

PROSTAGLANDINS, VASOACTIVE PEPTIDES AND OTHER AUTOCOIDS

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Autacoids

- endogenous compounds;
- play an important role in the physiological and pathological processes;
- *have very short $t_{1/2}$;*
- have local action.

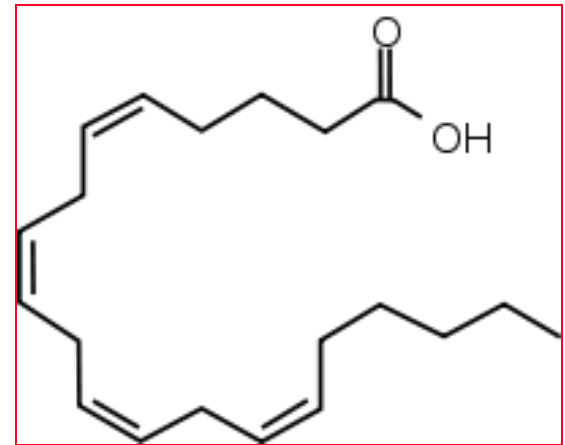
(eicosi = 20)

EICOSANOIDS

(20 carbon atoms!)

- **prostanoids**
 - **prostaglandins (PGs)**
 - **thromboxanes (TxS)**
- **leucotrienes (LTs)**
- **lipoxins**

- The eicosanoids are important mediators of inflammation and allergy.



- The main source of eicosanoids is arachidonic acid. It is a **20-carbon unsaturated fatty acid**.

Inflammatory stimulus



Phospholipids

Phospholipase A₂

Arachidonic acid

5-lipoxygenase

Cyclooxygenase (Cox)

