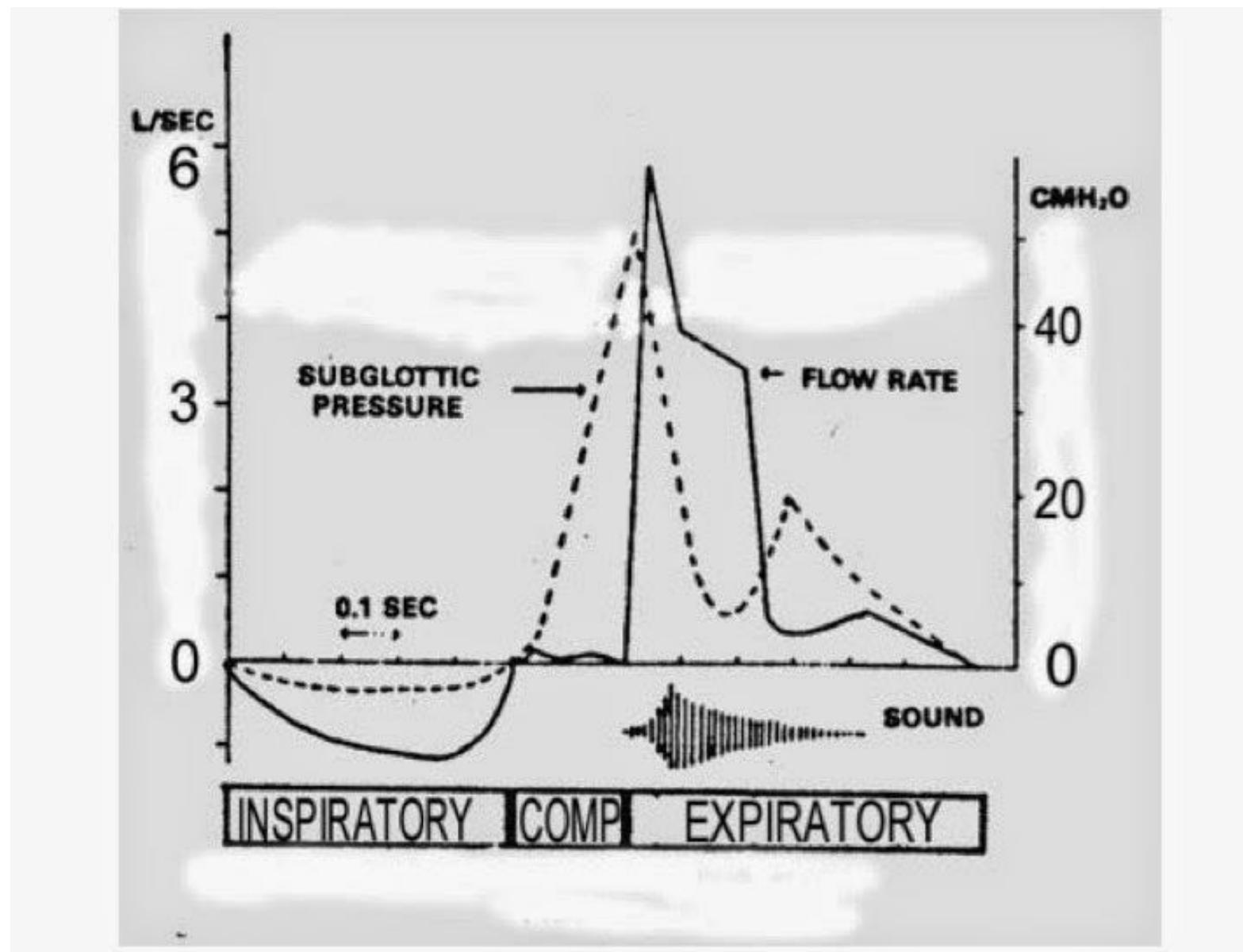
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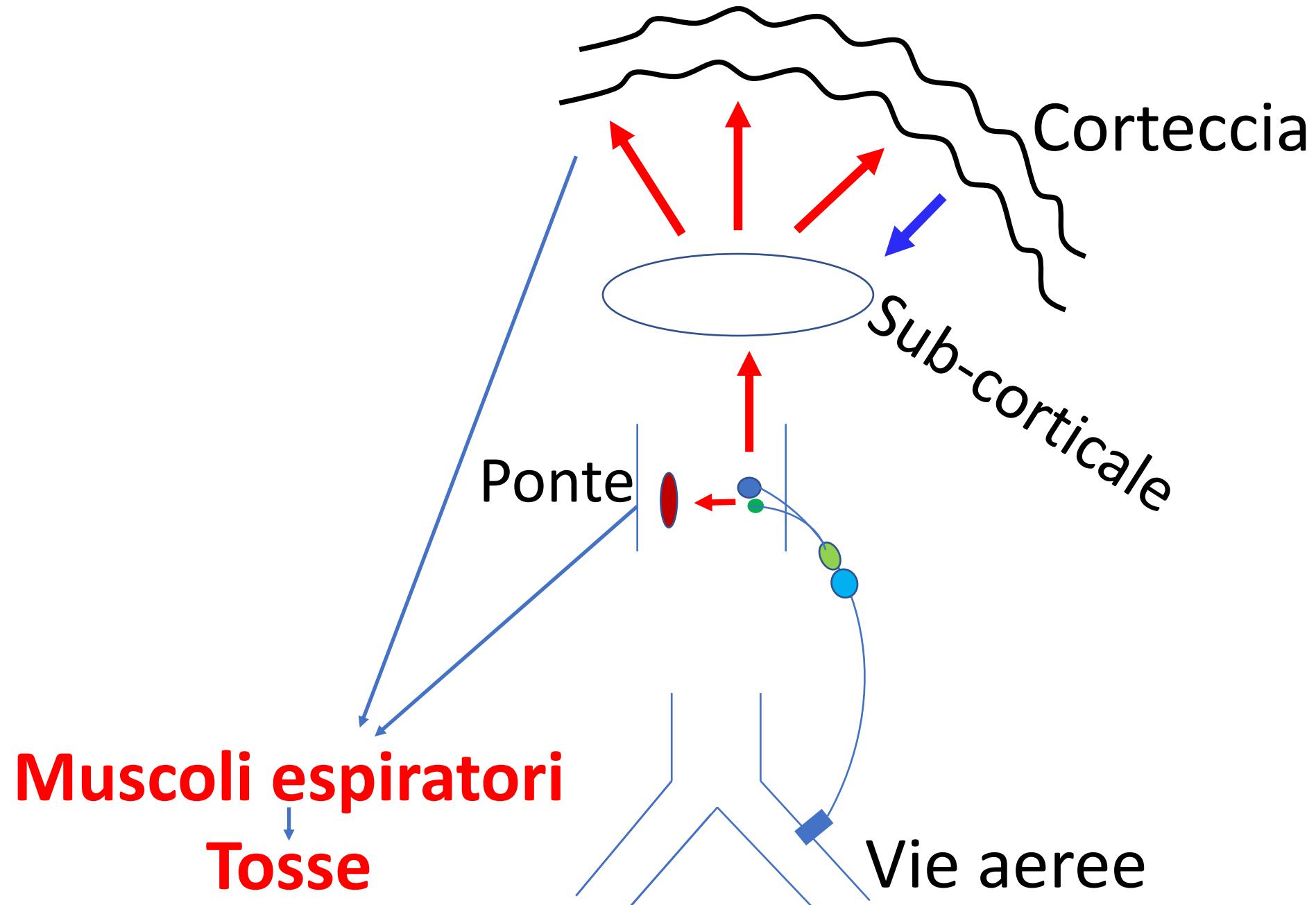
2006: L.G. ACCP.

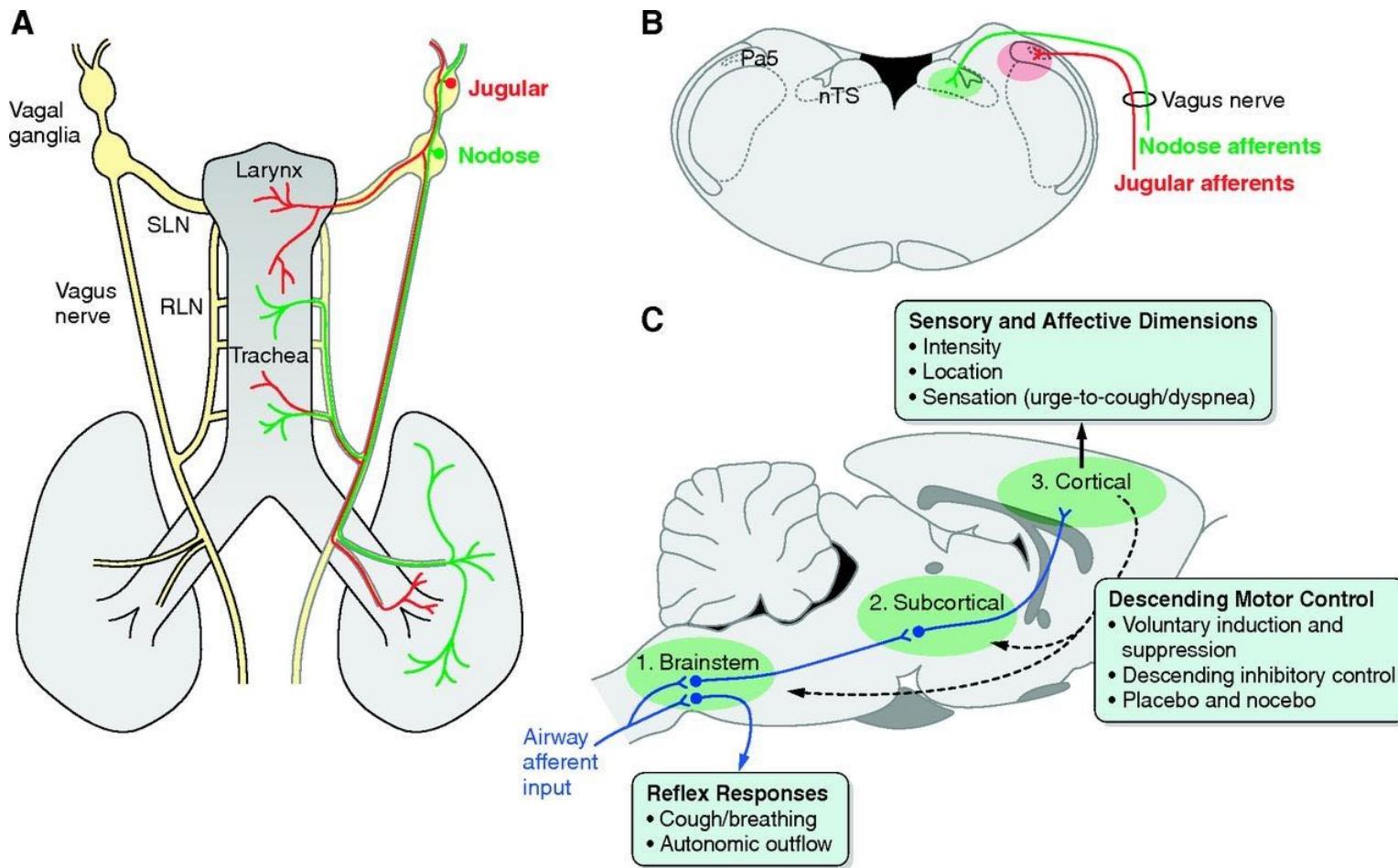
2008: Nuova definizione: **SINDROME DA IPERSENSIBILITA' O IPERREATTIVITA' ALLA TOSSE.** Motivazione: nel 12-42% dei pazienti la tosse non è spiegata dalla triade (Lung 2008; 186 Suppl 1: S78).





