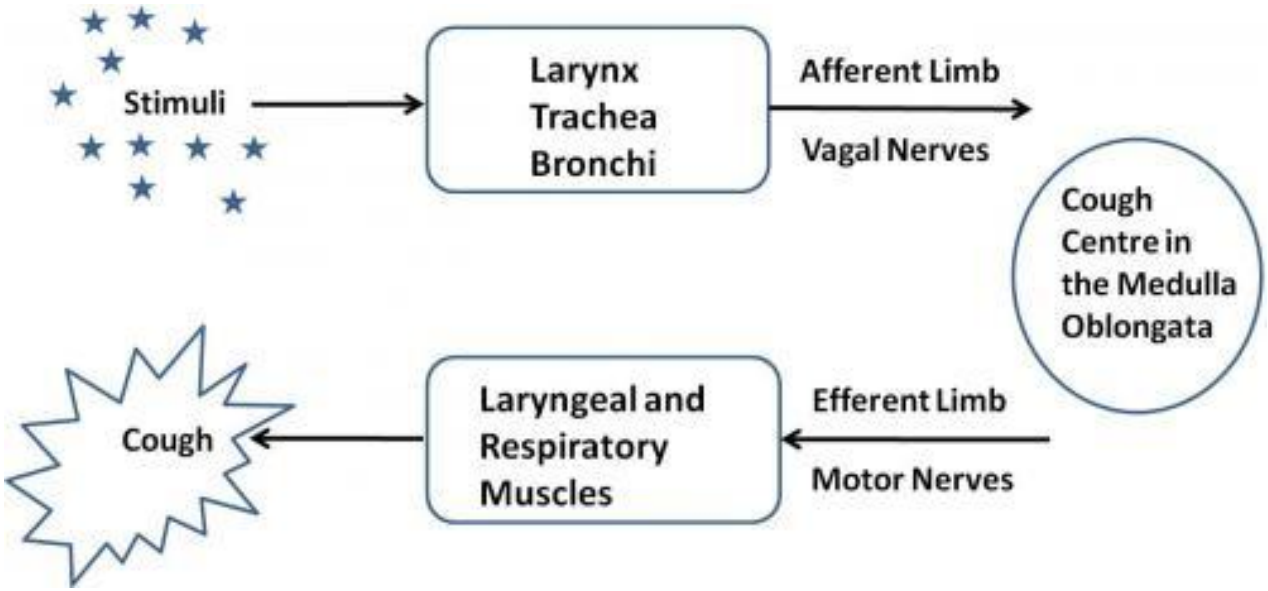
antitussivi



Tosse: espirazione forzata a glottide chiusa seguita dalla sua apertura con conseguente emissione di aria a velocita' elevata

La tosse e' uno dei principali meccanismi attraverso i quali l'albero tracheobronchiale viene mantenuto libero dalle secrezioni e da sostanze estranee eventualmente inalate.

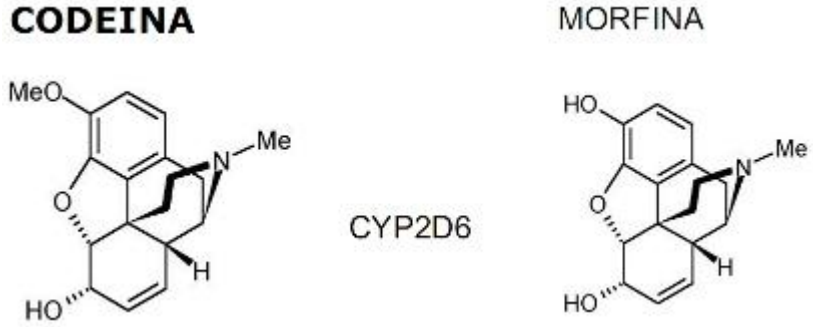
La tosse rappresenta quindi un meccanismo importante di protezione delle vie aeree. La tosse non va trattata se non quando cessa di essere un sintomo per divenire un problema che nuoce al paziente.

FARMACI ANTITOSSE

Azione centrale	oppioidi (codeina, destrometorfano) non oppioidi (cloperastina)
Azione periferica	levodropromazina, oxolamina
Azione periferica indiretta	mucoattivi broncodilatatori anestetici locali

Antitussivi ad azione centrale oppiodi

Codeina



Alcaloide naturale

Ottima biodisponibilita orale (> morfina)

$T_{1/2}$ 2-4h

ED_{50} antitussiva < ED_{50} analgesica

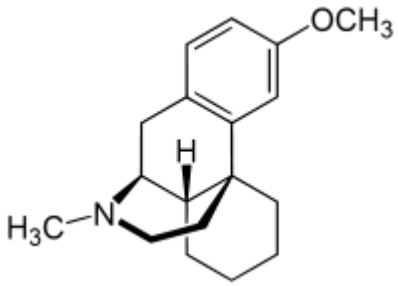
Dose 10-20 mg

Effetti collaterali – essenzialmente correlati alla formazione di morfina per demetilazione epatica quindi nause, stipsi, sedazione e per dosi elevate depressione respiratoria.

