



Farmakoterapi

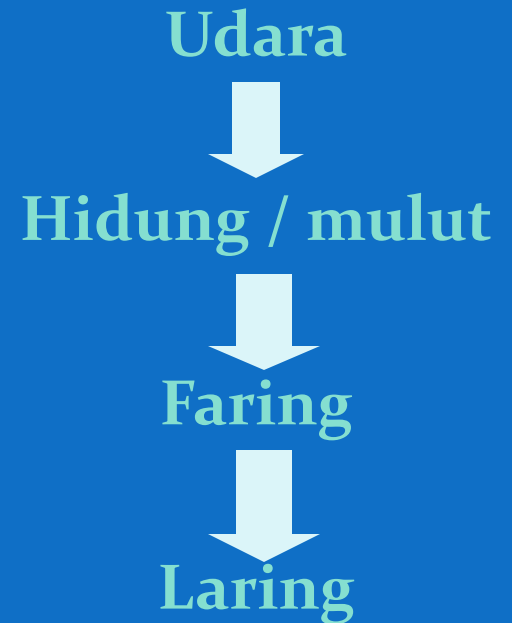
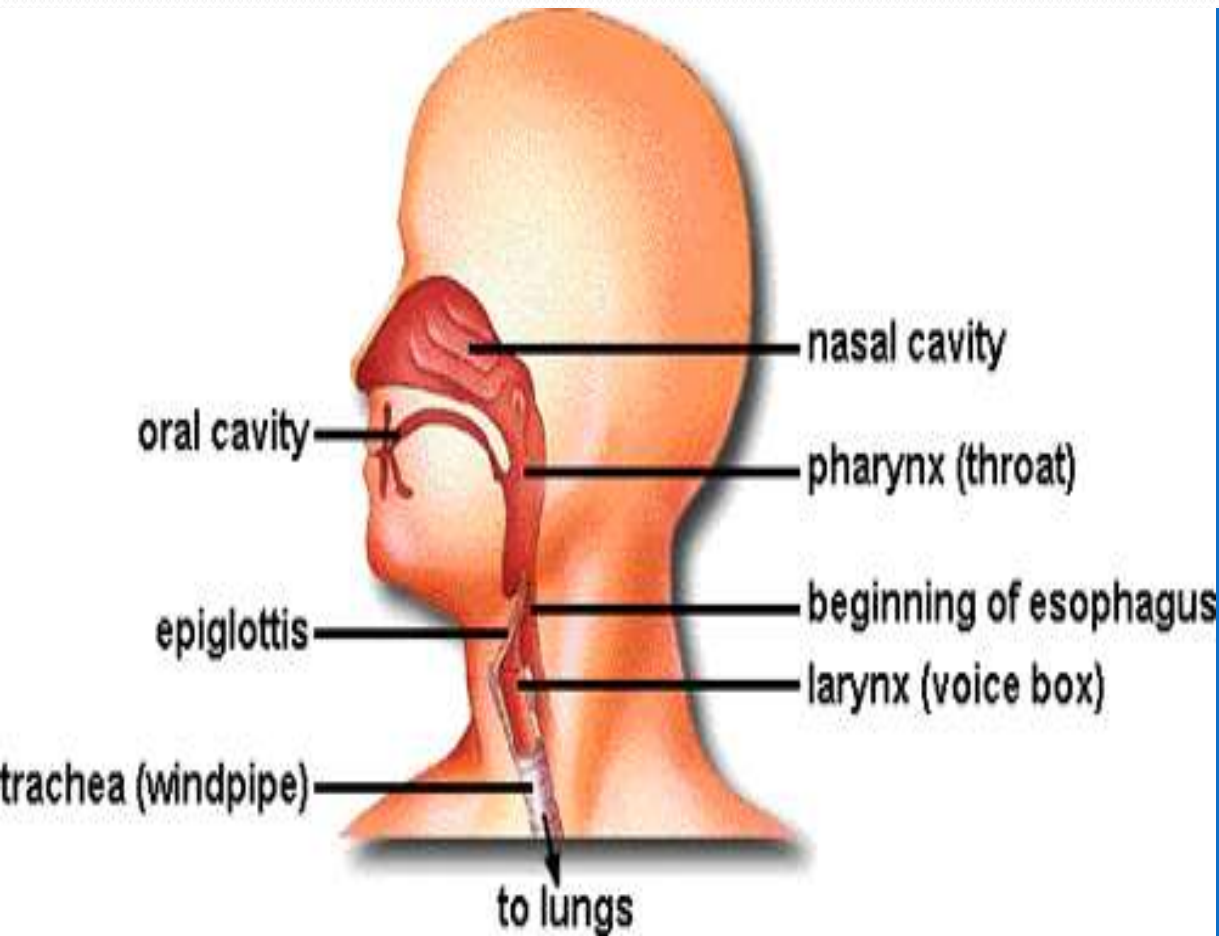
Obat Batuk dan Pilek

Fathiyah Safithri

Laboratorium Farmakologi FK-UMM

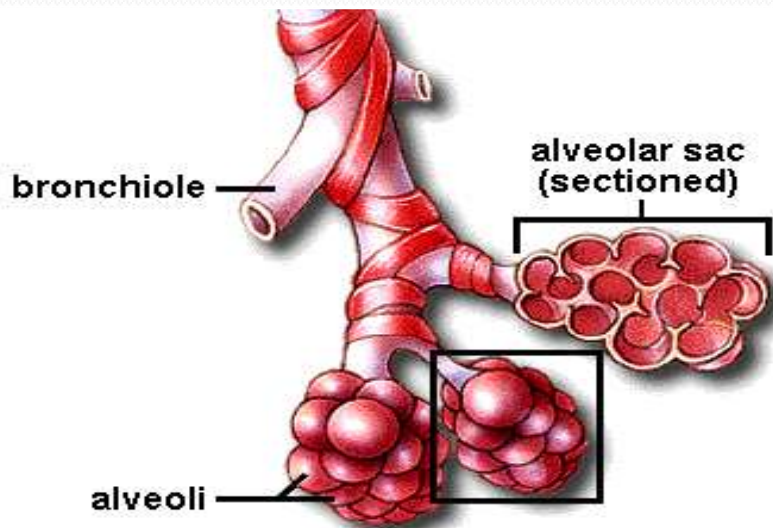
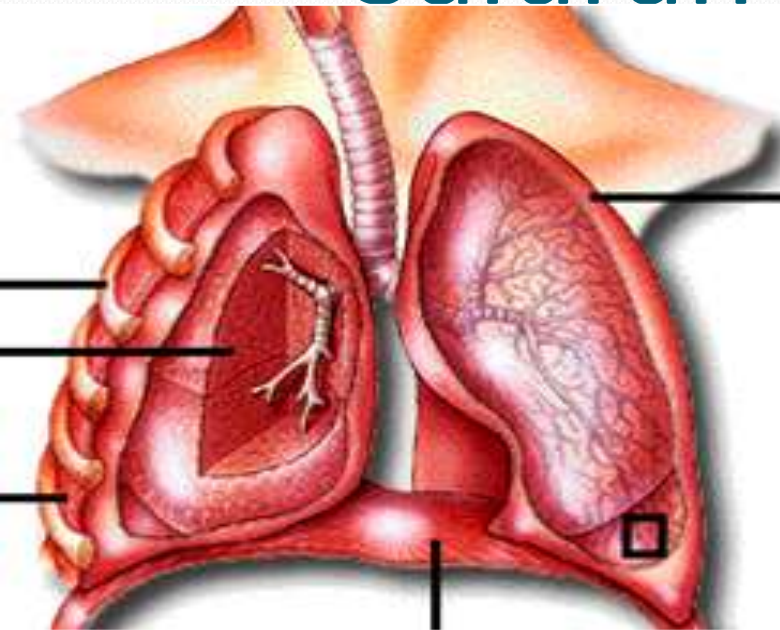
2019

