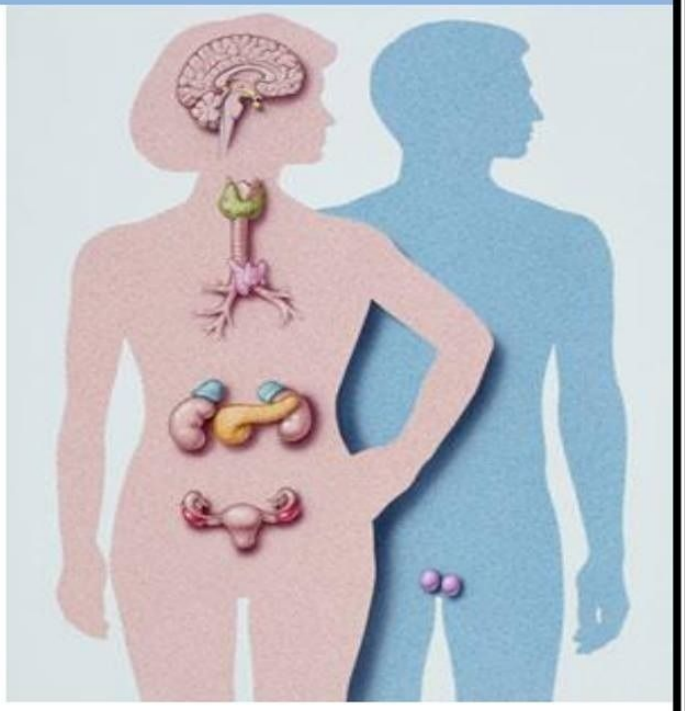
University of Jordan - Faculty of Medicine
(2013-19)

Medical Committee
The University of Jordan

Endocrine System



- [ ] Anatomy/Embryology/Histology
- [ ] Biochemistry
- [ ] Physiology
- [x] Pharmacology
- [ ] Pathology
- [ ] PBL

- [x] Slide
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- [ ] Handout
- [ ] Other

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Date:

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AUTACOIDS

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August, 2015

AUTACOIDS

Endogenous substances with complex physiologic and pathphysiologic functions; commonly understood to include histamine, serotonin, prostaglandins, and vasoactive peptides.

Histamine

- Occurs in plants, animals, venoms, and stinging secretions.
- Formed from l-histidine.
- Mediator of immediate allergic , and inflammatory reactions.
- Plays only a modest role in anaphylaxis.
- Gastric acid secretion.
- Neurotransmission.

Histamine

- Stored in granules in mast cells and basophils, and inactivated. Two types of release:
- **Immunologic Release:**
  - IgE and antigen interaction causes explosive degranulation and release of histamine, ATP, and other mediators.
- **Chemical and Mechanical Release:**
  - Drugs like morphine and tubocurarine.

Molecular Actions of Histamine

- G Protein Coupled Receptors:
- H 1, H2, H3, H4 types, no subfamilies.
- Activation of H1 receptors (in endothelium, smooth muscle cells, and nerve endings), elicits inositol triphosphate(IP3).
- Activation of H2 receptors(in gastric mucosa, cardiac muscle, and some immune cells), increases cAMP

TABLE 16–1 Histamine receptor subtypes.

Receptor Subtype	Distribution	Postreceptor Mechanism	Partially Selective Agonists	Partially Selective Antagonists or Inverse Agonists
H_1	Smooth muscle, endothelium, brain	G_q ↑ IP_3, DAG	Histaprodifen	Mepyramine,[1] triprolidine, cetirizine
H_2	Gastric mucosa, cardiac muscle, mast cells, brain	G_s ↑ cAMP	Amthamine	Cimetidine,[1] ranitidine,[1] tiotidine
H_3	Presynaptic autoreceptors and heteroreceptors: brain, myenteric plexus, other neurons	G_i ↓ cAMP	R-α-Methylhistamine, Imetit, Immepip	Thioperamide,[1] iodophenpropit, clobenpropit,[1] tiprolisant[1]
H_4	Eosinophils, neutrophils, CD4 T cells	G_i ↓ cAMP	Clobenpropit, Imetit, clozapine	Thioperamide[1]

[1] Inverse agonist.

cAMP, cyclic adenosine monophosphate; DAG, diacylglycerol; IP_3, inositol trisphosphate.

Pharmacologic Effects of Histamine

- Satiety effect
- Decrease BP and increase HR.
- Constricts bronchial muscle.
- Stimulates GI smooth muscle.
- Stimulates gastric acid secretion.
- *Triple Response: intradermal injection causes red spot, edema, and flare response.*
- Pain sensation.

Histamine Antagonists

- Physiologic Antagonists:
  - Epinehrine
- Release Inhibitors:
  - Cromolyn
  - Nedocromil
- Receptor Antagonists:
  - H1 antagonists
  - H2 antagonists

H1 Receptor Antagonists

- Reversible competitive binding to H1 receptors.
- Known long time ago, 60 years.
- Used in the treatment of allergy.
- Available without a prescription(OTC), both alone, or in combination as 'cold preparations" and 'sleep aids"

H1 Receptor Antagonists

- **First Generation:**
  - Strong sedatives because they can cross BBB. Dangers???.
  - Examples: Diphenhydramine, Chlorpheneramine
  - Have autonomic blocking effects
- **Second Generation:**
  - Less lipid soluble, so no sedative activity.
  - Examples: Fexofenadine, Loratidine, Cetrizine

Pharmacodynamics of H1 Antagonists

- **Sedation:**
  - Very common with first generation agents.
  - Varies among agents and patients.
  - No abuse potential.
  - Cause stimulation and convulsions at high doses.
- **Antinausea and antiemetic.**
- **Antiparkinsonism.**
- **Anticholinergic.**
- **Alpha blocking.**
- **Serotonin blocking.**
- **Local anesthesia**

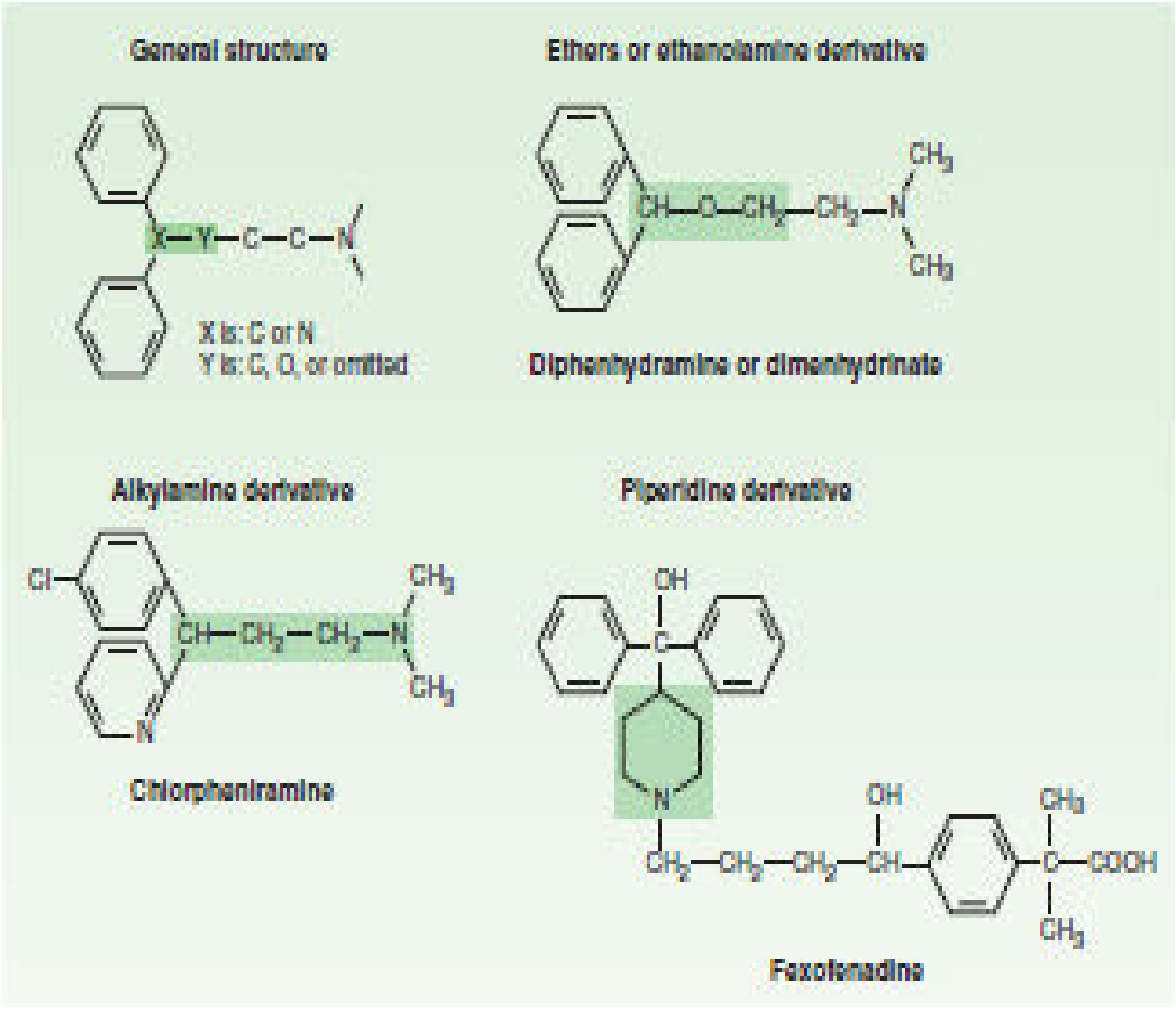


FIGURE 16–1 General structure of H_1-antagonist drugs and examples of the major subgroups. Chemical subgroups are indicated by shading.