Derivati diidrocodeina e folcodina

Antitussivi ad azione centrale oppiodi

Destrometorfano



Isomero destrogiro del metorfano

Bassa affinita' per recettori oppiodi (antagonista NMDA)

Efficacia antitussiva simile a quella della codeina

con minori effetti collaterali

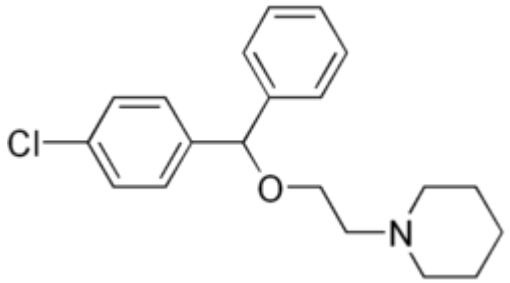
$T_{1/2}$ 5-6h

Dose 30-90 mg/die

Effetti collaterali – solo a dosi elevate depressione SNC

Antitussivi ad azione centrale non oppiodi

cloperastina



$T_{1/2}$ 3-4h

Dose 20-30 mg/die

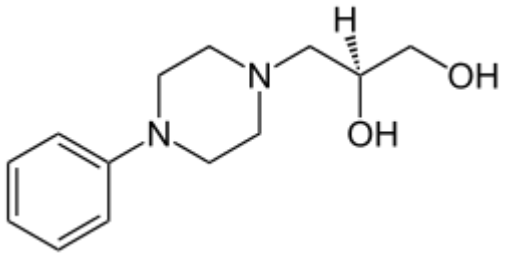
In genere ben tollerato

Effetti collaterali – secchezza delle fauci e sedazione

Clofenadiolo e zipeprolo – scarsamente utilizzati

Antitussivi ad azione periferica diretta

levodropropizina



Attivita' antiinfiammatoria e antiistaminica

Riduce iperattivita' bronchiale

Per os, $T_{1/2}$ 1-2h ma metabiliti attivi 3 volte/die

Dose 120 - 180 mg/die

In genere ben tollerato

Oxolamina simile a levodropropizina

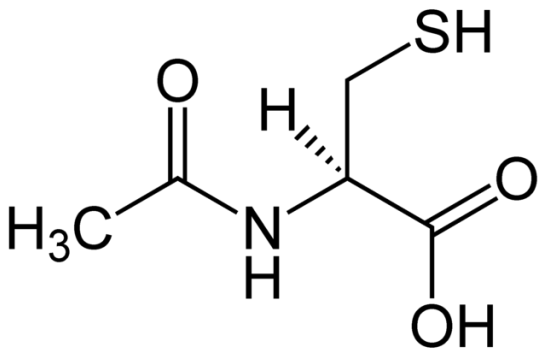
Antitussivi ad azione periferica indiretta

mucoattivi
broncodilatatori
anestetici locali (benzonatato)

MUCOATTIVI

Mucolitici	N-acetilcisteina
	peptidasi
Mucoregolatori	bromexina, ambroxolo

N-acetilcisteina



MoA - Il gruppo –SH libero si sostituisce a ponti -S-S- presenti tra le cisteine delle mucine.

Descritta attivita' antiossidante potenzialmente importante per ridurre la flogosi delle vie aeree.

Per os e aereosol

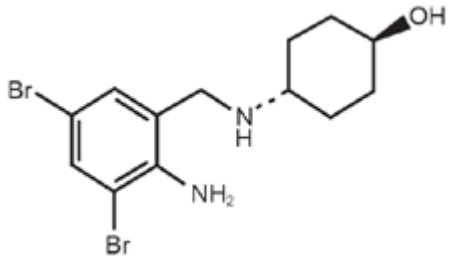
$T_{1/2}$ 10-12h

Dose 400 - 600 mg/die

Effetti collaterali: nausea, vomito, orticaria, broncospasmo.

