새롭게 이해하는 기침의 병태 생리

2015.9.5 제1회 기침연구회 심포지움

한양대학교 구리병원 호흡기내과

문 지 용

Contents

- Definition of Cough
- Anatomy & Neurophysiology
  - Airway Afferent Nerve Subtypes
  - Central Regulation of Cough
- Cough Hypersensitivity Syndrome

Contents

- Definition of Cough
- Anatomy & Neurophysiology
  - Airway Afferent Nerve Subtypes
  - Central Regulation of Cough
- Cough Hypersensitivity Syndrome

The Impact Of Cough On Health Is Substantial

1. an important **defense mechanism** that helps clear excessive secretions and foreign material from the airways
2. an important factor in the **spread of infection**
3. **one of the most common symptoms** for which patients seek **medical attention** and spend health-care dollars
    1. Acute cough (< 3 weeks): the most common complaint on primary care physicians
    2. Chronic cough (> 8 weeks): the most common reason for new patients visits to pulmonologists

Irwin RS. *Chest 2006;129:25S-7S.*

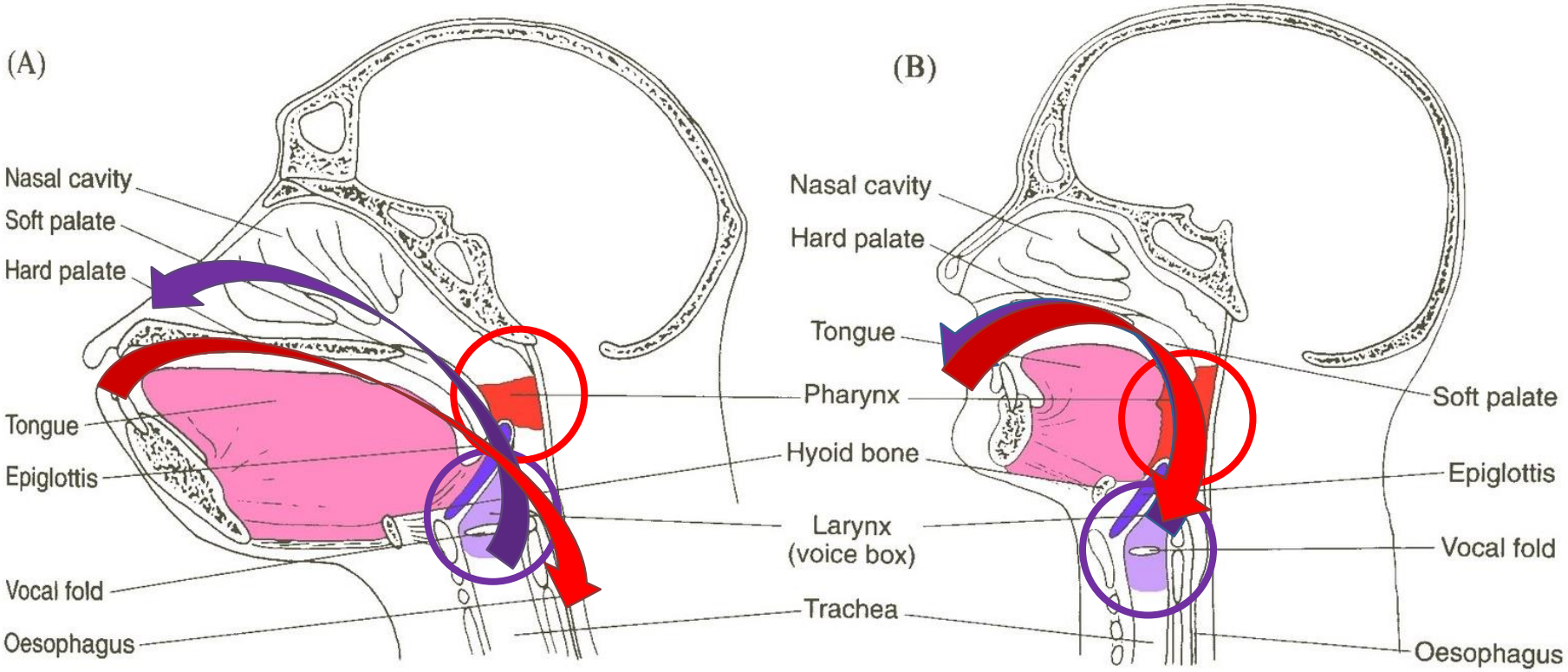
Potential Complications from Excessive Cough

- RESPIRATORY
  - Pneumothorax
  - Subcutaneous emphysema
  - Pneumomediastinum
  - Pneumoperitoneum
  - Laryngeal damage
- CARDIOVASCULAR
  - Cardiac dysrhythmias
  - Loss of consciousness
  - Subconjunctival hemorrhage
- CENTRAL NERVOUS SYSTEM
  - Syncope
  - Headaches
  - Cerebral air embolism
- MUSCULOSKELETAL
  - Intercostal muscle pain
  - Rupture of rectus abdominis muscle
  - Increase in serum creatine phosphokinase
  - Cervical disc prolapse
- GASTROINTESTINAL
  - Esophageal perforation
- OTHER
  - Social embarrassment
  - Depression
  - Urinary incontinence
  - Disruption of surgical wounds
  - Petechiae
  - Purpura

Chung KF, *et al.* Cough. Murray and Nadel's Textbook of Respiratory Medicine, Sixth Edition

The Evolution Of Language And Speech:

Chimpanzee Vs. Human



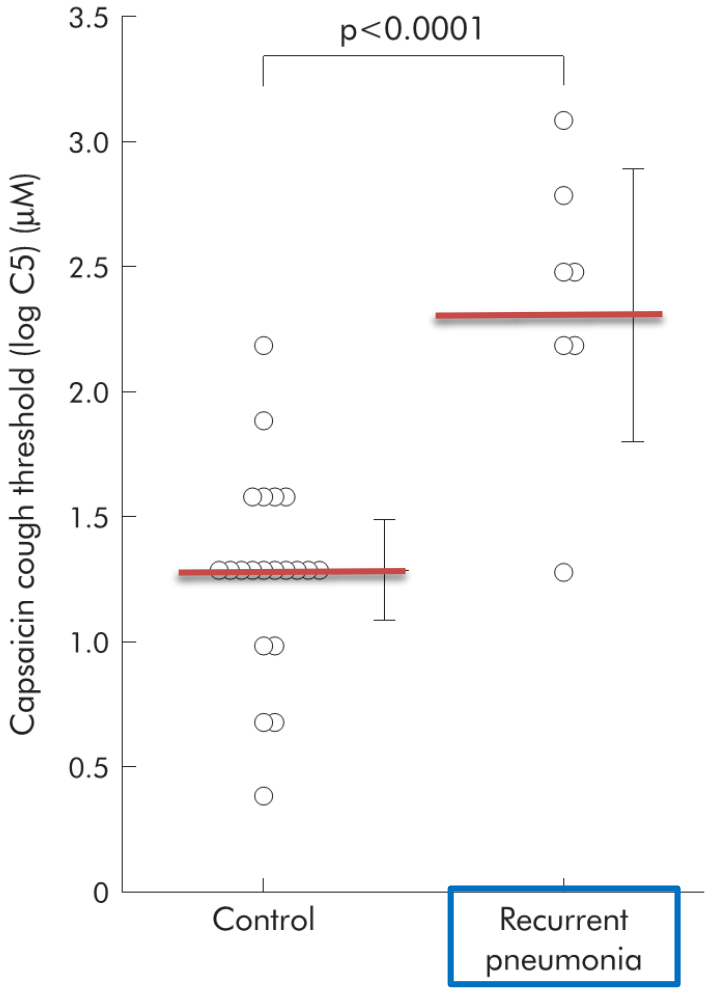
evolution of language and speech (development of "supralaryngeal vocal tract") → → increased risk of aspiration → → development of cough reflex and "urge-to-cough"

Brooks SM. *Cough (London, England) 2011;7:10-.*

Impaired cough reflex in patients with recurrent pneumonia

A Niimi, H Matsumoto, T Ueda, M Takemura, K Suzuki, E Tanaka, K Chin, M Mishima, R Amitani

Thorax 2003;**58**:152–153



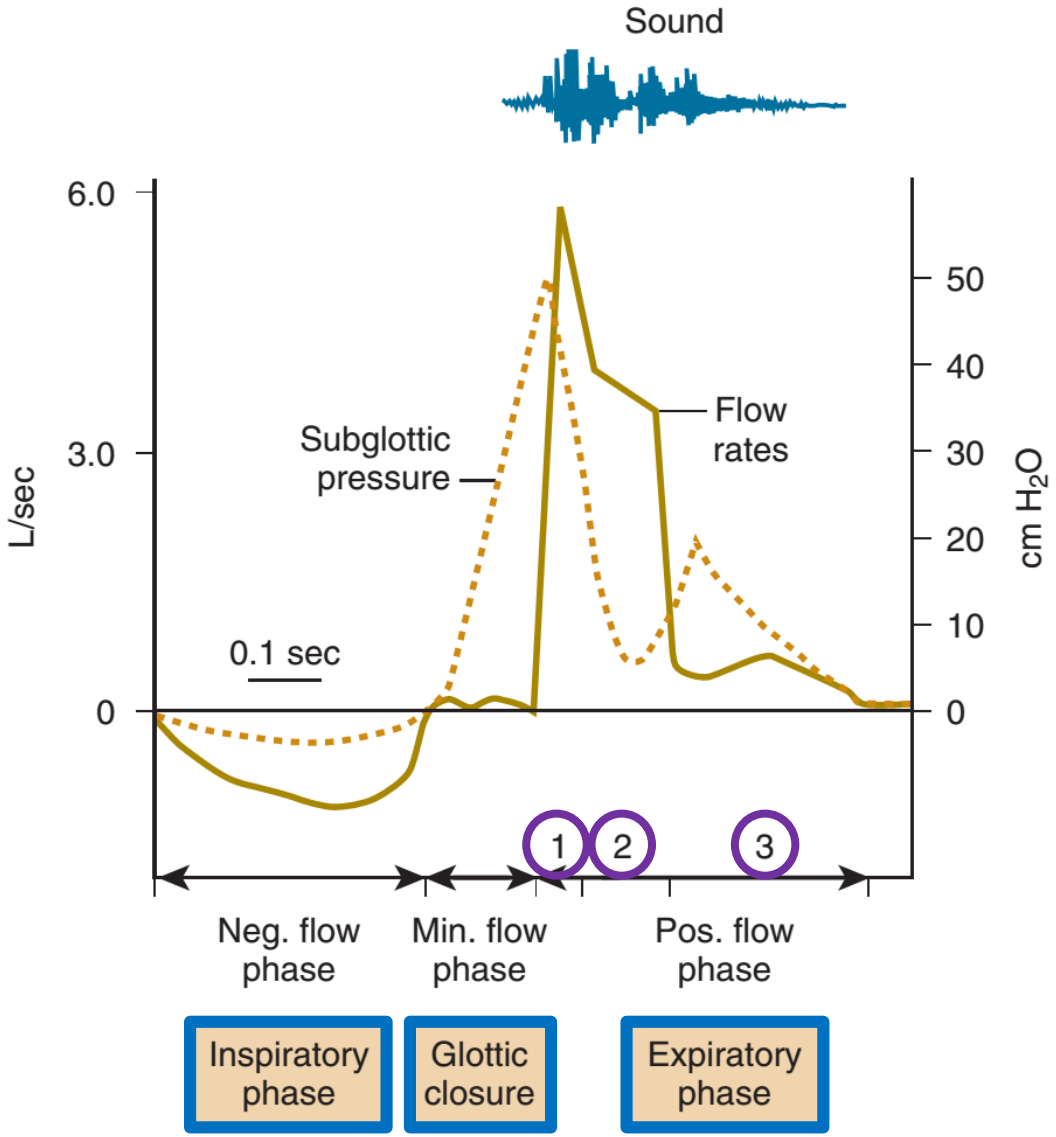
Niimi A, *et al. Thorax 2003;58:152-3.*

Phases of Cough

1. **흡입기(inspiratory phase)**
   - 1-2초, 성문(glottis)가 열리면서 공기를 흡입하는 기간
2. **압축기(compressive phase)**
   - 0.2-0.3초, 성문이 닫히고 호기근이 수축하여 흉강내와 폐포내 압력이 상승하는 시기
3. **호출기(expulsive phase)**
   - 0.5-0.8초, 성문이 갑자기 열리면서 빠른 속도로 압축되었던 폐내 공기가 배출되고 이와 함께 기도내 이물질과 분비물도 배출되는 시기

호흡기학, 대한결핵 및 호흡기학회, 2004

Phases of Cough



Chung KF, *et al.* Cough. Murray and Nadel's Textbook of Respiratory Medicine, Sixth Edition

