

AUTOCOIDS

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Definition

The term is derived from 'GREEK'

- Autos = self
- Akos = healing substance

or

Remedy or some times called Local
Hormones

Classification of autacoids

Amine Autacoids:

1. Histamine
2. Serotonin or 5-HT

Eicosanoids:

- 1.PGs
- 2.Thromboxane
- 3.Leukotriens

Peptides Autacoids:

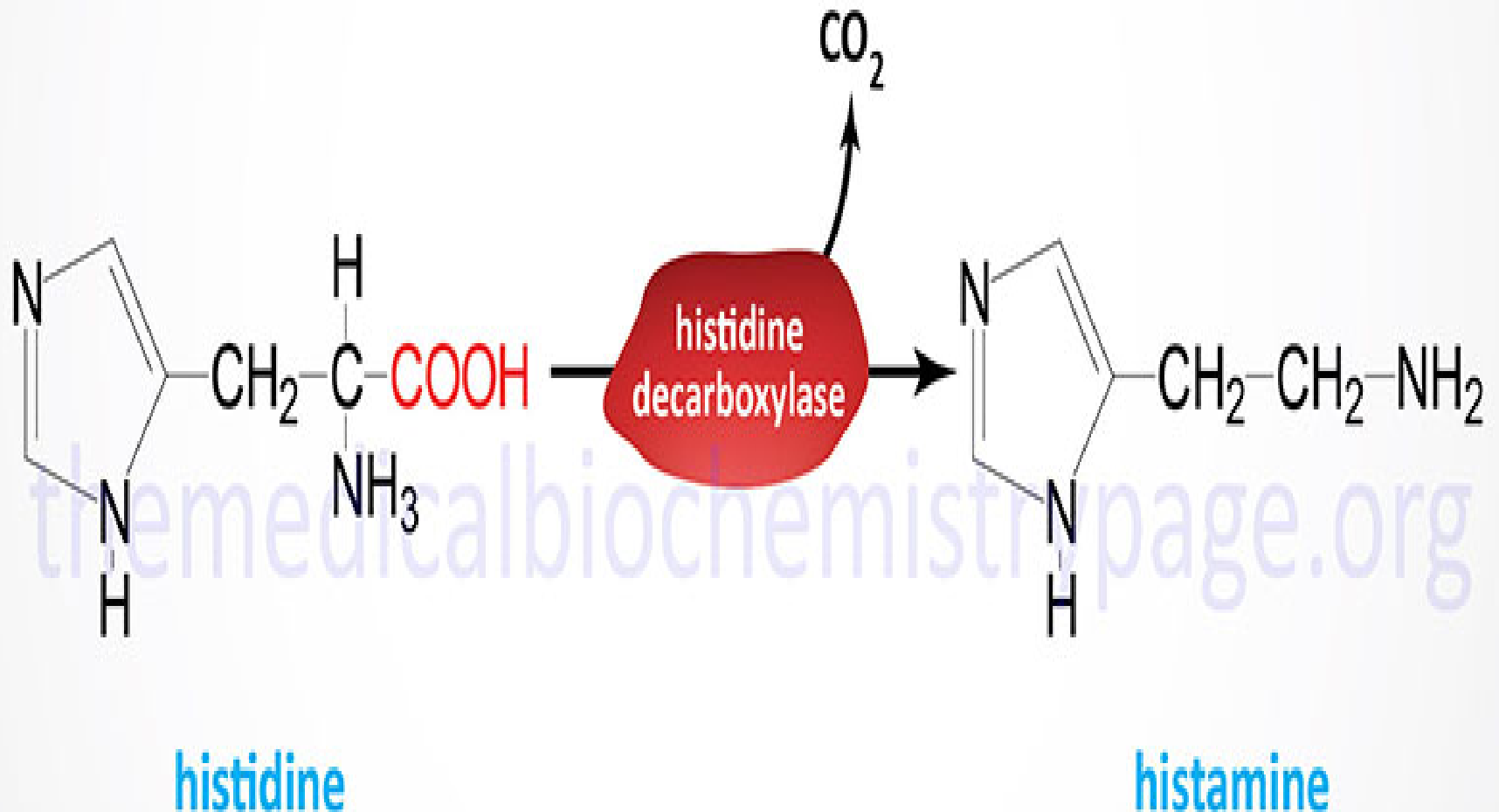
- 1).Kinins (bradykinin, kallidin)
- 2).Renin; Angiotensins etc