Controindicato nel pz ulceroso

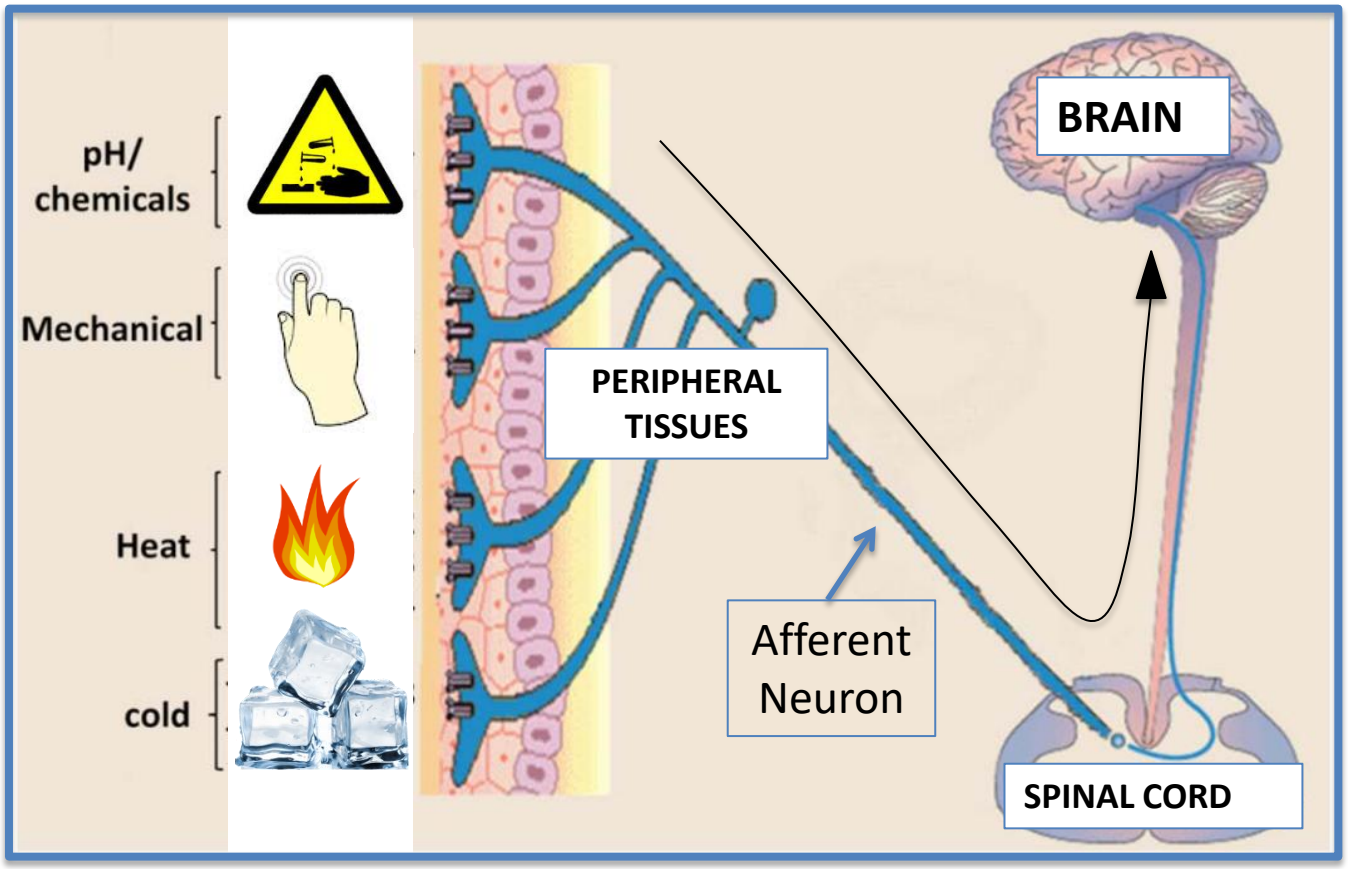
ambroxolo



Bromexina e neltexina sono profarmaci del ambroxolo
Effetti:
Riduzione adesivita' muco
Stimolazione epitelio ciliato
Stimolazione produzione surfactante

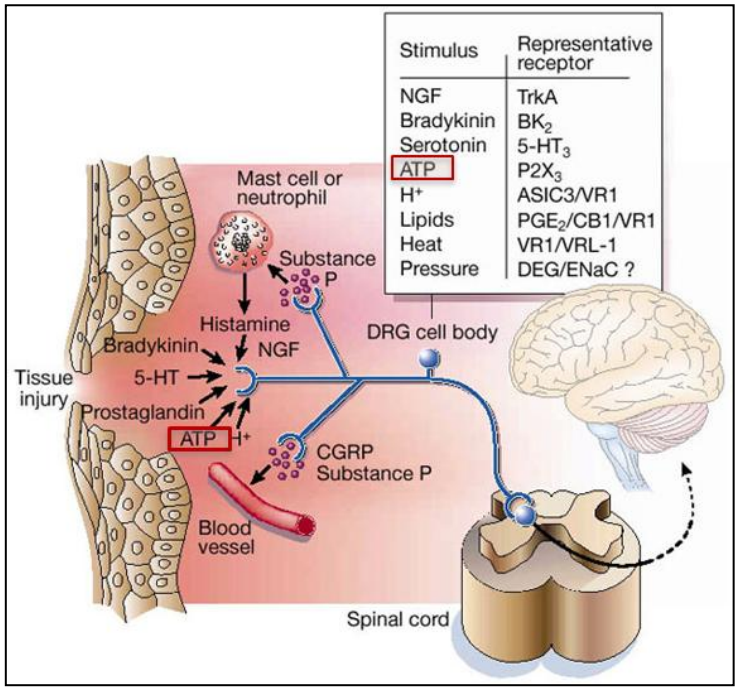
Per os
$T_{1/2}$ 7-12h
Dose 30 - 90 mg/die
Ben tollerato
raramente nausea, cefalea, disturbi GI.
Controindicato nel pz ulceroso

