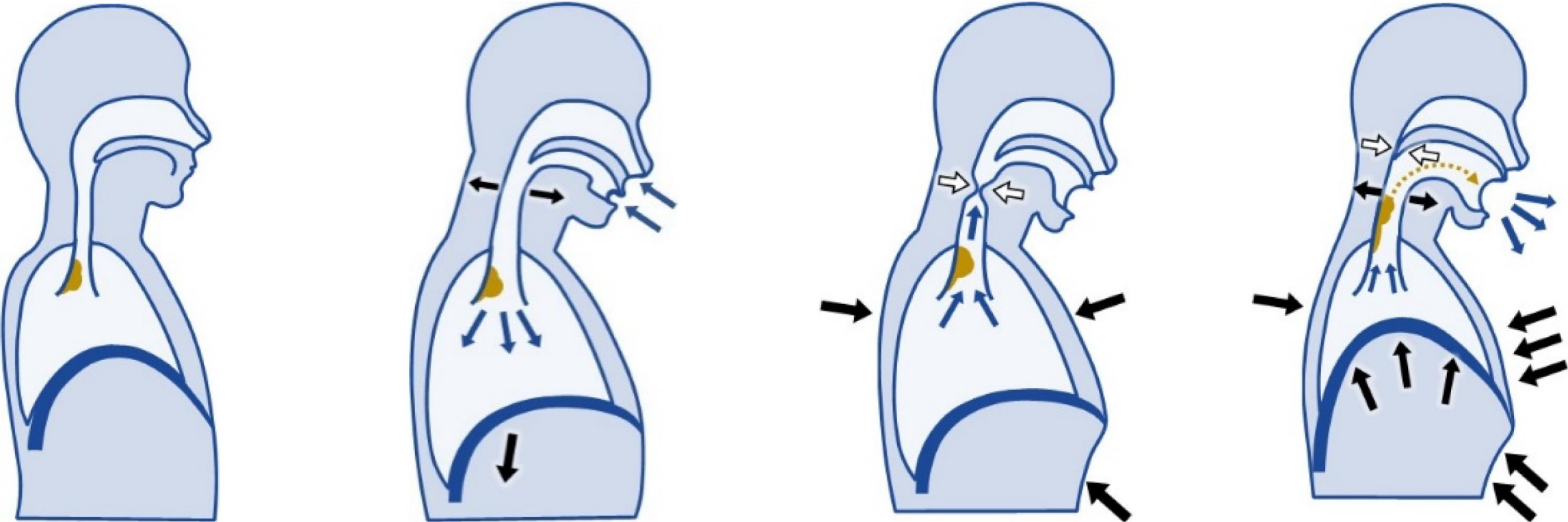


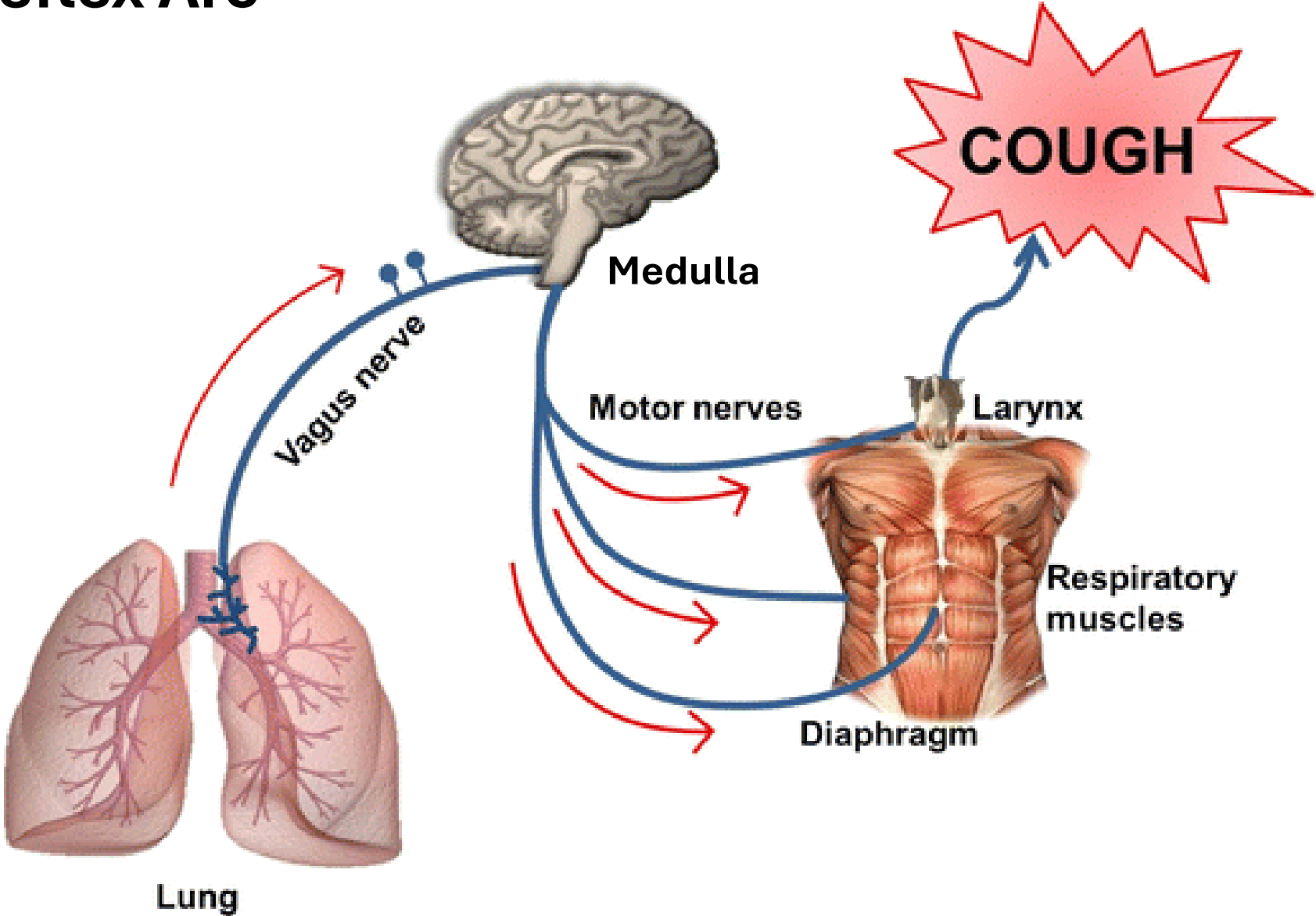
Pathophysiology and Mechanisms of Chronic Cough