AMINE AUTOCOIDS

Histamine

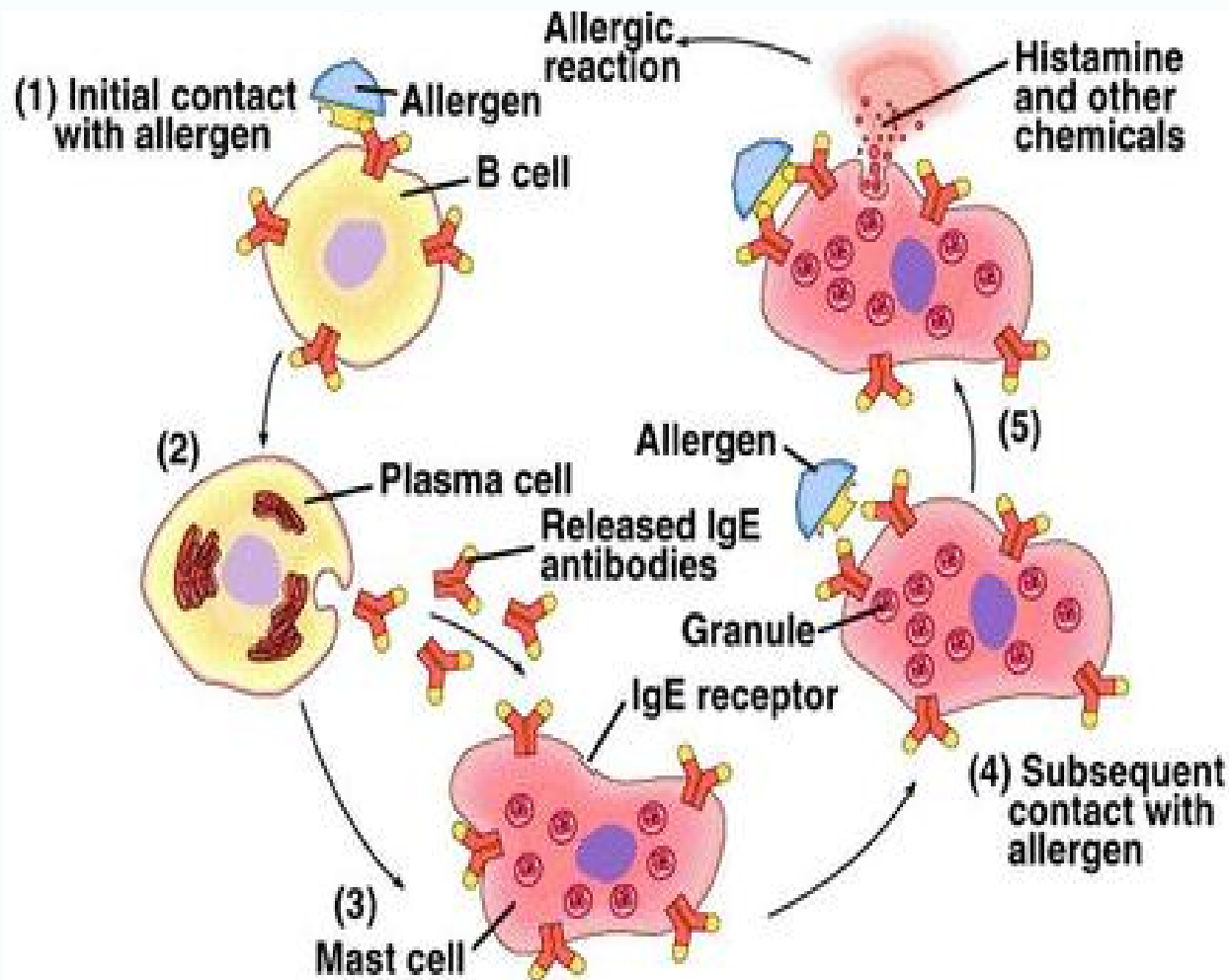
- Imidazole ethylamine
- Formed from the amino acid Histamine
- Important inflammatory mediator
- Potent biogenic amine and plays an important role in inflammation, anaphylaxis, allergies, gastric acid secretion and drug reaction
- As part of an immune response to foreign pathogens, its produced by Basophils and mast cells found in nearby connective tissues.

Synthesis of histamine



Mechanism of Release

- Histamine is released from storage granules as a result of the interaction of antigen with immunoglobulin E (IgE) antibodies

