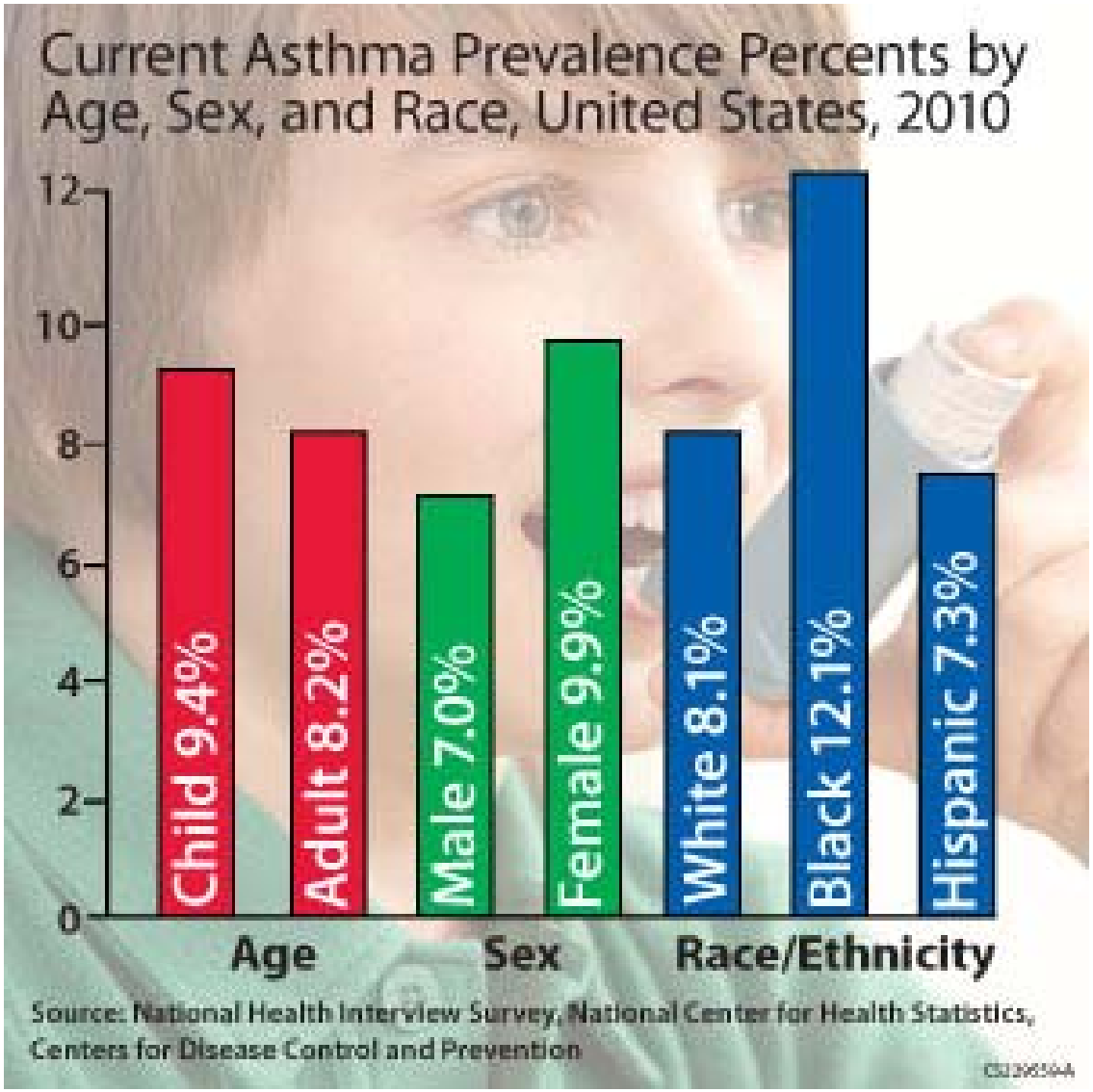
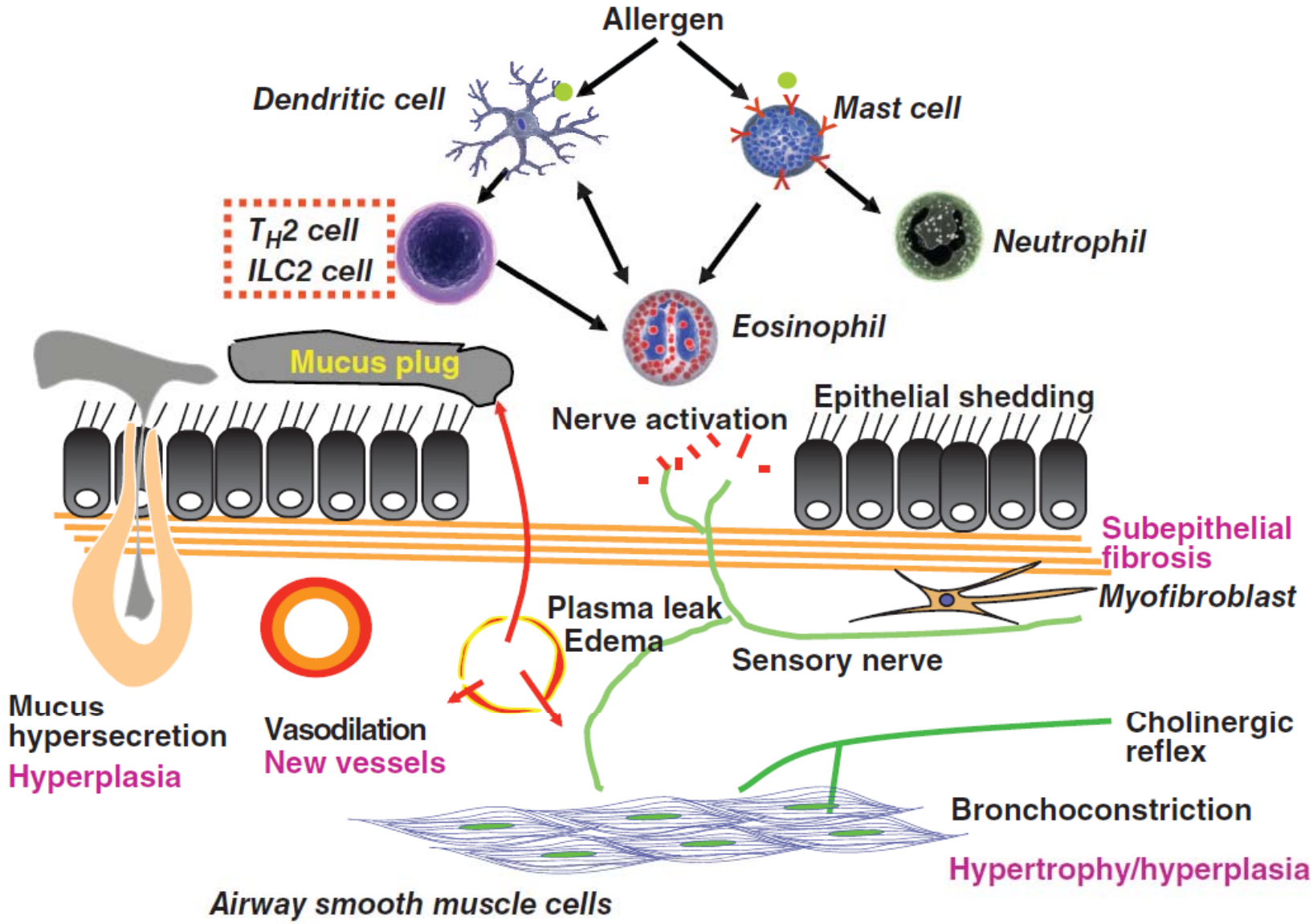
Pharmacology of Asthma


Current Asthma Prevalence Percents by Age, Sex, and Race, United States, 2010
12
10
8
6
4
2
0
Child 9.4%
Adult 8.2%
Male 7.0%
Female 9.9%
White 8.1%
Black 12.1%
Hispanic 7.3%
Age
Sex
Race/Ethnicity
Source: National Health Interview Survey, National Center for Health Statistics, Centers for Disease Control and Prevention

Pathophysiology of Asthma

- **Airway inflammation**
- **Bronchial hyperresponsiveness**
- **Airflow limitation**



Myriad inflammatory cells are recruited and activated in the airways, where they release multiple inflammatory mediators, which can also arise from structural cells. These mediators lead to bronchoconstriction, plasma exudation and edema, vasodilation, mucus hypersecretion, and activation of sensory nerves. Chronic inflammation leads to structural changes, including subepithelial fibrosis (basement membrane thickening), airway smooth muscle hypertrophy and hyperplasia, angiogenesis, and hyperplasia of mucus-secreting cells.

Pathologic Findings

- **Bronchoconstriction**
- **Hyperinflation of the lungs**
- **Hyperplasia of the smooth muscle surrounding the bronchial and bronchiolar walls**
- **Thickening of the basement membrane**
- **Mucosal edema**

Etiology

HOST FACTORS

Genetic, e.g.,
- Genes pre-disposing to atopy
- Genes pre-disposing to airway hyperresponsiveness

Obesity

Sex

ENVIRONMENTAL FACTORS

Allergens
- Indoor: Domestic mites, furred animals (dogs, cats, mice), cockroach allergen, fungi, molds, yeasts
- Outdoor: Pollens, fungi, molds, yeasts

Infections (predominantly viral)

Occupational sensitizers

Tobacco smoke
- Passive smoking
- Active smoking

Outdoor/Indoor Air Pollution

Diet

Examples of Agents Causing Asthma in Selected Occupations

Occupation/occupational field	Agent
	Animal and Plant Proteins
Bakers	Flour, amylase
Dairy farmers	Storage mites
Detergent manufacturing	*Bacillus subtilis* enzymes
Electrical soldering	Colophony (pine resin)
Farmers	Soybean dust
Fish food manufacturing	Midges, parasites
Food processing	Coffee bean dust, meat tenderizer, tea, shellfish, amylase, egg proteins, pancreatic enzymes, papain
Granary workers	Storage mites, *Aspergillus*, indoor ragweed, grass
Health care workers	Psyllium, latex
Laxative manufacturing	Ispaghula, psyllium
Poultry farmers	Poultry mites, droppings, feathers
Research workers, veterinarians	Locusts, dander, urine proteins
Sawmill workers, carpenters	Wood dust (western red cedar, oak, mahogany, zebrawood, redwood, Lebanon cedar, African maple, eastern white cedar)
Shipping workers	Grain dust (molds, insects, grain)
Silk workers	Silk worm moths and larvae
	Inorganic chemicals
Beauticians	Persulfate
Plating	Nickel salts
Refinery workers	Platinum salts, vanadium
	Organic chemicals
Automobile painting	Ethanolamine, dissocyanates
Hospital workers	Disinfectants (sulfathiazole, chloramines, formaldehyde, glutaraldehyde), latex
Manufacturing	Antibiotics, piperazine, methyldopa, salbutamol, cimetidine
Rubber processing	Formaldehyde, ethylene diamine, phthalic anhydride
Plastics industry	Toluene dissocyanate, hexamethyl dissocyanate, dephenylmethyl isocyanate, phthalic anhydride, triethylene tetramines, trimellitic anhydride, hexamethyl tetramine, acrylates

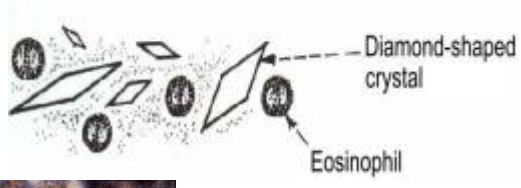
Factors that Exacerbate Asthma

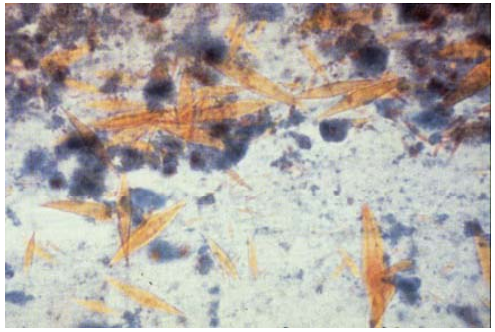
- Allergens
- Respiratory infections
- Exercise and hyperventilation
- Weather changes
- Sulfur dioxide
- Food, additives, drugs

Inflammatory cells in asthmatic airways

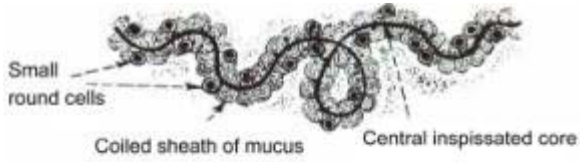
Sputum dg:

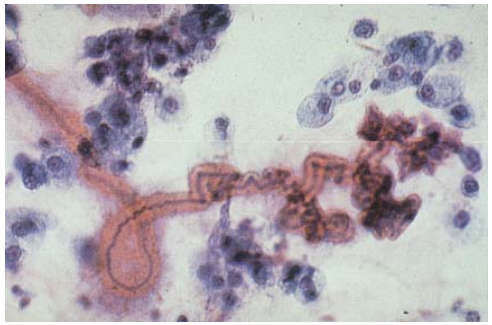
Charcot-Leyden christals





Curschmann's spirals





Mast cells: Activated mucosal mast cells release bronchoconstrictor mediators (histamine, cysteinyl leukotrienes, prostaglandin D_2)[93]. These cells are activated by allergens through high-affinity IgE receptors, as well as by osmotic stimuli (accounting for exercise-induced bronchoconstriction). Increased mast cell numbers in airway smooth muscle may be linked to airway hyperresponsiveness[94].

Eosinophils, present in increased numbers in the airways, release basic proteins that may damage airway epithelial cells. They may also have a role in the release of growth factors and airway remodeling[95].

T lymphocytes, present in increased numbers in the airways, release specific cytokines, including IL-4, IL-5, IL-9, and IL-13, that orchestrate eosinophilic inflammation and IgE production by B lymphocytes[96]. An increase in Th2 cell activity may be due in part to a reduction in regulatory T cells that normally inhibit Th2 cells. There may also be an increase in inKT cells, which release large amounts of T helper 1 (Th1) and Th2 cytokines[97].

Dendritic cells sample allergens from the airway surface and migrate to regional lymph nodes, where they interact with regulatory T cells and ultimately stimulate production of Th2 cells from naïve T cells[98].

Macrophages are increased in number in the airways and may be activated by allergens through low-affinity IgE receptors to release inflammatory mediators and cytokines that amplify the inflammatory response[99].

Neutrophil numbers are increased in the airways and sputum of patients with severe asthma and in smoking asthmatics, but the pathophysiological role of these cells is uncertain and their increase may even be due to glucocorticosteroid therapy[100].

Airway Structural Cells Involved in the Pathogenesis of Asthma

Airway epithelial cells sense their mechanical environment, express multiple inflammatory proteins in asthma, and release cytokines, chemokines, and lipid mediators. Viruses and air pollutants interact with epithelial cells.

Airway smooth muscle cells express similar inflammatory proteins to epithelial cells[101].