Clinical uses of H1 Antagonists

- Allergic reactions:
  - More effective when given before exposure.
  - Sedative effect reduces awareness of itching.
  - Local application may induce allergy by itself.
- Motion Sickness and Vestibular Disturbances: ***Menier's Syndrome***.
- Nausea and vomiting of Pregnancy (***Morning Sickness***):
  - Teratogenic in rodents.

H2 Antagonists

- Breakthrough treatment for peptic ulcer disease(1972).
- Do not completely abolish acid secretion(40-60%).
- Replaced by proton pump inhibitors(100% inhibition).
- Cimetidine.
- Ranitidine.
- Famotidine.
- Naziditine.

Serotonin and 5-Hydroxytryptamine

- **Serotonin**: a vsoconstrictor released from the blood clot.
- **Enteramine**: a smooth muscle stimulant found in intestinal mucosa.
- **5-Hydroxytryptamine**(synthesized in 1951)

Serotonin and 5-Hydroxytryptamine

- Widely distributed in nature, found in plant (Banana) and animal tissues, venoms, and stings.
- Synthesized from L-tryptophan.
- Stored or rapidly inactivated by MAO.
- 90% is found in the enterochromaffin cells of the GIT.
- Also found in platelets, enteric nervous system, nerve endings, and brain.
- Involved in mood, sleep, appetite, temperature control, and pain perception.
- Involved in depression, anxiety, migraine,

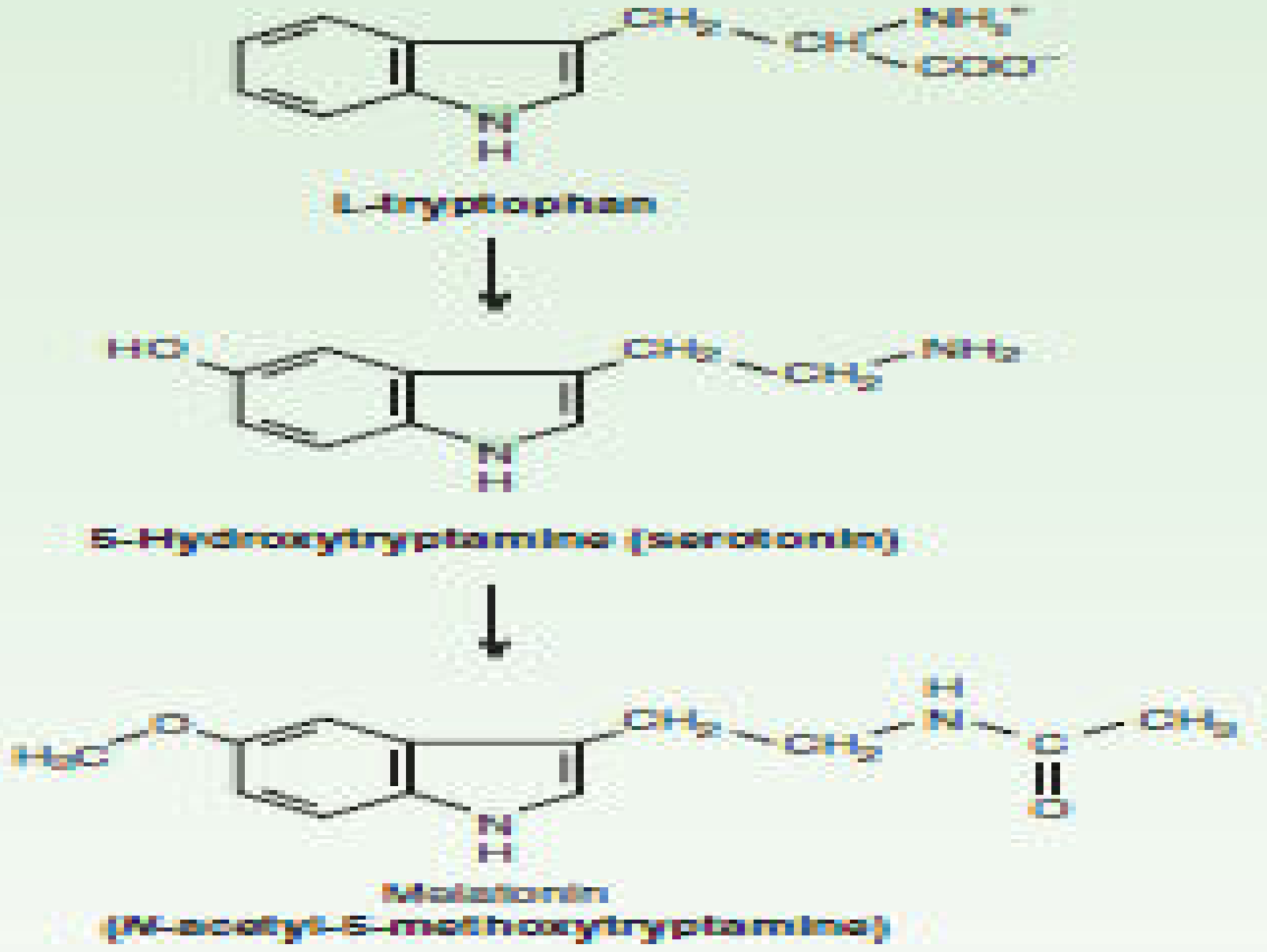


FIGURE 16–2 Synthesis of serotonin and melatonin from L-tryptophan.

TABLE 16–3 Serotonin receptor subtypes currently recognized. (See also Chapter 21.)

Receptor Subtype	Distribution	Postreceptor Mechanism	Partially Selective Agonists	Partially Selective Antagonists
5-HT_{1A}	Raphe nuclei, hippocampus	G_i, ↓ cAMP	8-OH-DPAT,[1] repinotan	WAY100635[1]
5-HT_{1B}	Substantia nigra, globus pallidus, basal ganglia	G_i, ↓ cAMP	Sumatriptan, L694247[1]	
5-HT_{1D}	Brain	G_i, ↓ cAMP	Sumatriptan, eletriptan	
5-HT_{1E}	Cortex, putamen	G_i, ↓ cAMP		
5-HT_{1F}	Cortex, hippocampus	G_i, ↓ cAMP	LY334864[1]	
5-HT_{1P}	Enteric nervous system	G_s, slow EPSP	5-Hydroxyindalpine	Renzapride
5-HT_{2A}	Platelets, smooth muscle, cerebral cortex	G_q, ↑ IP_3	α-Methyl-5-HT, DOI[1]	Ketanserin
5-HT_{2B}	Stomach fundus	G_q, ↑ IP_3	α-Methyl-5-HT, DOI[1]	RS127445[1]
5-HT_{2C}	Choroid, hippocampus, substantia nigra	G_q, ↑ IP_3	α-Methyl-5-HT, DOI,[1] lorcaserin	Mesulergine
5-HT_3	Area postrema, sensory and enteric nerves	Receptor is a Na^+/K^+ ion channel	2-Methyl-5-HT, m-chlorophenylbiguanide	Granisetron, ondansetron, others
5-HT_4	CNS and myenteric neurons, smooth muscle	G_s, ↑ cAMP	BIMU8,[1] renzapride, metoclopramide	GR113808[1]
5-$HT_{5A,B}$	Brain	↓ cAMP		
5-$HT_{6,7}$	Brain	G_s, ↑ cAMP		Clozapine (5-HT_7)

[1]Research agents; for chemical names see Alexander SPH, Mathie A, Peters JA: Guide to receptors and channels (GRAC). Br J Pharmacol 2009;158 (Suppl 1):S12.

cAMP, cyclic adenosine monophosphate; EPSP, excitatory postsynaptic potential; IP_3, inositol triphosphate.

Pharmacologic Effects of Serotonin

Nervous System:

- Melatonin
- Chemoreceptor Reflex(*Bezold-Jarish Reflex*): activation of 5-HT3 receptors in coronary arteries, leads to hypotension and bradycardia.

Respiratory System:

- Bronchoconstriction and hyperventilation.

Cardiovascular System:

- Vasoconstriction.
- Vasodilation in skeletal muscles and coronary arteries. Intact endothelium is required
- Platelets aggregation.

Pharmacologic Effects of Serotonin

GIT:

- Stimulation and diarrhea.
- *Carcinoid Syndrome*: due to a tumor of the enterochromaffin cells.

Skeletal Muscle:

- *Serotonin Syndrome:*
  - Due to excess serotnergic activity.
  - Potentially fatal .
  - Skeletal muscle contraction and hyperthermia
  - Predictable, not idiosyncratic.

