

Cough Hypersensitivity Syndrome

- From neurobiology to clinical phenotyping-

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Contents

- Cough hypersensitivity syndrome
- Mechanism/Neurobiology
- Phenotype
- Treatable trait

Chronic cough

- Cough $\geq$ 8 weeks
- 성인 인구의 약 9-10% 가 만성 기침을 경험하며, 전 세계적으로 가장 흔한 호흡기 증상 중 하나임.
(미국에서 호흡기내과 외래 방문환자의 38%가 기침임)
- 표준 진단 절차를 통해, 폐암, 흡연, 기침 유발 약물을 제외하고, 천식, GERD, allergic rhinitis 등 흔한 원인들을 배제하여도 최대 약 40% 에서는 기침이 지속되는 "Refractory cough", "Unexplained chronic cough"로 남음

Chronic cough as a neuropathic disorder

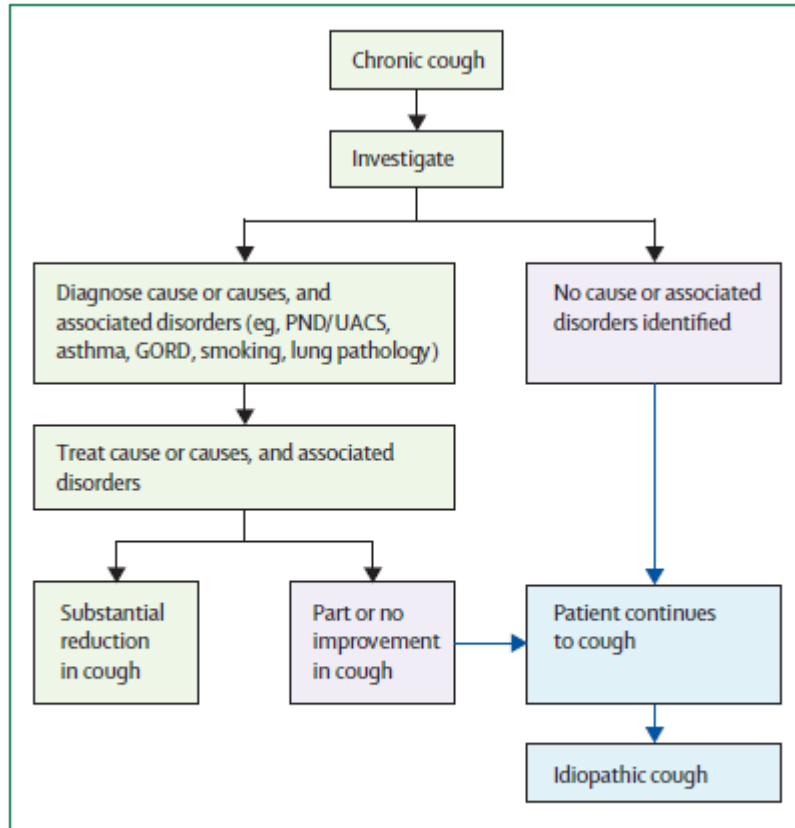


Figure 1: Diagnostic approach to chronic cough
PND/UACS—post-nasal drip/upper-airway cough syndrome.
GORD—gastro-oesophageal reflux disease.

- Urge to cough (목이 간질간질함), Allotussia (자극이 아닌데도 기침함), Hypertussia (작은 자극에도 기침함) 등의 증상을 경험하게 된다.
- 이에 대한 병태생리학적 기전은 "기침 반사 기전의 병적 변화", "sensory neuron 의 dysregulation" 으로 설명됨.
- Chronic cough 를 neuropathic disorder 로 보는 새로운 개념이 대두됨. (sensory neuropathy 를 유발하는 vitamin B₁₂ 결핍 기침 환자에서 vitamin B₁₂ 보충 후 기침 호전된 사례)

CHS demographics and characteristics

- Heightened response of afferent nociceptors within the upper airway
- Associated with discrete precipitating triggers
- Female > Male, most common age : 60-69 years

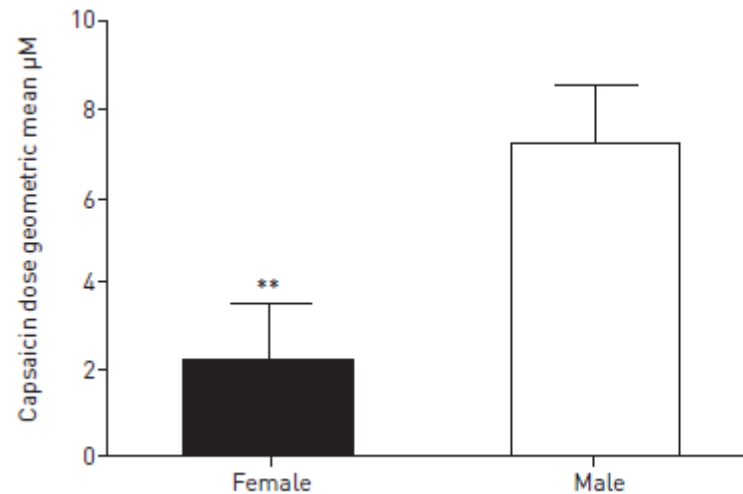


FIGURE 2 The maximum dose of capsaicin that could be inhaled without coughing was measured for a group of young, healthy females (n=10) and males (n=10). The geometric mean of the tolerable dose was significantly lower in females, the t-test with 18 degrees of freedom was 2.9. **: $p < 0.01$.

How to measure CHS?

- No objective measurement tool to define CHS
- Cough frequency measurement

	(/24hrs)
Healthy	16.8
Smokers	33
Asthma	107
Cough variant asthma/eosinophilic bronchitis	321
Unexplained	477

Table 2. Cough measurement tools and related outcomes

Category	Tools and outcomes
Subjective	
Cough-related quality of life	Leicester Cough Questionnaire, Cough-specific Quality-of-Life Questionnaire
Cough severity	Visual analog scale
Objective	
Cough frequency	Leicester Cough Monitor, Hull Automated Cough Counter, VitaloJAK
Cough reflex sensitivity	Tussigen inhalation challenge test (using capsaicin, citric acid, or ATP)/urge-to-cough, C2, C5, maximal cough responses evoked by any tussigen concentration (Emax)

ATP, adenosine triphosphate.

WJ Song, et al. *AAIR*, 2017

Mechanism of CHS

- TRPV1 : capsaicin 수용체, C-fiber 발현, 만성 기침에서 발현량 증가
- TRPA1 : thermosensor ($<17^{\circ}\text{C}$)
- ATP : damage-associated molecule
- P2X : ATP receptor