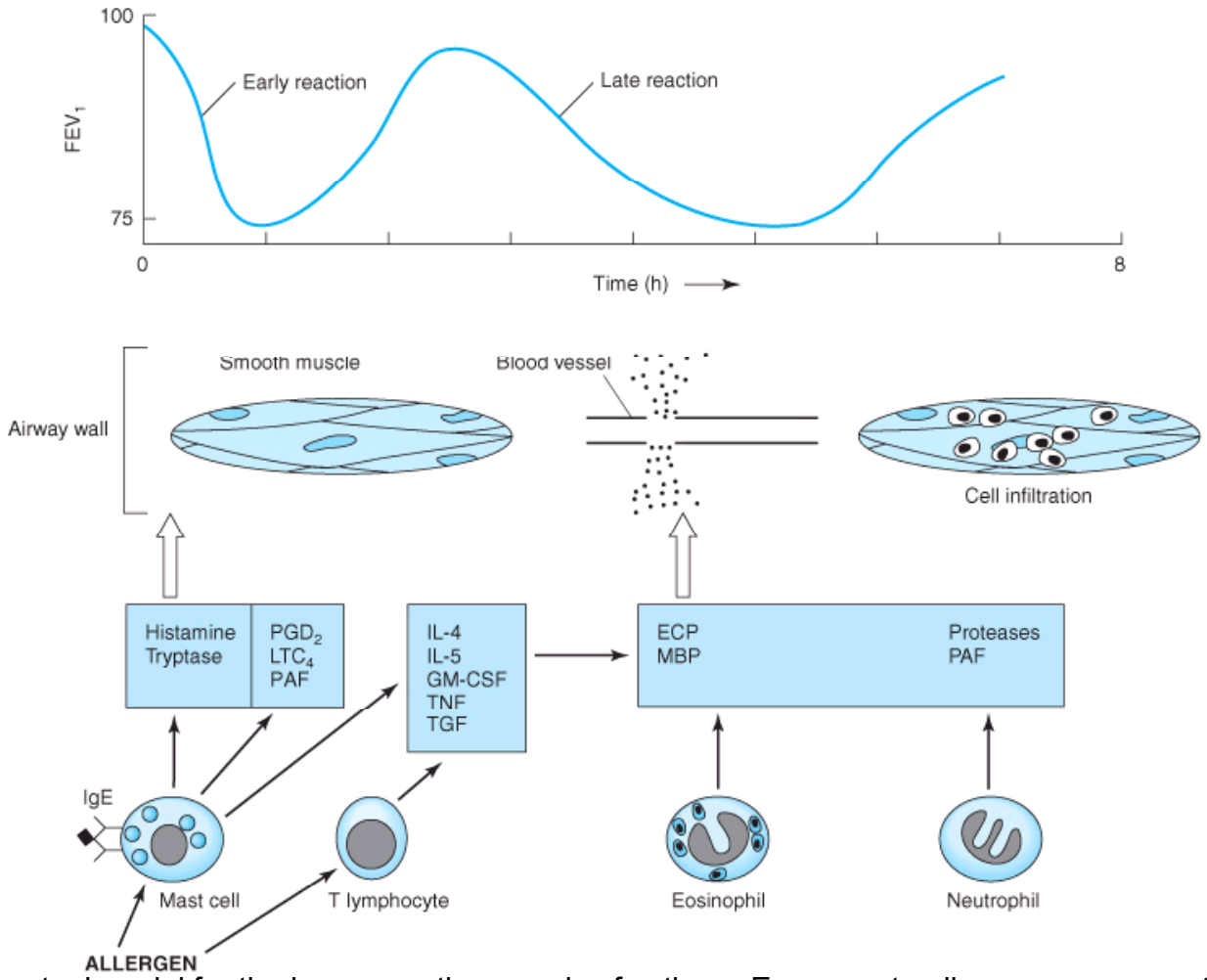
Endothelial cells of the bronchial circulation play a role in recruiting inflammatory cells from the circulation into the airway.

Fibroblasts and myofibroblasts produce connective tissue components, such as collagens and proteoglycans, that are involved in airway remodeling.

Airway nerves are also involved. Cholinergic nerves may be activated by reflex triggers in the airways and cause bronchoconstriction and mucus secretion. Sensory nerves, which may be sensitized by inflammatory stimuli including neurotrophins, cause reflex changes and symptoms such as cough and chest tightness, and may release inflammatory neuropeptides[102].

Chemicals Involved in Inflammation

- **IgE**
- **Histamine**
- **Tryptase**
- **Leukotrienes (LTC_4), SRS-A Slow Reactive Substance of Anaphylaxy**
- **Platelet activating factor (PAF)**
- **Prostaglandins (PGD_2)**
- **Interleukins (IL-4, IL-5)**
- **Granulocyte-macrophage colony stimulating factor (GM-CSF)**
- **Tumor Necrosis Factor (TNF)**
- **Major Basic Proteases (MBP)**
- **Eosinophil Cationic Protein (ECP)**



Conceptual model for the immunopathogenesis of asthma. Exposure to allergen causes synthesis of IgE, which binds to mast cells in the airway mucosa. On reexposure to allergen, antigen-antibody interaction on mast cell surfaces triggers release of mediators of anaphylaxis: histamine, tryptase, prostaglandin D2 (PGD2), leukotriene C4, and platelet-activating factor (PAF). These agents provoke contraction of airway smooth muscle, causing the immediate fall in FEV1. Reexposure to allergen also causes the synthesis and release of a variety of cytokines: interleukins 4 and 5, granulocyte-macrophage colony stimulating factor (GM-CSF), tumor necrosis factor (TNF), and tissue growth factor (TGF) from T cells and mast cells. These cytokines in turn attract and activate eosinophils and neutrophils, whose products include eosinophil cationic protein (ECP), major basic protein (MBP), proteases, and platelet-activating factor. These mediators cause the edema, mucus hypersecretion, smooth muscle contraction, and increase in bronchial reactivity associated with the late asthmatic response, indicated by a fall in FEV1 2-8 hours after the exposure.

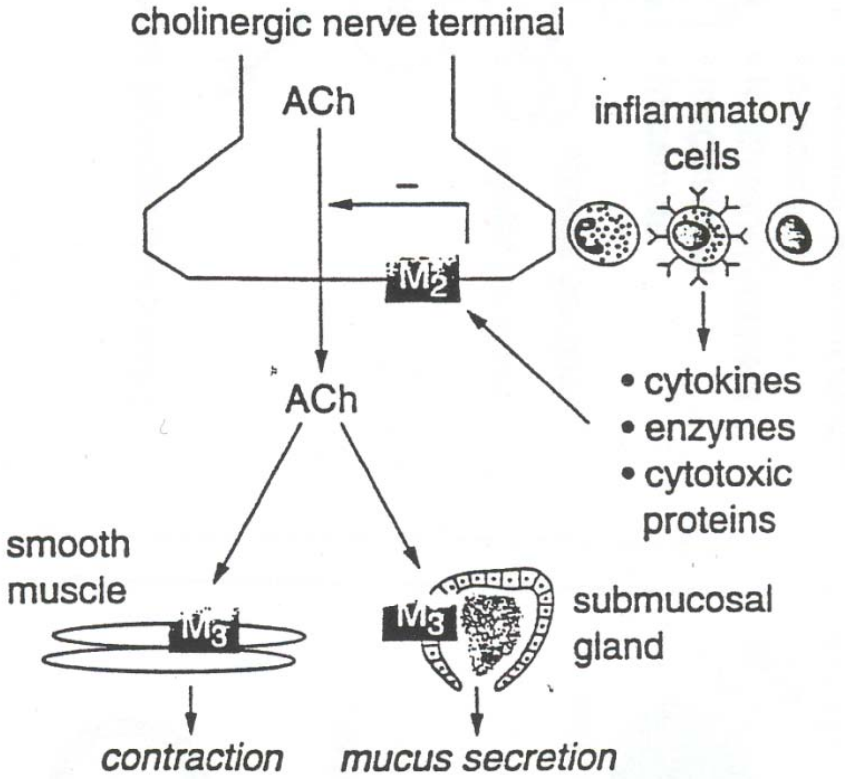
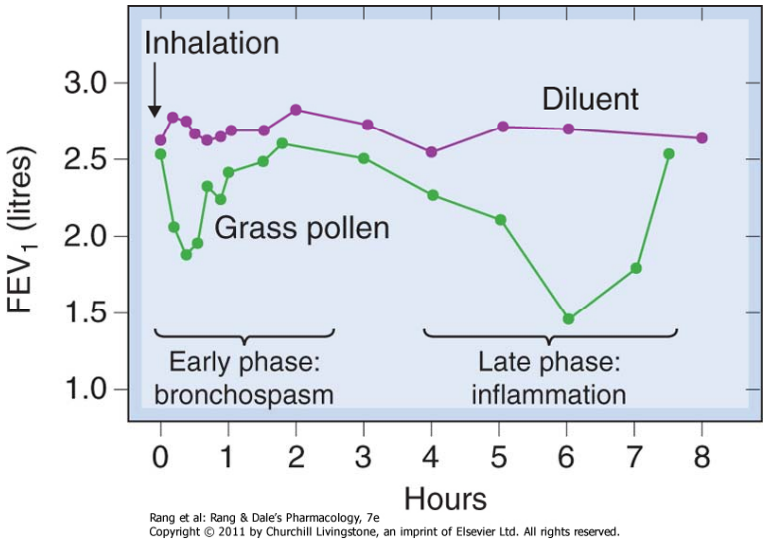
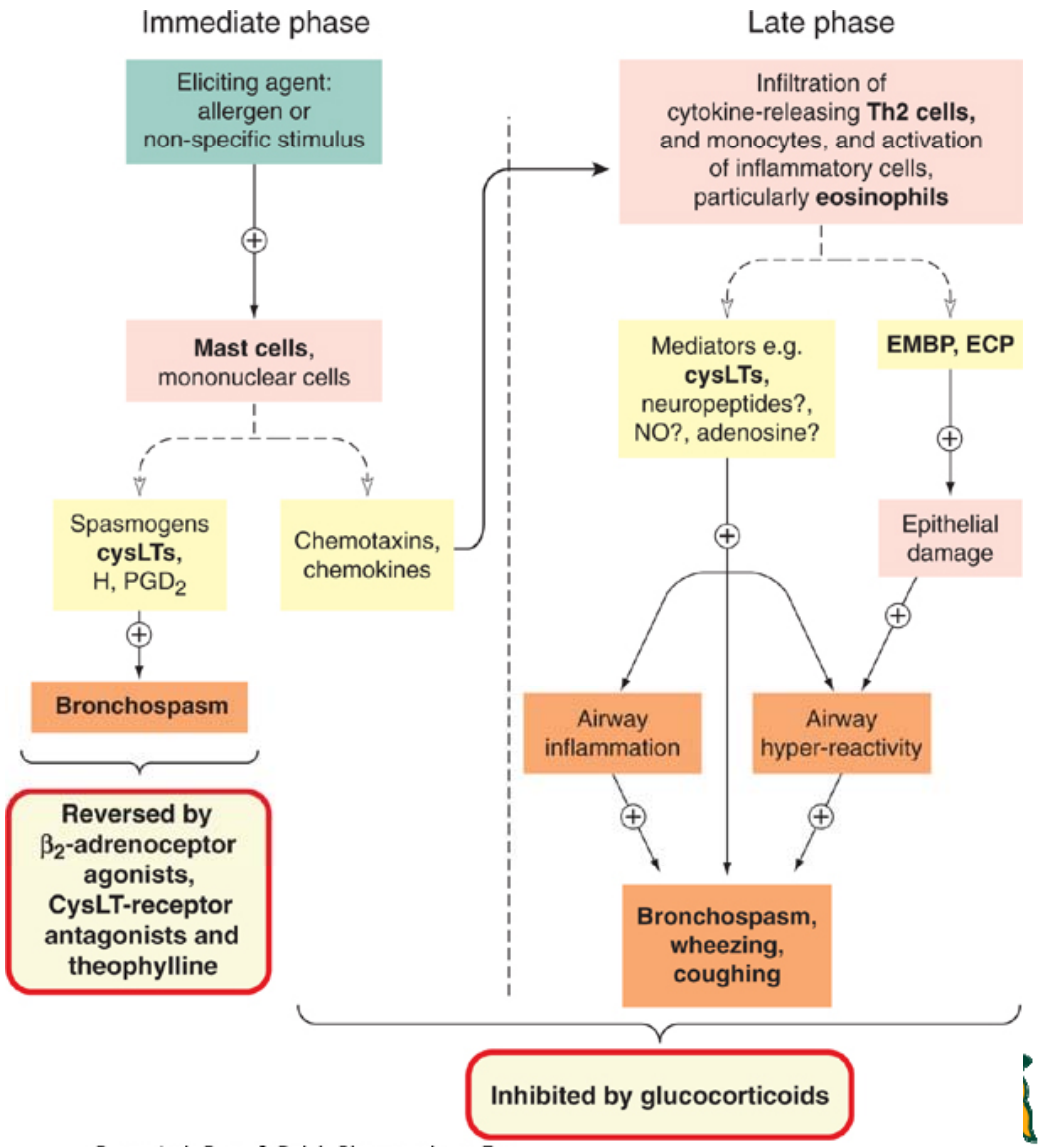


Fig. Putative mechanisms leading to M_2 muscarinic receptor dysfunction in asthma. Prejunctional M_2 muscarinic receptors are involved in the regulation of acetylcholine (ACh) through a feedback mechanism. In asthma, where inflammation is a prominent feature, inflammatory cell products such as cytokines (e.g. tumour necrosis factor α or interleukin 1β), enzymes (e.g. neuraminidase) and eosinophil cytotoxic proteins (e.g. major basic protein) alter the expression and function of M_2 receptors, which leads to an exaggerated ACh release. Acetylcholine then induces smooth muscle contraction and mucus secretion via the activation of postjunctional M_3 receptors (see text for details).

