Autocrine /Paracrine mediators (Autacoids)

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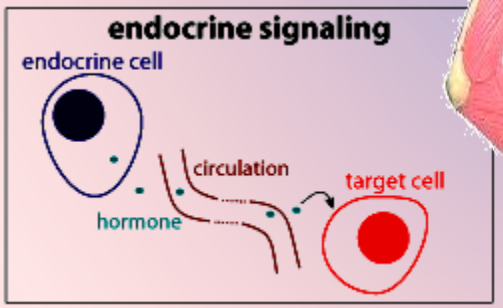
Cell-toCell COMMUNICATION

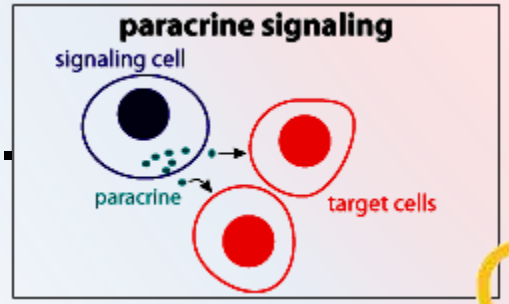
Distance

Via general routes → Blood

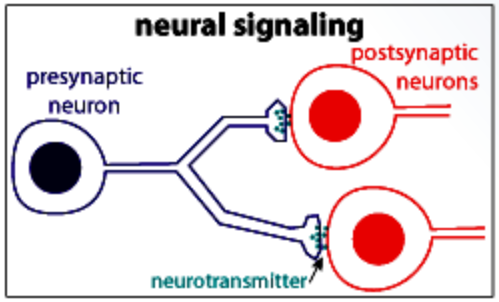


Local

Via → ECF, Gap junctions, ECM...

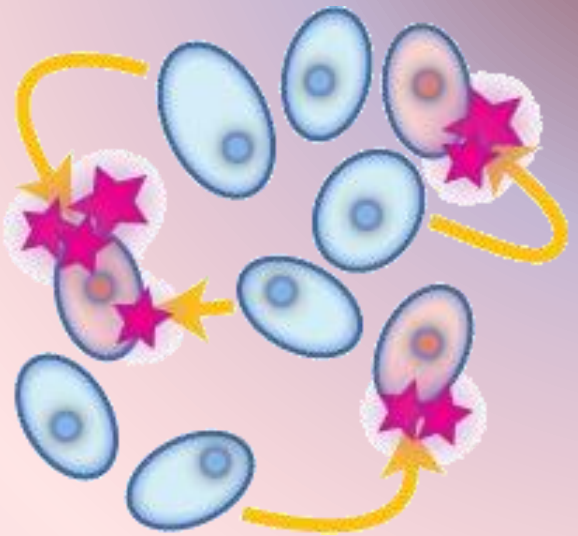


Along specified path → Nerves



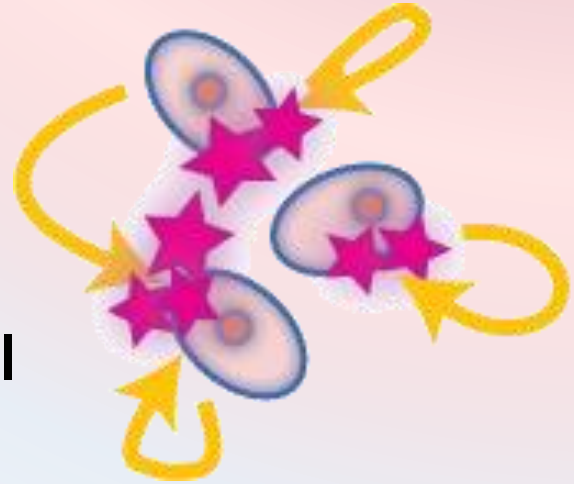
LOCAL COMMUNICATION

PARACRINE MEDIATORS



Secreted by one cell & acts upon adjacent cells or surrounding extracellular matrix [ECM]

AUTOCRINE MEDIATORS



Secreted from a cell and acts on the same cell

Paracrine Autocrine Mediators

Chemically they are classified into

EICOSANOIDS
Prostaglandins
Prostacyclines
Thromboxane A_2
Leukotrienes …etc

NO

OTHERS
Cytokines
Chemokine
Growth Factors
….etc.

