

AUTACOIDS

(LOCAL HORMONES)

Lecture -2

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Autacoids

- **Amines:**

- Histamine
- 5-Hydroxytryptamine

- **Peptide:**

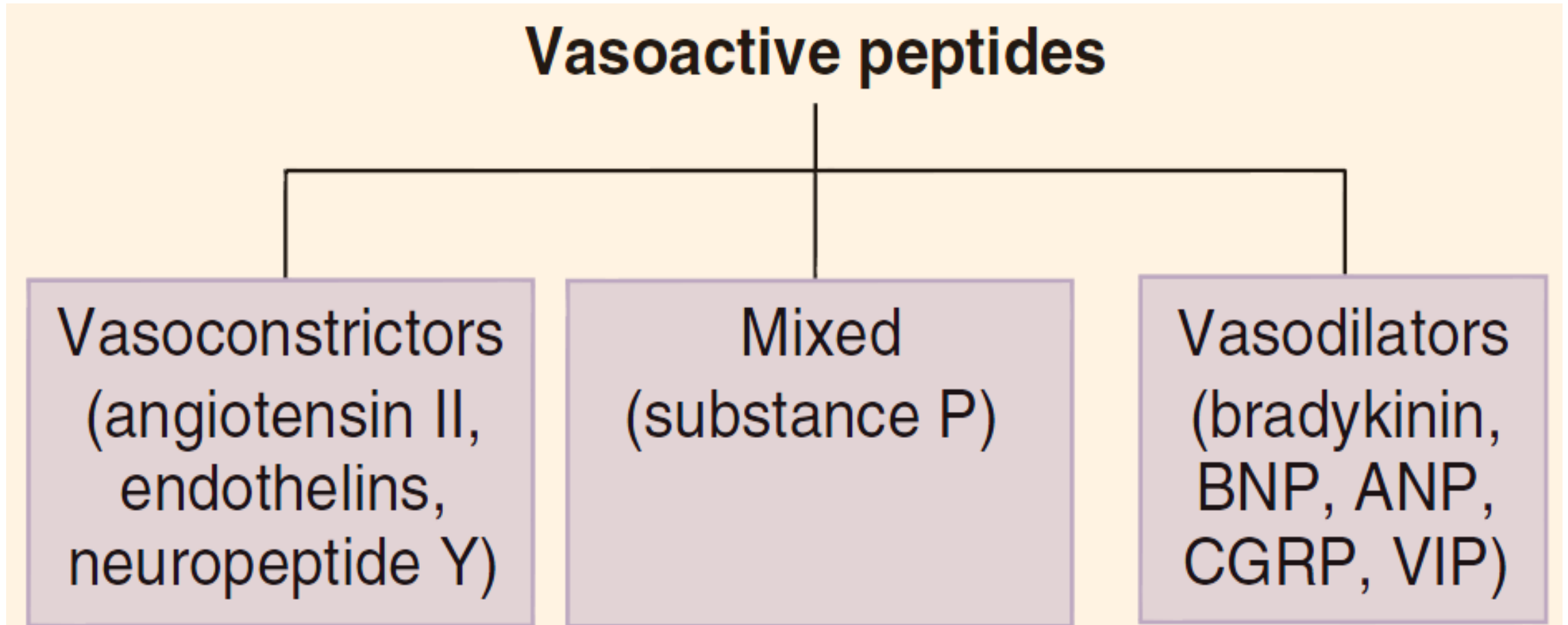
- Bradykinin
- Angiotensin

- **Lipids:**

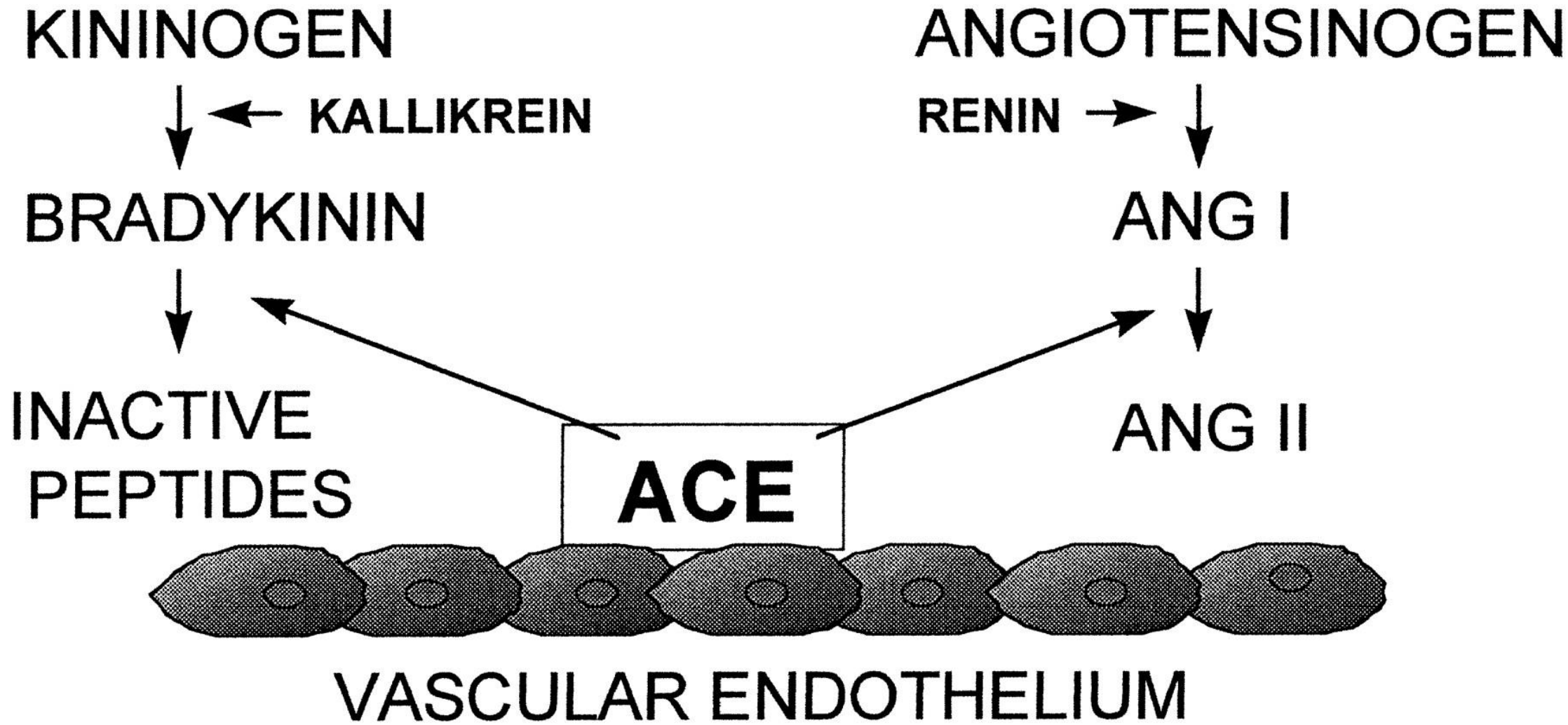
- Leukotriens
- Prostaglandins

Vasoactive Peptides

Vasoactive peptides are autacoids with significant actions on **vascular smooth muscle** as well as other tissues.



Bradykinin - Source and Disposition



Bradykinin - Source and Disposition

Bradykinin

- **Vasodilator**
- **Produced from kininogen by a family of enzymes, the kallikreins**
- **Bradykinin is rapidly degraded by ACE**