Clinical Uses of Serotonin Agonists

Serotonin:

- Has no clinical application.

Buspirone:

- 5HT1A agonist, anxiolytic, nonsedating.

Triptans: e.g. Sumatryptan

- 5HT1D/1B agonists
- First line drugs for migraine headache.

Cisapride:

- 5HT4 agonist used only in gastroesophageal reflux.

Tagaserod:

- 5HT4 agonist

Fluoxetine:

- SSRI, widely used in depression.

Serotonin Antagonists

Phenoxybenzamine:

- An alpha blocker

Cyproheptadine:

- 5HT2 and H1 blocker.
- Useful in carcinoid and serotonin syndrome.

Ketanserine:

- 5HT2 blocker, antihypertensive agent.

Ritanserine:

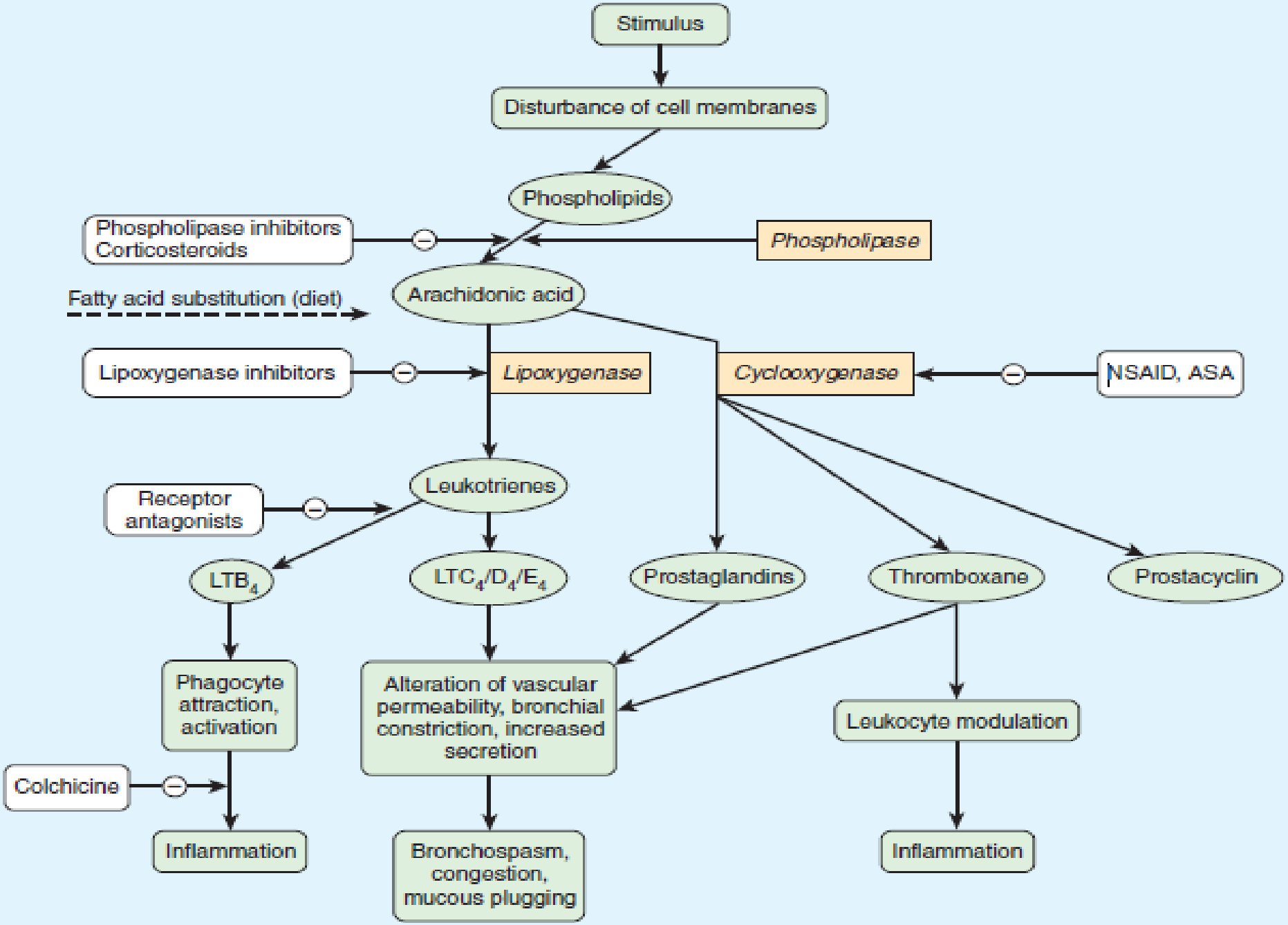
- 5HT2 blocker, prevents platelets sggregation.

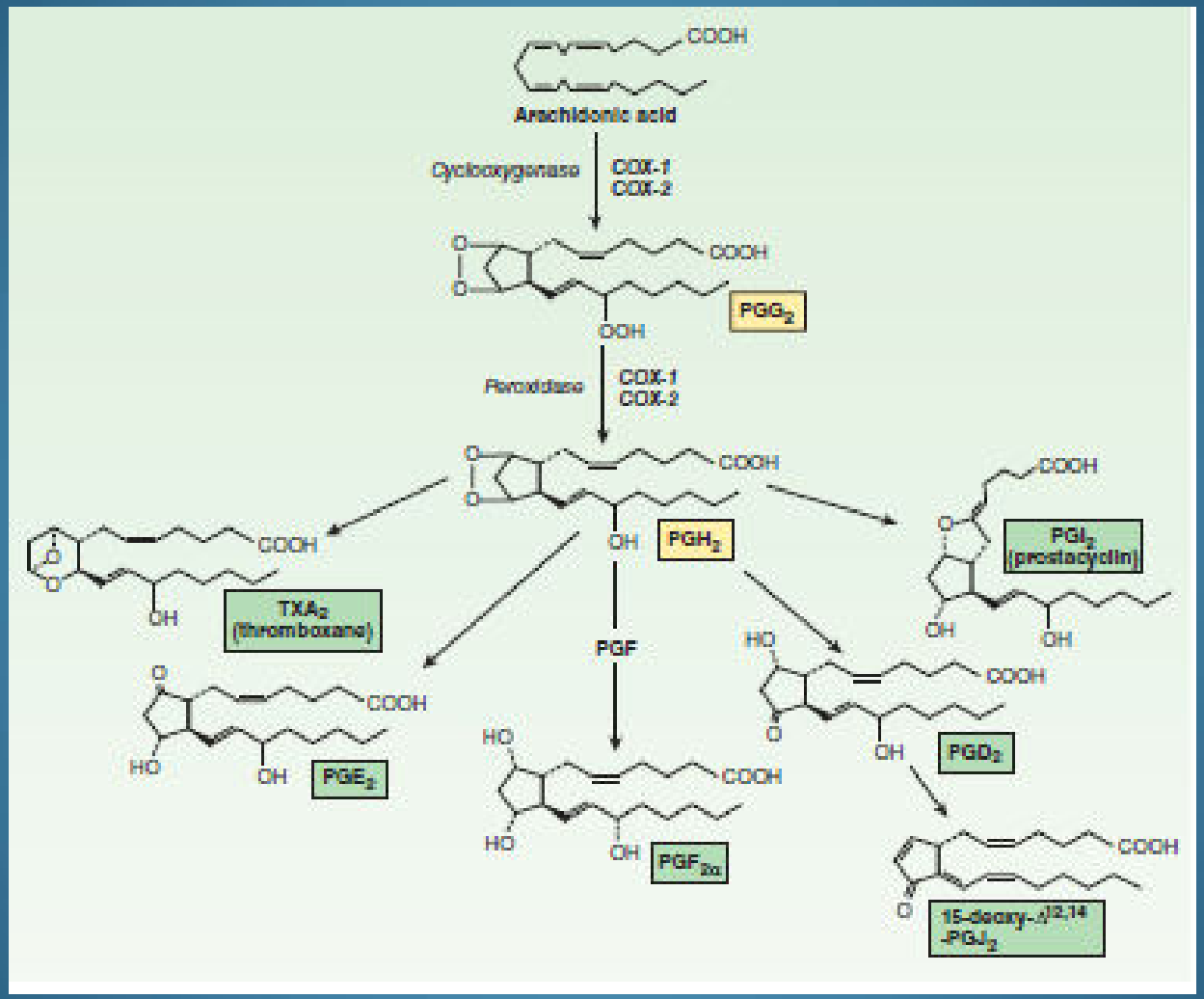
Ondansetron:

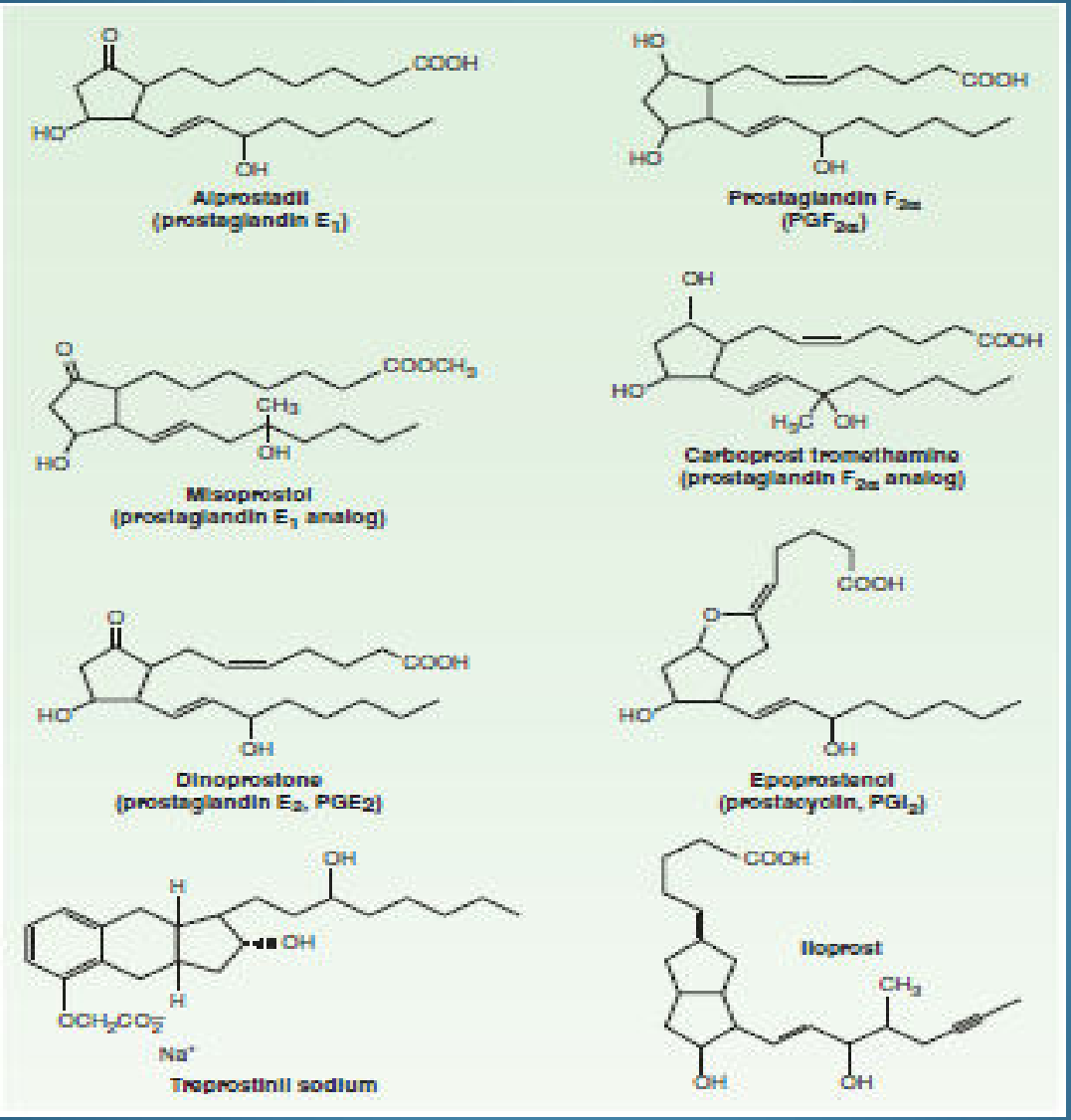
- 5HT3 blocker, used to prevent nausea and vomiting of cancer chemotherapy.

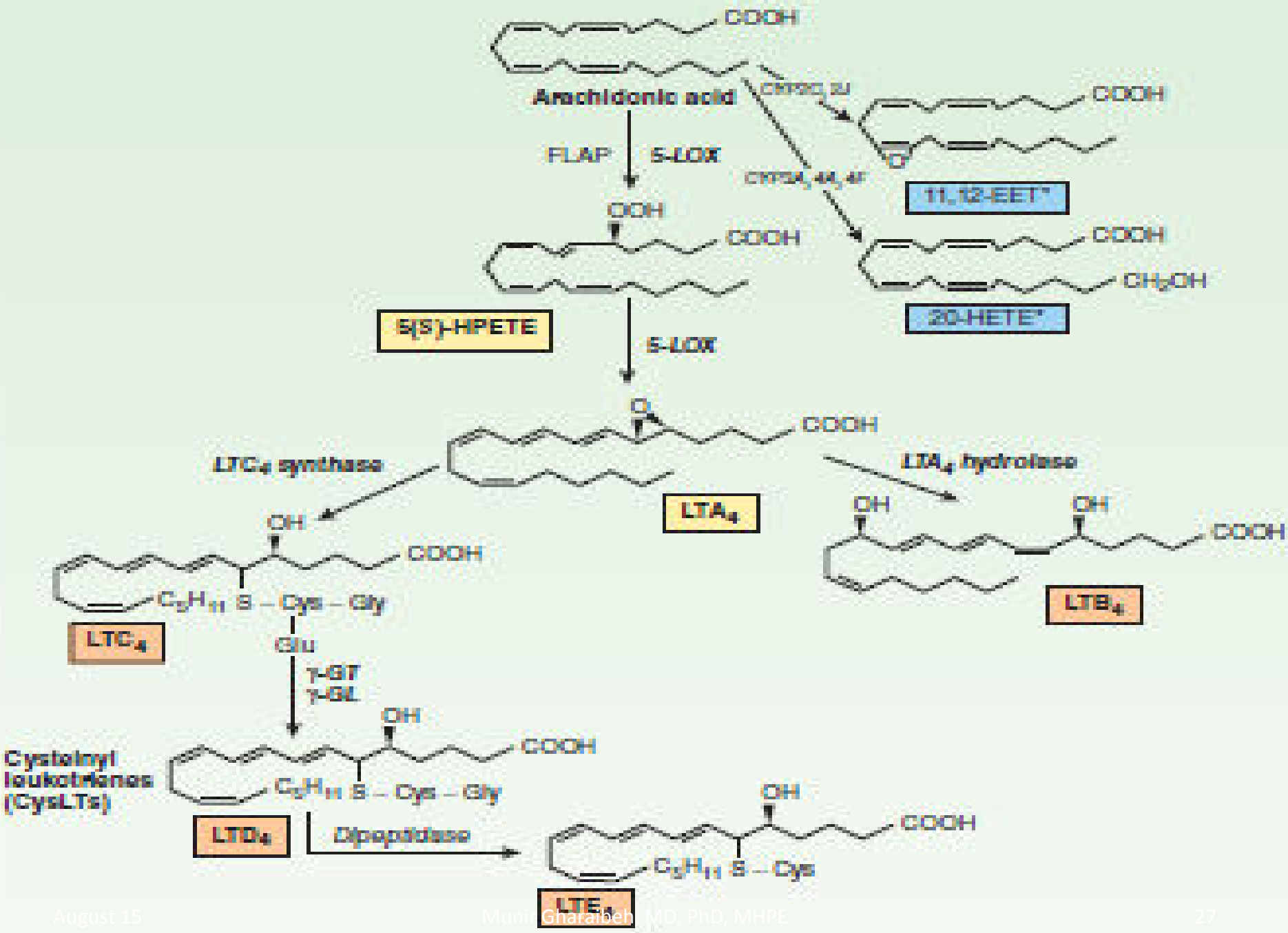
Ecosanoids

- Prostaglandins.
- Thromboxanes.
- Leukotrienes.


Stimulus
Disturbance of cell membranes
Phospholipids
Phospholipase inhibitors
Corticosteroids
Phospholipase
Fatty acid substitution (diet)
Arachidonic acid
Lipoxygenase inhibitors
Lipoxygenase
Cyclooxygenase
NSAID, ASA
Leukotrienes
Receptor antagonists
LTB4
LTC4/D4/E4
Prostaglandins
Thromboxane
Prostacyclin
Phagocyte attraction, activation
Alteration of vascular permeability, bronchial constriction, increased secretion
Leukocyte modulation
Colchicine
Inflammation
Bronchospasm, congestion, mucous plugging
Inflammation


COOH
Arachidonic acid
Cyclooxygenase
COX-1
COX-2
COOH
PGG2
OOH
Peroxidase
COX-1
COX-2
COOH
OH
PGH2
COOH
TXA2
(thromboxane)
OH
COOH
PGI2
(prostacyclin)
OH
OH
PGF
HO
COOH
PGE2
HO
OH
HO
COOH
PGD2
OH
HO
COOH
PGF2α
HO
OH
COOH
15-deoxy-Δ12,14
-PGJ2
O


Alprostadil
(prostaglandin E_1)
Prostaglandin $F_{2\alpha}$
($PGF_{2\alpha}$)
Misoprostol
(prostaglandin E_1 analog)
Carboprost tromethamine
(prostaglandin $F_{2\alpha}$ analog)
Dinoprostone
(prostaglandin E_2, PGE_2)
Epoprostenol
(prostacyclin, PGI_2)
Treprostinil sodium
Iloprost