Saluran Nafas Atas



Penyakit : flu, batuk

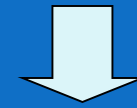
Saluran Nafas Bawah



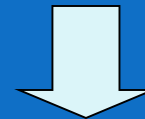
Laring



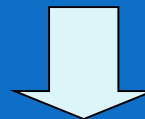
Trakhea



Bronkus



Bronkiolus



Alveoli

Penyakit : PPOM/ COPD
(asma bronkhiale, bronkhitis kronis, emfisema)

OBAT FLU & BATUK

Dekongestan

Antitussif

Mukokinetik (Ekspektoran, Mukolitik)

Antihistamin

GEJALA FLU

- Nasal congestion & obstruction
- Rhinorrhea
- Sneezing
- Cough
- Sore throat or scratchy throat
- “Post-nasal drip”
90% of OTC flu & batuk merupakan kombinasi dari : antitussif, ekspektoran, dekongestan, antihistamin, dengan / tanpa antipiretik.
- Fever
- Purulent postnasal discharge
- Increased malaise
- Dyspnea or localized pain
- Productive cough with expectoration of purulent material

Local use of α -**sympathomimetics** (nasal drops or spray)

Acetylsalicylic acid
Acetaminophen

Soreness
Headache
Fever

Decongestion of mucous membranes
H₁-Antihistamines
Caution: sedation

Sniffles, runny nose

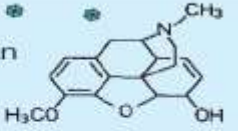
Common cold
Flu

Viral infection
Causal therapy impossible

Surface anesthetics
Caution: risk of sensitization

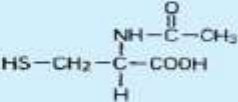
Sore throat

Antitussive:
Dextrometorphan
Codeine



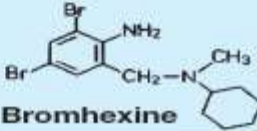
Cough

Mucolytics
Acetylcysteine



Airway congestion

Expectorants:
Stimulation of bronchial secretion
Give warm fluids
Potassium iodide solution
Bromhexine



Accumulation in airways of mucus, inadequate expulsion by cough

DEKONGESTAN

- Mek Kerja : agonis reseptor- α
vasokonstriksi → mukosa & sekresi ↓ → hidung longgar
- Sistemik (p.o) :
 - ☺ Pseudoephedrine (Sudafed, Actifed)
 - ☺ Phenylpropanolamine (PPA)
 - ☺ Phenylephrine (Neo-Synephrine)
- Lokal (nasal) :
 - ☺ ephedrine 0.25% Pretz-D (Parnell)
 - ☺ naphazoline HCl 0.05% Privine (Ciba)
 - ☺ oxymetazoline 0.025, 0.05% Afrin (Schering)
 - ☺ phenylephrine Neo-Synephrine (Win.)
 - ☺ xylometazoline HCl 0.025, 0.1% Otrivin (Ciba)

Dekongestan Nasal

- Cara pemberian :
 - **Spray** – utk dewasa , mencapai permukaan mukosa lebih luas.
 - **Drops** – utk anak-anak < 6 th.
- Efek Samping : **Rebound Congestion (rhinitis medicamentosa)**
 - Pada pemakaian jangka panjang → rebound vasodilation
 - Cara meminimalisir / menghindari ES tsb :
 - ✓ hanya digunakan utk 3-4 hari.
 - ✓ jangan memakai dosis besar atau memakai dg frekuensi lebih sering
 - ✓ Tidak dipakai untuk rhinitis alergi → overuse

Dekongestan Oral

- Kemampuan vasokonstriksi < dekongestan nasal (efikasi <)
- Phenylephrine - poor oral bioavailability (rapidly degraded in gut).
- ES rebound congestion (-)
- **ES sistemik >>> ~ Distribusi Reseptor**
- potential drug interactions: MAOIs, TCAs, dll

BATUK

Adalah reflek yg bisa disebabkan oleh stimuli mekanik, kimia di sal nfs atas atau stimuli sentral.

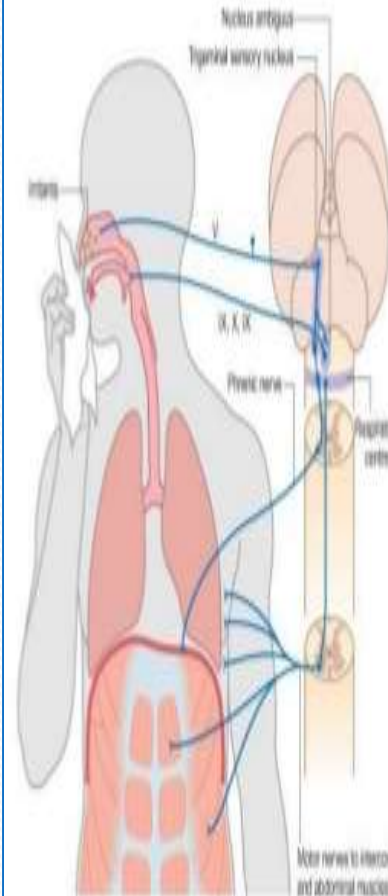
☐ Reflek Batuk :

Afferent limb – serabut sensoris terletak di ep. silia sal nafas (t.u laring, trakhea).