Definitions of Cough

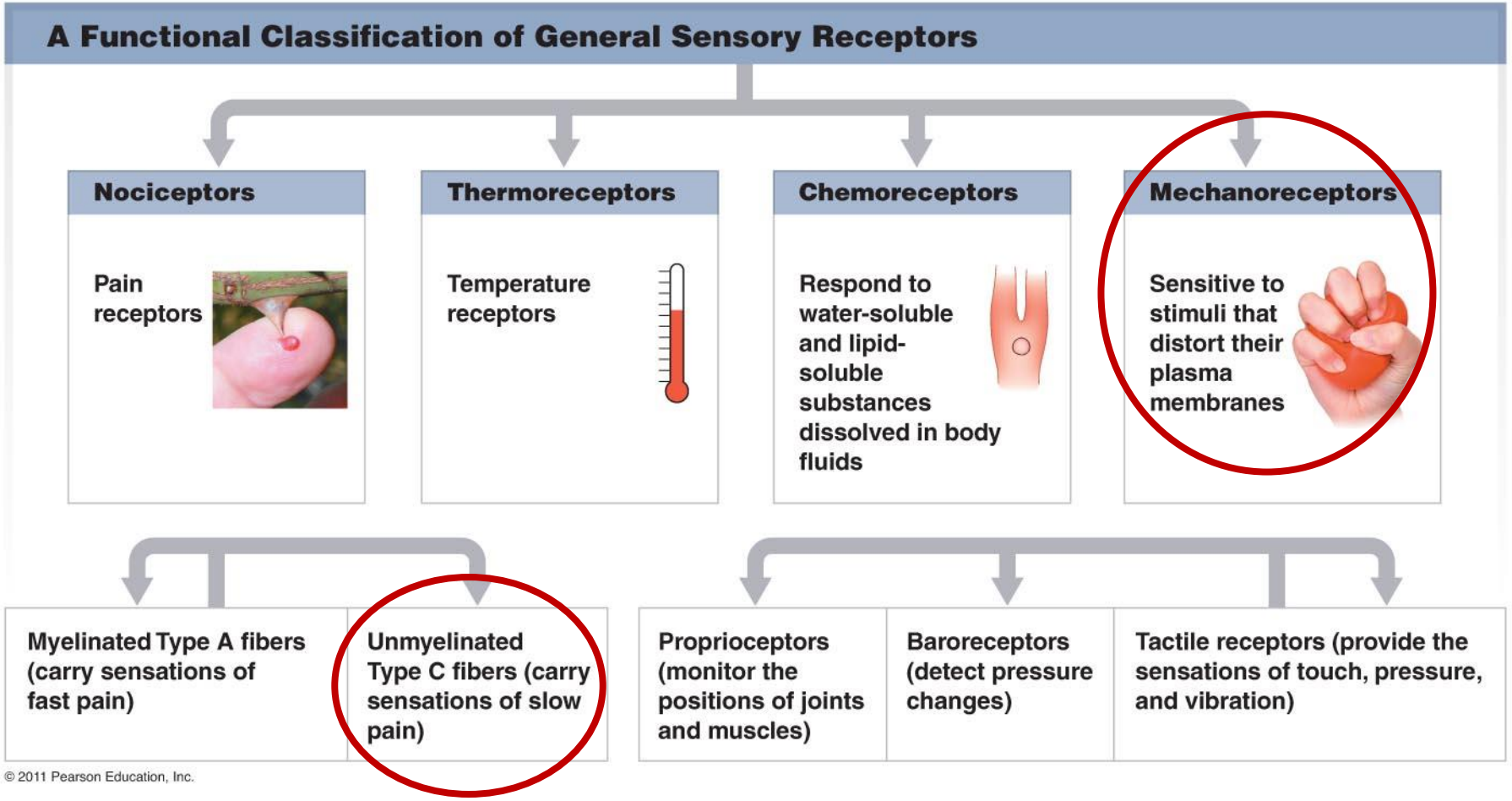
- **Induced cough**
  - usually preceded by an awareness of airway irritation and an "**urge-to-cough**,"
  - activation of sensory processing and limbic regions in the cerebral cortex
- **Evoked cough** (involuntary or voluntary)
  - involuntary (**reflexively** evoked)
    - mediated by sensory inputs at a brain-stem level
  - voluntary (a **behavioral** outcome in response to the urge-to-cough)
    - originating in motor regions of the cerebral cortex
- **Tic cough** (previously referred to as **habit cough**)
  - is a variant of voluntary cough, which may or may not be associated with an urge-to-cough

Chung KF*, et al.* Cough. Murray and Nadel's Textbook of Respiratory Medicine, Sixth Edition

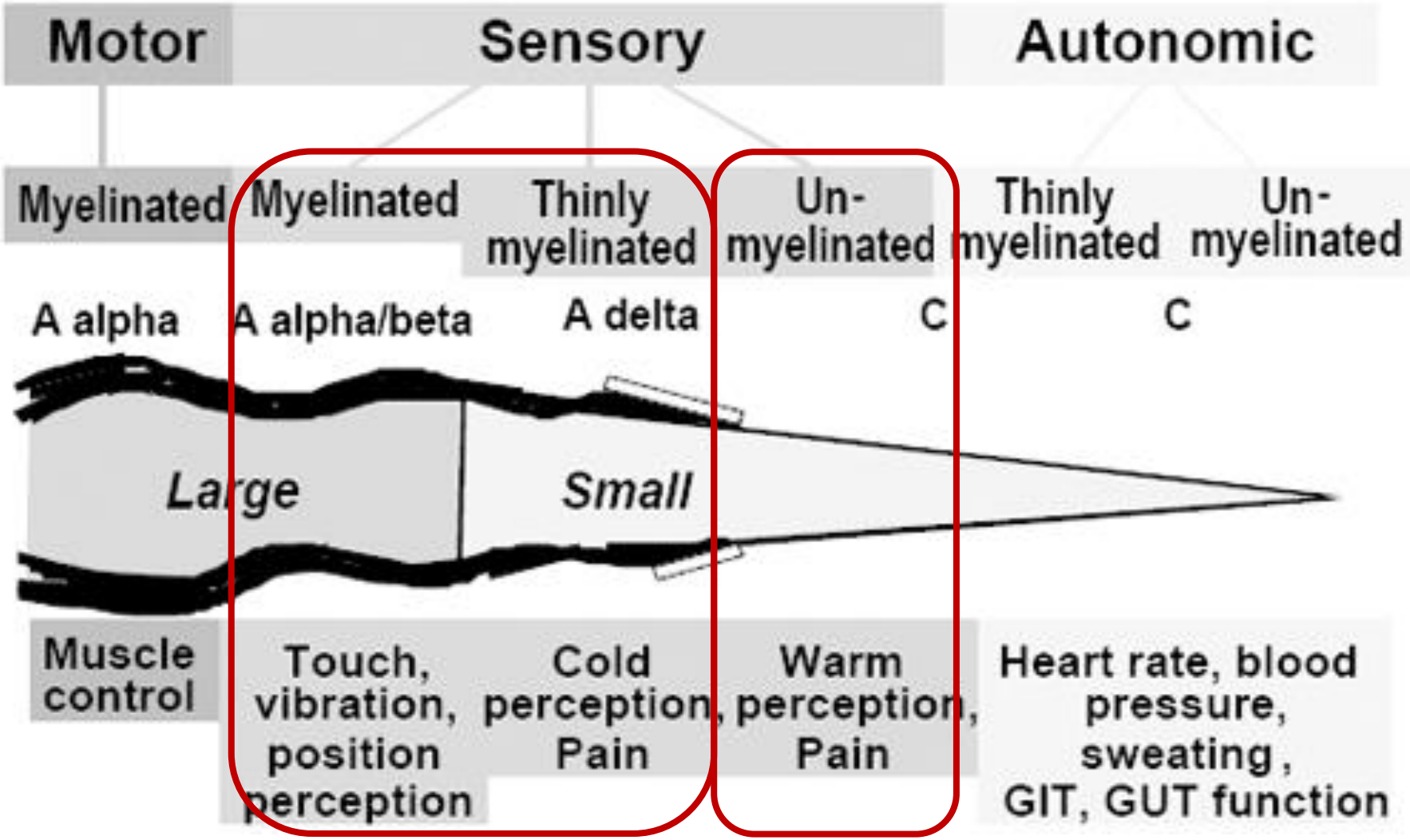
Contents

- Definition of Cough
- **Anatomy & Neurophysiology**
  - Airway Afferent Nerve Subtypes
  - Central Regulation of Cough
- Cough Hypersensitivity Syndrome

Sensory Receptors



Classification of Nerve Fibers



Casellini CM, *et al. Endocr Pract 2007;13:550-66.*

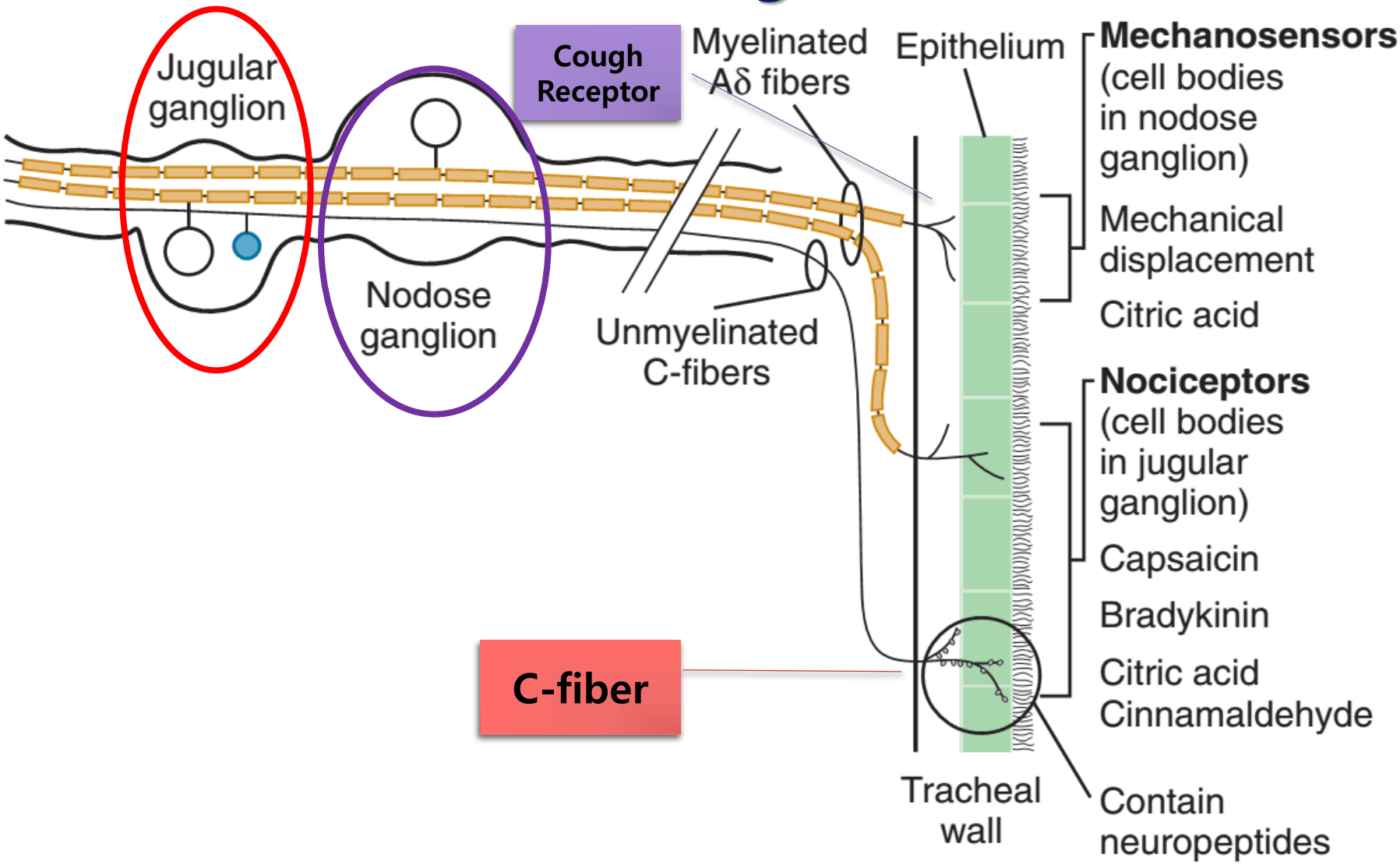
Vagal Airway Afferent Nerve Subtypes

- Understanding the differences in vagal afferent nerve subtypes is critical to understanding the physiology and pathophysiology of cough

- **C-fibers**
  - The **majority** of **bronchopulmonary** vagal afferent nerves
  - Unmyelinated
  - relative **insensitivity to mechanical stimulation** and lung inflation
- Widdicombe **Cough Receptors**
  - **Extrapulmonary** airways (trachea, mainstem, and segmental bronchi)
  - Myelinated
  - **mechanically sensitive**, capsaicin-insensitive
  - do not normally express the ion channels TRPV1 or TRPA1 and are, thus, **insensitive to the chemical irritants** capsaicin and allyl isothiocyanate.