서울대병원 윤정기

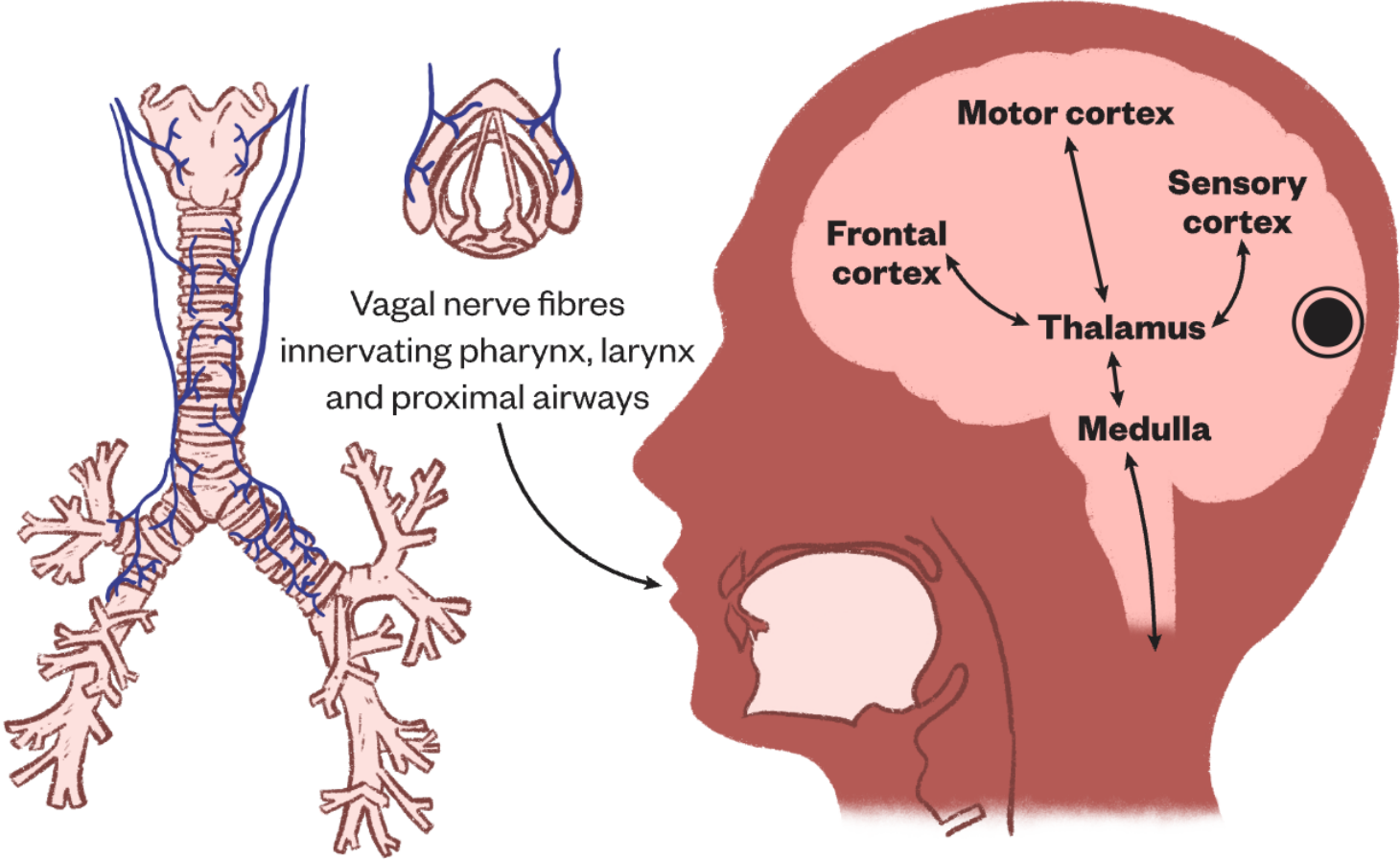
Phases of a Cough



Cough Reflex Arc



Central Nerve System of Cough

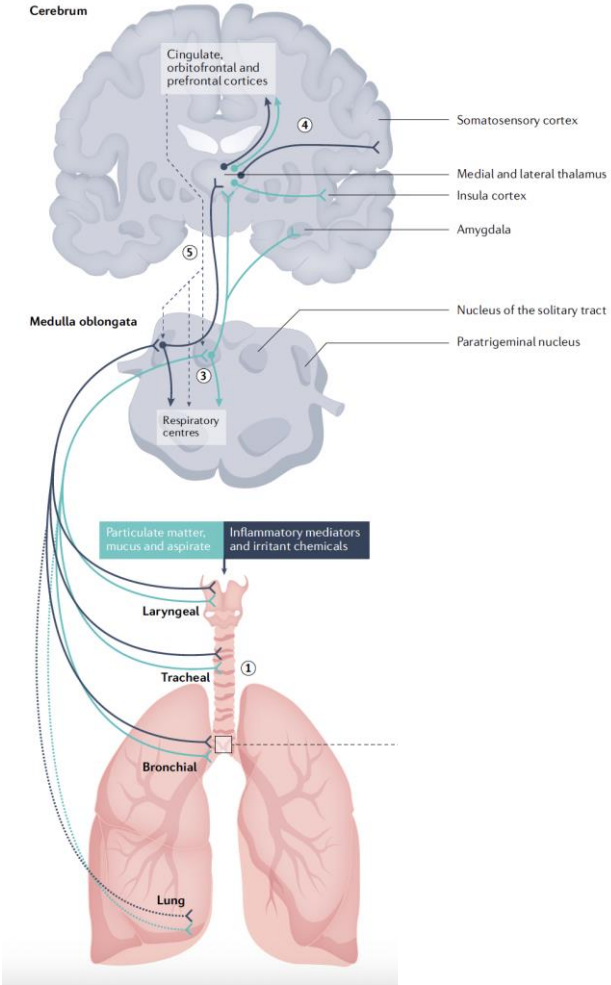


Neural Pathways

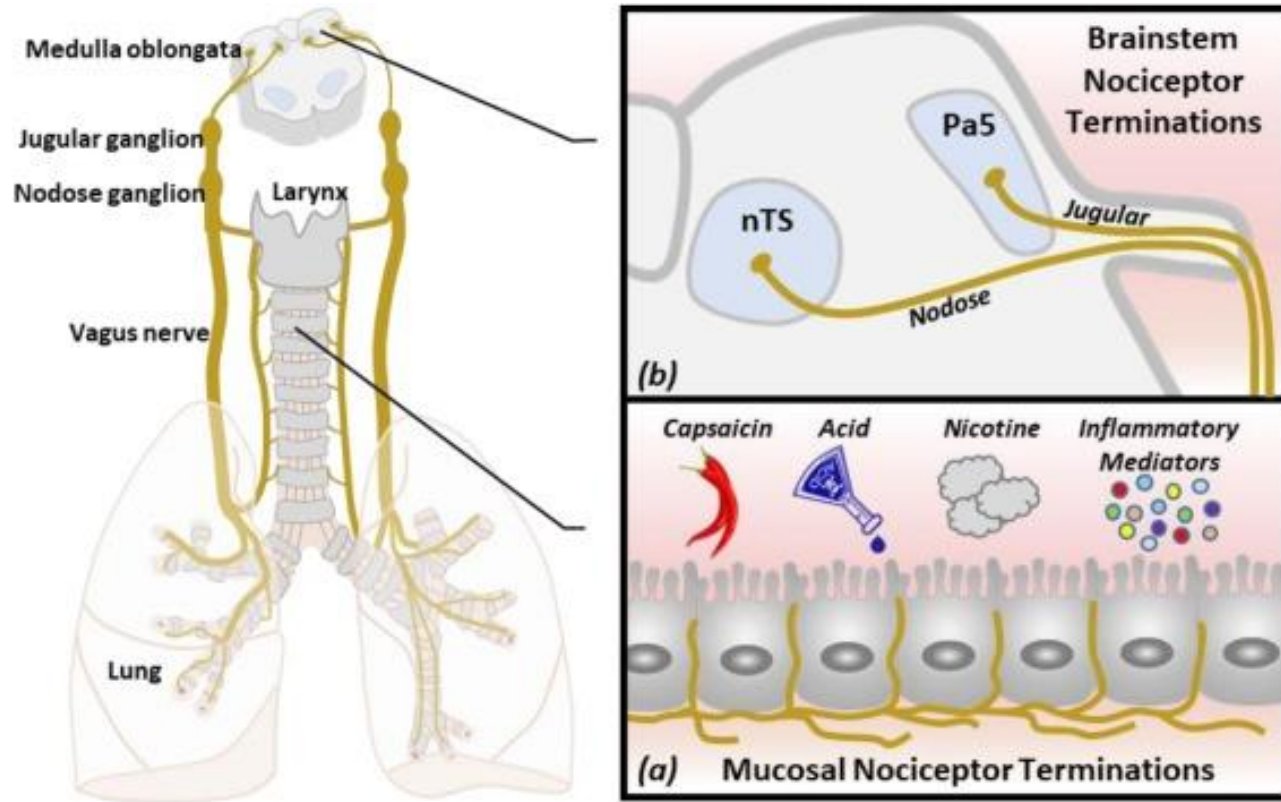
Cortex

Brainstem

Vagus nerves



Vagal Sensory Neurons



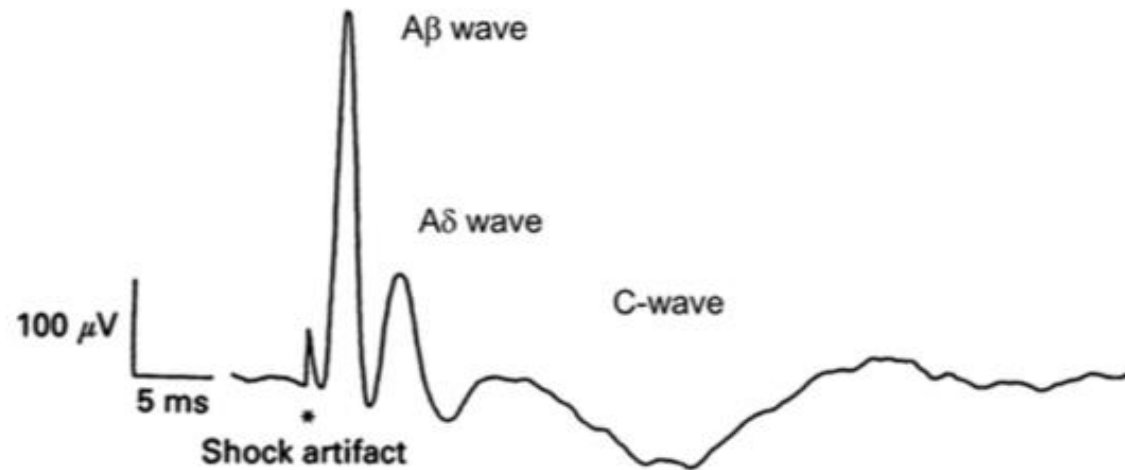
Nodose ganglia

- not-related to neural crest
- mechanical stimuli

Jugular ganglia

- neural crest origin
- neuropeptide

Vagal Sensory Neurons



A β /A δ -fiber

: myelinated

: 5~42m/s

C-fiber

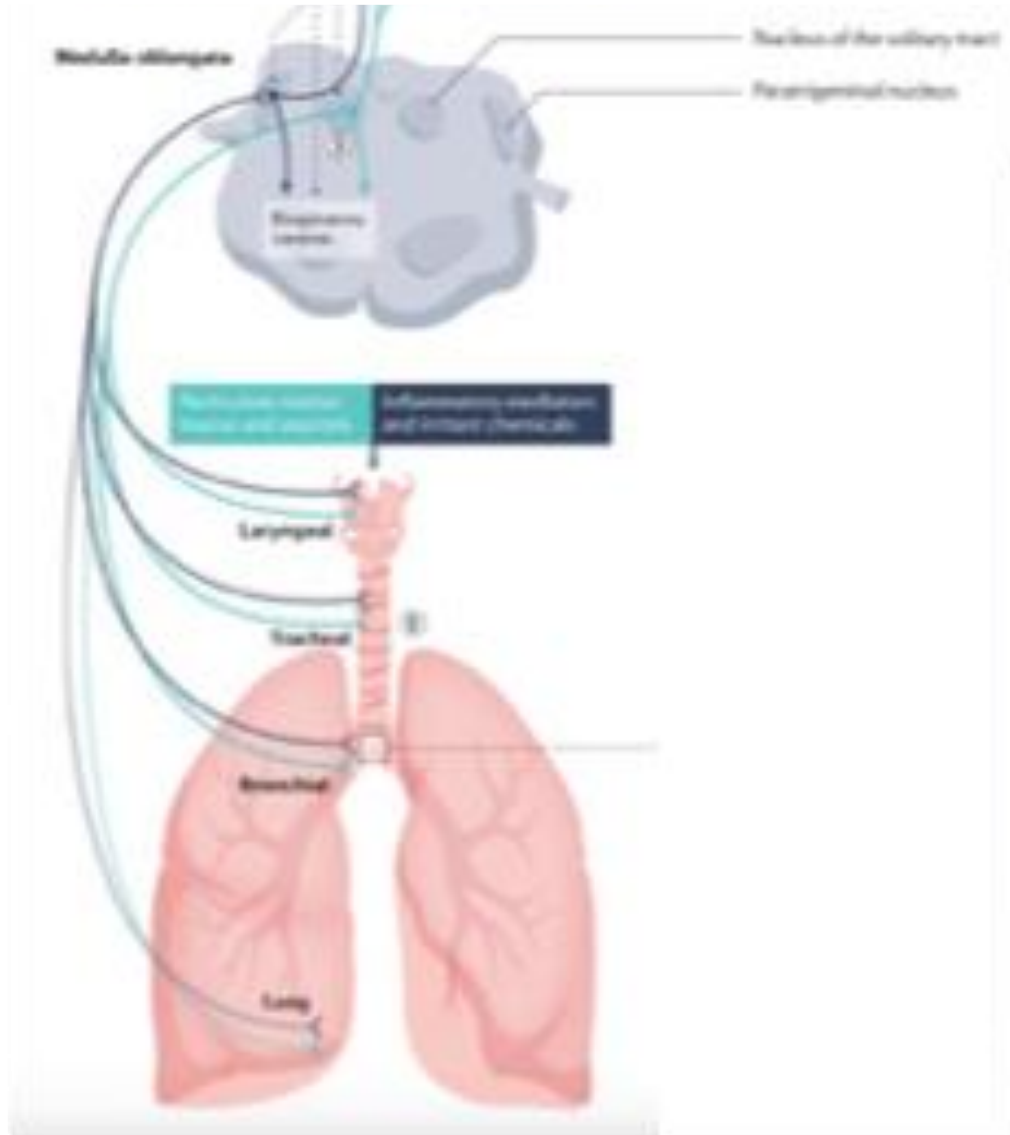
: unmyelinated

: 0.8~1.5m/s

Vagal Sensory Neurons

	Jugular Ganglia			Nodose Ganglia		
Defining molecular profiles	Runx1/Wnt1 (during development only), neuropeptides (SP/CGRP) ^a , P2X3, TRKA, GFR α 3		Phox2a/Phox2b	(during development only), 5-HT3 receptor, P2X2, P2X3, TRKB		
Fiber type	C-fibers	A δ -fibers	C-fibers	A δ -fibers	A β -fibers	
Common names	Nociceptors, chemosensors	A δ -nociceptors	Nociceptors, chemosensors	Cough receptors	RARs	SARs
Conduction velocity, m/s	~1	~6	~1	~5	~15	~18
Terminations						
Extrapulmonary	Many	Some	Few	Many	Few ^c	Few ^c
Intrapulmonary	Some	Some	Many	Some ^b	Many	Many
Responsivity						
Punctate mechanical ^d	No	No	No	Yes	Yes	Yes
Tissue stretch ^d	No	No	No	No	Yes	Yes
Bronchoconstriction	No	No	No	No	Yes	Yes
Capsaicin	Yes ^e	Yes	Yes ^e	No	No	No
Acid	Yes	Yes	Yes	Yes	Unknown	Unknown
ATP	No	No	No	No	Yes	Yes
Physiological responses	Apnea, cough	Unknown	Tachypnea, bronchoconstriction	Cough	Tachypnea, bronchoconstriction	Hering-Breuer, bronchodilation