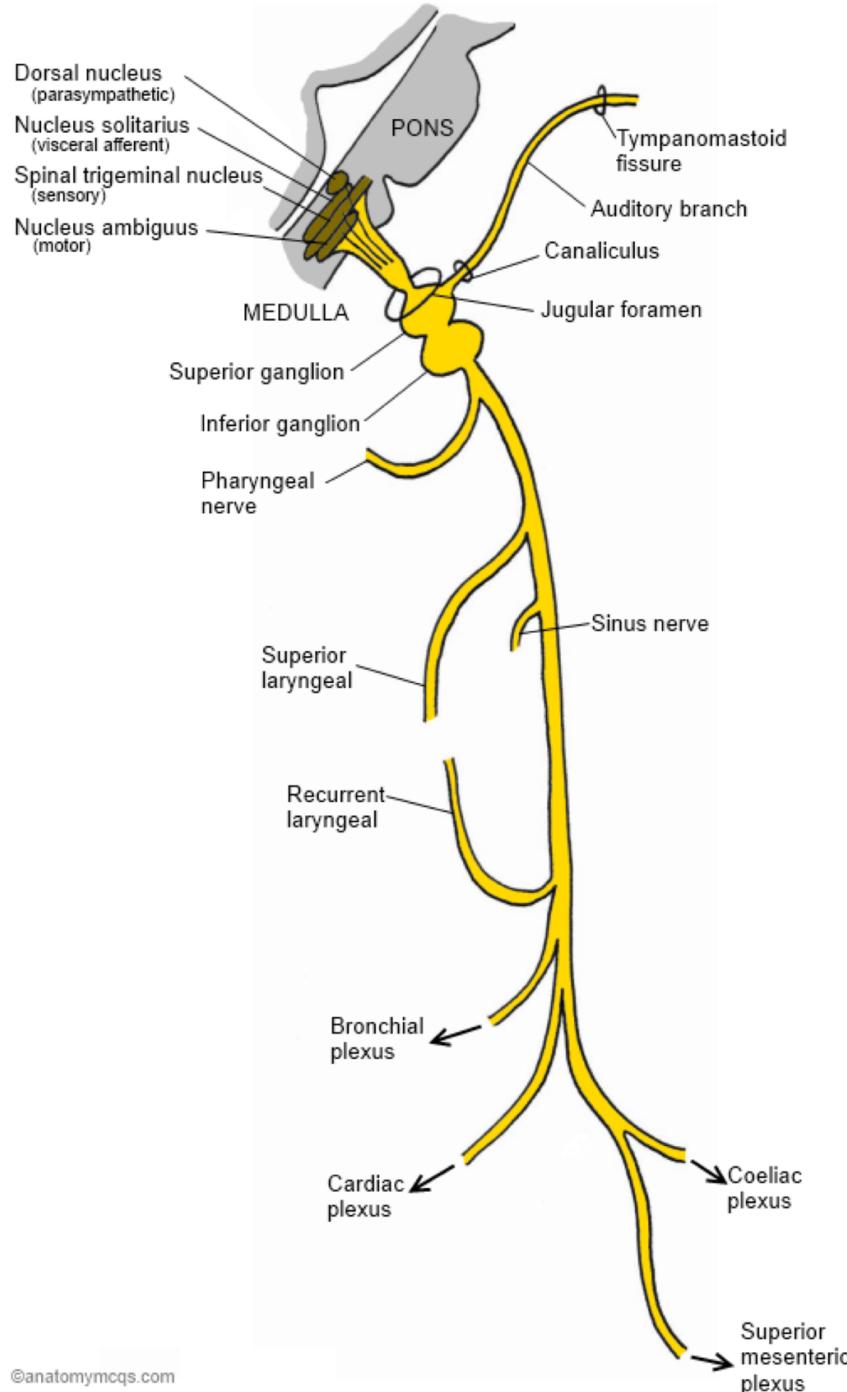


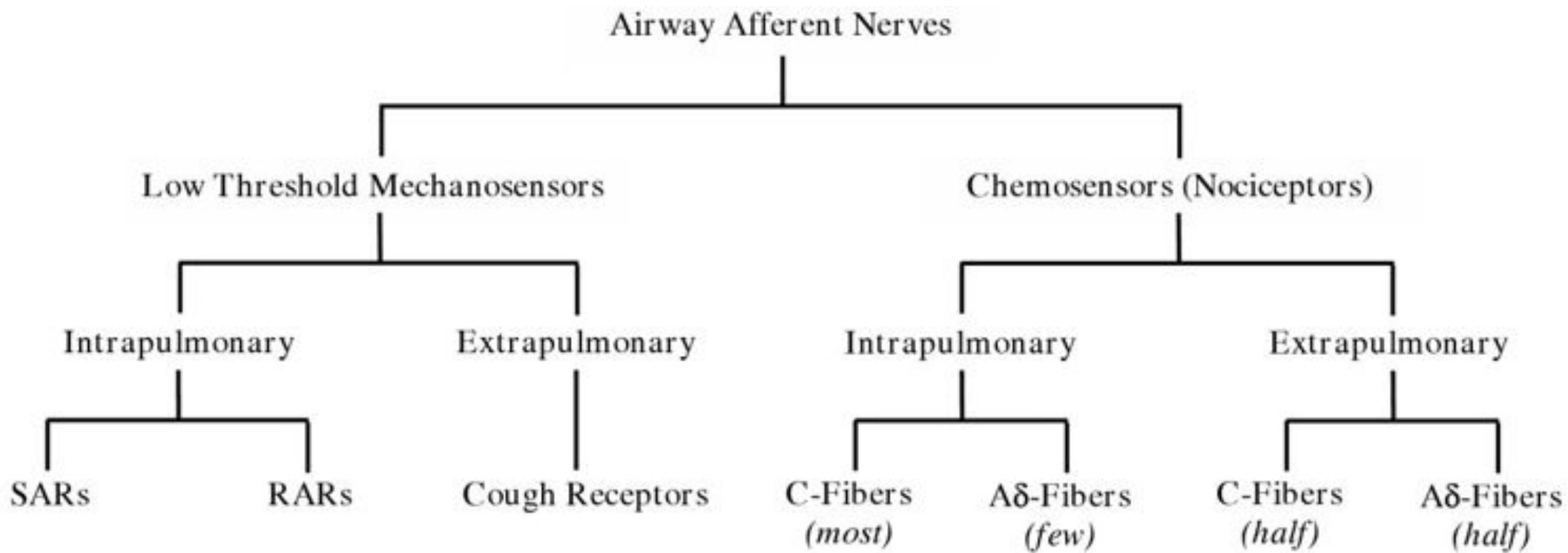




**FIGURE 5.** Schematic overview of the peripheral and central neural pathways regulating airway afferent processing. **A:** embryologically distinct neurons constituting the jugular (red) and nodose (green) vagal ganglia innervate the airways and lungs. The axons of these neurons reach the airways via distinct vagal branches, including the superior and recurrent laryngeal nerves (SLN/RLN, respectively). **B:** the brain stem terminal projections of jugular (red) and nodose (green) neurons are confined predominately to the paratrigeminal nucleus (Pa5) and the nucleus of the solitary tract (nTS), respectively. **C:** brain stem neurons in receipt of airway vagal sensory input in turn contribute to both reflex and higher order circuits that encode various involuntary and voluntary motor responses and perceivable sensations subsequent to airway sensory nerve stimulation. Descending control circuits help regulate airway sensory processing at multiple levels of the neuraxis.

## VAGUS NERVE





**Fibre C delle vie aeree extrapolmonari** (80-90% dal Ganglio giugulare attraverso il nervo laringeo superiore del vago, 10-20% dal ganglio nodoso attraverso il nervo laringeo ricorrente);

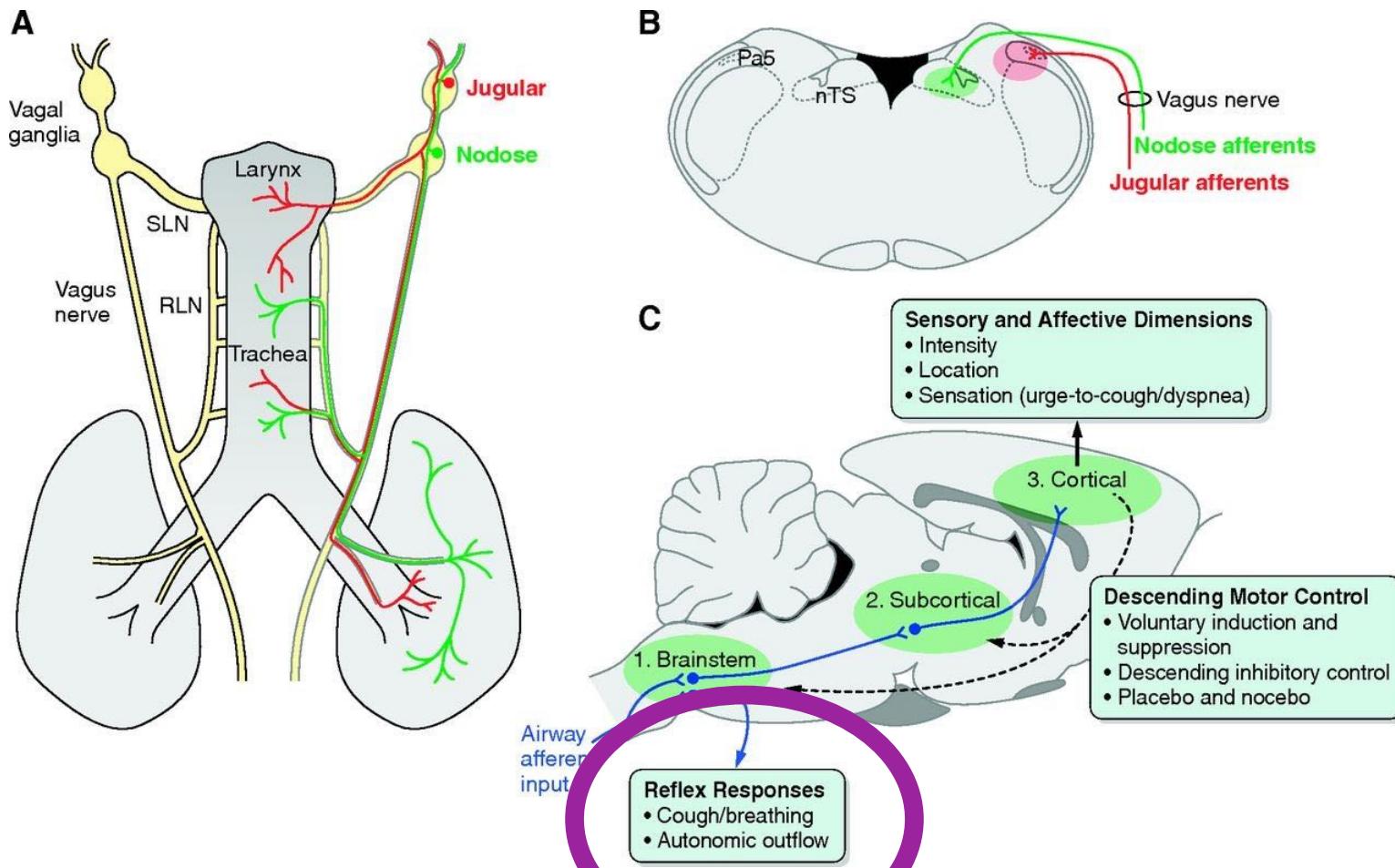
**Fibre C delle vie aeree intrapolmonari** (50% Ganglio giugulare, 50% ganglio nodoso attraverso il nervo ricorrente e branche polmonari del vago);

**Fibre A $\delta$**  terminano principalmente nei bronchi extrapolmonari, trachea e laringe) (100% ganglio nodoso);

Fibre C:A $\delta$  8:1.