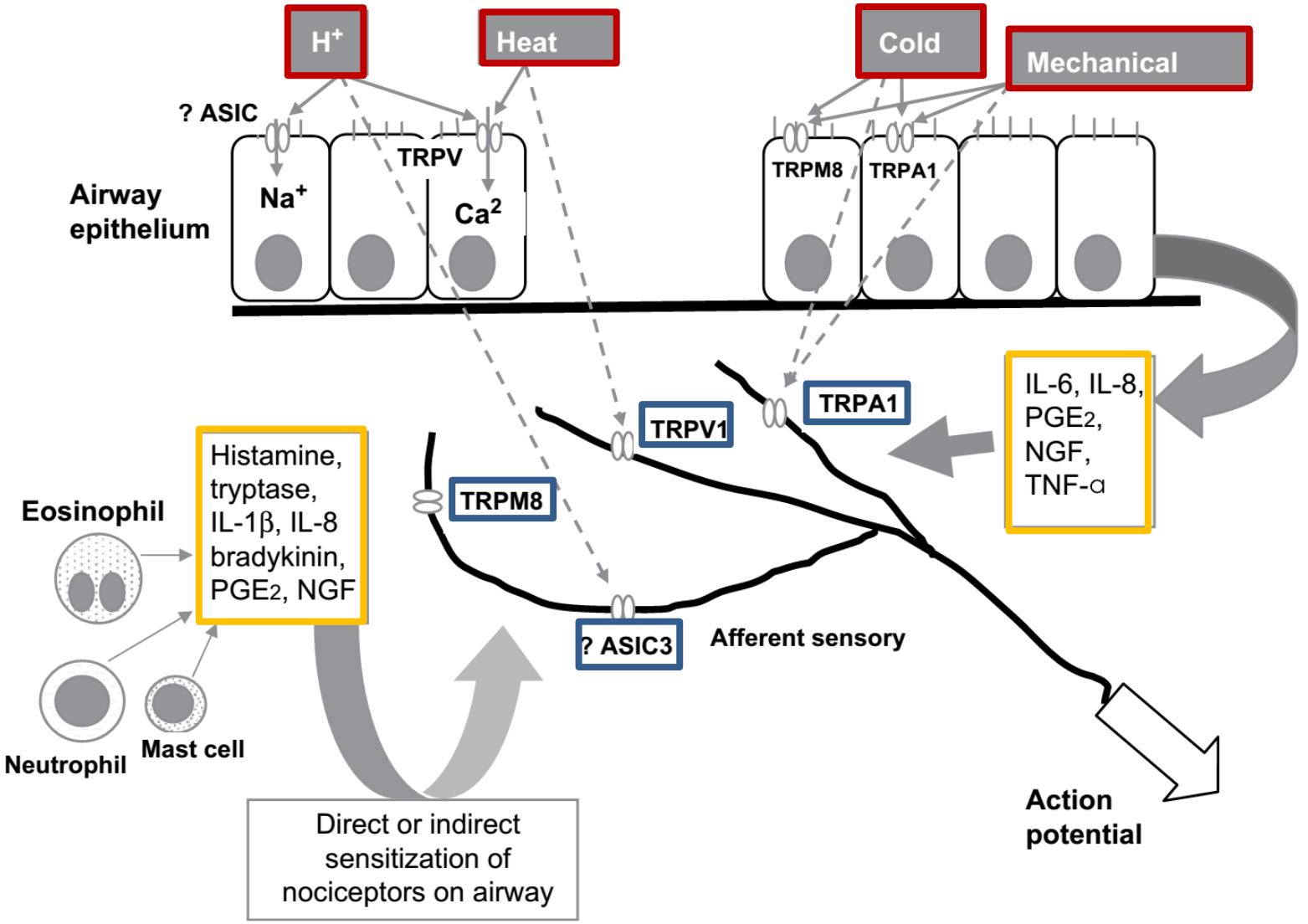
Canning BJ, *et al. Chest 2014;146:1633-48.*

Vagal Afferent Innervation Of Guinea Pig Trachea



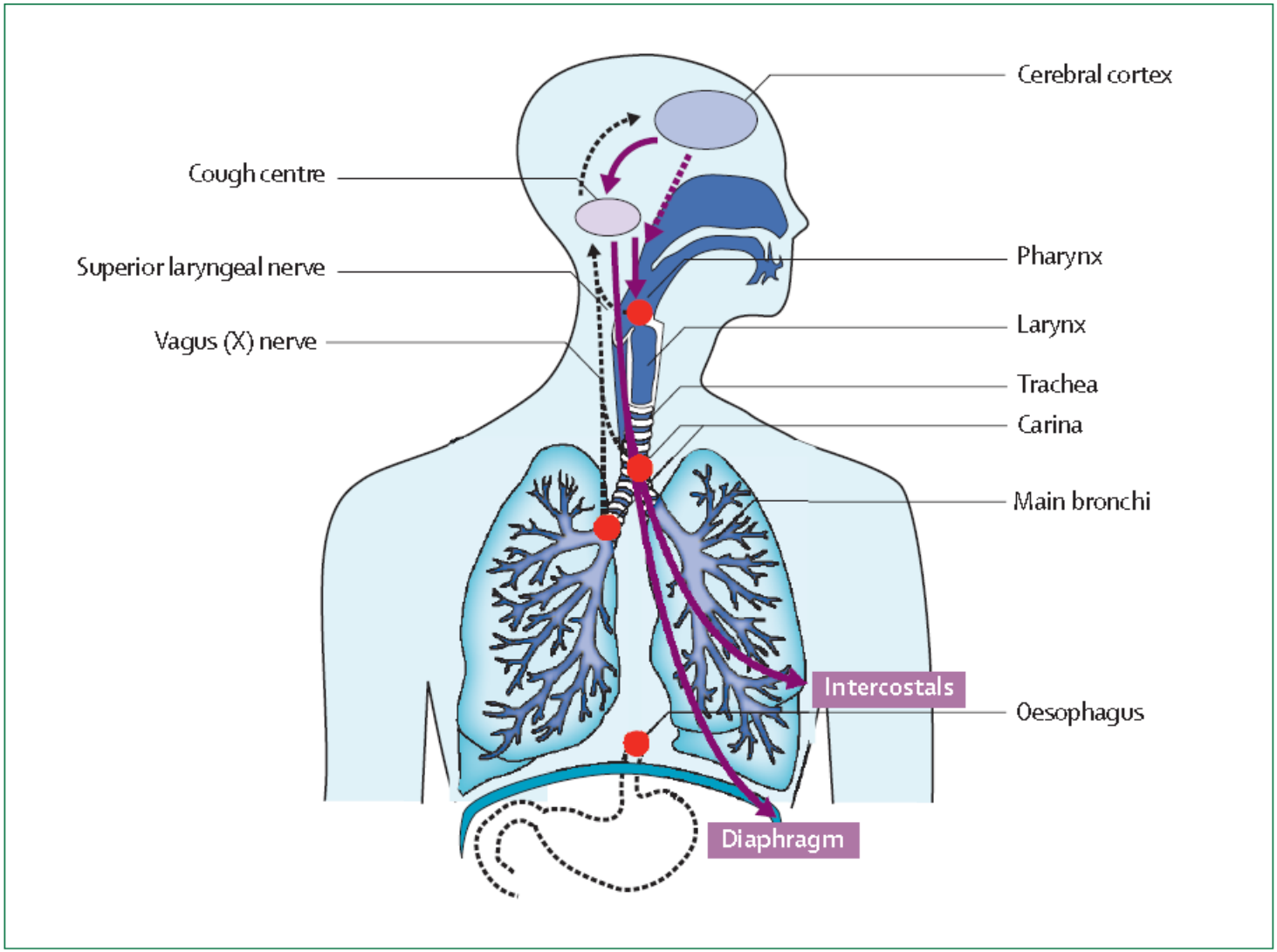
Chung KF, *et al.* Cough. Murray and Nadel's Textbook of Respiratory Medicine, Sixth Edition

Activation Of Nociceptors



McGarvey L, *et al. Pulm Pharmacol Ther 2009;22:59-64.*

Cough Receptors



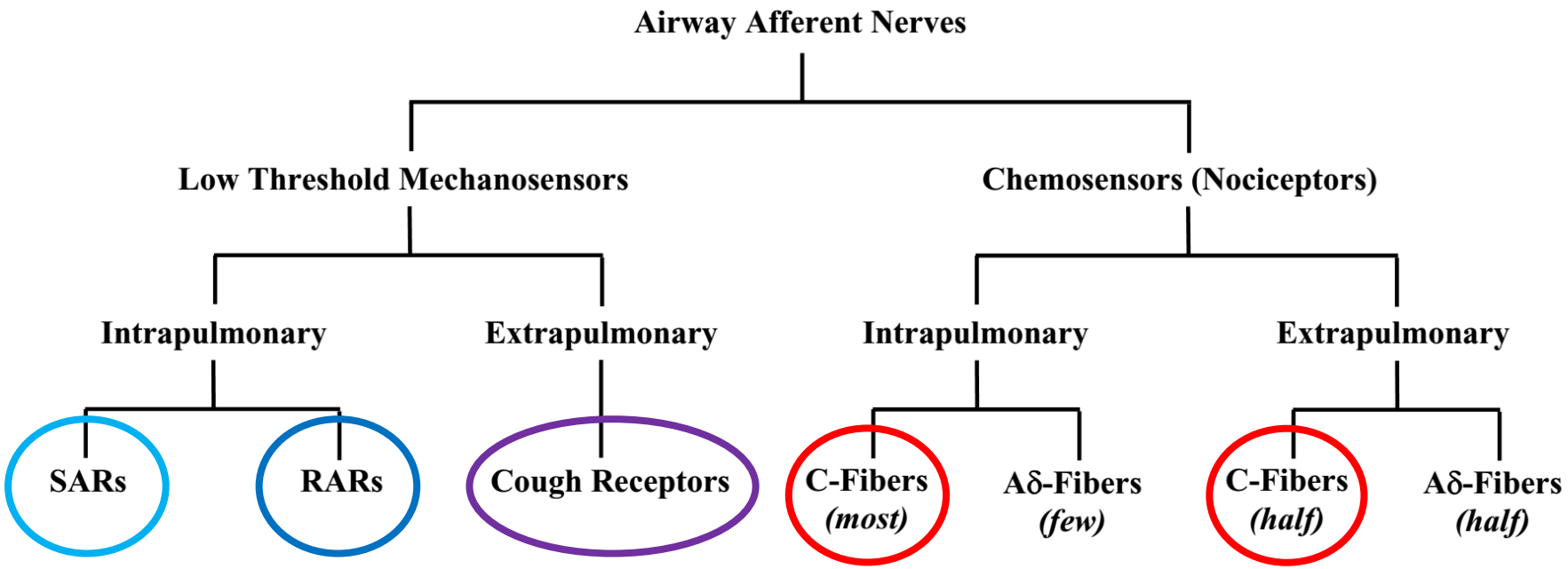
Chung KF, *et al. The Lancet 2008;371:1364-74.*

Vagal Airway Afferent Nerve Subtypes (2)

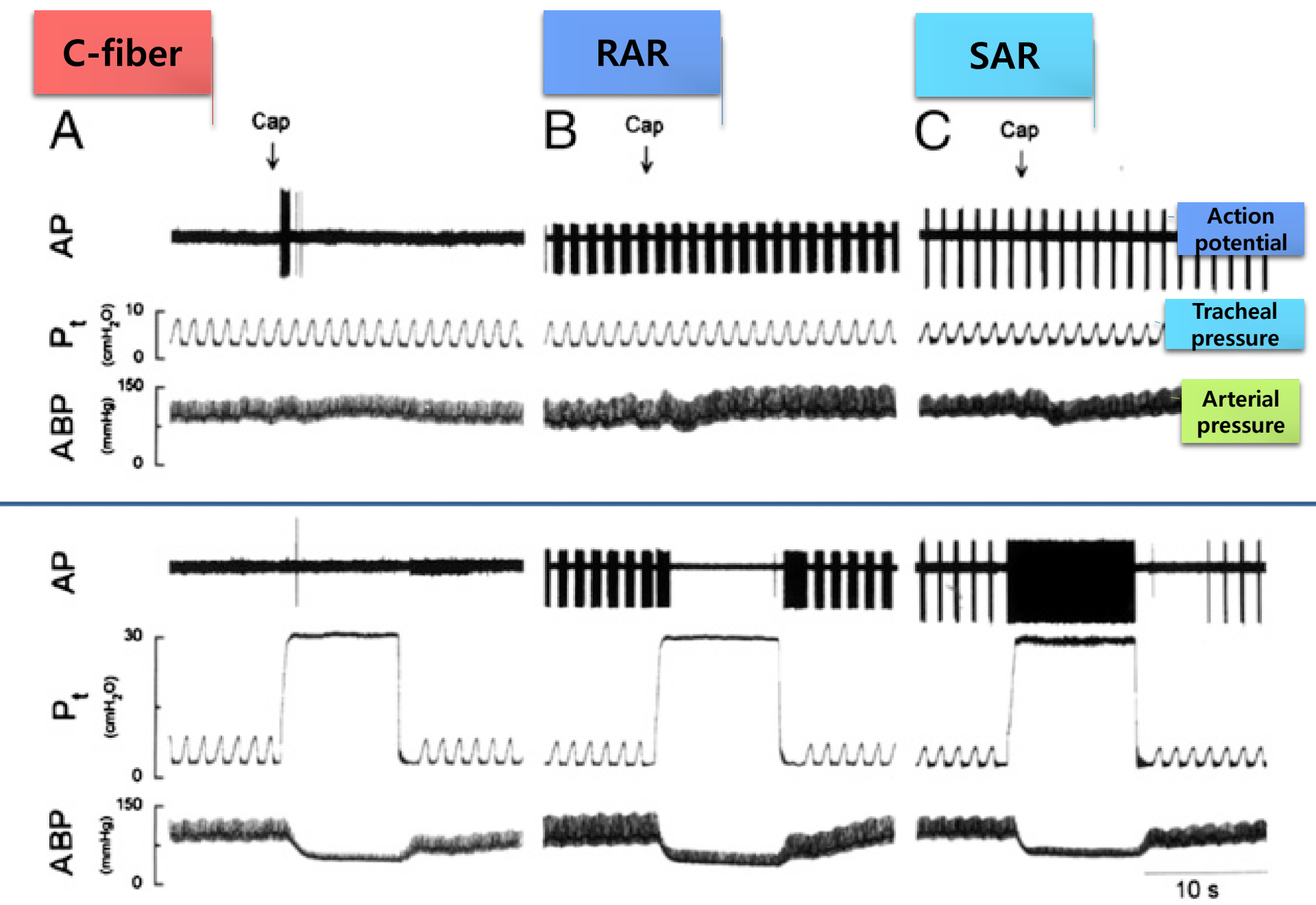
- **Pulmonary Stretch Receptors**
  - **Intrapulmonary** airways
  - a critical role in **regulating respiratory rate and tidal volumes** at eupnea
  - associated with the **airway smooth muscle**
  - **RAR** rapidly adapting mechanoreceptor
    - activated by sustained lung **inflation** and **deflation/lung** collapse
    - defined as dynamic airway **mechanoreceptors**
  - **SAR** slowly adapting mechanoreceptor
    - activated by sustained lung **inflation**
    - highly sensitive to the mechanical forces imposed upon the lung during breathing.
    - the primary afferent fibers involved in the **Hering-Breuer inflation reflex** (terminating inspiration and initiates expiration when the lungs are adequately inflated)

