AUTACOIDS
(LOCAL HORMONES)
Lecture - 1

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PhD Clinical Pharmacology

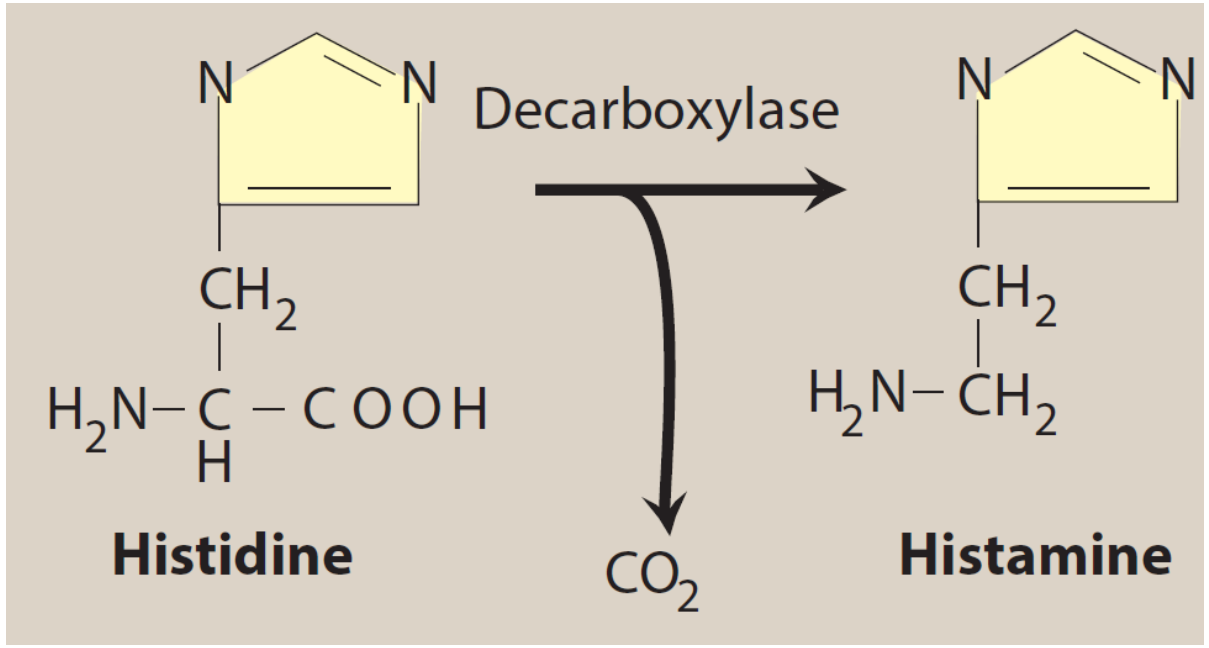
Autacoids

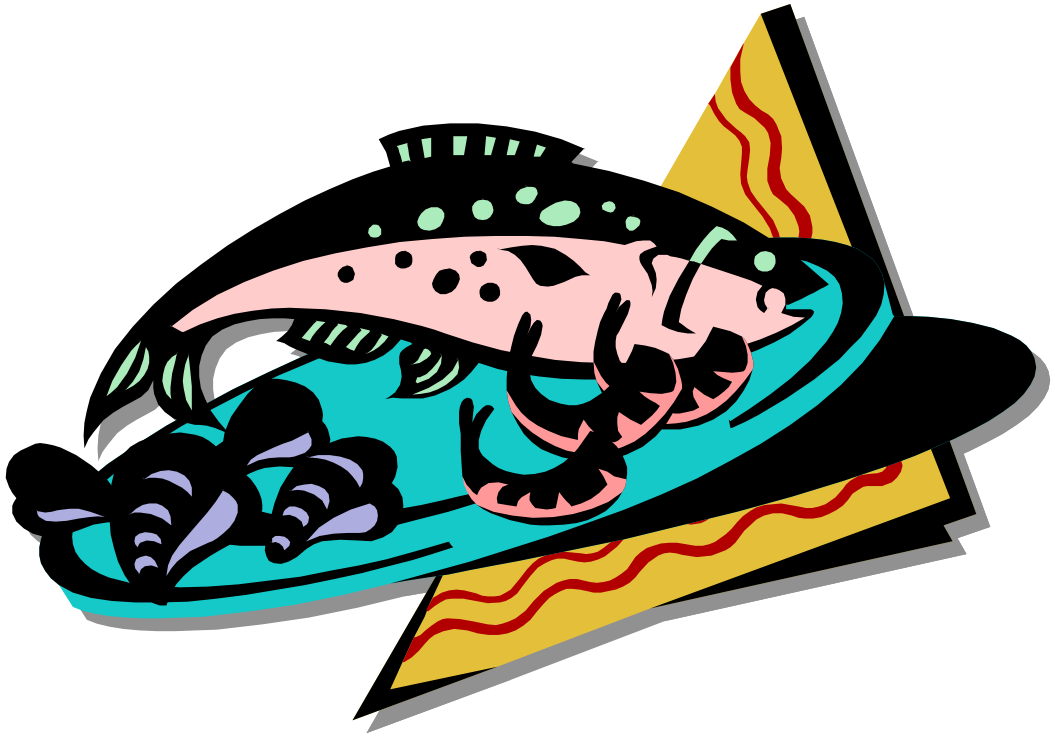
- ✓ **Auto = self Coids = Remedy**
- ✓ **Endogenious compounds**
- ✓ **Play an important role in the physiological and pathological processes**
- ✓ ***Have very short $t_{1/2}$***
- ✓ **Some times called Local Hormones**

Autacoids

- **Amines:**
  - Histamine
  - 5-Hydroxytryptamine
- **Peptide:**
  - Bradykinin
  - Angiotensin
- **Lipids:**
  - Prostaglandins
  - Leukotriens
  - Platelet activating factor