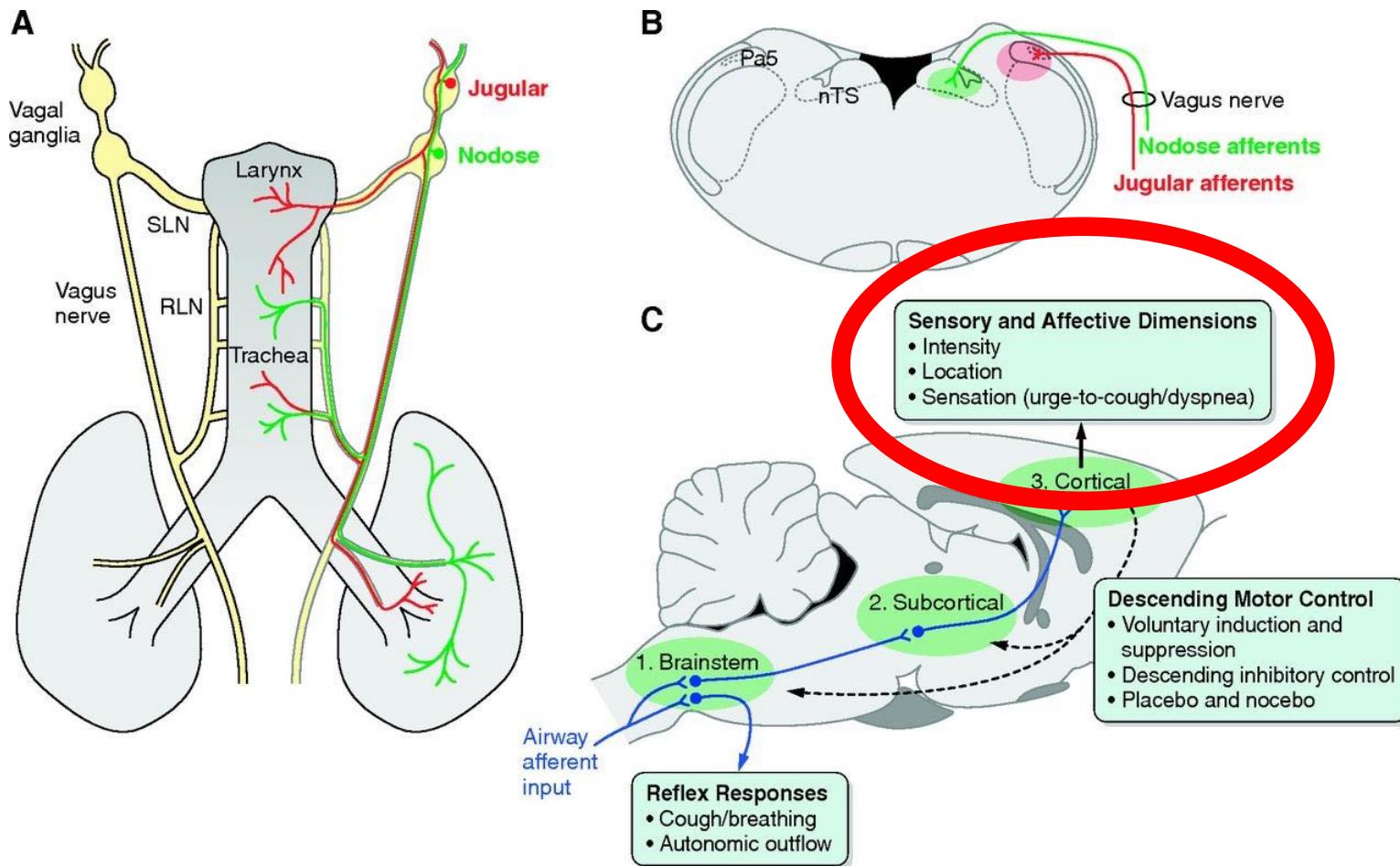
Fibre C: 0.4-3.0 m/s

Fibre A $\delta$  delta 3-10 m/s.



1.1152/physrev.00039.2015

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# OTOSSE CRONICA

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# **TOSSE CRONICA: ATOLOGIA NEUROSENSORIALE**

**Table 1. Evidences for neuropathology in cough hypersensitivity**

Category	Characteristics
Clinical profile	Cough triggered by trivial stimuli such as cold air, perfume, stress, exercise, singing, or talking (allotussia) Urge-to-cough sensation More coughs evoked by tussigen inhalation (hypertussia)
Sensory neural activation in the airways	Phenotypic switch of sensory neurons by respiratory virus infection, allergen, or air pollutant Increased neuropeptides in bronchoalveolar lavage fluids TRPV1 up-regulation in bronchial epithelial nerves
Central neural alterations in cough processing	Increased activation of midbrain areas (presumably related to descending modulatory pathways) Decreased activation in brain areas implicated in cough suppression
Clinical trials	Proven efficacy of drugs with neuro-modulatory properties

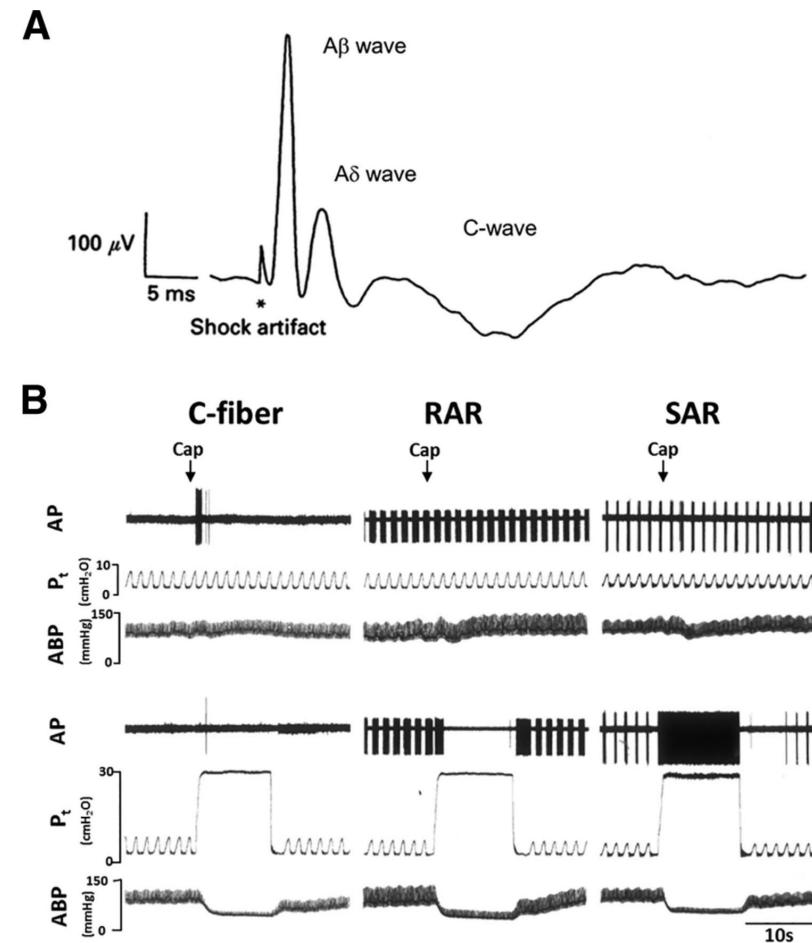
# **SENSORI PERIFERICI: FIBRE C e FIBRE A ( $\delta$ e $\beta$ )**

**Fibre C:** rispondono a stimolanti chimici (capsaicina, cinnamaldeide, isocianati, ozono, fumo di sigaretta, prostaglandine, prodotti di perossidazione, bradichinina), temperatura aria respirata, osmolarità e pH.

**Fibre A $\delta$  (RECETTORI DELLA TOSSE)** rispondono a stimoli meccanici e a basso pH solo in caso per rapida caduta.

Fibre A $\beta$  rispondono a alla distensione del polmone (RAR e SAR).

Interazioni positive tra fibre C e A $\delta$  e A $\beta$ .



**FIGURE 3.** Airway vagal afferent electrophysiology. **A:** example of a compound action potential recorded from the guinea pig recurrent laryngeal nerve. The vagus nerve was stimulated at asterisk with an electrical impulse of sufficient magnitude to stimulate all axons. The action potentials arrive at the recording electrode on the recurrent laryngeal nerve in three waves corresponding to the A $\beta$  (~20 m/s), A $\delta$  (~10 m/s), and C (0.3–3 m/s) waves. [From Canning et al. (62).] **B:** representative experimental records illustrating three different vagal afferent nerve phenotypes innervating the lungs of a rat. The first panel shows a pulmonary C fiber; conduction velocity of this fiber was 1.05 m/s. The second panel shows a RAR fiber; conduction velocity, 21.4 m/s. The last panel shows an SAR fiber; conduction velocity, 23.5 m/s. Capsaicin (Cap) was slowly injected at arrows, and hyperinflation was generated by maintaining a constant tracheal pressure (P<sub>t</sub>) at 30 cmH<sub>2</sub>O for 10 s, while the respirator was turned off. AP, action potentials; ABP, arterial blood pressure. [From Ho et al. (169), with permission from Elsevier.]

# RECETTORI DELLE FIBRE C

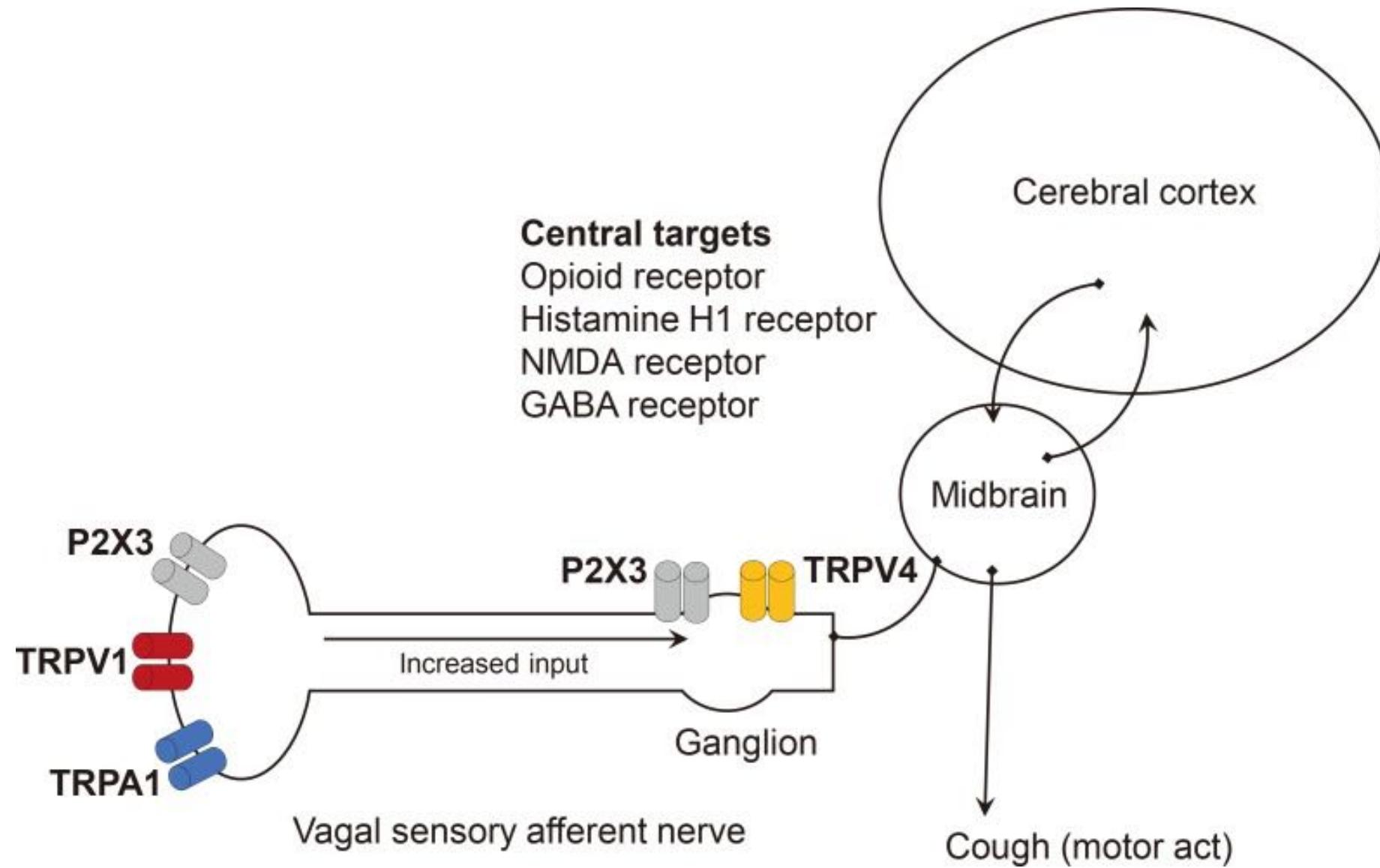
## 1. RECETTORI IONOTROPICI:

- A. RECETTORE DELLA NICOTINA
- B. RECETTORE SEROTONINERGICO PER 5 HT-3
- C. RECETTORI PURINERGICI P2X
- D. TRANSIENT RECEPTOR POTENTIAL:
  - I. TRPV1
  - II. TRPA1
  - III. TRPM8
- E. CANALI ACIDI

## 2. RECETTORI METABOTROPICI

- A. BRADICININA
- B. ISTAMINA
- C. 5HT
- D. ADENOSINA
- E. RECETTORI ATTIVATI DALLE PROTEASI
- F. EICOSANOIDI

## 3. RECETTORI DEI CANALI DEL $\text{Na}^+$ VOLTAGGIO DIPENDENTI E POTENZIALI D'AZIONE (NaVs)



## TRP

Famiglia di canali ionici espressi sui segmenti terminali delle **fibre C**.  
Stimolazione mediata preferenzialmente dagli ioni Ca<sup>++</sup>

### TRPV1

**Attivazione:** alte temperature ( $>42$  °C), range di ligandi esogeni ed endogeni (capsaicina, pH basso, resinoferotoxina e altri) e recettori accoppiati alla proteina G.