COOH
Arachidonic acid
CYP2C, 2J
COOH
O
11,12-EET*
FLAP
5-LOX
CYP4A, 4F
OOH
COOH
COOH
CH2OH
20-HETE*
5(S)-HPETE
5-LOX
O
COOH
LTC4 synthase
LTA4 hydrolase
LTA4
OH
COOH
OH
OH
COOH
C5H11 S – Cys – Gly
LTC4
LTB4
Glu
γ-GT
γ-GL
OH
COOH
Cysteinyl leukotrienes (CysLTs)
C5H11 S – Cys – Gly
LTD4
Dipeptidase
OH
COOH
C5H11 S – Cys
LTE4

Vasoactive Peptides

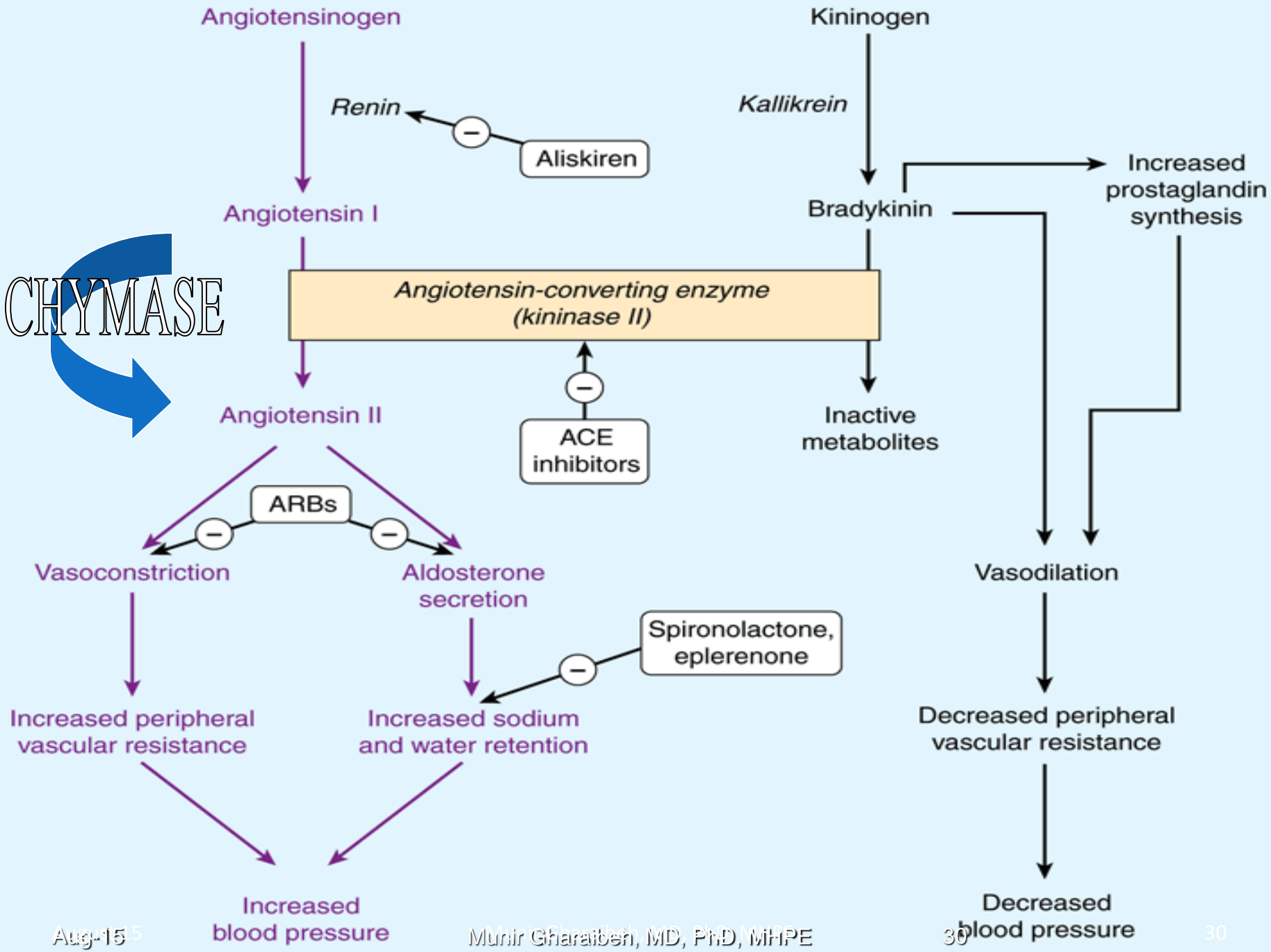
- Renin-Angiotensin- Aldosterone System(RAAS).
- Kinins.
- Vasopressin.
- Natriuretic Peptides.
- Endothelins.
- Vasoactive Intestinal Peptide.
- Subtance P.
- Neurotensin.
- Calctonin Gene-Related Peptide.
- Adrenomedullin.
- Neuropeptide Y
- Urotensin.

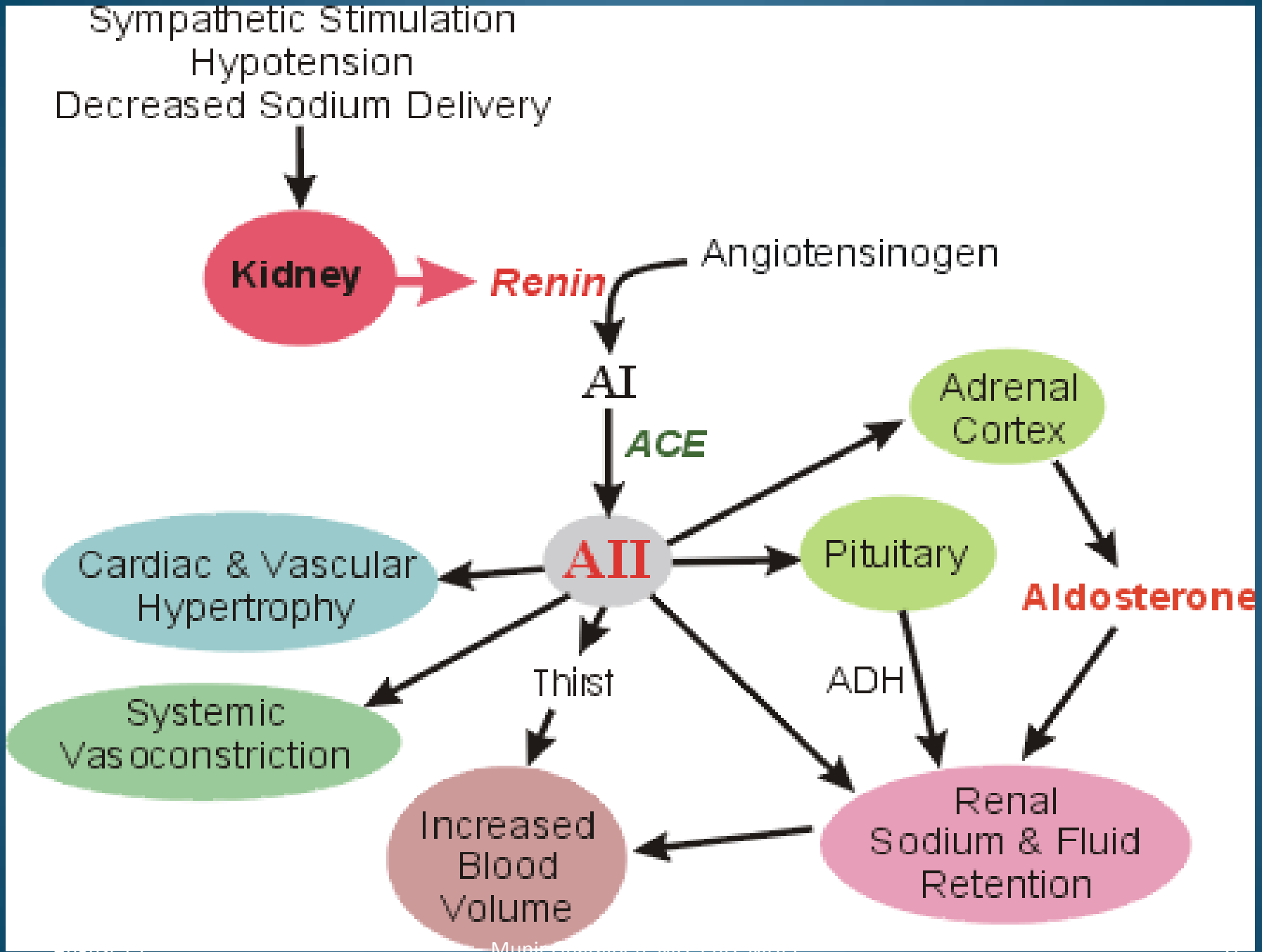
What is RAAS?

RAAS is a hormonal cascade that functions to control arterial pressure, tissue perfusion, and extracellular volume.

Pathophysiologic processes might occur when components of the RAAS are **overexpressed or inhibited**, thus disturbing the balance of this regulatory system

Dysregulation of the RAAS plays an important role in the pathogenesis of cardiovascular and renal disorders.


