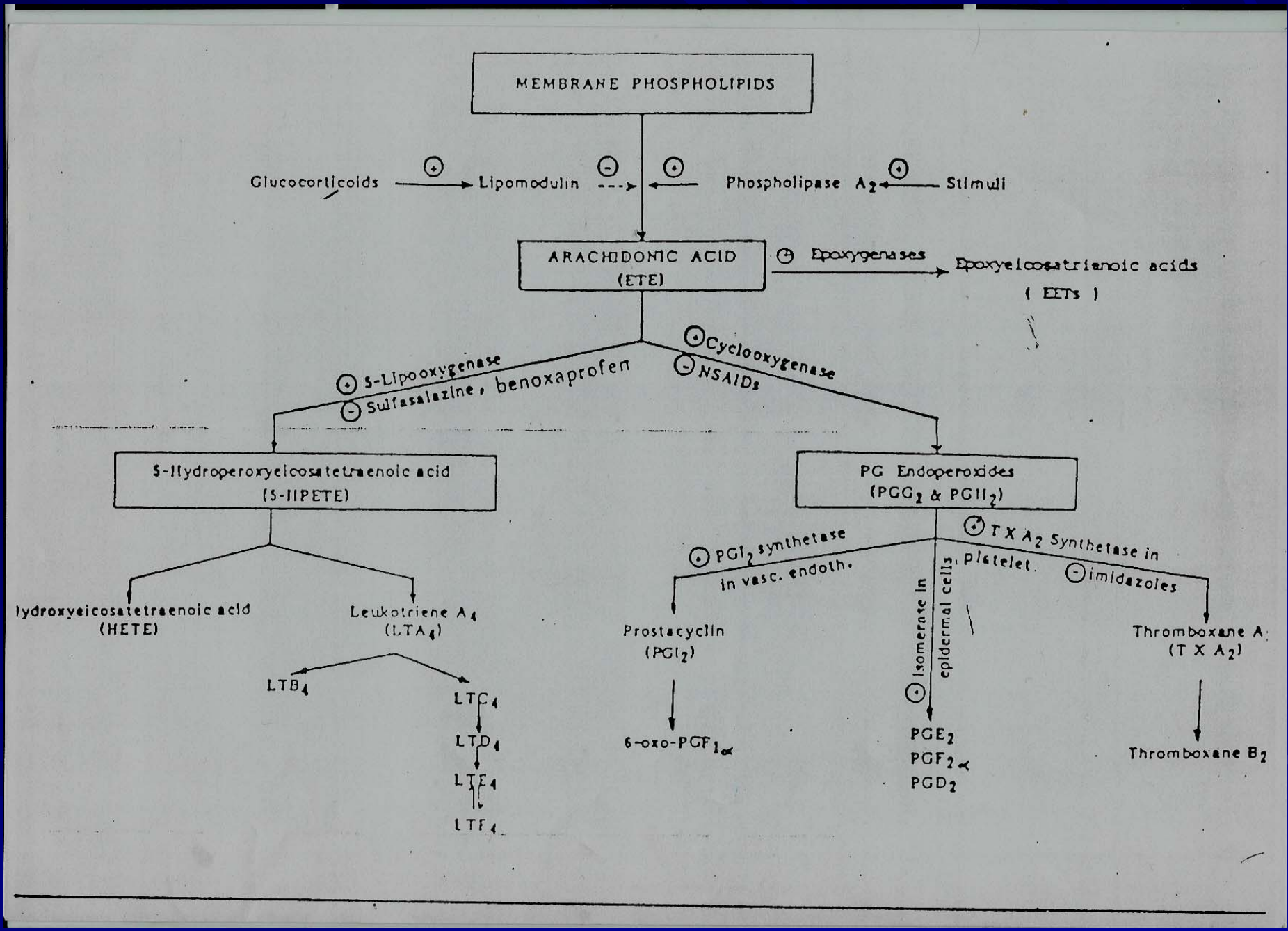