15-lipoxygenase

Endoperoxides

Leucotrienes

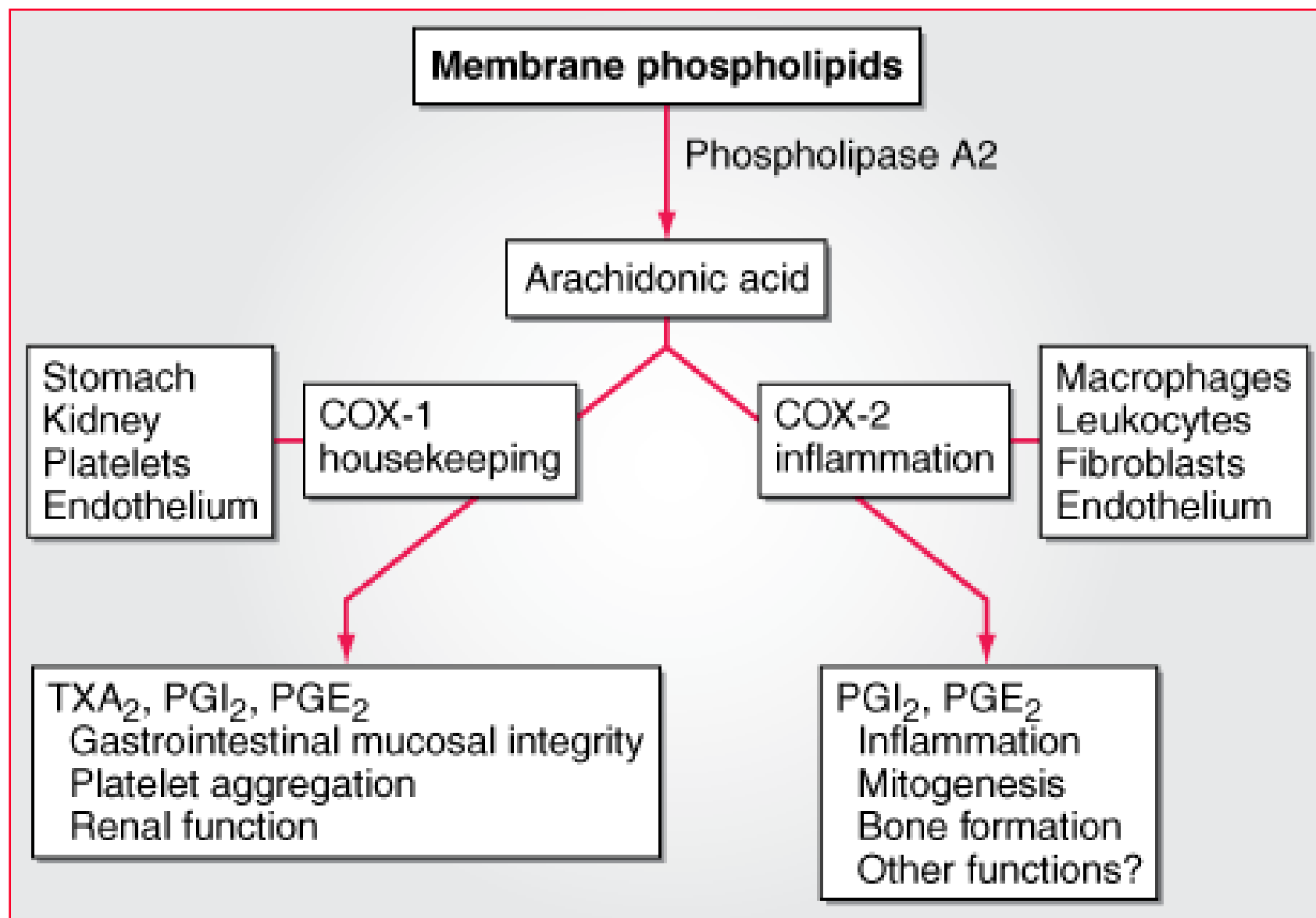
Lipoxins

PGs

TxA₂

Cyclooxygenase (COX) is found bound to the endoplasmatic reticulum. COX exists in 3 isoforms:

- **COX-1** (constitutive) acts in physiological conditions.
- **COX-2** (inducible) is induced in inflammatory cells by pathological stimulus.
- **COX-3** (in brain)



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: <http://www.accessmedicine.com>

Arachidonic acid

5-Lipoxygenase

Leukotrienes (LTs)

**LTC₄-
receptor**

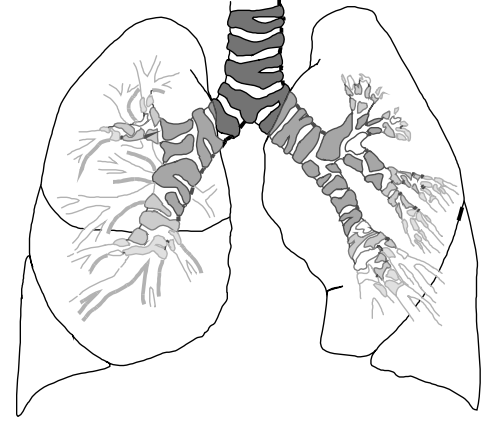
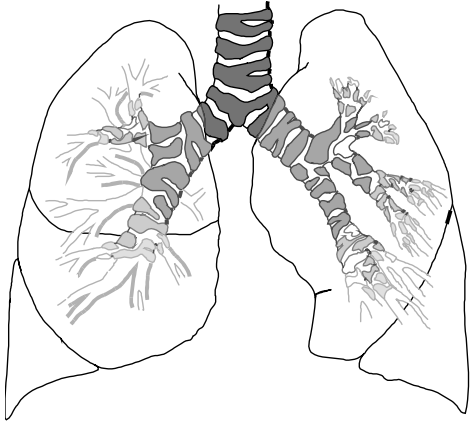
**LTD₄-
receptor**

**LTE₄-
receptor**

(-)

(-)

Montelukast, Zafirlukast



Aspirin-like drugs
inhibit mainly COX-1
and can cause peptic ulcer,
GI bleeding, bronchial
asthma, and nephrotoxicity.

PROSTANOIDS (PGs & Txs)

PGI₂ (prostacyclin) is located predominantly in vascular endothelium. Main effects:

- vasodilatation
- inhibition of platelet aggregation

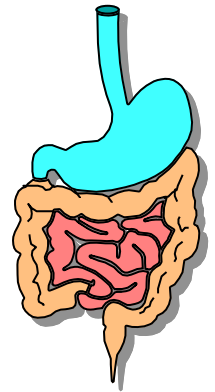
TxA₂ is found in the platelets.