**Espresso:** neuroni ganglio giugulare e nodoso e cellule non-neuronali.

**Effetti:** tosse negli animali e nell'uomo.

### TRPA1

**Attivazione:** bassa temperatura; isocianati, cannabinolo e allicina (mostarda, aglio, cannabis), acroleina (air pollution), idrocarburi policiclici aromatici del diesel, mediatori infiammatori (PGE2 e bradichinina).

**Espresso:** vago e trigemino nasale.

**Effetti:** tosse negli animali e nell'uomo.

## **TRPV4**

**Attivazione:** forbolo, soluzioni ipoosmolari, derivati dell'acido arachidonico.

**Espresso** nei gangli della radice dorsale e fibre A $\delta$  dei guinea pigs.

**Effetti:** tosse nei guinea pigs.

## **TRPM8**

**Attivazione:** basse temperature (15-28 °C), mentolo, eucaliptolo.

**Espresso** nei gangli della radice dorsale e trigeminali.

**Effetti:** tosse e broncocostrizione.

In realtà mentolo riduce la tosse (presumibilmente attraverso l'attivazione dei TRPM8 delle afferenze nervose del trigemino nasale o attraverso meccanismi non-TRPM8 dipendenti).

## P2X3

**Attivazione:** adenosina, AMP, ATP e  $\alpha\beta$ -Methylene ATP.

**Espresso** nelle fibre C dei bronchi di piccolo o medio diametro e fibre A $\delta$  dei gangli nodosi e giugulari.

**Effetti:** tosse e broncospasmo.

## **ASMA**

PGE e bradichinina stimolano TRPA1 e TRPV1 (ARRD 1989; 140: 137)

## **BPCO**

- ✓ Stimoli diretti: Acroleina e crotonaldeide del fumo di sigaretta stimolano TRPA1 (Chem Res Toxicol 2013; 26: 750)
- ✓ Stimoli indiretti: tachinine (Ann N Y Acad Sci 2003; 992: 218); aumento di ATP e stimolazione P2X3
- ✓ Aumento delle proteasi (elastase) per infiammazione neutrofila; stimolazione TRPA1 e TRPV4 (Br J Pharmacol 2014; 171: 3881)
- ✓ Aumento del muco (Eur Respir J 2004; 24: 893); stimolazione meccanica (fibre A $\delta$ )

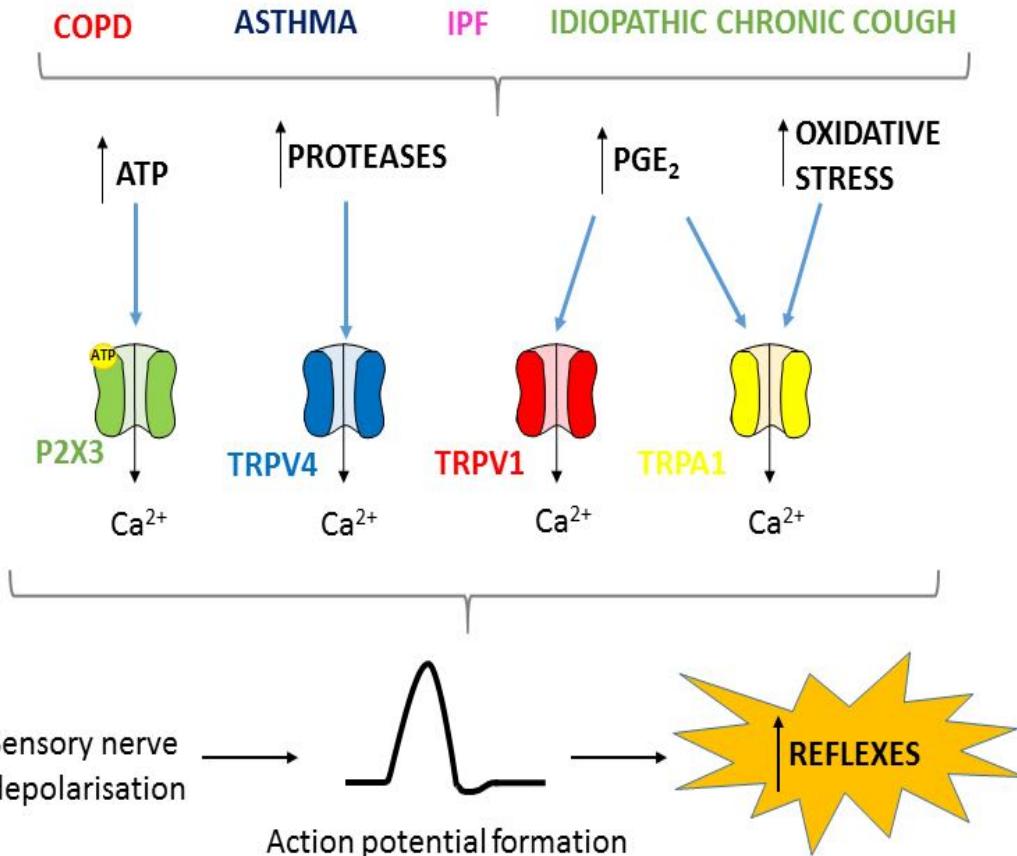
## **IPF**

- ✓ Stimolazione meccanica (Eur Respir Rev 2016; 25: 278) delle fibre A $\delta$
- ✓ Infiammazione subclinica del tessuto polmonare TRPA1 e TRPV1 (Respirology 2011; 16: 969)
- ✓ Aumento neurotrofine e ATP; stimolazione P2X3 (AJRCCM 2010; 182: 774)

## **SINDROME DI IPERREATTIVITA' DELLA TOSSE**

- ✓ Anomala risposta TRP (Clin Med 2016; 16: S92; J Allergy Clin Immunol 2013; 132: 847)
- ✓ Anomala risposta P2X3 (Lancet 2015; 385: 1198)

## AIRWAY DISEASE



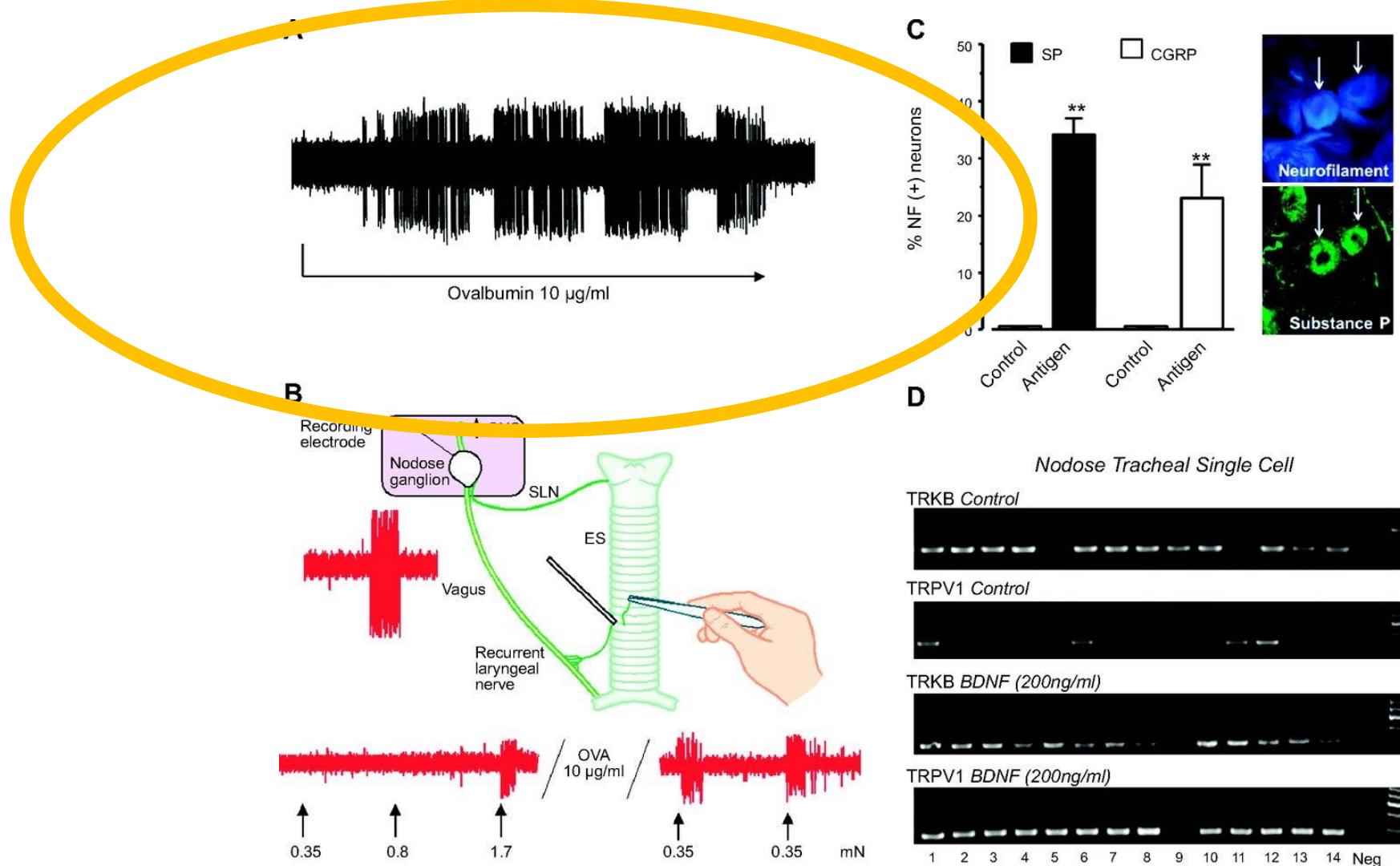
Bonvini SJ, Belvisi MG. Cough and airway disease: The role of ion channels. Pulm Pharmacol Ther 2017; 47: 21

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1. ATTIVAZIONE DEI NERVI AFFERENTI;
2. AUMENTO DELLA SENSIBILITÀ DEI NERVI AFFERENTI;
3. VARIAZIONI DEL FENOTIPO DEI NEURONI VAGALI AFFERENTI;
4. VARIAZIONI DELLA NEUROPLASTICITÀ E CAMBIAMENTI DELLA TRASMISSIONE SINAPTICA A LIVELLO CENTRALE.

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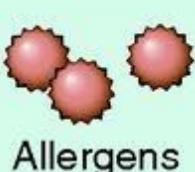


**FIGURE 9.** Examples of inflammation-induced modulation of guinea pig airway vagal afferent nerves. **A:** representative example of a nodose C-fiber responding with action potential discharge to allergen (ovalbumin) provocation (guinea pig was previously actively sensitized to ovalbumin). **B:** allergen (ovalbumin) challenge does not overtly activate nodose A $\delta$ -fibers in the guinea pig trachea, but increased the excitability of the fiber to mechanical activation. [From Riccio et al. (375).] **C:** allergen (ovalbumin) inhalation leads to phenotypic changes in the neurons expressing substance P and CGRP. In control animals, large neurofilament-positive (NF+) nodose neurons innervating the respiratory tract do not express these neuropeptides, but 1 day following allergen challenge, ~25% of these neurons become neuropeptide positive. [From Myers et al. (328).] **D:** another example of neuroplasticity showing a phenotypic switch in TRPV1 gene expression. In control animals, nodose fibers innervating the trachea do not express TRPV1, but 1 day following exposure to BDNF, TRPV1 is induced in a majority of the neurons. [From Lieu et al. (250).]

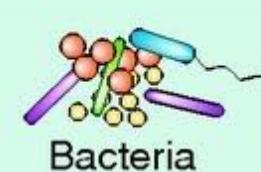
## Environmental exposures



Viruses



Allergens



Bacteria



Oesophageal  
refluxate

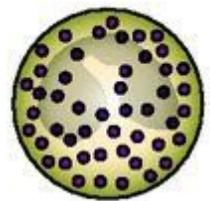


Smoke/pollution

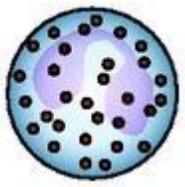
## Peripheral tissues

e.g.