Role of cholinergic nerves in bronchial asthma

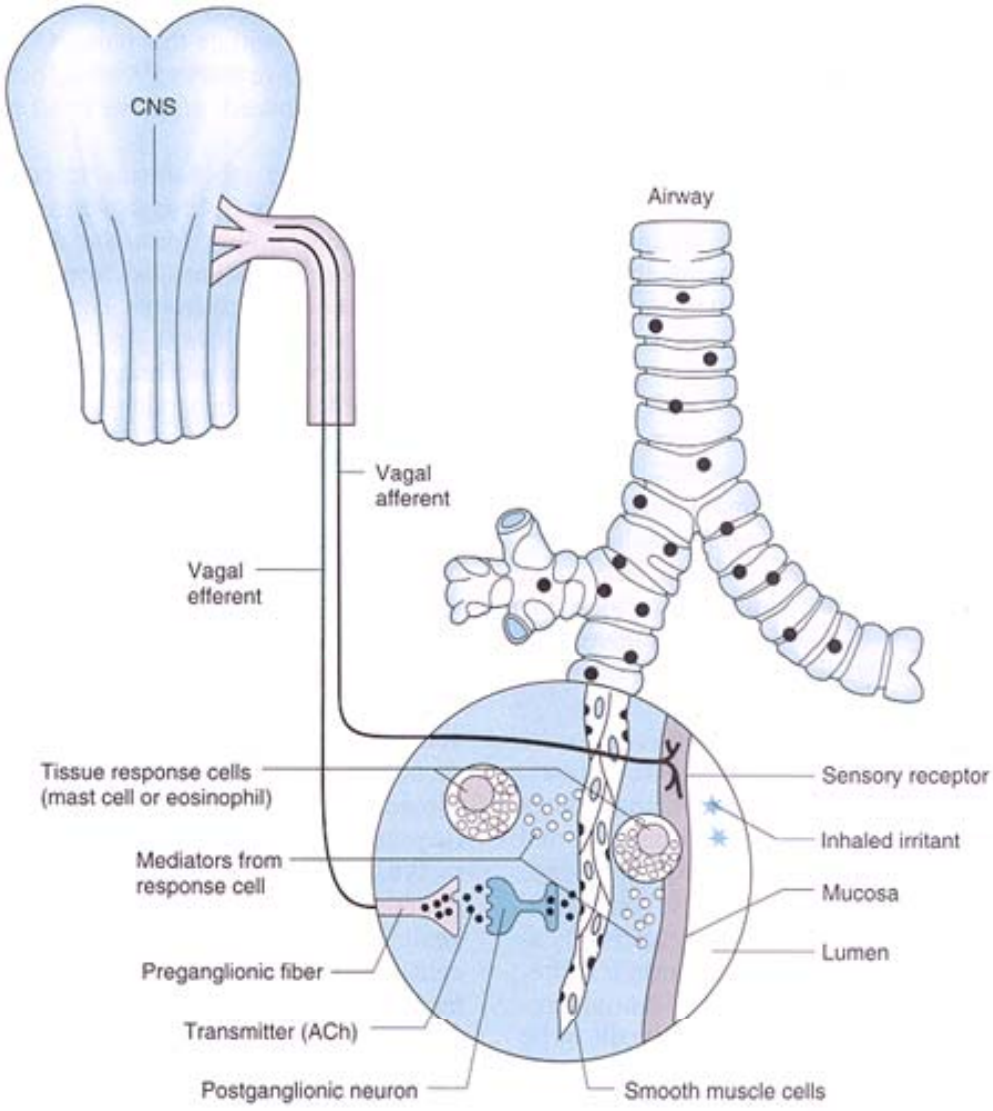
The two phases of asthma

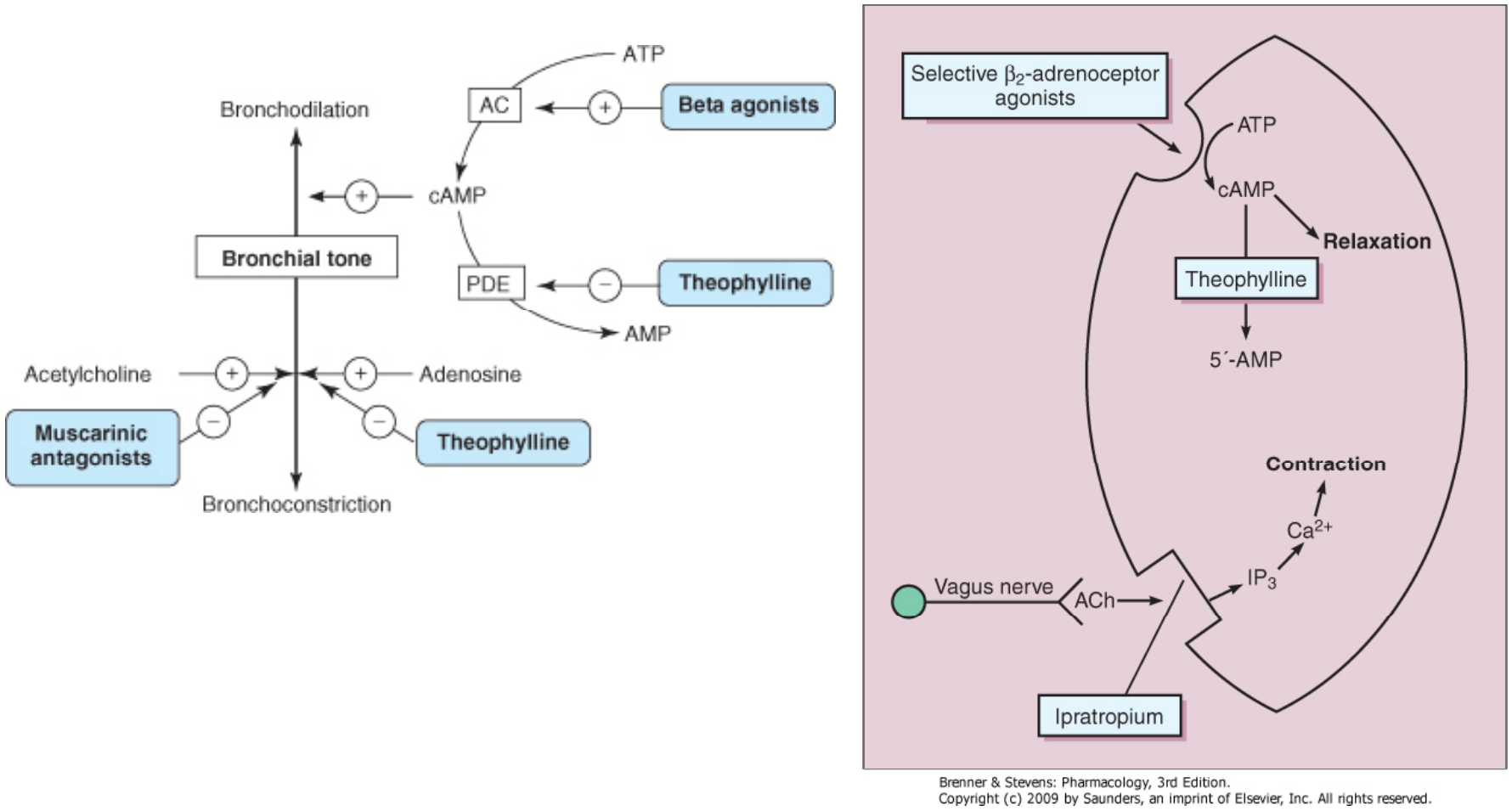




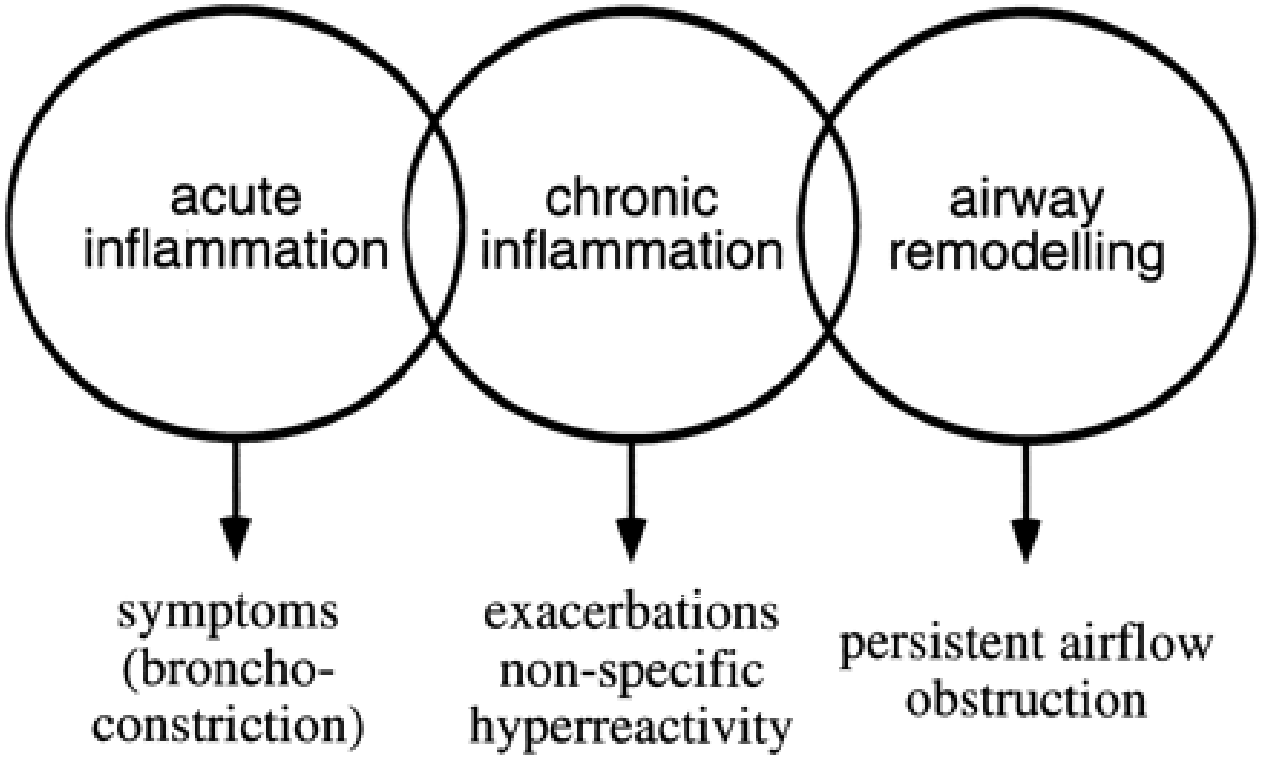
Mechanisms of response to inhaled irritants.

The airway is represented microscopically by a cross-section of the wall with branching vagal sensory endings lying adjacent to the lumen. Afferent pathways in the vagus nerves travel to the central nervous system; efferent pathways from the central nervous system travel to efferent ganglia. Postganglionic fibers release acetylcholine (ACh), which binds to muscarinic receptors on airway smooth muscle. Inhaled materials may provoke bronchoconstriction by several possible mechanisms. First, they may trigger the release of chemical mediators from mast cells. Second, they may stimulate afferent receptors to initiate reflex bronchoconstriction or to release tachykinins (eg, substance P) that directly stimulate smooth muscle contraction.





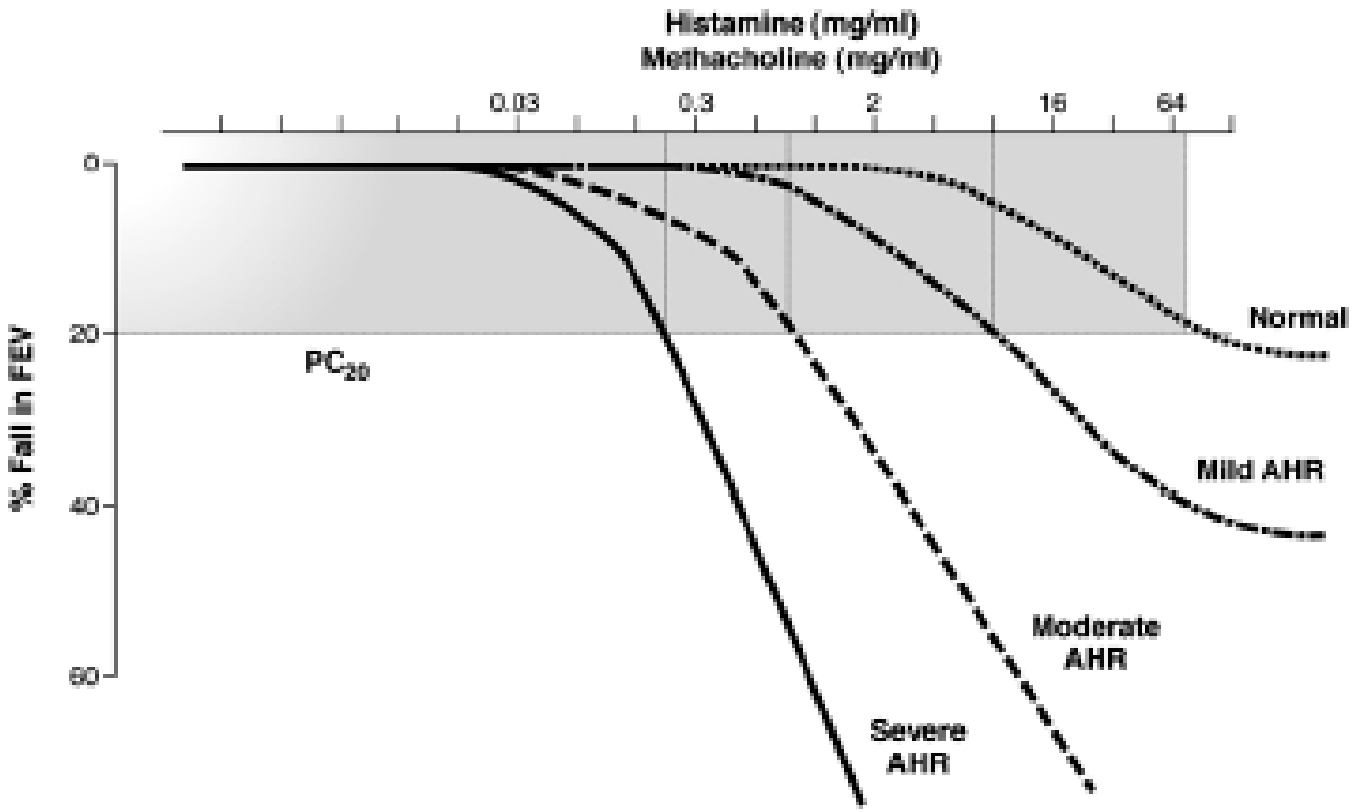
Bronchodilation is promoted by cAMP. Intracellular levels of cAMP can be increased by beta-adrenoceptor agonists, which increase the rate of its synthesis by adenylyl cyclase (AC); or by phosphodiesterase (PDE) inhibitors such as theophylline, which slow the rate of its degradation. Bronchoconstriction can be inhibited by muscarinic antagonists and possibly by adenosine antagonists.


acute inflammation
chronic inflammation
airway remodelling
symptoms (broncho-constriction)
exacerbations non-specific hyperreactivity
persistent airflow obstruction

Classification of Asthma Severity: Clinical Features Before Treatment

Severity	Days with Symptoms	Nights with Symptoms	PEF or $FEV_{1.0}$
Severe Persistent	Continual	Frequent	≤ 60%
Moderate Persistent	Daily	≥ 5/month	>60% < 80%
Mild Persistent	3-6/ week	3-4/month	≥ 80%
Mild Intermittent	≤ 2/week	≤ 2/month	≥ 80%

Figure 2-3. Measuring Airway Responsiveness*



*Airway responsiveness to inhaled methacholine or histamine in a normal subject, and in asthmatics with mild, moderate, and severe airway hyperresponsiveness. Asthmatics have an increased sensitivity and an increased maximal broncho- constrictor response to the agonist. The response to the agonist is usually expressed as the provocative concentration causing a 20% decline in FEV_1 (PC_{20}).