Main effects:

- platelet aggregation
- vasoconstriction

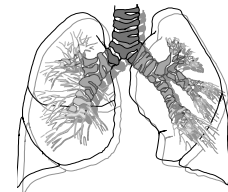
PGE₂ causes:

- contraction of pregnant uterus
- inhibition of gastric acid secretion
- contraction of GI smooth muscles

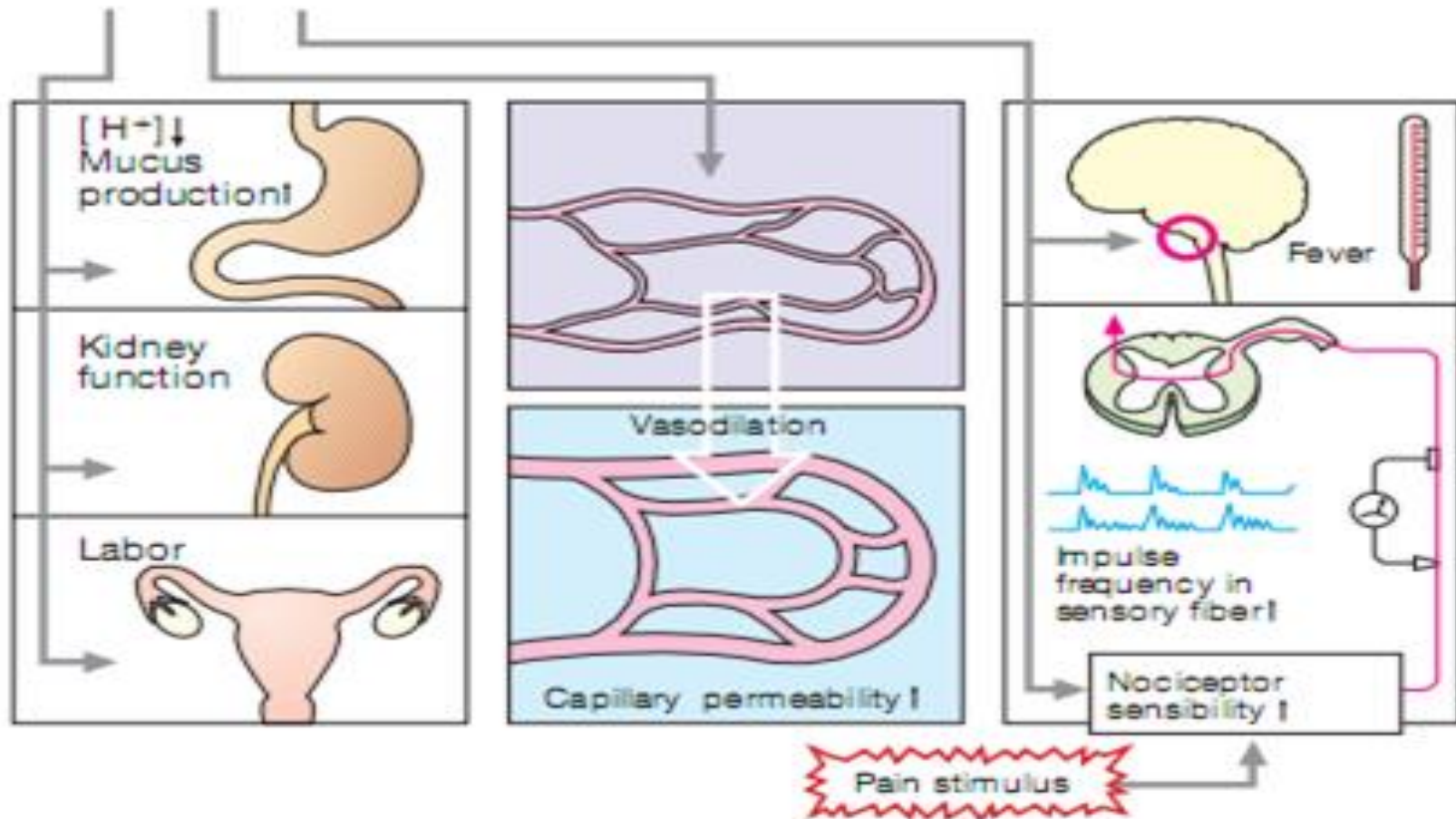


PGF_{2α} – main effects:

- contraction of bronchi
- contraction of myometrium



Main actions of the eicosanoids



Physiological and Pharmacological Actions of Eicosanoids

Mechanisms and Receptors:

Act on cell surface receptors

All coupled to G-protein.

PGI₂; PGE increases adenylate cyclase (decrease intracellular calcium) while TXA₂, PGF₂ α and leukotrienes increases IP₃ (increases intracellular calcium)

Their functions vary widely depending on the tissue

- The release of TxA_2 from platelets during tissue injury triggers platelet aggregation (the first step in clot formation) as well as local vasoconstriction
- PGI_2 , produced by endothelial cells, has opposite effects- inhibiting platelet aggregation and producing vasodilation

Actions

Inflammation, pain and fever

Most important mediators..