Angiotensinogen
Renin
Aliskiren
Angiotensin I
CHYMASE
Angiotensin-converting enzyme
(kininase II)
Angiotensin II
ACE
inhibitors
ARBs
Vasoconstriction
Aldosterone
secretion
Spironolactone,
eplerenone
Increased peripheral
vascular resistance
Increased sodium
and water retention
Increased
blood pressure
Kininogen
Kallikrein
Bradykinin
Increased
prostaglandin
synthesis
Inactive
metabolites
Vasodilation
Decreased peripheral
vascular resistance
Decreased
blood pressure


Sympathetic Stimulation
Hypotension
Decreased Sodium Delivery
Kidney
Renin
Angiotensinogen
AI
ACE
Adrenal Cortex
Cardiac & Vascular Hypertrophy
AII
Pituitary
Aldosterone
Thirst
ADH
Systemic Vasoconstriction
Increased Blood Volume
Renal Sodium & Fluid Retention

Local Renin-angiotensin Systems

- The renin-angiotensin system is a classic endocrine system.
- There are complete local renin-angiotensin systems existing entirely within organs and tissues .

  e.g. in the vascular endothelium, volume depletion increases angiotensinogen levels in aortic smooth muscle.

-Then either locally produced or systemic renin could initiate the sequential formation of angiotensin I and II.

The Cardiac Renin-Angiotensin System

-Stretch directly increases:

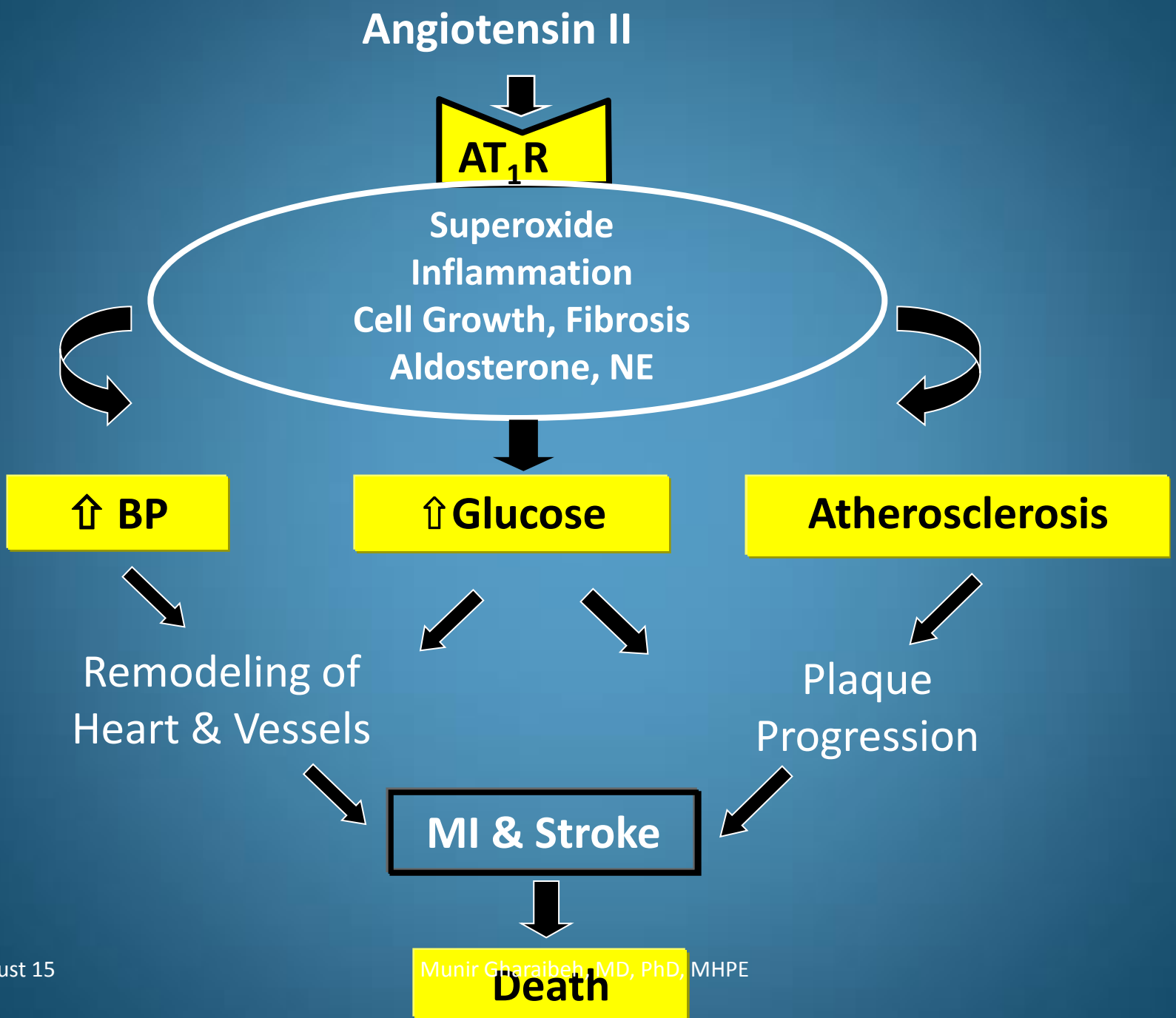
Release of angiotensin II from cardiac myocytes.

Expression of the angiotensinogen gene on the long-term.

-The apparent function of the cardiac RAAS is to maintain cellular balance of inhibition and cellular growth .

Effects of the Angiotensin II on the Heart

1- Inotropy .
2- Hypertrophy.
3- Ventricular remodeling
4- Electrical remodeling.
5- Pathogenesis of atherosclerosis

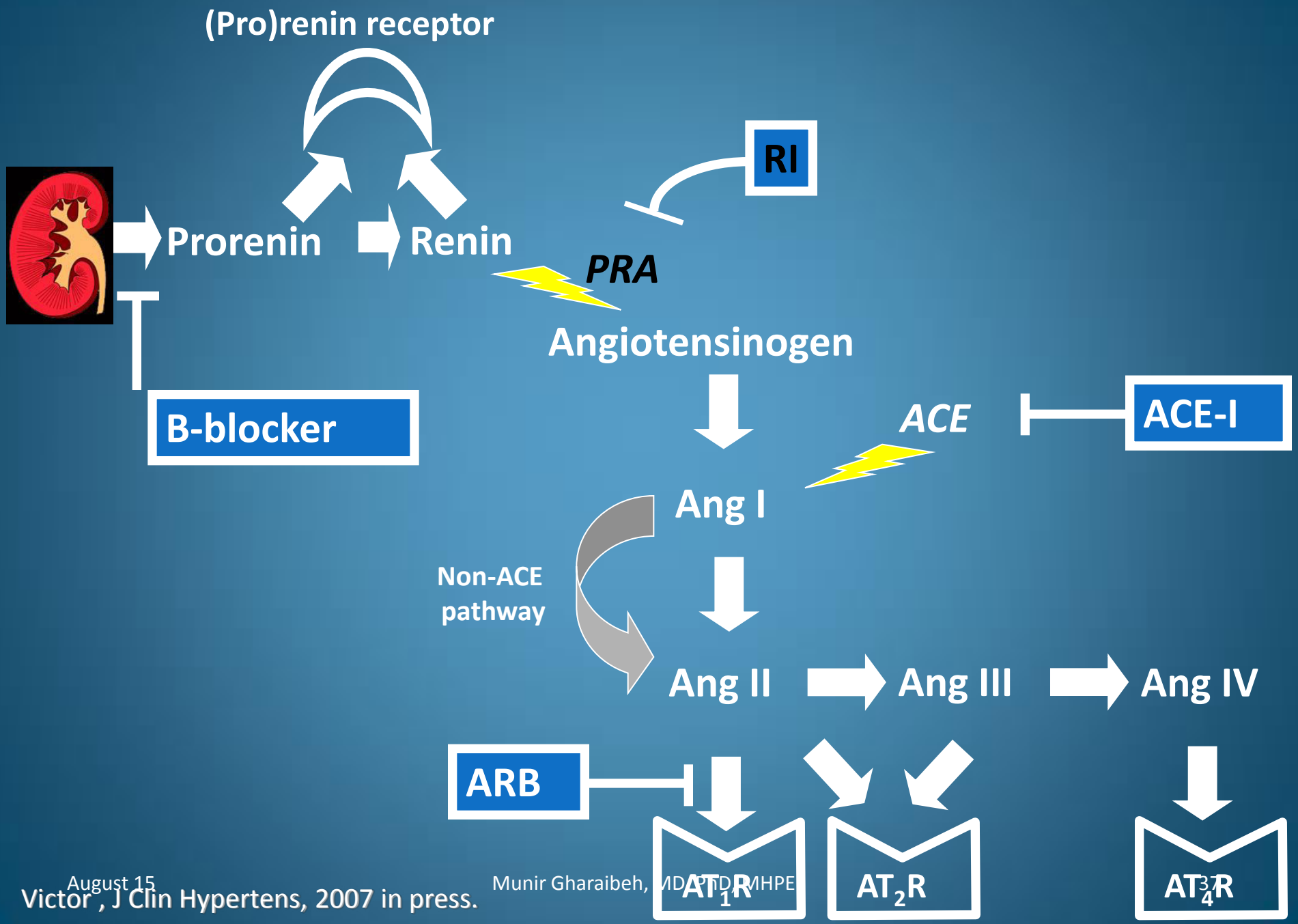

Angiotensin II
AT1R
Superoxide
Inflammation
Cell Growth, Fibrosis
Aldosterone, NE
⇧ BP
⇧Glucose
Atherosclerosis
Remodeling of Heart & Vessels
Plaque Progression
MI & Stroke
Death