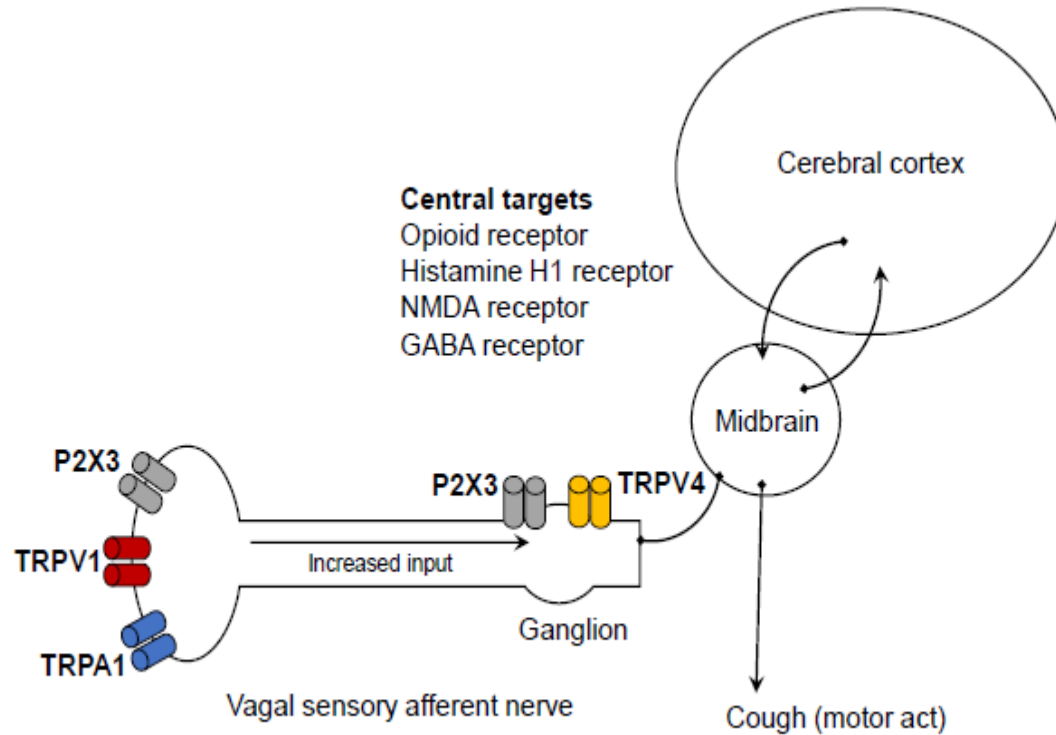
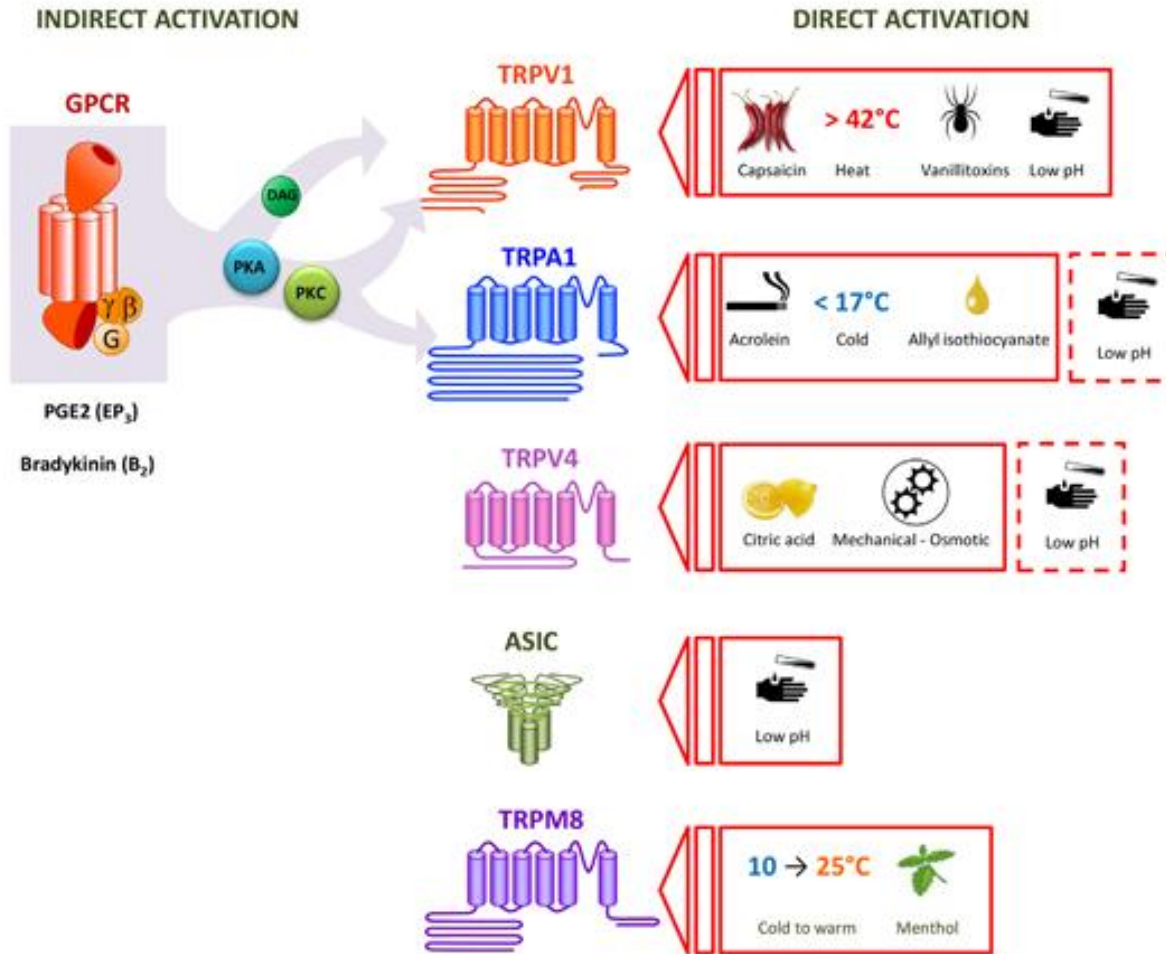


Fig. 2. Current potential therapeutic targets in cough hypersensitivity syndrome.

Transient receptor potential (TRP)



- TRP ion channels are widely expressed throughout the body
- Respond to a remarkable diversity of intracellular and extracellular stimuli
- PGE₂, Bradykinin 가 GPCR 에 결합하여 PKA, PKC 를 활성화 시키면 TRP 채널들을 활성화시켜, 채널이 더 쉽게 열리게 한다.

Transient receptor potential (TRP)

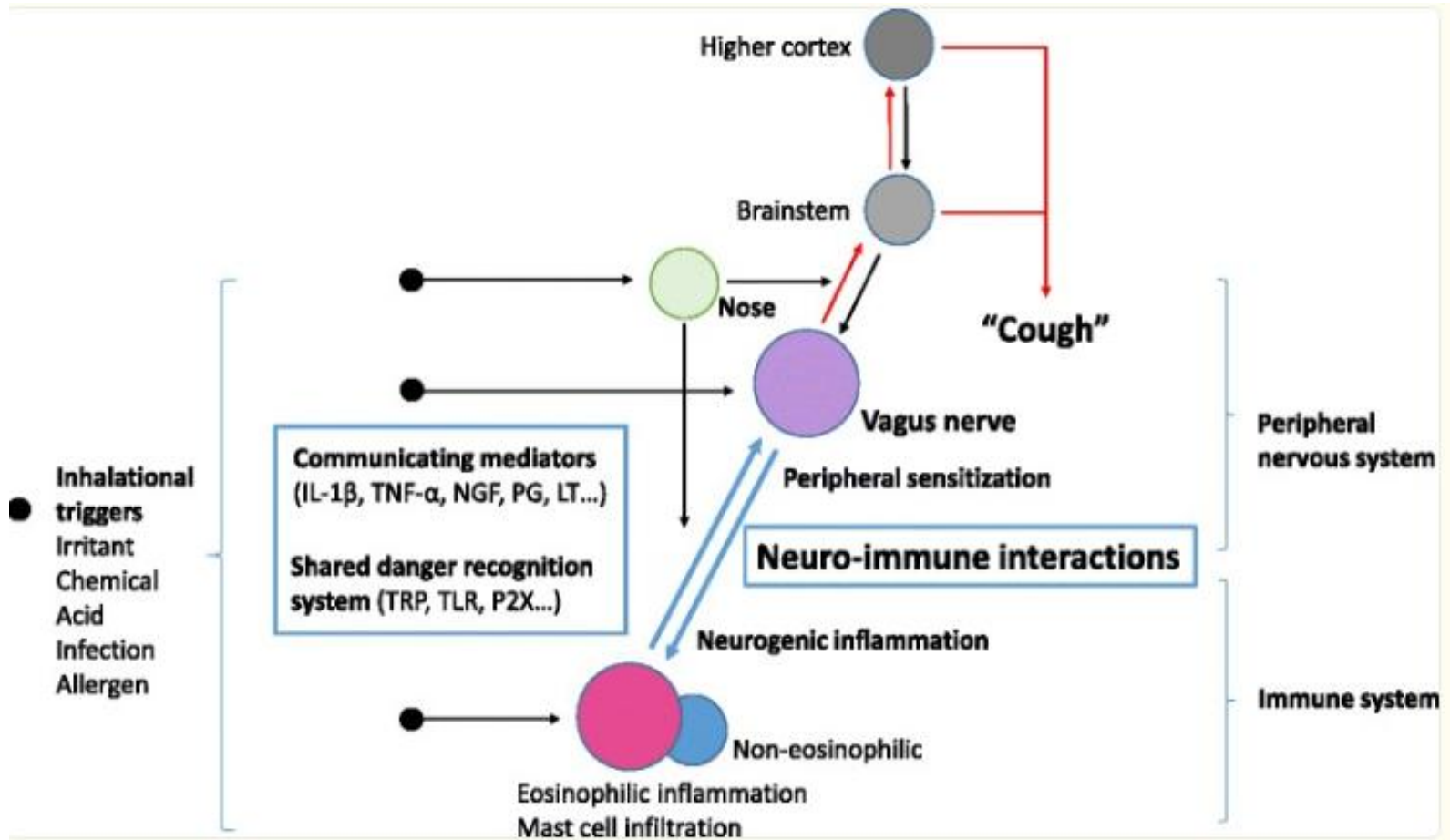
- TRPA1 and TRPV1 receptors are coexpressed in vagal pulmonary C-fiber sensory nerves.
- TRPA1 과 TRPV1 이 동시에 활성화될 경우 synergistic 작용을 통해 pulmonary C-fiber 반응성이 증폭됨.
- A δ cough receptor : thin myelin sheath, sensitive to mechanical stimulation and respond to acid