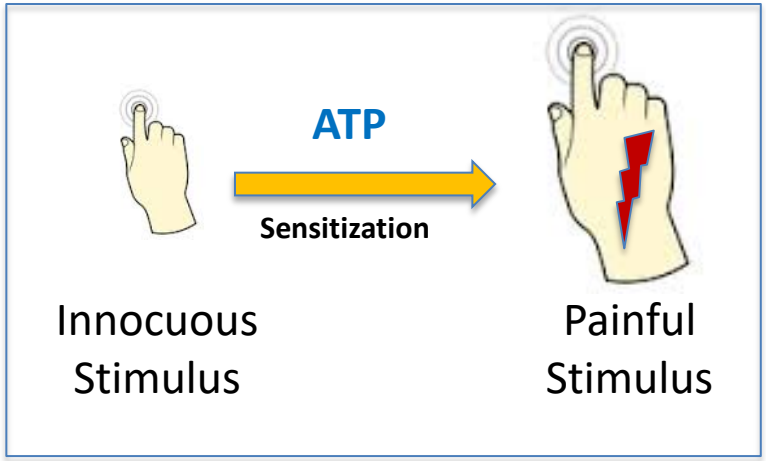
Sensory Afferents

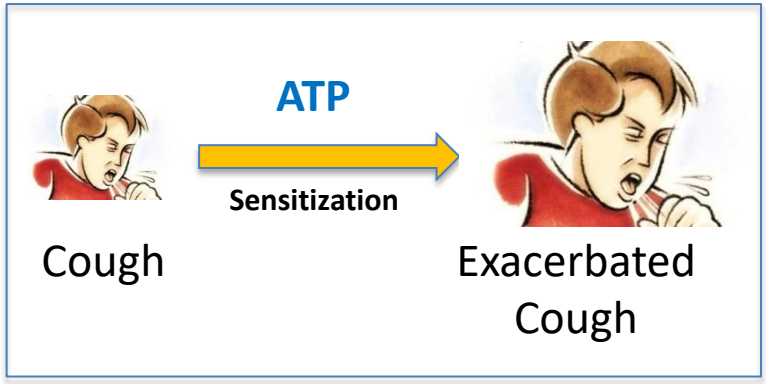


Sensory afferents carry impulses originated by diverse stimuli:
THERMAL (cold, heat), MECHANICAL, CHEMICAL

Sensory Afferents Sensitizarion

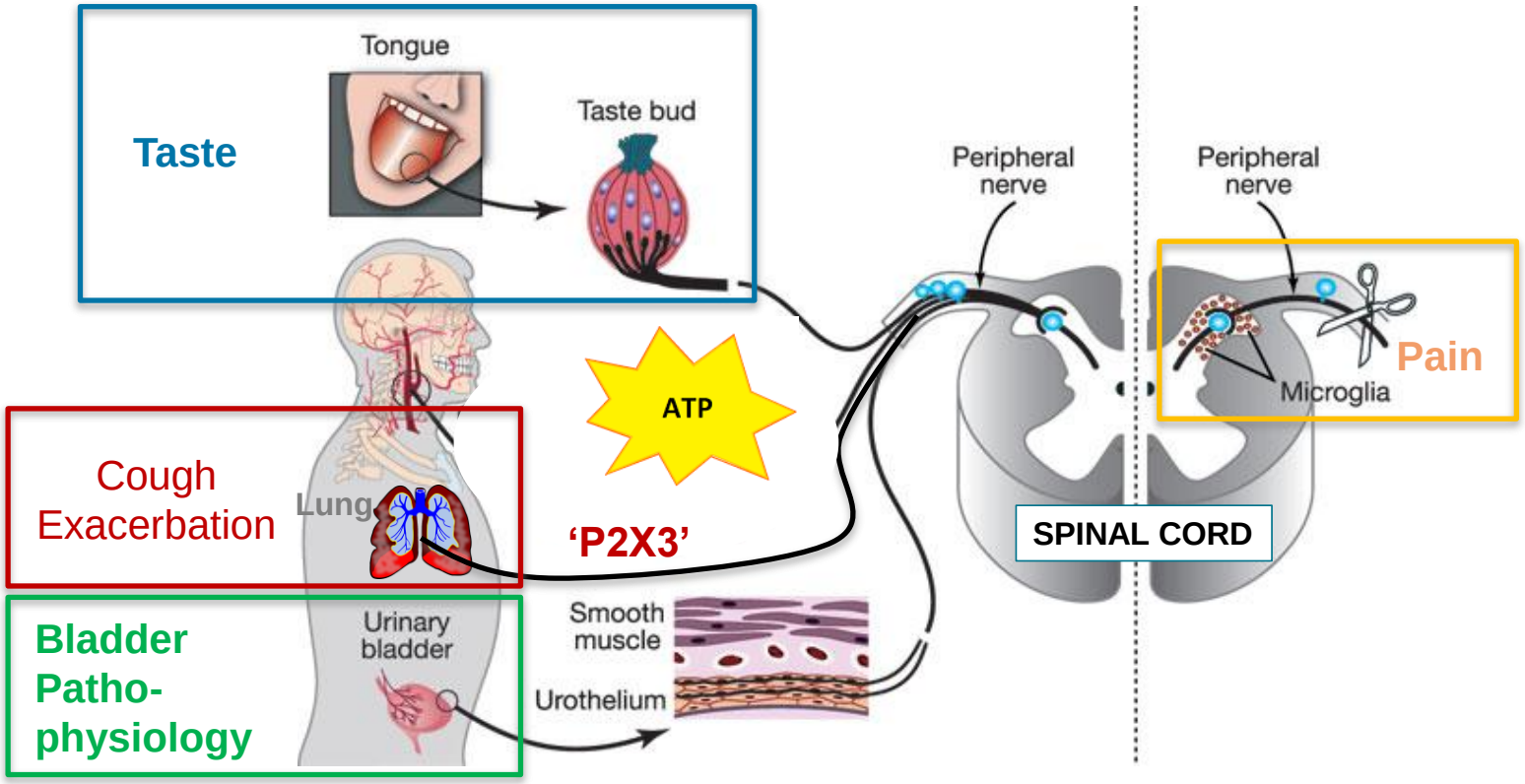




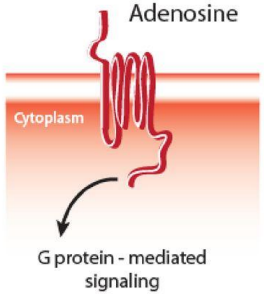
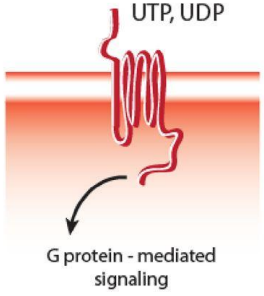
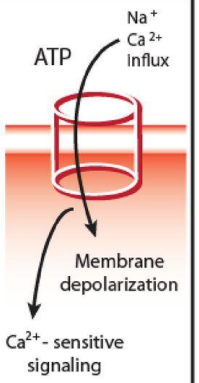