Alternative Pathways Of The Renin

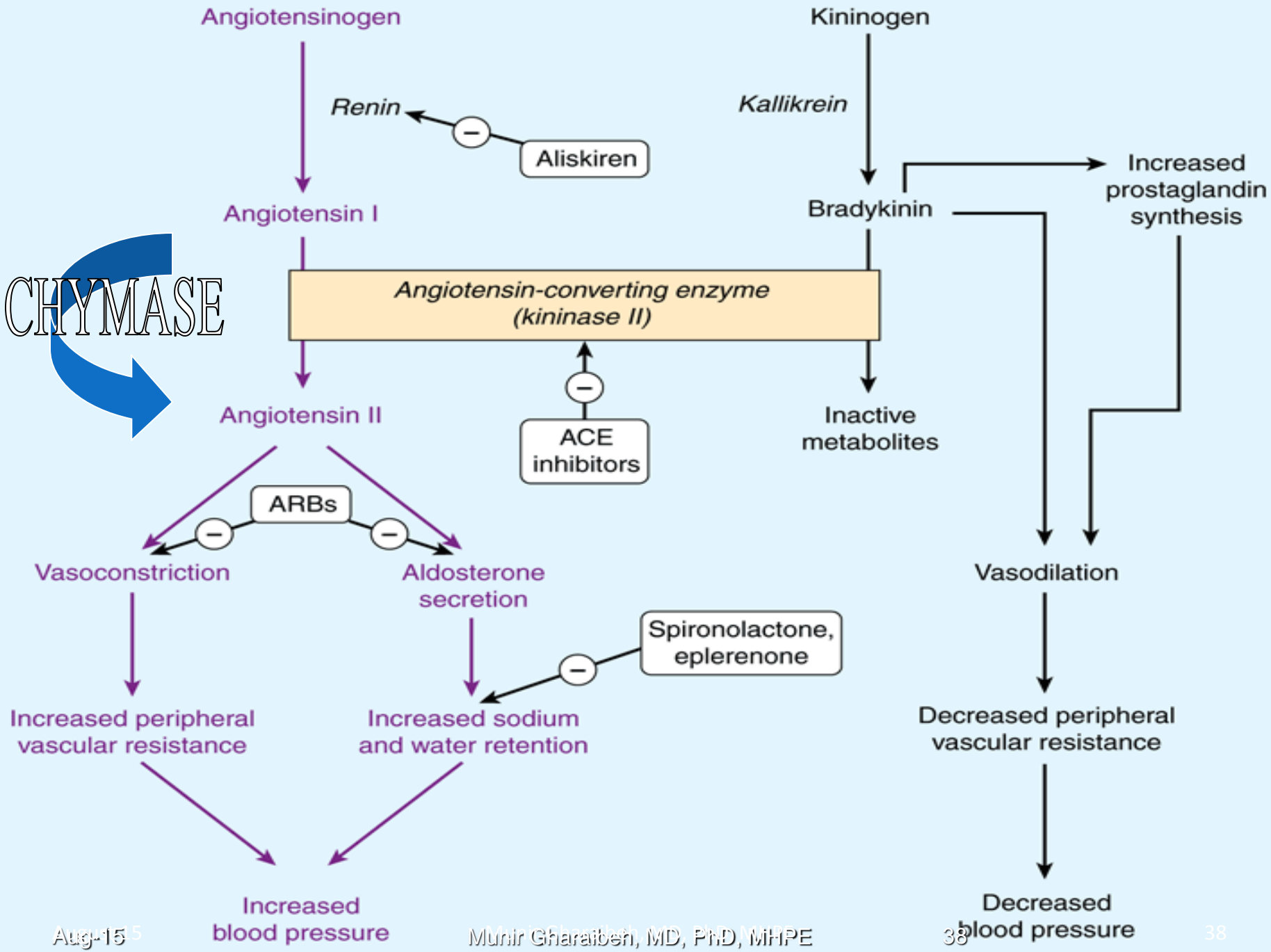
Alternative enzymatic pathways, not involving ACE, contribute to angiotensin II production.

Human heart chymase appears to be the most important of these pathways, particularly in the ventricles .

The physiologic importance of chymase is uncertain because of the presence of natural protease inhibitors in the interstitial fluid which inhibit chymase-induced angiotensin II production.



Victor, J Clin Hypertens, 2007 in press.


Angiotensinogen
Renin
Aliskiren
Angiotensin I
CHYMASE
Angiotensin-converting enzyme
(kininase II)
Angiotensin II
ACE
inhibitors
ARBs
Vasoconstriction
Aldosterone
secretion
Spironolactone,
eplerenone
Increased peripheral
vascular resistance
Increased sodium
and water retention
Increased
blood pressure
Kininogen
Kallikrein
Bradykinin
Increased
prostaglandin
synthesis
Inactive
metabolites
Vasodilation
Decreased peripheral
vascular resistance
Decreased
blood pressure

Direct Renin Inhibitors

The most recent class of agents that block the RAAS, are the direct renin inhibitors represented by **aliskiren,**

Recently approved for treatment of hypertension.

This compound differs from the ACEIs and ARBs in that, by blocking the catalytic activity of renin at the point of activation of the RAAS, it blocks the synthesis of all angiotensin peptides and prevents the compensatory increase in renin activity

Angiotensin-converting enzyme inhibitors (ACEI)

- **ACEI lower systemic vascular resistance and venous pressure, and reduce levels of circulating catecholamines, thus improving myocardial performance.**

Angiotensin-converting enzyme inhibitors ACEI

- **Captopril**
- **Benazepril**
- **Enalapril**
- **Fosinopril**
- **Lisinopril**
- **Moexipril**
- **Quinapril**
- **Ramipril**

Cardiorenal Effects of ACE Inhibitors

- Vasodilation (arterial & venous):
  - reduce arterial & venous pressure.
  - reduce ventricular afterload and preload.
- Decrease blood volume:
  - natriuretic.
  - diuretic.
- Depress sympathetic activity.
- Inhibit cardiac and vascular hypertrophy.

Angiotensin - Converting Enzyme Inhibitors (ACEI)

Therapeutic Benefits:

- High-rennin hypertension (present in 20% of cases).
- HF and Ischemic Heart Disease.
- Do not increase HR.
- Diabetic Nephropathy, dilate efferent arterioles which will reduce intraglomerular pressure and consequently protects against progressive glomerulosclerosis.
- No need for a diuretic but can be added.
- Can be combined with CCBs.
- Should not be combined with Beta blockers, except in HF.
- No metabolic effects(DM, Lipids, Uric Acid).

Angiotensin - Converting Enzyme Inhibitors (ACEI)

Side Effects:

Captopril is SH containing drug, so very toxic(bone marrow suppression, disguesia, proteinuria, allergic skin rash, fever)

- **Hypotension(*First Dose Phenomena*) especially with renovascular hypertension.**
- **K+ retention, especially in the presence of renal dysfunction or when combined with K+ sparing diuretics or ARBs.**
- **Cough(10% of patients).**
- **Angioedema.**

Angiotensin Receptor Antagonists(ARBs)

Losartan.

Irbersartan.

Candesartan.