Pusat batuk – terletak di batang otak atas & pons.

Efferent limb – impuls dari pusat batuk dikirim lewat N. vagus, phrenic & spinal motor menuju diaphragm, dinding abdomen & otot

Mechanism of cough



Stimulation of mechano-or chemoreceptors
(throat, respiratory passages or stretch
receptors in lungs)



Afferent impulses to cough center (medulla)



Efferent impulses via parasympathetic & motor
nerves to diaphragm, intercostal muscles & lung



Increased contraction of diaphragmatic, abdominal
& intercostal (ribs) muscles ⇒ **noisy expiration**
(cough)

Drugs for cough

- Cough can be treated as a symptom (nonspecific therapy) or with specific remedies (antibiotics, etc.)
- Nonspecific therapy
 - Pharyngeal demulcents: Lozenges, cough drops, linctuses containing syrup, glycerine, liquorice.
 - Expectorants:
 - (a) Directly acting: Sodium and potassium citrate or acetate, potassium iodide, guaiacol, guaiphenesin (glyceryl guaiacolate), balsum of tolu, vasaka and terpin hydrate.
 - (b) Mucolytics: Bromhexine, ambroxol, acetyl cysteine, carbocisteine.
 - (a) Antitussives (Cough center suppressants):
 - (a) Opioids: Codeine, pholcodeine, ethylmorphine, morphine.
 - (b) Nonopioids: Noscarpine, dextromethophan, oxeladin, chlorphedianol.
 - (c) Antihistamines: Chlorpheniramine, diphenhydramine, promethazine.

ANTITUSSIVE

- Obat penekan reflek batuk : **Antitussif**
- Batuk merup **mekanisme protektif tubuh** thd “benda asing” di sal nfs → pemakaian antitussive hrs sesuai indikasi
- Tuj : **“cough suppressants”**
- Indikasi : **batuk kering / non produktif**

ANTITUSSIVE

- Target kerja :
 - ☺ **di perifer** : me ↓ sensitivitas reseptor batuk thd substansi kimia spt bhn iritan, autokoid
 - ✓ uap menthol, minyak Eucalyptus (permen batuk)
 - ✓ anestesi lokal topikal (benzokain, lidokain : utk persiapan bronkoskopi)
 - ✓ benzonatate
 - ☺ **di pusat batuk** : me ↓ sensitivitas 'cough center'
 - ✓ Opioid : codein, morfin, hydrocodone (turunan codein)
 - ✓ Non Opioid : Dextromethorpan (*d*-isomer dari metil eter opiate), Chlopedianol, Diphenhydramin

Penggunaan Antitusif

- **Codein (Opiate agent)** : ES=mengantuk, konstipasi, addiksi. Peresepan tdk lebih dr 1 mgg
- **Dextromethorphan (non opiate)**
 - desktrometorfan = weak opiat, potensi antitusif ~ codein
 - **DMP (*D-3-methoxy-N-methyl-morphinan*)** = suatu dekstro isomer dari **levomethorphan**, suatu derivat morfin semisintetik.
 - Strukturnya mirip narkotik, DMP berinteraksi dg R/ sigma tp tidak berinteraksi dg R/ μ (R/ pd morfin / heroin), \rightarrow efek addiksi <<
 - Pd dosis >>>, DMP bekerja sbg antagonis R/ NMDA ~ mirip kerja dr **PCP / ketamin** \rightarrow **euforia, halusinasi penglihatan & pendengaran** \rightarrow **drug abuse DMP.**
 - teratogenic potential

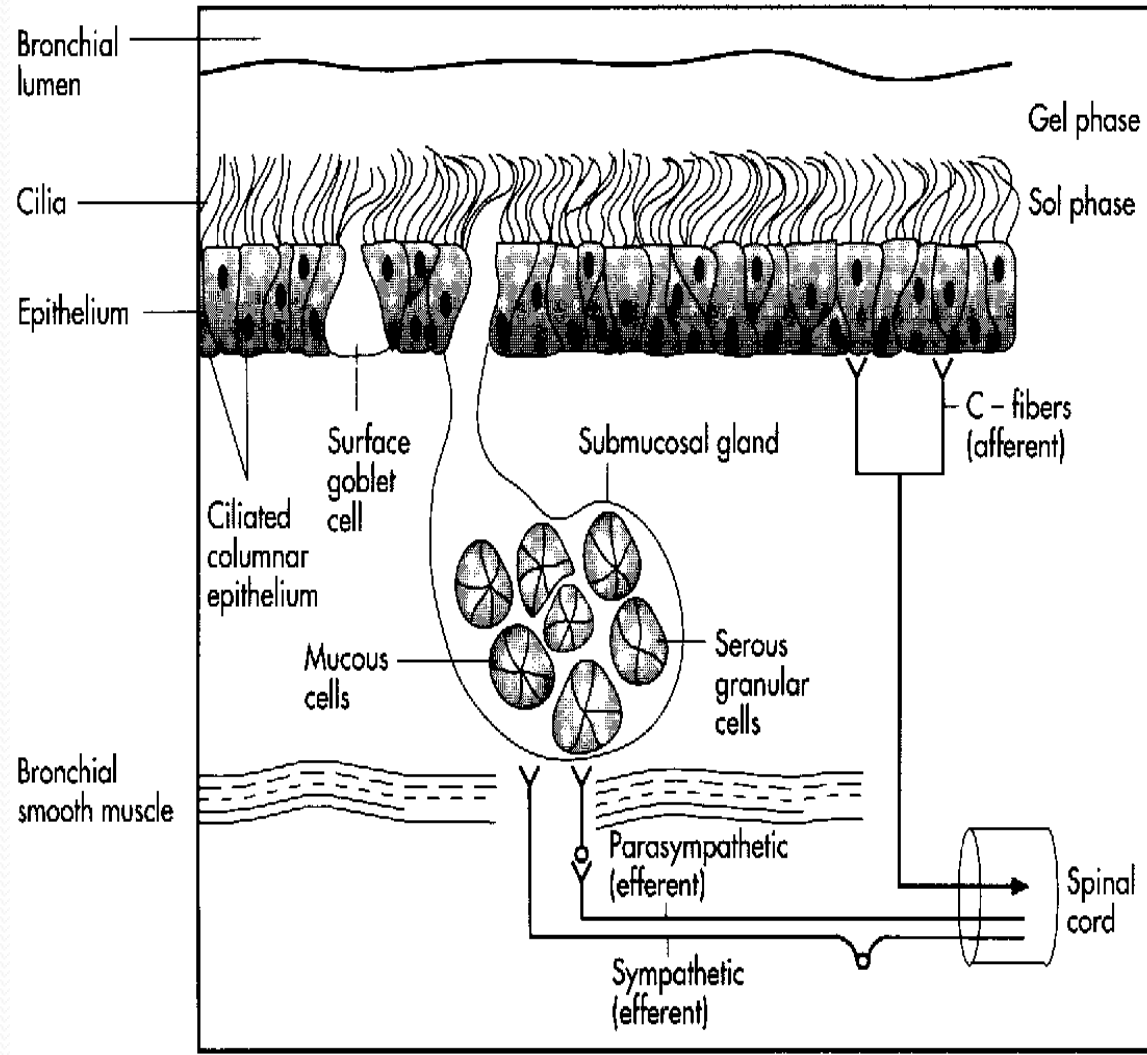
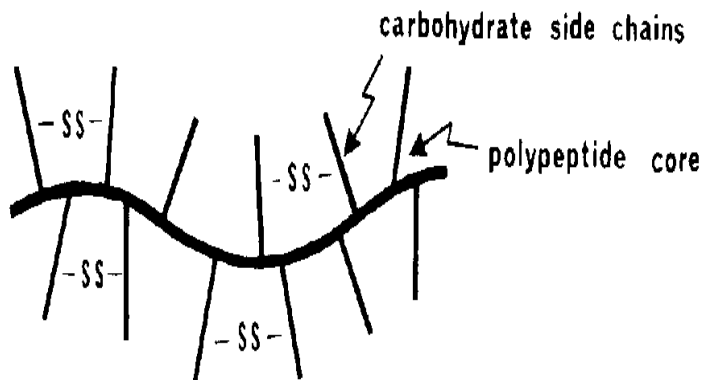
Penggunaan Antitusif