General Goals of Asthma Therapy

- Prevent chronic symptoms and asthma exacerbations during the day and night
- Maintain normal activity levels
- Have normal or near-normal lung function
- Have no or minimal side effects while receiving optimal medications

Historical Perspective

- Datura stramonium (1802)
- Epinephrine (1903)
- Ephedrine (1926)
- Isoproterenol (1940)
- Isoetharine (1951)
- Metaproterenol (1961)
- Beta$_2$-adrenergic agents via MDI (1973)
- Ipratropium bromide (1987)
- Salmeterol (1994)
- Levalbuterol (1999)

General Pharmacologic Approach to the Treatment of Asthma

- Asthma
  - "Relievers"
    - Short-acting bronchodilators
      - β_2-adrenergic agents
      - Anti-cholinergic (Parasympatholytic) agents
  - "Controllers"
    - Corticosteroids
    - Long-Acting bronchodilators
      - β_2-adrenergic agents
      - Methylxanthines
    - Cromolyn sodium
    - Leukotriene inhibitors
    - Anti-IgE monoclonal antibodies

DRUGS USED IN BRONCHIAL ASTHMA

I. BRONCHODILATORS

1. METHYLXANTHINES

   Theophylline, Aminophylline,

   Enprophylline

2. β2-ADRENERG RECEPTOR AGONISTS

   Salbutamol, Terbutalin, Fenoterol, Clenbuterol (short)

   Salmeterol, Formoterol (long)

3. MUSCARIN RECEPTOR ANTAGONISTS

   Atropine, Ipratropium bromide, Tiotropium bromide

II. ANTIINFLAMMATORY DRUGS

1. MAST CELL STABILIZERS

Disodium cromoglycate, Nedocromil

2. GLUCOCORTICOSTEROIDS

Budesonid, Fluticason, Beclomethason, Ciclesonid

3. LIPOXIGENASE INHIBITORS

Zileuton

4. LEUKOTRIENE RECEPTOR ANTAGONISTS

Zafirlukast, Montelukast

5. COX-2 INHIBITORS: Valdecoxib

6. PDE4 ENZYME INHIBITORS

Rolipram

7. MONOCLONAL ANTIBODIES

Omalizumab (anti-IgE)

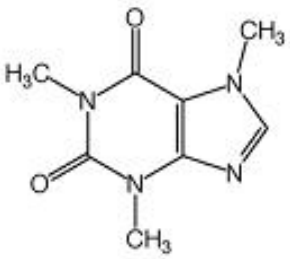
III. FUTURE DRUGS

ET1 RECEPTOR ANTAGONISTS

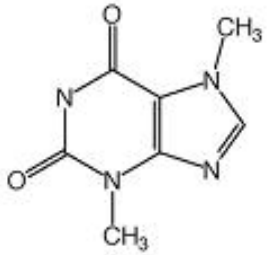
TACHYKININ (NK1/NK2) RECEPTOR ANTAGONISTS

ANTISENSE OLOGONUCLEOTIDES against NF-kB, MBP, IL-4, IL-5, A1 ADENOSINE RECEPTORS

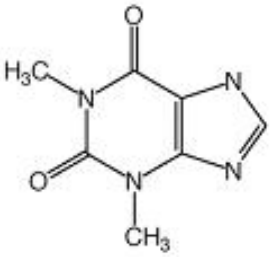
Methylxanthines



Caffeine



Theobromine



Theophylline

Natural sources:

(Coffea arabica)
(Cola vera)
(Ilex paraguensis)
(Theobroma cacao)
(Camellia sinensis)

Theobroma cacao
Ilex paraguariensis
Camellia sinensis
Coffea arabica

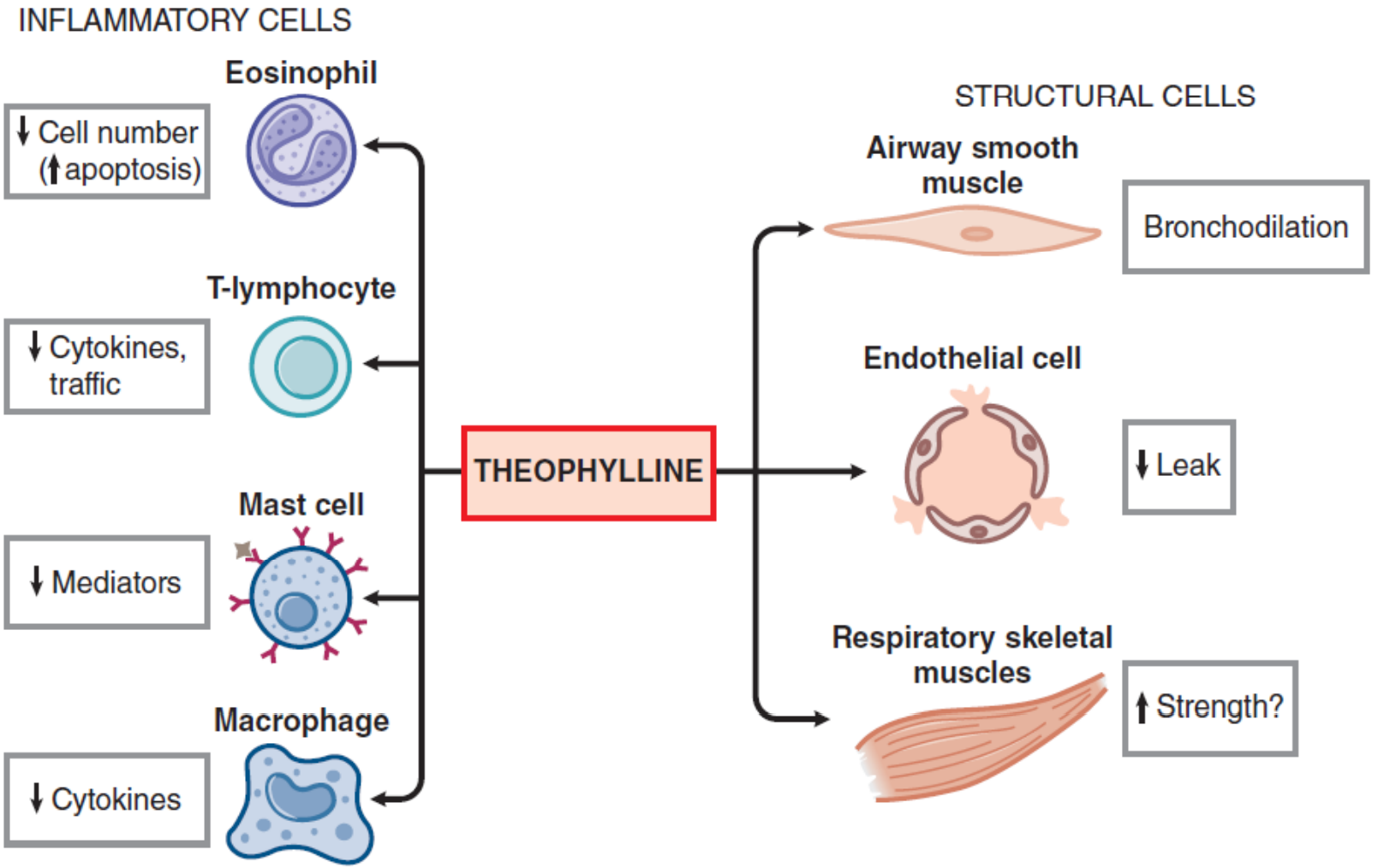
Thea sinensis

1. Inhibition of phosphodiesterase

(millimolar concentration range)!!!

2. Adenosine receptor antagonist action(therapeutic blood level: 20-50 μM)
3. Antiinflammatory effects (less than 5 μM blood level)

Theophylline affects multiple cell types in the airway



Antiasthmatic action of theophylline

1. Relaxation of bronchial smooth muscle
2. Inhibition of mast cell degranulation
3. Inhibition of mucus secretion
4. Increased release of noradrenaline
5. Antiinflammatory effect
6. Increased contraction of diaphragma
7. Adrenaline liberation from suprarenal glands
8. Can be used mainly in COPD

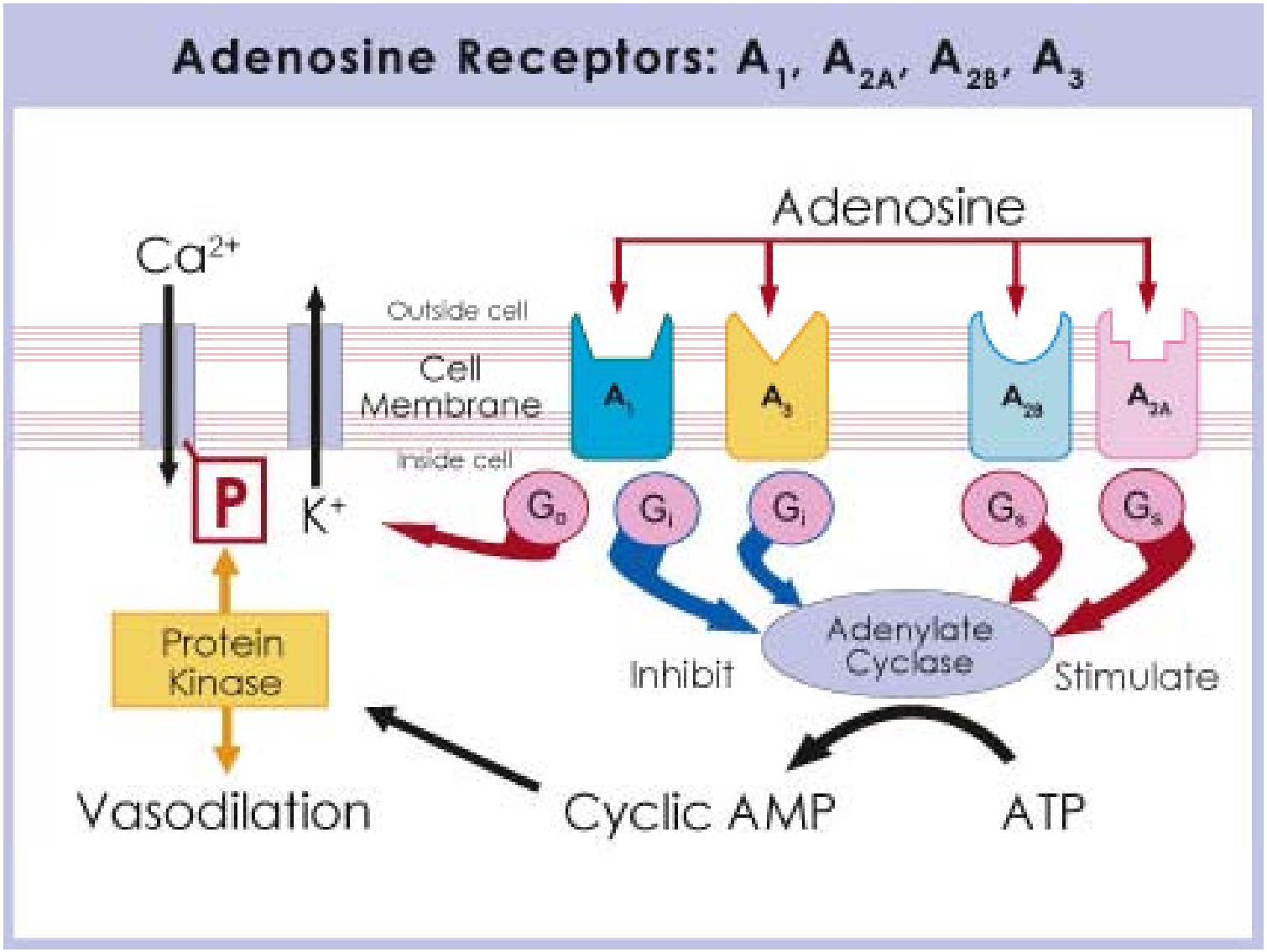
Disadvantages and adverse reactions of theophylline

1. Narrow therapeutic index
2. Gastrointestinal symptoms
3. CNS effects (excitation, epileptiform convulsions)
4. Relaxing effect on the esophageal sphincter (reflux, initiation of asthma)

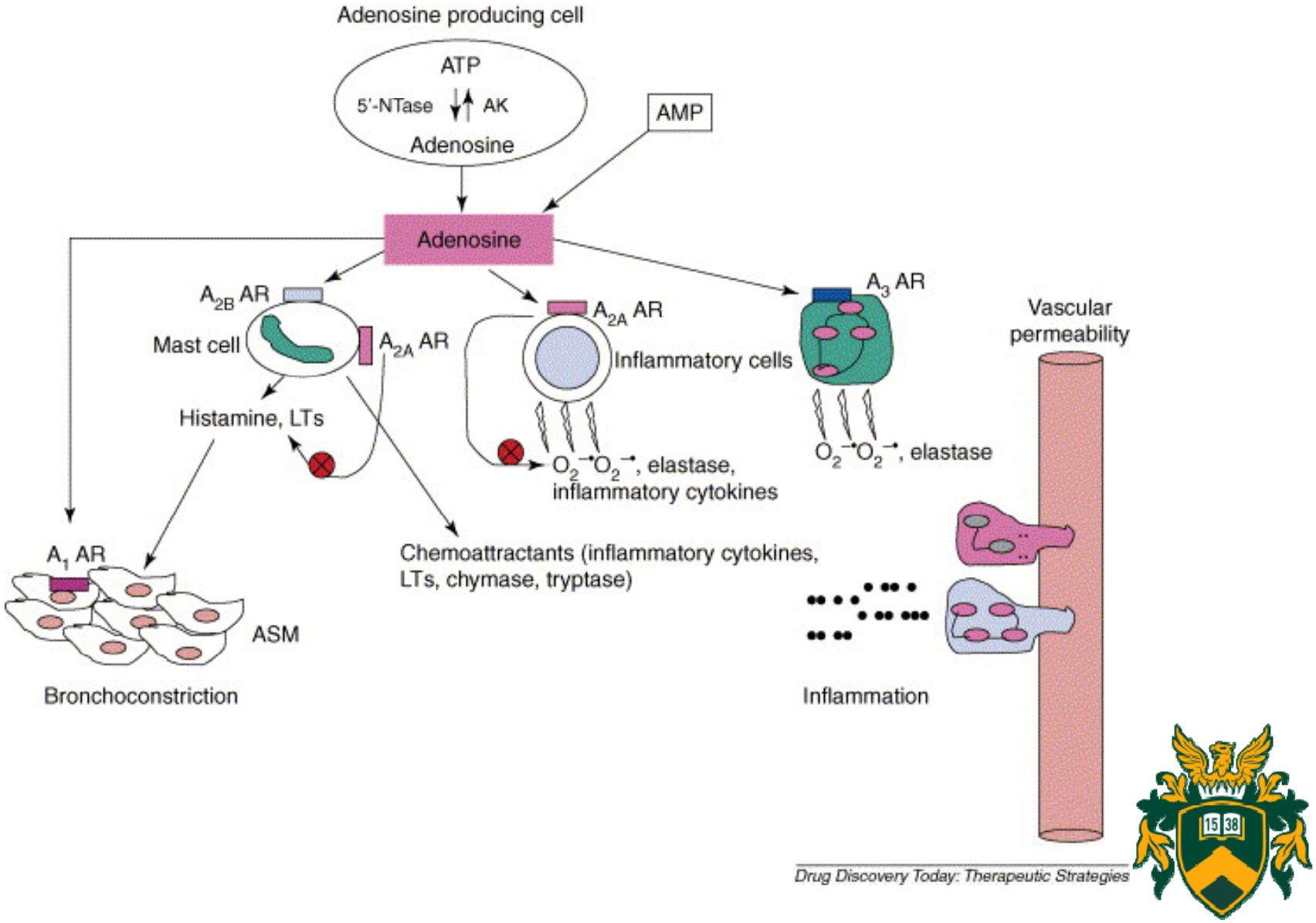
SIDE EFFECT	PROPOSED MECHANISM
Nausea and vomiting	PDE4 inhibition
Headaches	PDE4 inhibition
Gastric discomfort	PDE4 inhibition
Diuresis	A_1 receptor antagonism
Behavioral disturbance (?)	?
Cardiac arrhythmias	PDE3 inhibition, A_1 receptor antagonism
Epileptic seizures	A_1 receptor antagonism

A, adenosine.