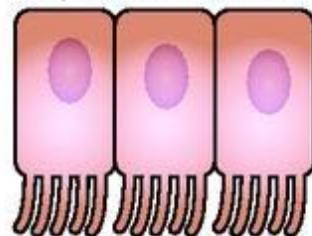
Mast cell



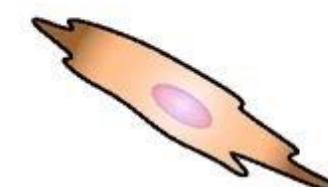
Eosinophil



Epithelial cells



Fibroblasts



Activation/recruitment  
of inflammatory or  
structural cells

## Inflammatory mediators

e.g.

5-HT

Cys-LTs

PGE<sub>2</sub>

ILs

TNF- $\alpha$

Bradykinin

PARs

NGF

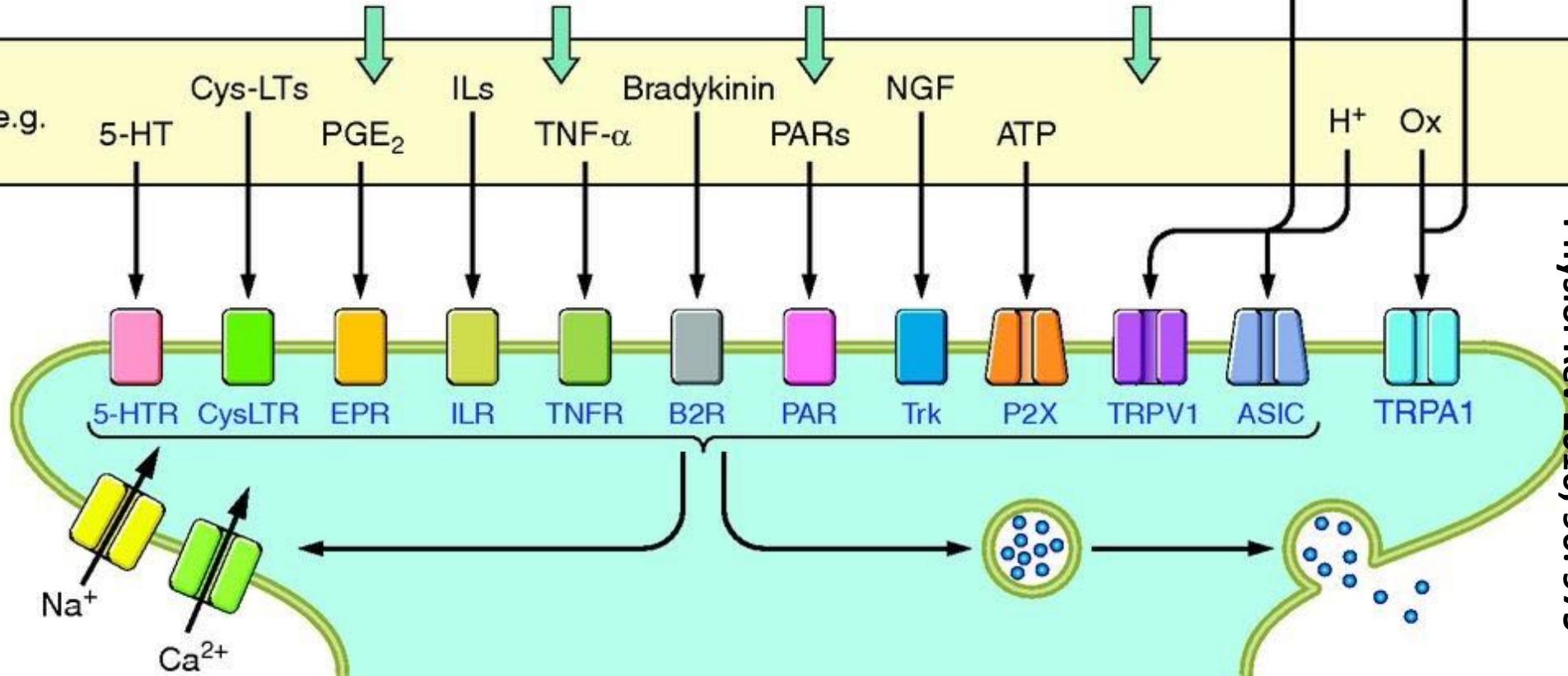
ATP

H<sup>+</sup>

Ox

## Sensory nerve terminal

Activation, sensitization and  
neuropeptide release



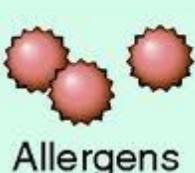
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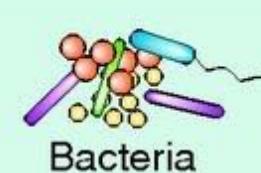
## Environmental exposures



Viruses



Allergens



Bacteria



Oesophageal  
refluxate

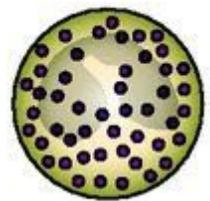


Smoke/pollution

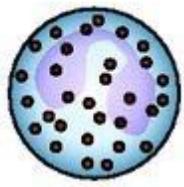
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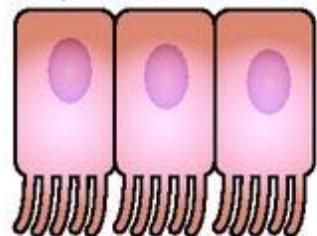
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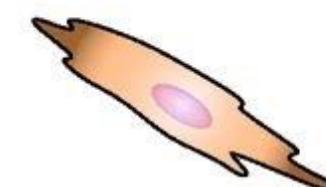
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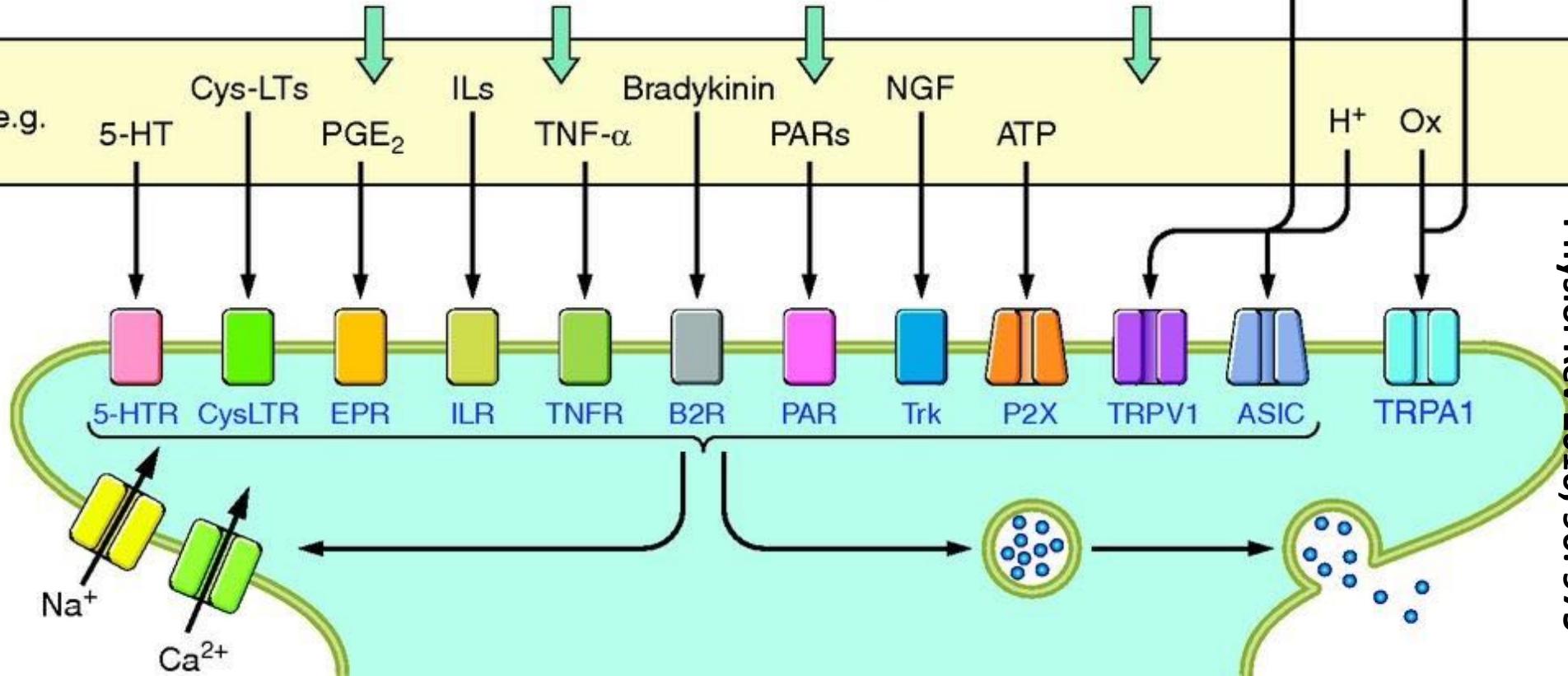
NGF