Bradykinin acts through at least 2 receptors (**B1 and B2**)

Causes the production of cAMP, nitric oxide and prostaglandins

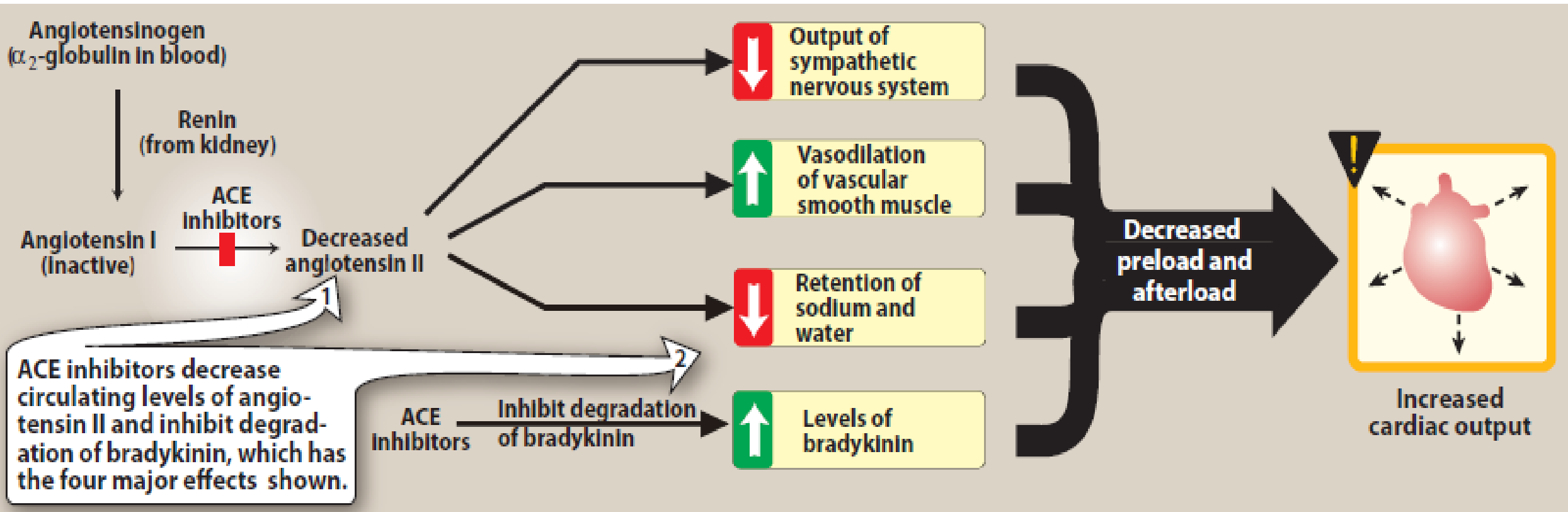
Involves in [inflammation and causes edema and pain](#)

Plays a role in the antihypertensive action of ACE inhibitors and in hereditary angioedema.

Ecallantide (parenteral kallikrein inhibitor) and **icatibant** (oral bradykinin B2-receptor antagonist), are approved for use in **angioedema**.



Bradykinin



NATRIURETIC PEPTIDES



Atrial natriuretic peptide (ANP)

Brain natriuretic peptide (BNP)

They act as:

- Vasodilators
- Natriuretic (sodium excretion-enhancing) agents
- Decrease proximal tubular sodium reabsorption
- Inhibit renin, ANGII and aldosterone.