Canning BJ, *et al. Chest 2014;146:1633-48.*

Classification of Airway Afferent Nerve Subtypes



Mazzone SB. *Cough 2005;1:1-9.*



Canning BJ, *et al. Chest 2014;146:1633-48.*

Name	Fiber type	Conductive Property	Distribution / location	Receptor types	Sensitivity
C-fiber	Nocice ptor (chemo -sensor)	Unmyelinat ed	Intra-pulmonary / mucosal surface	TRPV-1, TRPA-1	chemicals such as bradykinin (a mediator released during inflammation), capsaicin (a vanilloid extract of peppers), and Hydrogen ions (acid pH)
Cough recept-or	Mechan osensor	Myelinated, RAR "irritant receptor"	Extra-pulmonary /subepitheli al layer	voltage-gated sodium channels (acid-sensing ion channel family)	mechanical and acid stimuli (insensitive to capsaicin and bradykinin)
Lung stretch receptor	Mechan osensor	Myelinated, **RAR** "irritant receptor"	Intra-pulmonary	TRPV-1	• cigarette smoke, acidic and alkaline solutions, hypotonic and hypertonic saline, mechanical stimulation, pulmonary congestion, atelectasis, bronchoconstriction, and reduction in lung compliance • Autacoids / inflation /deflation
	Mechan osensor	Myelinated, **SAR**	Intra-pulmonary		Lung inflation

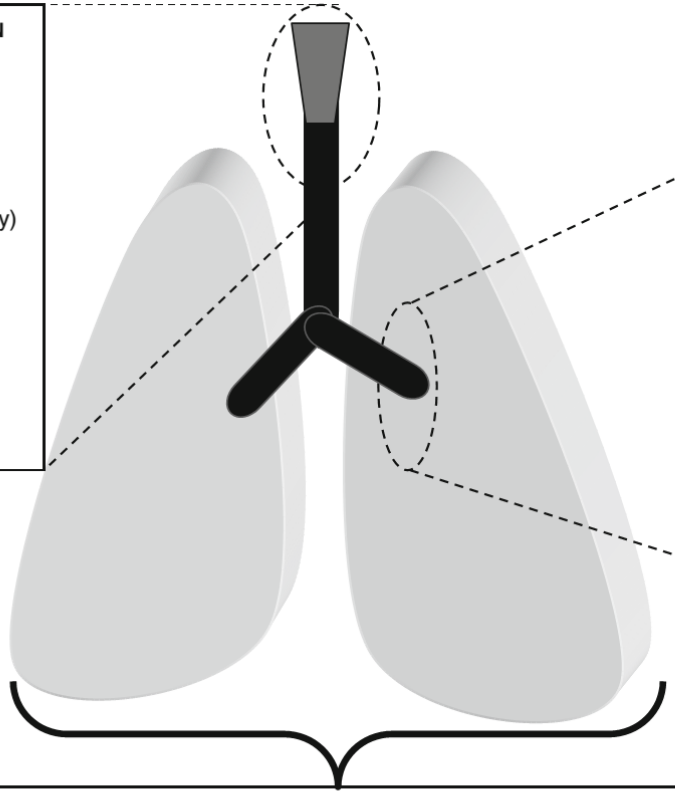
RAR, rapidly adapting mechanoreceptor; SAR, slowly adapting mechanoreceptor; TRPV-1, transient receptor potential vanilloid-1; TRPA-1, transient receptor potential A1

Canning BJ, *et al. Chest 2014;146:1633-48.*
Chung KF, *et al. The Lancet 2008;371:1364-74.*

Sensory Afferent and Receptors

VAGAL AFFERENT SUBTYPES AND RECEPTORS IN LARYNX AND TRACHEA

Sensory afferents	*Activated by*
RAR	Mechanical distention, Punctuate stimulation (foreign body)
Aδ nociceptors bradyknin	Low pH, capsaicin,
'Cough' receptors	Mechanical, low pH (citric acid)
C fibres	Bradykinin, low pH, SO_2



VAGAL AFFERENT SUBTYPES AND RECEPTORS IN LARGE BRONCHI AND PERIPHERAL AIRWAYS

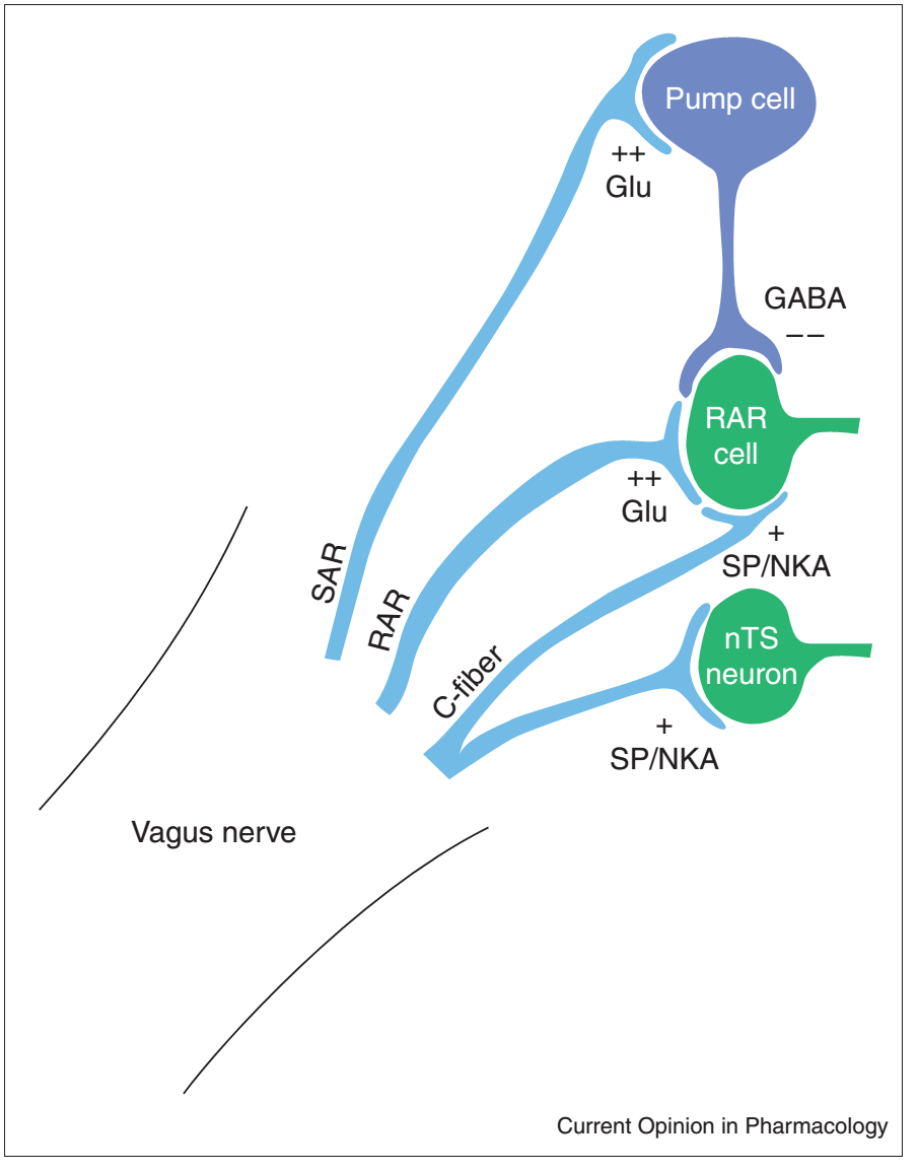
Sensory Afferents	*Activated by*
RAR	mechanical distention, mucus, oedema,
Aδ nociceptors	low pH (citric acid), capsaicin
'Cough' receptors	mechanical, low pH (citric acid)
C fibres	capsaicin, bradykinin, prostaglandins

UPPER AND LOWER AIRWAY AFFERENT RECEPTORS

Receptor	*Activated by*
TRPV1:	heat, low pH, capsaicin
TRPA1:	noxious cold, mechanical, Cigarette smoke, low pH, pungent chemicals (cinnamon, wasabi)
TRPM8	Cool, menthol, Thymol
ASICs	low pH (citric acid), mechanical