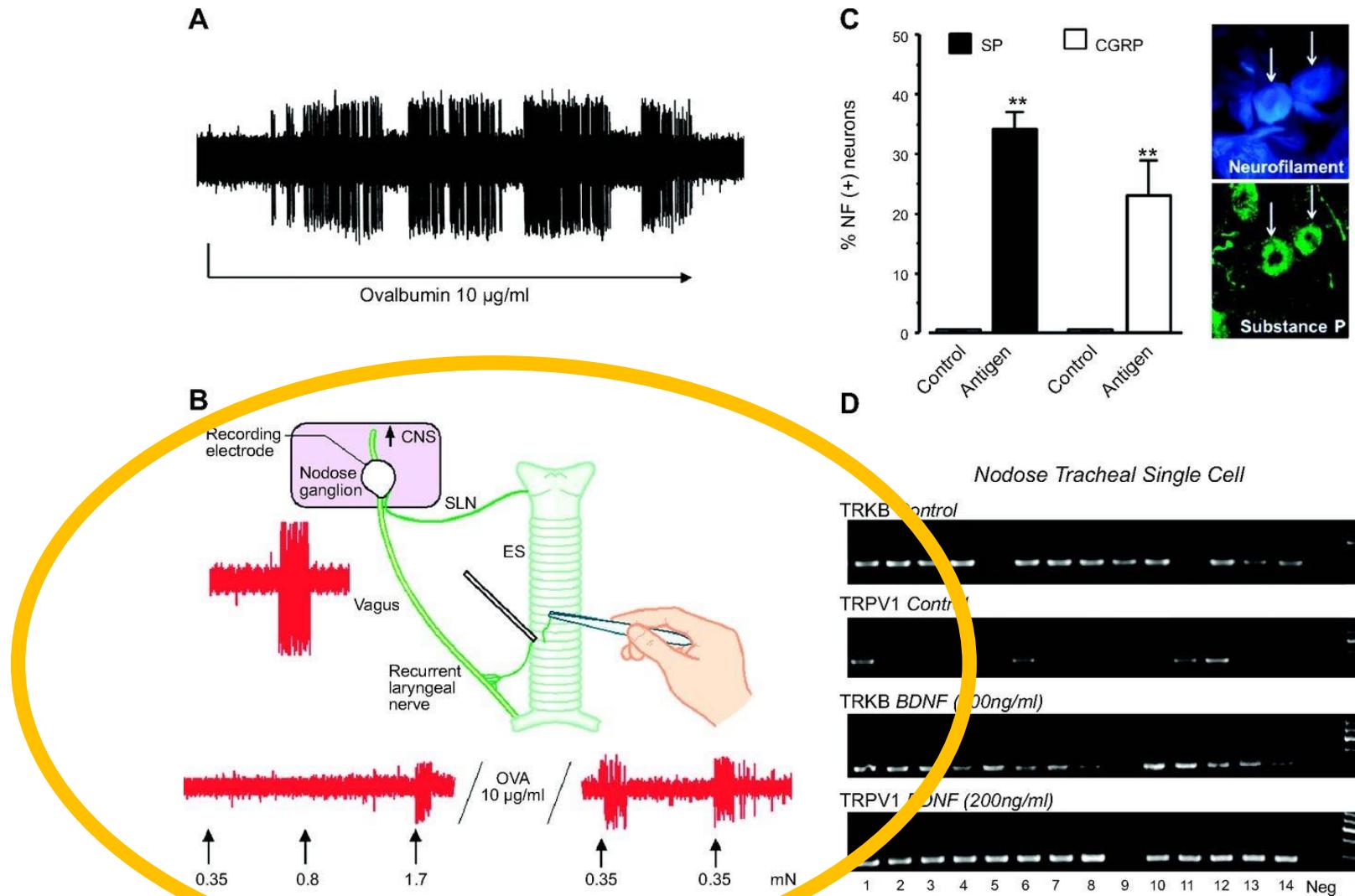
ATP

H<sup>+</sup>  
Ox

## Sensory nerve terminal

Activation, sensitization and  
neuropeptide release

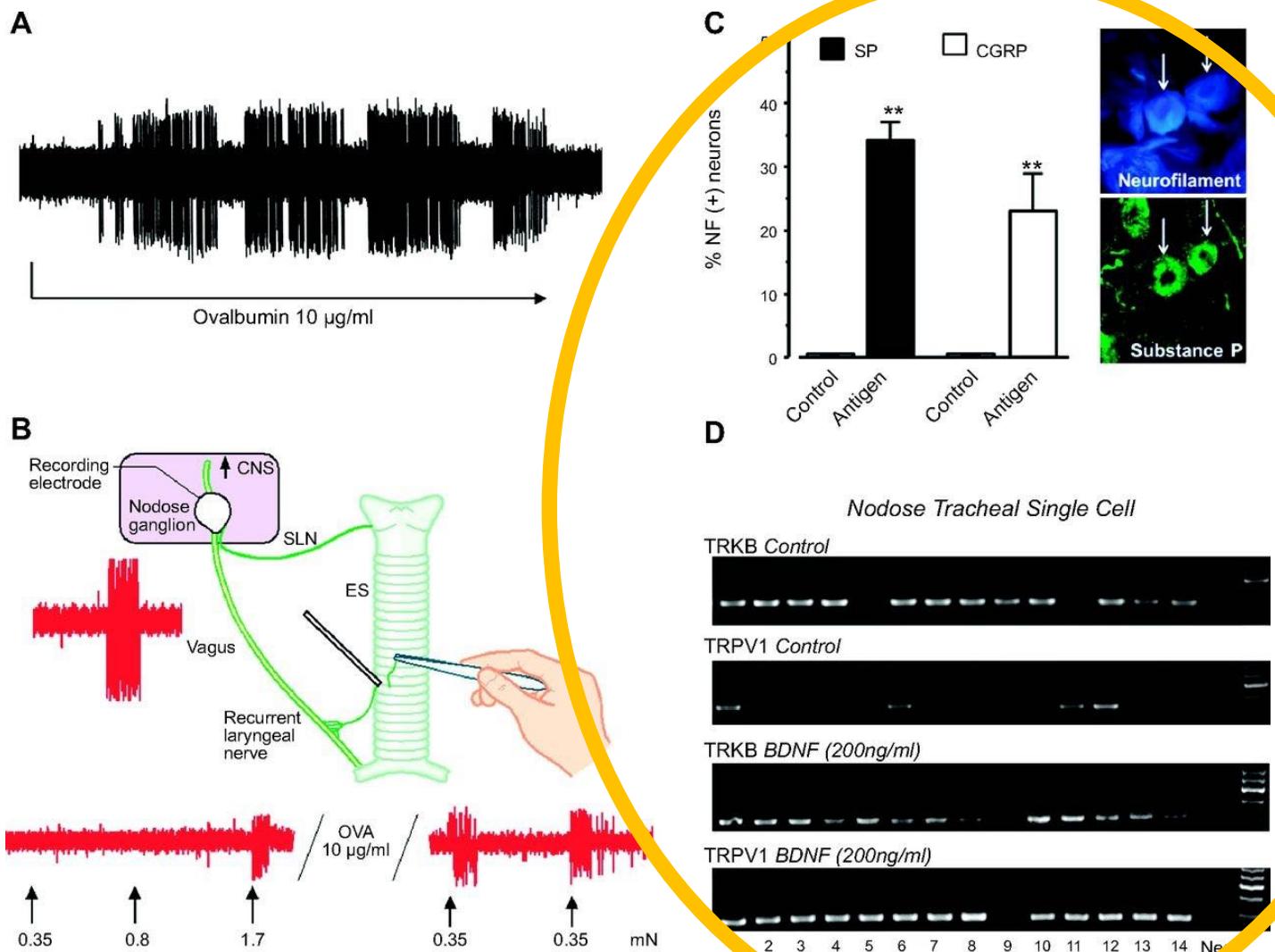




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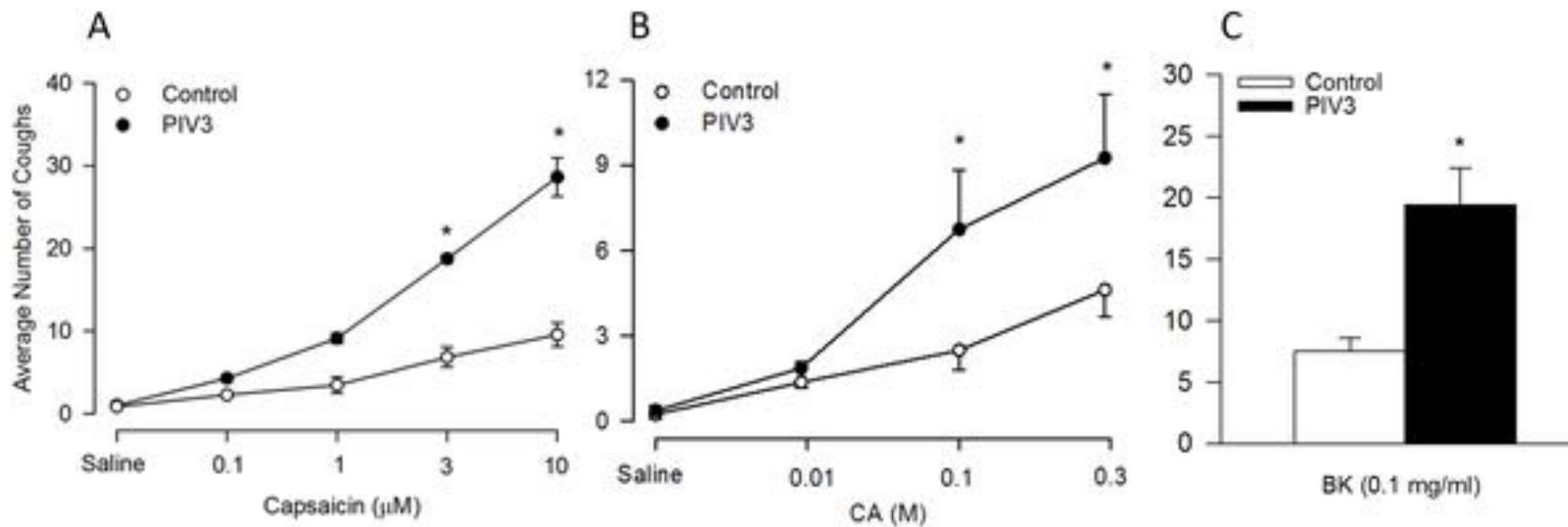
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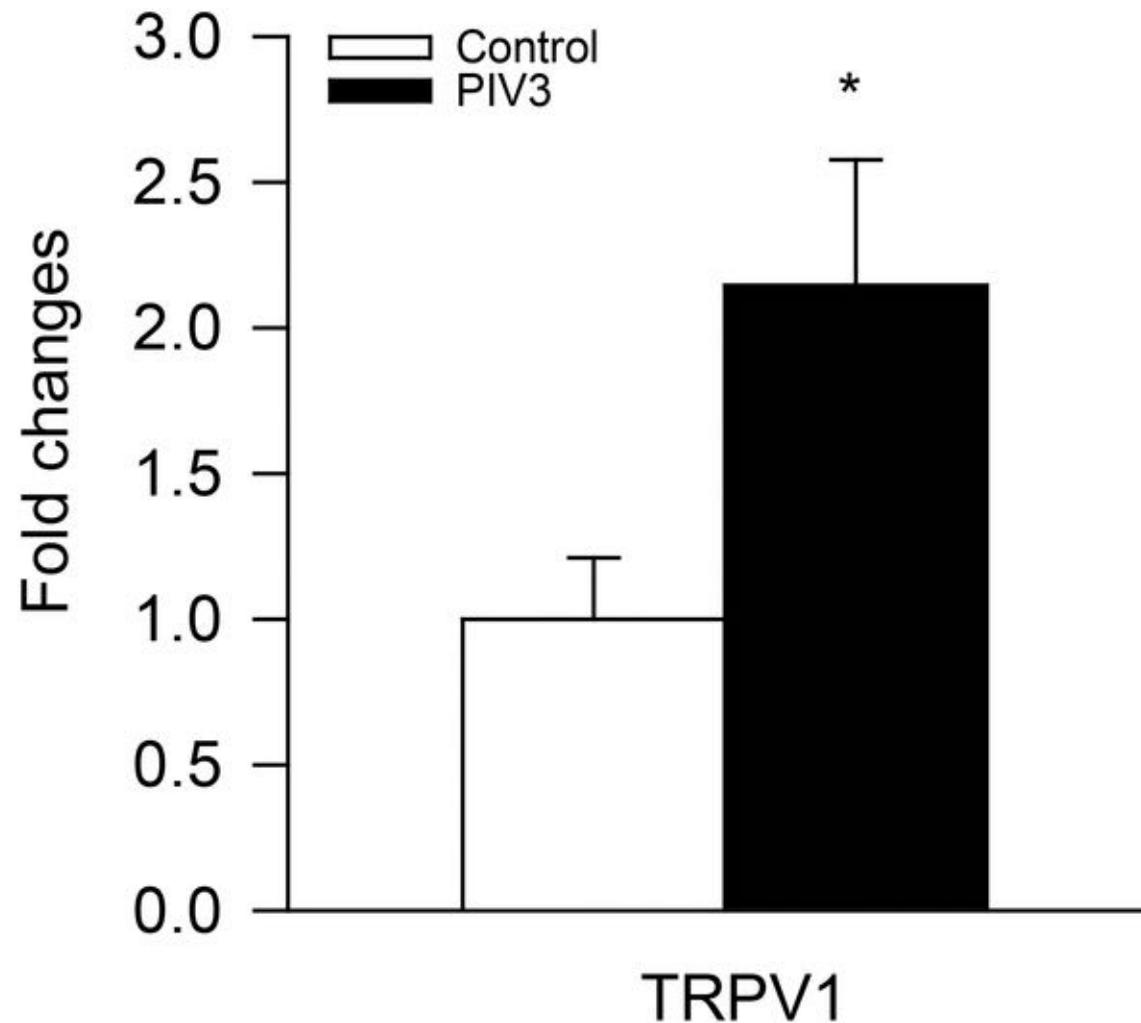
**FIGURE 9.** Examples of inflammation-induced modulation of guinea pig airway vagal afferent nerves. **A:** representative example of a nodose C-fiber responding with action potential discharge to allergen (ovalbumin) provocation (guinea pig was previously actively sensitized to ovalbumin). **B:** allergen (ovalbumin) challenge does not overtly activate nodose A $\delta$ -fibers in the guinea pig trachea, but increased the excitability of the fiber to mechanical activation. [From Riccio et al. (375).] **C:** allergen (ovalbumin) inhalation leads to phenotypic changes in the neurons expressing substance P and CGRP. In control animals, large neurofilament-positive (NF+) nodose neurons innervating the respiratory tract do not express these neuropeptides, but 1 day following allergen challenge, ~25% of these neurons become neuropeptide positive. [From Myers et al. (328).] **D:** another example of neuroplasticity showing a phenotypic switch in TRPV1 gene expression. In control animals, nodose fibers innervating the trachea do not express TRPV1, but 1 day following exposure to BDNF, TRPV1 is induced in a majority of the neurons. [From Lieu et al. (250).]