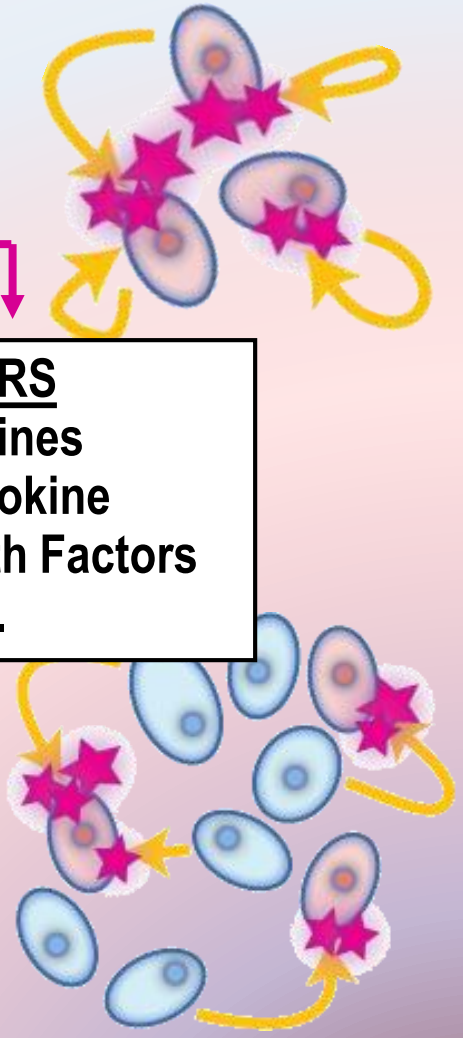
PURINES
ATP / ADP
Adenosine

MONOAMINES
Histamine
Serotonin …etc

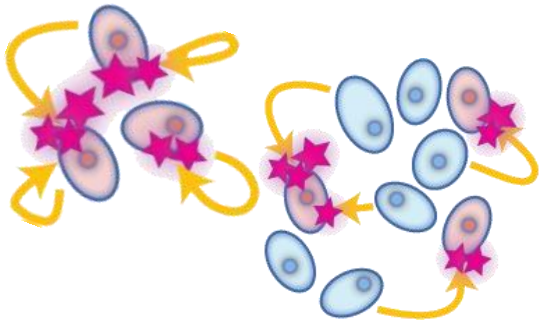
PEPTIDES

Contractants
Angiotensin
Endothelin
NPY
Vasopressin

Relaxants
Kinines
ANP
Tachykinins [SP]
VIP ….etc

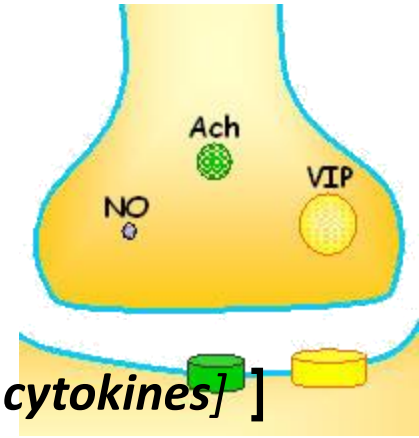


Paracrine Autocrine Mediators



General Features

- **Act mostly on**:
  smooth muscles (SMC) vascular,or non vascular.
  nerve endings [> nonadrenergic non-cholinergic (NANC) co-transmission]
  + heart + exocrine glands + CNS +kidney…etc



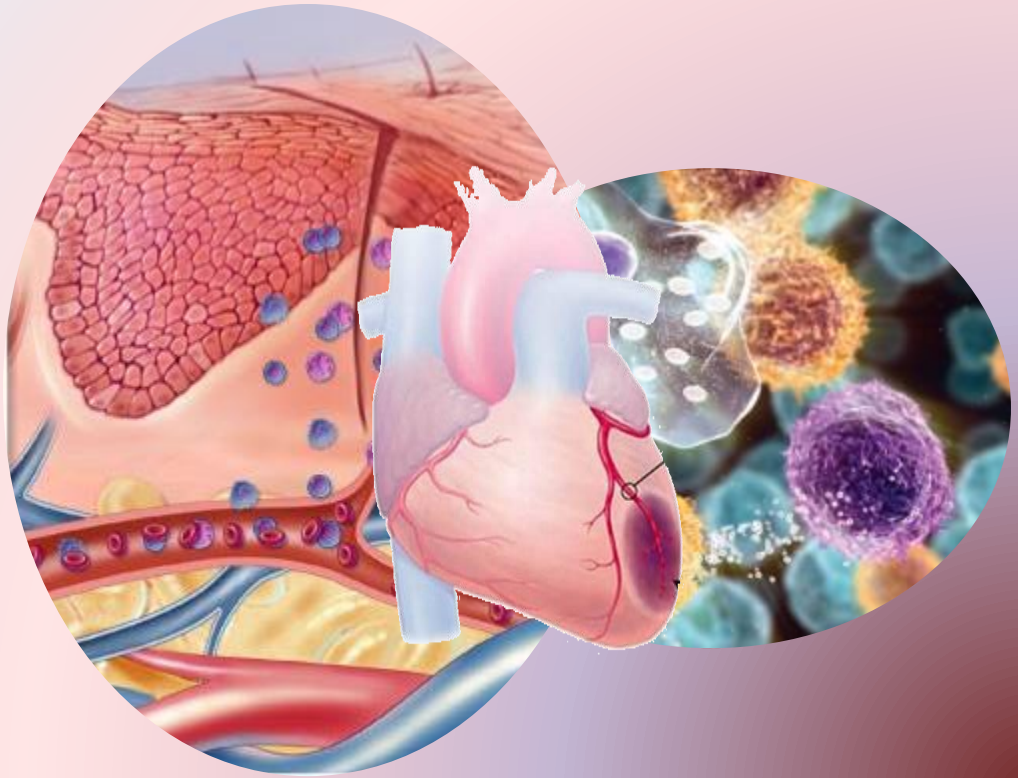
- **Exist either**:
  Preformed & stored in tissues & released by a stimulus
  [Monamines (histamine), most peptides]
  Formed in response to a stimulus
  [NO, eicosanoids, some peptides(angiotensin II ,bradykinins), cytokines]

- **Their presence is either**:
  Constitutive: present all times, to share in normal basic functional regulation within the cells (eNOS / COXI)
  Inducible: only present upon demand i.e. gets expressed [gene transcription, mRNA formation and ribosomal translation into protein] (iNOS / COXII)

DRUGS Acting On Paracrine Autocrine Mediators

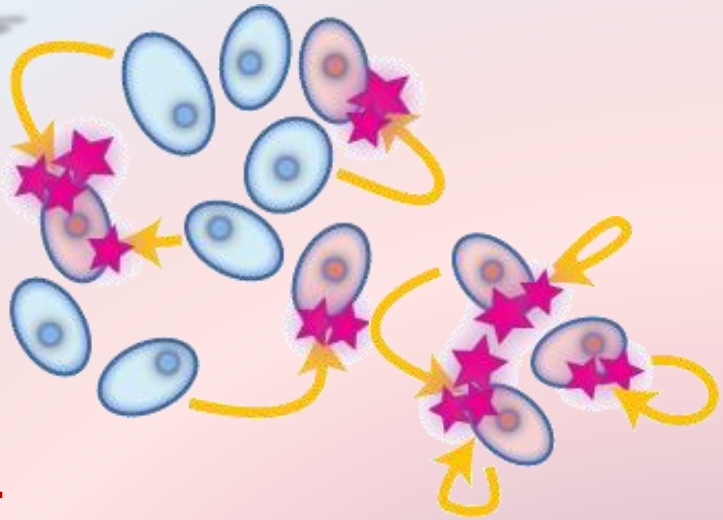
- Nitric Oxide
- Angiotensin & Bradykinin

- Eicosanoids
- Histamines



DRUGS Acting OnParacrine Autocrine Mediators

Part I



ILOs

By the end of this lecture you will be able to:

- Recognize the role of NO in cellular communication.
- Classify the different NOS available
- Expand on its formation, actions termination and pharmacological modulation.
- Identify role of angiotensin in body homeostasis and local regulation.
- Explain its formation, target receptors, feedback regulatory actions, breakdown, intersection with the kinin system and pharmacological modulation.