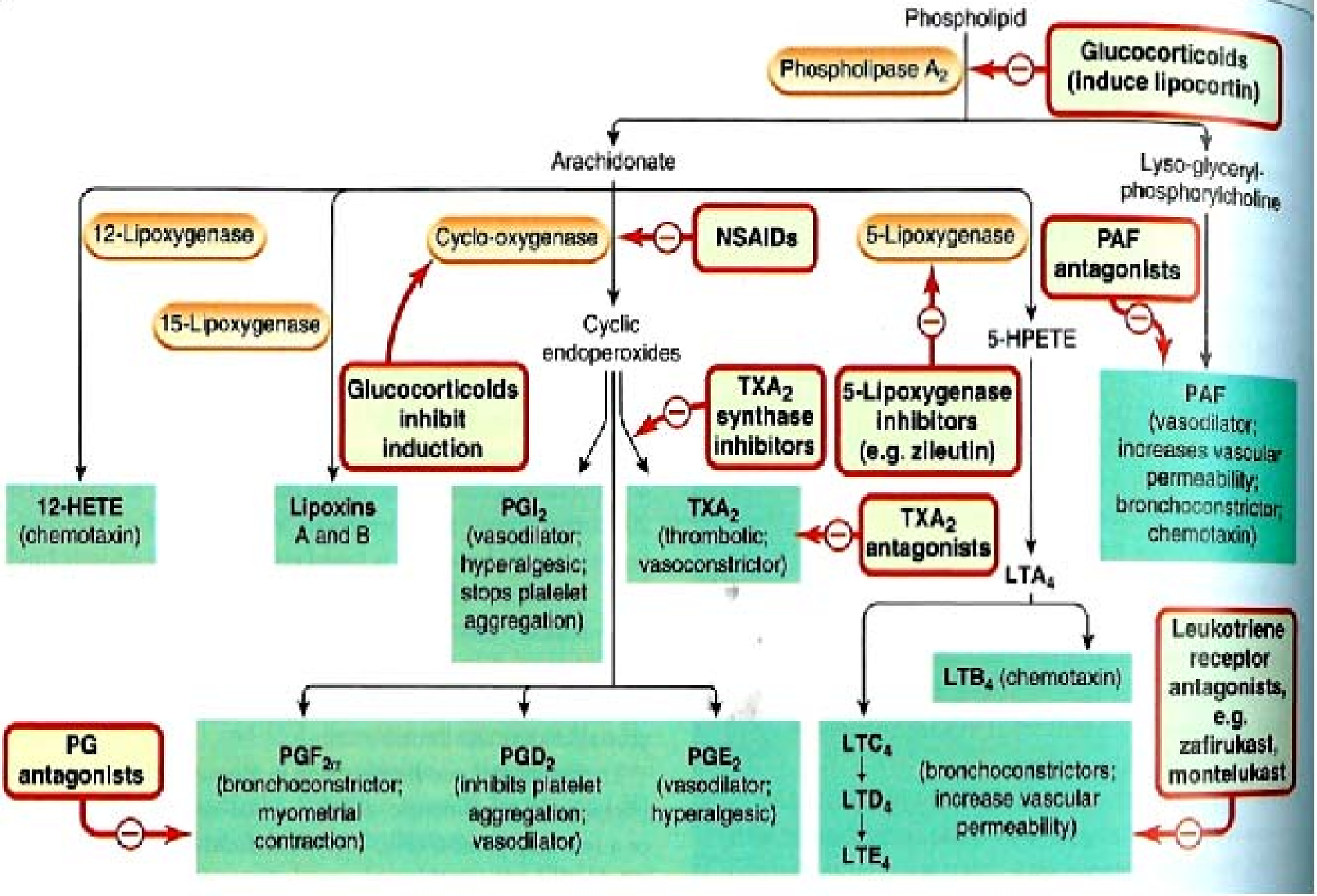
Lipid-Derived autacoids