NSAIDS-their inhibitors

Actions – Vascular smooth muscles

Blood vessels

PGE_2 , PGI_2 (Prostacycline) -
vasodilatation

Thromboxane A_2 – constriction

Actions :Smooth muscle

Bronchus

PGE_2

PGI_2

• BRONCHODILATION

$\text{PGF}_{2\alpha}$

TXA_2

LT

• CONSTRICTION

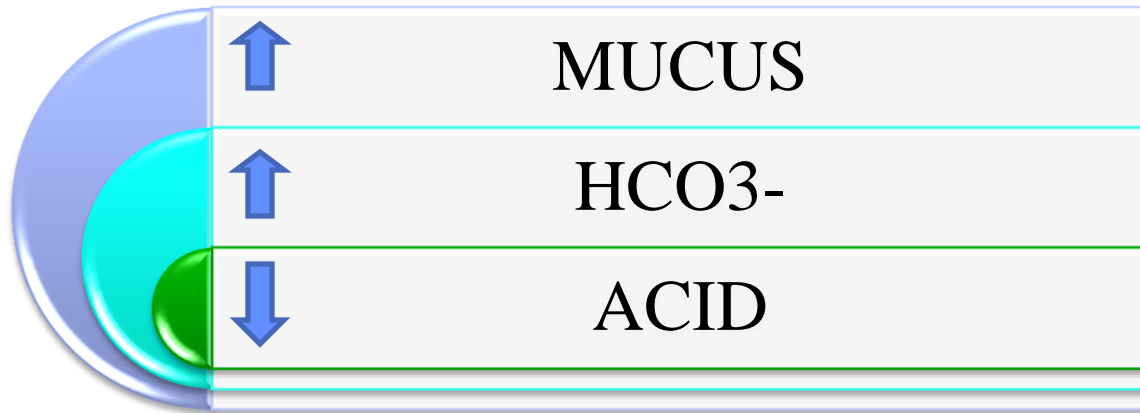
Uterus

Both uterus & cervix

Cervical
ripening

- PgE_2

Actions- GIT



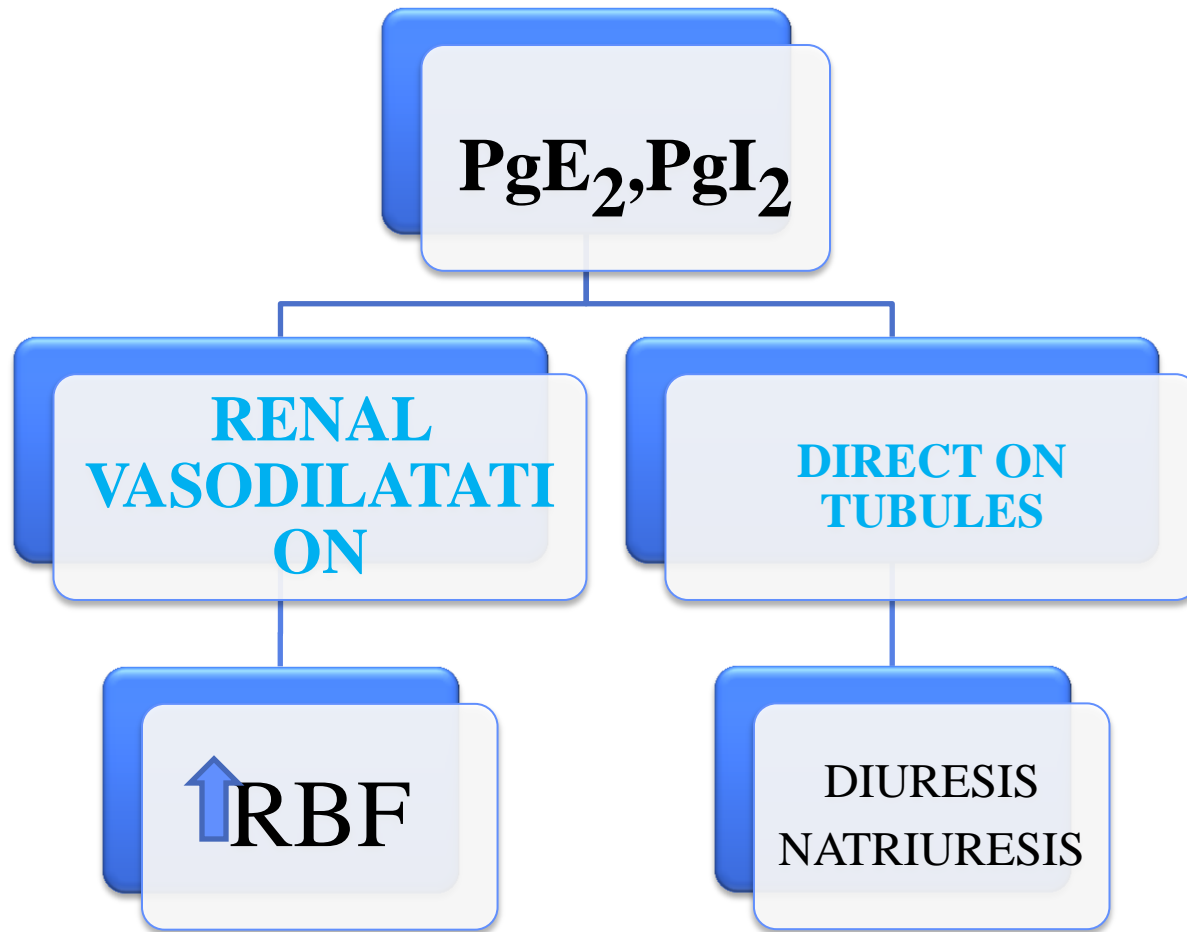
Natural ulcer protectants..