Histamine





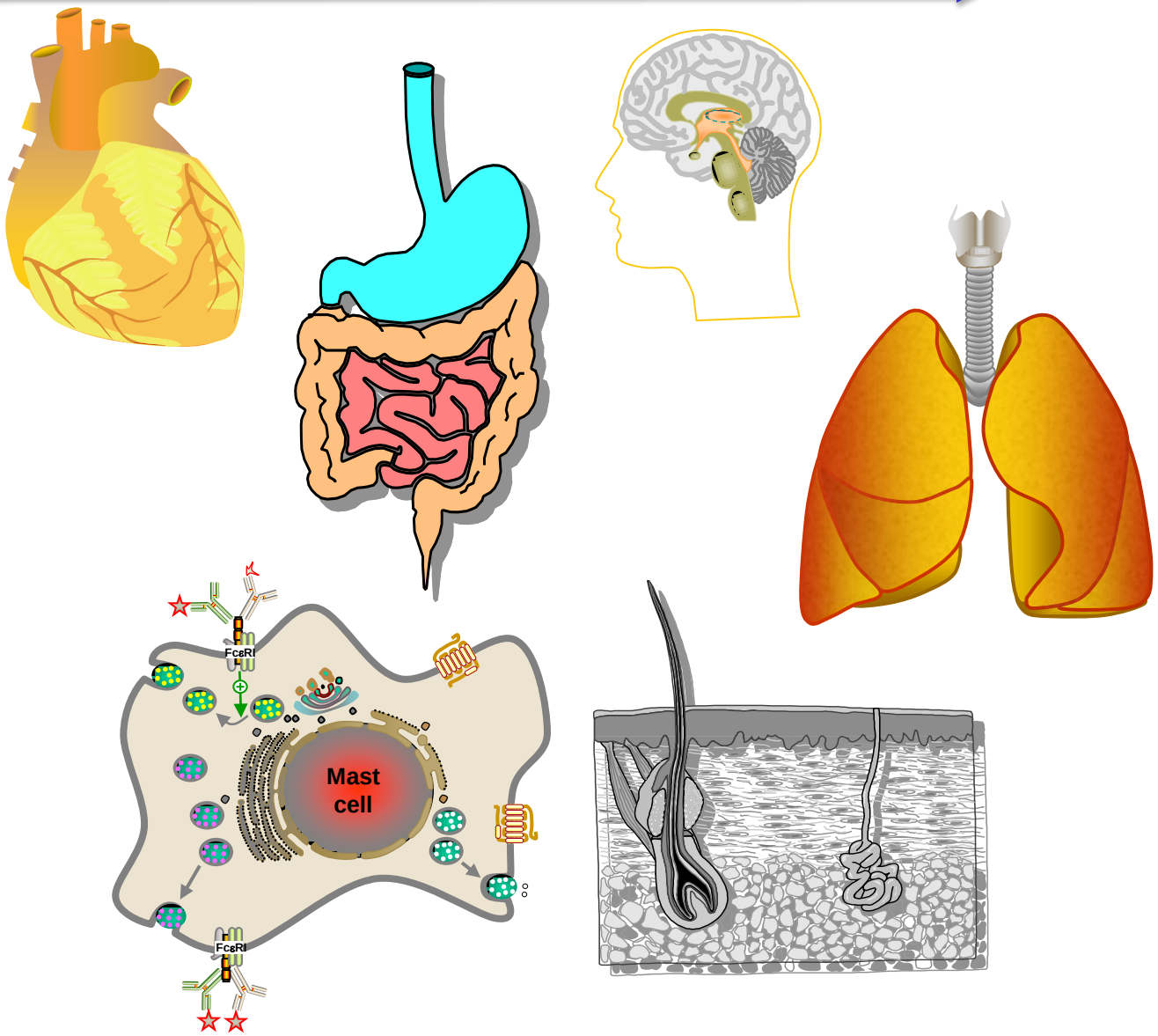
fish contains histidine!

Mechanism of Action

Histamine binds to three types of Receptors , namely H1 , H2 , H3

Receptor sub type	Distribution
H_1	Smooth muscle , endothelium , brain
H_2	Gastric mucosa , Cardiac muscle , mast cells , brain.
H_3	Presynaptic: brain, myentric plexus, other neurons