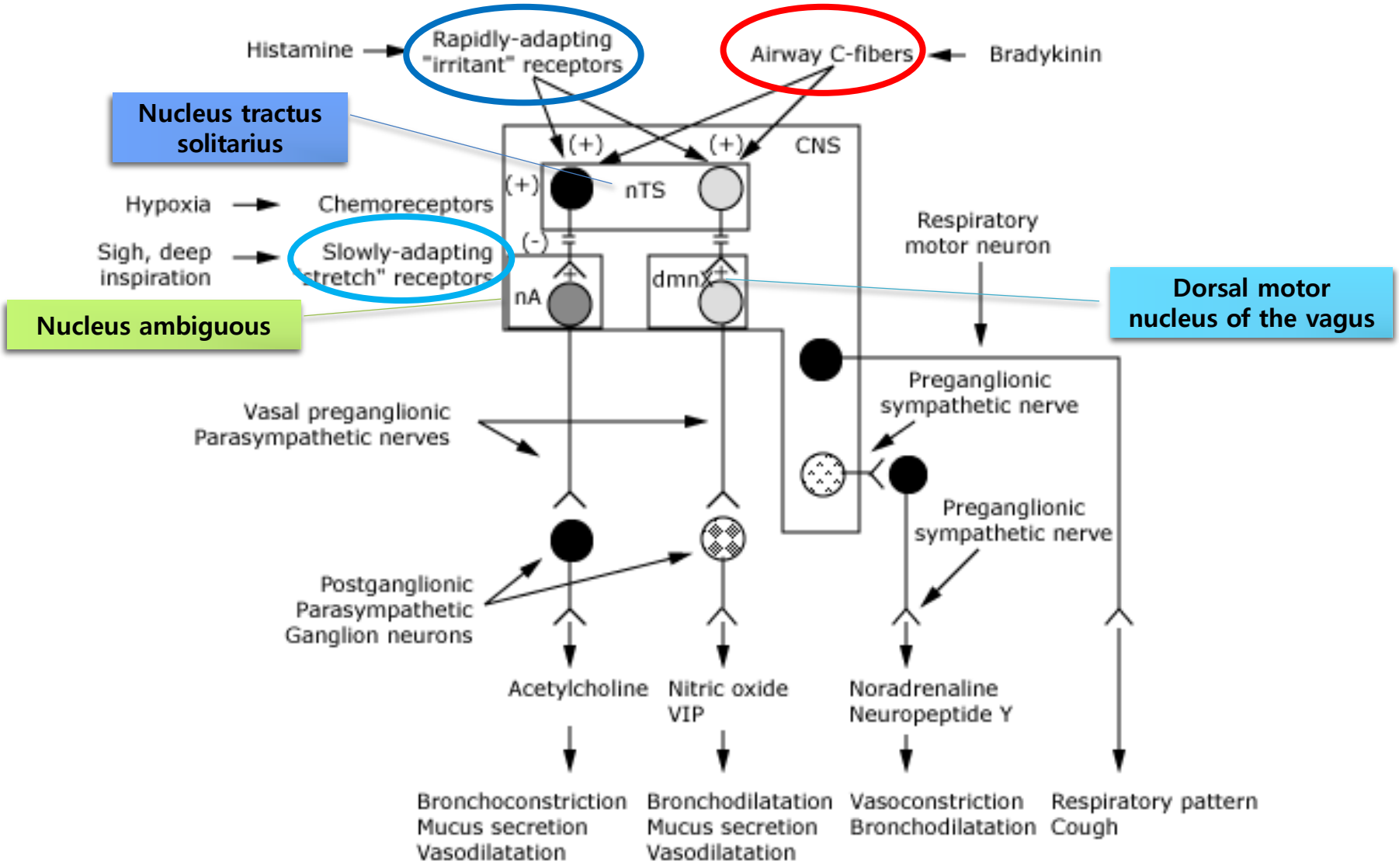
McGarvey L. *Lung 2014;192:459-65.*

Organization Of Airway Afferent Nerve



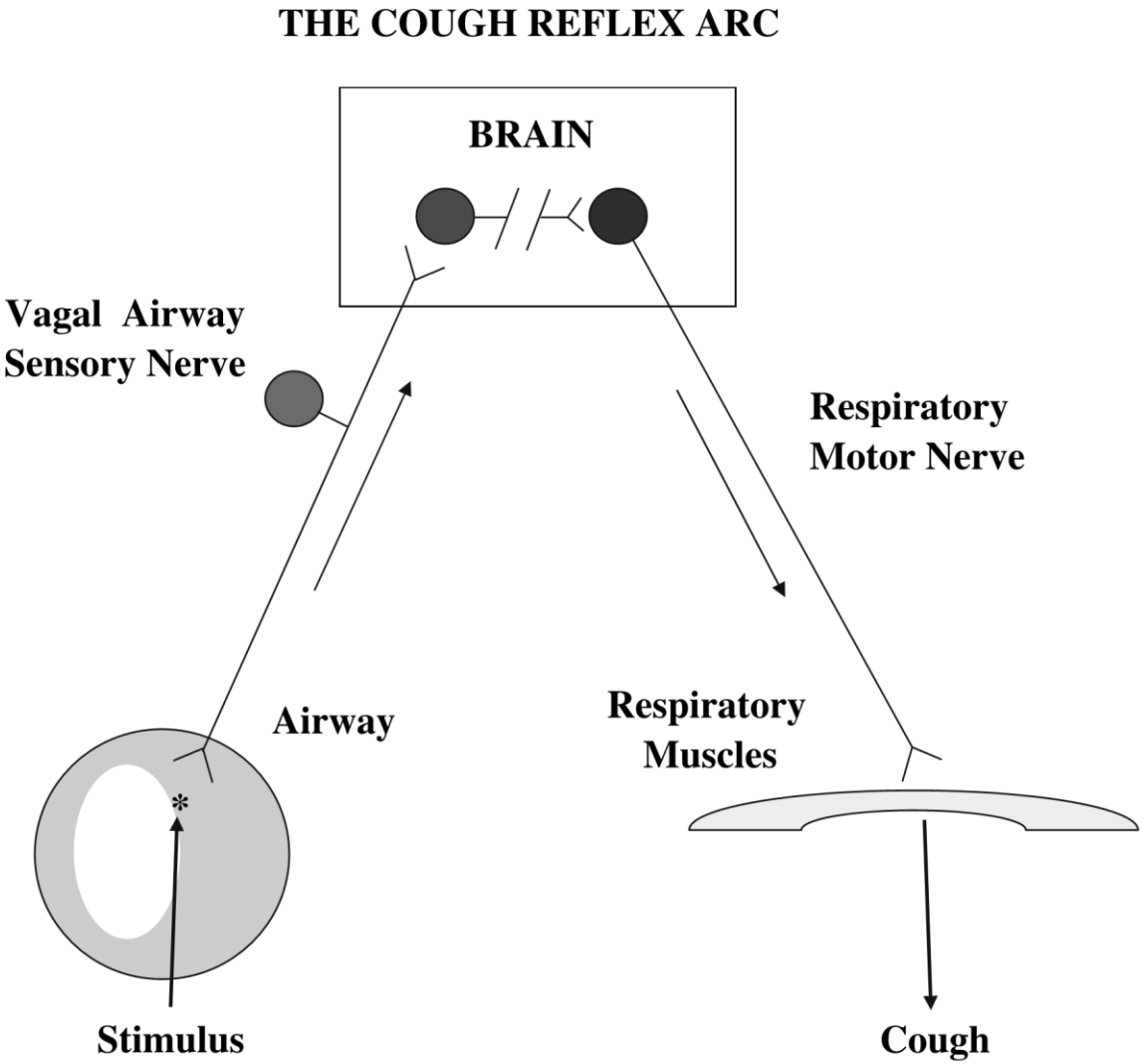
Mazzone SB, *et al. Curr Opin Pharmacol 2002;2:220-8.*

The Neural Pathways Controlling Airway Function



Mazzone SB, *et al. Curr Opin Pharmacol 2002;2:220-8.*

Cough Reflex



Canning BJ. *Lung 2008;186 Suppl 1:S23-8.*

Stimuli Evoking Cough In Humans And Animals

- **Mechanical** stimulation
  - Mucus
  - Foreign body
  - Tumor
- **TRPV1** receptor activation
  - Capsaicin
  - Acid
  - Autacoids and second messengers (e.g., HETEs, bradykinin, adenosine)
- **Bradykinin**
  - Asthma
  - Viral infections
  - ACE inhibitor
- Citric **acid** and tartaric acid
  - Aspiration
  - Airway acidification in disease as measured by exhaled breath condensate
- Low chloride and/or nonisosmotic **aerosols**
  - Aspiration
  - Fog

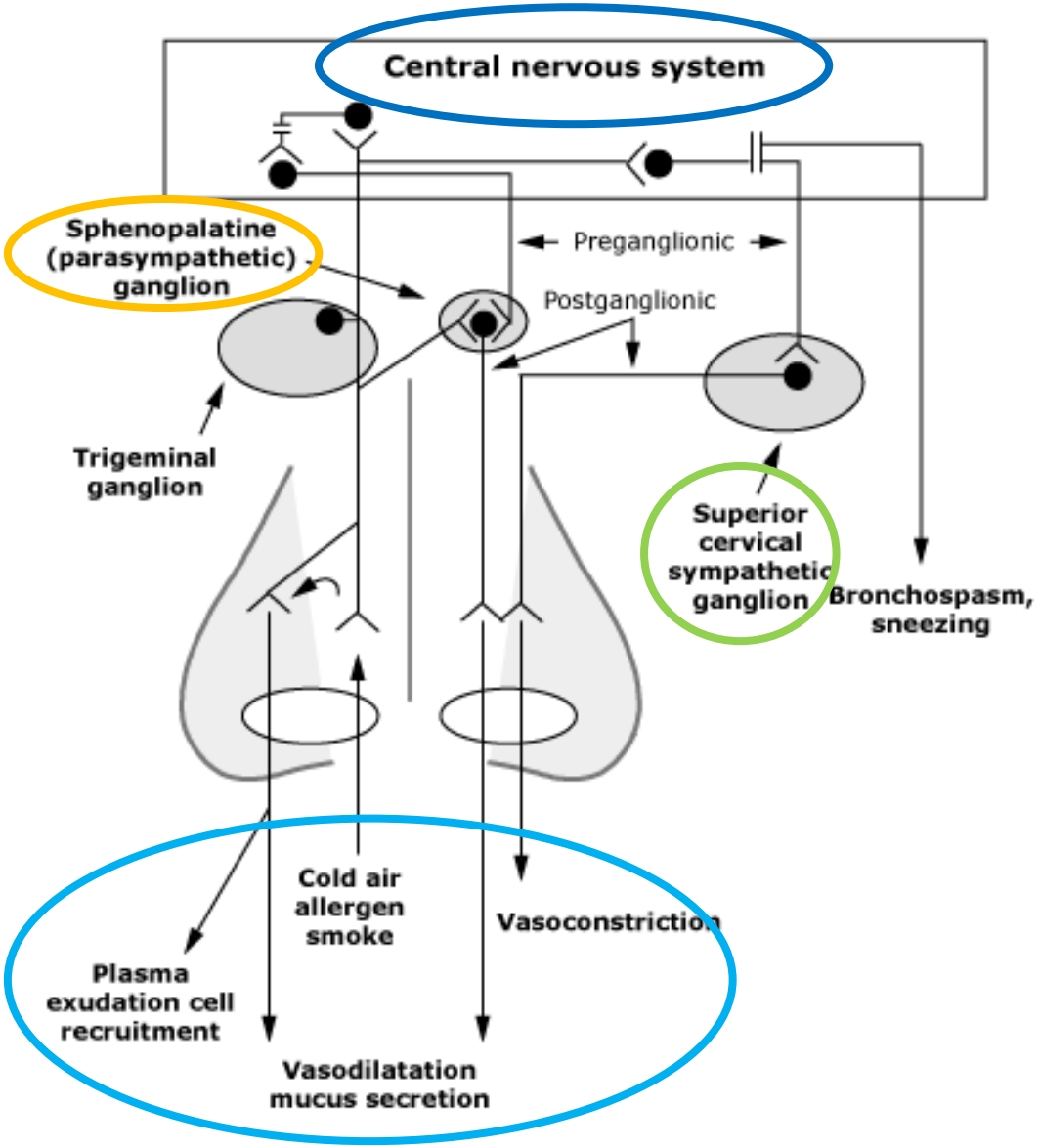
Canning BJ. *Lung 2008;186 Suppl 1:S23-8.*

Stimuli That Do Not Reliably Evoke Cough In Humans Or Animals

- Airways obstruction
  - Methacholine
  - Histamine
  - Cysteinyl-leukotrienes
- Lung inflation/hyperinflation
- Direct nasal stimulation
- Acidification of the esophagus

Canning BJ. *Lung 2008;186 Suppl 1:S23-8.*

The Innervation Of The Upper Airways



Canning BJ. *Curr Allergy Asthma Rep 2002;2:210-5.*

Nasal Afferent Nerve Regulation Of The Cough Reflex

- Enhanced cough reflex
  - **trigeminal afferent pathways** can promote the likelihood of cough **by lowering the threshold** of the central cough pattern generator to subsequent vagal afferent input
- Activating the ion channel transient receptor potential M8 (**TRPM8**)
  - Menthol
  - Soothing, a **counterirritant to effects** evoked by nociceptors
  - Reducing cough frequency and responsiveness

Canning BJ, *et al. Chest 2014;146:1633-48.*

Potential Mechanisms Of Gastro-oesophageal Cough

- Direct effect of reflux contents (acid or pepsin) or volume on **lower oesophageal** afferent nerves
- Direct effect of reflux contents (acid or pepsin) or volume on **laryngeal** afferents or tracheobronchial afferents
- Stimulation of oesophageal-bronchial **interconnecting** neural pathways
- **Increased cough reflex**
- Increased gastro-oesophageal reflux caused by **cough**

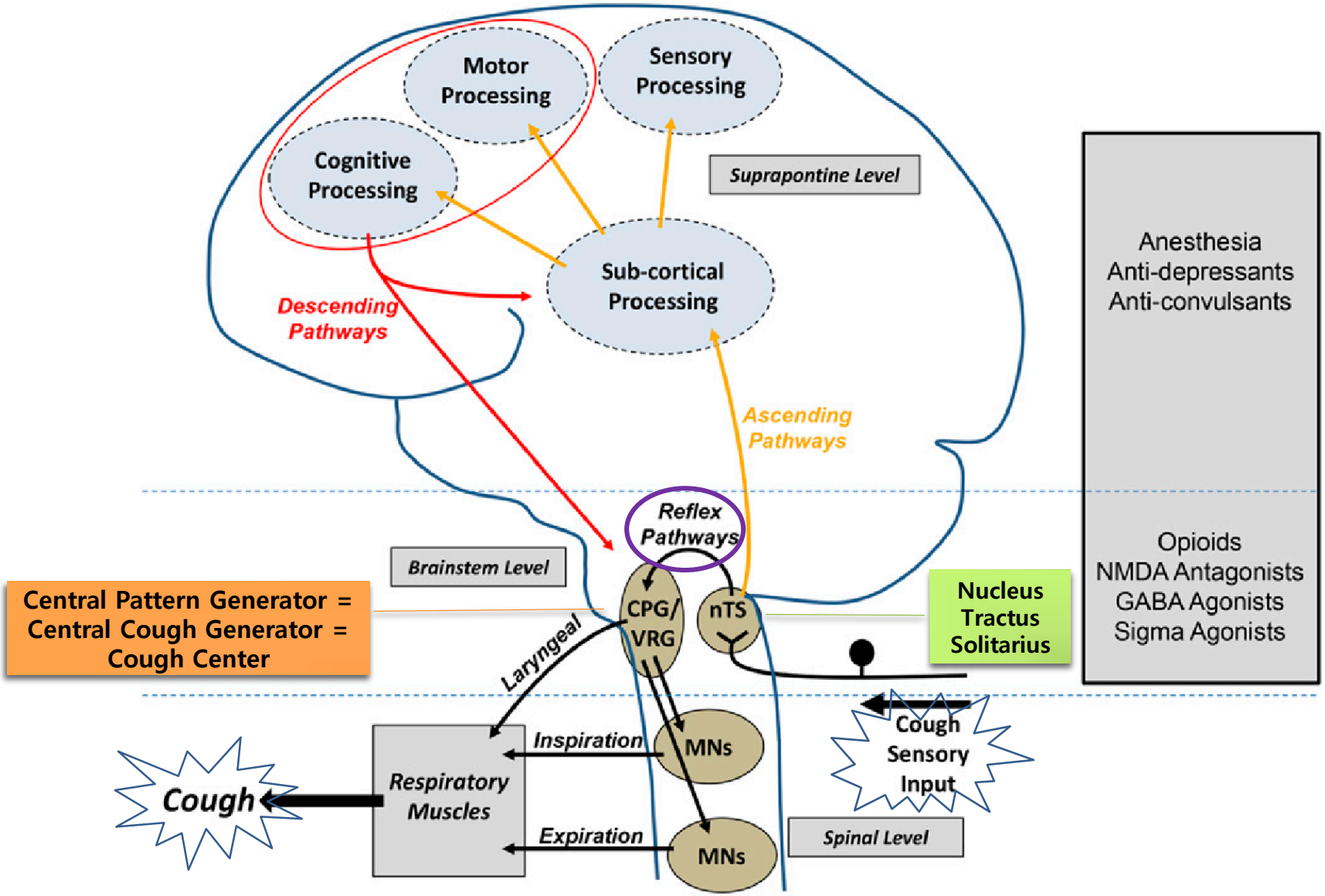
Chung KF, *et al. The Lancet 2008;371:1364-74.*