- **GIT**

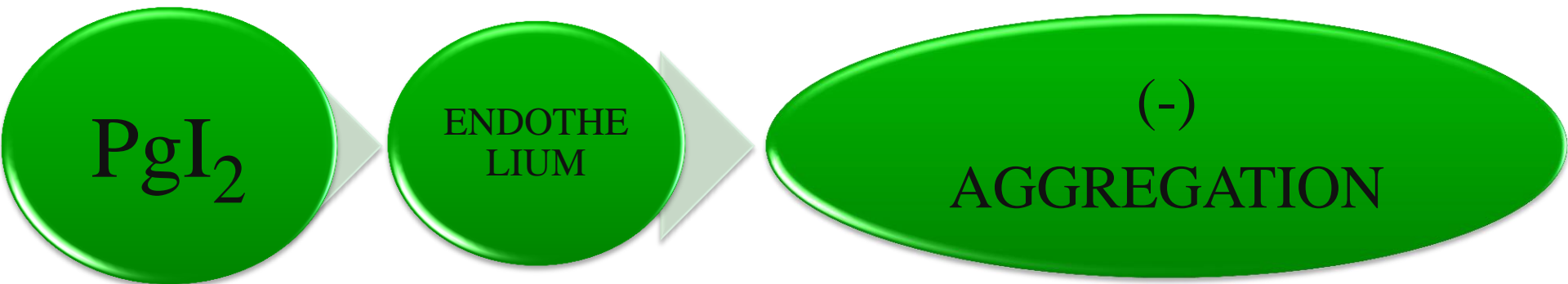


RENAL

PgE₂, Prostacyclin (PGI₂) -protective..



Coagulation



Clinical Uses of Eicosanoids and Inhibitors:

A. Uses of Eicosanoids:

Misoprostol (a PGE1 analogue)

- **It is used to protect the mucosal lining of the stomach during chronic NSAID treatment**
- **Reducing gastric acid secretion, stimulating mucus and bicarbonate production**
- **Increasing uterine contraction- off-label uses in obstetric settings for labor induction**

ADRs: Category X, potential risk to induce abortion, diarrhea, abdominal pain, spotting, headache

Uterine damage, fetal bradycardia, infection, death

- Mifepriston + misoprostol-

Complete abortion rates exceeding 95 percent

Iloprost (a analog of PGI₂)

Pulmonary vasodilator (cAMP inc., TxA₂ inh.)