Adenosine Receptors: A_1, A_{2A}, A_{2B}, A_3



Role of adenosine receptors in development of asthma



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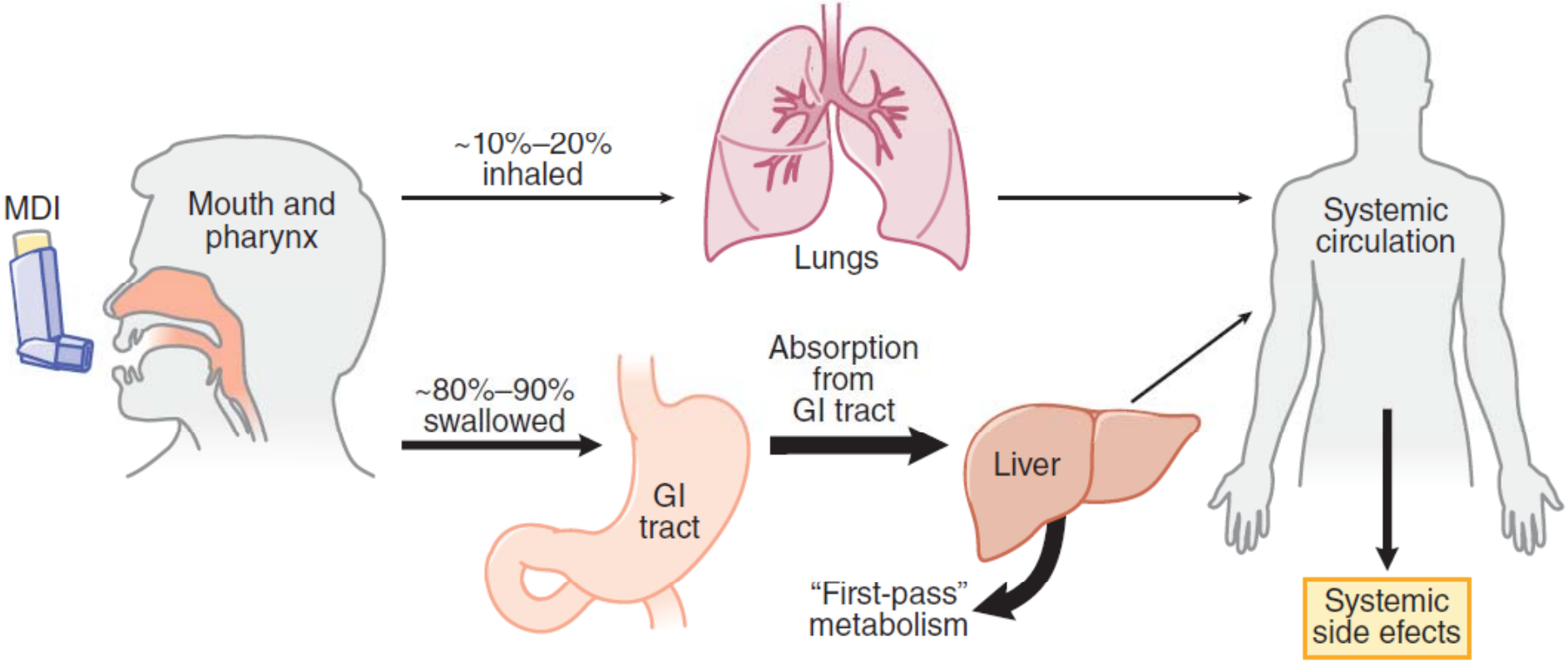


Schematic representation of the deposition of inhaled drugs (e.g., corticosteroids, β2 agonists). Inhalation therapy deposits drugs directly, but not exclusively, in the lungs. Distribution between lungs and oropharynx depends mostly on the particle size and the efficiency of the delivery method. Most material will be swallowed and absorbed, entering systemic circulation after undergoing the first-pass effect in the liver. Some drug will also be absorbed into the systemic circulation from the lungs. Use of a large-volume spacer will reduce the amount of drug deposited on the oropharynx, thereby reducing the amount swallowed and absorbed from the GI tract, thus limiting systemic effects.

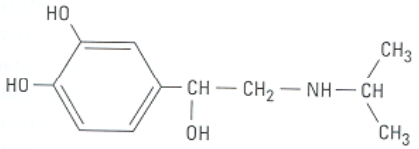
Inhaled Short-Acting β2 Agonists (SABAs)

Albuterol,
Albutamol
Levalbuterol
Metaproterenol
Terbutaline
Pirbuterol
Fenoterol
Tulobuterol
Rimiterol

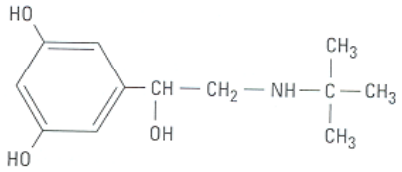
Table 27-2. Pharmacologic Properties of Selected β_2-Adrenoceptor Agonists Administered by Inhalation

Drug	Onset of Action (Minutes)	Duration of Action (Hours)	Dosage
Albuterol	5	3-8	2 puffs every 4-6 hours
Formoterol	5	12	1 inhalation every 12 hours
Pirbuterol	5	5	2 puffs every 4-6 hours
Salmeterol	20	12	2 puffs every 12 hours
Terbutaline	5-15	3-6	2 puffs every 4-6 hours

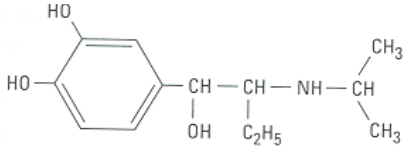
Arformoterol, the active (R,R)-isomer of formoterol, is available as a inhalation solution for the twice-daily treatment of bronchoconstriction in patients with **chronic bronchitis** or **emphysema**. Salmeterol and formoterol are available as single ingredients and in combination products that contain fluticasone or budesonide, respectively.



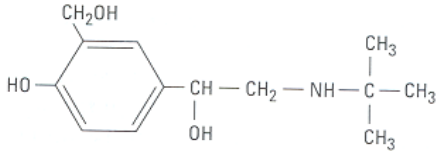
Isoproterenol



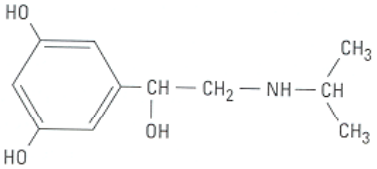
Terbutaline



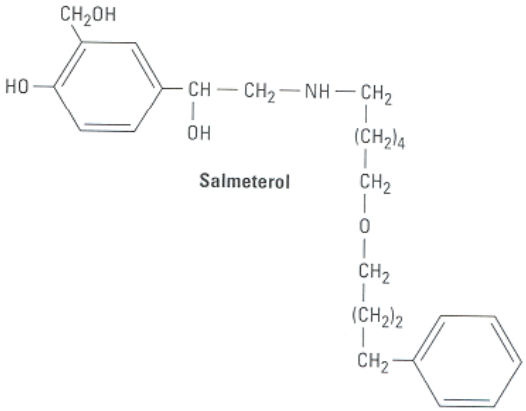
Isoetharine



Albuterol (salbutamol)



Metaproterenol



Salmeterol

Side effects of β2 agonists

•Muscle tremor (direct effect on skeletal muscle β2 receptors)
• Tachycardia (direct effect on atrial β2 receptors, reflex effect from increased peripheral vasodilation via β2 receptors)
• Hypokalemia (direct β2 effect on skeletal muscle uptake of K+)
• Restlessness
• Hypoxemia (↑ V/Q mismatch due to reversal of hypoxic pulmonary vasoconstriction)
• Metabolic effects (↑ FFA, glucose, lactate, pyruvate, insulin)

Antiastmatic mechanism of action of β2 agonists

1. Bronchodilation
2. Anti-inflammatory action: inhibits the release of inflammatory mediators from mast cells, eosinophils, basophils and macrophages
3. Reduce the non-specific bronchial hyperreactivity
4. Increase the mucus secretion and ciliary movement
5. Decrease the permeability of the vessels and edema

Long-Acting Inhaled β2 Agonists: The LABAs

Salmeterol
Formoterol
Arformoterol
Indacaterol
Vilanterol
Olodaterol

Duration of action is longer than 24 hrs.

Combination inhalers: LABA + corticosteroid (e.g. fluticasone+salmeterol)

Side Effects Seen with Beta Agonist

- Tremor
- Palpitations and tachycardia
- Headache
- Insomnia
- Rise in blood pressure
- Nervousness
- Dizziness
- Nausea
- Freon gase: increases beta receptor sensitivity

DRUGS USED IN BRONCHIAL ASTHMA

I. BRONCHODILATORS

1. METHYLXANTHINES

   Theophylline, Aminophylline,

   Enprophylline

2. β2-ADRENERG RECEPTOR AGONISTS

   Salbutamol, Terbutalin, Fenoterol, Clenbuterol (short)

   Salmeterol, Formoterol (long)

3. MUSCARIN RECEPTOR ANTAGONISTS

   Atropine, Ipratropium bromide, Tiotropium bromide

II. ANTIINFLAMMATORY DRUGS

1. MAST CELL STABILIZERS

Disodium cromoglycate, Nedocromil

2. GLUCOCORTICOSTEROIDS

Budesonid, Fluticason, Beclomethason, Ciclesonid

3. LIPOXIGENASE INHIBITORS

Zileuton

4. LEUKOTRIENE RECEPTOR ANTAGONISTS

Zafirlukast, Montelukast

5. COX-2 INHIBITORS: Valdecoxib

6. PDE4 ENZYME INHIBITORS

Rolipram

7. MONOCLONAL ANTIBODIES

Omalizumab (anti-IgE)

III. FUTURE DRUGS

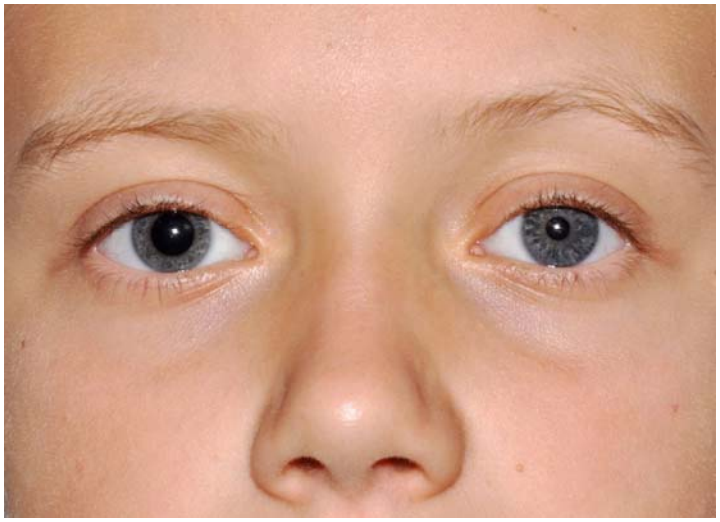
ET1 RECEPTOR ANTAGONISTS

TACHYKININ (NK1/NK2) RECEPTOR ANTAGONISTS

ANTISENSE OLOGONUCLEOTIDES against NF-kB, MBP, IL-4, IL-5, A1 ADENOSINE RECEPTORS

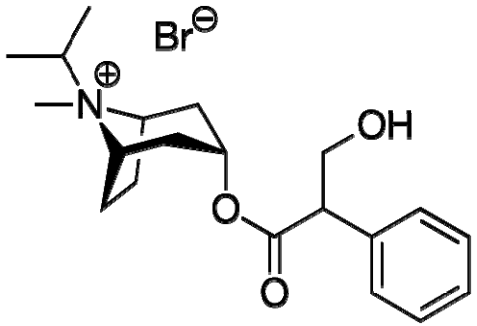
Atropa belladonna

Deadly nightshade

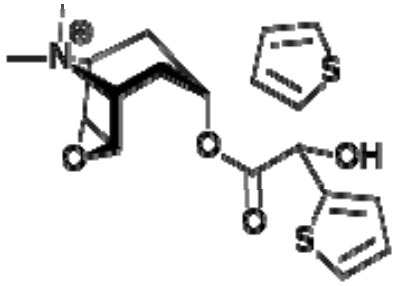


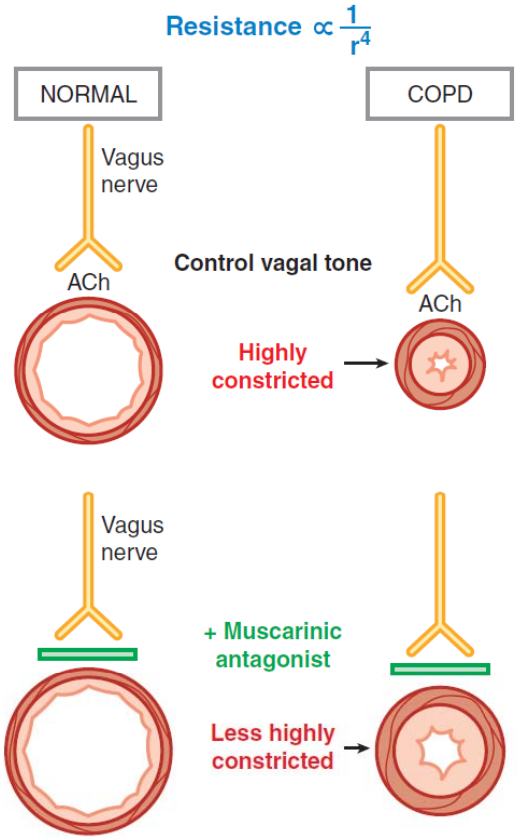
Klotho
Lakhesis
Atropos

Quaternary amines

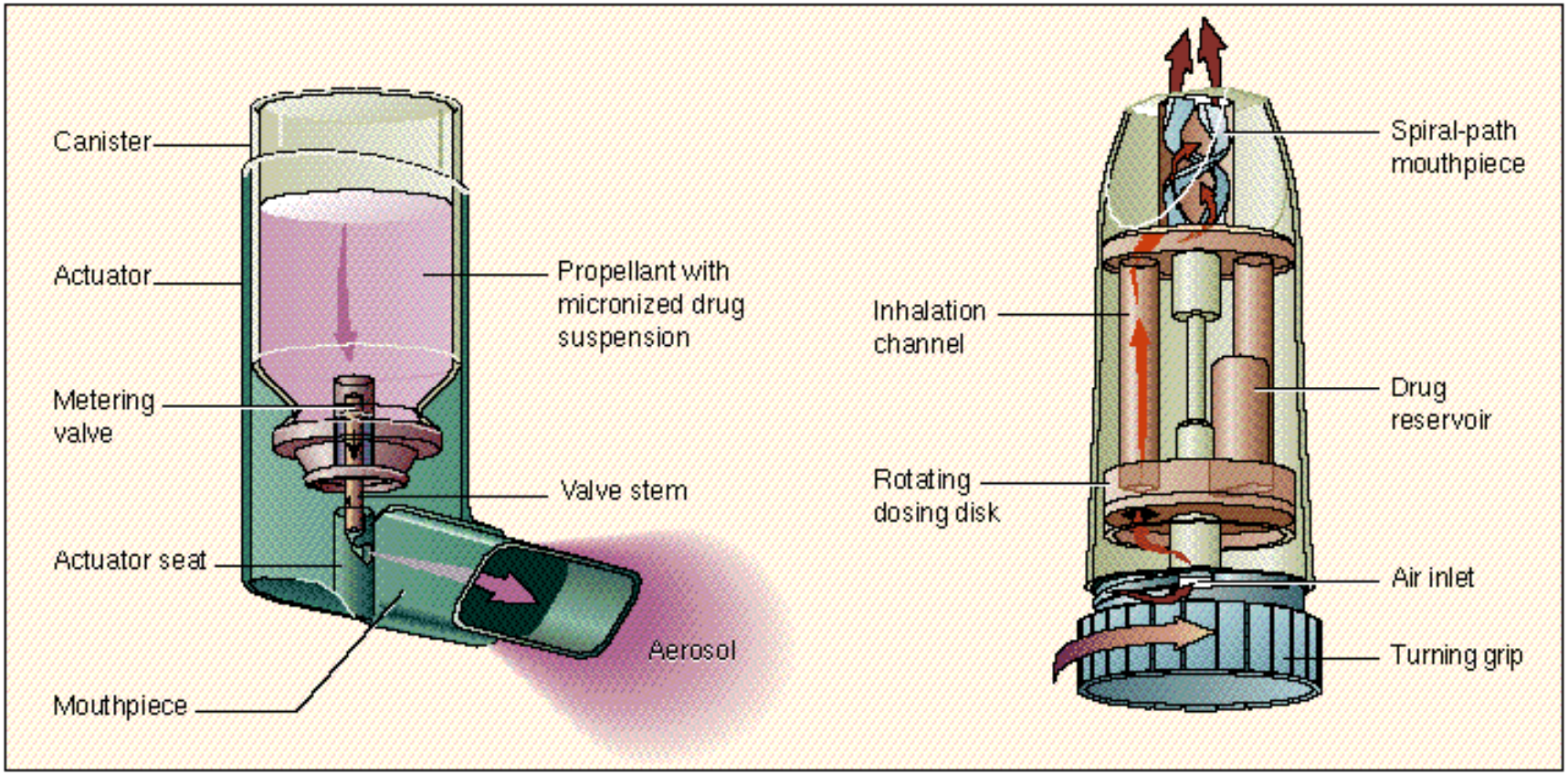


SAMA: Ipratropium bromide
LAMA: Tiotropium bromide





nebulizer


Canister
Actuator
Metering valve
Actuator seat
Mouthpiece
Propellant with micronized drug suspension
Valve stem
Aerosol
Spiral-path mouthpiece
Inhalation channel
Rotating dosing disk
Drug reservoir
Air inlet
Turning grip