Histamine Distribution and Effects on Organs



Histamine-related Drugs/ Antagonists

A) Physiological Antagonism by epinephrine

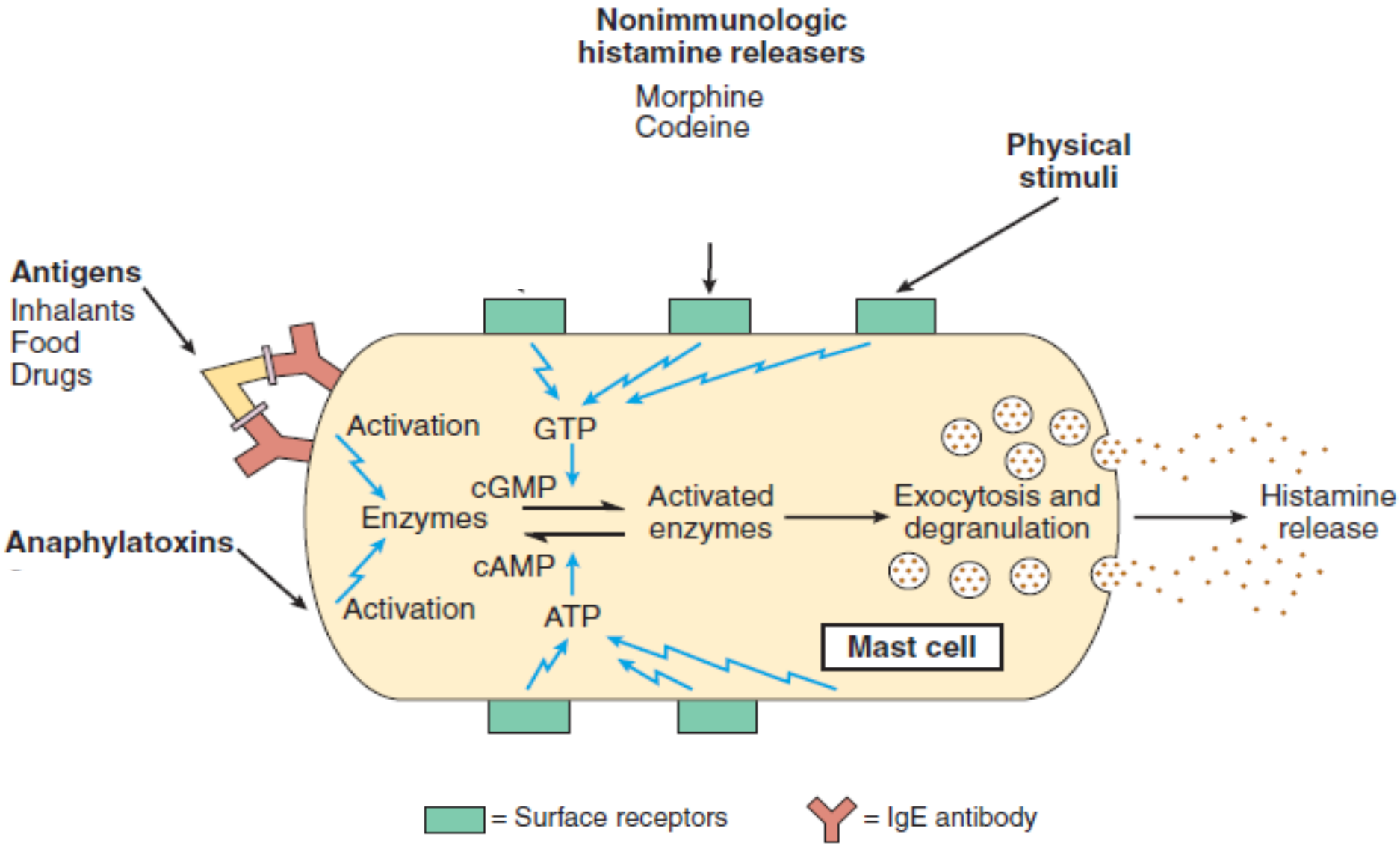
B) Mast cell release inhibitors

- ✓ **(Sodium Chromoglycate, Ketotifen)**
- ✓ **Prevent transmembrane influx of calcium ions, provoked by antigen-IgE antibody reaction on the mast cell membrane. They prevent degranulation and release of histamine and other autacoids from mast cells**

C) Histamine Receptors Antagonists

- **H1 Receptor Antagonists (1st and 2nd generation)**
- **H2 Receptor Antagonists (Ranitidine, Cimetidine)**

Mast Cells Activation/ Histamine release



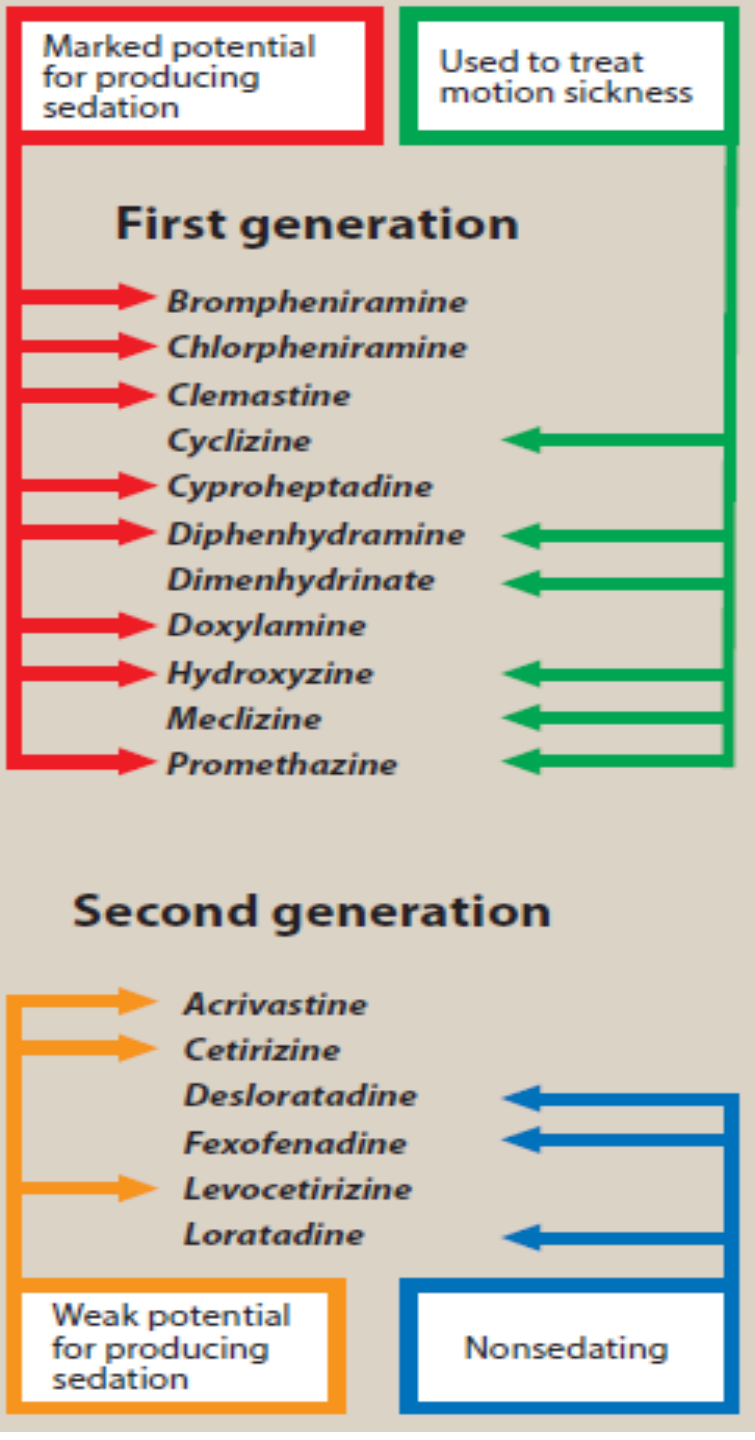
H1-receptors blockers/ antihistamine

The first-generation (older)

- widely used (effective and inexpensive)
- penetrate the **CNS** (sedation)
- interact with **other receptors** (adverse effects)

The second-generation

- **Specific** for peripheral H1 receptors (polarity/ carboxyl groups)
- Do **not penetrate** the blood–brain barrier (less CNS depression/ sedation)



H1-receptors blockers/ **Therapeutic uses**

Allergic and inflammatory conditions:

- Antigens - immunoglobulin E antibody reaction .
- e.g allergic rhinitis, urticarial, allergic conjunctivitis **BUT NOT bronchial asthma, WHY?**

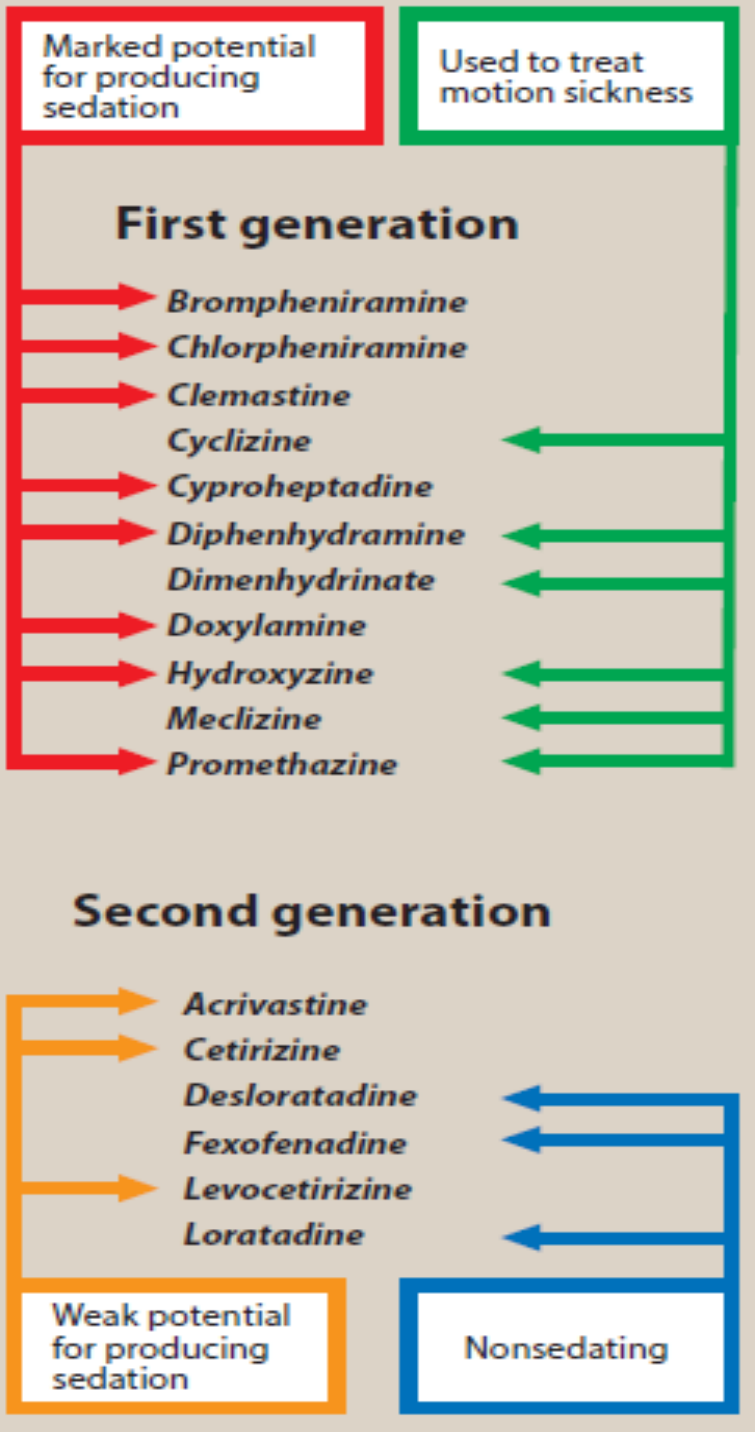
Motion sickness and nausea (First Gen.)

- **Not effective if symptoms are already present, WHY?**

Somnifacients (treatment of insomnia)

- **First- or second generation H1 antihistamines ?????**

Strong serotonin blockade (Cyproheptadine) !!!!!!



H1-receptors blockers/ **Pharmacokinetics**

Generally

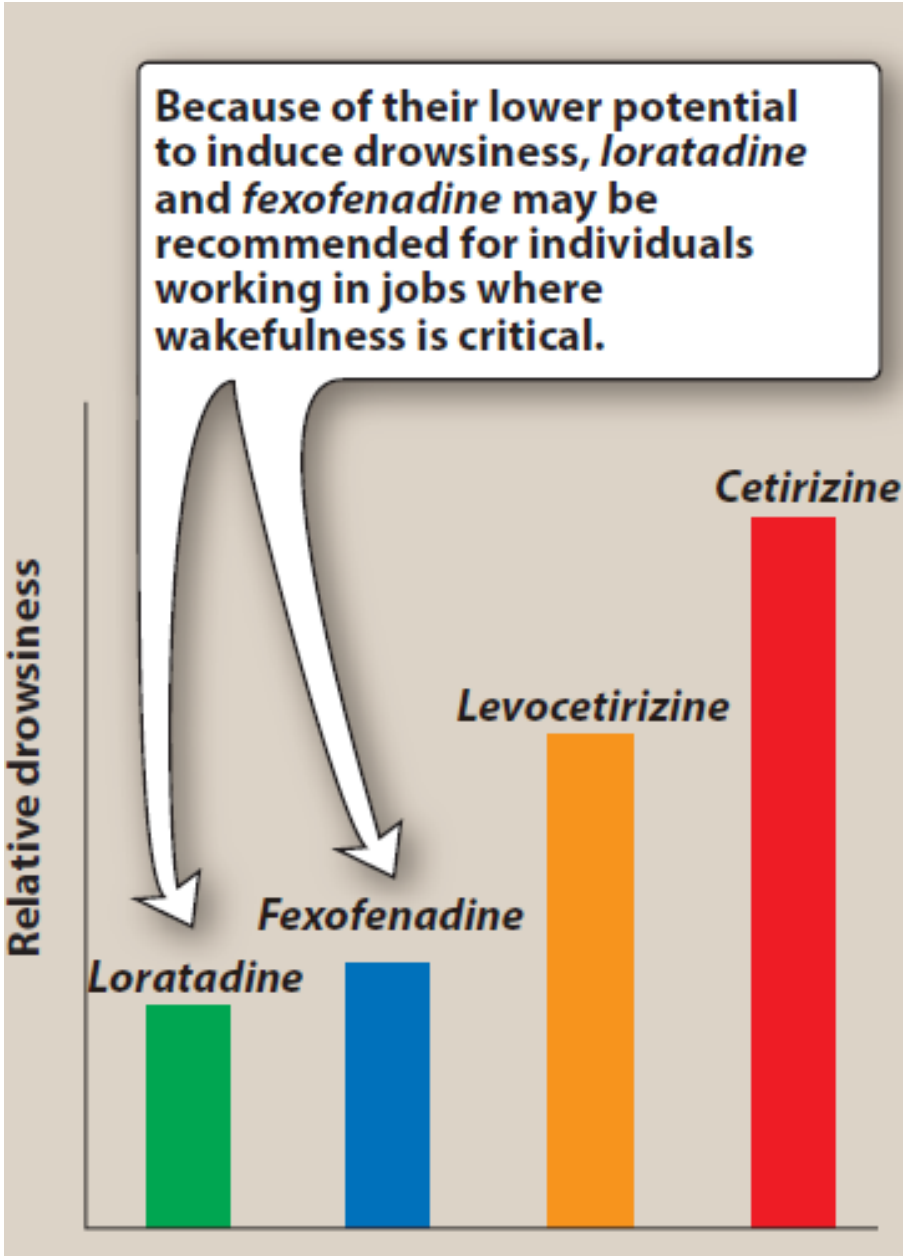
- Oral, ophthalmic, intranasal formulations