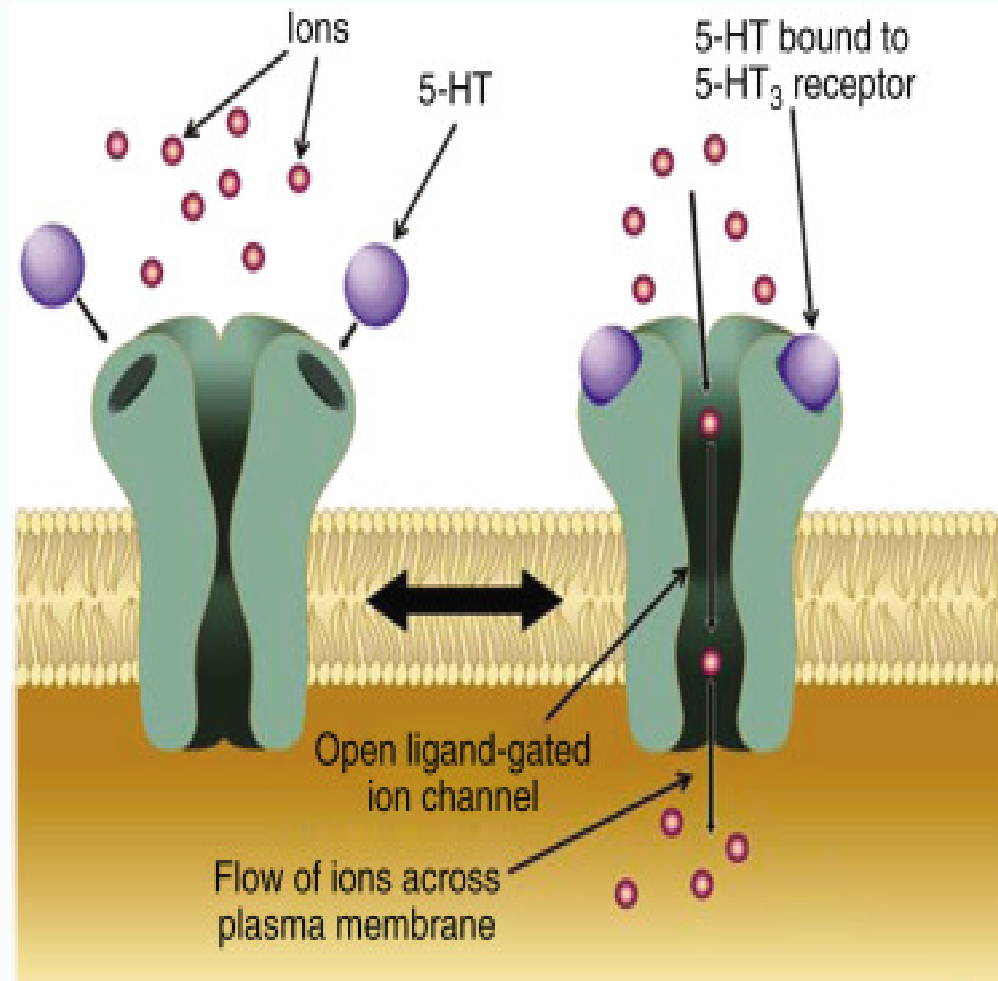


Adverse effects of Histamine release

- Itching
- Urticaria
- Flushing
- Hypotension
- Tachycardia
- Bronchospasm
- Angioedema
- Wakefulness
- Increased acidity (Gastric acid secretion)

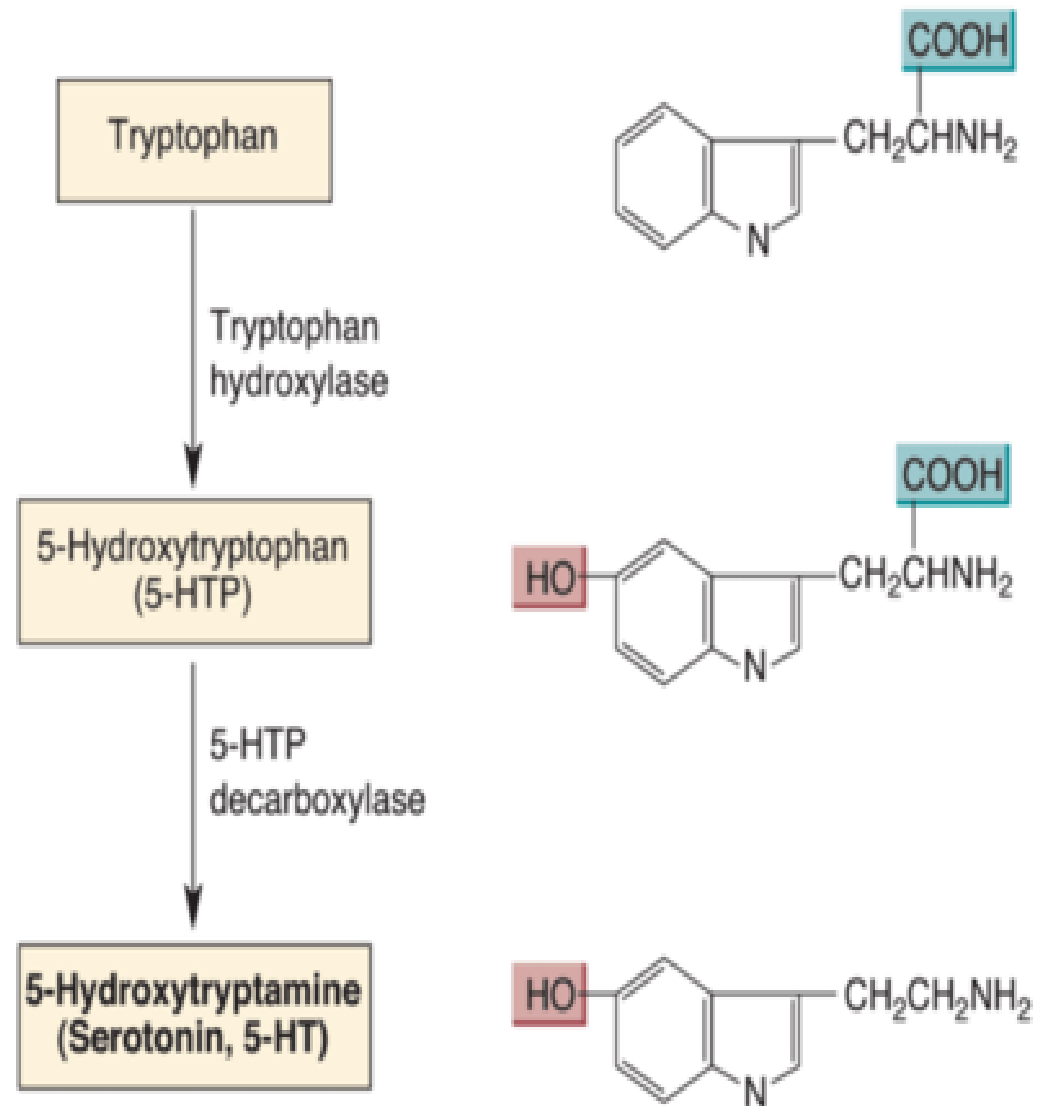
Serotonin or 5-Hydroxytryptamine (5-HT)

- It is a neurotransmitter found in enterochromaffin cells in GIT (90%) , and in plateletes and in raphe nuclei of brain stem.
- The remainder is synthesized in serotonergic neurons of the CNS, where it has various functions including the



Synthesis

- Serotonin is synthesized from the amino acid L-tryptophan by a short metabolic pathway consisting of two enzymes:
- Tryptophan hydroxylase (TPH)
- Amino acid decarboxylase (DDC)



Pharmacological actions of Serotonin

CVS:

Blood vessels: Potent and direct contractions on smooth muscle (via 5- HT₂)

EXCEPT : Skeletal Muscles and Heart blood vessels.