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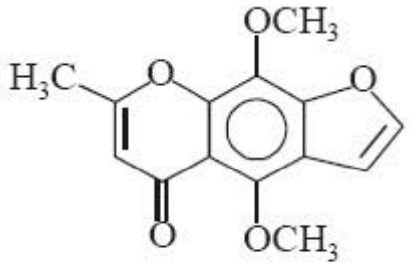
ANTISENSE OLOGONUCLEOTIDES against NF-kB, MBP, IL-4, IL-5, A1 ADENOSINE RECEPTORS

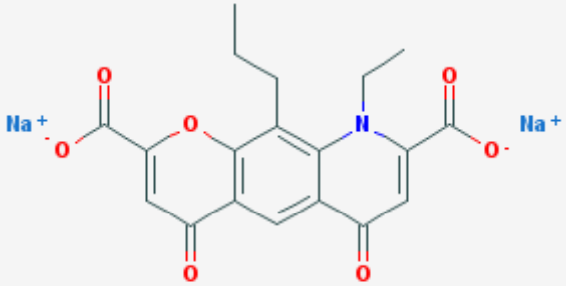
Mast cell stabilizers

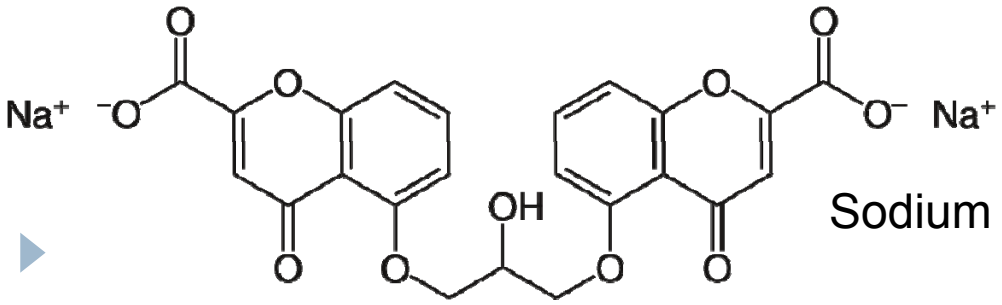


Khellin

Cromolyn sodium (sodium cromoglycate) is a derivative of khellin, an Egyptian herbal remedy.

Nedocromyl sodium





Sodium cromoglycate

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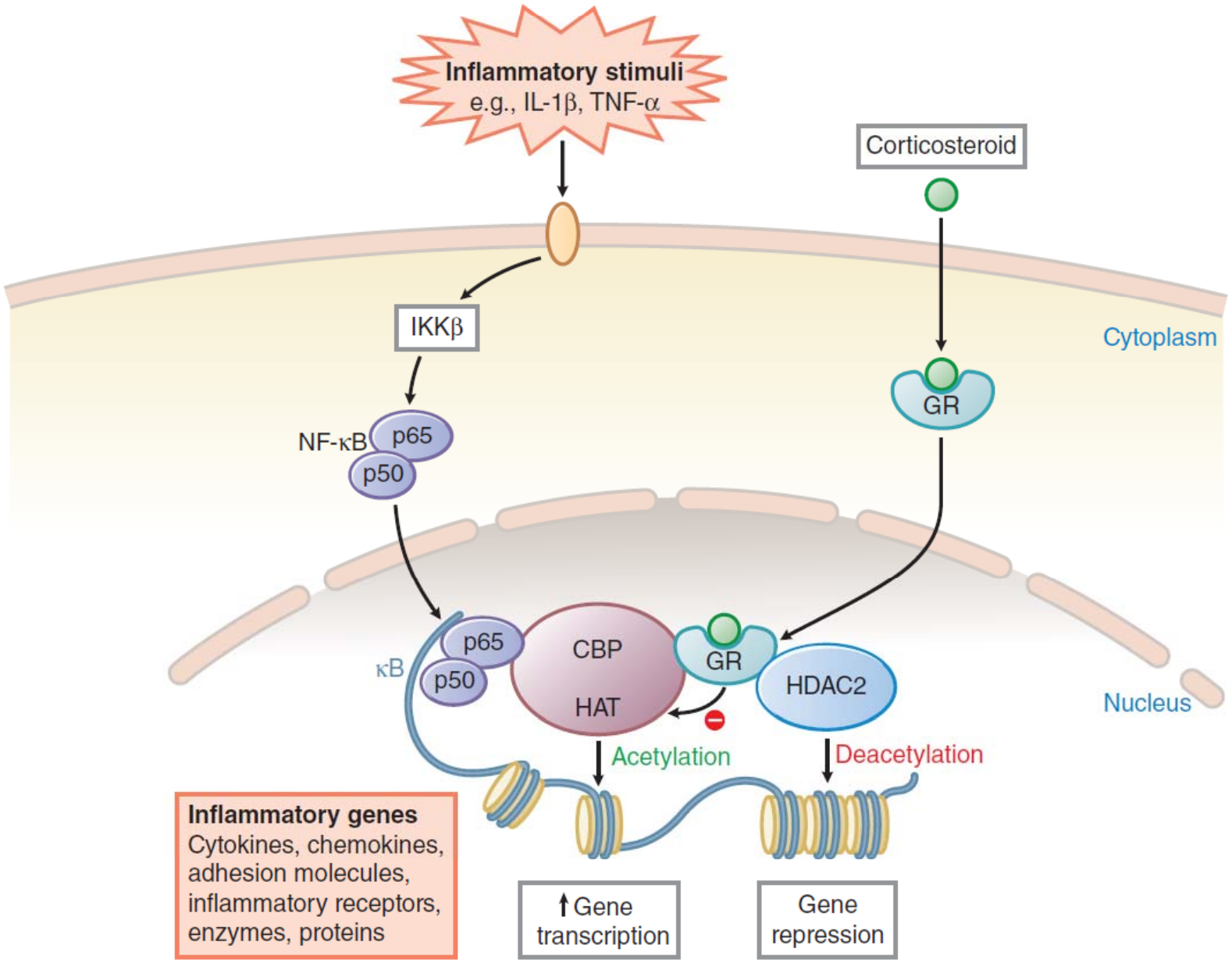
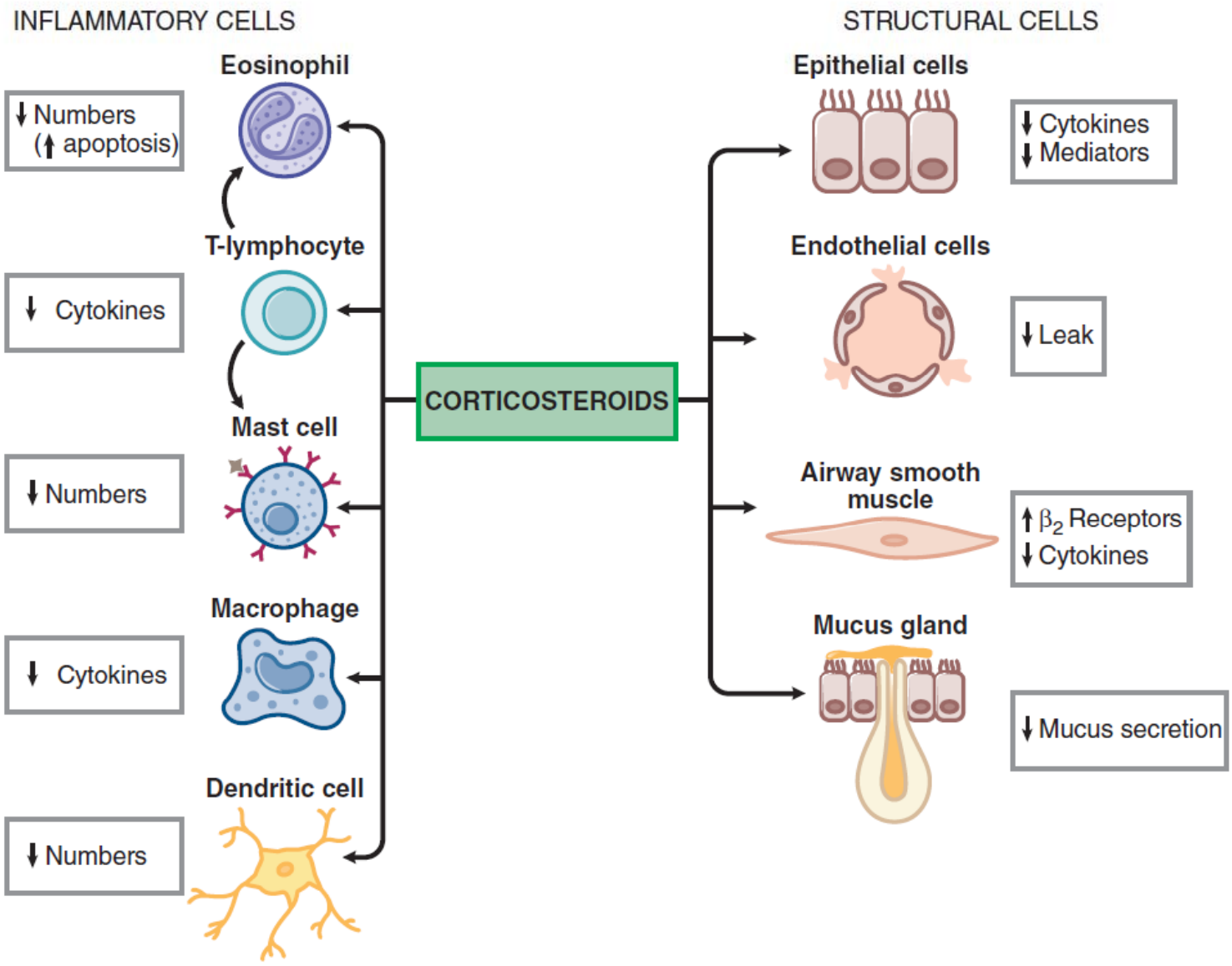
Mechanism of anti-inflammatory action of corticosteroids in asthma.



Effect of corticosteroids on inflammatory and structural cells in the airways



Corticosteroids

1. Reduce citokine production, synthesis of adhesion molecules, production of inflammatory mediators
2. Inhibit migration and activation of inflammatory cells
3. Reduce the bronchial hyperreactivity
4. Side effects: oral candidiasis, minimal systemic reactions
5. Aphonia, dysphonia

Prodrugs: Beclomethasone dipropionate and ciclesonide

Budesonide and fluticasone propionate

Inhaled Glucocorticoids

- Beclomethasone dipropionate
  - Dosage: 200-1000µg
- Budesonide
  - Dosage: 200-800µg
- Flunisolide
  - 500-2000µg
- Fluticasone
  - 100-500µg
- Tramcinolone acetonide
  - 400-2000µg

		UK licence covers		
Steroid	**Equivalent dose**	**> 12 years**	**5 – 12 years**	**< 5 years**
Beclometasone dipropionate CFC	400 micrograms	**No longer available**		
Beclometasone				
Clenil modulite	400 micrograms	✓	✓	✓
Clickhaler		✓	Over age 6	×
Aerobec Autohaler		✓	×	×
Asmabec Clickhaler		✓	Over age 6	×
Dry powder (Becodisks)		✓	✓	✓
Easyhaler		✓	×	×
Pulvinal		✓	Over age 6	×
Filair		✓	✓	✓
Qvar*	200 to 300 micrograms	✓	×	×
Fostair	200 micrograms	Over age 18	×	×
Budesonide				
Turbohaler	400 micrograms	✓	✓	×
Metered dose inhaler		✓	✓	Over age 2
Easyhaler		✓	Over age 6	×
Novolizer		✓	Over age 6	×
Symbicort		✓	Over age 6	×
Symbicort (regular and as required dosing)		Over age 18	×	×
Fluticasone				
Metered dose inhaler (HFA)	200 micrograms	✓	✓	Over age 4
Accuhaler		✓	✓	Over age 4
Seretide HFA		✓	✓	Over age 4
Seretide (Accuhaler)		✓	✓	Over age 4
Mometasone	200 micrograms	✓	×	×
Ciclesonide	200 to 300 micrograms	✓	×	×

Systemic Glucocorticoids

- Mode of administration
  - Oral
  - Parenteral
- Mechanisms of action
  - Same as for inhaled Glucocorticoids however systemic Glucocorticoids may reach different target cells than inhaled drugs
- Role in therapy
  - Long-term oral Glucocorticoids therapy (daily or alternate-day) may be required to control severe persistent asthma.