Vagal Sensory Neurons for Cough



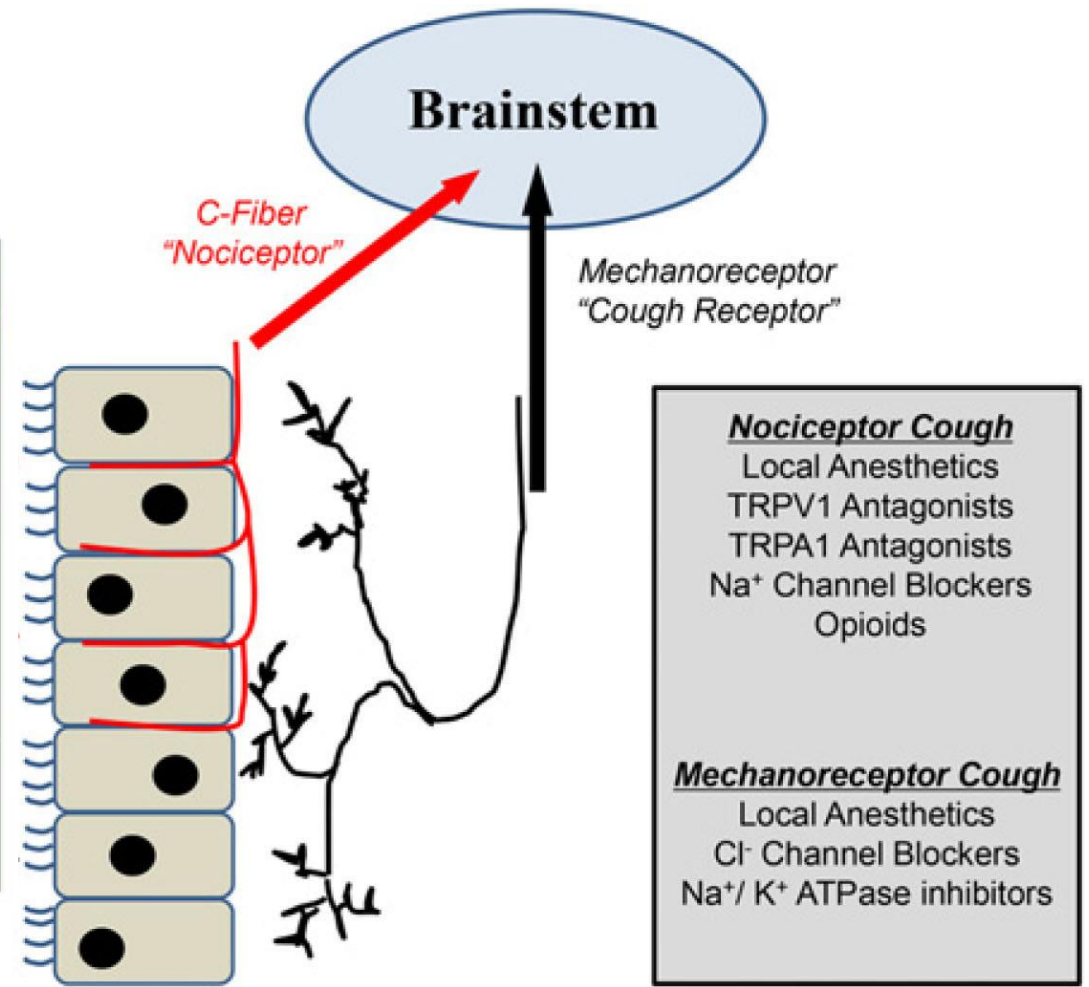
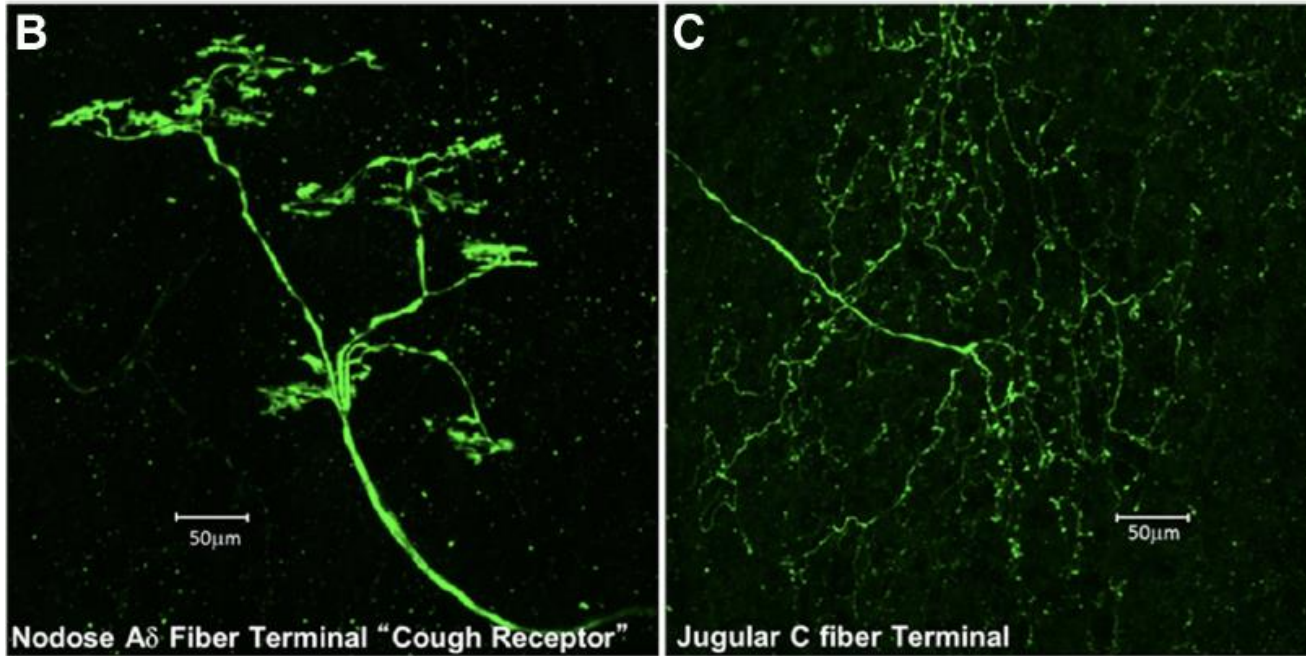
**A δ -fiber from nodose ganglia
= cough receptor**

Mechanical stimuli
(aspirated particles, mucus, gastric contents)

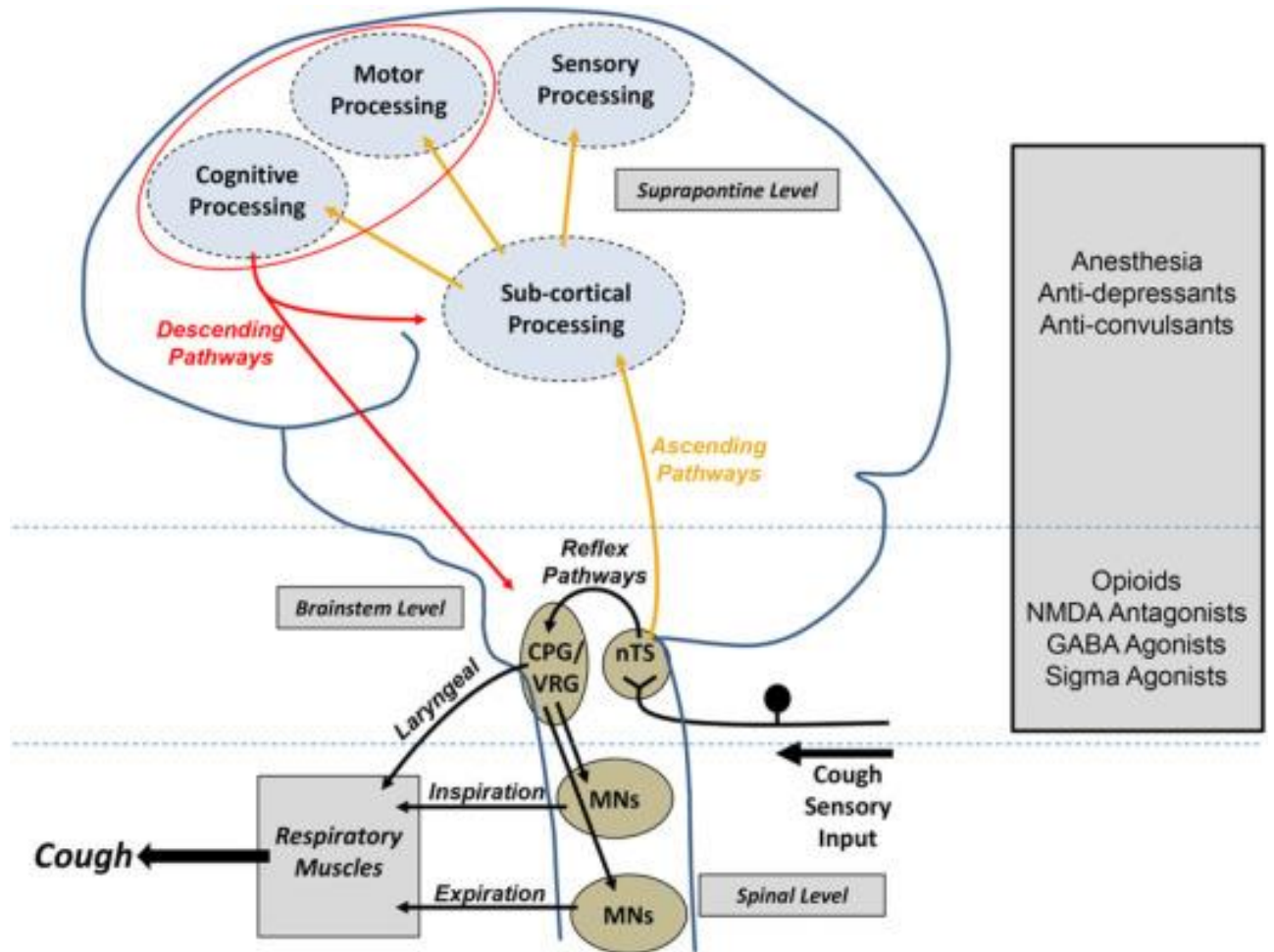
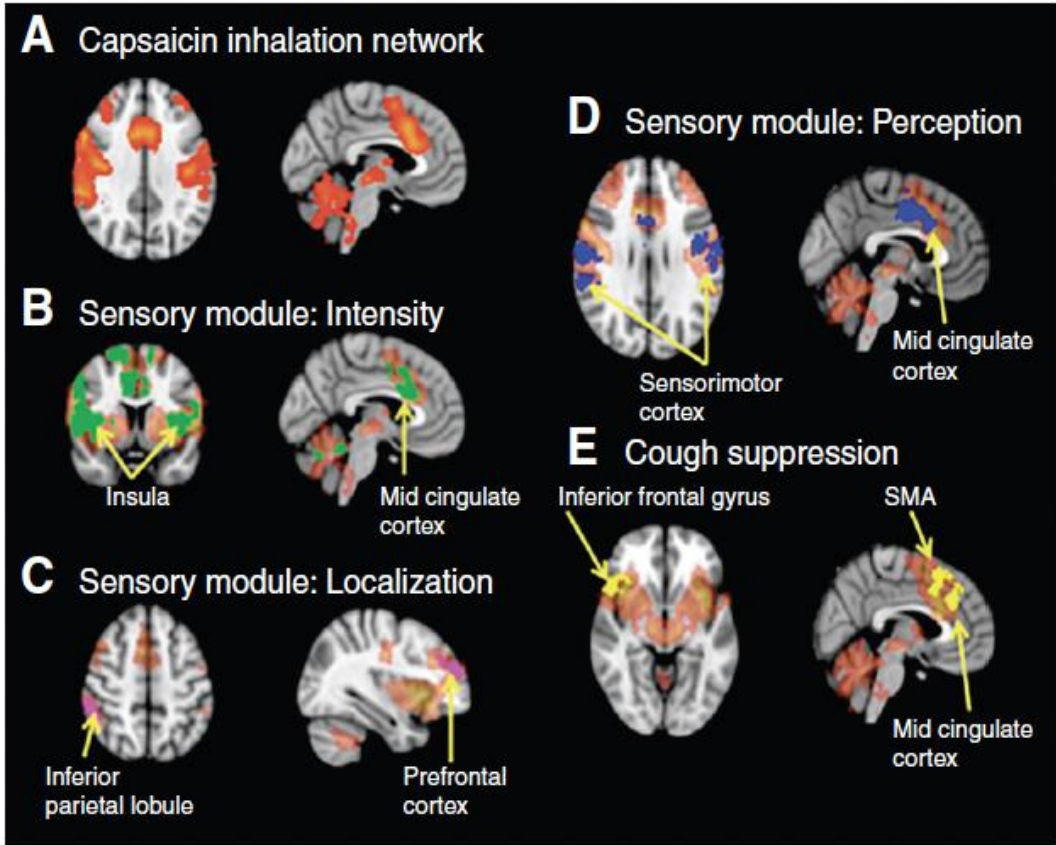
**C-fiber from jugular ganglia
= nociceptor**