Nitric Oxide

Nitric Oxide

Is a highly diffusible stable gas

Synthesis

NADPH, FAD, CaCAM

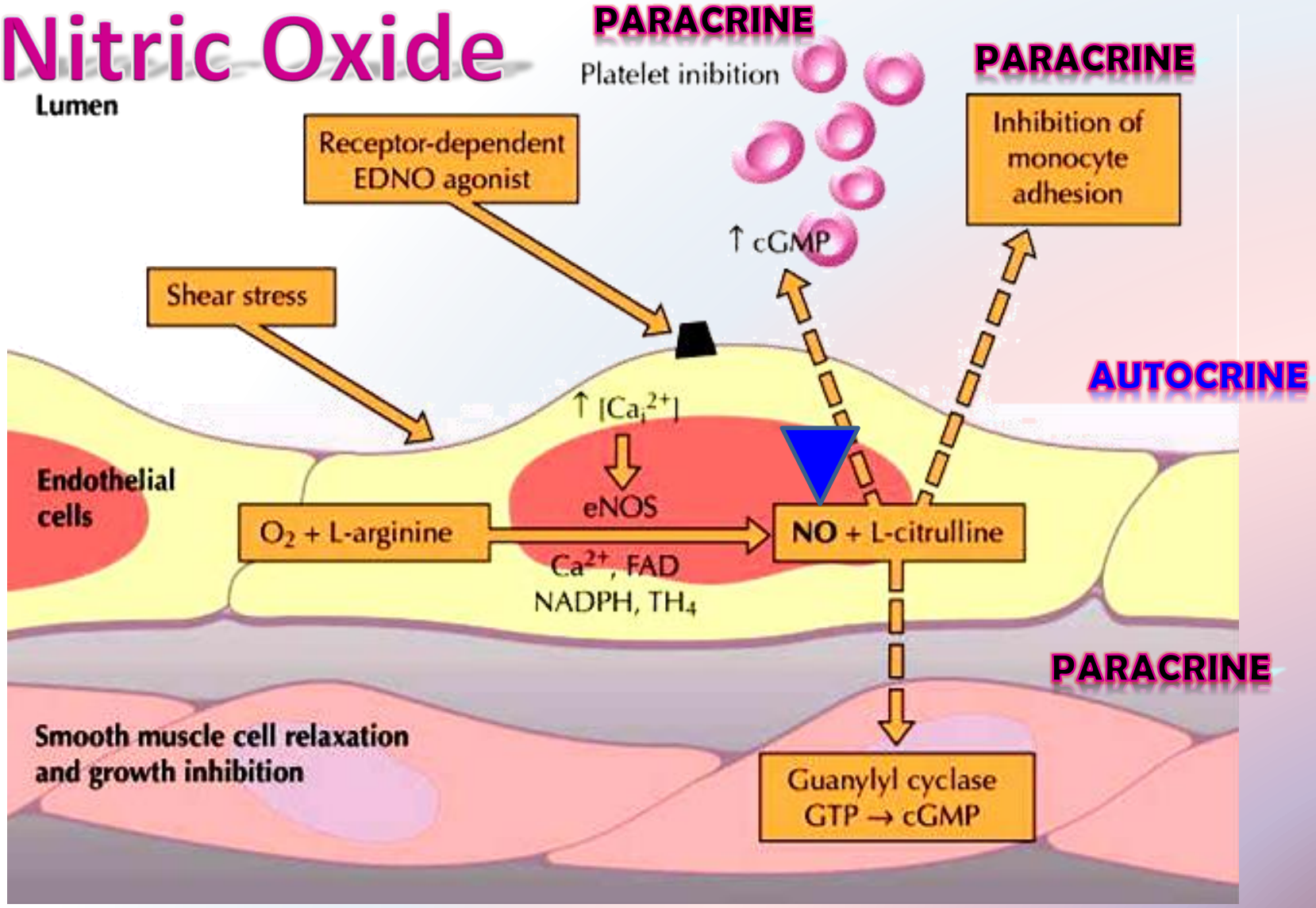
L-arginine + O_2 → NO + Citrulline + H_2O

Nitric oxide synthase (NOS)

NOS Isoforms	Type I [n-NOS] Neuronal NOS	Type III [E-NOS] Endothelial NOS	Type II [I-NOS] Inducible NOS
	Cytosol of Neuronal cells	Bound to membrane of endothelial cell [EC], platelets …etc.	Cytosol of macrophage, neutrophil, kupffer cells … etc
	Constitutive	Constitutive	Inducible
	Neuronal messenger Cytoprotective	Relaxation of VSMC Cytoprotective	Immunocytotoxicity

Shear Stress or Agonists as; Ach, histamine, bradykinin, …..when bind to receptors ↑ intracellular Ca ➔activate eNOS ➔NO formation

Nitric Oxide



Role of NO in blood vessels

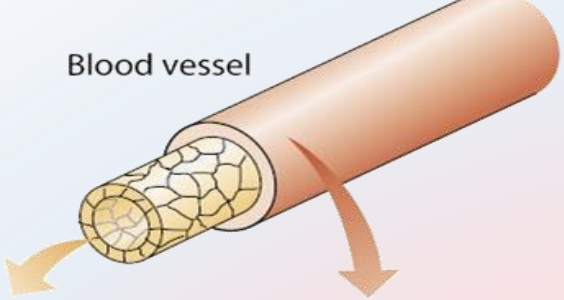
Relaxation of VSMC (Vasodilatation) + Cytoprotection on ECs