GIT:

- 1) increase contraction of smooth muscle (via 5- HT₄ stimulated the release of ACH).
- 2) Nausea and vomiting (via 5-HT₃)

Respiration :

5-HT may produce weak bronchoconstriction.

CNS:

very important.(Appetite; depression and mania; Pain; reduce Anxiety; Schizophrenia).

Serotonin syndrome

Serotonin syndrome (SS) is a potentially life-threatening drug reaction. It causes the body to have too much serotonin, a chemical produced by nerve cells.

Causes

SS most often occurs when two medicines that affect the body's level of serotonin are taken together at the same time. The medicines cause too much serotonin to be released or to remain in the brain area.

For example, you can develop this syndrome if take **migraine** medicines together with antidepressants called selective serotonin reuptake inhibitors (SSRIs), and selective serotonin/norepinephrine reuptake inhibitors (SSNRIs).

Rapid onset

Combination of 2+ serotonin agonists



Mental status changes

Agitation

Pressured speech



Autonomic instability

Tachycardia

Diarrhea

Shivering

Diaphoresis

Mydriasis



Neuromuscular abnormalities

Clonus

Hyperreflexia (lower > upper)

Tremor

Seizure

Rx

Benzodiazepines

Hydration/Cooling

Cyproheptadine

Eicosanoid

- "Eicosanoid" is derived from a Greek word "eicosa" meaning "twenty"
- Eicosanoids is the collective term for the signaling molecules made by oxidation
- Eicosanoids are oxygenated derivatives of 3 different 20-carbon fatty acids:
 1. Eicosapentanoic acid
 2. Arachidonic acid
 3. Di-homo-gamma-linolenic acid

Classification

Eicosanoids are classified into two main groups

1) Prostanoids

2) Leukotrienes and Lipoxins

- Prostanoids are further sub-classified into three groups

a) Prostaglandins (PGs)

b) Prostacyclins (PGIs)

c) Thromboxanes (TXs)

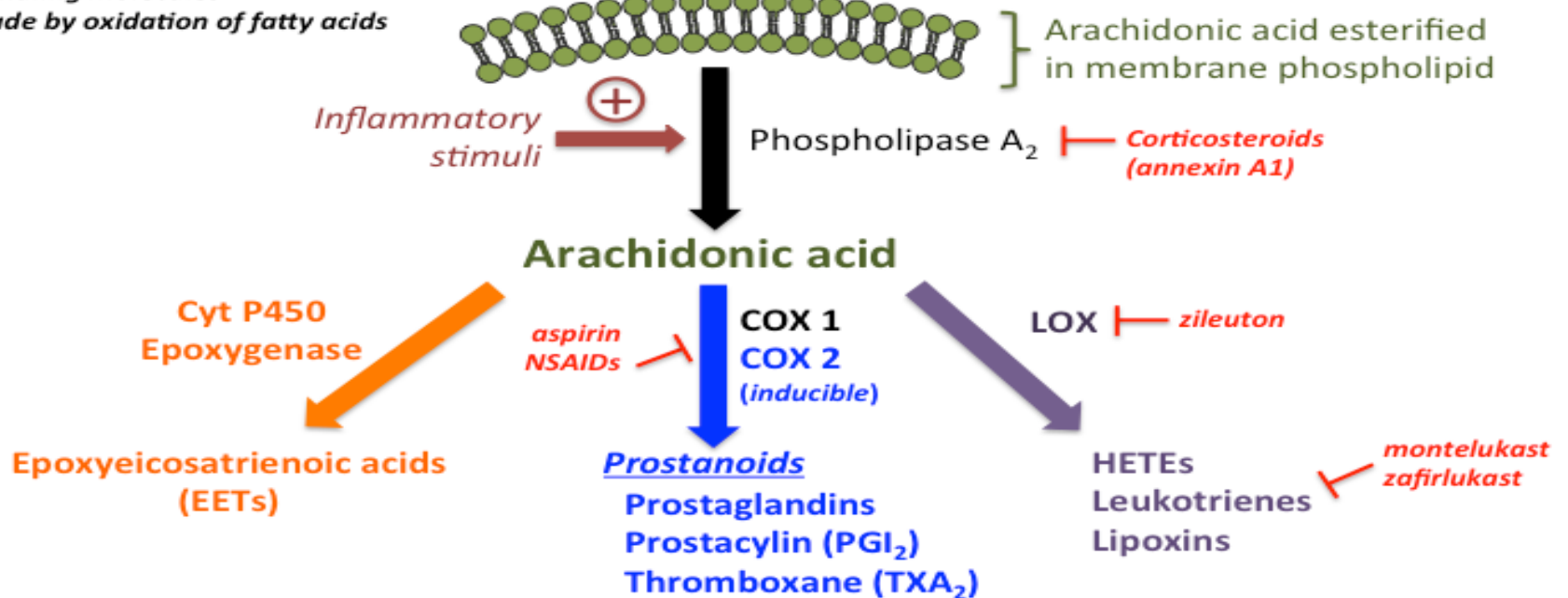
Biosynthesis

Two families of enzyme catalyze fatty acid oxygenation to produce the eicosanoids:

- **Cyclooxygenase** , or COX, generates the prostanoids.
- **Lipoxygenase** , or LOX, in several forms.

Eicosanoids

signaling molecules
made by oxidation of fatty acids



Actions

prostanoids

Prostanoids mediate local symptoms of inflammation:

- vasoconstriction or vasodilation
- coagulation
- pain and fever
 - COX-2 is responsible for pain and inflammation, while COX-1 is responsible for platelet clotting actions
 - Inhibition of cyclooxygenase, specifically the inducible COX-2 isoform, is the hallmark of NSAIDs (non-steroidal anti-inflammatory drugs).