Valsartan

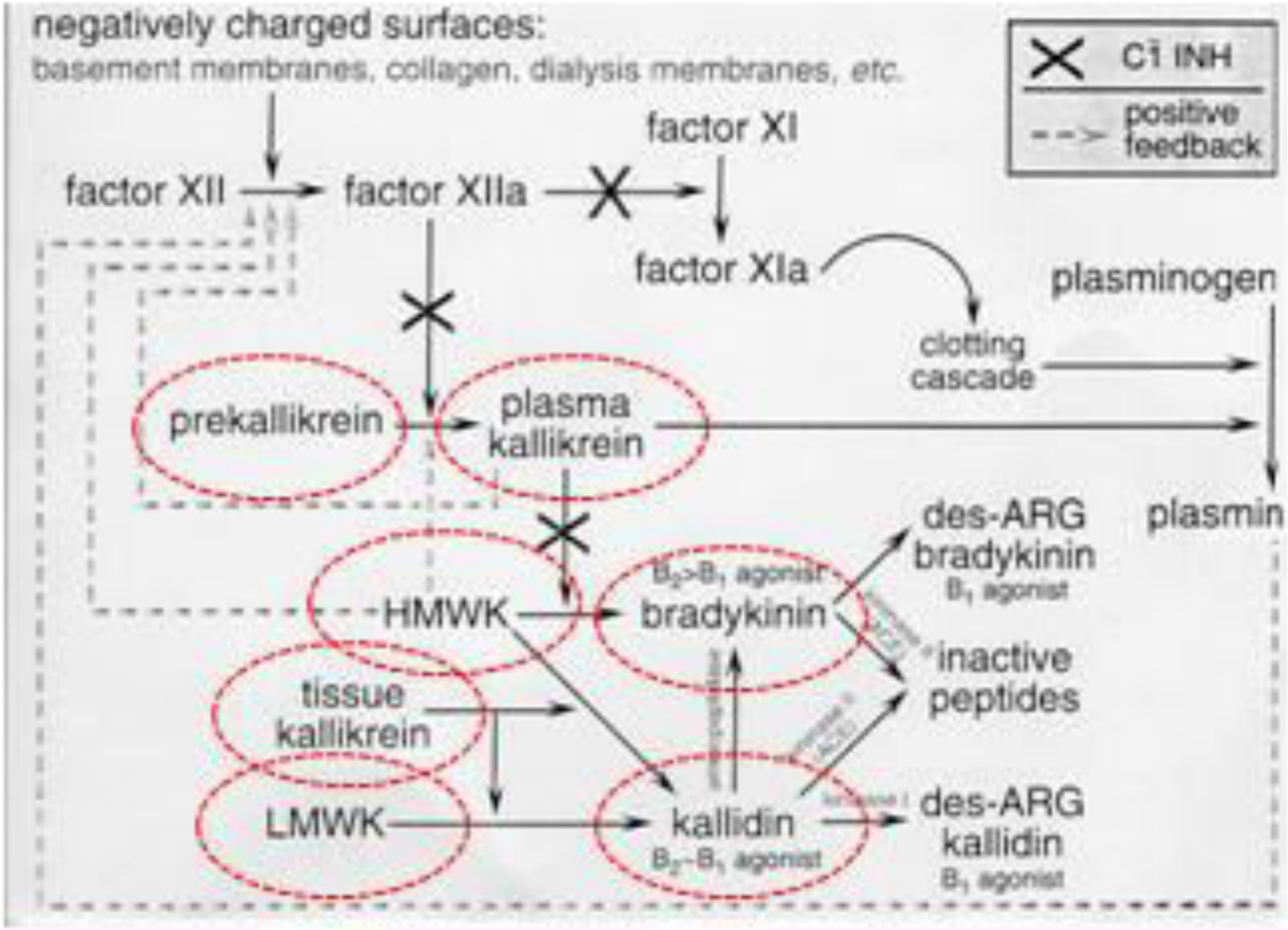
Have similar haemodynamic effects to ACEI

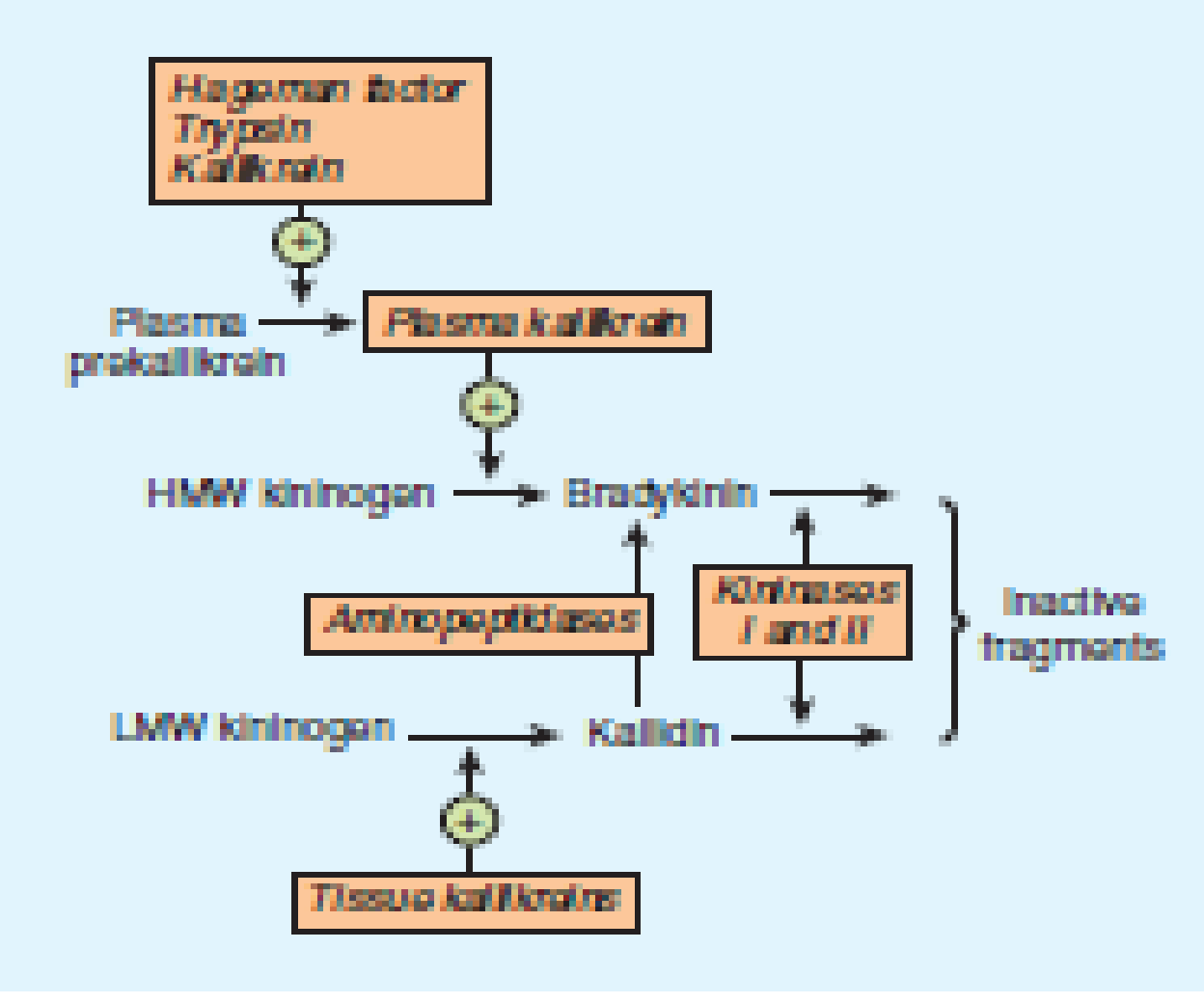
Do not affect bradykinin metabolism.

Do not cause cough.

Block the effects of Angiotensin II generated from both pathways (chymase &ACE)

Kallikrein Kinin System




Hageman factor
Trypsin
Kallikrein
Plasma prekallikrein
Plasma kallikrein
HMW kininogen
Bradykinin
Aminopeptidases
Kininases I and II
Inactive fragments
LMW kininogen
Kallidin
Tissue kallikrein

Actions of Kinins

Cardiovascular System:

- Arteriolar vasodilation: direct & endothelium-dependent via the release of NO and PGI_2
- Venous constriction: direct and via $PGF_{2\alpha}$
- Increased capillary permeability
- Response to iv bradykinin:
  - Transient decrease in BP: direct arteriolar dilation
  - Restoration of normal BP: reflex sympathetic discharge

Actions of Kinins

Other Effects:

- Pro-inflammatory
- Algesic: via PGE_2
- Constrict visceral smooth muscle

Putative Effects:

- Local modulators of blood flow
- Modulate tone of salivary and pancreatic ducts
- Regulate transport of H_2O, electrolytes, aa in GIT

Kinin Receptors

B_1:

- Sensitive to des-Arg metabolites
- Kallidin is 10x more potent than BK
- limited tissue distribution
- VSM contraction, proliferation,
- Collagen synthesis, inflammation
- Induced by trauma

B_2 (B_{2A}, B_{2B}):

- Sensitive to intact peptides
- GPCR; wide tissue distribution
- Vasodilation, permeability, pain.
- Ca^{++} mobilization, Cl^- transport, NO, PLC, PLA_2, AC

B_3: Unknown function

Kinins

Table 25–2
Structure of Kinin Agonists and Antagonists, Listed from Carboxyl Terminus

NAME	STRUCTURE*	FUNCTION
Bradykinin	Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg	Agonist, $B_2 > B_1$
Kallidin	Lys-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg	Agonist, $B_2 \simeq B_1$
des-Arg^9-bradykinin	Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe	Agonist, B_1
des-Arg^{10}-kallidin	Lys-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe	Agonist, B_1
des-Arg^9-[Leu^8]-bradykinin	Arg-Pro-Pro-Gly-Phe-Ser-Pro-Leu	Antagonist, B_1
[D-Phe^7]-bradykinin	Arg-Pro-Pro-Gly-Phe-Ser-[D-Phe]-Phe-Arg	Antagonist, B_2 (also B_1 to some extent)
HOE 140	[D-Arg]-Arg-Pro-Hyp-Gly-Thi-Ser-Tic-Oic-Arg*	Antagonist, B_2
WIN 64338	Nonpeptide	Antagonist, B_2

*Hyp, *trans*-4-hydroxy-Pro; Thi, β-(2-thienyl)-Ala; Tic, [D]-1,2,3,4-tetrahydroisoquinolin-3-yl-carbonyl; Oic, (3as,7as)-octahydroindol-2-yl-carbonyl.
SOURCE: Modified from Trifilieff *et al.*, 1993.

Kinins

Potential Clinical Uses of KKS Antagonists:

- Allergic conditions
- Anti-inflammatory
- Anti-nociceptive