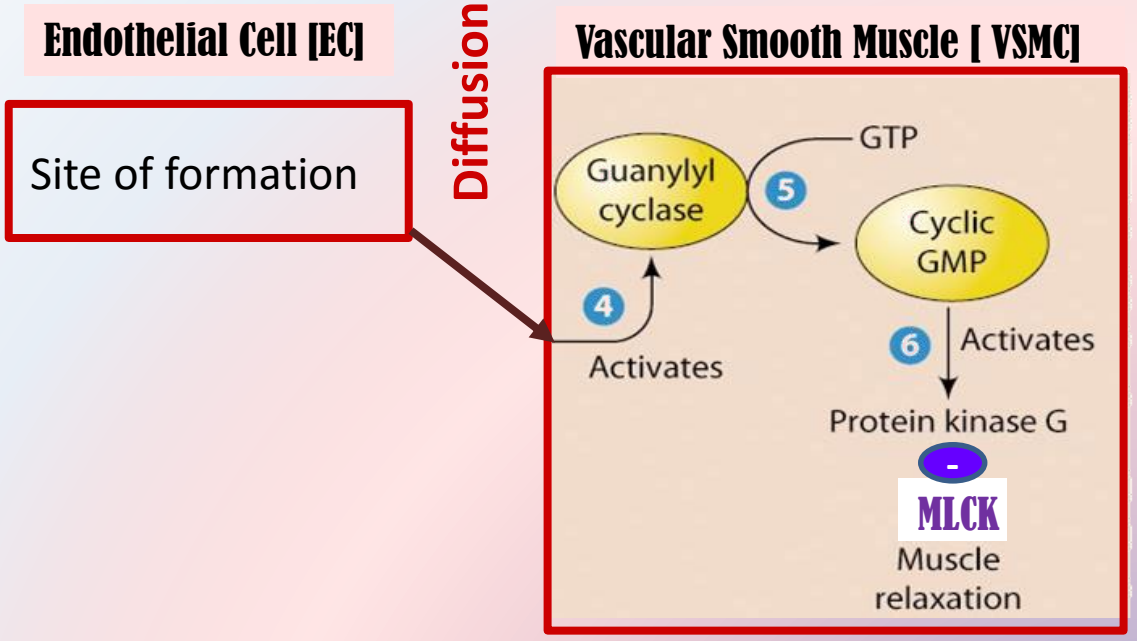
Nitric Oxide

Action

1. Vasodilatation PARACRINE

Diffuse to VSMC
Binds soluble GC
Change GTP to cGMP
↓
Activate PKG &
↓Ca
Inactivate MLCK
Prevent actin myosin cross link
No contraction
RELAXATION

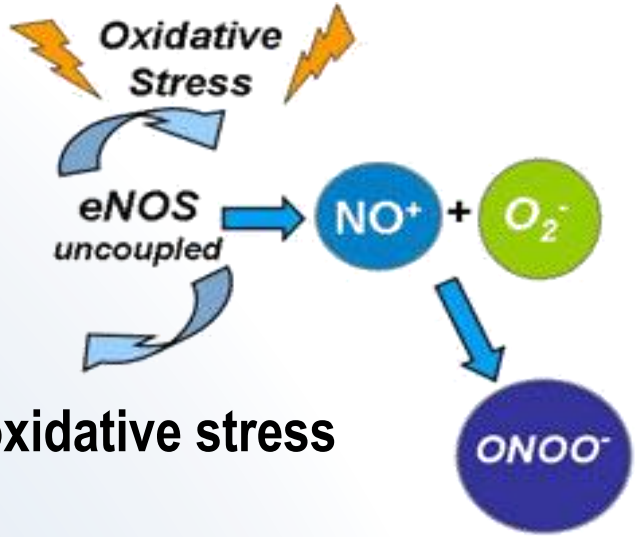




2. Cytoprotection PARACRINE AUTOCRINE

↓platelet aggregation
↓inflammatory cell recruitment
↓ Cholesterol deposition…etc.