- Overdosis DMP → hiper-eksitabilitas, kelelahan, berkeringat, bicara kacau, hipertensi, & mata melotot (*nystagmus*).
- **Interaksi** dg MAOI dpt menyebabkan adrenergic crisis, dizziness, spasm, tremor, hyperten., intracerebral bleed., psychosis, coma.
- Interaksi dg alkohol, dapat menyebabkan kematian.
- **Diphenhydramine (non opiate) :**
 - anticholinergic effects (hati2 pd lansia).
 - 25-50 mg = 15 mg codeine

MUKOKINETIK AGENT

Komposisi Mukus :

- 95% is water
- 3% is protein
- $\leq .03\%$ DNA



Airway Anatomy

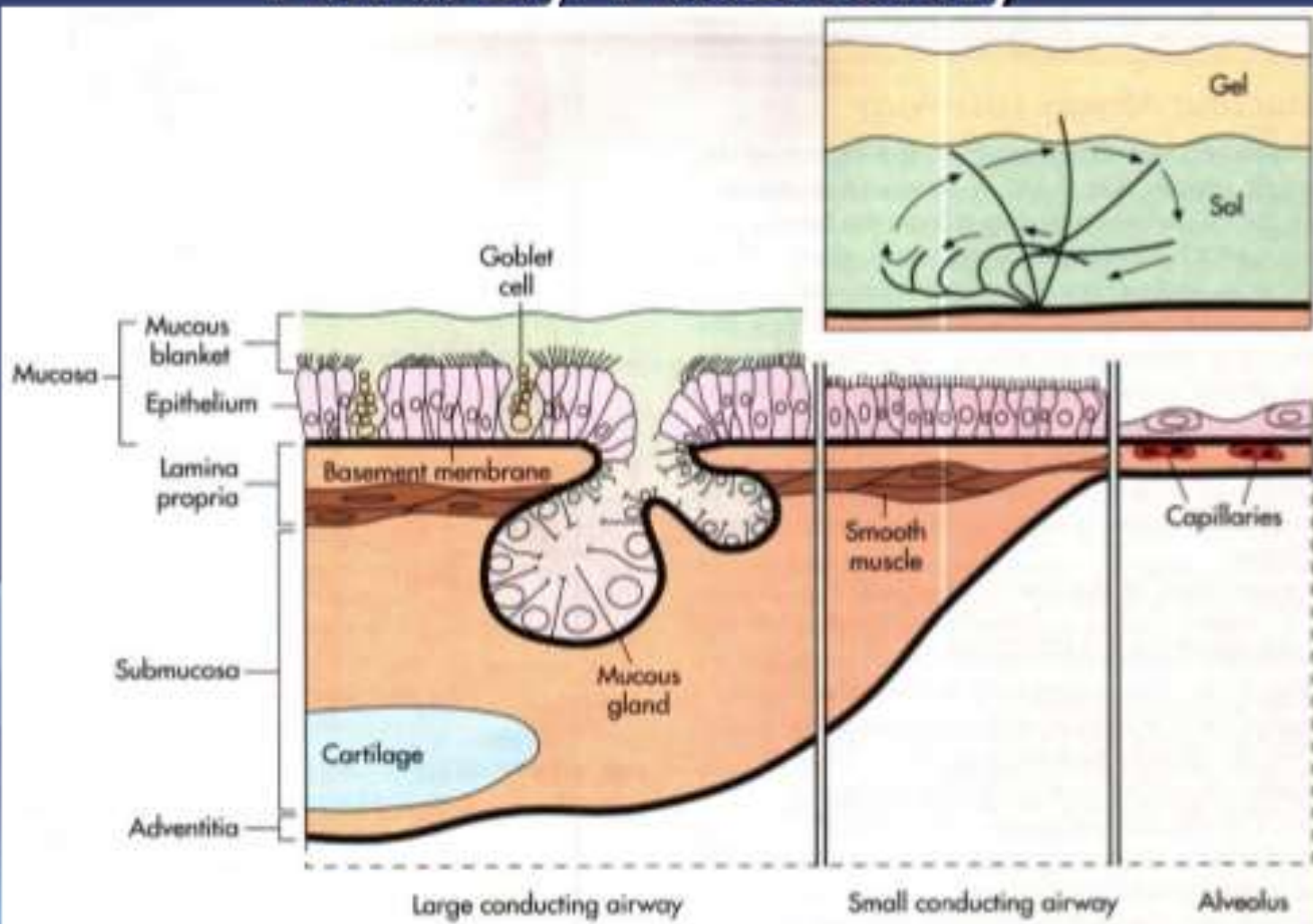
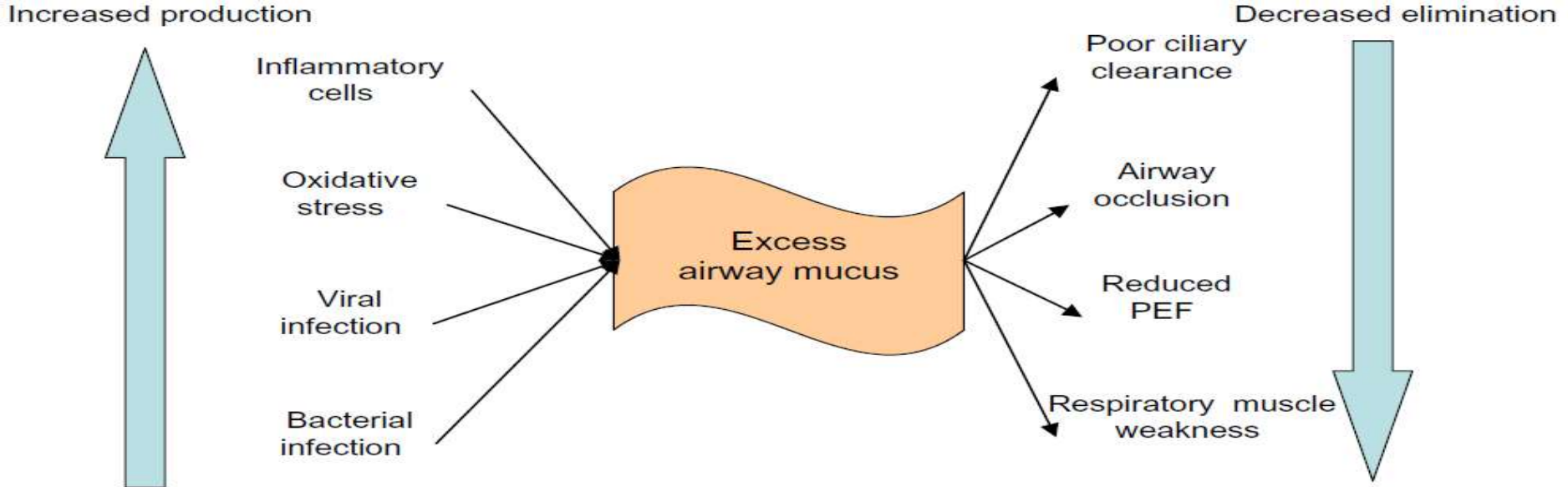