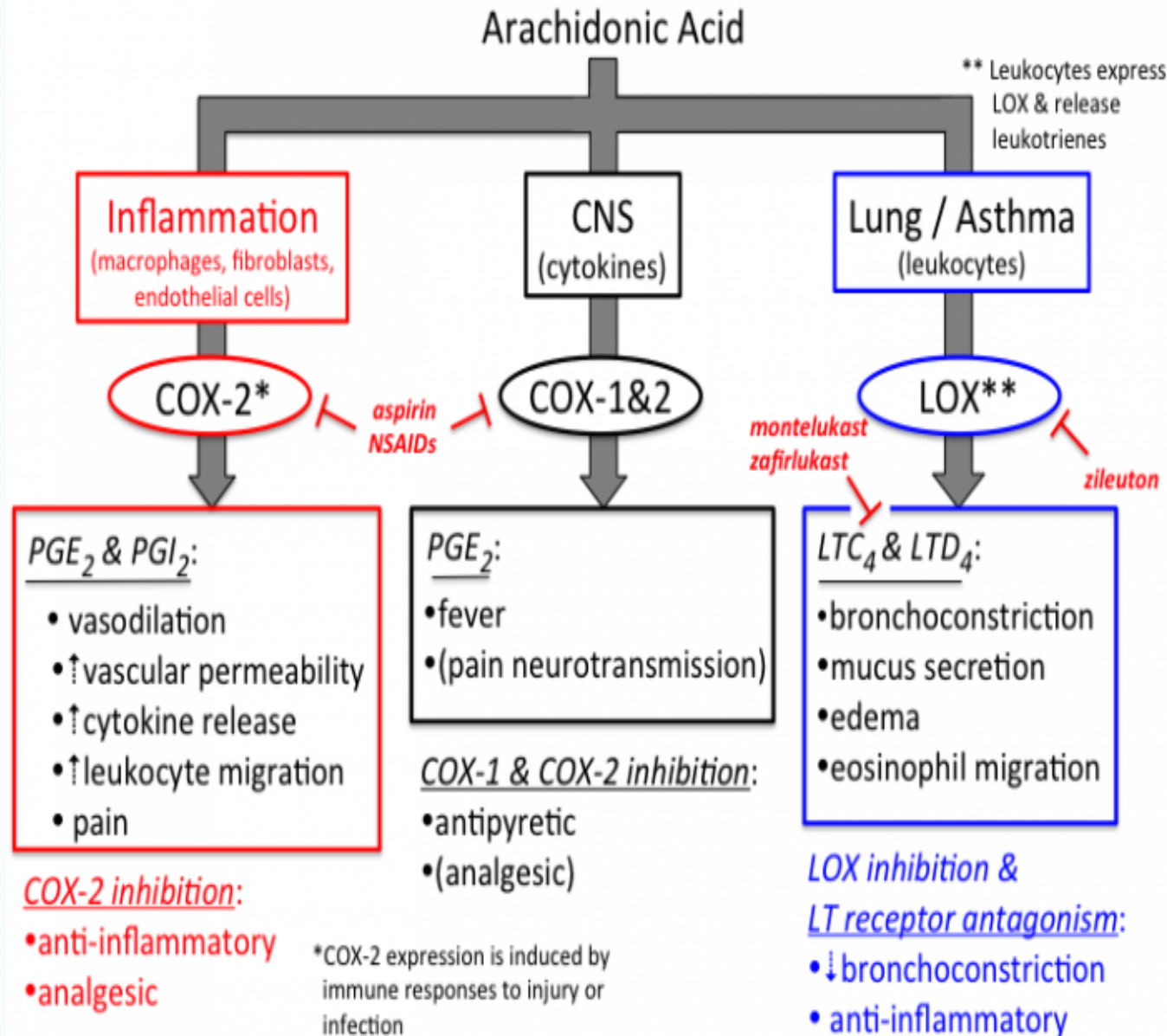
leukotrienes

- Leukotrienes play an important role in inflammation. There is a neuroendocrine role for LTC₄ in luteinizing hormone secretion.
- LTB₄ causes adhesion and chemotaxis of leukocytes and stimulates aggregation, enzyme release, and generation of superoxide in neutrophils.
- Blocking leukotriene receptors can play a role in the management of inflammatory diseases such as asthma (by the drugs montelukast and zafirlukast), psoriasis, and rheumatoid

Role of Aspirin in Inflammation

Aspirin inhibits the COX pathway and consequently diverts arachidonic acid metabolites to the LO pathway.

This also leads to a decrease in the levels of PGE₂, the anti-inflammatory PG.



Pharmacological applications of Eicosanoids

- **Cardiovascular uses-** pulmonary arterial hypertension, peripheral vascular disease
- **Digestive Uses-** indicated in the treatment of gastro duodenal ulcer and for the prevention of NSAID-induced ulcers.
- **Gynecological and obstetrical uses** - They induce cervical dilatation and uterine contractions, particularly in late pregnancy.
- **Bronchial Asthma-** PGE₂ agonists and leukotrienes receptor antagonists are used for the treatment of bronchial asthma.