ATP Participates to Sensory Afferents Sensitization

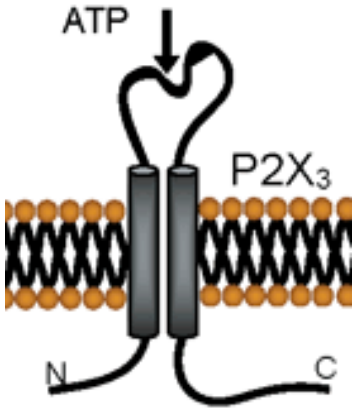
ATP signaling in sensory afferents patho-physiology



Purinergic Receptors

Purinergic Receptors			
Family	Adenosine/P1 receptors (P1Rs)	P2 receptors (P2Rs)	
Subfamily	-	P2Y	P2X
Receptor Subtypes	A1, A2A, A2B, A3	P2Y1, P2Y2, P2Y4, P2Y6, P2Y11, P2Y12, P2Y13, P2Y14	P2X1, P2X2, P2X3, P2X4, P2X5, P2X6, P2X7
Structure	G protein-coupled receptors	G protein-coupled receptors	Ligand-gated ion channels
Ligands			

$P2X_3$ is a ligand-gated ion channel…

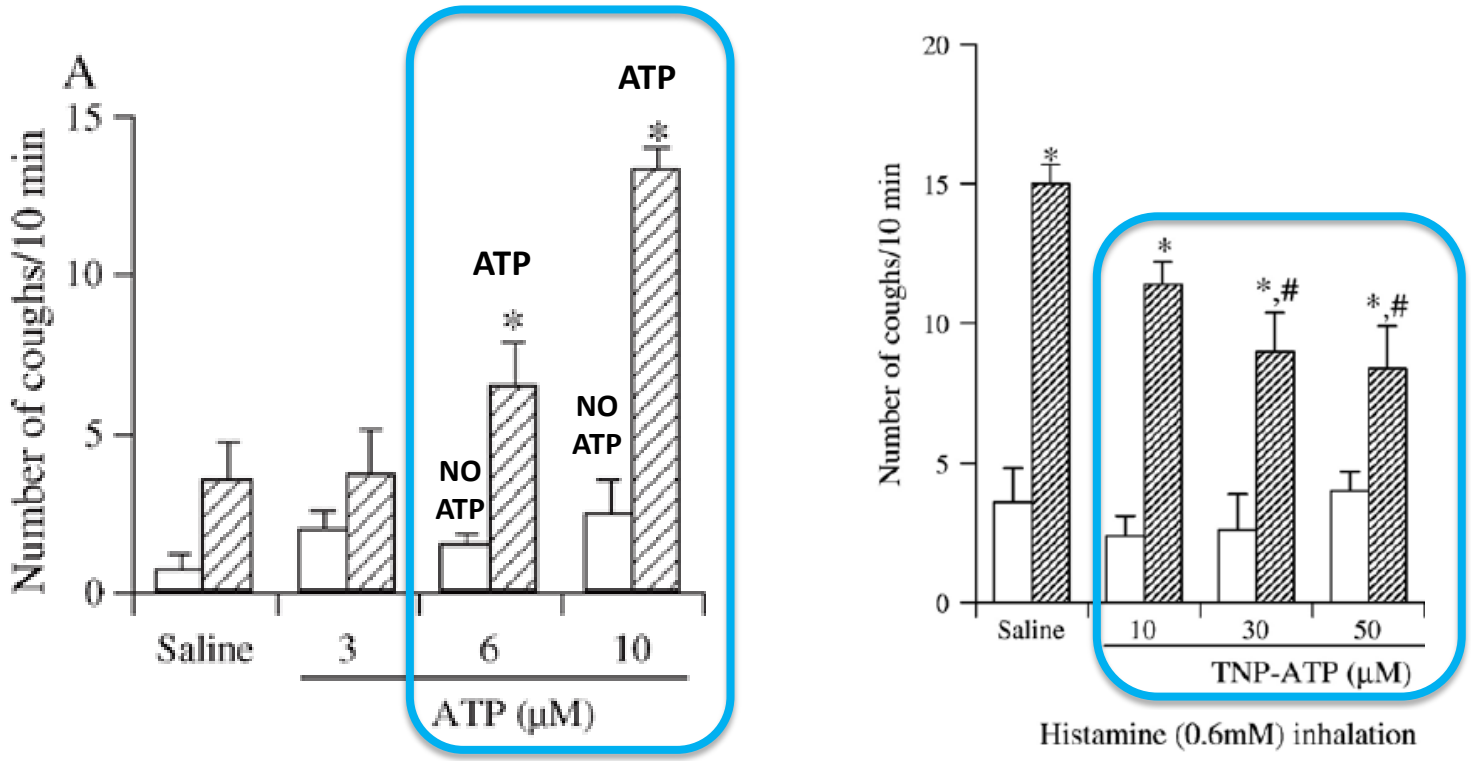


…that transduces ATP-evoked afferents activation/sensitization

Therapeutic Rationale:

Blocking P2X3 activity may diminish sensory neurons discharge and sensitization

ATP as a cough exacerbating mediator



Aerosolised ATP exacerbated Citric acid-induced cough in Guinea Pigs
ATP mediates Histamine-induced cough exacerbation in Guinea Pigs

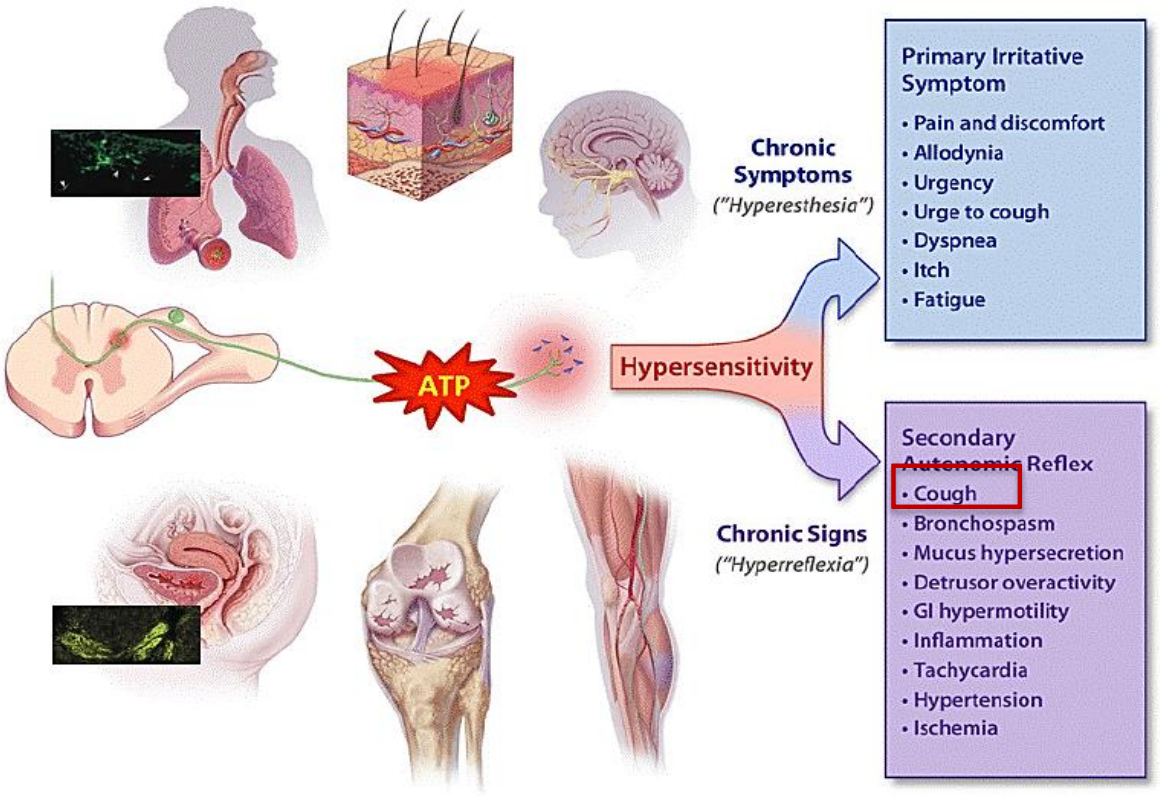
European Journal of Pharmacology 528 (2005) 158–161
European Journal of Pharmacology 547 (2006) 160–164