**Fig 2. Guinea pig cough responses to inhaled capsaicin (0.1, 1, 3, 10  $\mu$ M), citric acid (CA; 0.01, 0.1, 0.3 M) and bradykinin (BK; 0.1 mg/ml) 4 d after viral inoculation.**



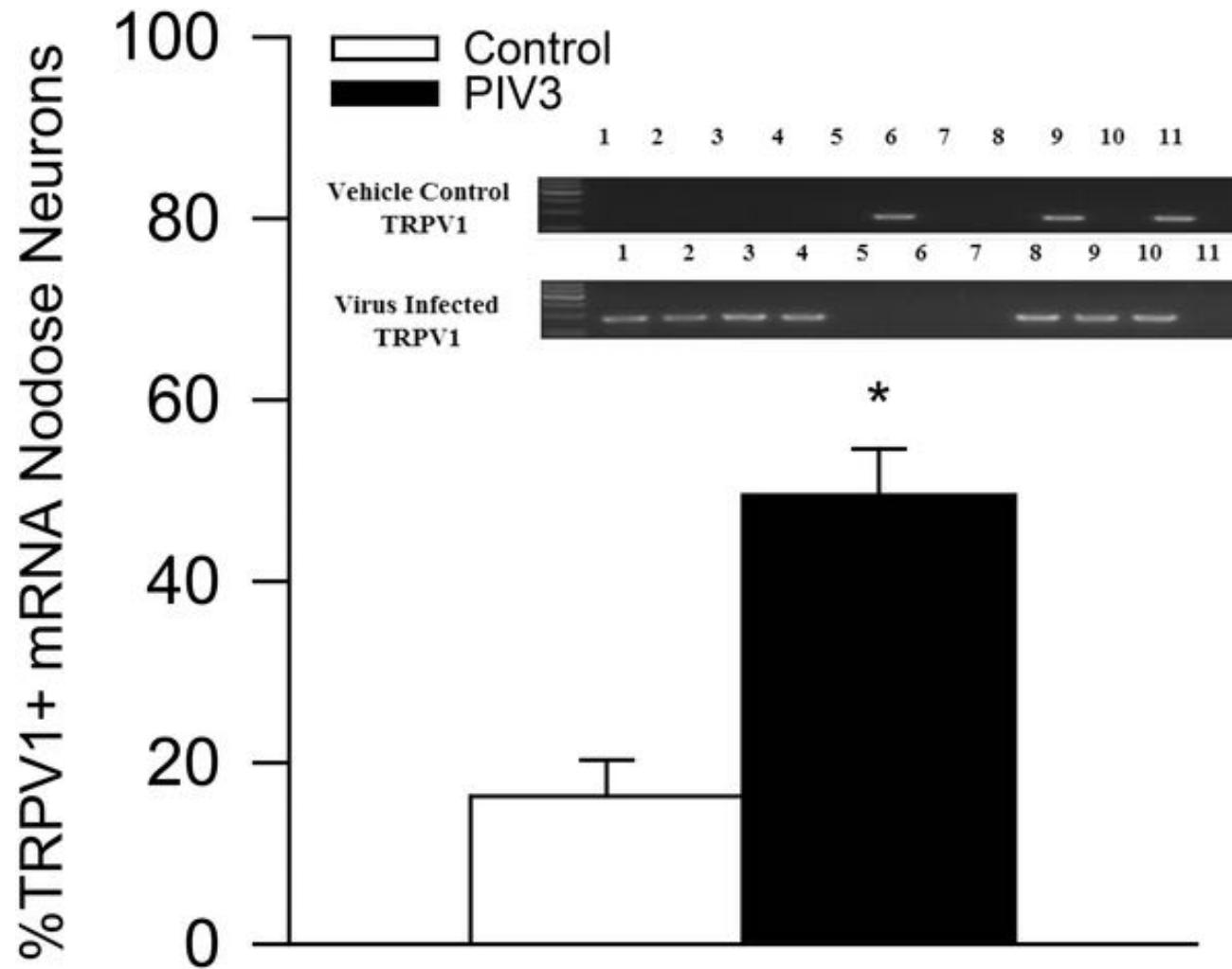
Zaccone EJ, Lieu T, Muroi Y, Potenzieri C, Undem BE, et al. (2016) Parainfluenza 3-Induced Cough Hypersensitivity in the Guinea Pig Airways. PLOS ONE 11(5): e0155526. <https://doi.org/10.1371/journal.pone.0155526>

**Fig 3. TRPV1 expression in the jugular ganglia in control animals compared to those inoculated with PIV3 (day 4).**



Zaccone EJ, Lieu T, Muroi Y, Potenzieri C, Undem BE, et al. (2016) Parainfluenza 3-Induced Cough Hypersensitivity in the Guinea Pig Airways. PLOS ONE 11(5): e0155526. <https://doi.org/10.1371/journal.pone.0155526>

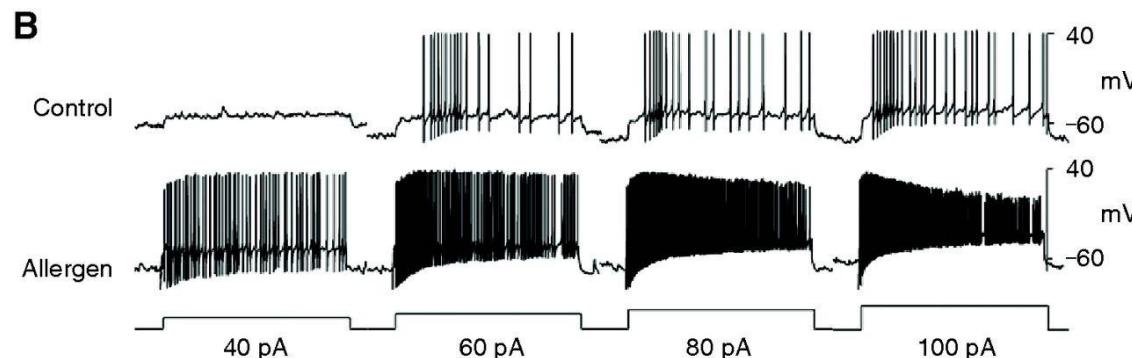
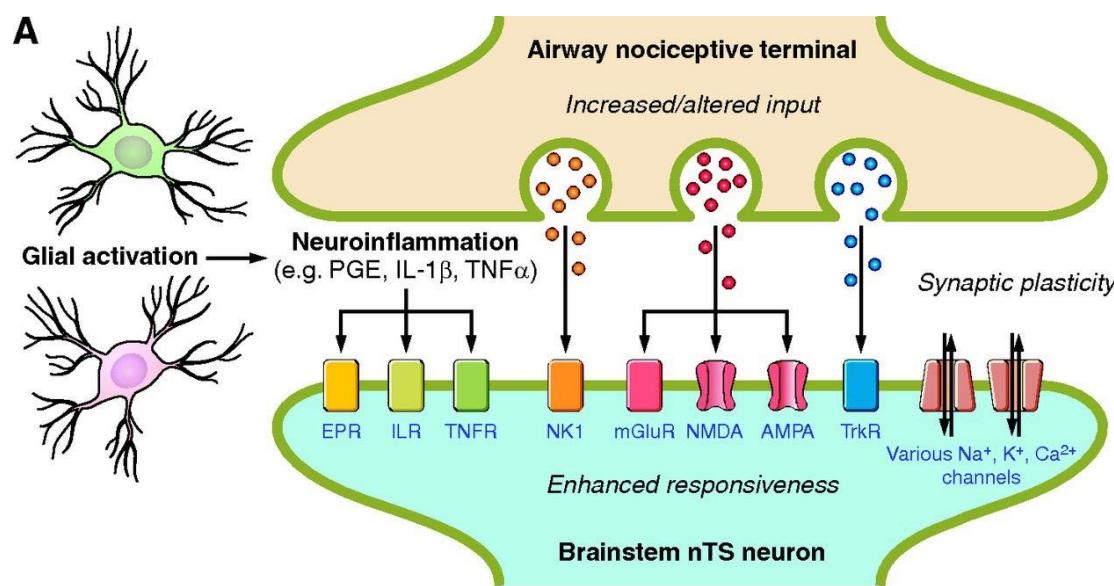
**Fig 4. Percentage of guinea pig tracheal-specific nodose neurons that express TRPV1 in controls compared to those inoculated with PIV3 (day 4).**



Zaccone EJ, Lieu T, Muroi Y, Potenzieri C, Undem BE, et al. (2016) Parainfluenza 3-Induced Cough Hypersensitivity in the Guinea Pig Airways. PLOS ONE 11(5): e0155526. <https://doi.org/10.1371/journal.pone.0155526>

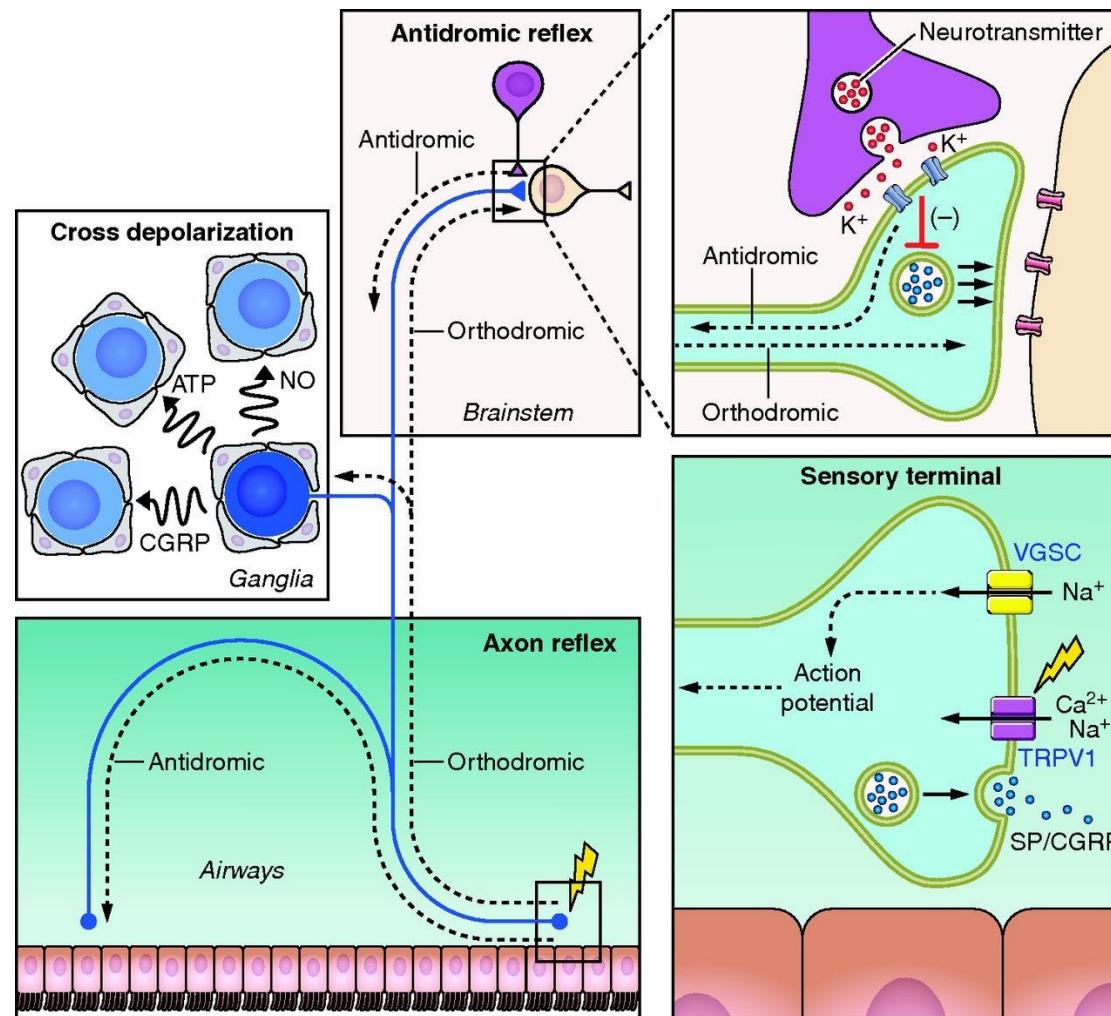
# **MECCANISMI DI IPERSENSIBILITÀ NEUROSENSORIALE NELLE MALATTIE RESPIRATORIE:**

- 1. ATTIVAZIONE DEI NERVI AFFERENTI;**
- 2. AUMENTO DELLA SENSIBILITÀ DEI NERVI AFFERENTI;**
- 3. VARIAZIONI DEL FENOTIPO DEI NEURONI VAGALI AFFERENTI;**
- 4. VARIAZIONI DELLA NEUROPLASTICITÀ E CAMBIAMENTI DELLA TRASMISSIONE SINAPTICA A LIVELLO CENTRALE.**