Systemic Glucocorticoids

- Side effects
  - Osteoporosis
  - Arterial hypertension
  - Diabetes
  - Hypothalamic-pituitary axis suppression
  - Cataracts
  - Glaucoma
  - Obesity
  - Skin thinning leading to cutaneous striae
  - Easy bruising
  - Muscle weakness
  - Fatal herpes virus infections have been reported among patients who are exposed to these viruses when they are taking systemic Glucocorticoids

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Zileuton

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Zafirlukast, Montelukast

5. COX-2 INHIBITORS: Valdecoxib

6. PDE4 ENZYME INHIBITORS

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7. MONOCLONAL ANTIBODIES

Omalizumab (anti-IgE)

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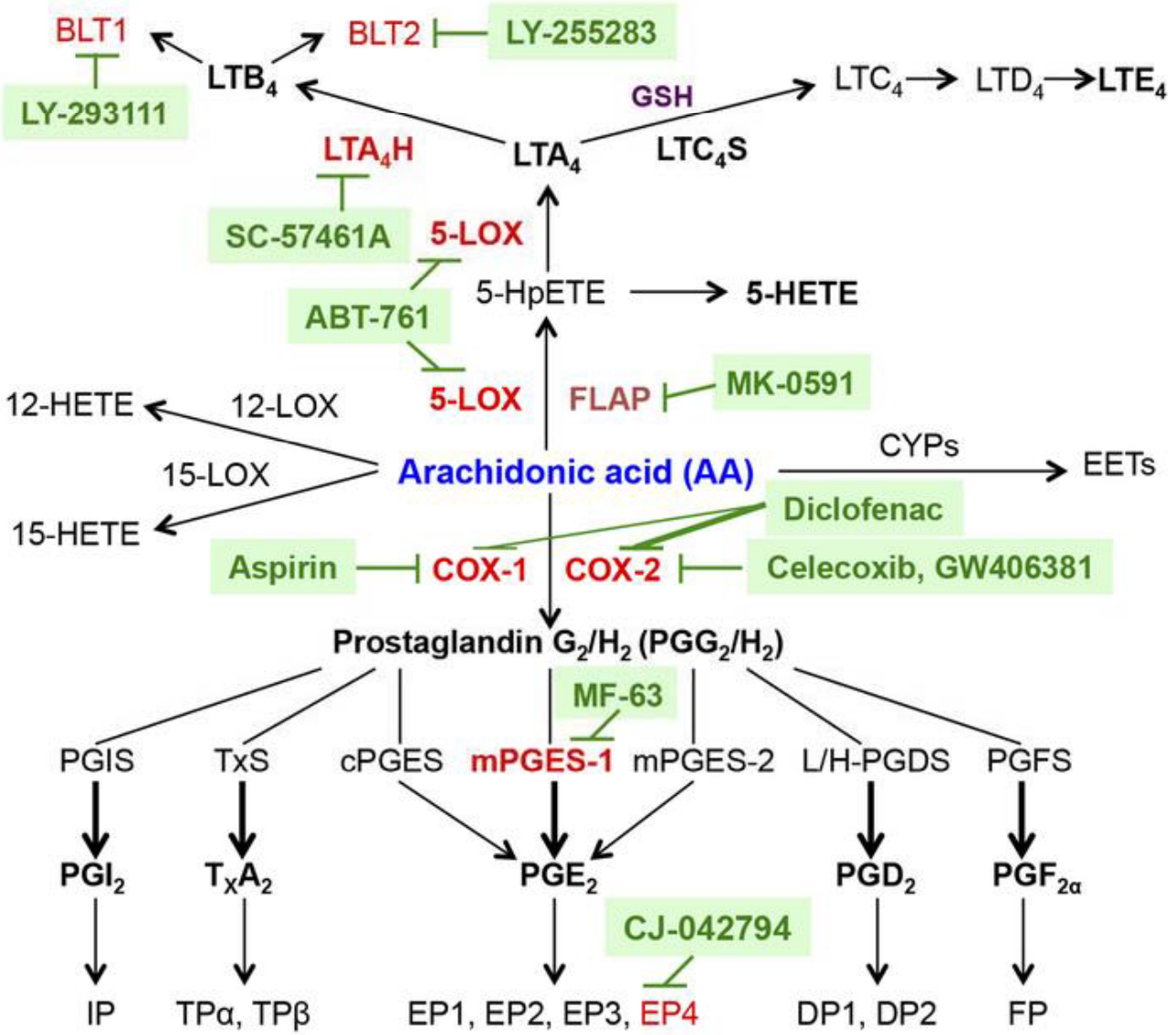
ET1 RECEPTOR ANTAGONISTS

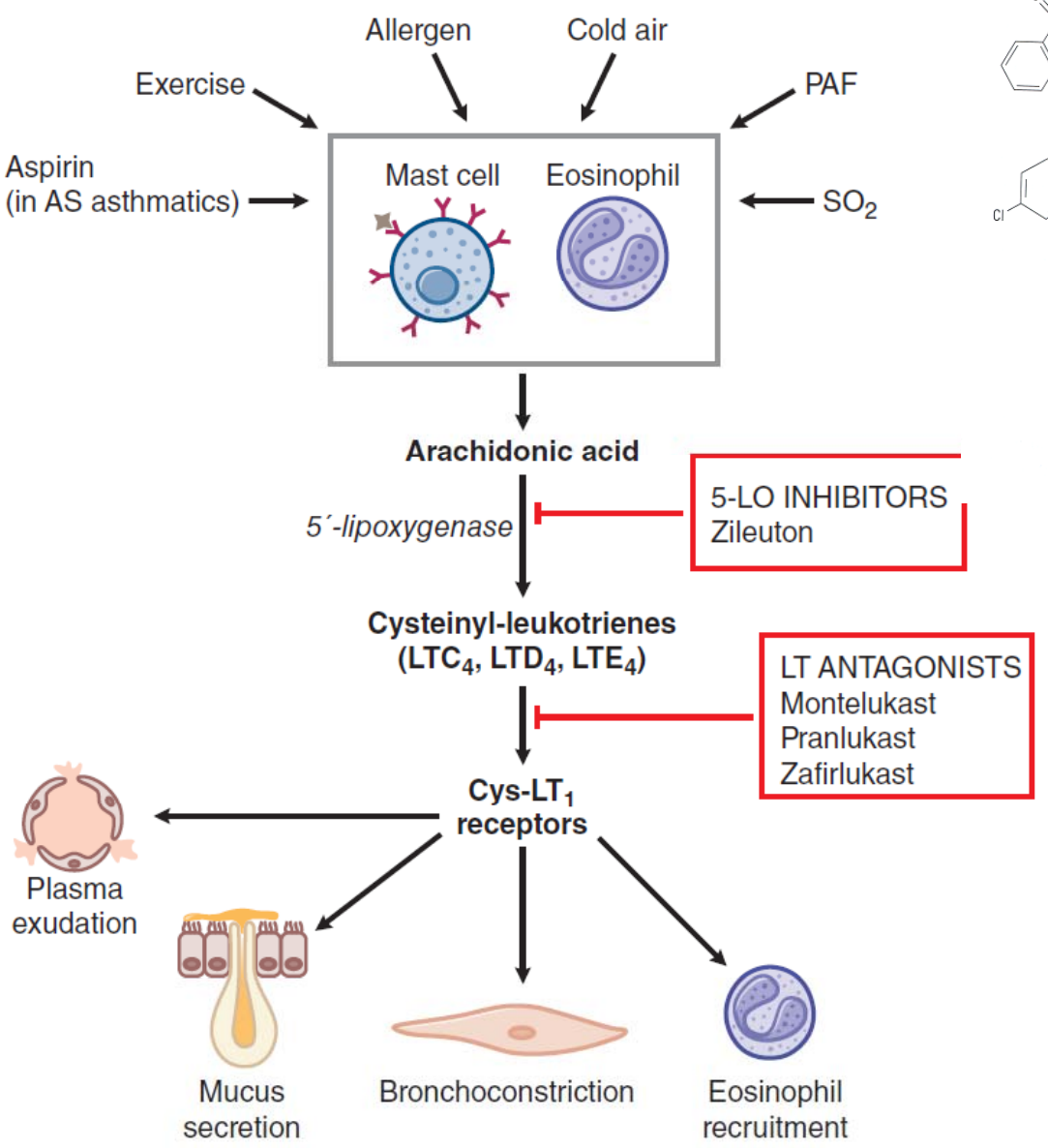
TACHYKININ (NK1/NK2) RECEPTOR ANTAGONISTS

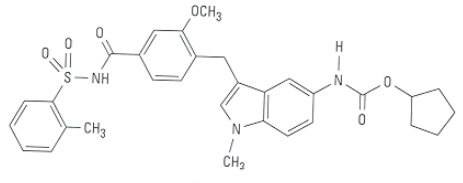
ANTISENSE OLOGONUCLEOTIDES against NF-kB, MBP, IL-4, IL-5, A1 ADENOSINE RECEPTORS

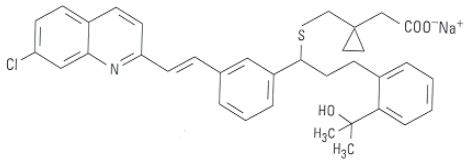
Lipoxigenase pathway

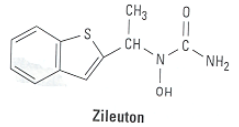


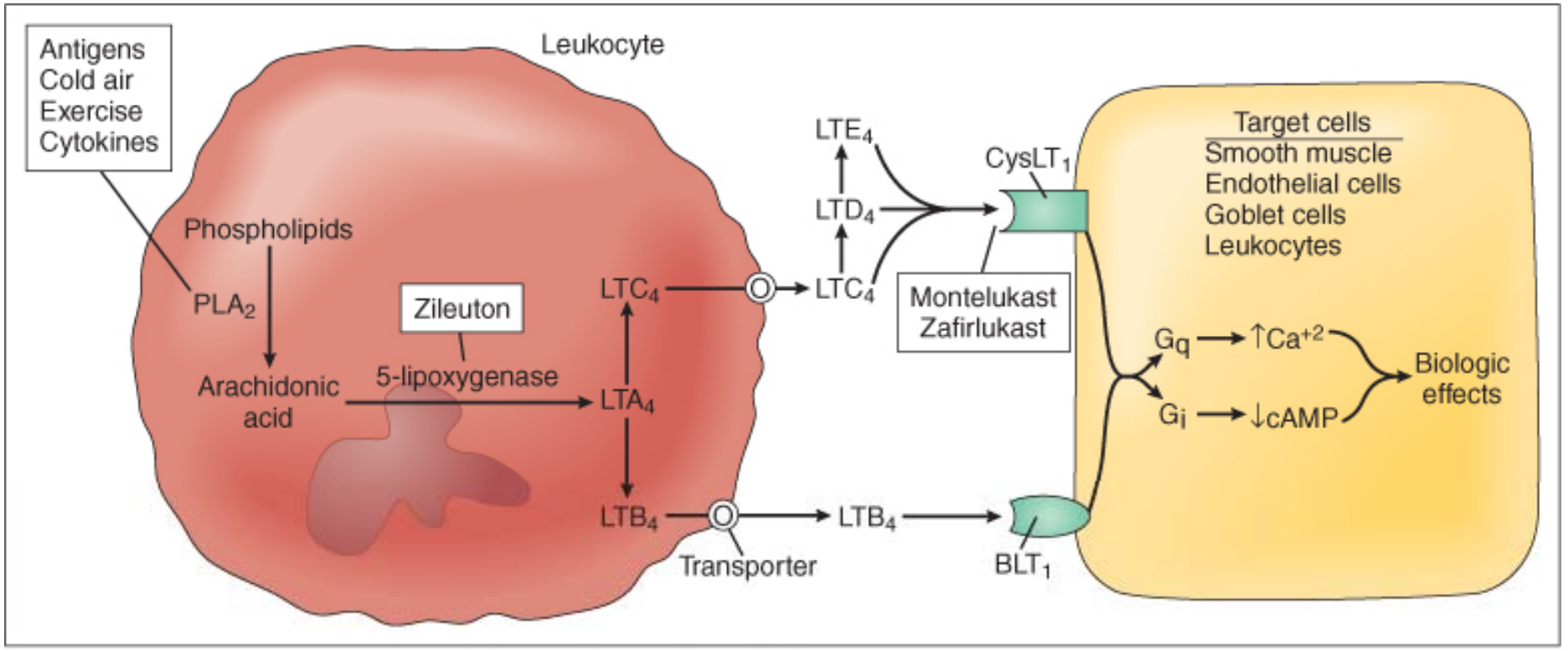
Effects of cysteinyl-LTs on the airways and their inhibition by anti-LTs. AS, aspirin sensitive.




Zafirlukast


Montelukast


Zileuton



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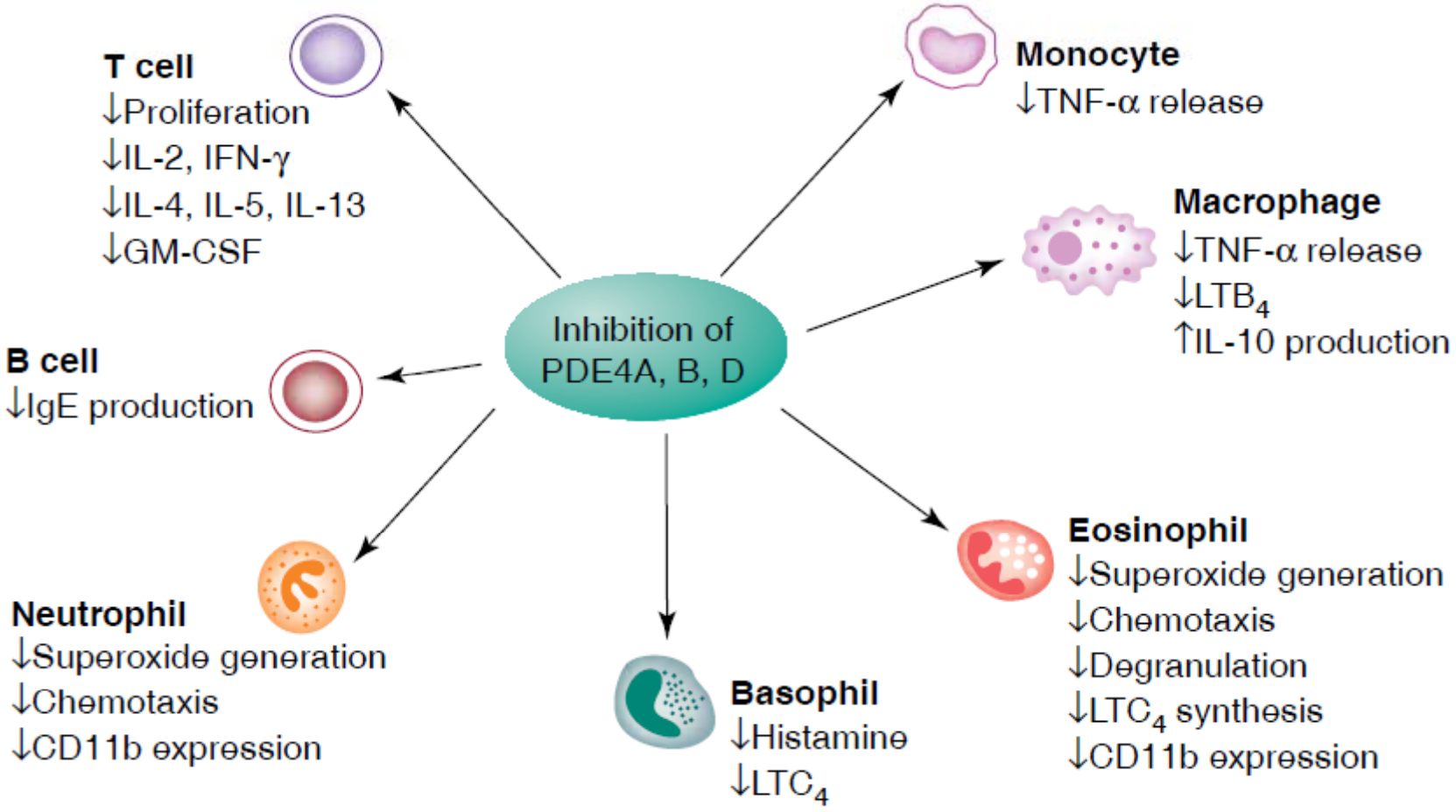