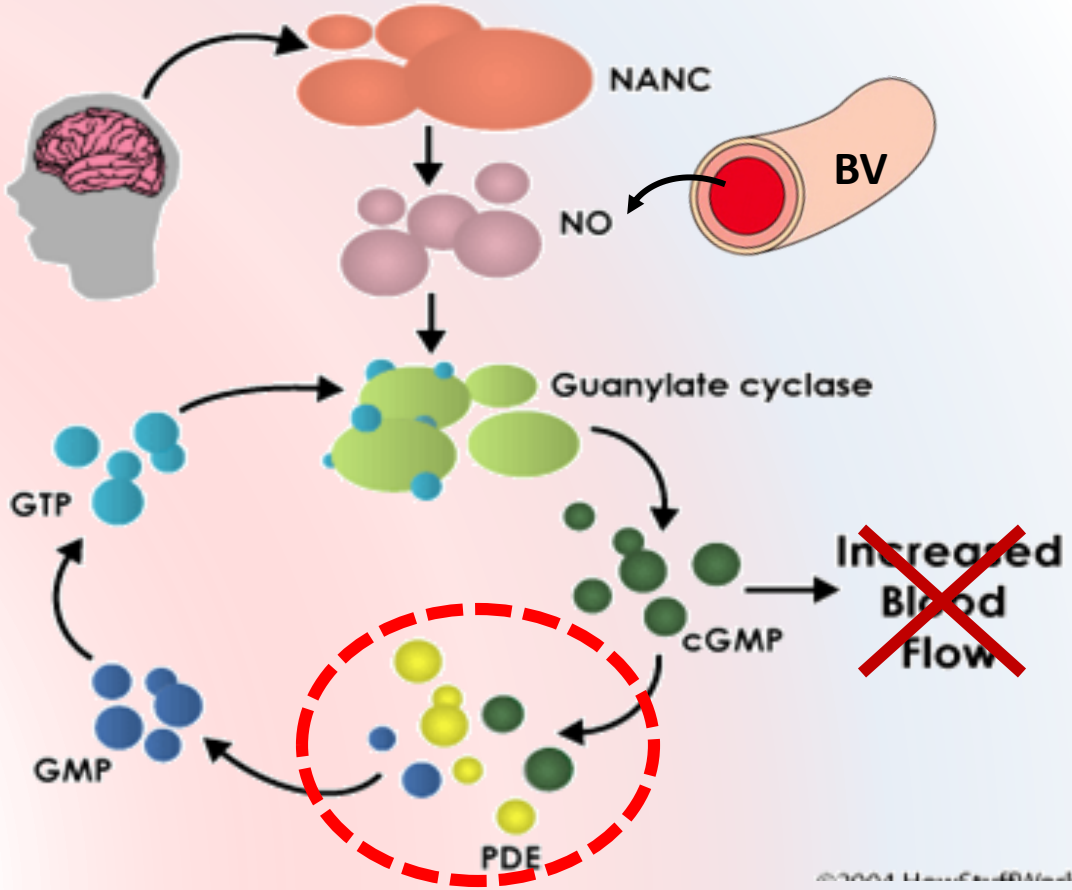
Nitric Oxide



Termination of action

By formation of
1. Stable analogues ➔ with proteins containing SH ….
2. Free radical ➔Peroxynitrite ➔ in oxidative stress

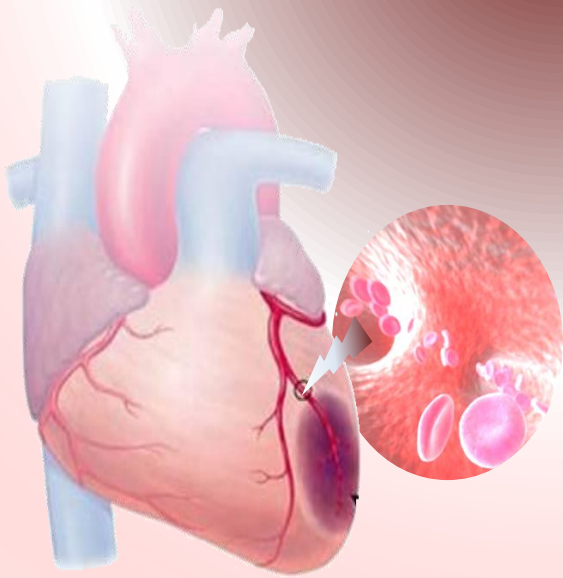
By break down of its downstream signal [cGMP] by PDE to form GMP