Nesiritide (BNP)

- Approved for IV administration in acute severe heart failure
- But has very significant toxicity

ENDOTHELINS



Vasoconstrictors/ more potent than norepinephrine

Formed in and released by endothelial cells in blood vessels

Three endothelin peptides (**ET-1**, **ET-2**, and **ET-3**)

Two receptors, **ETA** and **ETB**, have been identified

Stimulate the heart, increase natriuretic peptide release

Bosentan and ambrisentan

- ✓ ETA antagonists
- ✓ Treatment of pulmonary hypertension

Neurokinins

substance P, neurokinin A, and neurokinin B

Act at NK1 and NK2 receptors in the CNS and the periphery

Dilate arterioles,

Contract veins and intestinal and bronchial smooth muscle, cause diuresis

Transmitter in sensory pain neurons

Capsaicin

Component of chili peppers

Releases **substance P** from its stores in nerve endings and **depletes the peptide**

Approved for topical use on **arthritic joints and for neuralgia.**

Aprepitant (oral antagonist at NK1 receptors)

Approved for use in **chemotherapy-induced** nausea and vomiting

Some vasoactive peptides and their Properties

Calcitonin gene-related peptide (CGRP)

An extremely potent **vasodilator**; causes hypotension and reflex tachycardia

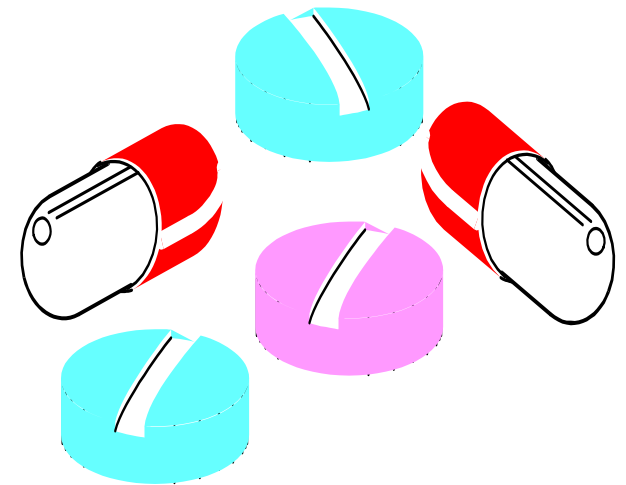
Neuropeptide Y

Causes **vasoconstriction** and stimulates the heart.

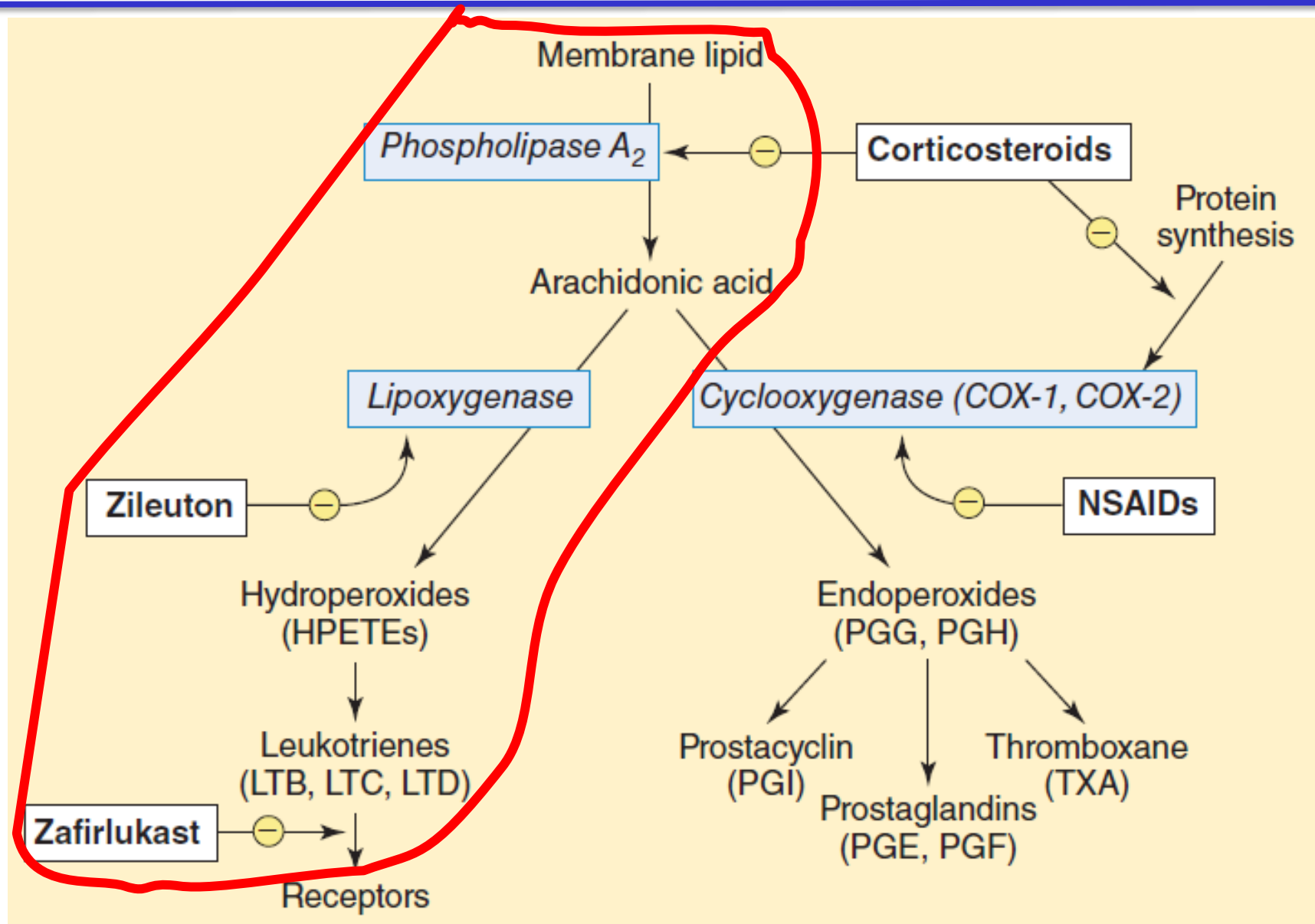
Vasoactive intestinal peptide (VIP)

↑ cAMP via G protein-coupled receptors VPAC1 and VPAC2.