1. Platelet activating factor (PAF).
2. Eicosanoids
   - Leukotrienes
   - Prostanoids


MEMBRANE PHOSPHOLIPIDS
Glucocorticoids
Lipomodulin
Phospholipase A2
Stimuli
ARACHIDONIC ACID (ETE)
Epoxygenases
Epoxyeicosatrienoic acids (EETs)
5-Lipooxygenase
Sulfasalazine, benoxaprofen
Cyclooxygenase
NSAIDs
5-Hydroperoxyeicosatetraenoic acid (5-HPETE)
PG Endoperoxides (PGG2 & PGH2)
PGI2 synthetase in vasc. endoth.
TXA2 Synthetase in platelet.
imidazoles
Isomerase in epidermal cells
Hydroxyeicosatetraenoic acid (HETE)
Leukotriene A4 (LTA4)
Prostacyclin (PGI2)
Thromboxane A2 (TXA2)
LTB4
LTC4
LTD4
LTE4
LTF4
6-oxo-PGF1α
PGE2
PGF2α
PGD2
Thromboxane B2


Phospholipid
Phospholipase A_2
Glucocorticoids (induce lipocortin)
Arachidonate
Lyso-glyceryl-phosphorylcholine
12-Lipoxygenase
Cyclo-oxygenase
NSAIDs
5-Lipoxygenase
PAF antagonists
15-Lipoxygenase
Cyclic endoperoxides
5-HPETE
Glucocorticoids inhibit induction
TXA_2 synthase inhibitors
5-Lipoxygenase inhibitors (e.g. zileutin)
PAF (vasodilator; increases vascular permeability; bronchoconstrictor; chemotaxin)
12-HETE (chemotaxin)
Lipoxins A and B
PGI_2 (vasodilator; hyperalgesic; stops platelet aggregation)
TXA_2 (thrombolic; vasoconstrictor)
TXA_2 antagonists
LTA_4
LTB_4 (chemotaxin)
Leukotriene receptor antagonists, e.g. zafirukast, montelukast
PG antagonists
$PGF_{2\alpha}$ (bronchoconstrictor; myometrial contraction)
PGD_2 (inhibits platelet aggregation; vasodilator)
PGE_2 (vasodilator; hyperalgesic)
LTC_4
LTD_4
LTE_4
(bronchoconstrictors; increase vascular permeability)

Platelet aggregating factor (PAF)

- Produced by platelets, macrophages and eosinophils
- Platelet aggregation
- mediator of inflammation
- Vasodilatation
- Increased capillary permeability (Oedema)
- Chemotactic for leucocytes
- smooth muscles contraction (bronchoconstriction).

Leukotrienes

- Mediators of inflammation and allergy in asthma.
- Vasodilatation.
- Increase capillary permeability.
- Bronchoconstriction.
- Chemotactic action.
- Intestinal contraction

Types

LTA4

LTB4 (Chemotaxis)

LTC4, LTD4, LTE4 (Bronchoconstriction)

Leukotriene Blockers

Treatment of asthma

Zileuton (5-Lipo-oxygenase inhibitor).

Zafilurkast (Leukotriene D4 antagonist).

Prostaglandins

Chemistry

Synthesis

the action of Phospholipase A2 on arachidonic acid and then by cyclooxygenase to PGs.

Metabolism

PG dehydrogenase

Types

Prostacyclin (PGI2) - PGE2 –PGF2α - PGD2

TABLE 13-1 Physiologic and pharmacologic effects of prostaglandins and related eicosanoids

Biologic process	Eicosanoid	Effect
Reproduction	PGE_2	Contract pregnant uterus
	$PGF_{2\alpha}$	Destruct corpus luteum
		Contract pregnant uterus
Blood pressure regulation	PGE_1, PGE_2, PGI_2	Dilate blood vessels
	$PGF_{2\alpha}$	Constrict veins
	TXA_2	Constrict arteries
Gastric secretion	PGE_1, PGE_2	Contract longitudinal smooth muscle, stimulate bicarbonate secretion
	$PGF_{2\alpha}$, LTC_4, LTD_4	Contract smooth muscle
Inflammation	PGE_1, PGE_2, PGI_2	Increase local blood flow, increase vascular permeability
	LTB_4	Chemotactic for leukocytes
	LTC_4, LTD_4	Increase vascular permeability
Bronchoconstriction	PGD_2, $PGF_{2\alpha}$, TXA_2, LTC_4, LTD_4	Cause bronchoconstriction
	PGE_1, PGE_2, PGI_2	Cause bronchodilation
Platelet aggregation	PGE_1, PGD_2, PGI_2	Inhibit platelet aggregation
	PGG_2, PGH_2, TXA_2	Induce platelet aggregation