First-generation

- **half-life is 4 to 6 hours/ multiple doses per day**
- **Distributed in all tissues, including the CNS/ sedation**

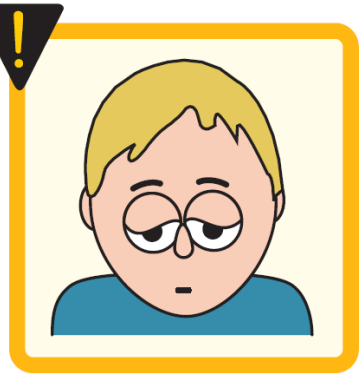
Second-generation

- **half-life is 12 to 24 hours/ once daily dosing**
- **Less CNS penetration/ less sedation**



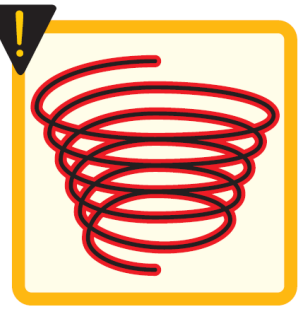
H1-receptors blockers/ **Adverse effects**

Drowsiness

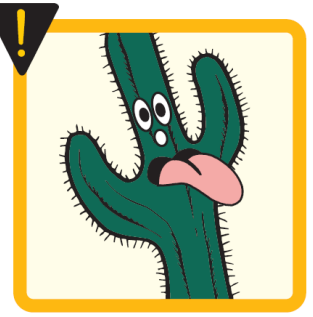


Hypotension

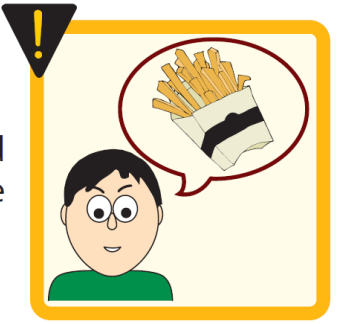
Vertigo



Dry mouth

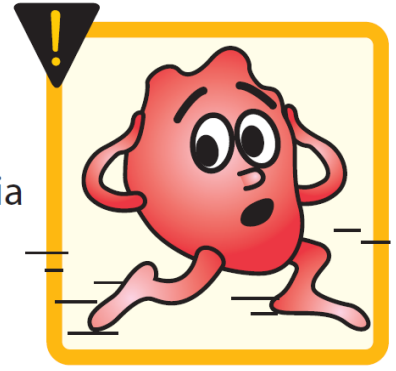


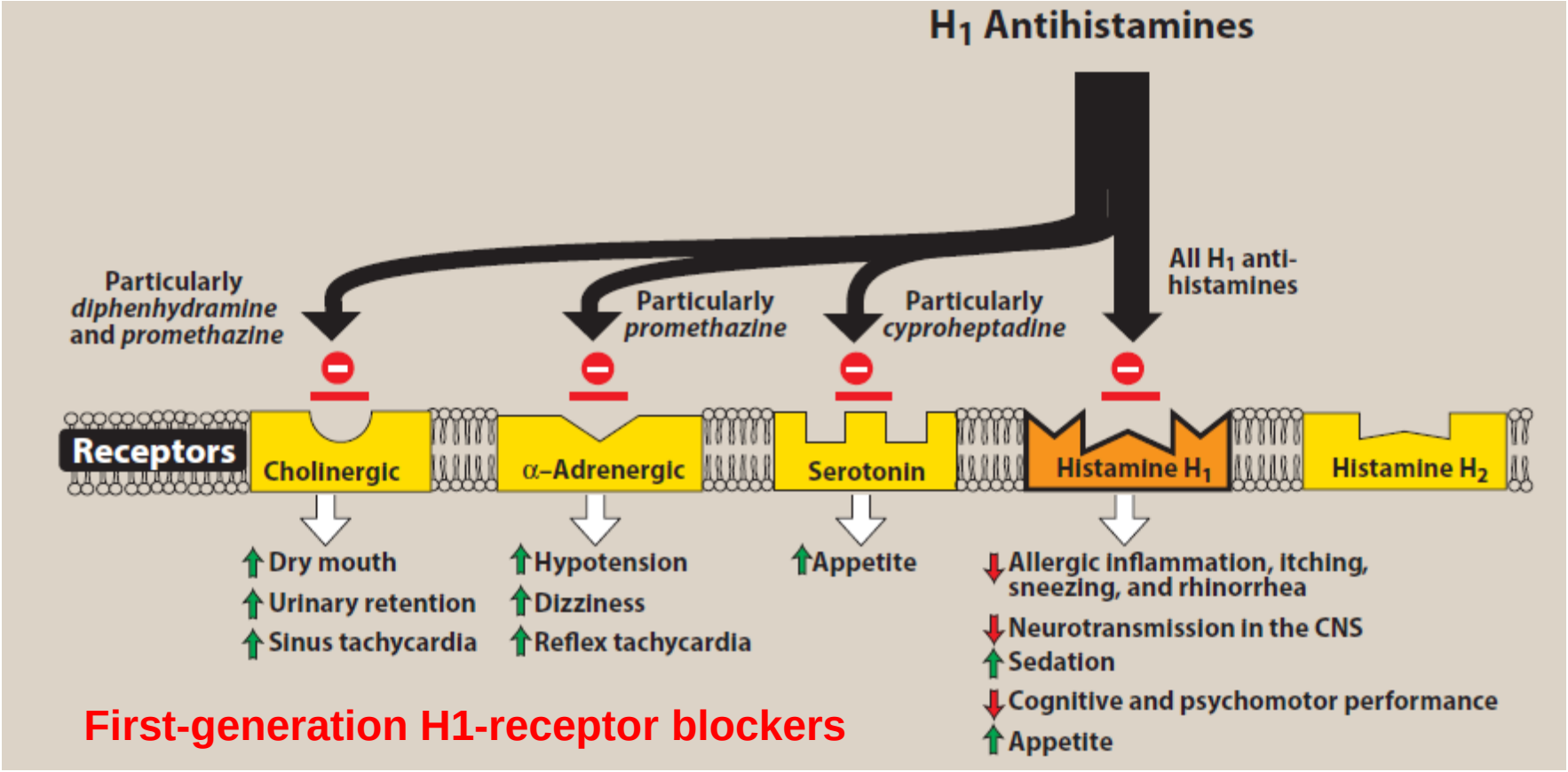
Increased appetite



Urinary retention

Tachycardia

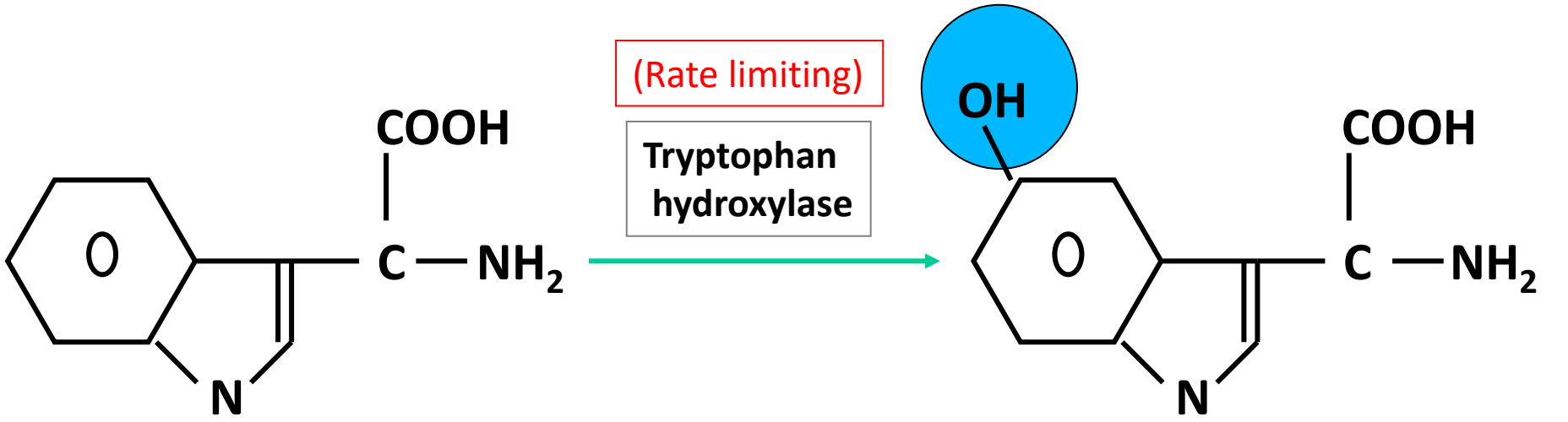




HISTAMINE **H2**-RECEPTOR BLOCKERS

- Little affinity for H1 receptors
- Treatment of ulcers and heartburn.
- Cimetidine (? . . .), ranitidine, famotidine, and nizatidine

Serotonin (5-Hydroxytryptamine: 5-HT)



Tryptophan

In diet. Active CNS transport

5-Hydroxytryptophan

Serotonin Receptors

At least **15 types** and subtypes