Dilates vessels, relaxes bronchi and intestinal smooth muscle



Lipids/ Leukotrienes



Lipids/ Leukotriens

Leukotrienes (LT) B₄ and the cysteinyl leukotrienes, LTC₄, LTD₄, and LTE₄, are products of the 5-lipoxygenase pathway of arachidonic acid metabolism

5-Lipoxygenase is found in cells such as mast cells, basophils, eosinophils, and neutrophils

Pharmacologic effects

Potent vasoconstrictor

Potent bronchoconstrictor

↑ permeability of venules

↑ mucus secretion

potent chemoattractant for neutrophils and eosinophils

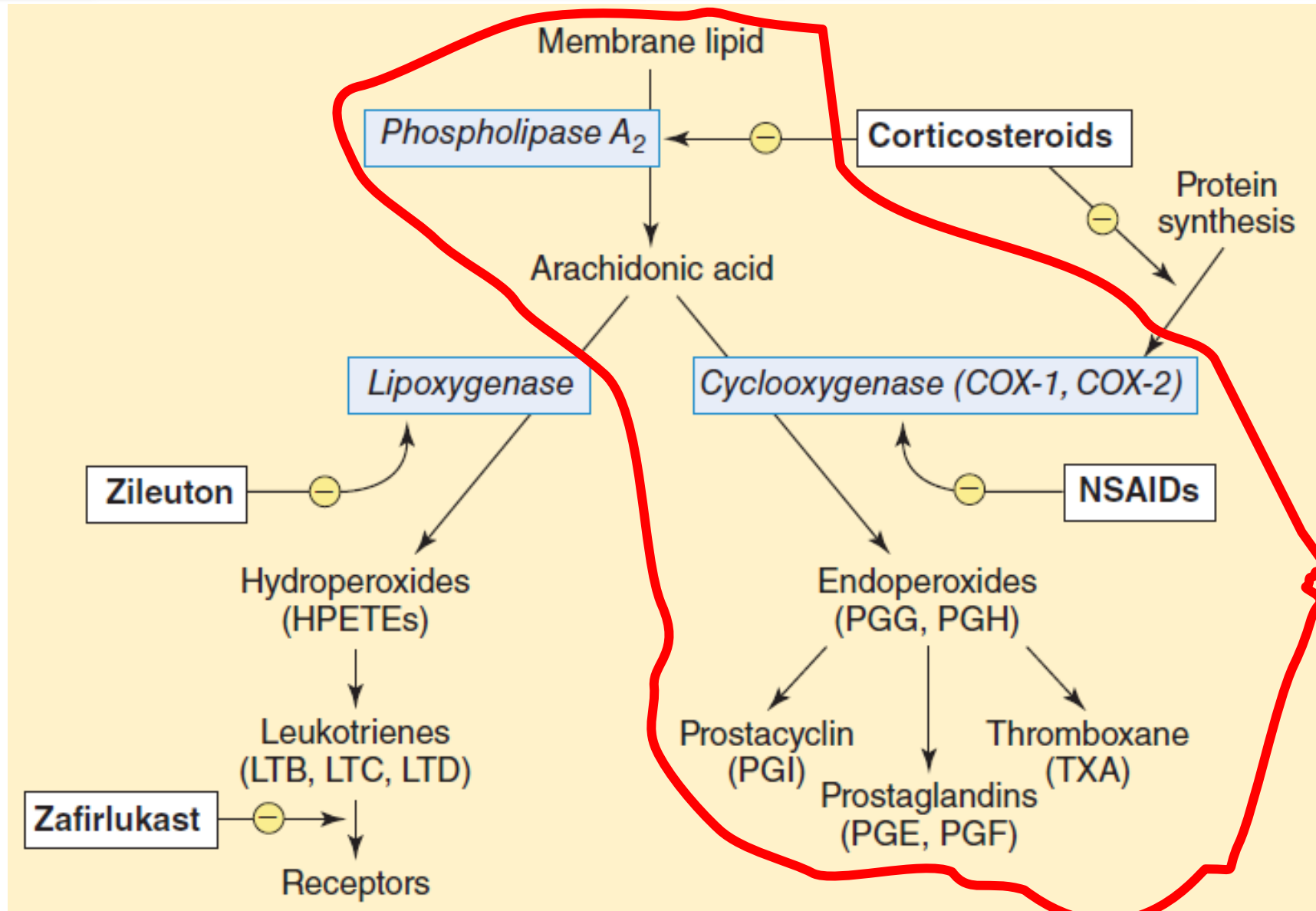
Zileuton - selective inhibitor of 5-lipoxygenase, preventing the formation of both LTB₄ and the cysteinyl leukotrienes

Zafirlukast and **montelukast** are selective antagonists of the cysteinyl leukotriene-1 receptor, they block the effects of cysteinyl leukotrienes