Irritant chemicals, inflammatory mediators
or tissue damages

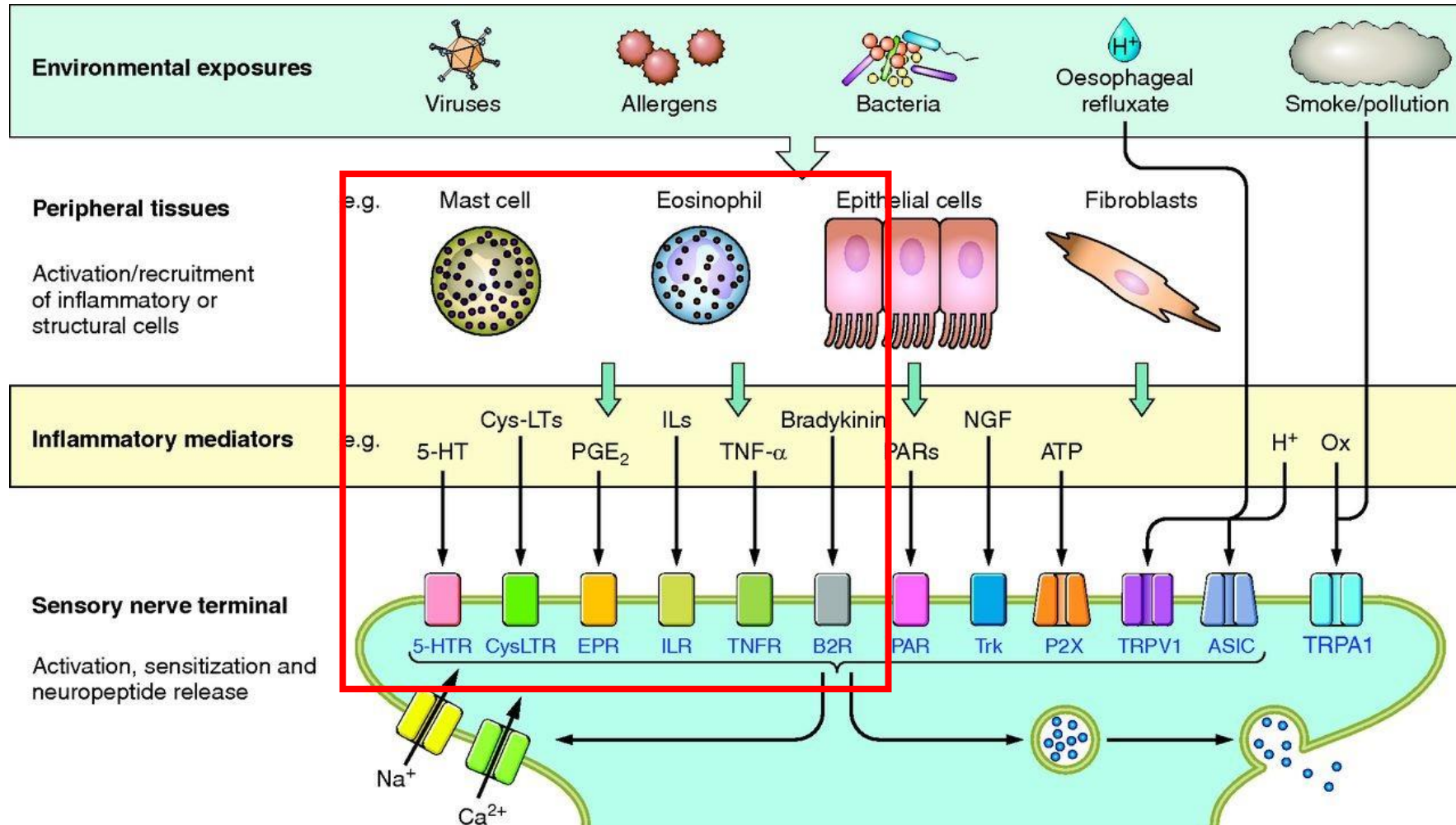
Vagal Sensory Neurons for Cough



Central Areas for Cough

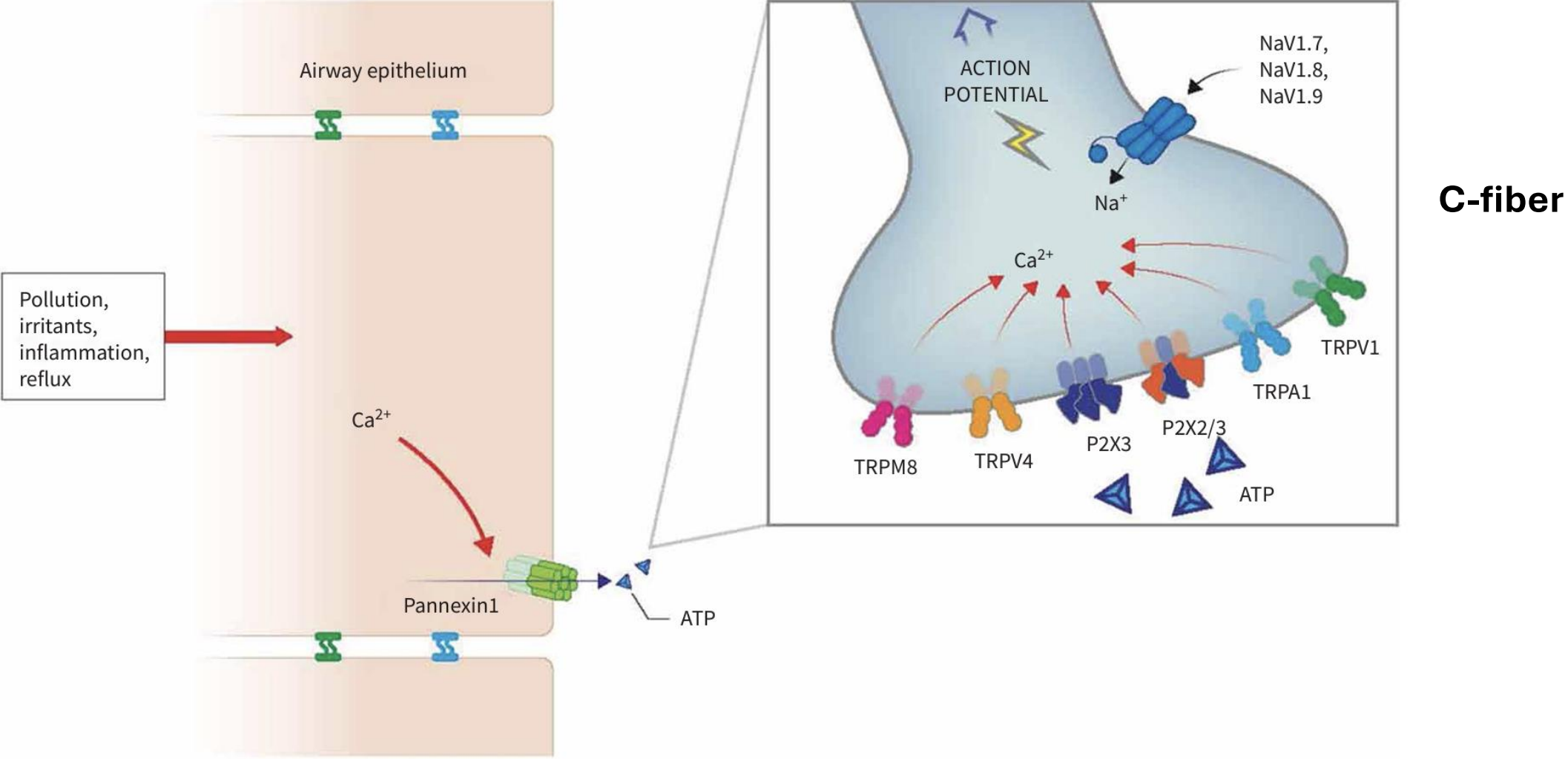


Peripheral Activations (Cytokine-mediated)

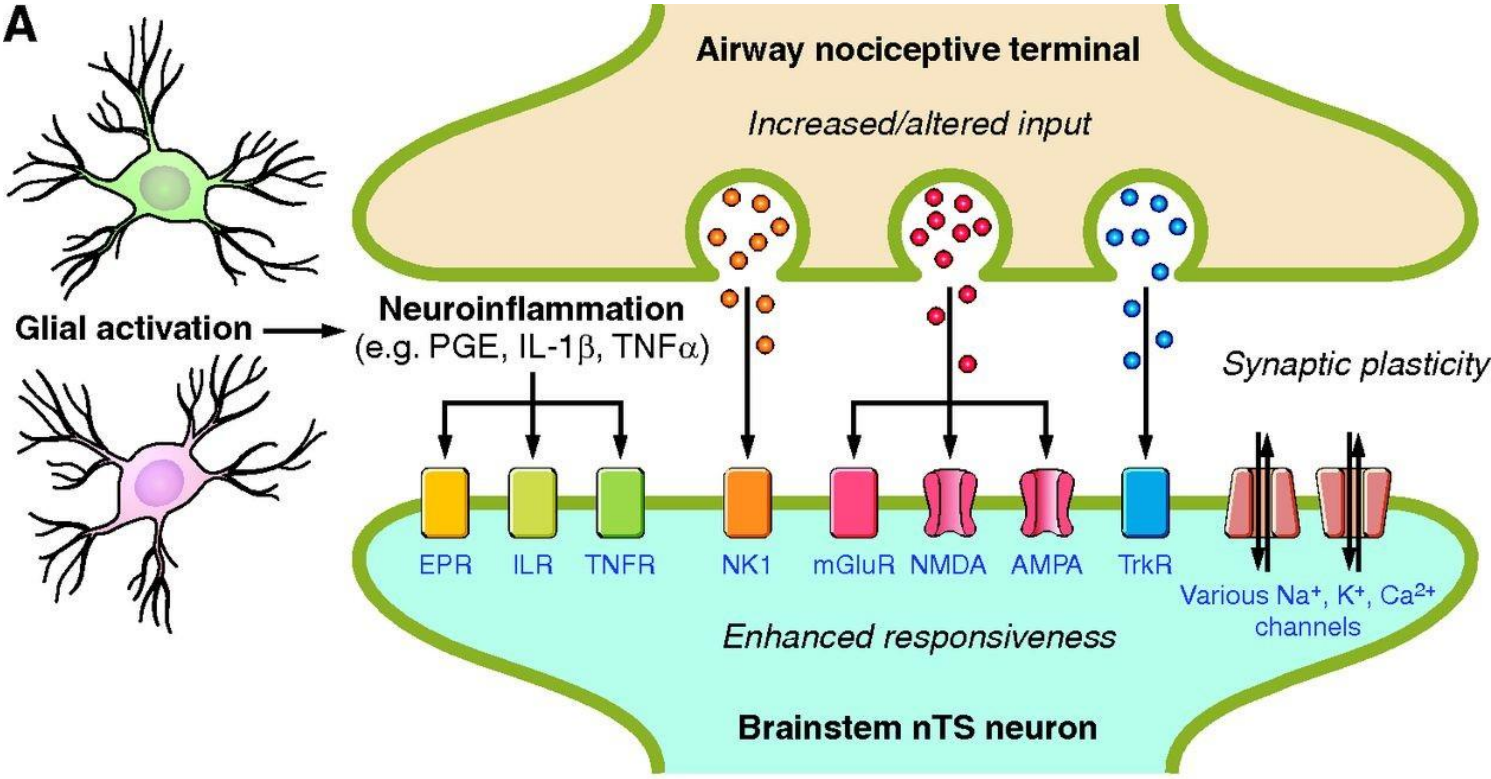


Peripheral Activations (Peptide/lipid-mediated)