PGI 2	TXA2
Increase cAMP	IP3 & DAG
Inhibits platelet aggregation	Stimulate platelet aggregation
Vasodilatation .	Vasoconstriction
Bronchodilation .	Bronchoconstriction
Endothelium	Platelets
Increase GFR Diuretic Natriuretic actions	Renal vasoconstriction ADH-like action

PGE2	PGF2α
IP3 &DAG or cAMP	IP3 &DAG
Vasodilatation	Vasoconstriction
Bronchodilation	Bronchoconstriction
GIT contraction	GIT contraction
Contraction of pregnant uterus	Contraction of pregnant uterus
↑GFR ↑H2O & Na excretion Gastroprotective action Mediator of fever	No action No action

Uses

- **Misoprostol (PGE1)**
  - **NSAID-induced gastritis (peptic ulcer)**
- **alprostadil (PGE1)**
  - **Impotence, Placed in urethra (minisuppositories).**
  - **Maintain ductus arteroisus patent before surgery.**

Dinoprostone(PGE2) Intravaginally

- induction of labour or abortion

Carboprost tromethamine (PGF2α)

- Induction of labour or abortion (intramaniotic injection, I.M. Intravaginally).

Epoprostenol (PGI2) I.V.

- Pulomonary hypertension
- antithrombotic (inhibit platelet aggregation)

Polypeptide autacoids

Renin -Angiotensin -Aldosterone System (RAAS)

Metabolism:

- Short duration of action
- Metabolized by aminopeptidase into Ang III& angiotensinase into peptide fragments

Actions:

Blood pressure: Hypertension

- Direct vasoconstriction
- Release of catecholamines
- +Ve inotropic effect
- Increased sympathetic outflow

Adrenal cortex:

- aldosterone synthesis and secretion
- Renal blood vessels: vasoconstriction
- CNS: increased secretion of ADH & ACTH

RAA blockers

- Renin: B-blockers
- ACE inhibitors: captopril - enalpril
- Ang II blockers: losartan-candesartan

Vasoactive polypeptides

Vasoconstrictors

Angiotensin – Endothelin-Vasopressin-Urotensin – neuropeptide Y

Vasodilators kinins –natriuretic peptides-

Vasoactive intestinal peptide-substance P- neurotensin - adrenomedullin

Endothelin

RECEPTORS

ET A : Smooth muscles

ET B : Vascular endothelial cells

Actions

1. Vasoconstriction
2. Direct positive inotropic and chronotropic effects.
3. Decrease GFR
4. Constriction of bronchial smooth muscles
5 . Increase secretion of renin, aldosterone, ANP.

Bosentan :