GIT (chromaffin cells and enteric neurons), platelets, CNS

5HT-1A: role in anxiety/depression
5HT-1D: role in migraine
5HT-2: role in CNS various behaviors, and in cardiovascular system
5-HT3: role in nausea and vomiting (chemotherapy)

Clinical Uses of Serotonergic **Agonists**:

Agents	Receptor	Use
Buspirone	5-HT_{1A}	Anxiolytic
Sumatriptan	5-HT_{1D}	Migraine (Treatment and prophylactic)
Metoclopromide	5-HT_4	Prokinetic (gastroesophagial reflex)
Fluoxetine	SSRI	Depression
Cisapride Removed due to fatal arrhythmias	5-HT_4	Decreases gastro-eosopggeal reflux
LSD/ Lysergic acid diethylamide	5-HT_{2A}	Hallucinogen
Ergot alkaloids/ Dihydroergotamine	5-HT_{1D}	Acute migraine

Clinical Uses of Serotonergic **Antagonists**

Agents	Receptor	Use
Ondan**setron** & Grani**setron**	5-HT3	Chemotherapy-induced nausea and vomiting
Cyproheptadine	H1 5-HT1,2 Cholinergic	Carcinoid tumor (5HT-secreting tumour) Increase appetite
Ketanserin	5-HT2 antagonist a1-adrenergic blocker.	Antihypertensive
Clozapine	5HT2A/2C H1-receptors	schizophrenia