Peptides Autacoids

1. Hormones from non-neural sources:

(angiotensin and bradykinin, as well as other hormones such as insulin, endothelin, atrial natriuretic peptide)

2. Neuroendocrine mediators

(vasopressin, somatostatin, hypothalamic releasing hormones, ACTH, LH, FSH and TSH)

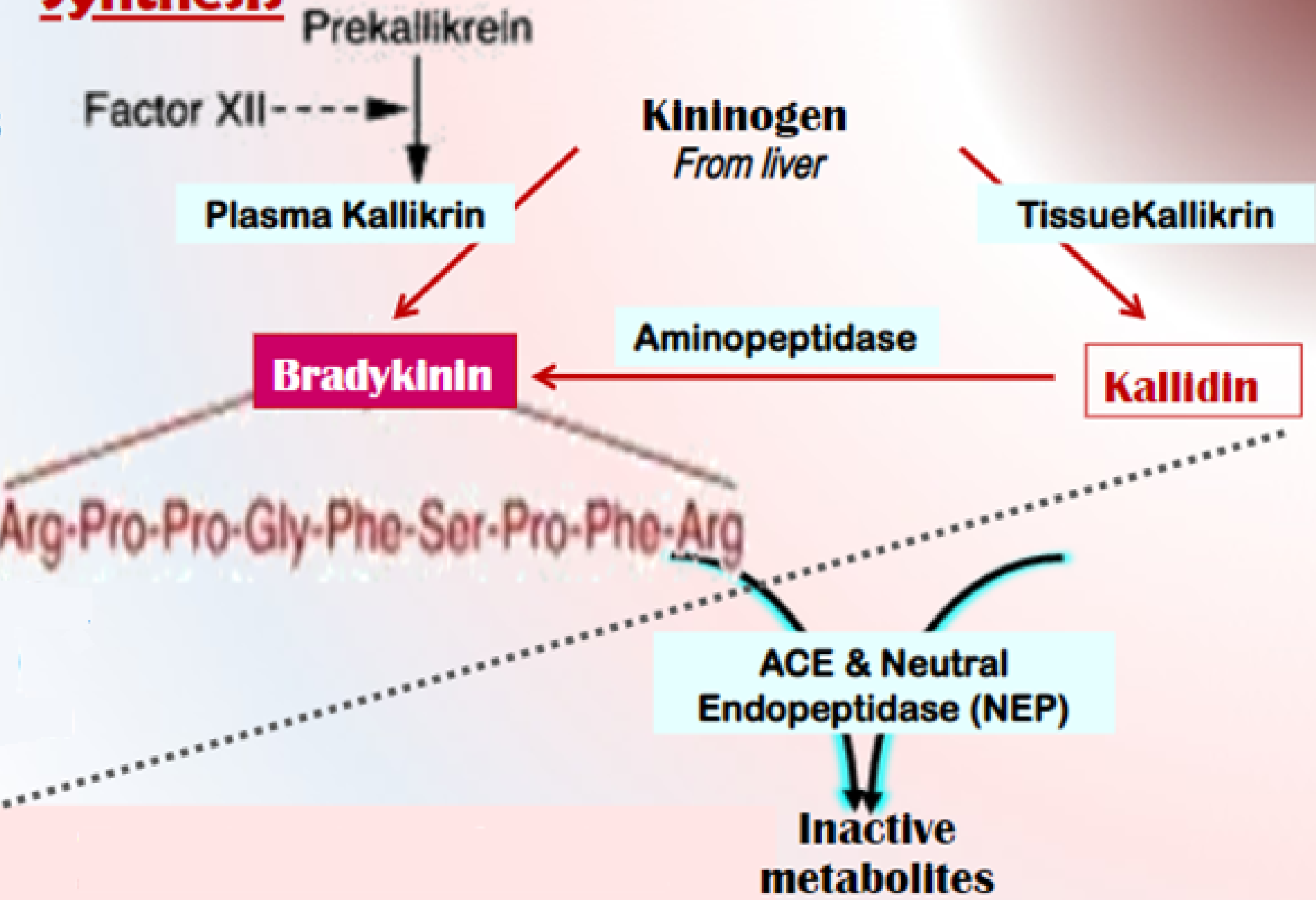
3. Mediators of the immune system

(cytokines)

Bradykinin

- ❑ (Greek brady-, **slow**; -kinin, kīn(eîn) **to move**) is an inflammatory mediator.
- ❑ It is a peptide that causes blood vessels to dilate via the release of **prostacyclin and nitric oxide**
- ❑ Bradykinin is active peptide ,consisting of **nine amino** acid,
- ❑ formed by proteolytic cleavage of circulating protein termed **kininogen** by the serine protease **Kallikrein**.

Synthesis



Bradykinin receptor

- Two receptors, designated B1 and B2.
- Both are G protein-coupled receptors
- **B1 receptors**
 - ✓ are normally expressed at very low levels but are strongly induced in inflamed or damaged tissues by cytokines such as IL-1.
 - ✓ It respond to des-Arg9-bradykinin but not to bradykinin
 - ✓ significant role in inflammation
 - ✓ its antagonists could be used in cough and neurological disorders
- **B2 receptors**
 - ✓ are constitutively present in many normal cells and are activated by bradykinin.
 - ✓ It stimulates Na⁺ excretion.
- **Antagonists:** Deltibant, Icatibant

Pharmacological actions:

- – Vasodilatation
- – Increased vascular permeability
- – Stimulation of pain nerve endings
- – Stimulation of epithelial ion transport and fluid secretion in airways and gastrointestinal tract
- – Contraction of intestinal and uterine smooth muscle
- – Contribute to inflammatory responses as autacoids that act locally.