FIG. 1-14 A, The respiratory mucosal epithelium. Most airways contain ciliated, pseudostratified columnar epithelium. **B**, Detail of ciliary action. Cilia reach up into the gel mucous layer during the forward propulsive stroke, withdrawing and retracting in the sol layer.



Penyakit yg Disertai Hipersekresi Mukus

- **Chronic Bronchitis**
 - hyperplasia of submucosal glands & goblet cells
- **Asthma**
 - mucus plugging
- **Cystic Fibrosis**
 - mucoviscidosis

Faktor yg Mempengaruhi Transpor Mukus

- Age-related factors (>56 years old)
- Presence of COPD
- General Anesthetics
- Use of Atropine
- Presence of tracheostomy
- Use of endotracheal suctioning techniques
- Cigarette Smoke
- Atmospheric pollutants
- Hyperoxia and hypoxia

MUKOKINETIK AGENT

- Kelompok obat yang digunakan u/ membersihkan mukus dari jalan nafas (trakhea, brokus, paru)
- Bds mekanisme kerjanya ada 4 gol :
 - **Expectorants** : mengencerkan mukus shg mudah dikeluarkan
 - **mucolytic agents** : merusak struk kimia mukus shg viskositas turun & mdh dikeluarkan
 - **wetting agents / hypoviscosity agents**
 - **abhesives / surfactants** : menurunkan adhesivitas sputum & meningkatkan efisiensi transfer energi dari silia ke lapisan mukus