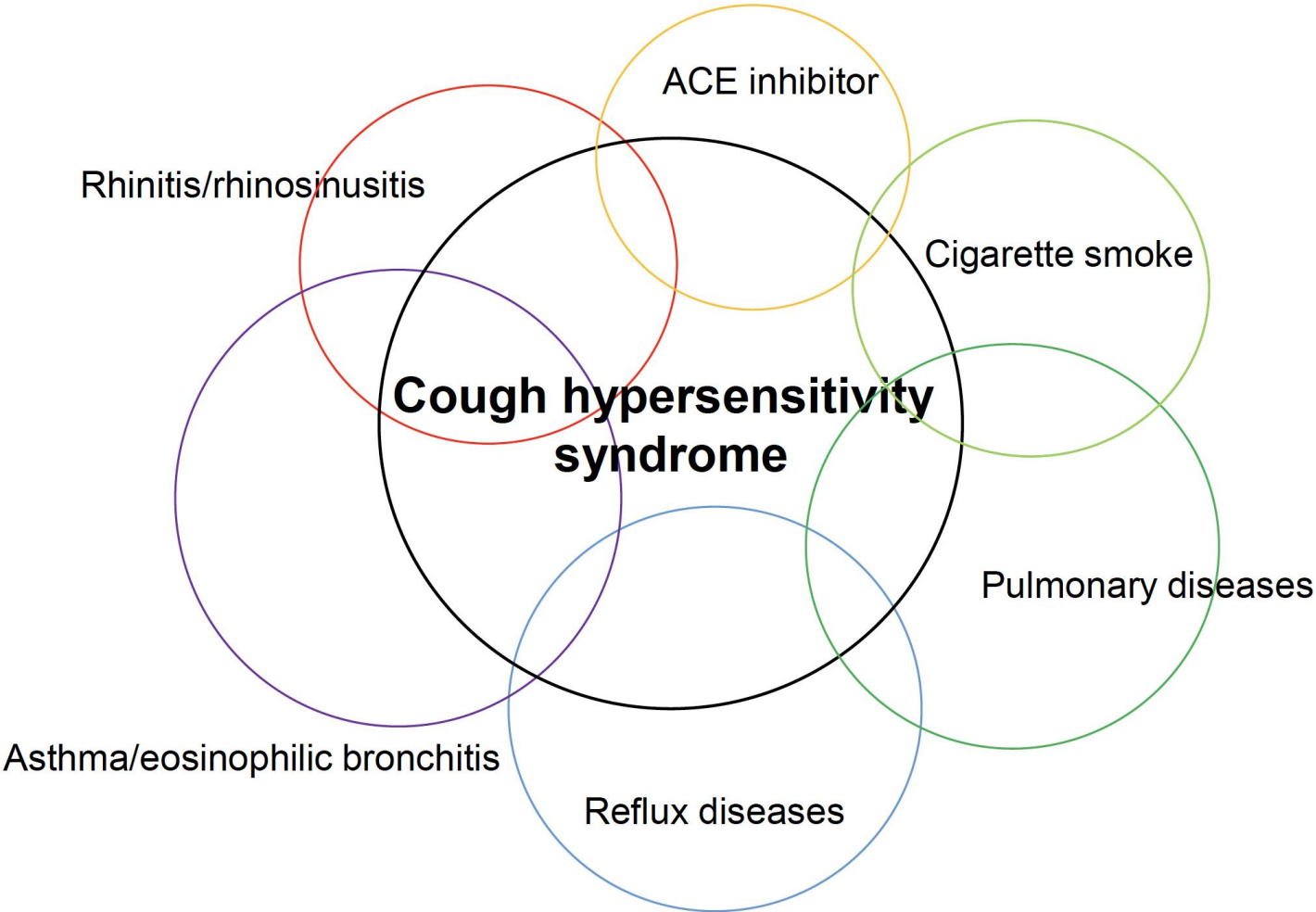
b)