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Lipids/ Eicosanoid



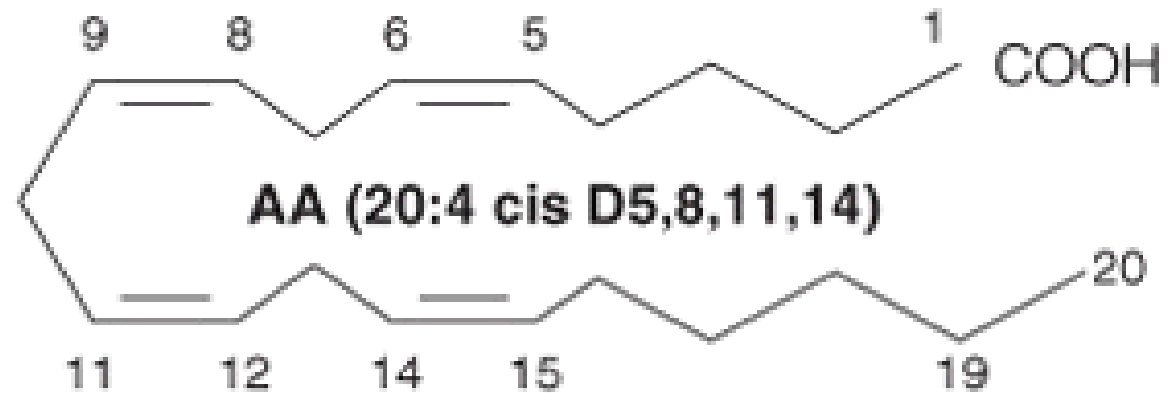
Lipids/ Eicosanoid

The principal eicosanoid subgroups are:

- Leukotrienes
- Prostaglandins
- Prostacyclin
- Thromboxane

Main sites of eicosanoid biosynthesis

- Endothelial cells
- Leukocytes
- Platelets
- Kidney



**Eicosanoid “eicosa”
compounds containing a 20-carbon core**

- **Unlike histamine, eicosanoids are NOT synthesized in advance and stored in granules – when needed, they can be produced very quickly from arachidonate released from membranes**

Eicosanoid / Main steps of eicosanoid biosynthesis

- 1) Variety of stimuli (eg, physical injury, immune reactions) activate **phospholipase A2**
- 2) Release of **arachidonic acid** from membrane phospholipase A2
- 3) **Eicosanoid synthesis:** Arachidonic acid is then metabolized by **lipoyxygenase**, which results in straight-chain leukotrienes, and **cyclooxygenase (COX)**, which results in cyclization to prostacyclin, prostaglandins, or thromboxane.

Eicosanoid/ Synthesis

COX exists in at least 2 forms. COX-1 is found in many tissues; the prostaglandins produced by COX-1 appear to be important for a variety of normal physiologic processes

Gastric cytoprotection

Vascular homeostasis

Platelet aggregation

Control of several reproductive functions, such as the induction of labor

Kidney functions

In contrast, COX-2 is found primarily in inflammatory cells; the products of its actions play a major role in tissue injury (eg, inflammation and chronic disease).

- **Thromboxane is preferentially synthesized in platelets, whereas prostacyclin is synthesized in the endothelial cells of vessels.**

Eicosanoid / Actions

Effects of some important eicosanoids.

Effect	PGE ₂	PGF _{2α}	PGI ₂	TXA ₂	LTB ₄	LTC ₄	LTD ₄
Vascular tone	↓	↑ or ↓	↓↓	↑↑↑	?	↑ or ↓	↑ or ↓
Bronchial tone	↓↓	↑↑	↓	↑↑↑	?	↑↑↑↑	↑↑↑↑
Uterine tone	↑, ↓ ^a	↑↑↑	↓	↑↑	?	?	?
Platelet aggregation	↑ or ↓		↓↓↓	↑↑↑	?	?	?
Leukocyte chemotaxis	?	?	?	?	↑↑↑↑	↑↑	↑↑

^aLow concentrations cause contraction; higher concentrations cause relaxation.

?, unknown effect.

Eicosanoid/ Therapeutic uses

Alprostadil

PGE1 that is naturally produced in tissues

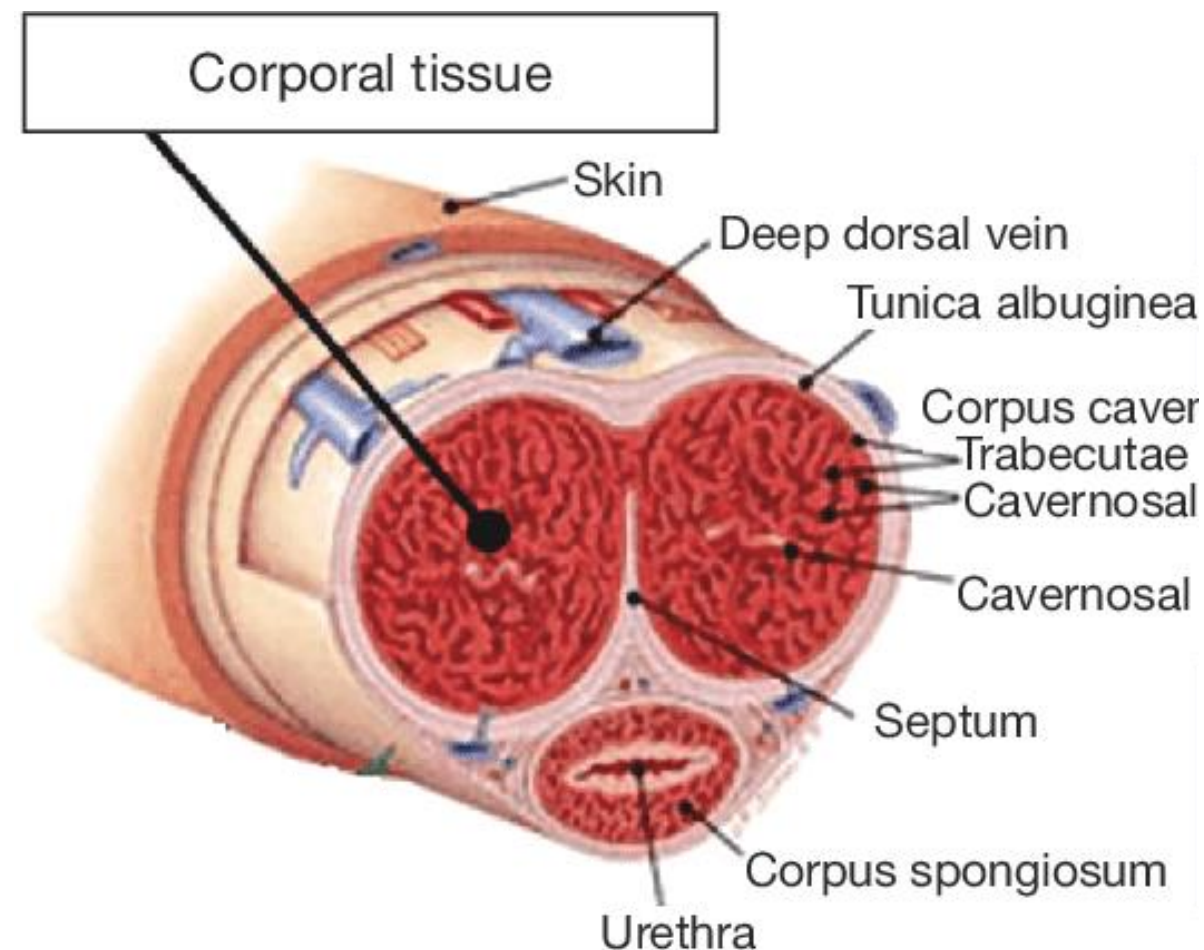
- Seminal vesicles
- Cavernous tissues
- Placenta,
- Ductus arteriosus of the fetus.