TNP-ATP: P2X receptor antagonist

Scientific rationale for various indications

P2X3 Receptors

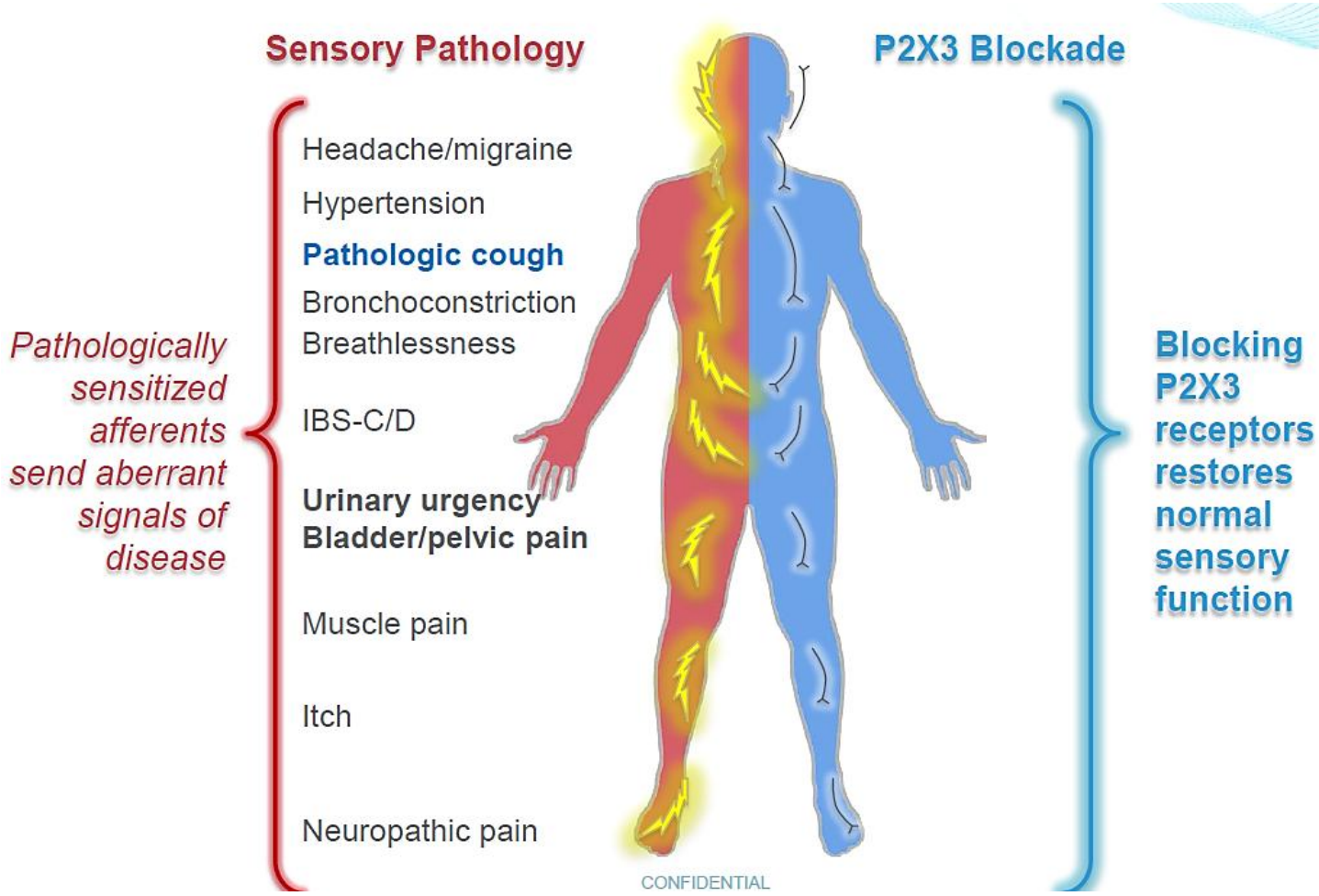
- ATP sensitizes afferents via P2X3 channels
- P2X3 up-regulated in pathology
- Highest P2X3 expression in C-fiber afferents
- Dense innervation to skin, muscles, viscera
- Absent in higher brain centers
- ATP evokes symptoms in preclinical and clinical studies
- P2X3 and P2X2 knock-out/downs result in attenuated afferent responses in the setting of sensitization



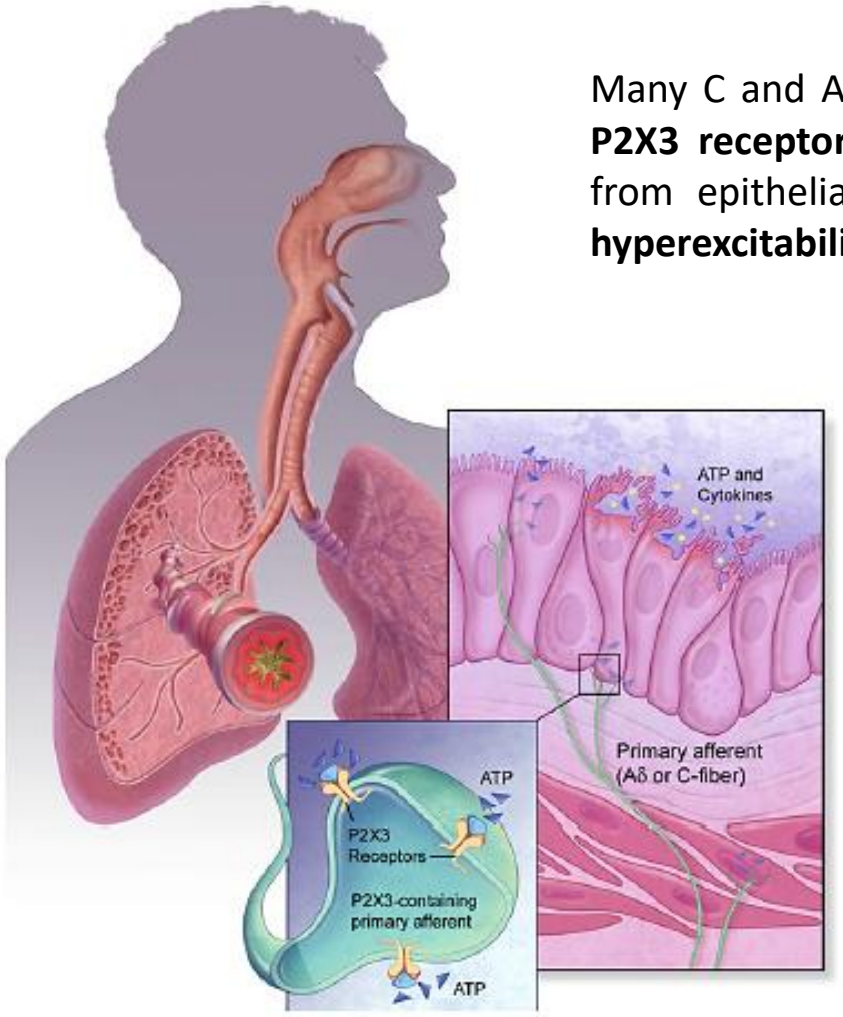
Targeting P2X3 in order to treat significant unmet medical needs

Scientific rationale for various indications

Blocking sensitization of afferents: a fundamental mechanism in many sensory disorders