YJ Lin, et al. *J Applied Physiology*, 2014;MS Grace, et al. *Pulm Pharmacology & Therapeutics*, 2012

ATP-P2X3

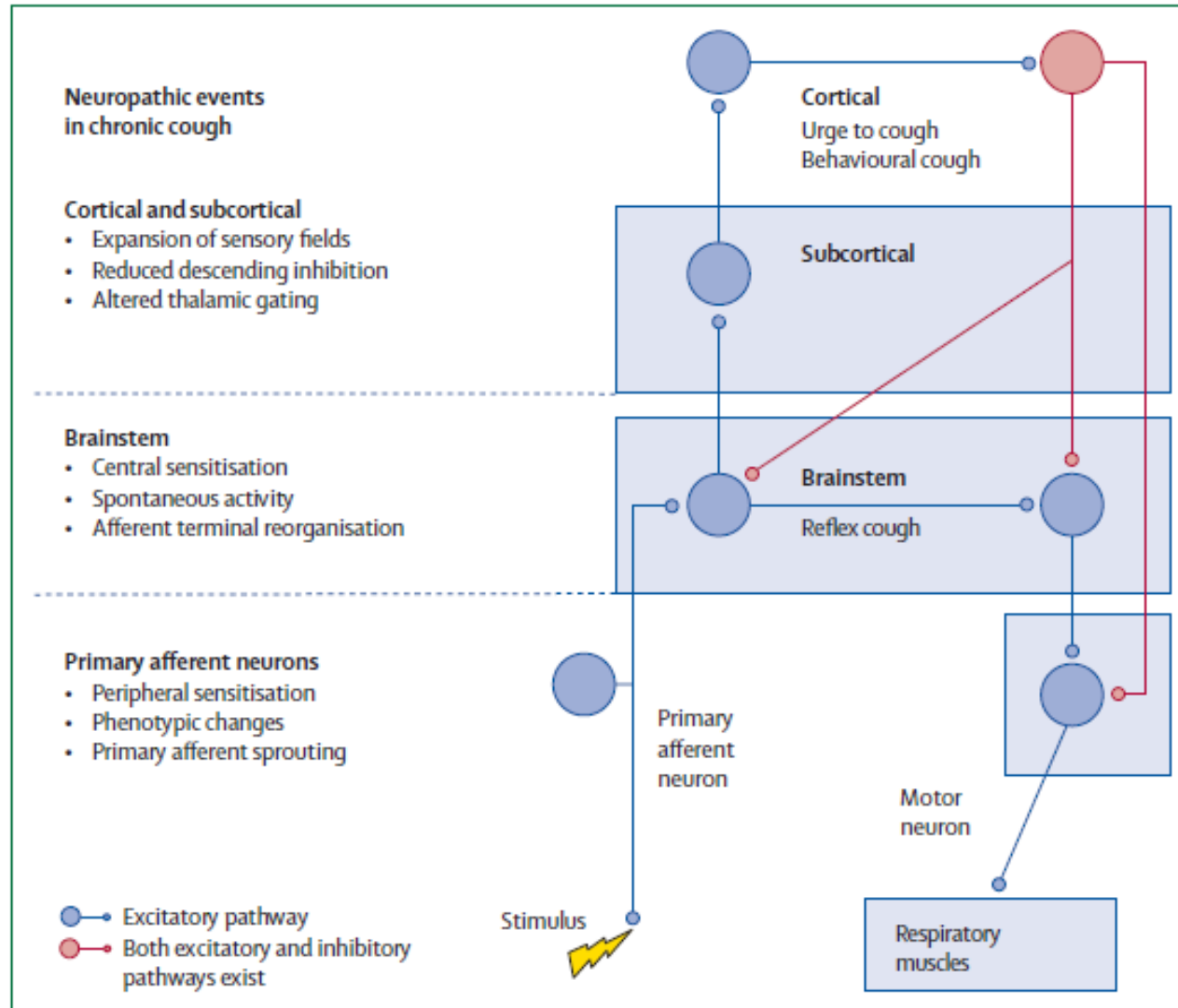
- 손상되거나 염증이 있는 기도 상피 세포는 ATP를 방출
- COPD 환자는 breath condensate 에 ATP 농도가 높음.
- ATP 는 P2X3 에 결합함.
- Gefapixant (P2X3 antagonist) – 만성기침 환자에서 기침 감소 함.

Neuro-immune reaction



- 기침과 면역 반응 모두 exogenous danger 에 대한 방어 반응이라는 점에서 유사하다.
- inhaled trigger 가 peripheral nerve 와 immune system을 동시에 자극한다.
- vagus nerve 가 면역 반응을 유도하고, 활성화된 면역 반응이 peripheral sensitization 을 유발하기도 한다.
- 호산구 과립은 C-fiber를 자극한다.
- 신경 혹은 면역 반응 조절에 이상이 생기면 CHS

Neurobiology

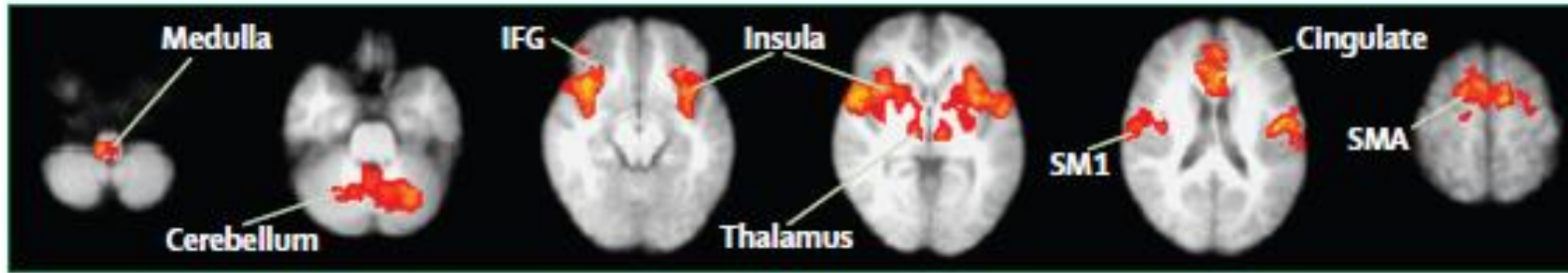


- 1차 구심 신경이 예민해짐.
- Brain stem: reflex cough, 예민, 자극이 없어도 activate, reorganize
- Brain stem 의 신호가 더 올라가게 되면, 기침하고 싶은 충동과 의식적으로 하는 기침이 만들어진다.
- Cortical/subcortical에서는 감각을 느끼는 영역이 넓어지고, 억제 신호가 약해지고, 문지기의 기능이 이상이 생긴다.