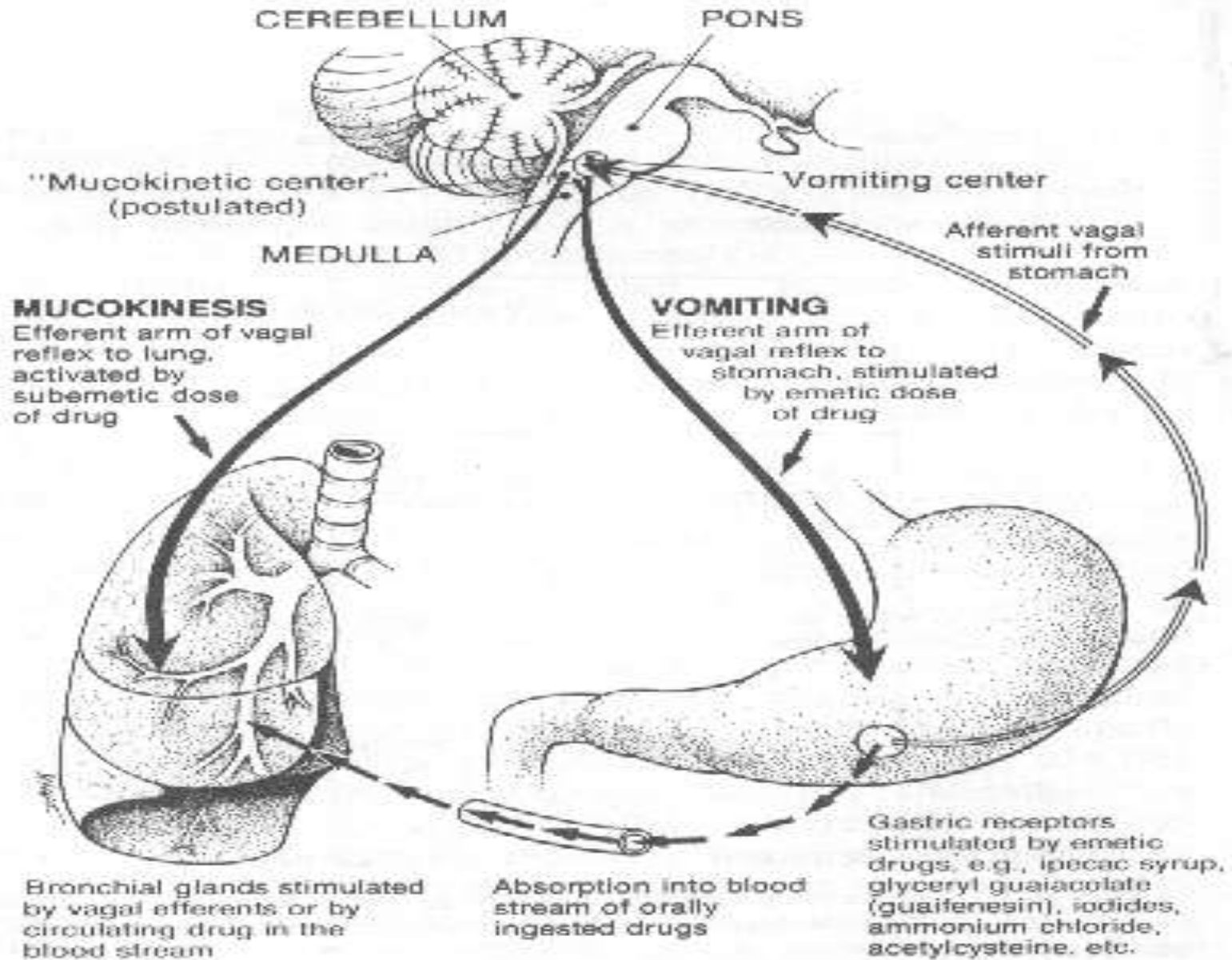
Mucoactive Agents

Mucoactive Agent	Potential Mechanisms of Action
Expectorants	
Hypertonic (7%) saline	Increases secretion volume and perhaps hydration
Dry powder mannitol	Increases mucus secretion
Guaifenesin	Not shown to be effective
Classical mucolytics	
N-acetylcysteine	Severs disulfide bonds that link mucin oligomers. Anti-oxidant and anti-inflammatory
Nacystelyn	Increases chloride secretion and severs disulfide bonds
Peptide mucolytics	
Dornase alfa	Hydrolyzes DNA polymer and reduces DNA length
Thymosin β_4	Depolymerizes filamentous actin
Nondestructive Mucolytics	
Heparin	May break both hydrogen and ionic bonds
Cough clearance promoters	
Bronchodilators	Can improve cough clearance by increasing expiratory flow
Surfactants	Decreases sputum adhesiveness

EKSPEKTORAN

- Tujuan : mengencerkan sekret → perbaiki produktivitas batuk → merangsang pengeluaran sekret / mukus dr sal nfs
- Indikasi : batuk produktif
- Efektifitas terbatas (NONE ARE FDA APPROVED)
- Ekspektoran terbaik : Air
- Contoh
 - ☺ Guaifenesin (Gliseril guaiakolat) : reduces mucus adhesion & surface tension. ES : diarrhea, drowsiness, nausea /vomiting, stomach pain
 - ☺ Menthol & Camphor
 - ☺ Amonium klorida (NH_4Cl) : may induce metabolic acidosis
 - ☺ Ipekak : local irritant stimulates secretions
 - ☺ Potassium iodide : long term or over use can induce goiter

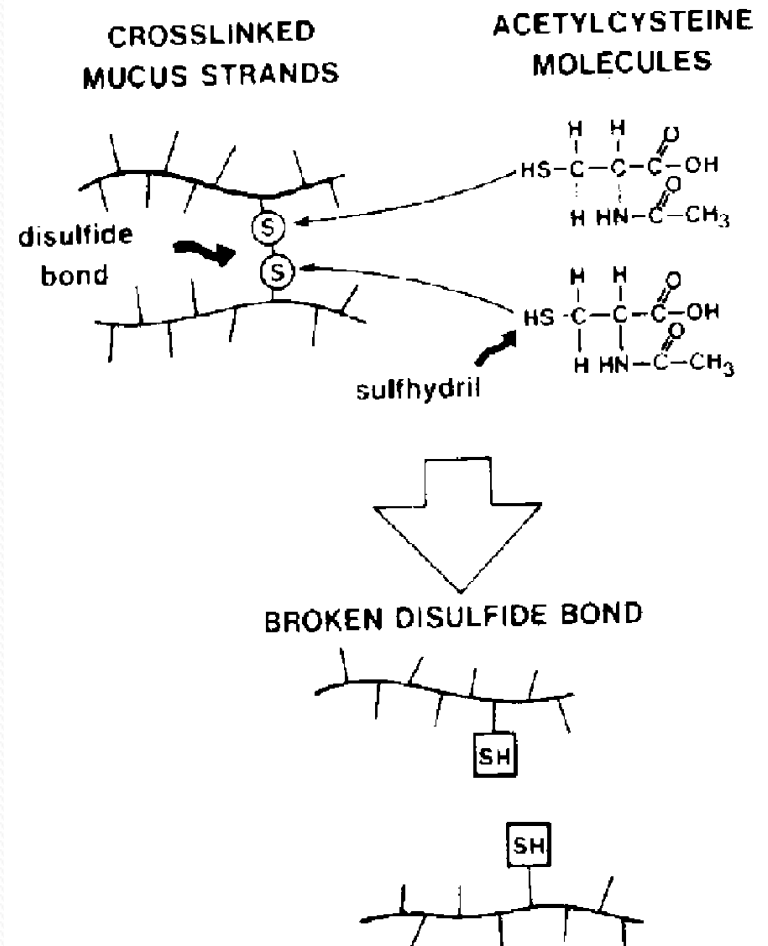
Vagal Stimulation and Mucokinesis



MUKOLITIK

- **Acetylcysteine (Mucomist)**

- ⊕ Mek. Kerja : menurunkan viskositas sekret dg cara merusak ikatan disulfida.
- ⊕ p.o, aerosol
- ⊕ ES : Bronchospasm (utk asma, shg perlu dipakai bersama bronkodilator), Stomatitis, Nausea, Rhinorrhea
- ⊕ Indikasi lain : antioksidan pd COPD, antidotum intoksikasi parasetamol



MUKOLITIK

Bromhexin (Bisolvon)

- Mek. Kerja : me↑ sekresi serous mukus pd jln nfs (sekretolitik), sekret. Lbh tipis & mdh dikeluarkan oleh cilia, merusak struk mukopolisakarida.
- p.o (tablet, sirup)
- ES = merusak barrier mukosa gaster (jarang)