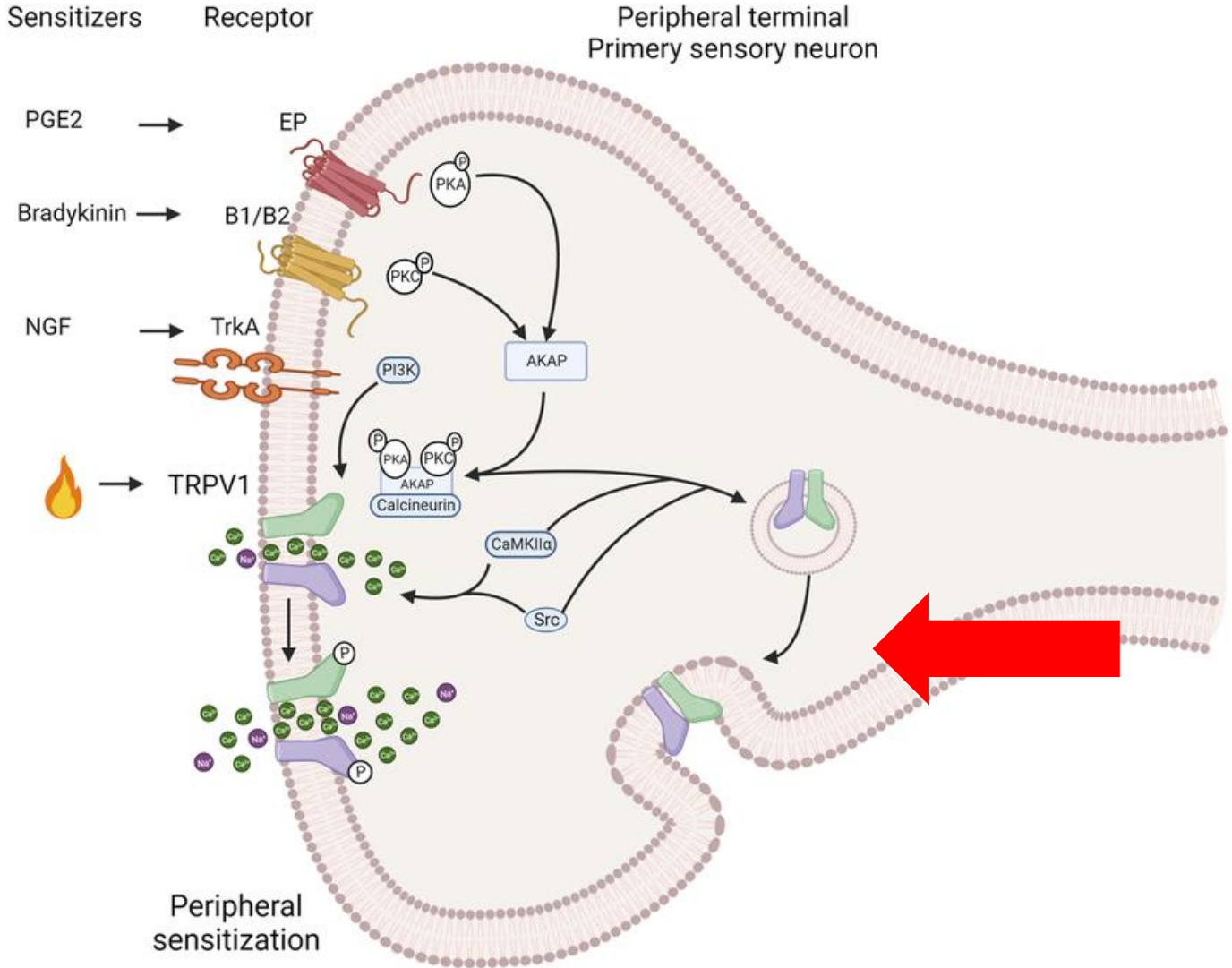
Central Activations



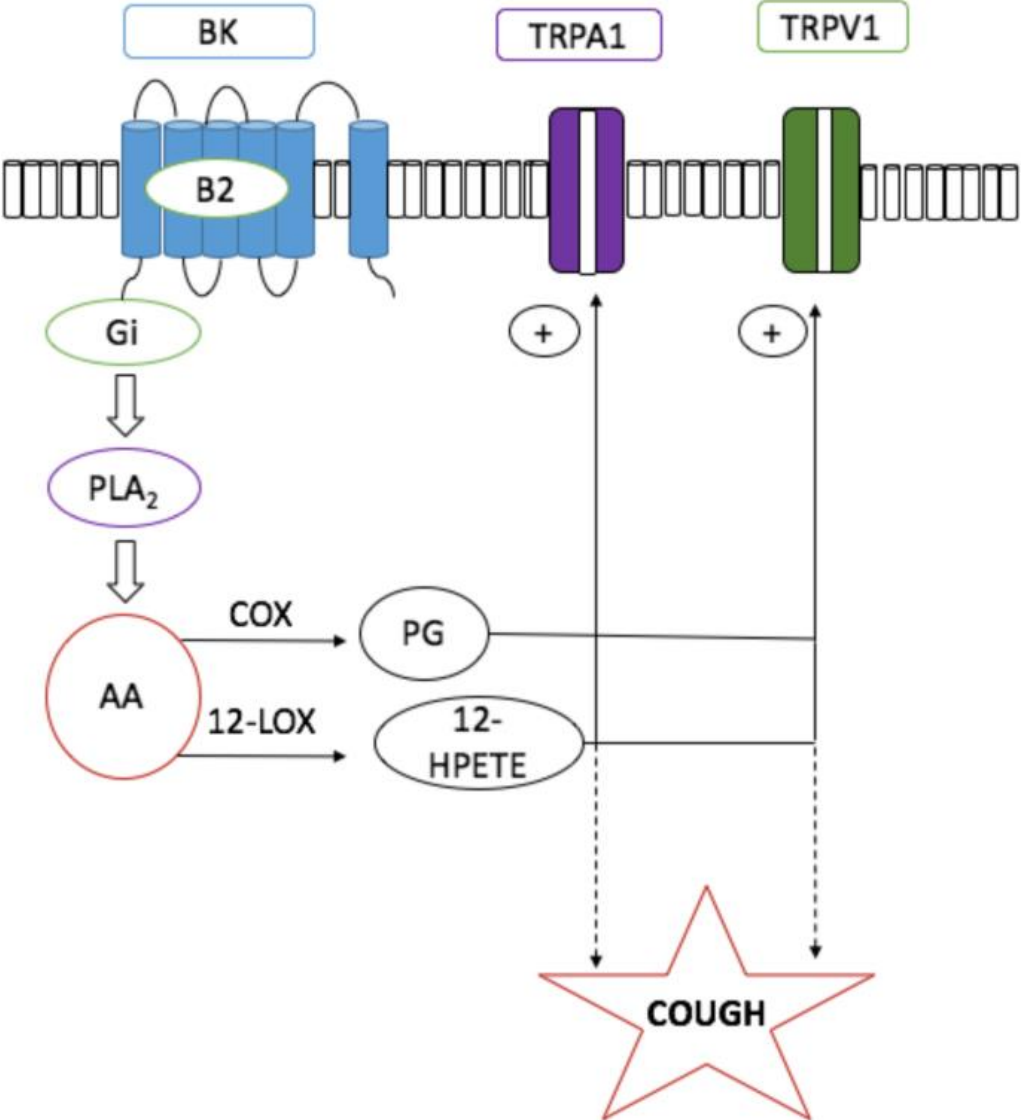
Cough Hypersensitivity Syndrome



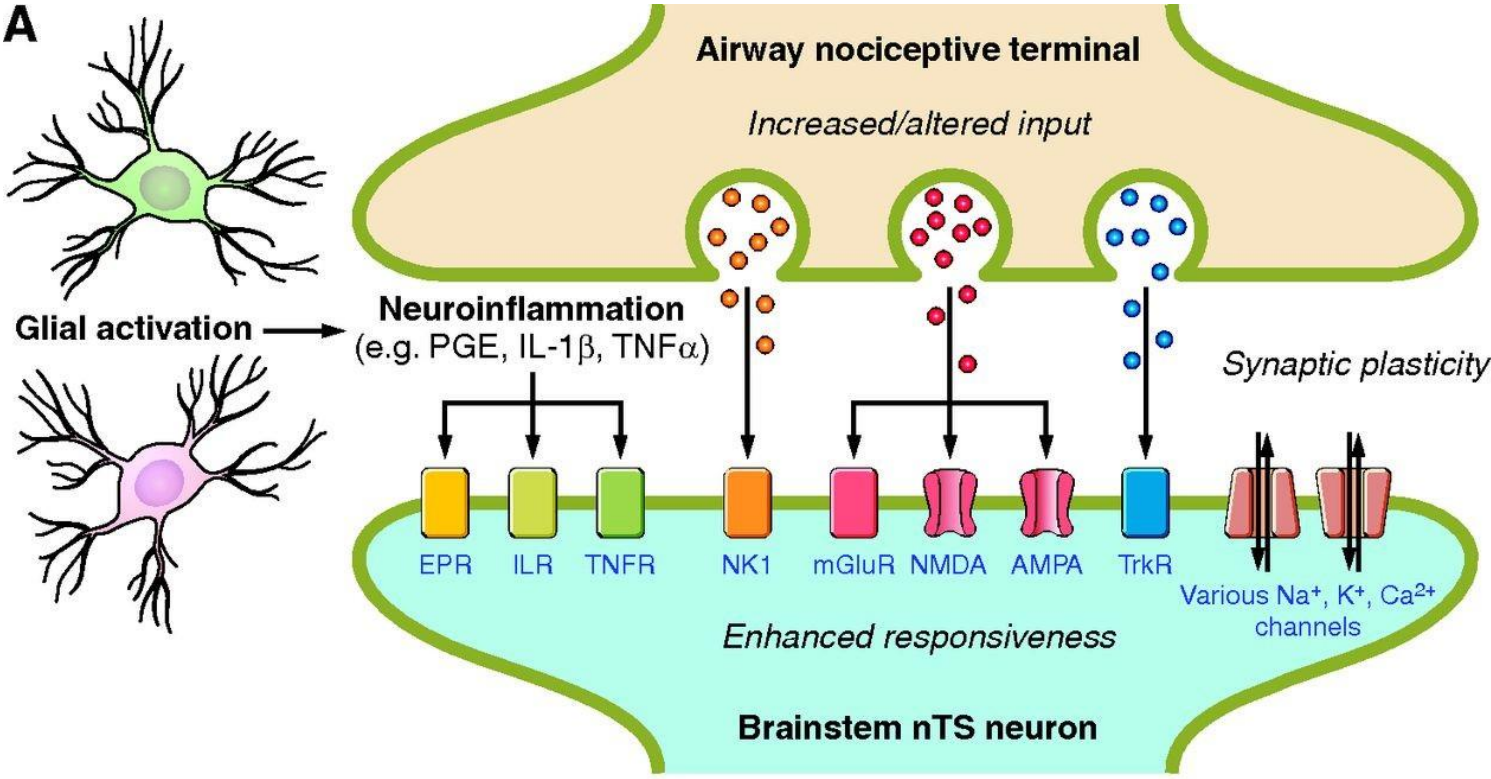
Peripheral Sensitization



Peripheral Sensitization (Bradykinin)



Central Sensitization



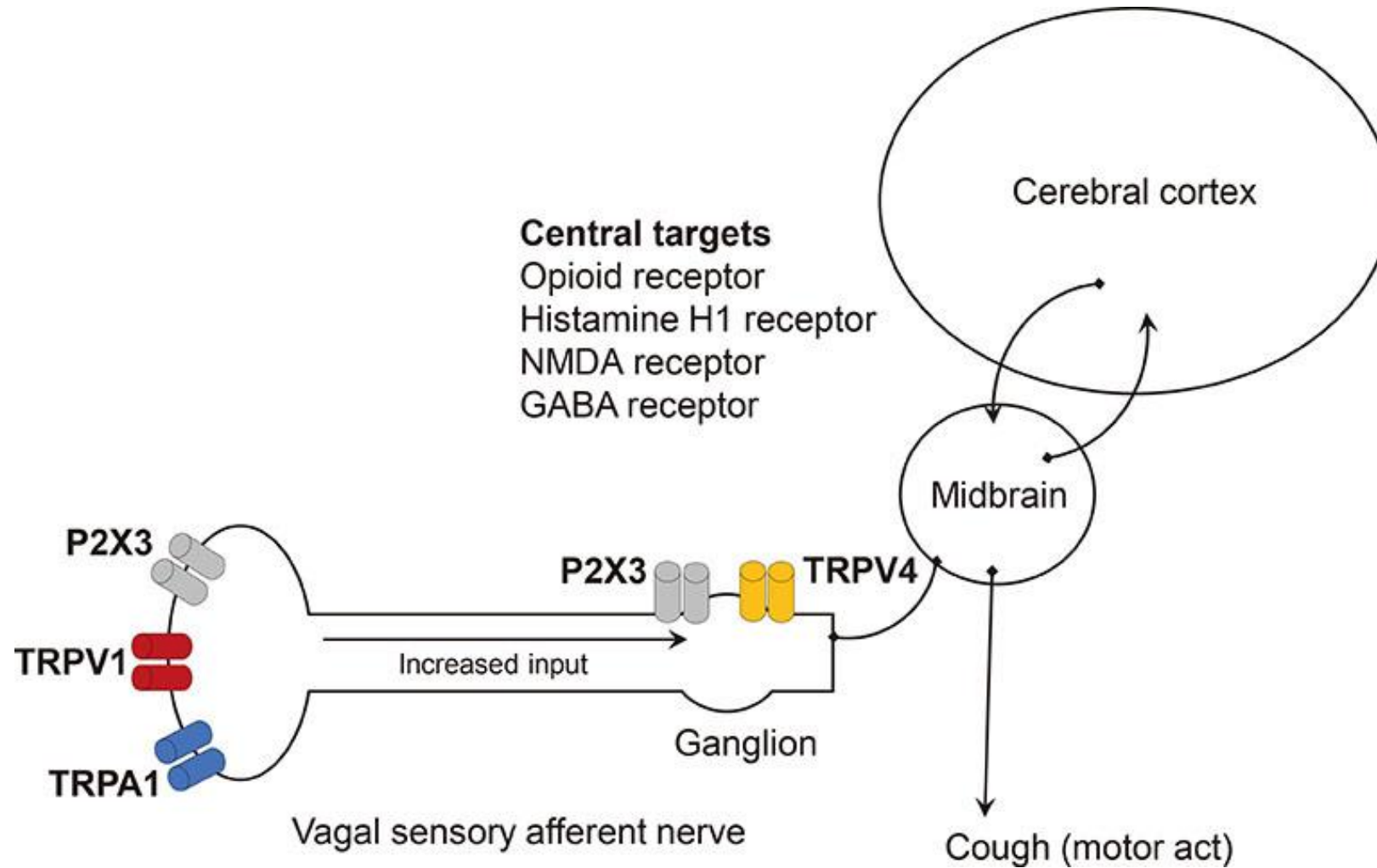
Anti-tussive Drugs

- **Codeins/morphine**: central acting, opioid receptors
- **Gabapentin, pregabalin**: central acting, opioid receptors
- **Dextromethorphan**: central acting

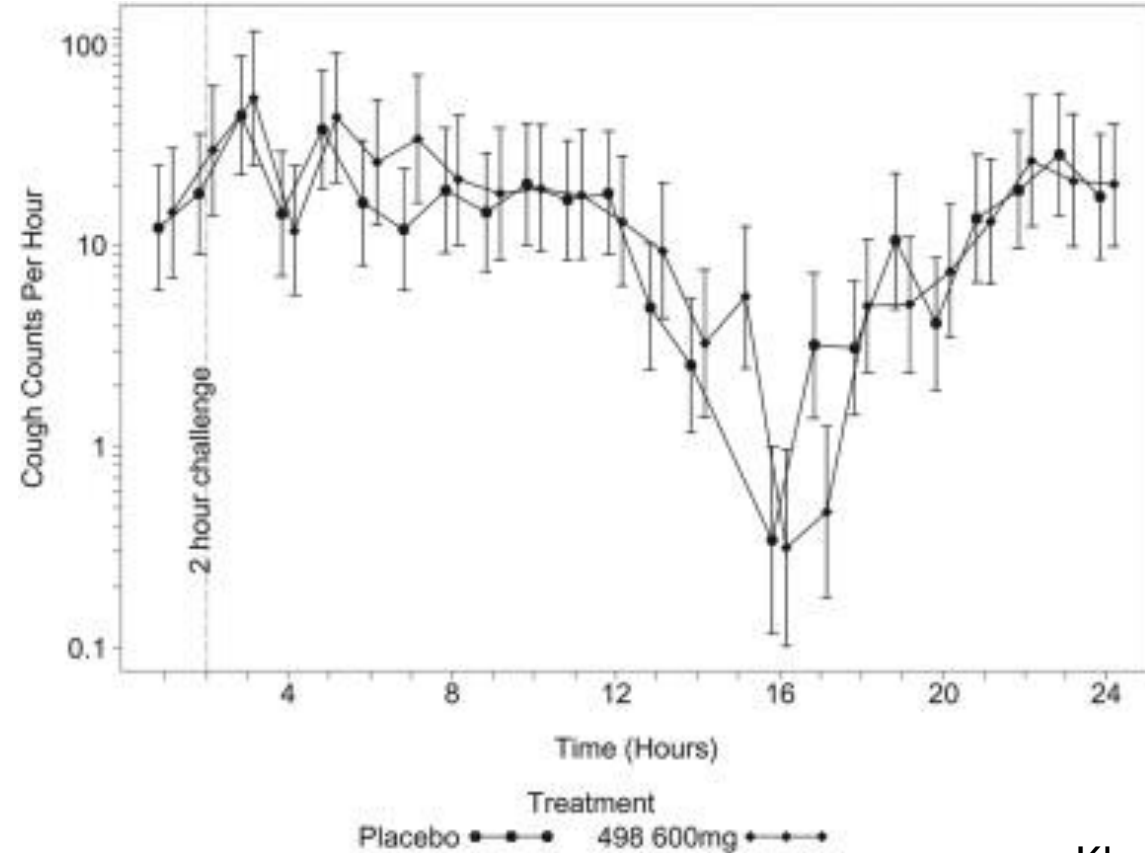
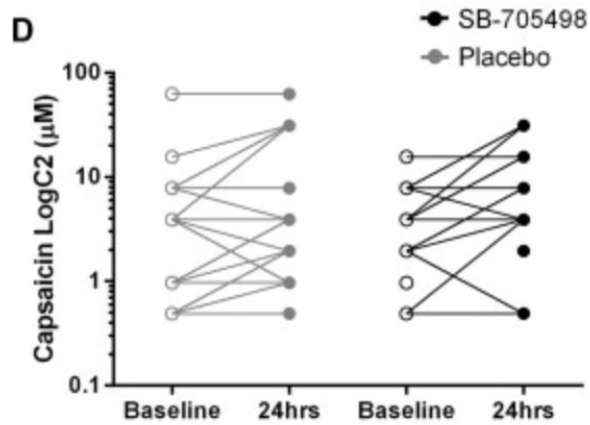
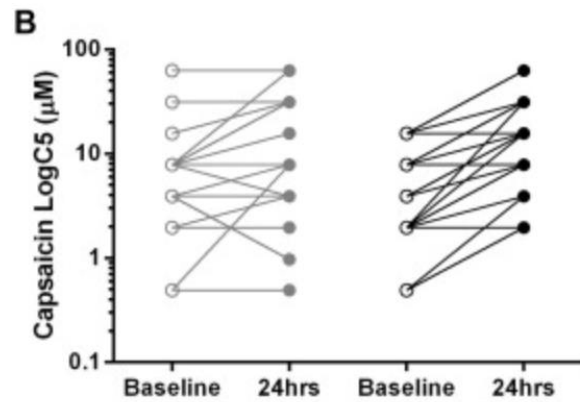
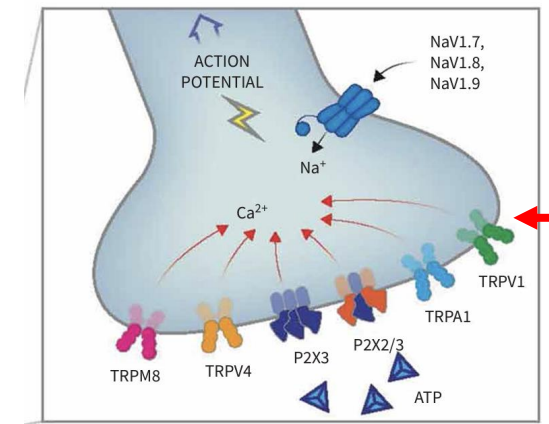
- **Levodropropizine**: peripheral acting (suppress C-fiber activity)
- **Theobromine** : alkaloid, suppress vagal activity