: 말초 신경이 예민해져 있고, brain stem의 기능이 고장나 있고, inhibitory system에도 문제가 생김.

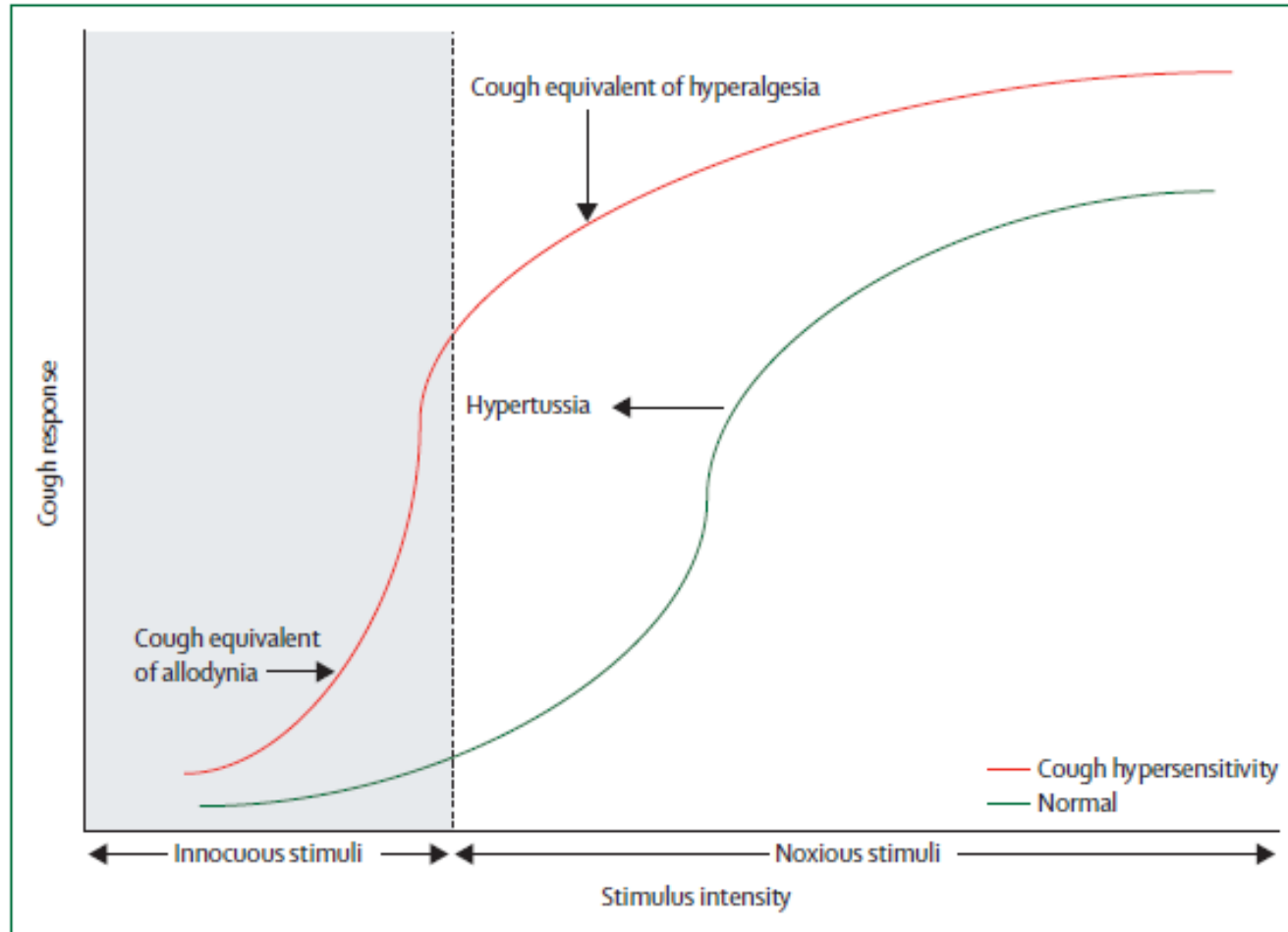
Central neural mechanism of CHS

기침은 brain stem 한 곳에서만 끝나는 것이 아니라, 감각을 느끼는 부위부터, 그것을 억제/조절하는 부위까지 뇌 전체에 걸친 광범위한 네트워크가 함께 작동한다.



- Altered expression of neuronal ion channels
- Normal afferent signals are amplified by central events
- Simultaneous subthreshold inputs can substantially lower the cough-reflex threshold of second order neurons in the brainstem
- Second order medullary neurons project to subcortical nuclei (pons, thalamus, hypothalamus, midbrain and amygdala)
- 1) Changes in thalamic gating, 2) loss of descending inhibitory control, 3) altered brain response

CHS = neuropathy?



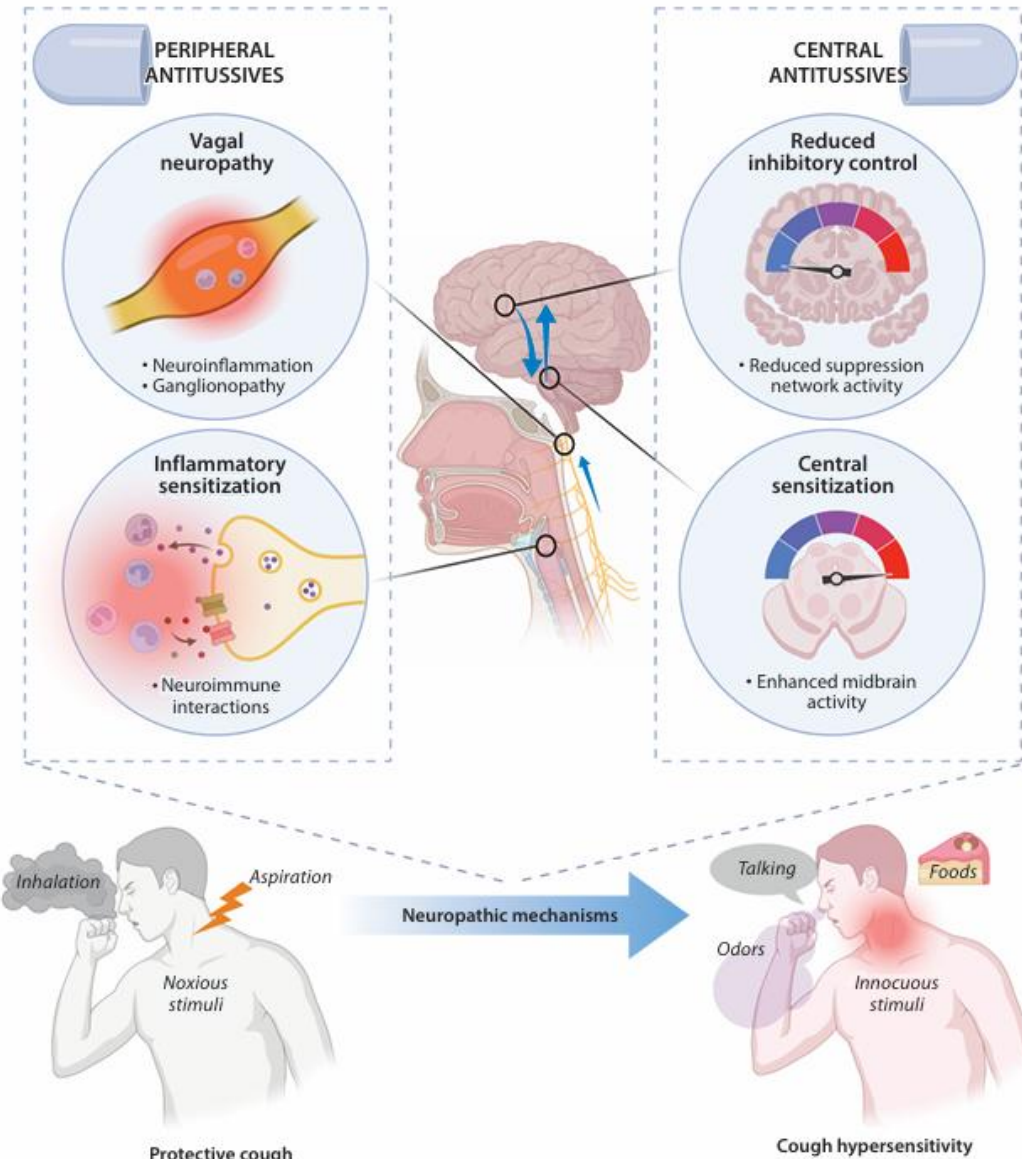
Kian Fan Chung, et al. *Lancet Respir Med*, 2013

CHS = neuropathy?