Central Regulation of Cough

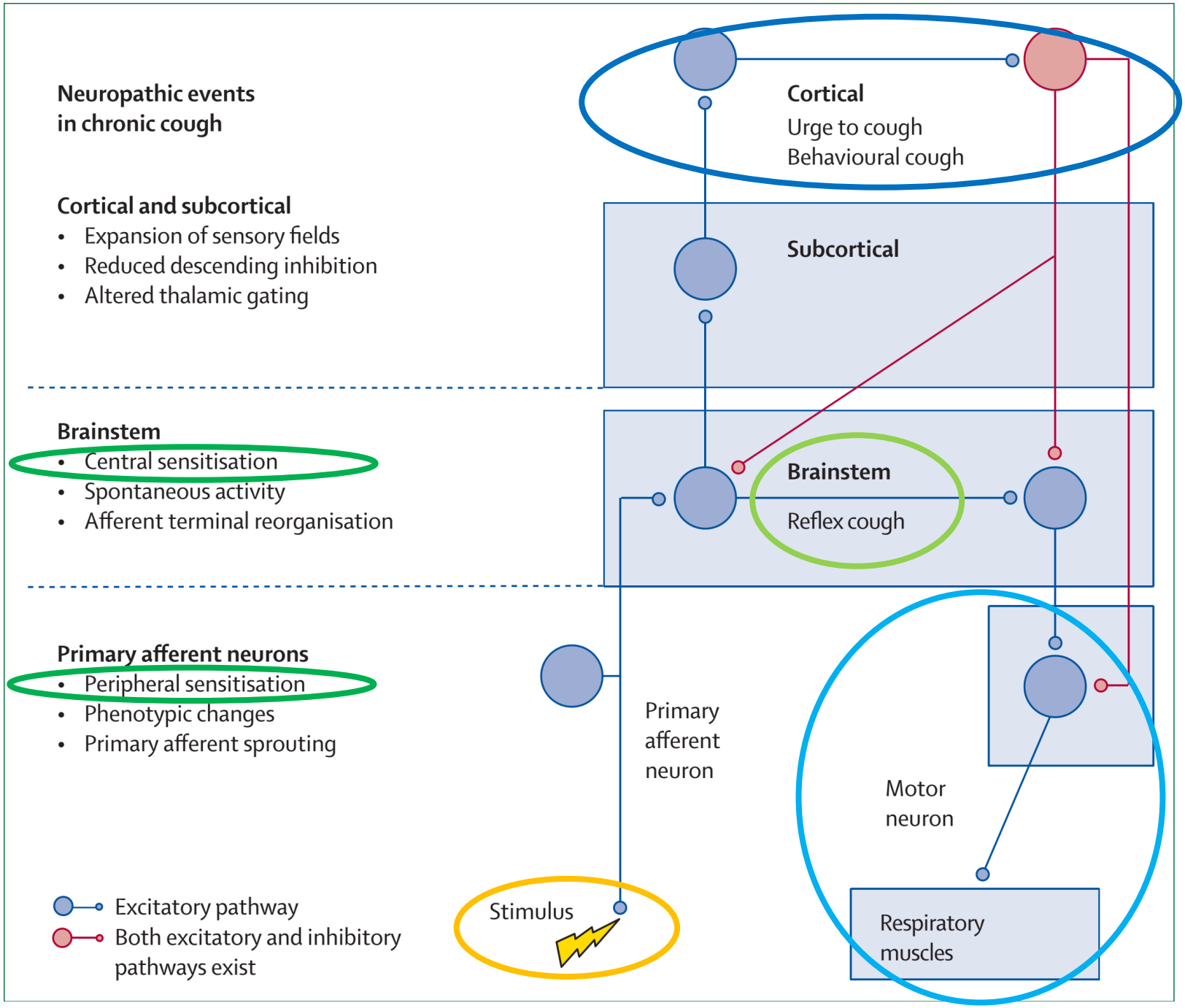
1. **Brainstem** processing of afferent **information**
2. **Organization** of the brainstem control **network**
3. **Higher brain** (encompassing subcortical and cortical) circuits that support the role of consciousness, perception, and emotion in the expression of cough

Canning BJ, *et al. Chest 2014;146:1633-48.*

Central Mechanisms Regulating Cough



Canning BJ, *et al. Chest 2014;146:1633-48.*

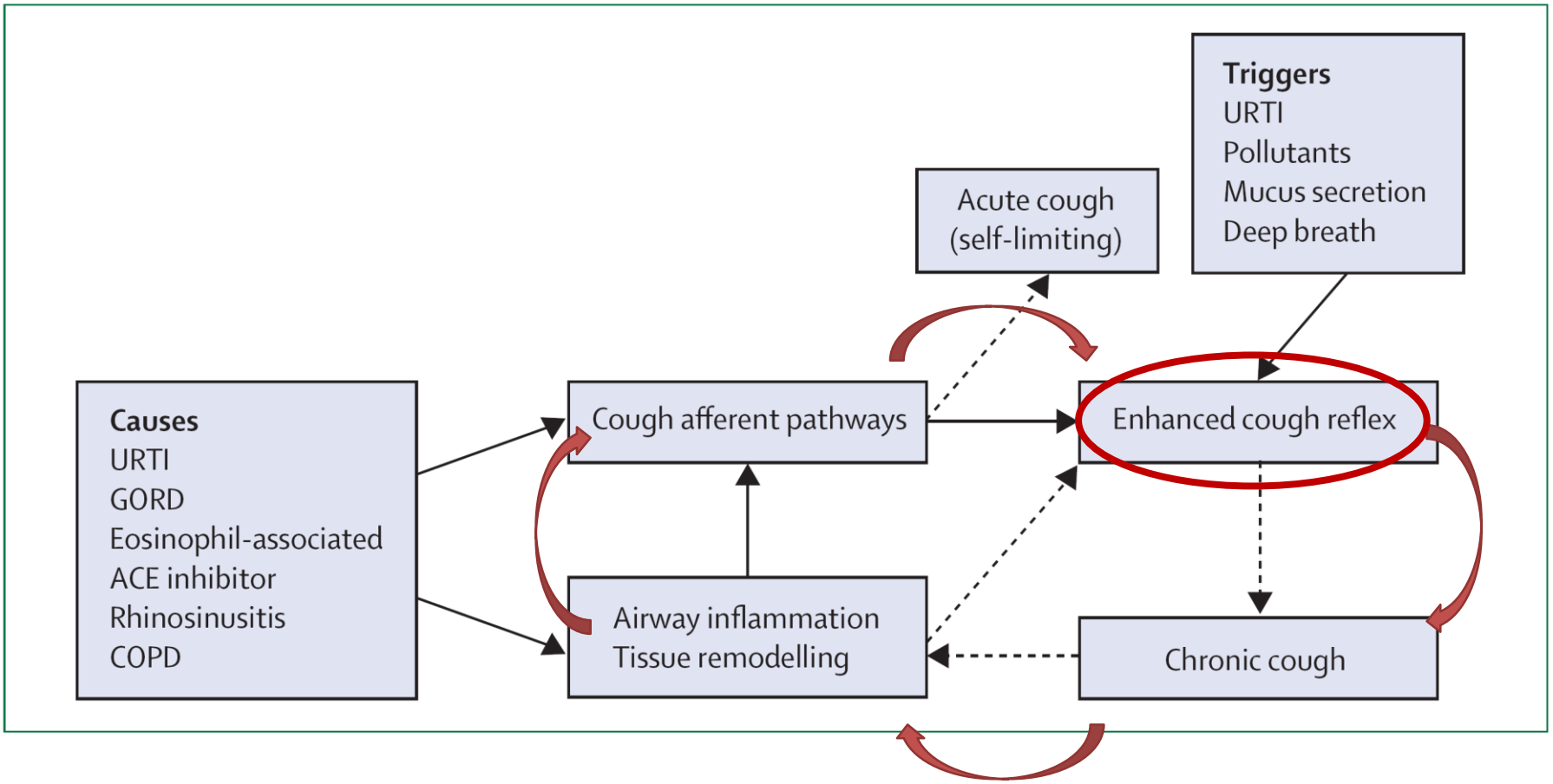


Chung KF, *et al. The Lancet Respiratory Medicine 2013;1:414-22.*

Contents

- Definition of Cough
- Anatomy & Neurophysiology
  - Airway Afferent Nerve Subtypes
  - Central Regulation of Cough
- **Cough Hypersensitivity Syndrome**

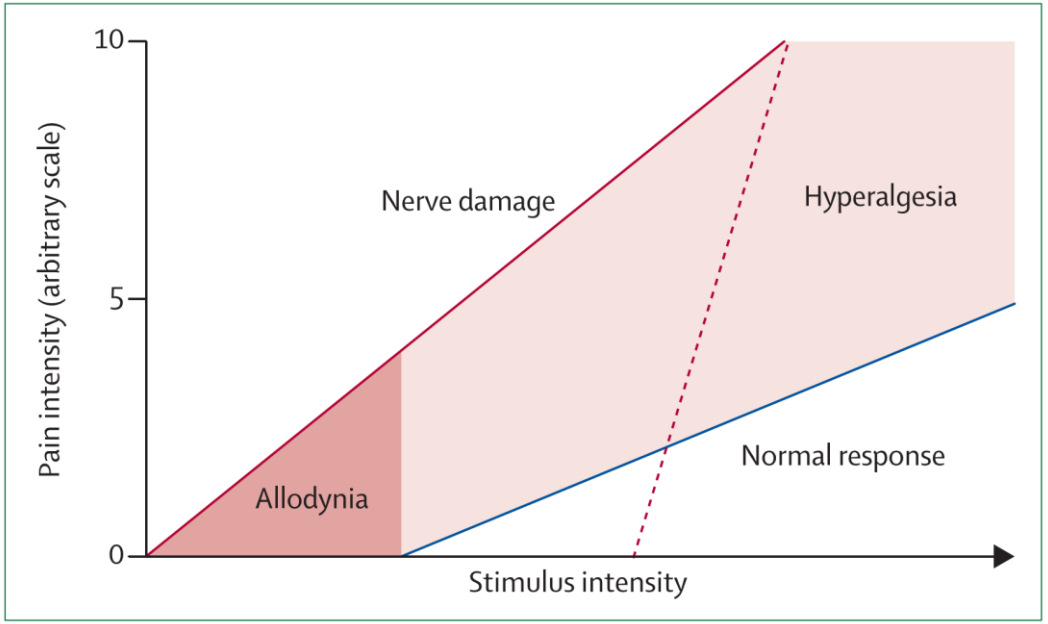
Interactions Between Causes, Cough Pathways, And Airway Inflammation