Therapeutically,

Used to treat erectile dysfunction

keep the ductus arteriosus open in neonates with congenital heart conditions until surgery is possible.

PGE1 maintains the patency of the ductus arteriosus during pregnancy. The ductus closes soon after delivery to allow normal blood circulation between the lungs and the heart. Infusion of the drug maintains the ductus open as it naturally occurs during pregnancy, allowing time until surgical correction is possible



Eicosanoid/ Therapeutic uses

Lubiprostone (PGE1 derivative)

- Chronic idiopathic constipation
- Opioid-induced constipation
- Irritable bowel syndrome with constipation.

MoA,

It stimulates chloride channels in the luminal cells of the intestinal epithelium, thereby increasing intestinal fluid secretion .

S/E

Nausea and diarrhea (most common)
Decreased if taken with food.



Nausea



Diarrhea

Eicosanoid/ Therapeutic uses

Misoprostol (PGE1 analog)

MoA

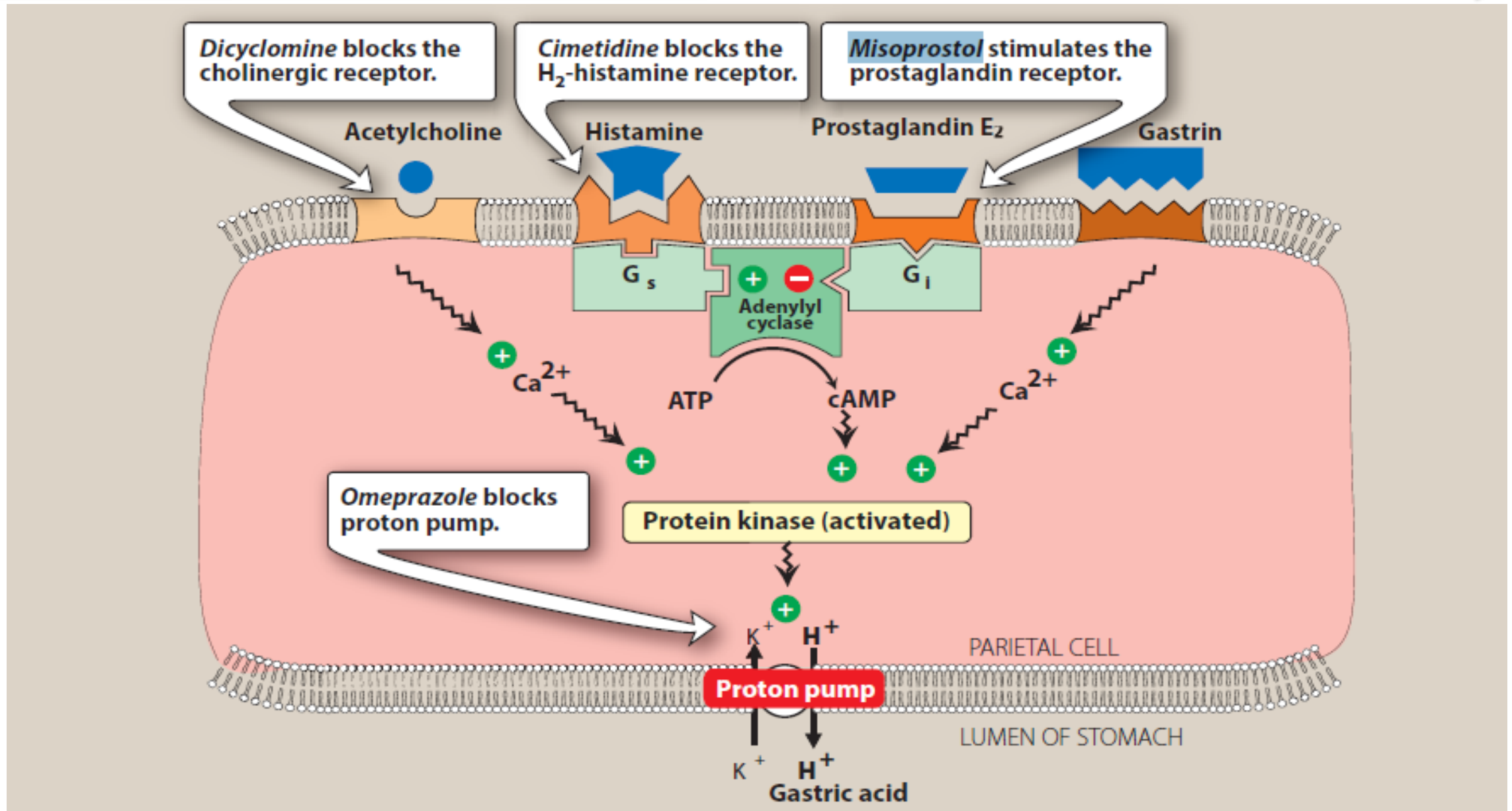
- Interacts with PGE receptors on parietal cells within the stomach, reducing gastric acid secretion
- GI cytoprotective effect by stimulating mucus and bicarbonate production
- Used for labor induction, since it increases uterine contractions by interacting with prostaglandin receptors in the uterus