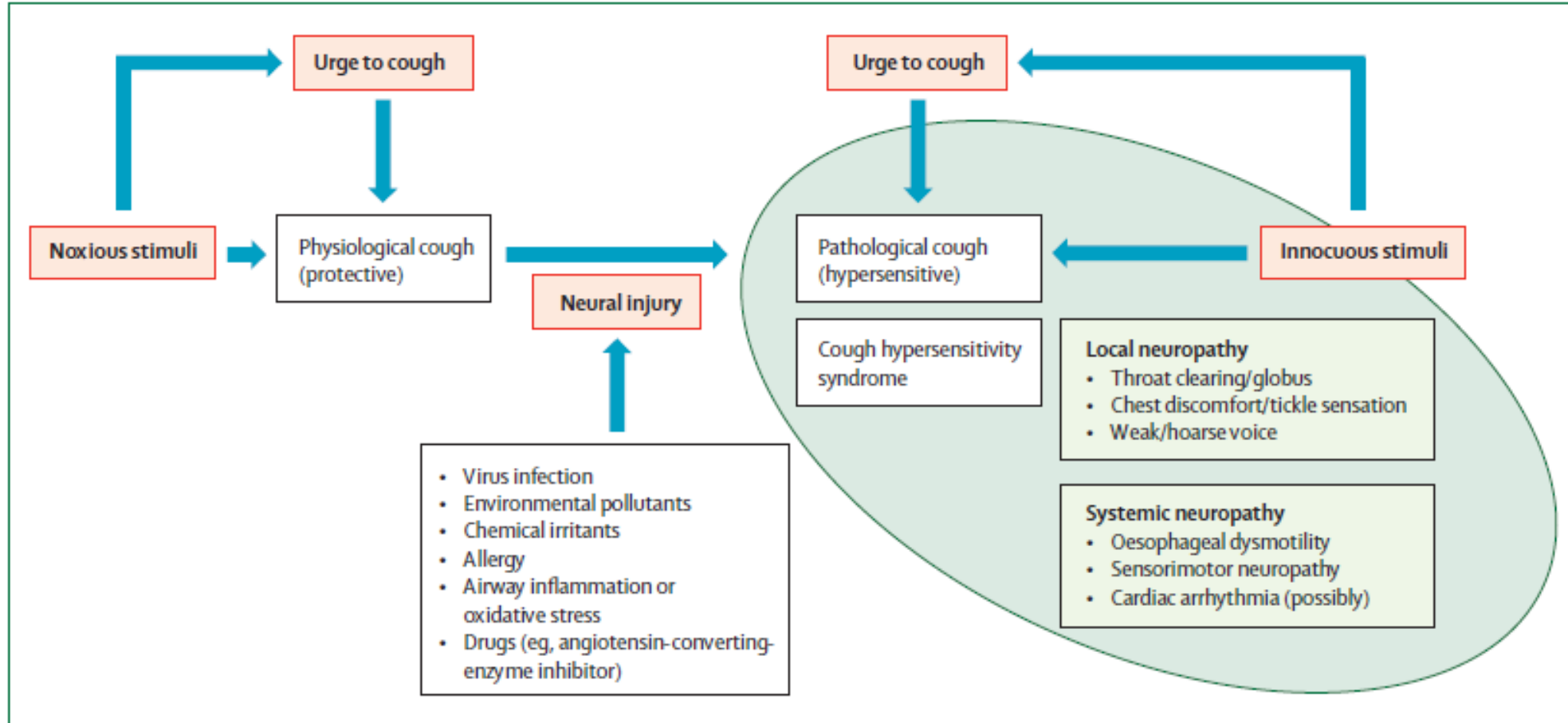
- 미주신경의 염증과 신경절 손상, 면역 세포가 신경말단을 자극
- 억제회로의 손상, 중추의 감작

말초를 표적으로 하는 약 : P2X3 (gefapixant)

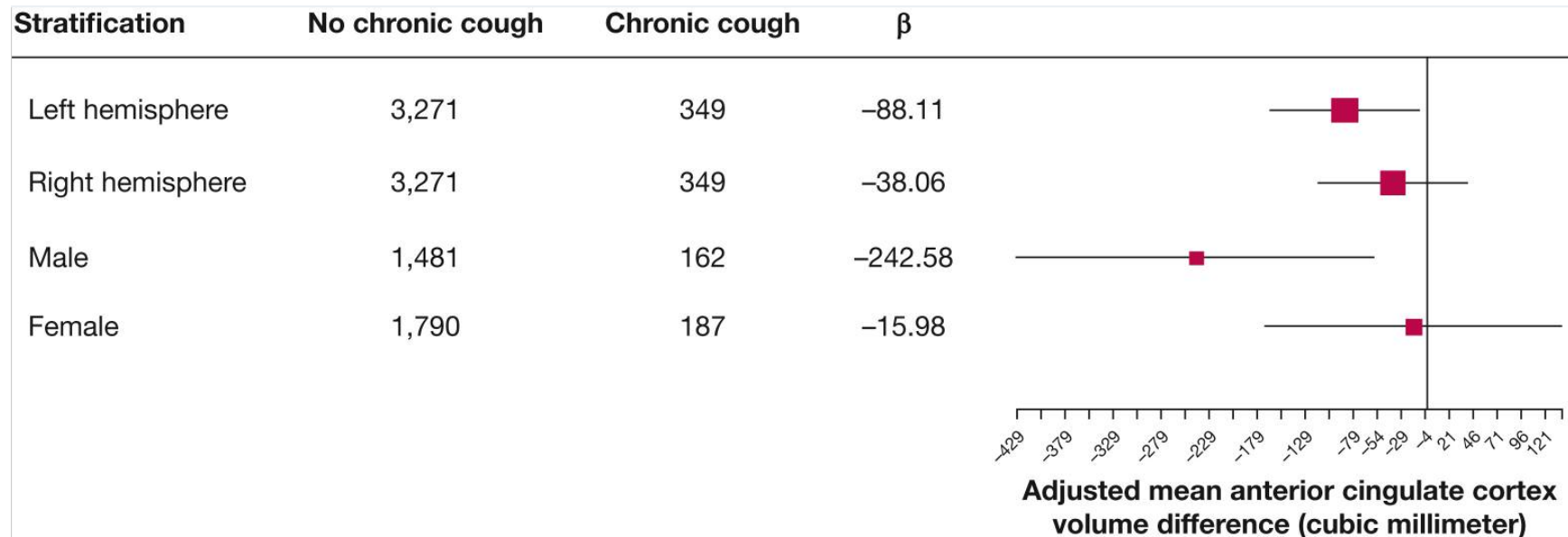
중추를 표적으로 하는 약 : gabapentin, pregabalin, 저용량 opioid



CHS = neuropathy?