➔ Off-label use!

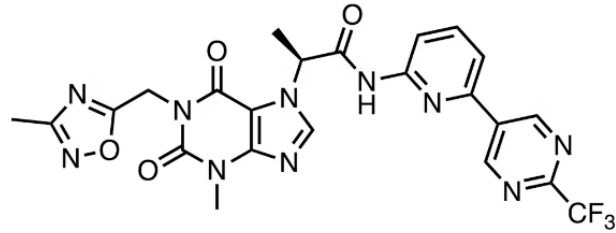
Targets in Chronic Hypersensitivity Syndrome



TRPV1 antagonist (SB-705498)



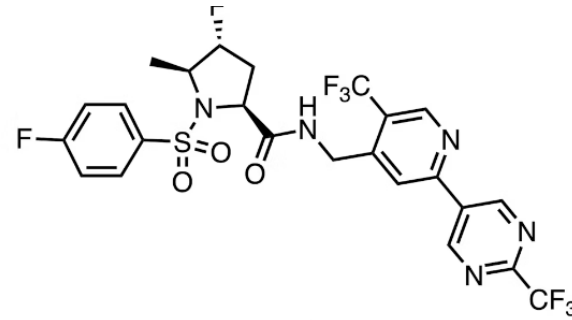
TRPA1 antagonists



LY3526318

TRPA1 antagonist
Ph. II - recruiting

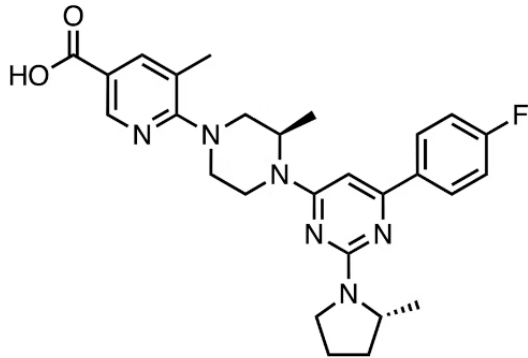
HYDRA BIOSCIENCES & LILLY



GDC-0334

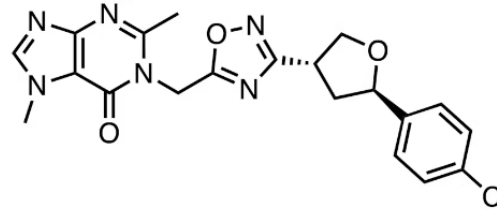
TRPA1 antagonist
Ph. I - terminated

cyno/dog neurological findings
GENENTECH



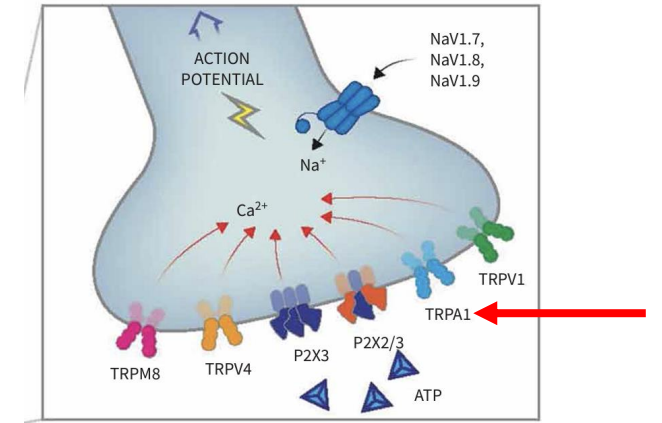
MK-2295

TRPV1 antagonist
Ph. II - discontinued
NEUROGEN & MERCK

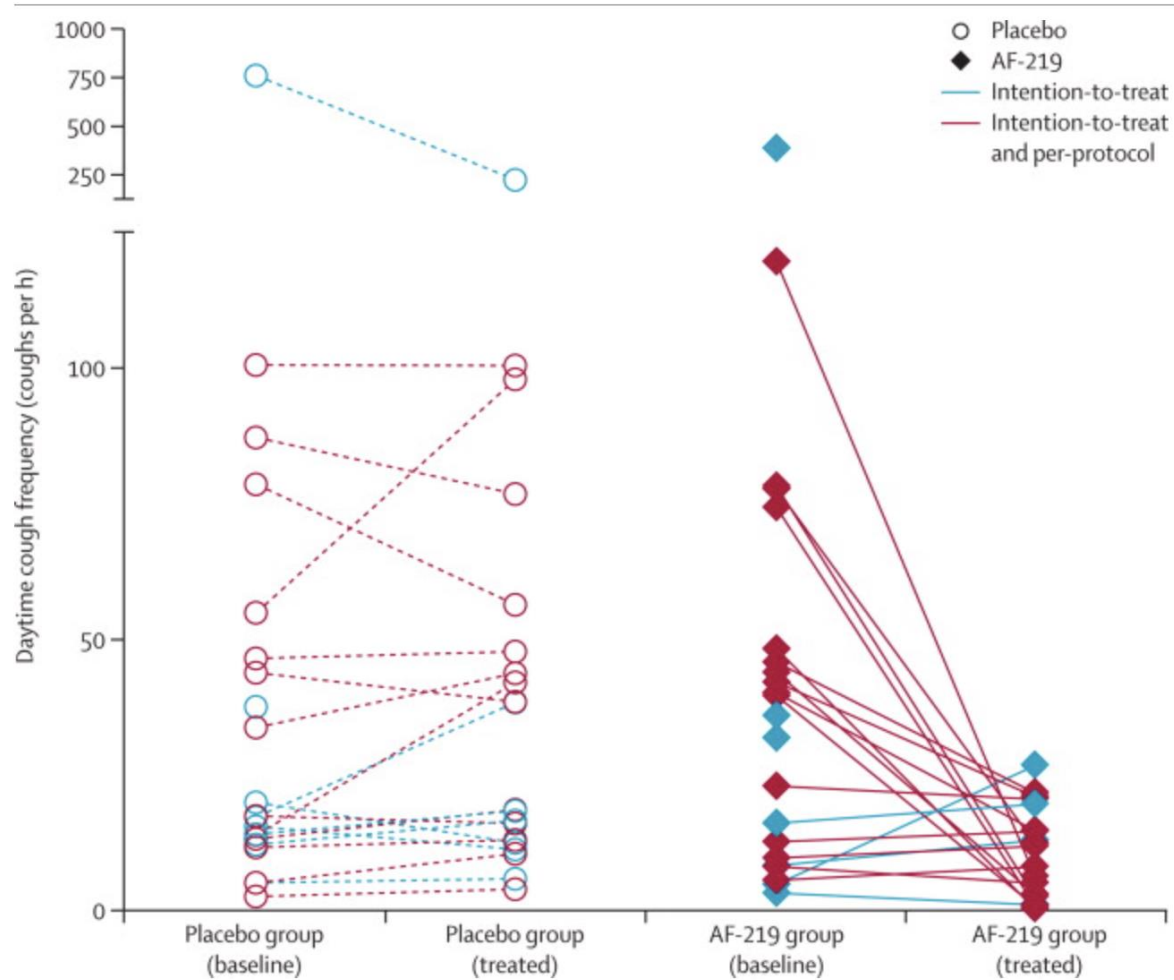
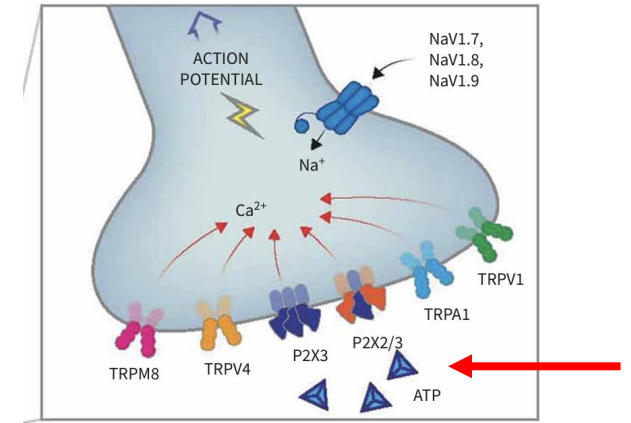