Autacoids

- **Amines:**
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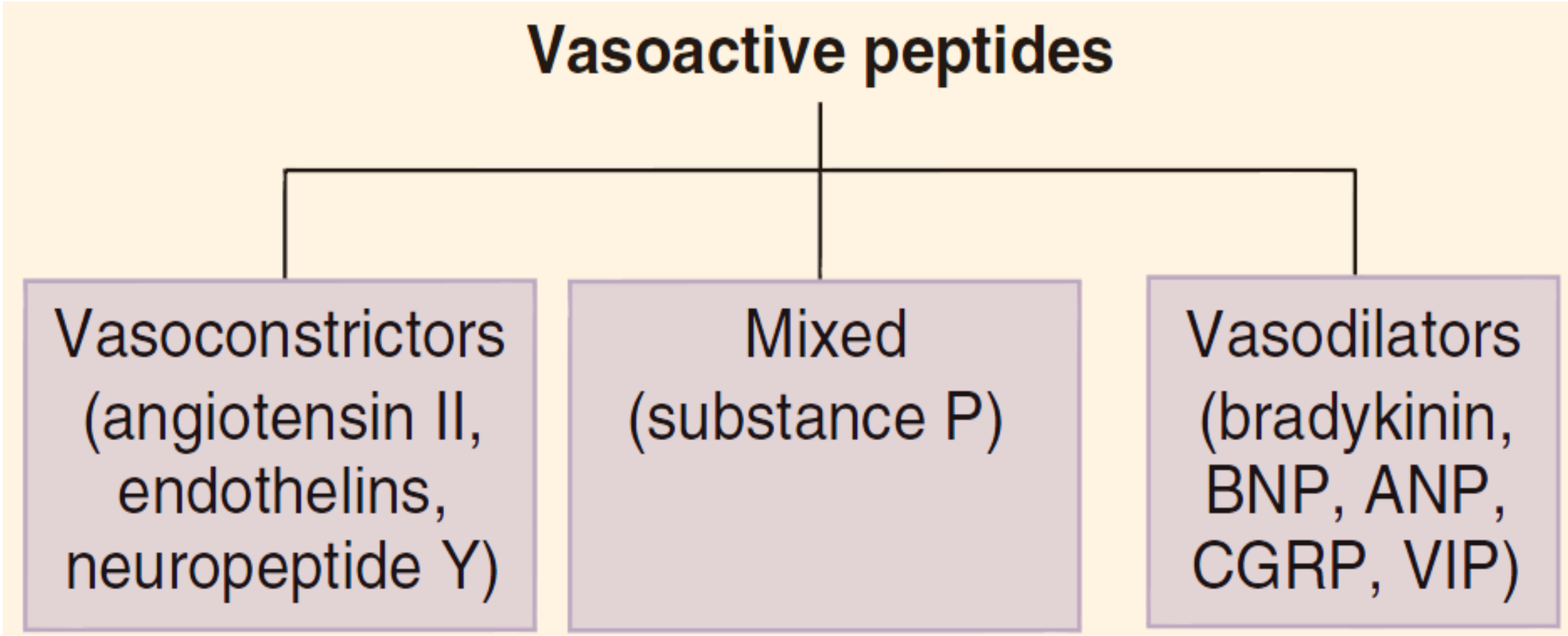
  - 5-Hydroxytryptamine
- **Peptide:**
  - Bradykinin
  - Angiotensin
- **Lipids:**
  - Leukotriens
  - Prostaglandins