CHS – smaller anterior cingulate cortex

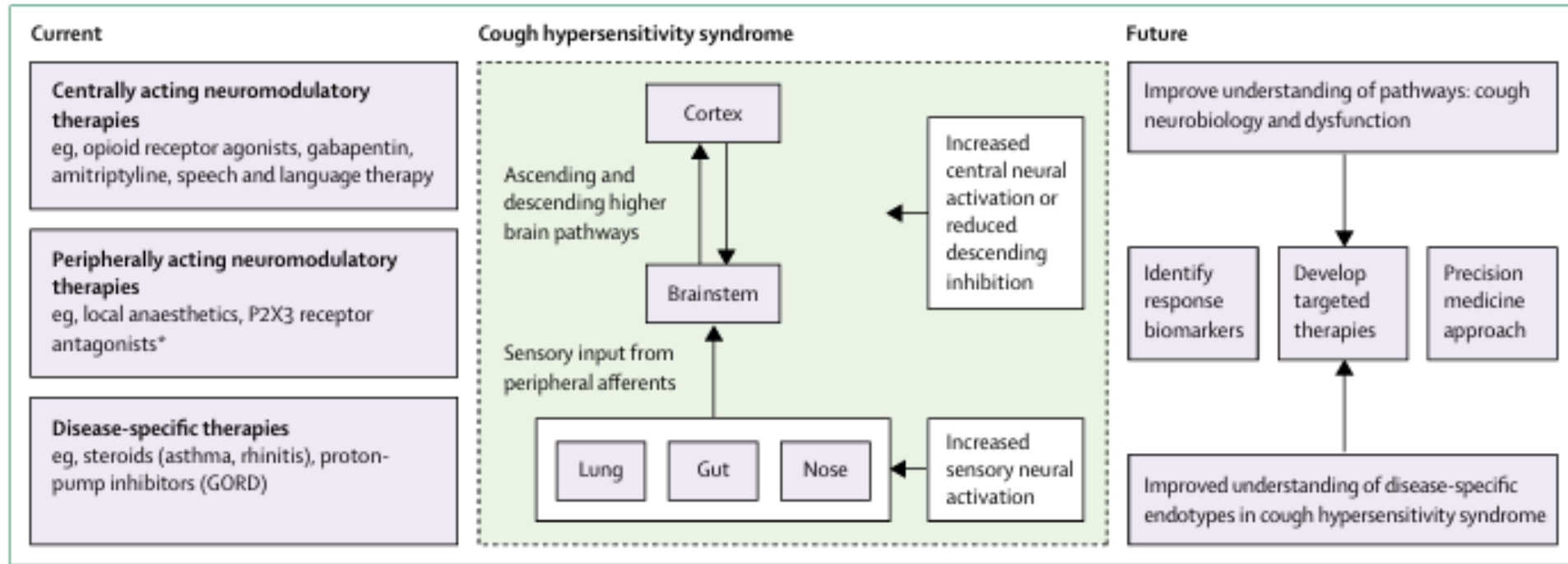


- Individuals with chronic cough have a smaller volume of the anterior cingulate cortex, which is a brain region involved in cough suppression

CHS = neuropathy?

- Inflammatory pain and neuropathic pain evoked by
 - 1) altered neural activity associated with tissue damage
 - 2) disease of peripheral sensory nerve system or its central projection pathway
- Centrally acting neuromodulator (Gabapentin, pregabalin, baclofen and amitriptyline) action on the spinal and higher brain networks regulating pain processing
- Slow-release morphine (not universally recommended)

Heterogeneity of cough in the clinic



Heterogeneity of cough (Phenotype)