Nitric Oxide

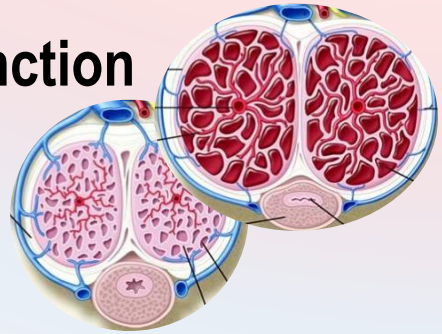
Drugs modulating

1. Express eNOS:
   Statins, like atorvastatin and Estrogens → CVS Cytoprotection

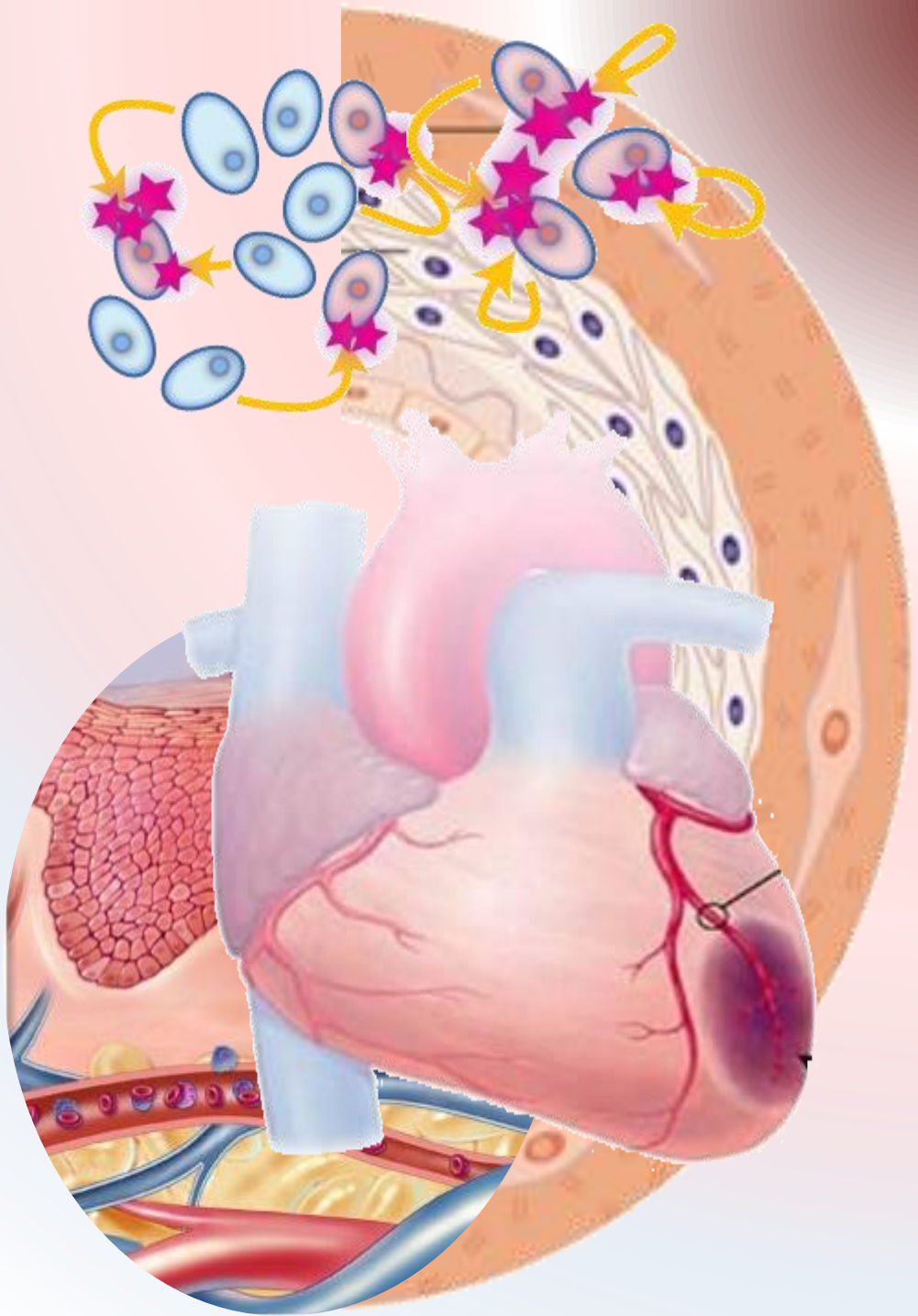


2. Act as NO donners:
   a. Nitrates → >Venulodilators in angina
   b. Na Nitroprusside → Arteriolar dilator in hypertension

Selective PDE_5 Inhibitors; Sildenafil → Erectile dysfunction



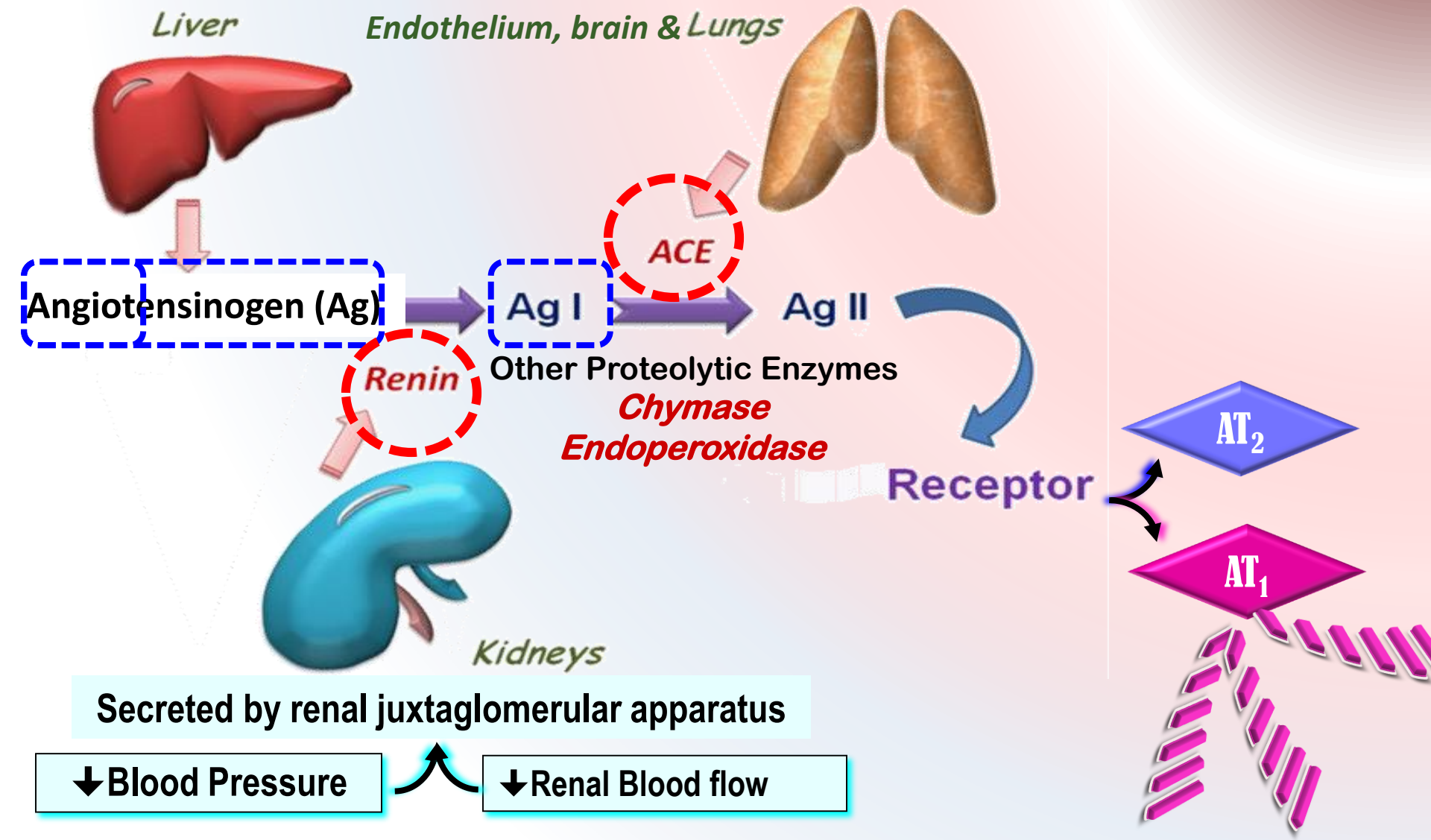
Angiotensin



Angiotensin [Ag]