It is used for the treatment of pulmonary arterial hypertension

It is given via inhalation

- short half life- requires frequent doses

Side effects: dizziness, headache, flushing and fainting

Bronchospasm and cough can also occur after iloprost inhalation

Latanoprost (PGF2 α analogue)

Treatment of open-angle glaucoma and elevated intraocular pressure

Travoprost (pro-drug)

Reducing intraocular pressure

Bimatoprost (mimics endogenous prostamides)

Reduction of intraocular pressure

Increase eyelash prominence, length, darkness-
approved for eyelash hypotrichosis

Side effects: blurred vision, iris color change (increased brown pigmentation), increased number and pigment of eyelashes, ocular irritation and foreign body sensation

Alprostadil (PGE₁)

that is naturally produced in tissues (seminal vesicles, cavernous tissues, placenta, ductus arteriosus of the fetus)

use to treat erectile dysfunction or to keep the ductus arteriosus open in neonates with congenital heart conditions until surgery is possible

Side effects: symptomatic hypotension, dizziness and syncope

Local adverse reactions: penile, urethral and testicular pain, prolonged erections and priapism

When admin. i.v in neonates- apnea, fever, sepsis, seizures

Lubiprostone (a PGE1 derivative)

Treatment of chronic idiopathic constipation
and irritable bowel syndrome with
constipation

(via opening chloride channels in the luminal
cells of the intestinal epithelium)

Side effects: nausea (can be decreased if taken
with food)

Dose-dependent diarrhea, headache,
abdominal pain

B – Uses of eicosanoids blockers:

- Asthma: Leukotrien antagonists (Zafirlukast; Montelukast); or Lipoxygenase inhibitor e.g. Zileuton**
- Anti-inflammatory and RA (NSAIDs)**
- Antiplatelet action (Aspirin)**
- Dysmenorrhea (NSAIDs)**

ADRs

- Vomiting, Diarrhea, Abdominal cramps
- Uterine cramps
- Bronchospasm

Platelet activating factor (PAF)

- **PLA₂ releases PAF in inflammation.**
- **PAF causes vasodilatation, increases vascular permeability, activates platelet aggregation.**

Vasoactive Peptides

- A. Vasoconstrictors** (angiotensin II; vasopressin; endothelins and neuropeptide Y.
- B. Vasodilators** (Bradykinin and related Kinins; Natriuretic Peptides; Vasoactive Intestinal Peptide; substance P; Neurotensin)

Kinins : (e.g. : Bradykinin & kallidin)

- Polypeptides present in plasma and several tissues including the kidneys, pancreas, intestine, sweat and salivary glands.

ACTIONS :

CVS : Very potent vasodilator (direct and via increase EDRF). Also, increases the body capillary permeability

- **Bronchioles** : Contraction of bronchial smooth muscles (cough).
- **Inflammation** : Kinins can produce all the symptoms of inflammation (pain and edema when injected to tissue).
- **Pain** : Intradermal injection of kinins elicited potent pain (Stimulate nociceptive nerve afferent fibers)