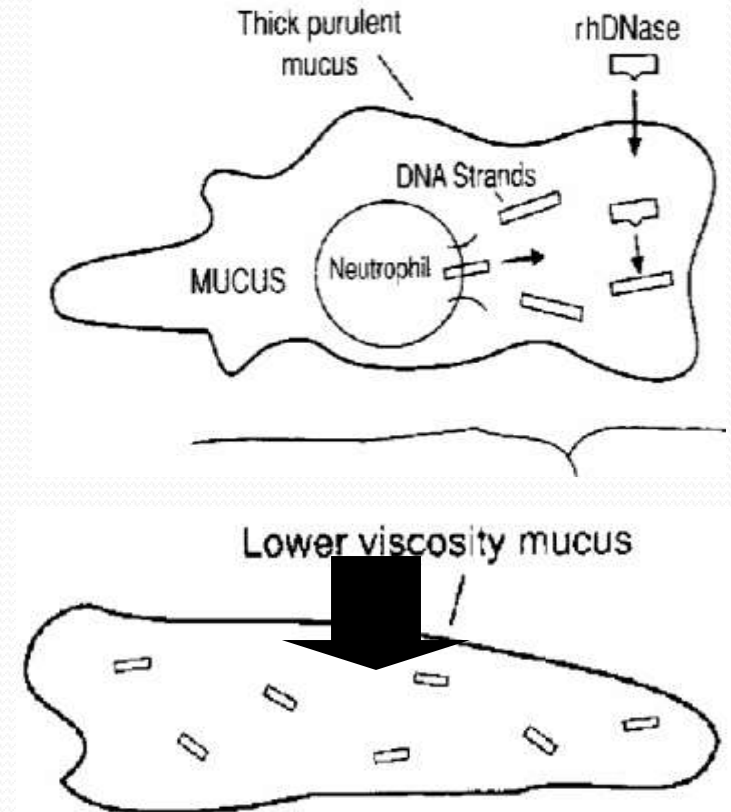
Ambroxol (Mucosolvan)

- Merup metabolit Bromhexin
- Mek kerja hampir sama
- Mempunyai efek antiinflamasi, antioksidan, lokal anestesi (?)

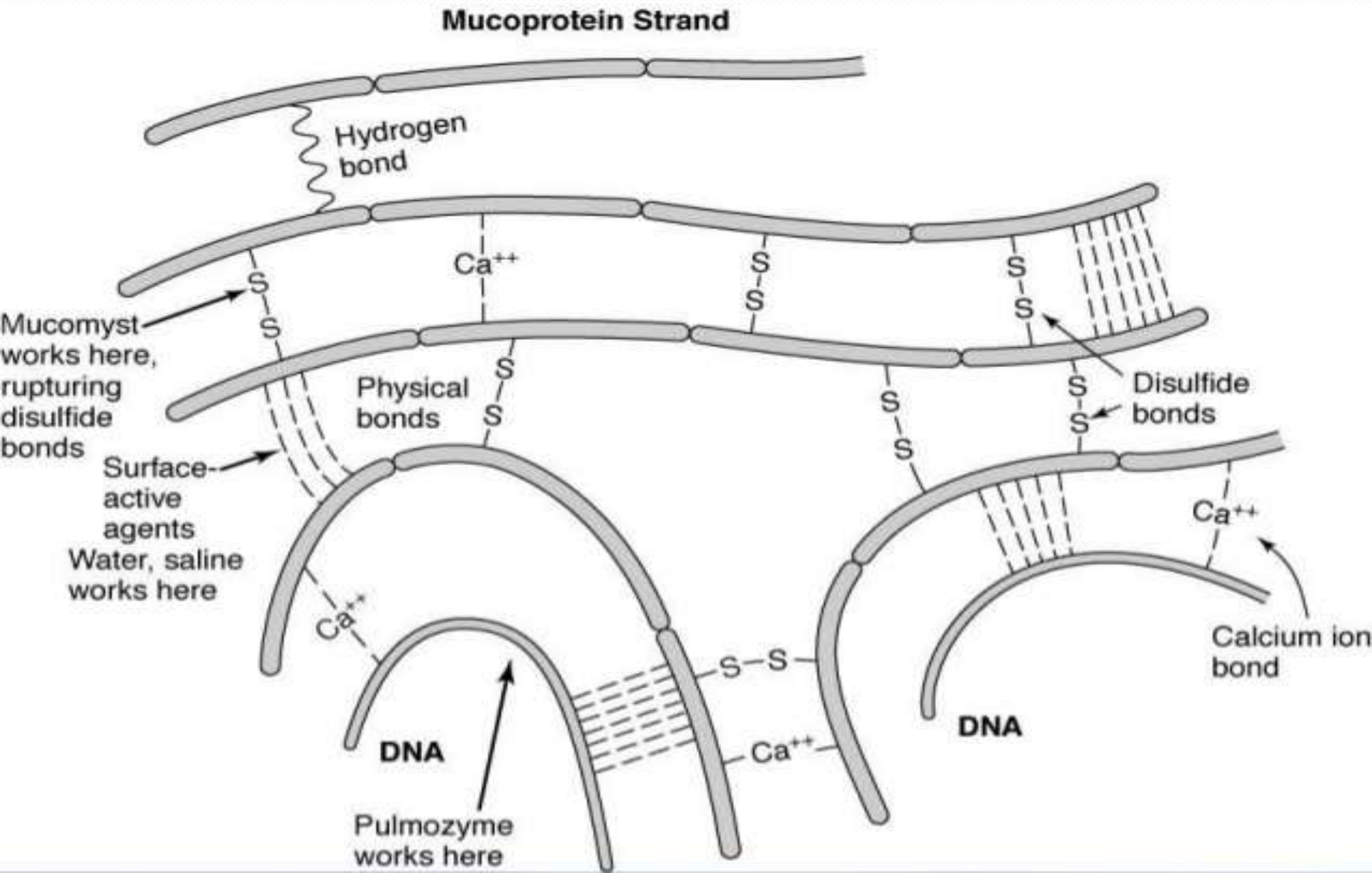
MUKOLITIK

DNAase (Pulmozyme)

- Mekanisme kerja : merusak DNA mukus dg reaksi enzimatik
- Digunakan pd kasus kistik fibrosis
- Lebih efektif d.p asetilsistein
- ES : Voice changes, laryngitis
- rash, conjunctivitis, chest pain