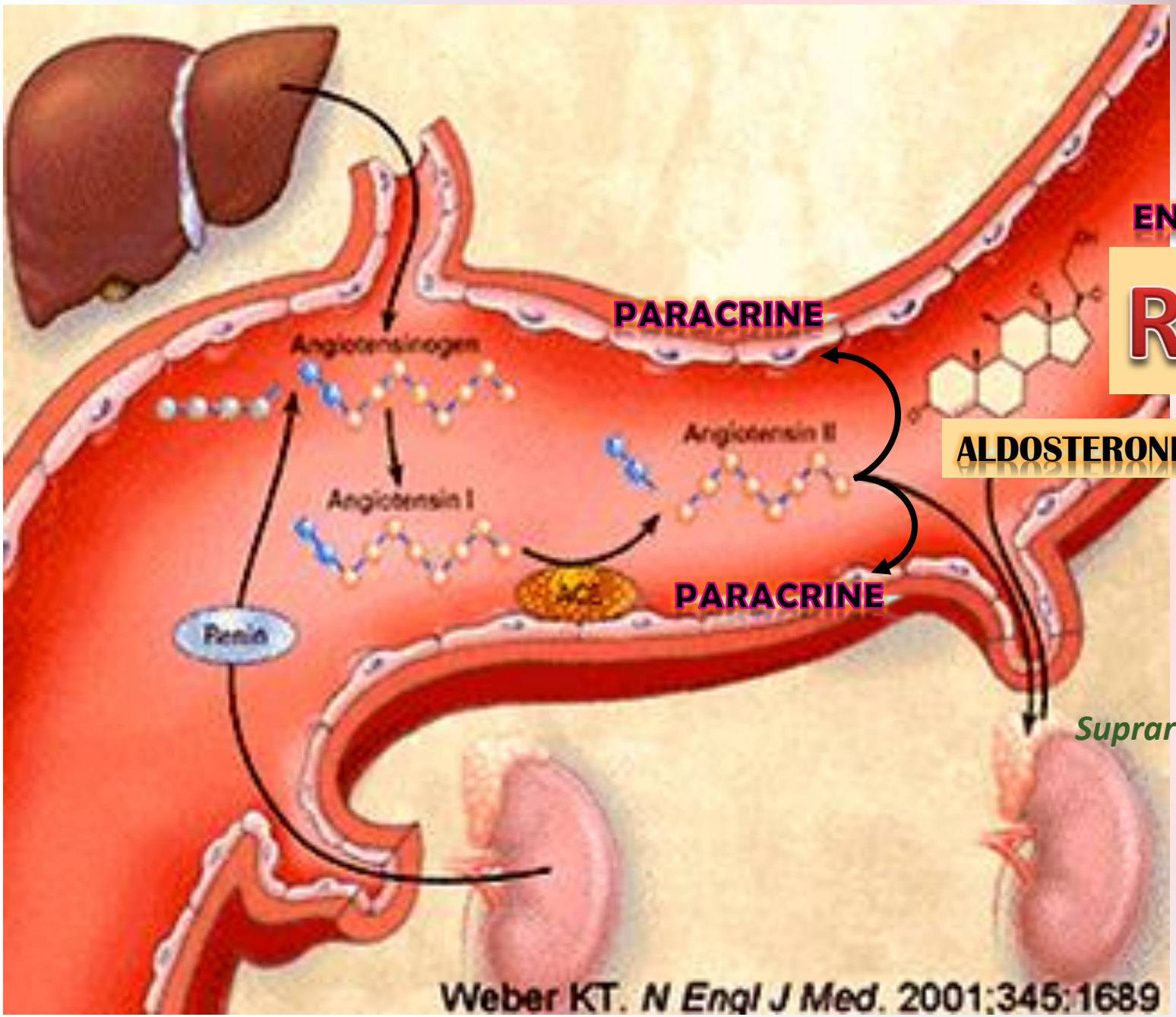
A vasoconstrictor peptide

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



Secreted by renal juxtaglomerular apparatus

↓Blood Pressure ← ↓Renal Blood flow



ENDOCRINE

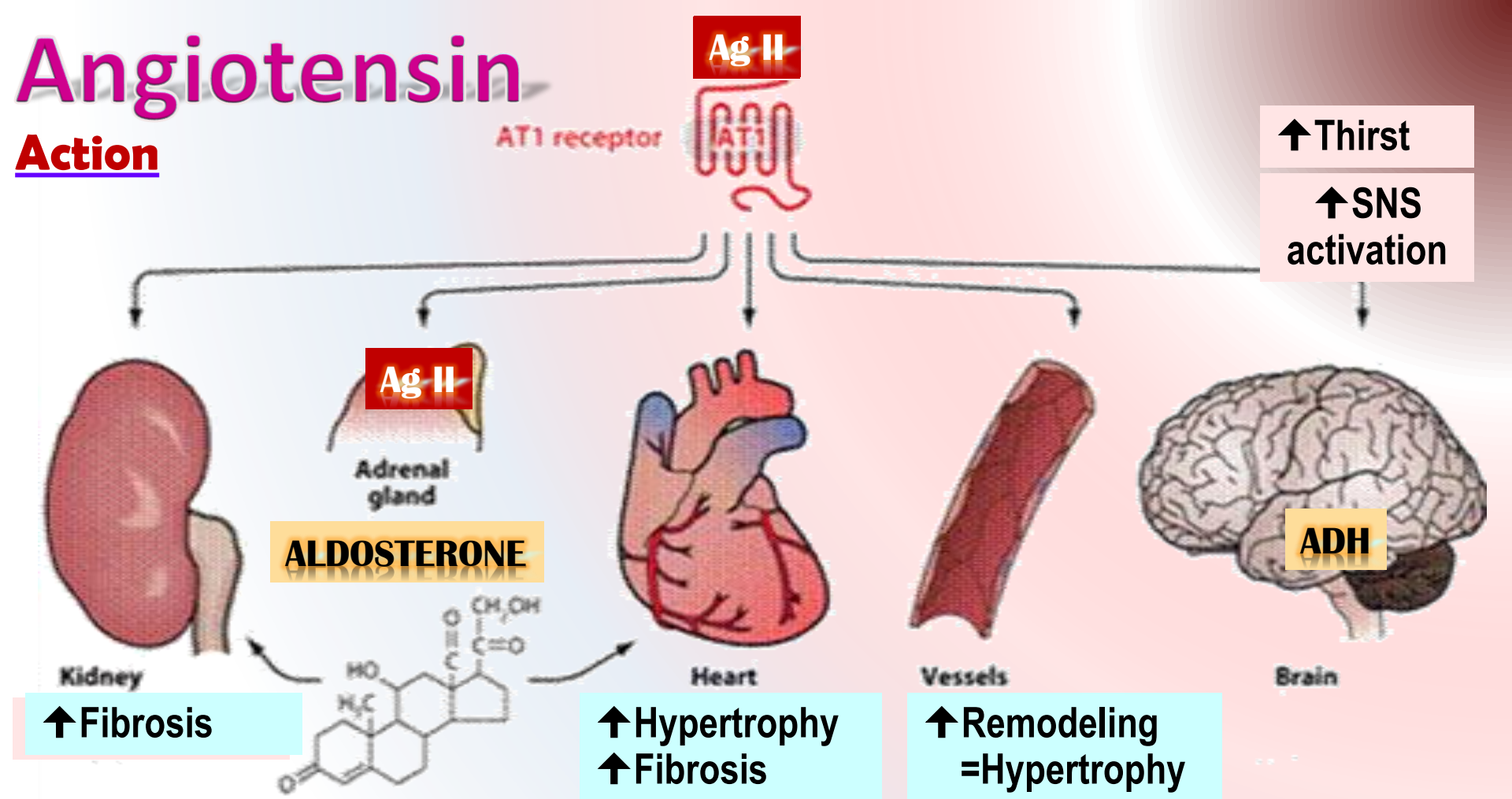
RAAS