GDC-6599

TRPA1 antagonist
Ph. IIa - ongoing
GENENTECH



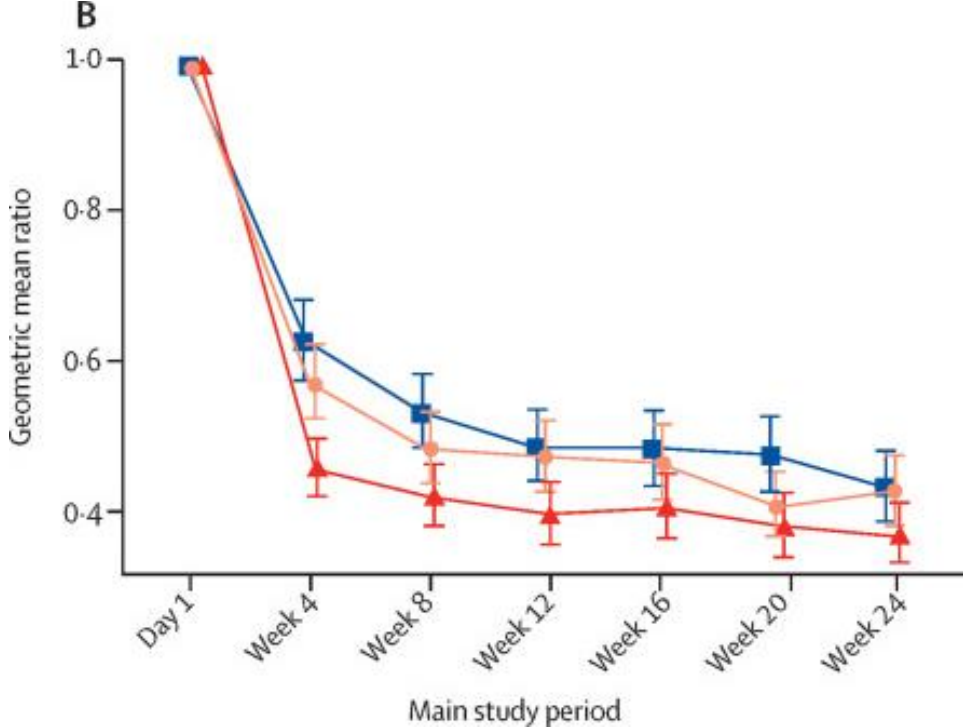
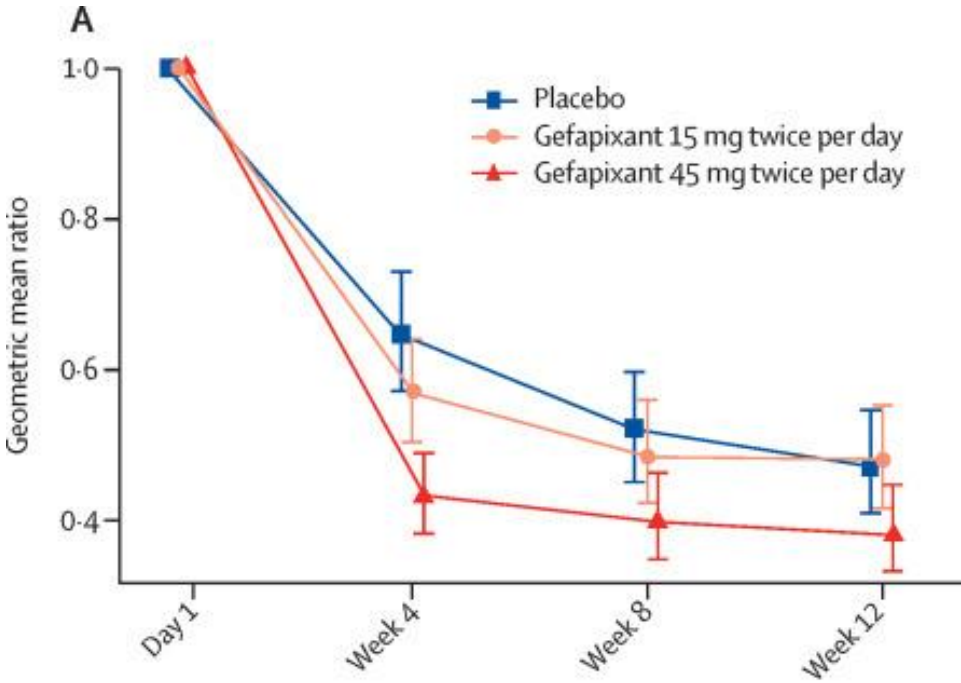
P2X2/3 Receptor Antagonist; Gefapixant



88% reporting tasting disturbance
→ Dose-related

P2X2/3 Receptor Antagonist; Gefapixant

COUGH-1, COUGH-2



P2X2/3 Receptor Antagonist; Gefapixant → Lyfuna

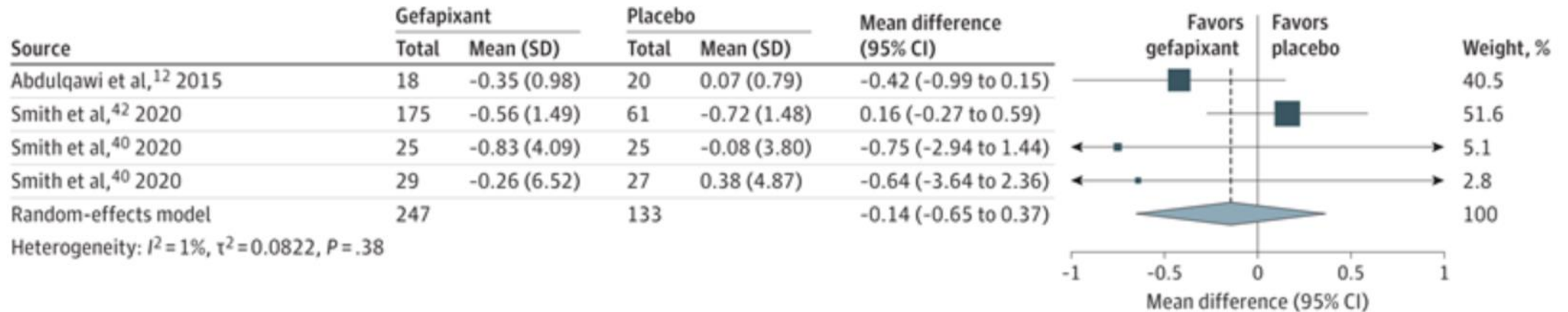


First approved drug for Refractory or Unexplained chronic cough

P2X2/3 Receptor Antagonist; Gefapixant

Meta-analysis

C Pooled mean difference in log-transformed sleep cough frequency among patients with refractory or unexplained chronic cough who received gefapixant vs placebo in 4 RCTs



→ FDA declined to approval due to lack of efficacy

Highly Selective P2X3 Receptor Antagonists

Eliapixant

PAGANINI study (Phase 2b)

Dysgeusia 1~16%

→ Terminated d/t toxicity issue

Sivopixant

Phase 2a

31% reduced 24h cough count

Dysgeusia 6%

Filapixant

Phase 2a

25% reduced

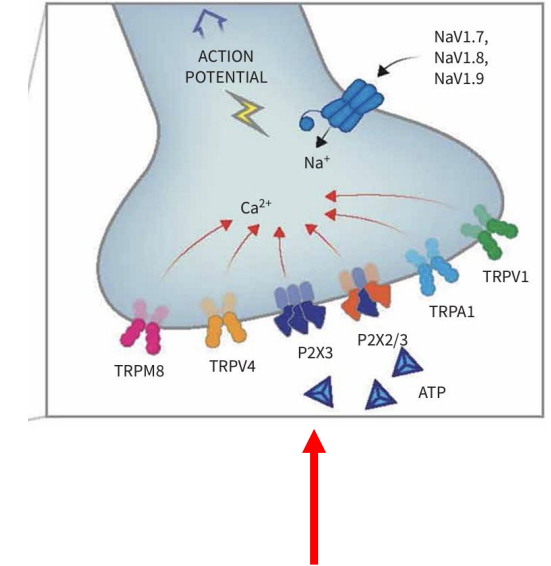
Dysgeusia 20%

Camlipixant

SOOTHE study (phase2b)

30% reduced

Dysgeusia 5%



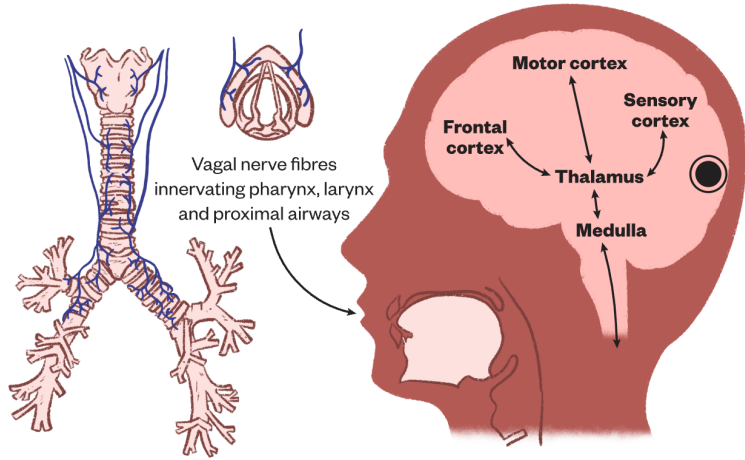
Dicpinigaitis, Lung, 2023

Niimi, ERJ, 2022

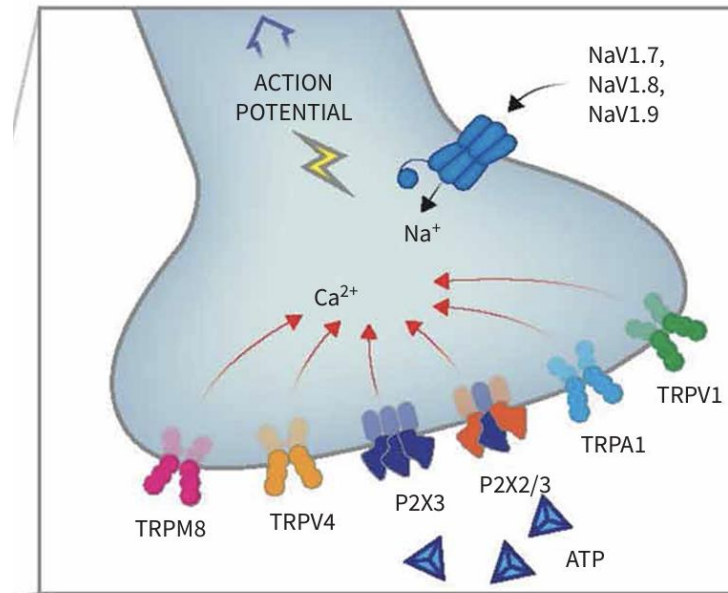
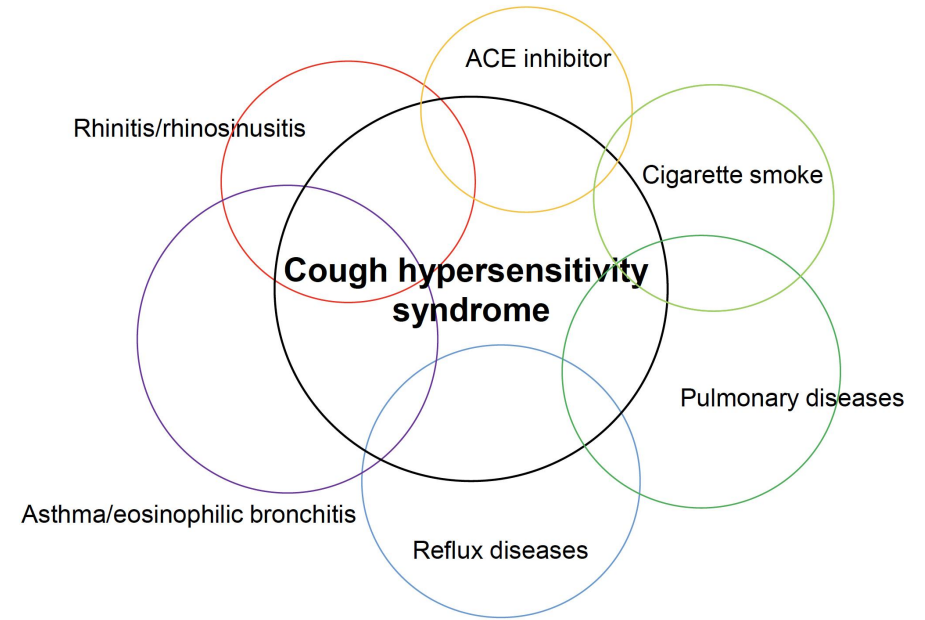
Morice, ERJ, 2021

Bonuccelli, AJRCCM, 2021

Summary



A δ -fiber
C-fiber



C-fiber