Resume : target of mucokinetics agents

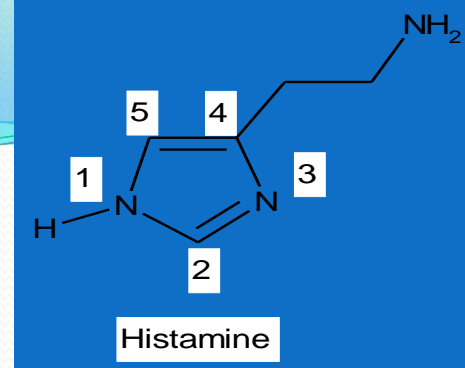


ANTIHIISTAMIN

- Mek kerja : blok reseptor histamin-1 (H1) t.u di sal nfs atas
- Tujuan : me↓ sekresi sekret
sedative effect → p istirahat
- Mis :
 - Chlorpheniramin maleat (chlortrimeton=ctm)
 - Diphenhydramin (delladryl, benadryl)
 - Prometazin (Phenergan)
- ES antihistamin :
 - Mucous membrane kering
 - Cardiac stimulation
 - Pandangan kabur
 - Retensi urine



HISTAMIN



- ☺ dibentuk dr asam amino histidin & disimpan dlm konsentrasi tinggi di sel mast jaringan dan basofil darah.
- ☺ Lokasi \Rightarrow paru, kulit, GIT
- ☺ Produksi & sekresi histamin oleh mast sel me \uparrow pd :
 - ♥ Reaksi alergi yg diperantarai Ig-E (immediate), mis : seasonal rhinitis (hay fever), urticaria, and angioneurotic edema.
 - ♥ **Pemakaian Obat** spt tubocurarine, morfine dll
 - ♥ Tissue injury

Efek Aktivasi Reseptor Histamin

H₁ receptor ⇒ release IP3 & DAG ↑ ⇒ Ca²⁺ intake

- ☺ Kontraksi otot polos (bronkhokonstriksi, peristaltik ↑)
 - ☺ Arteri vasodilatasi (H1 & H2), akibat dr pe ↑ release endothelium-derived relaxing factor (EDRF) & PGI₂., Permeabilitas vaskuler ↑ → edema
 - ☺ Kontraksi jantung ↑, aliran koroner ↑
 - ☺ Sekresi kelenj eksokrin hidung & bronkus ↑
 - ☺ Headache, kewaspadaan ↓
 - ☺ Release katekolamin oleh adrenal ↑
- ➔ manifest pd : allergic reactions .

ANTI-HISTAMIN - H₁

- **Sedative (1st Generation)**

difenhydramin

chlorpheniramine

embramin

prometazin

cyproheptadin

bisulepin

dimetinden

azatadin

klemastin



- **Non sedative (2nd Generation)**

terfenadine

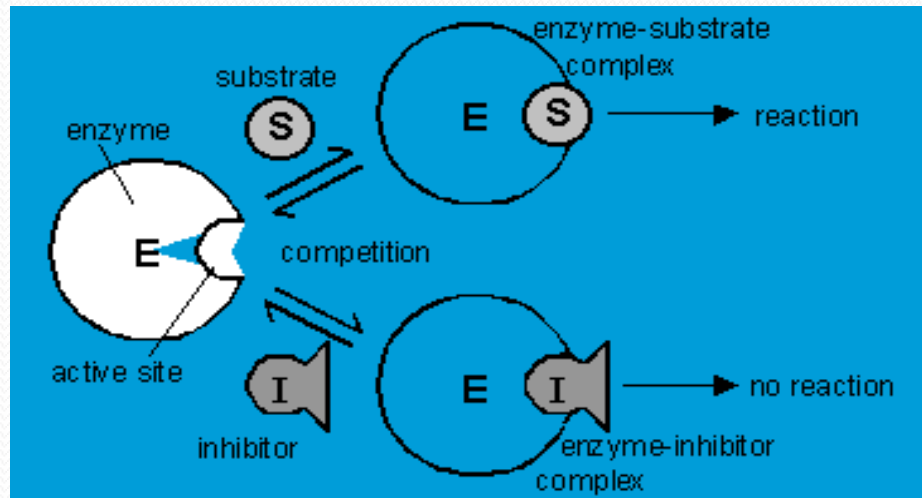
astemizol

cetirizin

loratadin

Mekanisme Kerja AH1

☺ Mek kerja AH1 : kompetitif inhibitor pd reseptor H_1



- ☺ Struktur sgt mirip dg muscarinic blockers & alpha adrenoceptor blockers (anti H_1 sedatif) → efek antikolinergik & antagonis adrenergik
- ☺ Bbrp bisa memblok resept serotonin (cetirizine).
- ☺ efek pd resept H_2 (-)

Anti-H1 sedatif

- Prototipe : **Diphenhydramine** & chlorpheniramine
- Aktif pd pemberian per oral, absorpsi baik.
- metabolized extensively in the **liver**
- Durasi 4-6 jam
- ES :
 - ✓ efek ↓ pd pemakaian kronis (induksi enz mikrosomal)
 - ✓ Antikolinergik effect (mulut kering, dll)
 - ✓ Drowsiness (penetrasi SSP ok lipofilik)
 - ✓ Mual, muntah, nafsu mkn ↓

Anti-H₁ Non sedatif

- Prototipe : terfenadine
- Durasi > 12 jam
- Low lipid soluble → penetrasi SSP (-)
- Terikat protein plasma ⇔ bioav <
- Antikolinergik effect <<
- Metab di hepar

EFEK AH1

1. **Antialergi** (Blok pd H_1 receptors perifer) → u/ reaksi alergi ringan (insect bite, urtica, dll)
2. **Sedasi** (blok reseptor H_1 & M di SSP)
3. **Anti emetik** → u/ motion sickness (Dimenhidrinat)
4. **Antikolinergik** (retensi urine, pandangan kabur, konstipasi, mulut kering)
5. **Blok α -adrenergik** (hipotensi ortostatik)

Toksistas:

- Sedasi (t.u AH1 sedatif)
- Antimuscarinic effects (dry mouth, blurred vision etc.)
- α -blocking actions (orthostatic hypotension).

Interaksi

- ⊗ Obat dg efek **sedatif** (benzodiazepines, alcohol).
- ⊗ Obat yg menghambat metab di hepar (ketaconazole) → kdr AH 1 ↑ → lethal arrhythmia (terfenadin).

Kombinasi Obat Batuk-Pilek

- Preparat obat flu & batuk umumnya merup kombinasi 3-4 jenis obat
- Pilih secara teliti preparat yg cocok (komposisi) dengan 'the actual symptoms'
- Perhatikan efisiensi, safety, suitability pada pasien
- Penggunaan yg tdk sesuai pd pasien asma dpt menyebabkan kematian!
- ES tgt kandungan msg2 obat



THANK YOU