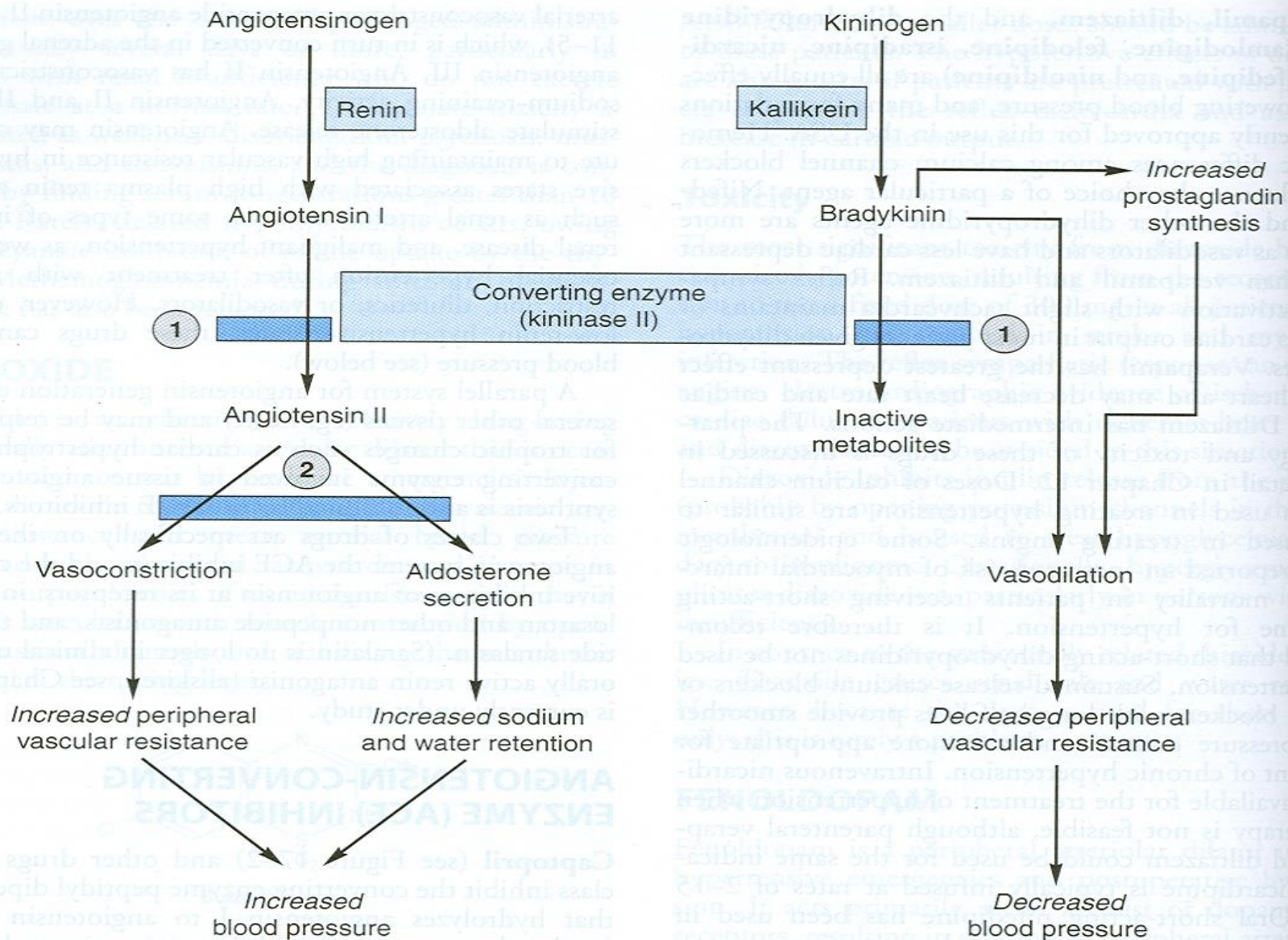


Figure 11-5. Sites of action of ACE inhibitors and angiotensin II receptor blockers. ① Site of angiotensin-converting enzyme blockade. ② Site of receptor blockade.

2. Vasoconstrictor peptides:

Angiotensin II

1. the most potent vasoactive agent in the body (direct and via NE)
2. Stim release of aldosterone and renin as well.
3. Centrally, stim. Drinking and increase the secretion of vasopressin and ACTH.

ACE inhibitors and AngII antagonists- hypertension, congestive heart failure

Endothelins:

- Widely distributed in the body (in endothelial cells of blood vessels)
- **ACTIONS:** Dose-depen. Vasoconstriction in most vascular beds, Thus:
 - Decrease GFR
 - Increase aldosterone, vasopressin and ANP
 - Potent bronchoconstriction
- **Endothelin Antagonists:** (Bosentan, ambrisentan) (pulmonary HTN)

Cytokines

Soluble proteins and glycoproteins that interact with specific cellular receptors.

Cytokines are involved in inflammatory and immune response.

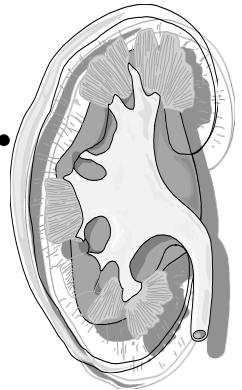
INTERLEUKINES (ILs)

IL-1 participates in the pathogenesis of rheumatoid arthritis.

Glucocorticosteroids and glucosamine depress the synthesis of IL-1.

IL-2: used i.v. in renal carcinoma but has ADRs!

IL-11 stimulates thrombocytopoiesis.



IL-18:

- **Upregulated interferon production**

IL-23:

- **Anti-viral activity**
- **Stimulates T-cell, macrophage, and**
- **Used therapeuticaly in viral and autoimmune conditions**

INTERFERONS (INFs)

- **Interferon alpha-2b (Intron[©]):**
 - in chronic hepatitis B and C
 - lymphomas, melanomas, etc.
- **Interferon beta-1b (Betaferon[©])**
s.c. in multiple sclerosis.
- **Interferon gamma** –
in the regulation of the immune system.

Colony-stimulating factors:

- Filgrastim, Molgramustim, Lenograstim
(to treat agranulocytosis and leukopenia)