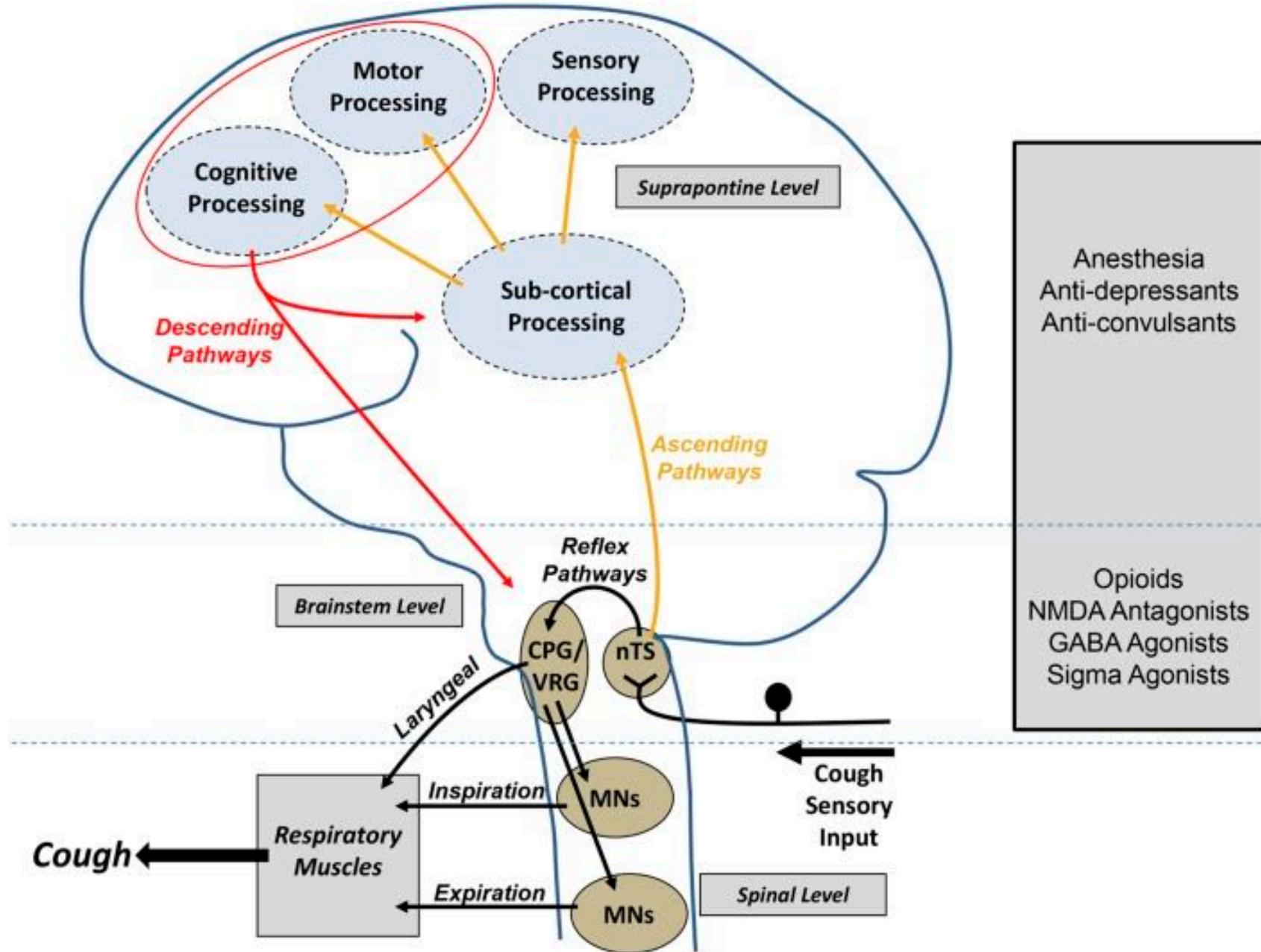
**FIGURE 10.** Mechanisms of central sensitization of brain stem neurons in receipt of airway afferent inputs. *Top:* schematic showing how aberrant sensory input to the central nervous system leads to a series of events that culminate in persistent hypersensitivity of the central neural circuits receiving sensory input. Sensory neurotransmitters substance P (SP) and glutamate (Glu) and neurotrophins (NTs) act postsynaptically to induce wind up and/or to lower the activation threshold of second-order brain stem neurons. In addition, activation of the brain's immune cells (glia) facilitates the upregulation of synaptic processes by orchestrating neuroinflammatory events. Collectively, these mechanisms drive synaptic plasticity, fundamental to generating heightened sensory nerve-dependent responses. *Bottom:* an example of central sensitization evoked by pulmonary antigen sensitization and challenge. Electrophysiological recordings of two neurons within the nucleus of the solitary tract (nTS) *in vitro*, one from a control animal and a second from an animal after prior *in vivo* allergic sensitization and challenge in monkeys. In the control cell, injection of increasing current (40–100 pA) produces stimulus-dependent action potential formation (spikes). Prior allergic inflammation in the airways lowers the current threshold needed for brain stem neuron action potential formation and dramatically increases the number of spikes per current step. PGE, prostaglandin E2; IL-1 $\beta$ , interleukin-1 $\beta$ ; TNF $\alpha$ , tumor necrosis factor- $\alpha$ ; EPR, E prostanoid receptor; NK1, neurokinin 1 receptor; mGluR, metabotropic glutamate receptor; NMDA, N-methyl-d-aspartate; AMPA,  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; TrkR, tropomyosin receptor kinase. [From Chen et al. (73), with permission from Elsevier.]

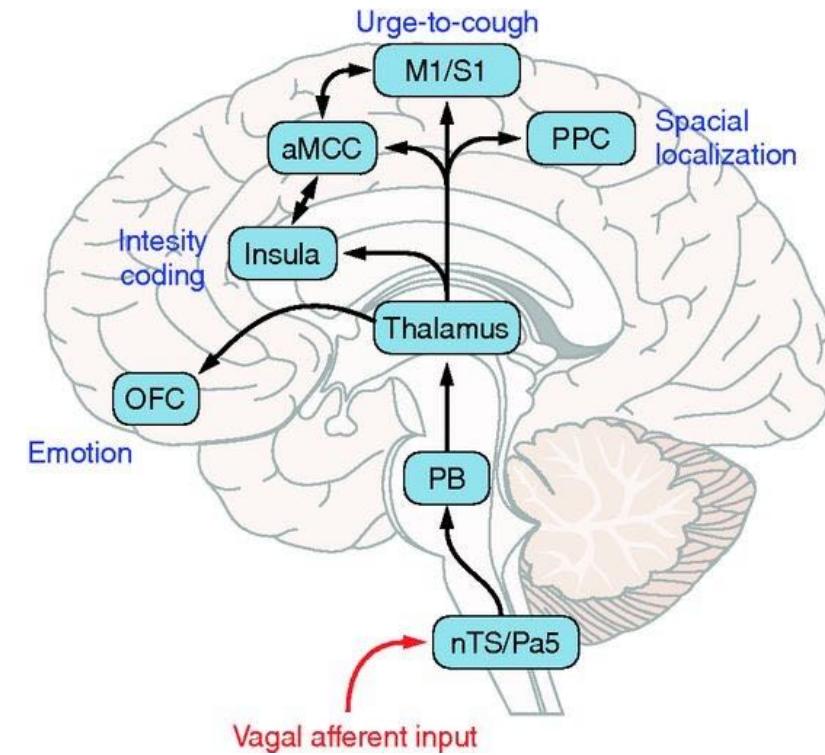
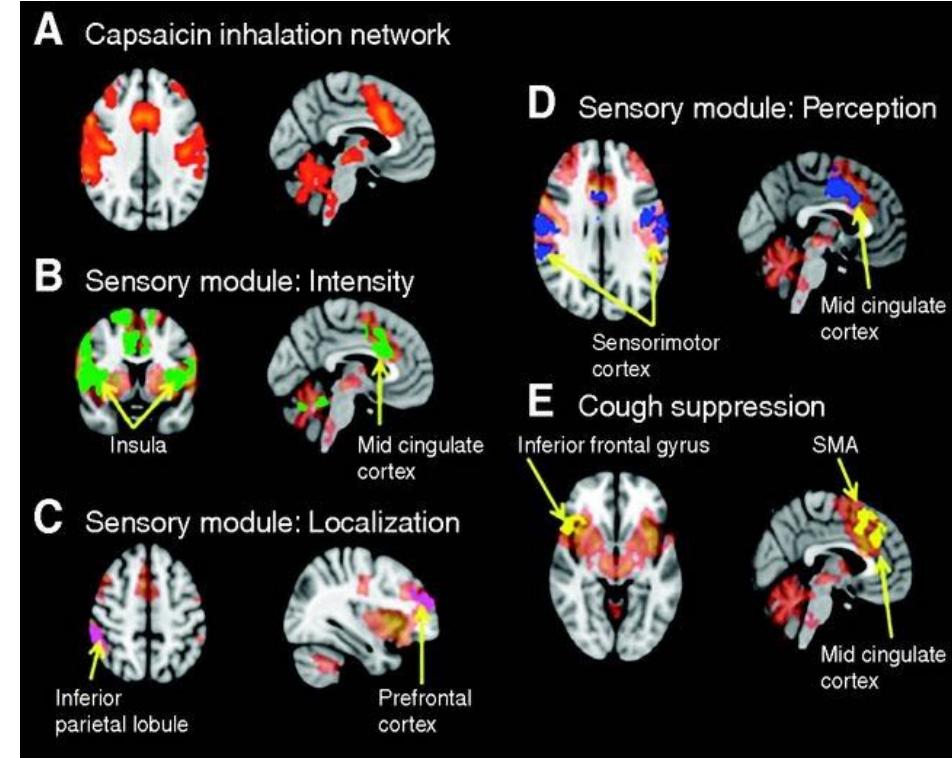
# RIFLESSI PERIFERICI ASSONICI



**FIGURE 7.** Axon reflexes, cross depolarization and antidromic reflexes, alternate modes of sensory dependent responses in the airways. Subsets of airway afferents, namely, the peptidergic nociceptors, can produce local end organ effects within the airways via classic axon reflexes. Thus peripheral stimuli can lead to Ca<sup>2+</sup> and Na<sup>+</sup> entry into the nerve terminal that leads to both the local release of neurotransmitters substance P and calcitonin gene-related peptide (SP/CGRP) at the site of stimulation, or at distal sites secondary to the antidromic conduction of action potentials along collateral sensory branches. Orthodromic action potential conduction depolarizes sensory neuron soma in the vagal ganglia leading to the somal release of signaling molecules such as CGRP, ATP, and nitric oxide (NO), which can act in a paracrine fashion to cross depolarize neighboring sensory soma. Within the central nervous system, presynaptic inputs to primary afferents help regulate synaptic transmission by depolarizing primary afferent terminals (serving to inhibit transmission). A build-up of extracellular K<sup>+</sup> and/or presynaptic transmitters can induce antidromic action potential formation within primary afferents, capable of conduction to peripheral tissues. TRPV1, transient receptor potential vanilloid receptor 1; VGSC, voltage-gated sodium channel.

# **SISTEMA NERVOSO CENTRALE: TERMINAZIONI NEUROSENSORIALI E RISPOSTE MOTORIE**





**FIGURE 6.** Central processing of the urge to cough in humans. Inhalation of the nociceptive afferent stimulant capsaicin evokes cough and related sensations. The central neural correlates of these sensorimotor processes have been studied using functional brain imaging. *Left*, A: capsaicin inhalation activates a distributed network that can be functionally divided in several subnetworks (modules) that relate to the intensity of the stimulus (B), the spatial localization of the sensation (C), the intensity of the perceivable sensation (urge to cough) (D), and the resultant voluntary suppression of cough dictated by the imaging protocol (participants were instructed not to cough) (E). [Adapted from Mazzone et al. (291).] *Right*: a summary figure of the putative central networks regulating cough sensory processing. nTS, nucleus of the solitary tract; Pa5, paratrigeminal nucleus; OFC, orbitofrontal cortex; aMCC, anterior mid-cingulate cortex; M1/S1, primary motor and sensory cortices; PPC, posterior parietal cortex.