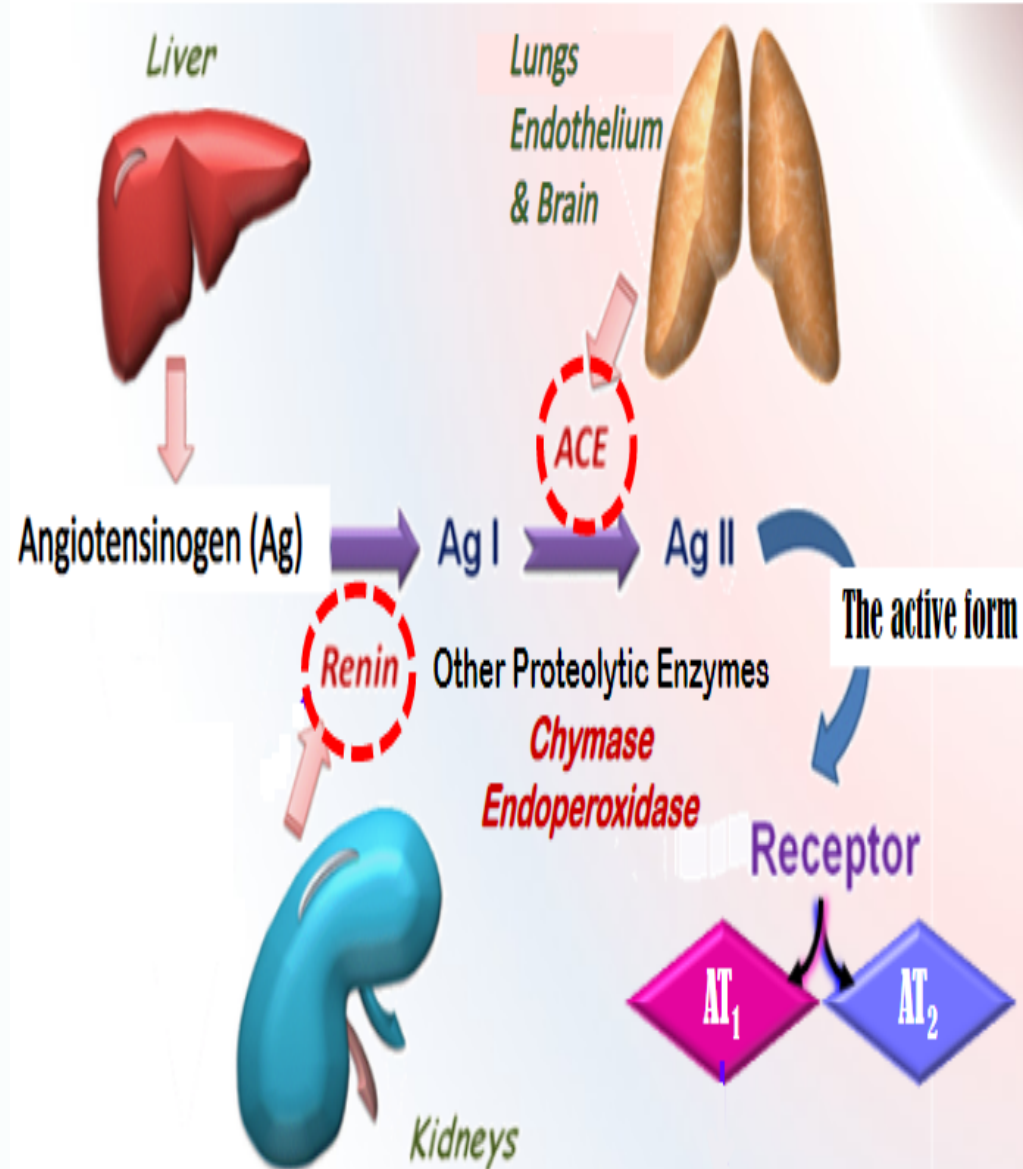
Angiotensin

- is a peptide hormone that causes vasoconstriction

- Synthesis**

Precursor is Angiotensinogen; a plasma α -globulin synthesized in the liver.

- Biosynthesis of angiotensinogen is stimulated by inflammation, insulin and estrogens



Receptor

- Angiotensin II binds to specific GPCRs, designated AT1 and AT2.
- Effects mediated by **AT1 receptors** include:
 - ✓ generalised vasoconstriction
 - ✓ increased noradrenaline release, reinforcing sympathetic effects
 - ✓ proximal tubular reabsorption of Na⁺
 - ✓ growth of cardiac and vascular cells.
- **AT2 receptors** are expressed during fetal life and in distinct brain regions in adults. They may be involved in growth, development and exploratory behaviour

Natriuretic peptide

- These peptides produce vasodilation, natriuresis, and inhibition of the renin-angiotensin system
- The family includes atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP).

Atrial natriuretic peptide

- Release of ANP occurs during volume overload in response to stretching of the **atria**, and intravenous saline infusion is sufficient to stimulate its release.

Brain natriuretic peptide

- BNP is synthesized primarily in the **heart** and released from ventricular muscle and opposes ventricular fibrosis; its plasma concentration is increased in patients with heart failure and is used as an aid to diagnosis

■ C-type natriuretic peptide

CNP is located predominantly in the **central nervous system** but is also present in other tissues including the vascular endothelium, kidneys, and intestine. potent vasodilator

□ Receptor

The actions of the natriuretic peptides are mediated by natriuretic peptide receptors (NPRs)