Use: to protect the mucosal lining of the stomach during chronic NSAID treatment
Labour induction

Contraindication: pregnancy (potential risk to induce abortion)

SE- diarrhea and abdominal pain

Eicosanoid/ Therapeutic uses



Eicosanoid/ Therapeutic uses

Prostaglandin F_{2α} analogs (Bimatoprost, latanoprost, tafluprost and travoprost)

MoA,

Increase uveoscleral outflow reducing intraocular pressure

Use: open-angle glaucoma (ophthalmic solutions)

✓ as effective as timolol in reducing intraocular pressure

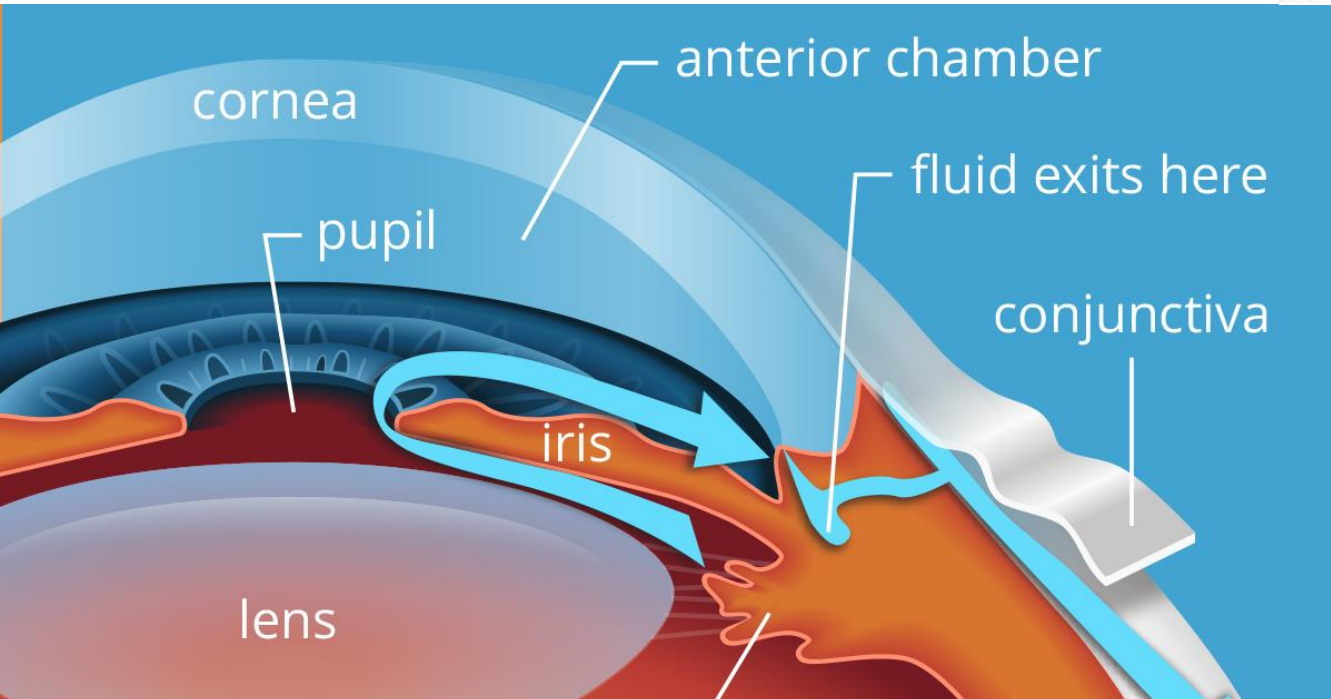
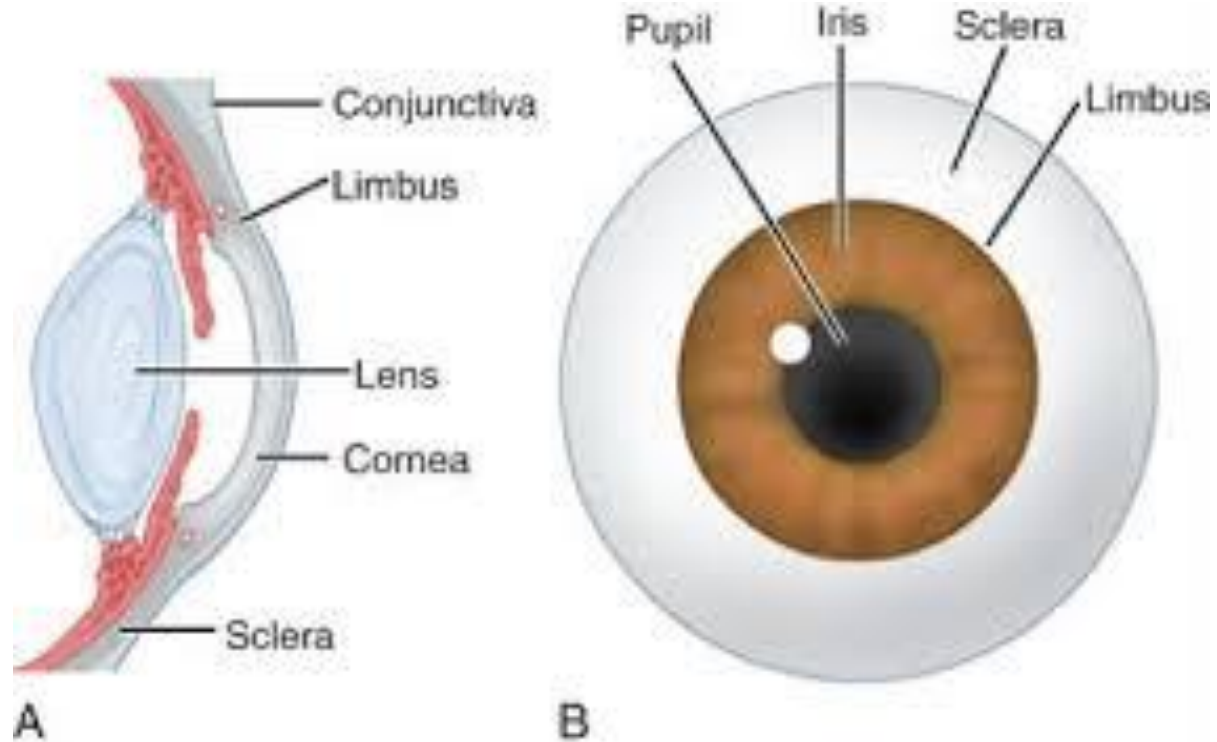
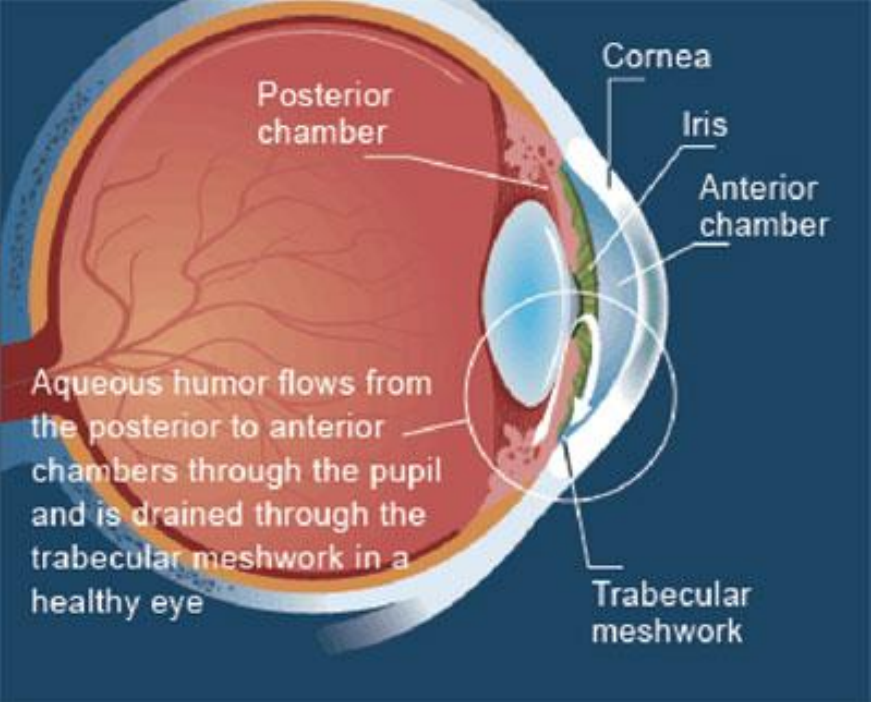
Bimatoprost