Chung KF, *et al. The Lancet 2008;371:1364-74.*

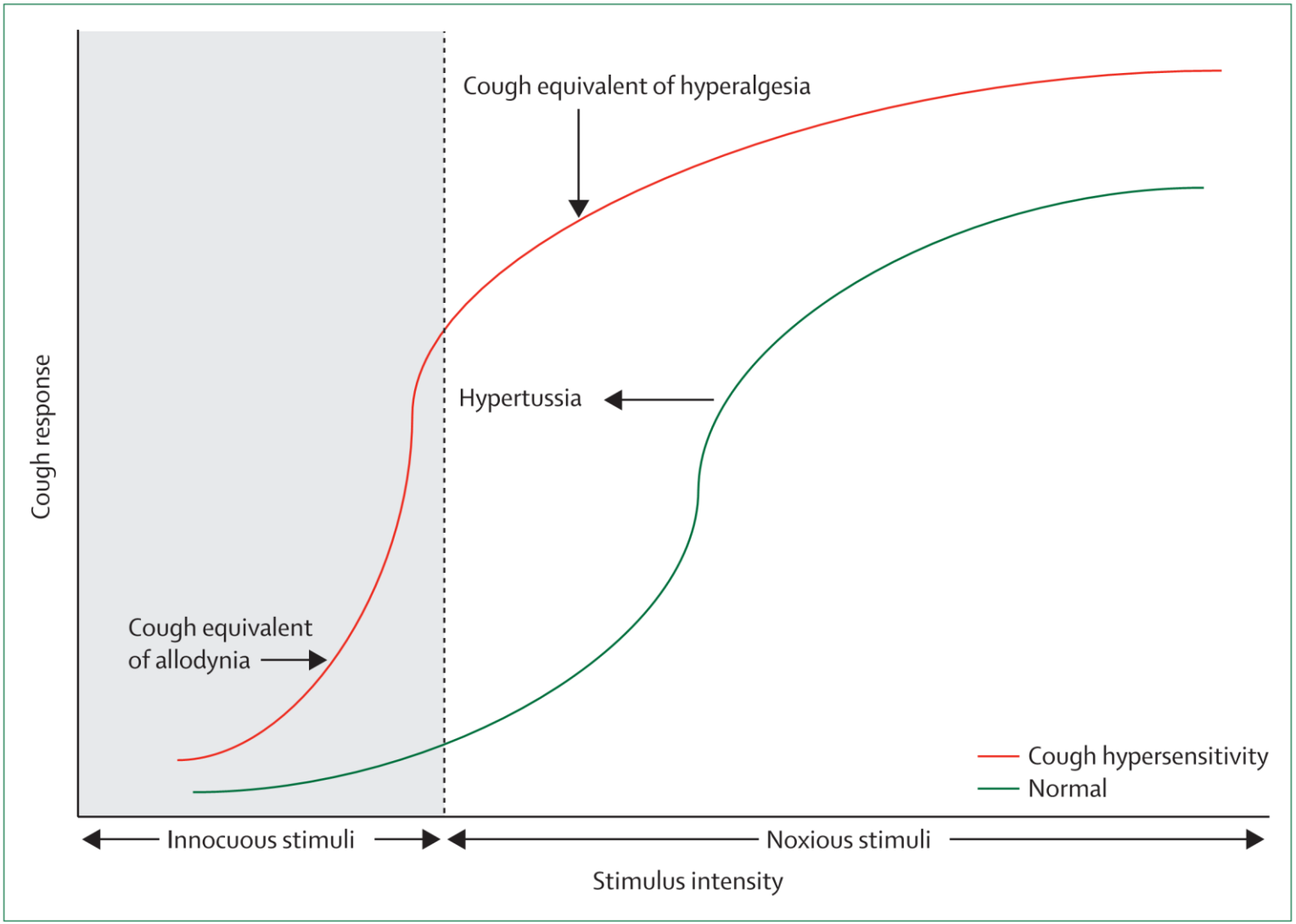
Allodynia And Hyperalgesia

- Neuropathic pain
  - Allodynia - pain due to a stimulus that does not usually provoke pain
  - hyperalgesia - increased pain from a stimulus that usually provokes pain



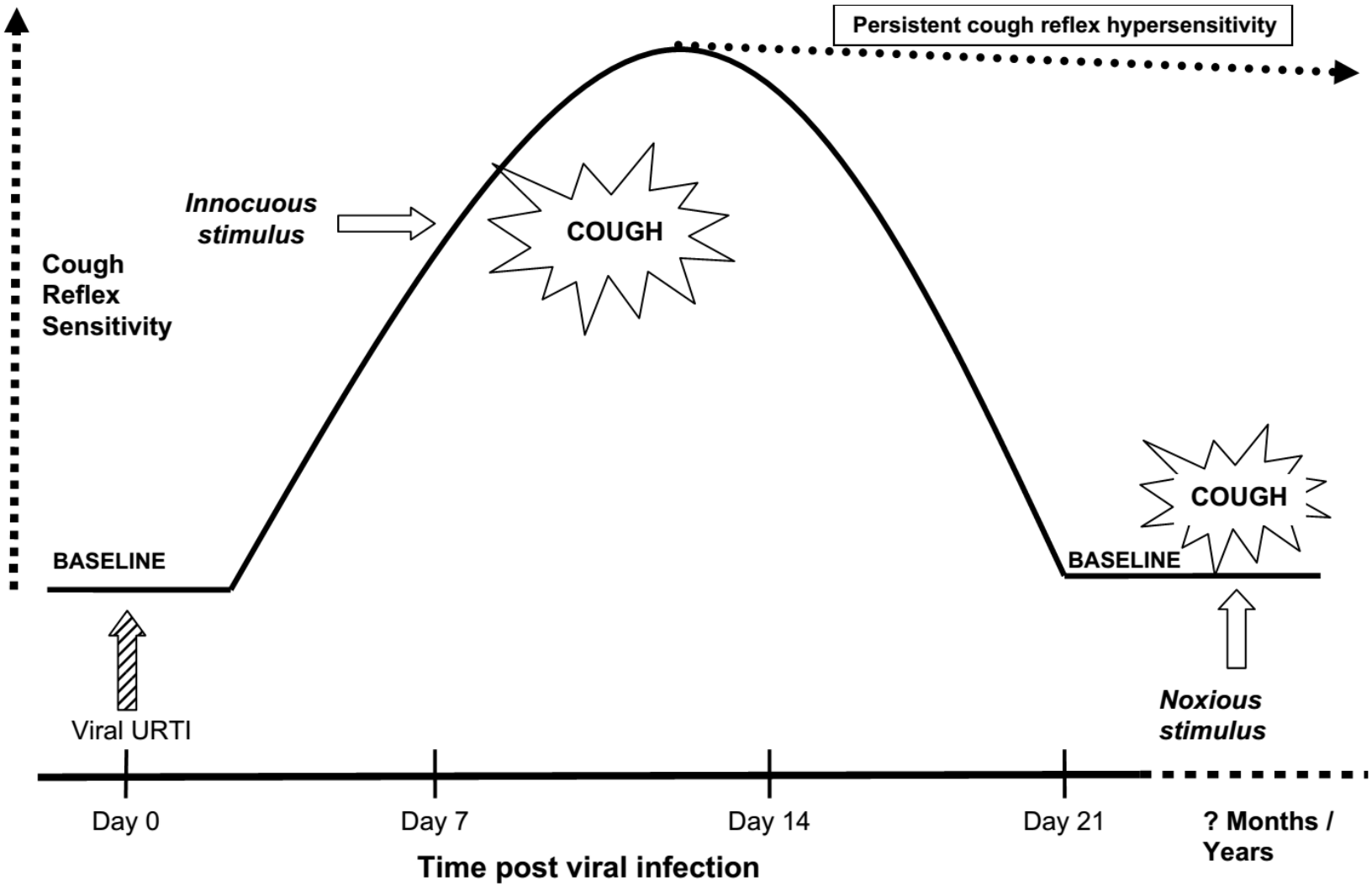
Jensen TS, *et al. Lancet Neurol 2014;13:924-35.*

'Allotussivity' And 'Hypertussivity'



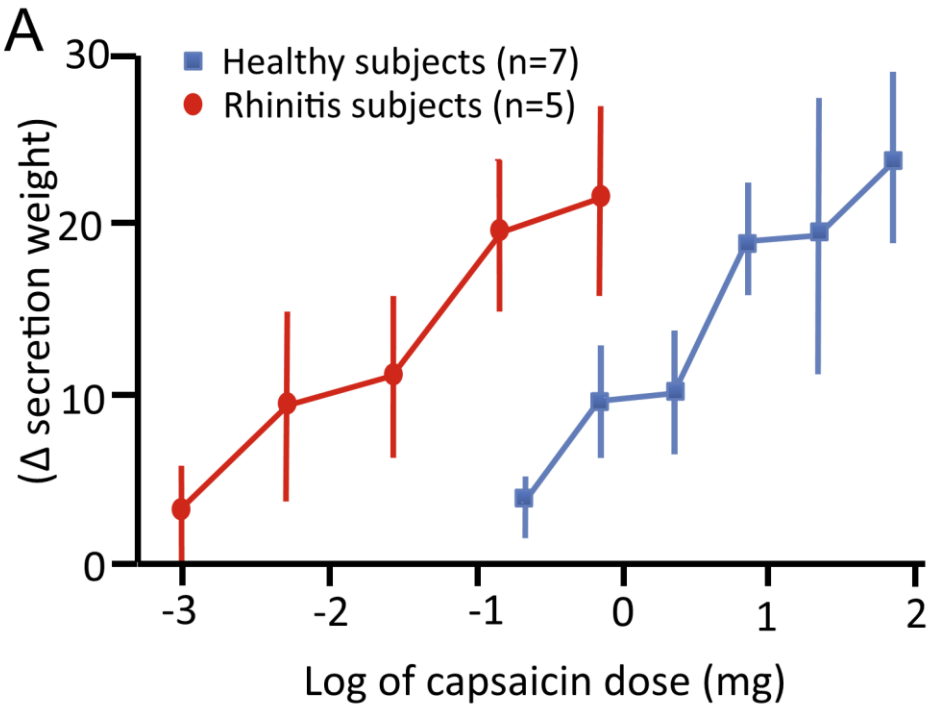
Chung KF, *et al. The Lancet Respiratory Medicine 2013;1:414-22.*
Chung KF, *et al. Pulm Pharmacol Ther 2013;26:475.*