Roflumilast in COPD

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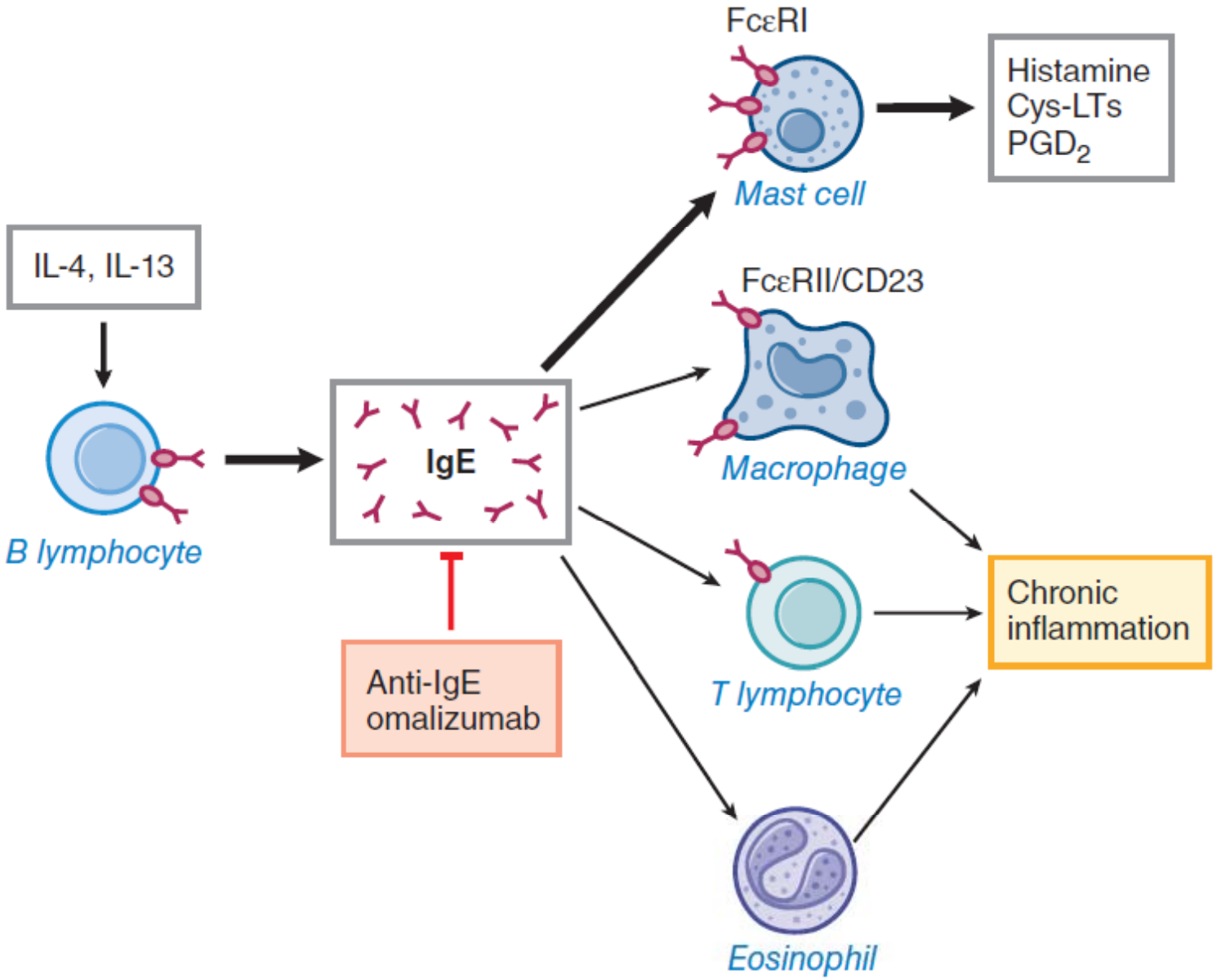

FcεRI
Histamine
Cys-LTs
PGD_2
Mast cell
IL-4, IL-13
FcεRII/CD23
IgE
Macrophage
B lymphocyte
Chronic
inflammation
T lymphocyte
Anti-IgE
omalizumab
Eosinophil

Anti-IgE Antibodies

- Agents directed at diminishing the production of IgE through effects on interleukin 4 or on IgE itself have been evaluated
  - Soluble recombinant IL-4 receptor that can be delivered by aerosol
  - Recombinant human monoclonal antibody that forms complexes with free IgE (rhuMAb or omalizumab blocks the interaction of IgE with mast cells and basophils.
    - Attenuates the early-phase and late phase airway obstruction response to allergen and suppressed the accumulation of eosinophils in the airways

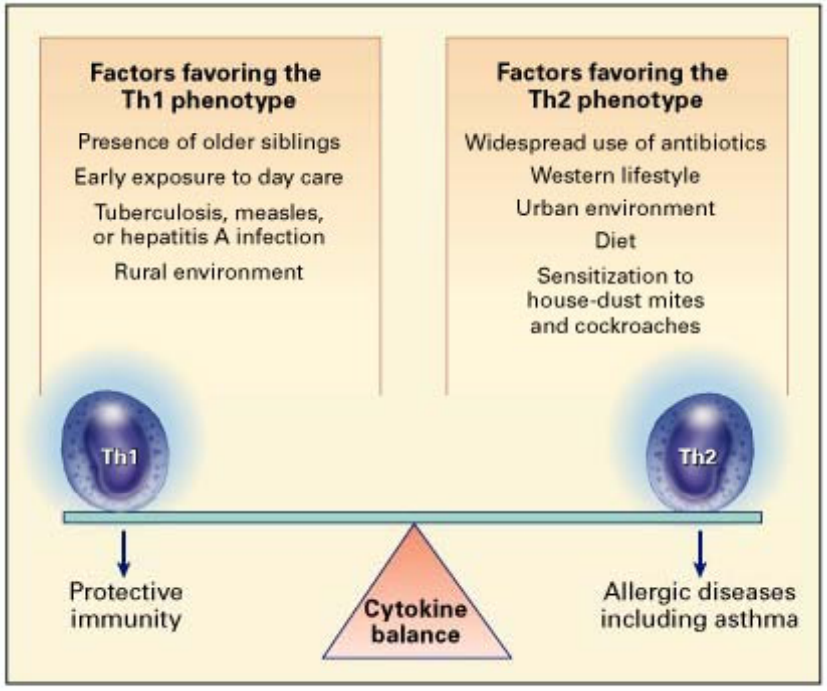
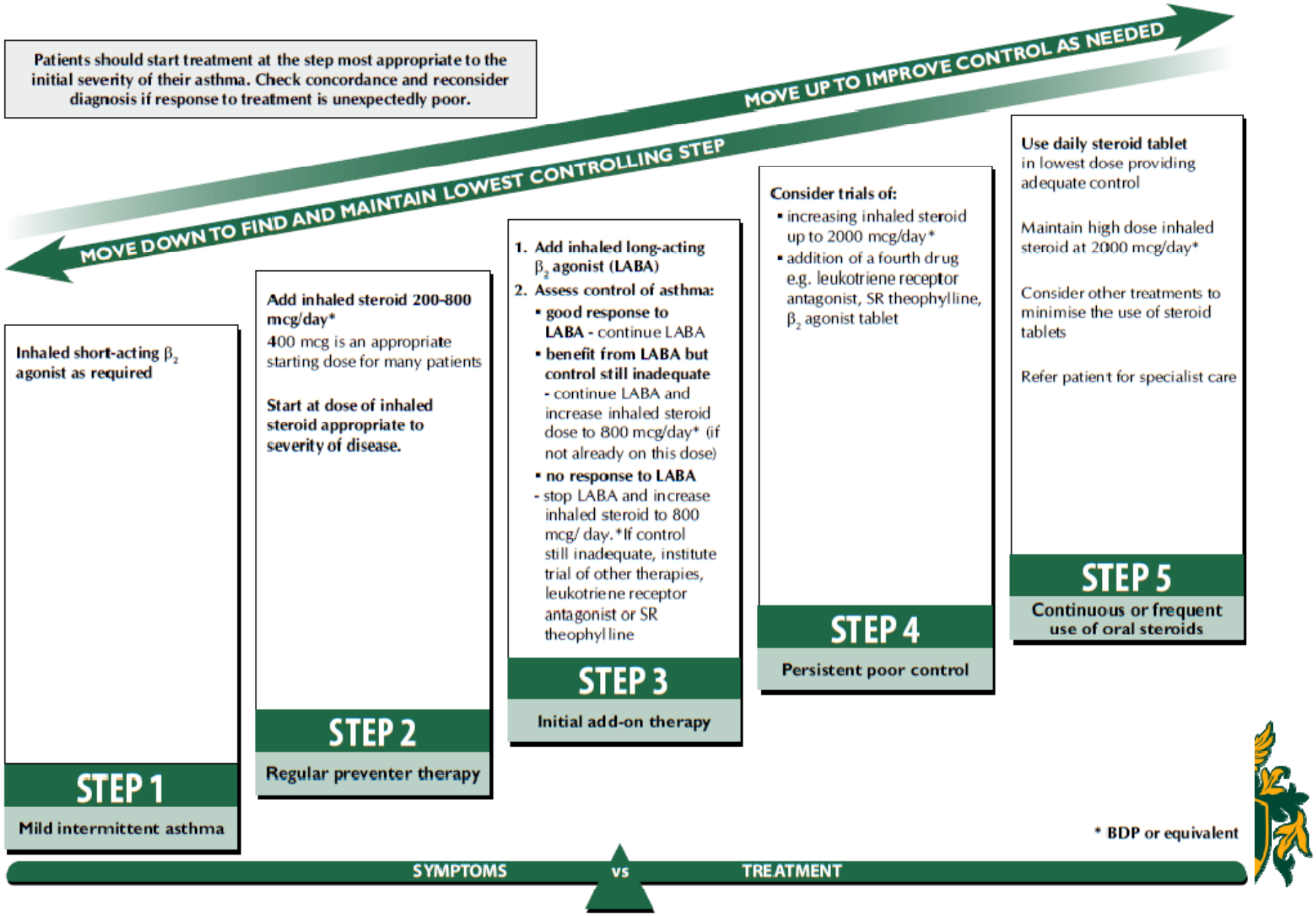


Table 27-1. Relative Efficacy of Anti-inflammatory Drugs, Bronchodilators, and Miscellaneous Agents in the Management of Respiratory Tract Disorders*

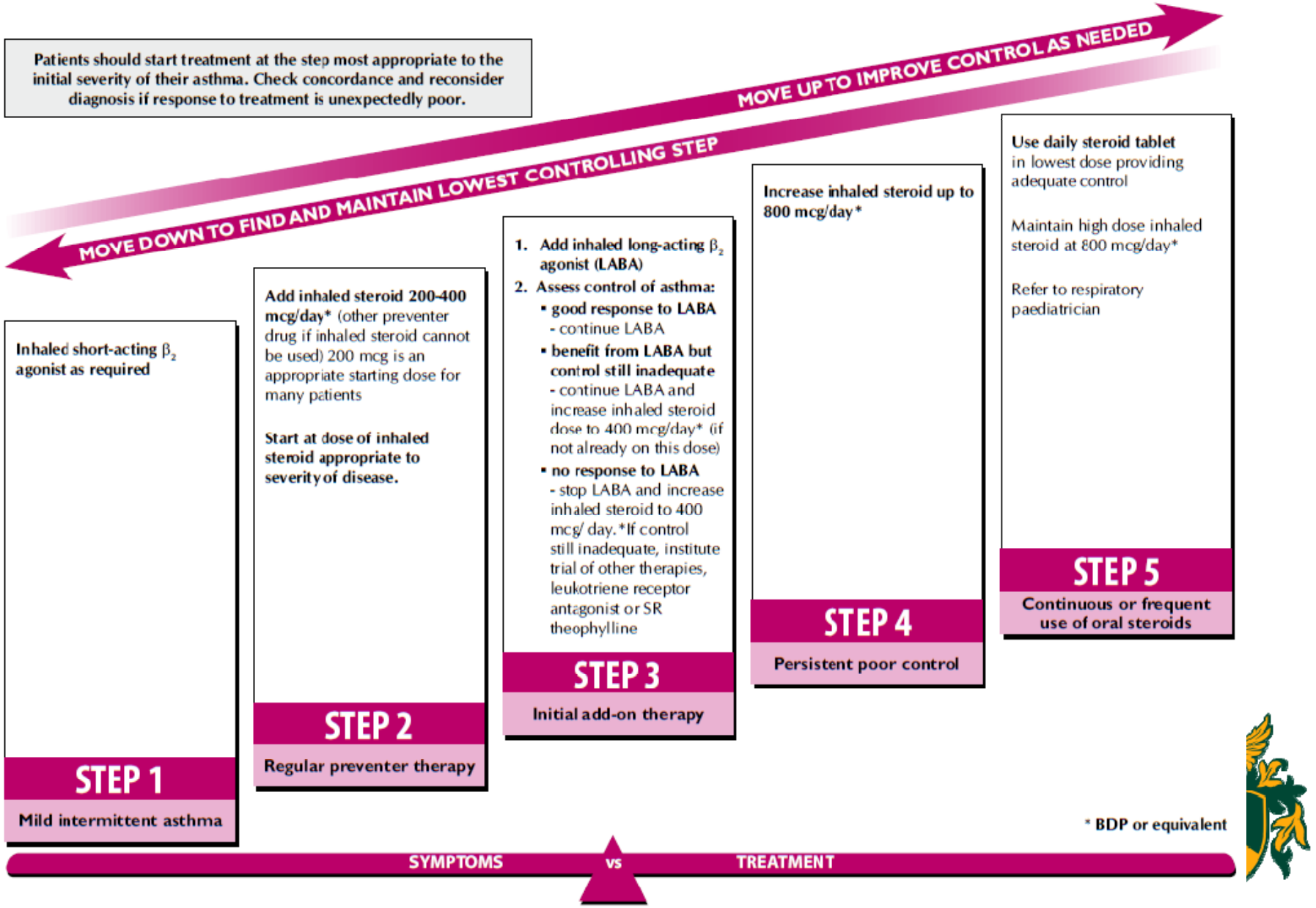
Drug	Asthma	COPD	Allergic Rhinitis	Viral Rhinitis
Anti-inflammatory Drugs				
Glucocorticoids	++++	0 to ++	++++	0
Mast cell stabilizers	+++	0 to ++	+++	0
Leukotriene inhibitors	+++	0 to +	Unknown	0
Bronchodilators				
Selective β_2-adrenoceptor	++++	++	0	0
agonists				
Other bronchodilators				
- Ipratropium	+	+++	++	++
- Theophylline	++ to +++	++ to +++	0	0
Miscellaneous Agents				
Analgesics	0	0	0	+++
Antihistamines	0 to ++	0	++++	+
Decongestants	0 to ++	0 to ++	+++	+++

*Ratings range from 0 (not efficacious) to ++++ (highly efficacious).
COPD = chronic obstructive pulmonary disease (e.g., emphysema).

Stepwise management in adults



Stepwise management in children



Stepwise management in children less than 5 years