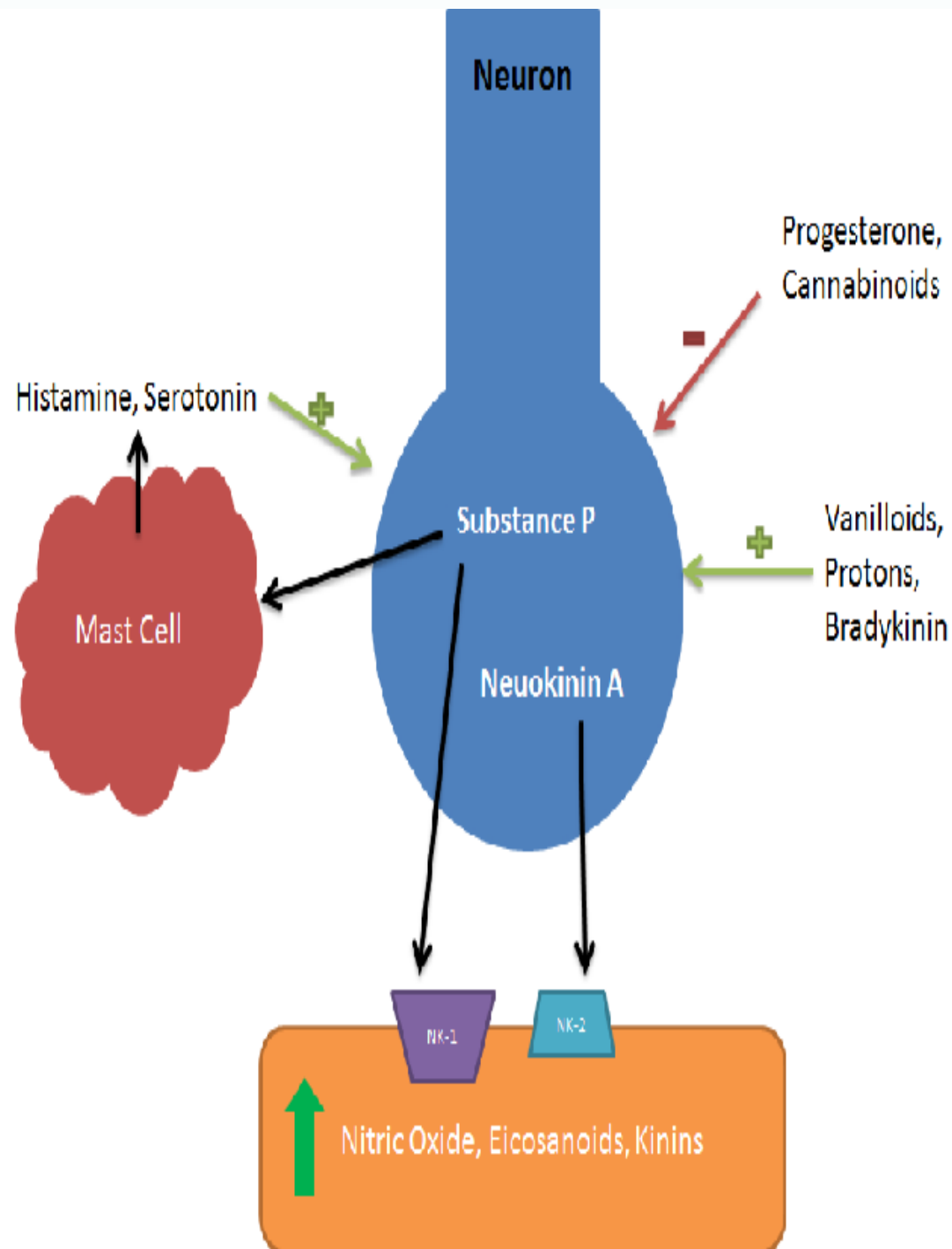
NPR-A & NPR-B are coupled to membrane-bound guanylyl cyclases GC

- ❖ They are metabolized in the kidneys, liver, and lungs by the neutral Endopeptidase
- ❖ short half-life in the circulation
- Natriuretic peptides may be administered as recombinant ANP (**carperitide**) or BNP (**nesiritide**).

Substance P

- is an **undecapeptide**, member of the **tachykinin** neuropeptide family.
- is a **neuropeptide**, acting as a neurotransmitter and as a neuromodulator
- is secreted by nerves and inflammatory cells such as macrophages, eosinophils, lymphocytes
- The endogenous receptor for substance P is **neurokinin 1 receptor (NK1R)**.
- Antagonists at the neurokinin NK1 receptor such as **aprepitant** and **fosaprepitant** are used to treat **emesis**, particularly that associated with cancer chemotherapy

- ❑ Substance P act on mast cells, releasing histamine and other mediators, and producing smooth muscle contraction, mucus secretion and vasodilatation (**potent vasodilator**)



Vasopressin

- Antidiuretic hormone, also known as vasopressin, is a **nine amino** acid peptide secreted from the posterior pituitary.
- vasopressin is also released in response to **stress, inflammatory signals, and some medications**
- Antidiuretic hormone binds to receptors in the distal or collecting tubules of the kidney and promotes reabsorption of water back into the circulation
- Three subtypes of AVP receptors have been identified; all are G protein-coupled.
- **V1a receptors** mediate the vasoconstrictor action
- **V2 receptors** mediate the antidiuretic action.
- used to treat patients with bleeding **oesophageal varices**

Cytokines

- are polypeptides that are rapidly induced and released during inflammation. They regulate the action of inflammatory and immune system cells.
- The cytokine superfamily includes the **interferons, interleukins, chemokines and colony-stimulating factors**.
- They exert complex effects on leukocytes, vascular endothelial cells, mast cells, fibroblasts, haemopoietic stem cells and osteoclasts, controlling proliferation, differentiation and/or activation.

- **IL-1 and TNF- α** are important primary inflammatory cytokines, inducing the formation of other cytokines.
- Chemokines, such as **IL-8**, are mainly involved in the regulation of cell trafficking.
- Interferons **IFN- α and IFN- β** have antiviral activity, and IFN- α is used as an adjunct in the treatment of viral infections.
- IFN- γ has significant immunoregulatory function and is used in the treatment of multiple sclerosis.