- Clinical phenotype

- 1) Upper airway cough syndrome

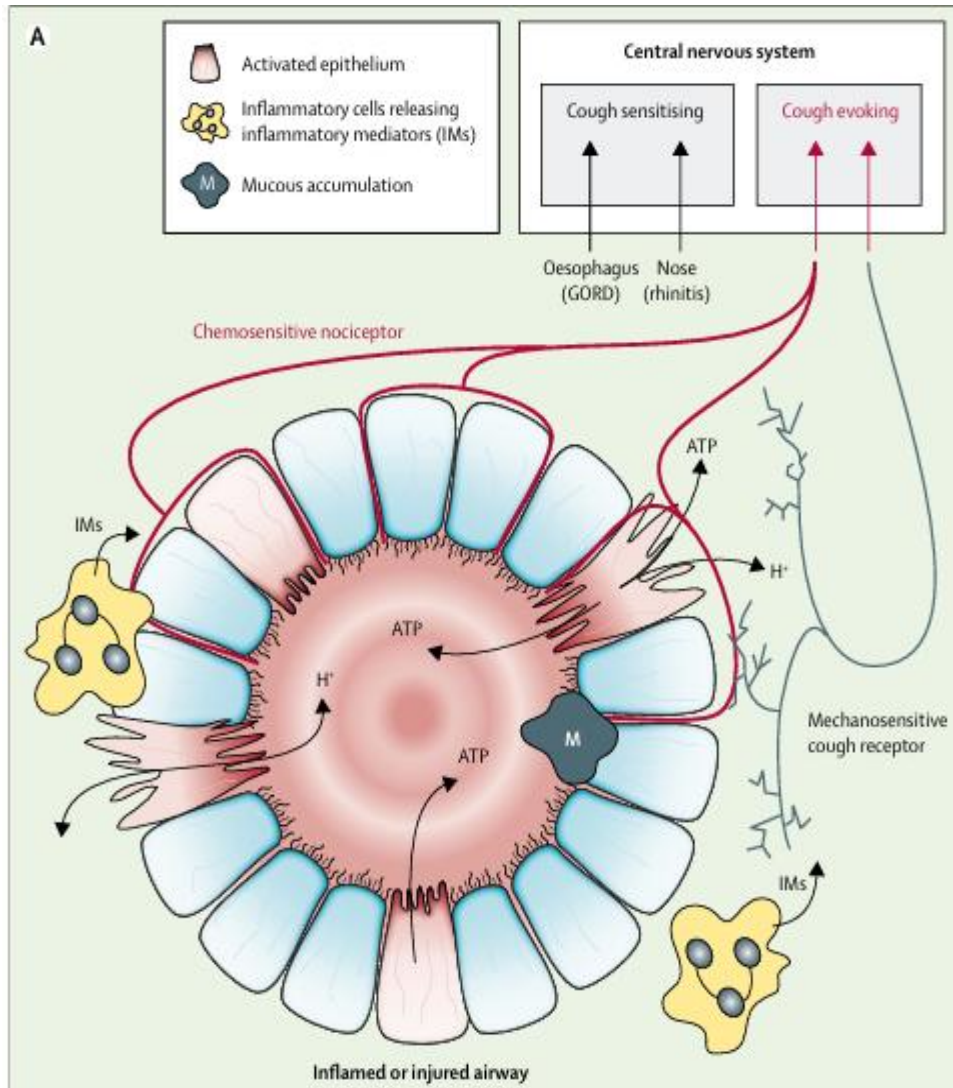
- 2) Rhinitis and rhinosinusitis

- 3) Obstructive sleep apnea and laryngeal hyperresponsiveness

- 4) Lower airway cough syndrome

- 5) Reflux –related cough syndrome

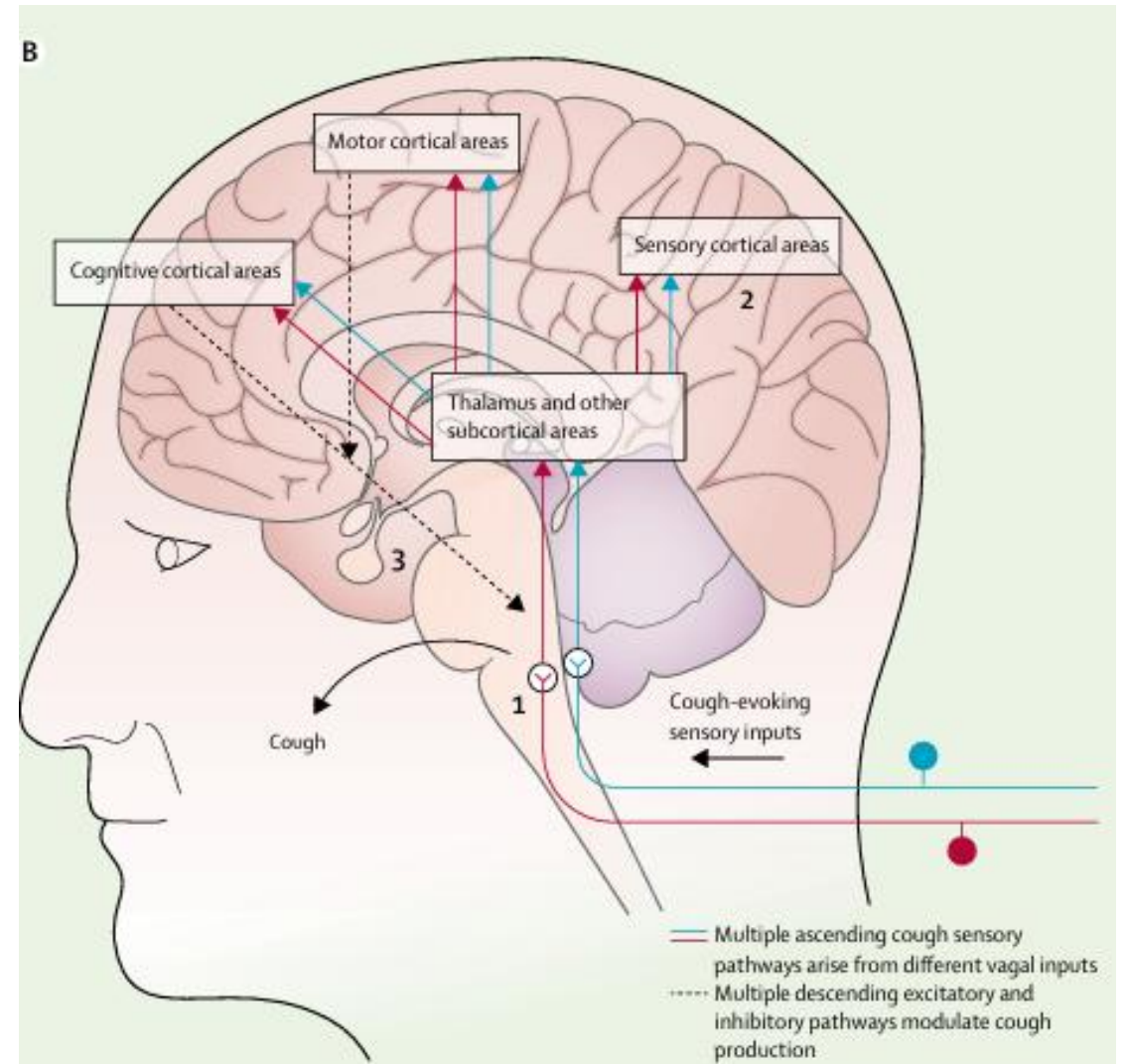
Heterogeneity of cough (Endotype)



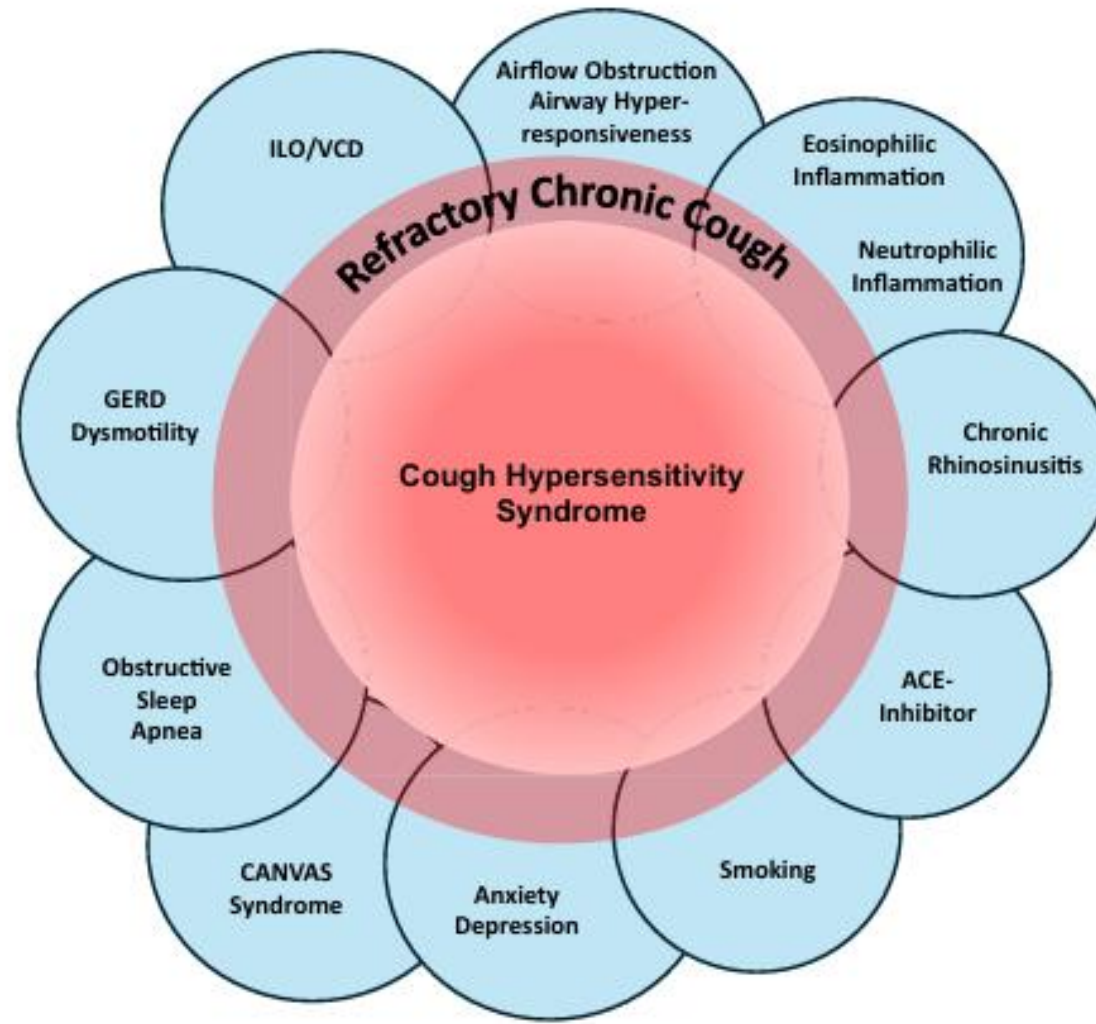
- 손상된 세포에서 ATP, H⁺ 를 방출하고, 염증세포에서 염증매개체를 방출한다.
 - Chemosensitive receptor (TRPV1, TRPA1, P2X3), Mechanosensitive receptor – cough evoking
 - GORD, rhinitis – cough sensitising
- 어느 단계가 우세한지는 환자마다 다를 수 있다.