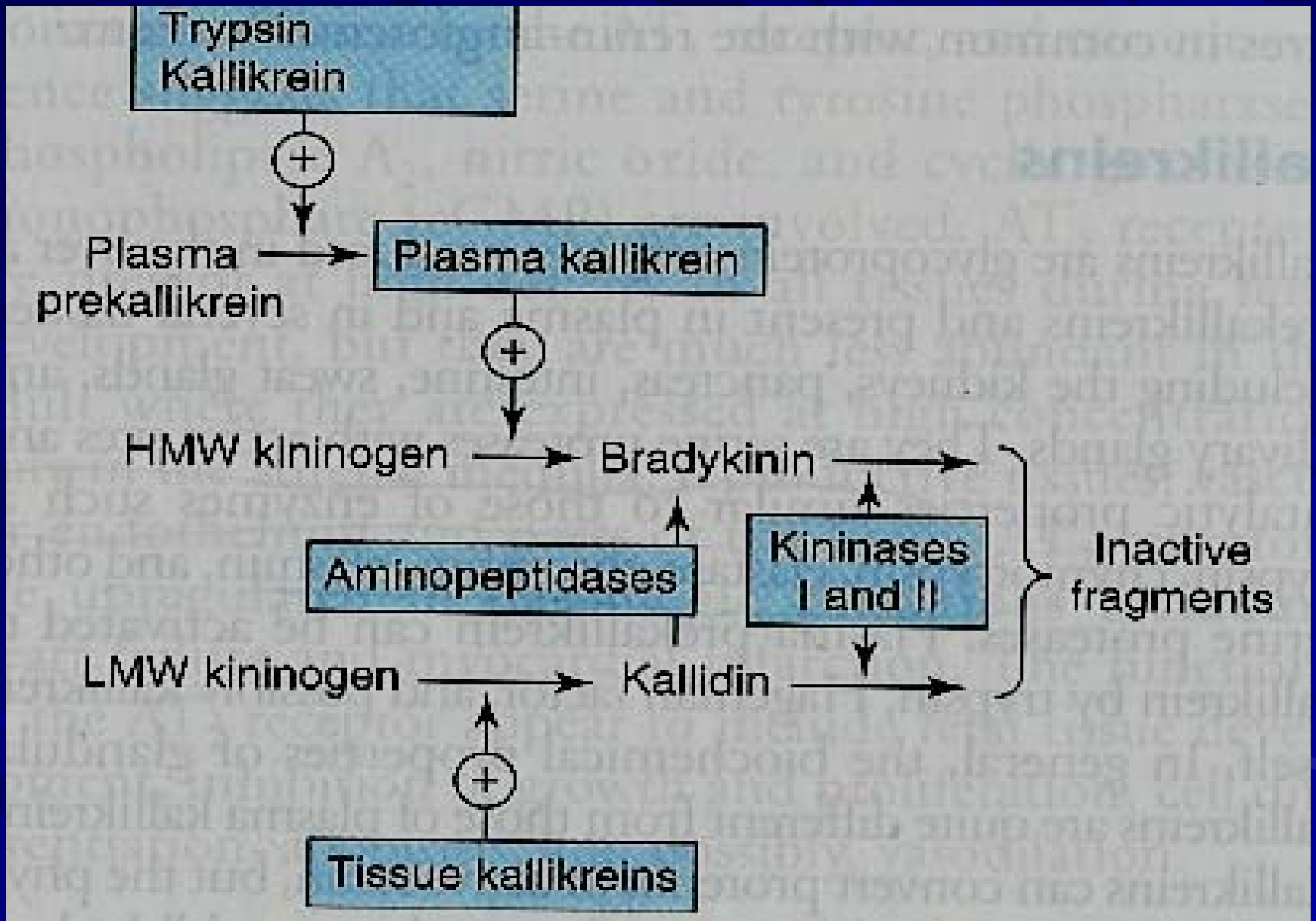
- Endothelin receptor antagonist (A+B).
- Orally and intravenously.
- used for treatment of pulmonary hypertension

The Kallikrein-Kinin System

- Present in plasma and tissues as kidney, pancreas, intestine, sweat and salivary glands.
- Kinins:

Bradykinnin – lysyl-Bradykinnin (kallidin)

- Released from high molecular weight protein precursors by kallikrein
- Degraded by kininase II, ACE


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

Receptors

- **B1 receptors:**
  - stimulated by kallidin (lys-bradykinin), bradykinin.
  - Limited in mammalian tissue

- **B2 receptors:**
  - G-protein coupled
  - mainly stimulated by bradykinin- kallidin.

Actions of Kinins

- Mediators of inflammation (pain & oedema)
- Pain sensation (i.d.) by stimulation of afferents in skin
- Oedema
- Vasodilatation of arterioles (direct and via EDRF).
- Reflex increase HR, cardiac output, contractility.
- Smooth muscle contraction (the intestine, bronchi and uterus).

USES

kallikrein inhibitor, aprotonin (Trasylol):

acute pancreatitis, carcinoid syndrome.