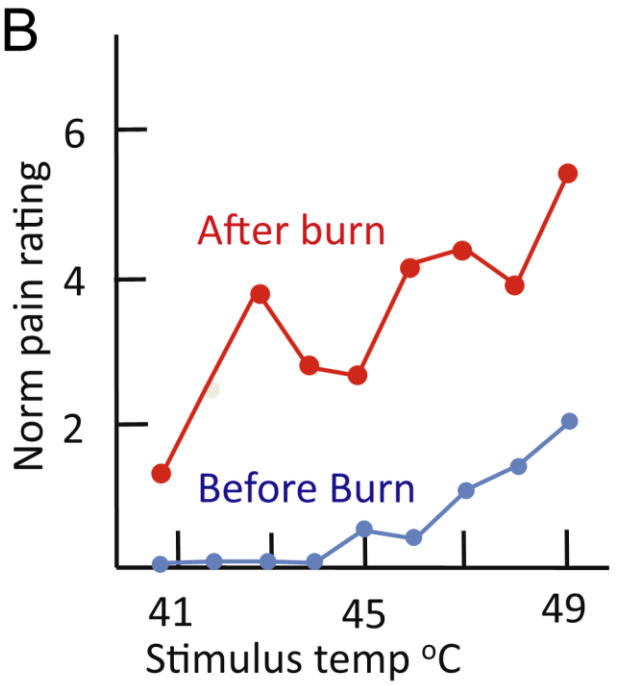
Cough Reflex Hypersensitivity



McGarvey L, *et al. Pulm Pharmacol Ther 2009;22:59-64.*

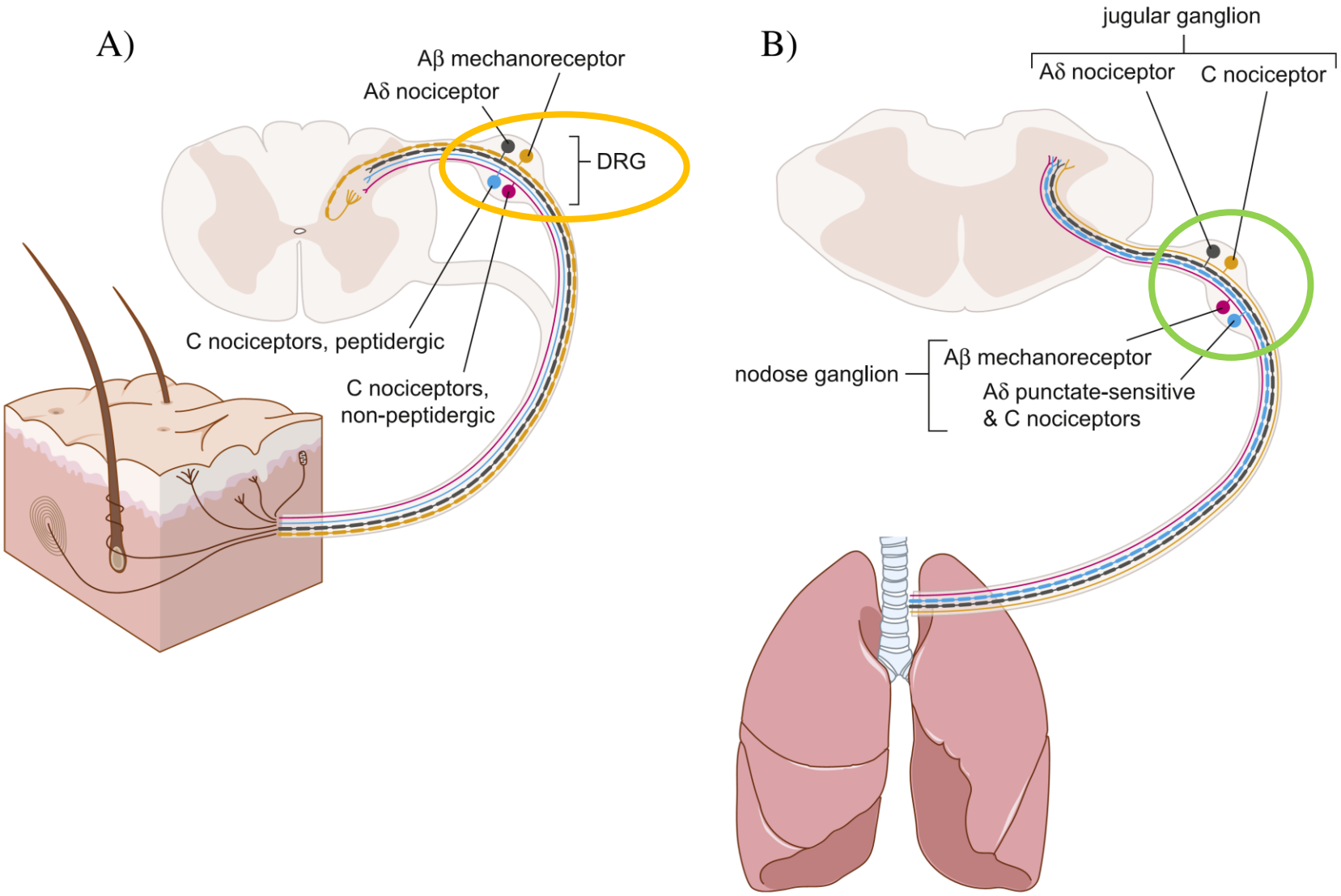
Hypersensitivity In Cough And Pain





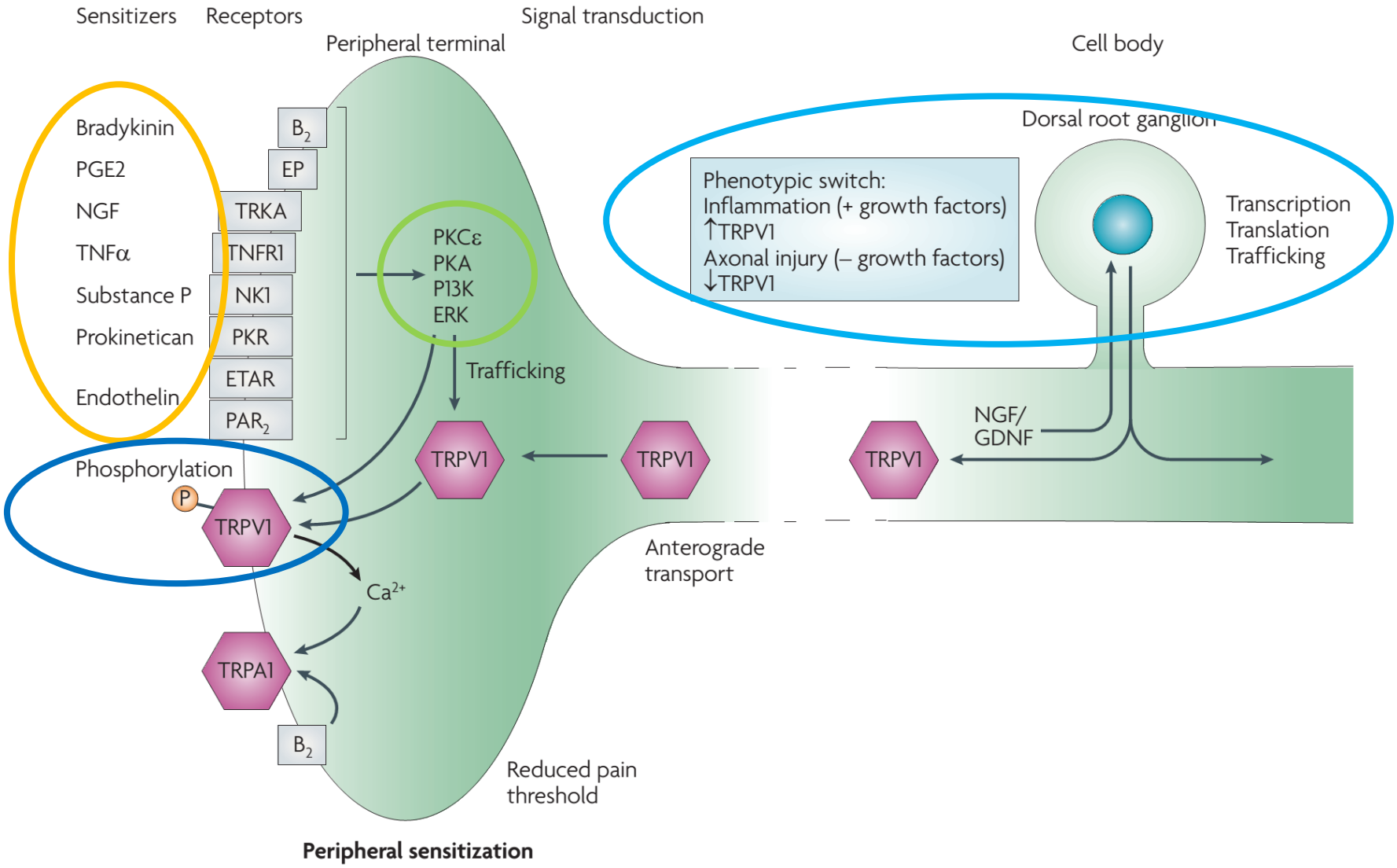
O'Neill J, *et al. Pulm Pharmacol Ther 2013;26:476-85.*

Skin vs. Airway Innervation



O'Neill J, *et al. Pulm Pharmacol Ther 2013;26:476-85.*

Changes In Trp Channels Produced By Inflammation



Patapoutian A, *et al. Nat Rev Drug Discov 2009;8:55-68.*

Cough Hypersensitive Response

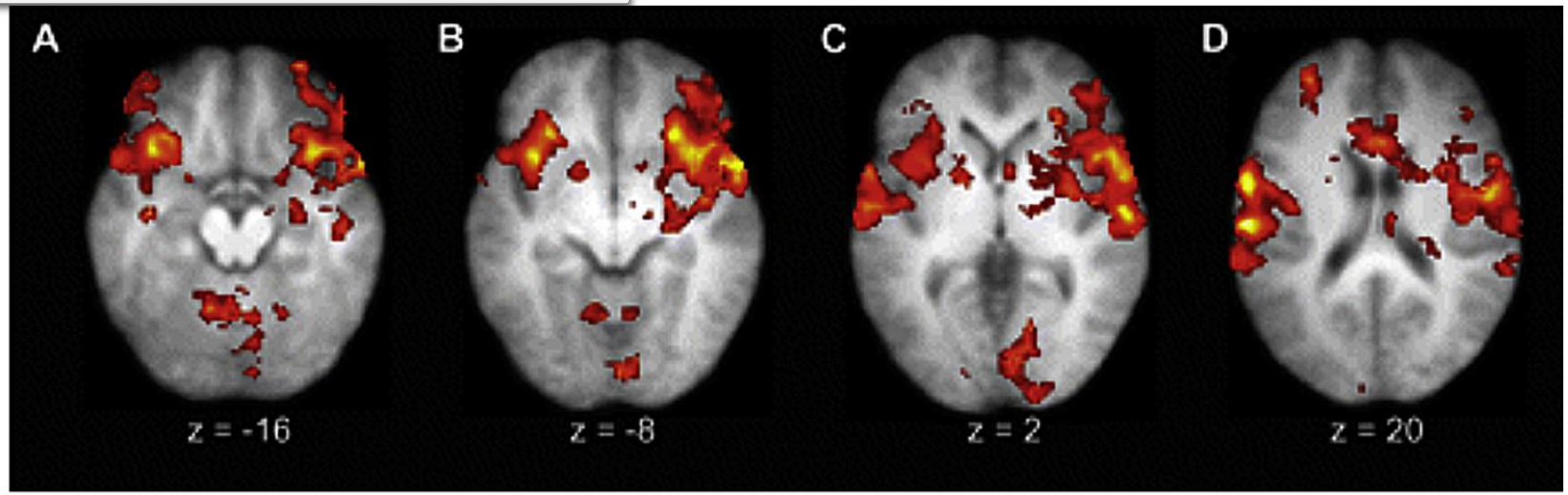
- peripheral sensitization
  - increased sensitivity of cough receptors
- central sensitization
  - changes in central processing, brainstem

Canning BJ, *et al. Chest 2014;146:1633-48.*
Chung KF, *et al. The Lancet 2008;371:1364-74.*

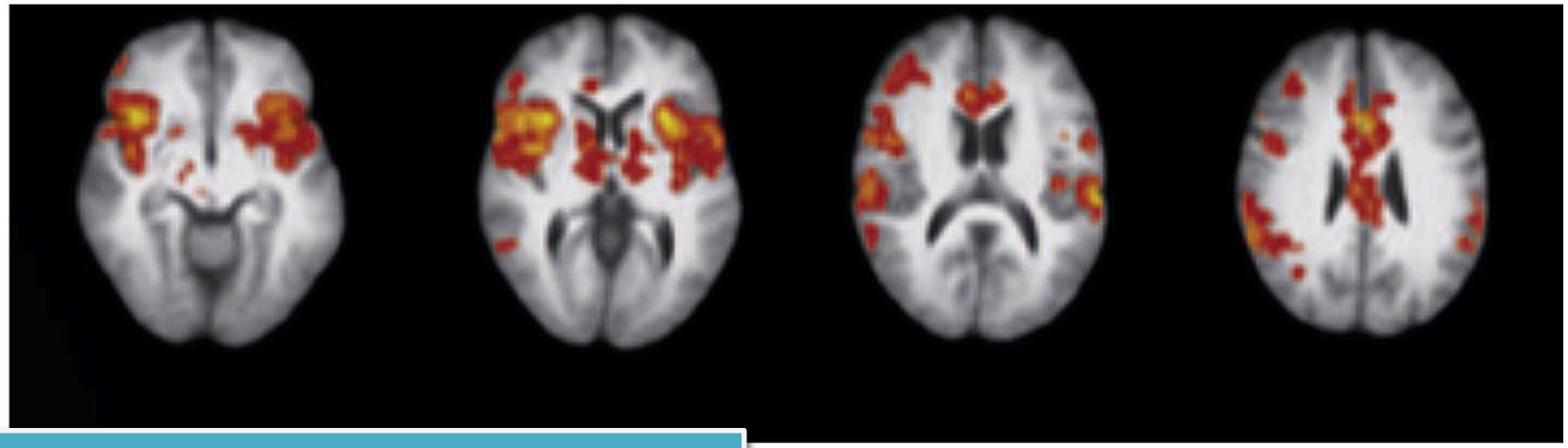
Neural Correlation of Pain & Cough

Post-inhalation of capsaicin

A



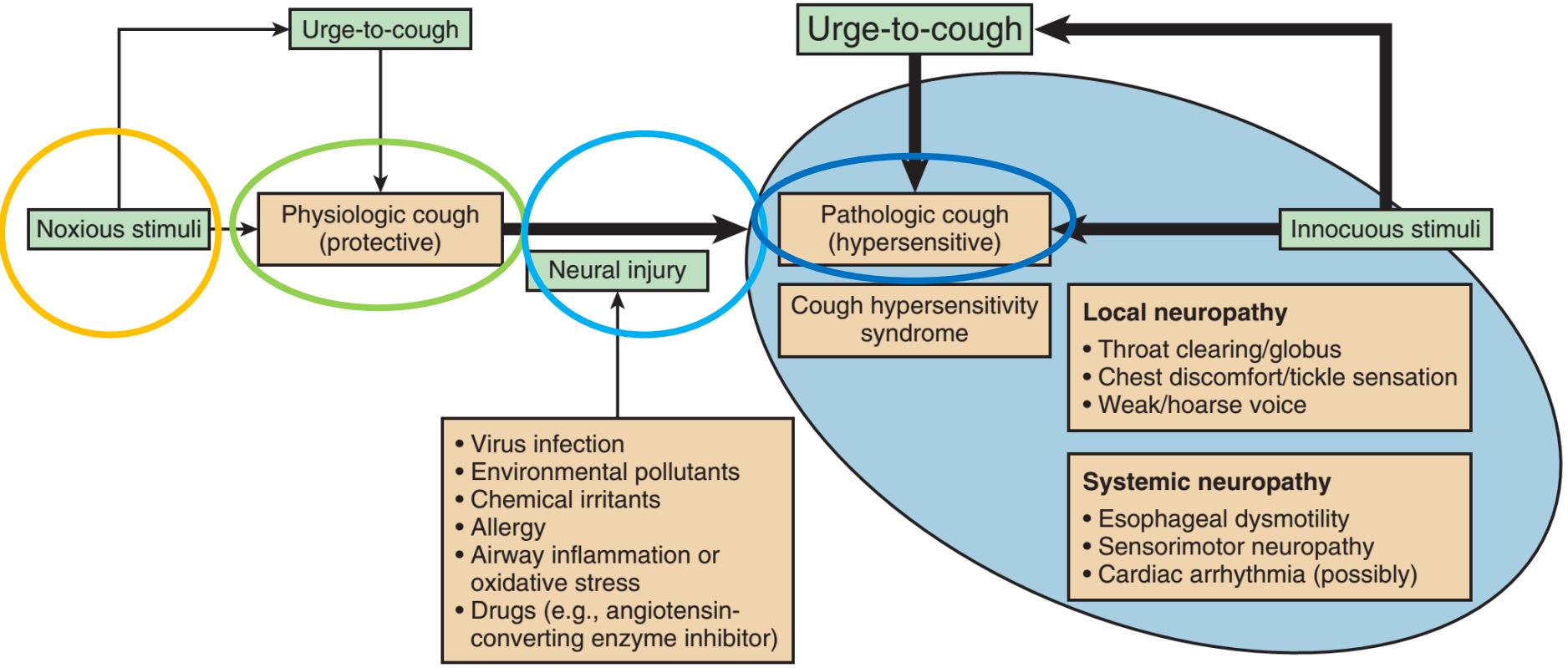
B



Noxious heat applied to the hand

O'Neill J, *et al. Pulm Pharmacol Ther 2013;26:476-85.*

Cough Hypersensitivity Syndrome



Chung KF, et al. The Lancet Respiratory Medicine. 2013;1:414-22.