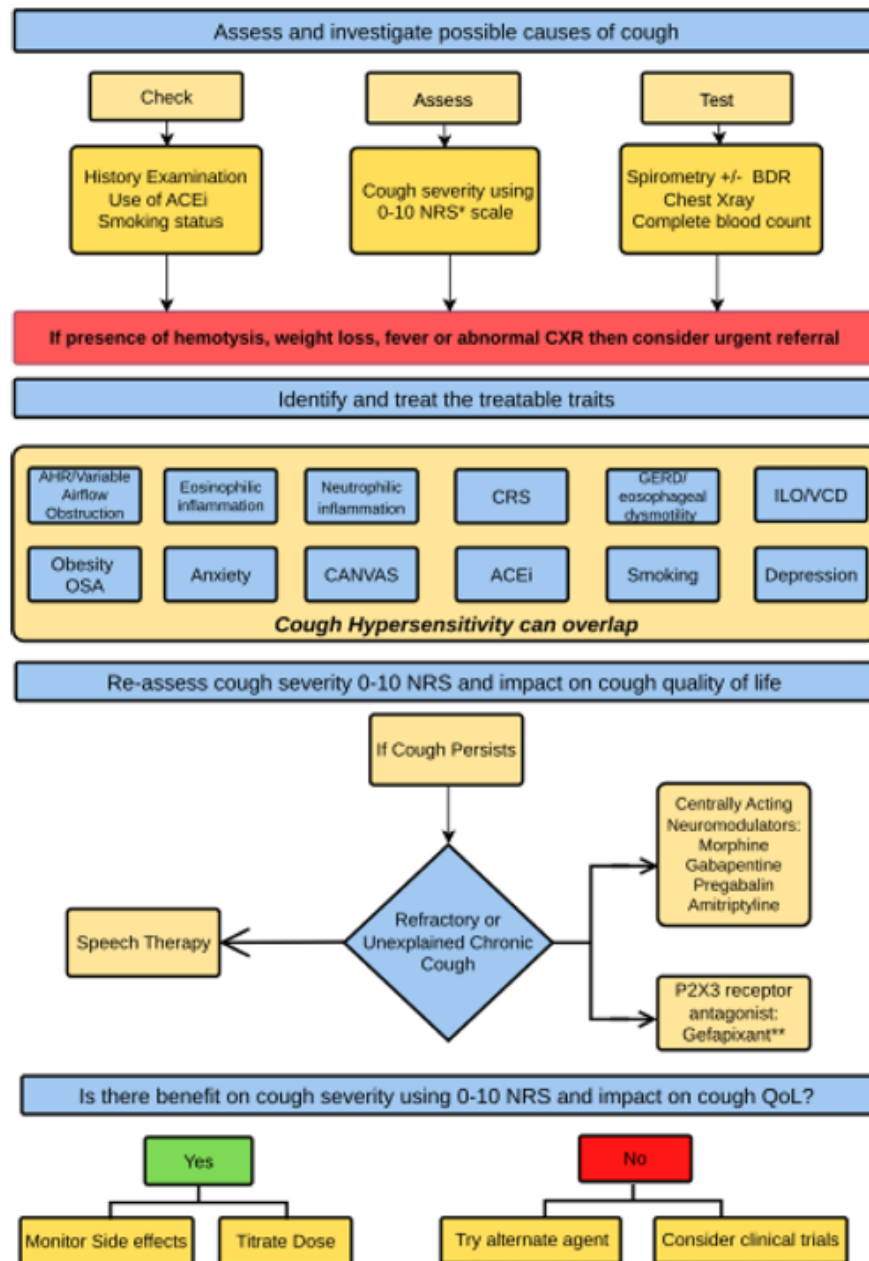
Heterogeneity of cough (Endotype)

- peripheral nerve -> brain stem -> thalamus and other subcortical area -> motor cortical area, sensory cortical area, cognitive cortical area
- cognitive, motor cortical area : excitatory and inhibitory pathways
- "cough hypersensitivity syndrome" 은 같은 임상 현상이더라도, 말초에서는 화학수용체 우성/기계수용체 우성/감작형, 중추에서는 과활성화형, 하행억제 저해 형 등으로 분류할 수 있다.



Heterogeneity of cough (Treatable traits)





- Treatable trait approach

1) Check, Assess, Test

2) CHS can overlap

Assessment of cough

- Capsaicin and citric inhalation cough challenge
- Cough visual analogue scale (VAS)
- Leicester cough questionnaire (LCQ)
- Chronic cough impact questionnaire (CCIQ)
- Cough Assessment Test (COAT)

AH Morice, et al, *Eur Respir J*, 2007

- ☐ Airway hyper-responsiveness and variable airflow obstruction
 - asthma related cough : ICS/bronchodilator, LAMA, Leukotriene receptor antagonist

- ☐ Airway eosinophilia
 - type 2 high biomarker (blood eosinophil $>0.3 \times 10^9/L$), FENO > 25 ppb , ICS

- ☐ Chronic bronchitis/neutrophilia
 - smoking ,cough with phlegm

- ☐ Gastroesophageal reflux disease
 - Lifestyle changes, high-dose antacid trial

☐ Dysmotility

- Metoclopramide/Domperidone/Macrolides ~ limited evidence

☐ Upper airway symptoms

- Postnasal drip, 1,2 generation non-sedating antihistamines

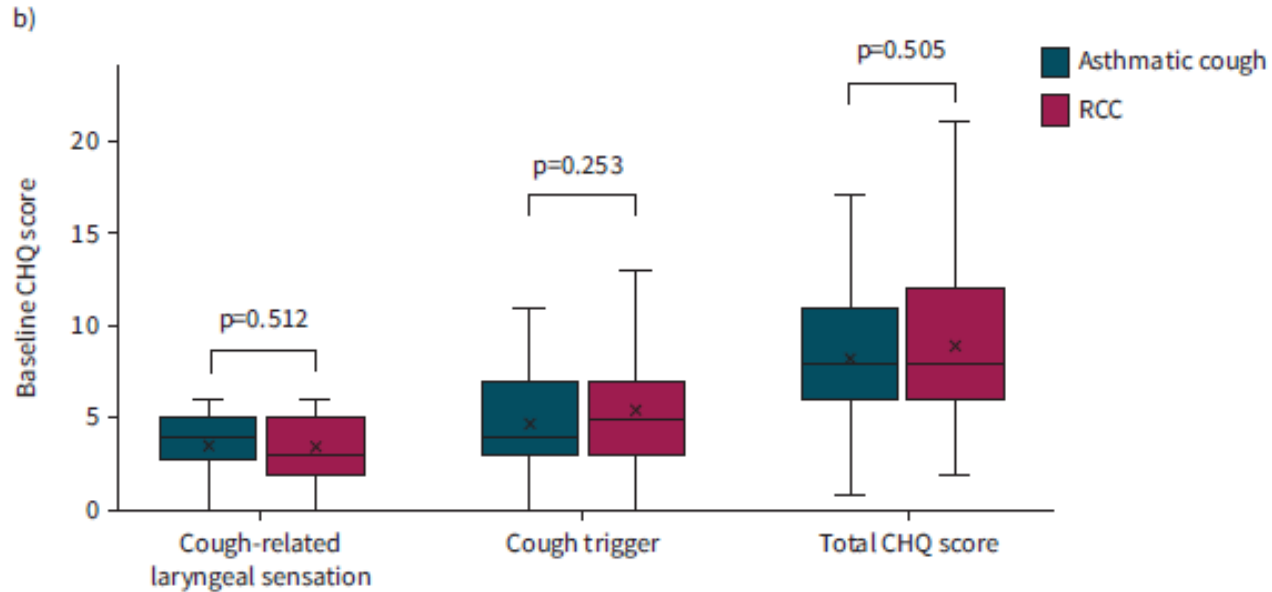
☐ Inducible laryngeal obstruction/vocal cord dysfunction

- Paradoxical vocal cord dysfunction, laryngeal hypersensitivity, speech and language therapy

☐ Obstructive sleep apnea

- Exacerbate cough reflex sensitivity , CPAP

Chronic cough in both phenotypes



- Baseline CHQ scores were similar between the groups
- Symptoms of cough hypersensitivity may not distinguish between asthmatic cough and RCC
- Shared mechanism in different treatable traits

MY Kim, et al. *ERJ open* , 2024

Summary

- 만성 기침의 상당수는 원인 불명이며 이는 neuropathy 와 유사한 특징을 가진다.
- TRPV1, TRPA1, P2X3 등 말초 감각수용체의 감작, 중추 신경계의 변화, neuroimmune reaction 이 CHS 를 형성한다.
- CHS는 단일 질환이 아니라 여러 표현형이 중첩되는 공통 경로이며, 증상만으로는 기전이 다른 표현형을 구별하기 어렵다.
- Treatable trait approach (check-assess-test), multi-axis approach