Scientific rationale for chronic cough



Many C and Aδ fiber afferents in the upper and lower airways express **P2X3 receptors** that can be sensitized and activated by ATP liberated from epithelial and smooth muscle cells may contribute to **airway-hyperexcitability** and **chronic cough**

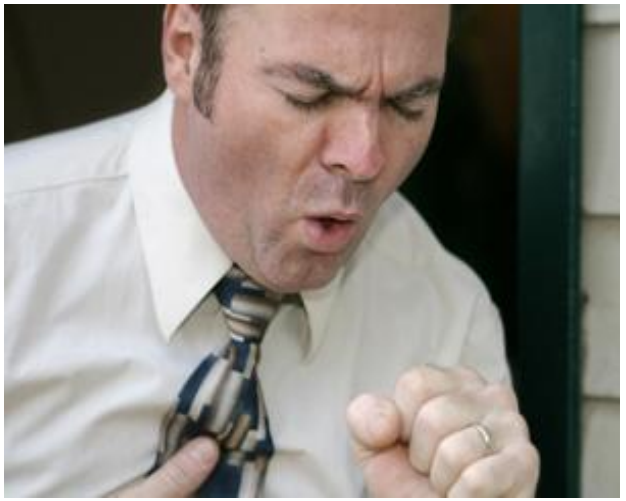
P2X3 receptors are ATP-gated ion channels selectively localized on populations of primary sensory nerves

<u>Antagonism of these receptors is predicted to normalize afferent sensitivity</u>

Chronic cough background: an unmet clinical need

- **Chronic cough is one of the major reasons for physician visits in the US**

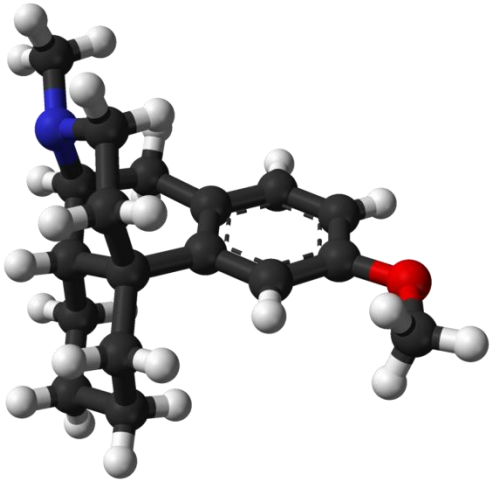
- Cough disrupts patients' lives with physical, social, and psychological effects, yet effective, safe, and well tolerated antitussive treatments are an **important unmet clinical need**



Chronic Cough: a cough lasting over 8 weeks that is associated with significant morbidity, particularly in subjects with idiopathic cough or who are resistant to treatment of common triggers

Chronic cough is associated with many pulmonary disorders (e.g., asthma, COPD, lung cancer, and interstitial lung disease), some drugs (e.g., ACE inhibitors), and extrapulmonary disorders (e.g., nasal disease and gastro-oesophageal reflux)

State of the art in therapy: current treatment options



- **Very few options** exist when coughing does not respond to treatment for underlying disorders
- There is **little high-quality evidence an few placebo-controlled studies** to suggest that available licensed antitussive drugs are effective for cough in any disorder
- The **last new cough therapy** to receive approval was *dextromethorphan* over **50 years ago**
  - Subsequent investigations have highlighted its poor efficacy (only 12% reduction in cough frequency)
  - Safety concerns have emerged restricting the use of dextromethorphan and other antitussive drugs in children

P2X3 receptor antagonist (AF-219) in refractory chronic cough: a randomised, double-blind, placebo-controlled phase 2 study

Rayid Abdulqawi, Rachel Dockry, Kimberley Holt, Gary Layton, Bruce G McCarthy, Anthony P Ford, Jaclyn A Smith

Summary

Background Preclinical studies suggest that P2X3 receptors are expressed by airway vagal afferent nerves and contribute to the hypersensitisation of sensory neurons. P2X3 receptors could mediate sensitisation of the cough reflex, leading to chronic cough. We aimed to investigate the efficacy of a first-in-class oral P2X3 antagonist, AF-219, to reduce cough frequency in patients with refractory chronic cough.

Methods We did a double-blind, placebo-controlled, two-period, crossover study at one UK centre. With a computer-generated sequence, we randomly assigned patients with refractory chronic cough to AF-219, 600 mg twice a day, or to placebo (1:1), and then, after a 2 week washout, assigned patients to receive the other treatment. Patients, health-care providers, and investigators were masked to sequence assignment. We assessed daytime cough frequency (primary endpoint) at baseline and after 2 weeks of treatment using 24 h ambulatory cough recordings. The primary analysis used a mixed effects model with the intention-to-treat population. This study was registered at ClinicalTrials.gov, number NCT01432730.

Findings Of 34 individuals assessed between Sept 22, 2011, and Nov 29, 2012, we randomly assigned 24 patients (mean age 54·5 years; SD 11·1). In the observed case analysis, cough frequency was reduced by 75% when patients were allocated to AF-219 compared when allocated to placebo (p=0·0003). Daytime cough frequency fell from a mean 37 coughs per h (SD 32) to 11 (8) coughs per h after AF-219 treatment versus 65 (163) coughs per h to 44 (51) coughs per h after placebo. Six patients withdrew before the end of the study because of taste disturbances, which were reported by all patients taking AF-219.

Interpretation P2X3 receptors seem to have a key role in mediation of cough neuronal hypersensitivity. Antagonists of P2X3 receptors such as AF-219 are a promising new group of antitussives.