✓ Increases **eyelash** prominence, length, and darkness

✓ Approved for the treatment of **eyelash hypotrichosis**

✓ SE- Ocular reactions include blurred vision, iris color change (increased brown pigmentation), increased number and pigment of eyelashes, ocular irritation, and foreign body sensation.





Eicosanoid/ Therapeutic uses

Prostacyclin (PGI₂) analogs

Epoprostenol - the pharmaceutical form of naturally occurring prostacyclin (IV infusion)

Treprostinil - the **synthetic** analogs of prostacyclin (**orally** or via inhalation or SC infusion)

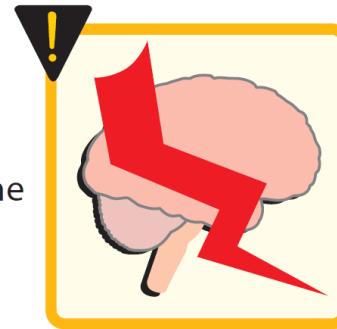
Potent pulmonary vasodilators (treatment of pulmonary arterial hypertension)

SE- Dizziness, headache, flushing, and fainting

Iloprost

- Inhaled
- Requires frequent dosing (short half-life)
- **SE-** Bronchospasm and cough (occur after inhalation)

Headache



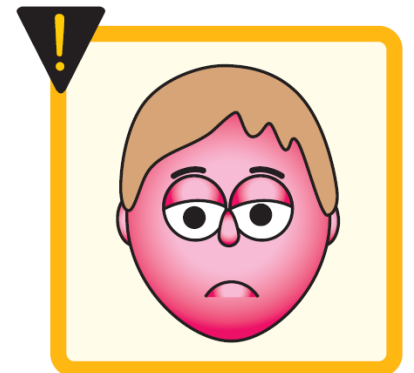
Dizziness



Fainting



Flushing



Iloprost SE