Vasoactive Peptides

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

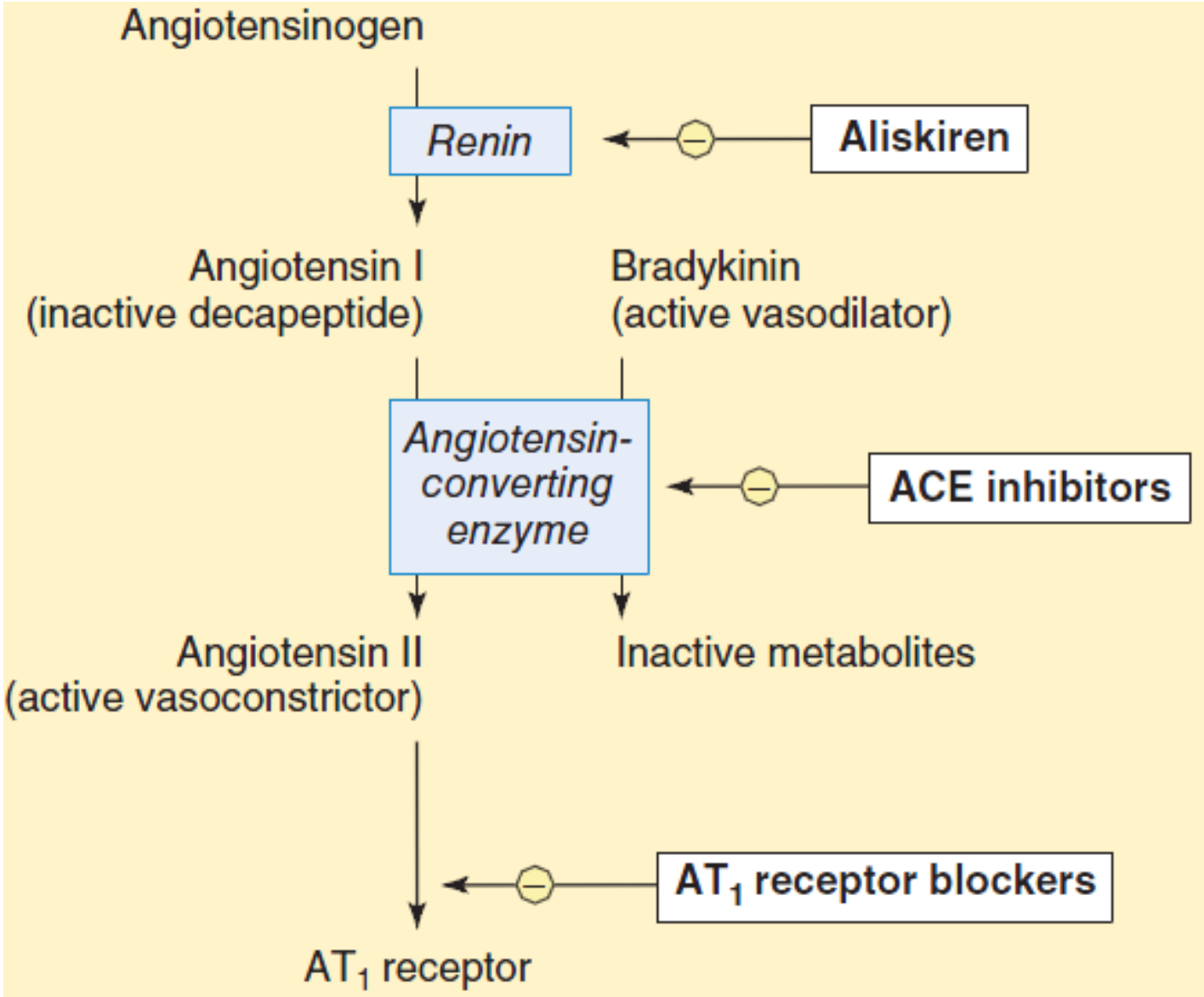


Vasoactive Peptides

The better-known vasoactive peptides include

- Angiotensin,
- Bradykinin,
- Natriuretic peptides,
- Calcitonin gene-related peptide (CGRP)
- Endothelin,
- Neuropeptide Y (NPY)
- Substance P
- Vasoactive intestinal peptide (VIP)

ANGIOTENSIN & ITS ANTAGONISTS



ANGIOTENSIN & ITS ANTAGONISTS

Angiotensin I is produced from circulating angiotensinogen by renin, an enzyme released from the juxtaglomerular apparatus of the kidney.

Angiotensin I is an inactive decapeptide, and is converted into angiotensin II, an active octapeptide, by angiotensin-converting enzyme (**ACE**), also known as **peptidyl dipeptidase** or **kininase II**.

Angiotensin II, the active form of the peptide, is rapidly degraded by peptidases (**angiotensinases**).

ANGII directly **increases peripheral vascular resistance** and, through **aldosterone**, causes renal sodium retention. It also facilitates the release of **norepinephrine** from adrenergic nerve endings via presynaptic heteroreceptor action

ANGIOTENSIN & ITS ANTAGONISTS

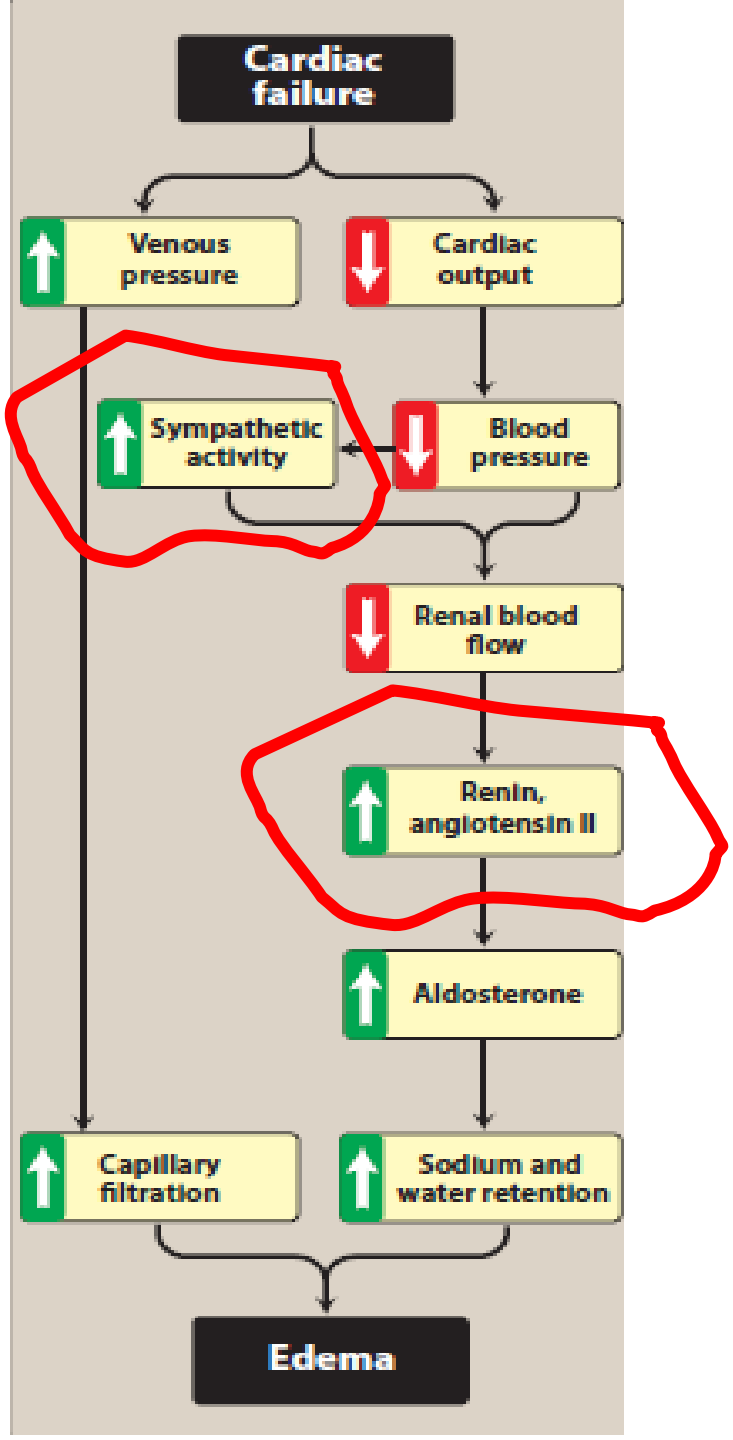
All these effects are mediated by the angiotensin **AT1 receptor**, a Gq-coupled receptor

The **AT2 receptor** appears to mediate vasodilation via nitric oxide and is probably most important during fetal development

ACE inhibitors (eg, captopril, enalapril, others) and **Angiotensin II antagonists (eg, losartan, valsartan,** others) have demonstrated clinical benefits in hypertension and heart Failure

Aliskiren, an orally active renin inhibitor, reduces angiotensin I as well as angiotensin II and is approved for use in hypertension.

The AT1 receptor antagonists lack the effect on bradykinin levels, which may explain the lower incidence of cough observed with these agents


Cardiac failure
Venous pressure
Cardiac output
Sympathetic activity
Blood pressure
Renal blood flow
Renin, angiotensin II
Aldosterone
Capillary filtration
Sodium and water retention
Edema