ALDOSTERONE

Suprarenal Gland

Angiotensin

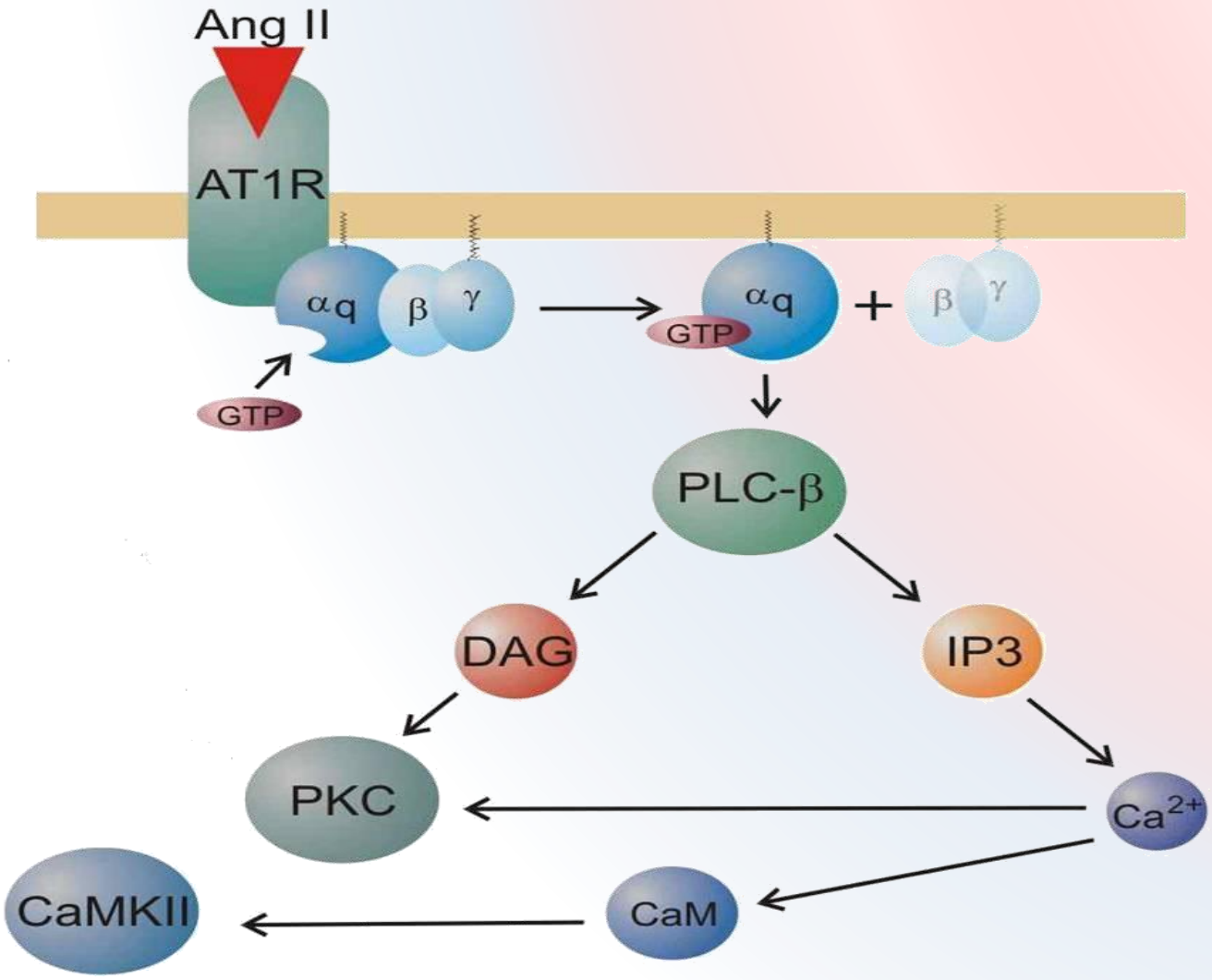
Action



↑Blood Pressure

Angiotensin

Ag II



Termination of action

AgII acted upon by peptidases aminopeptidases (angiotensinase) to Ag III [a less active] & then to fragmentation products

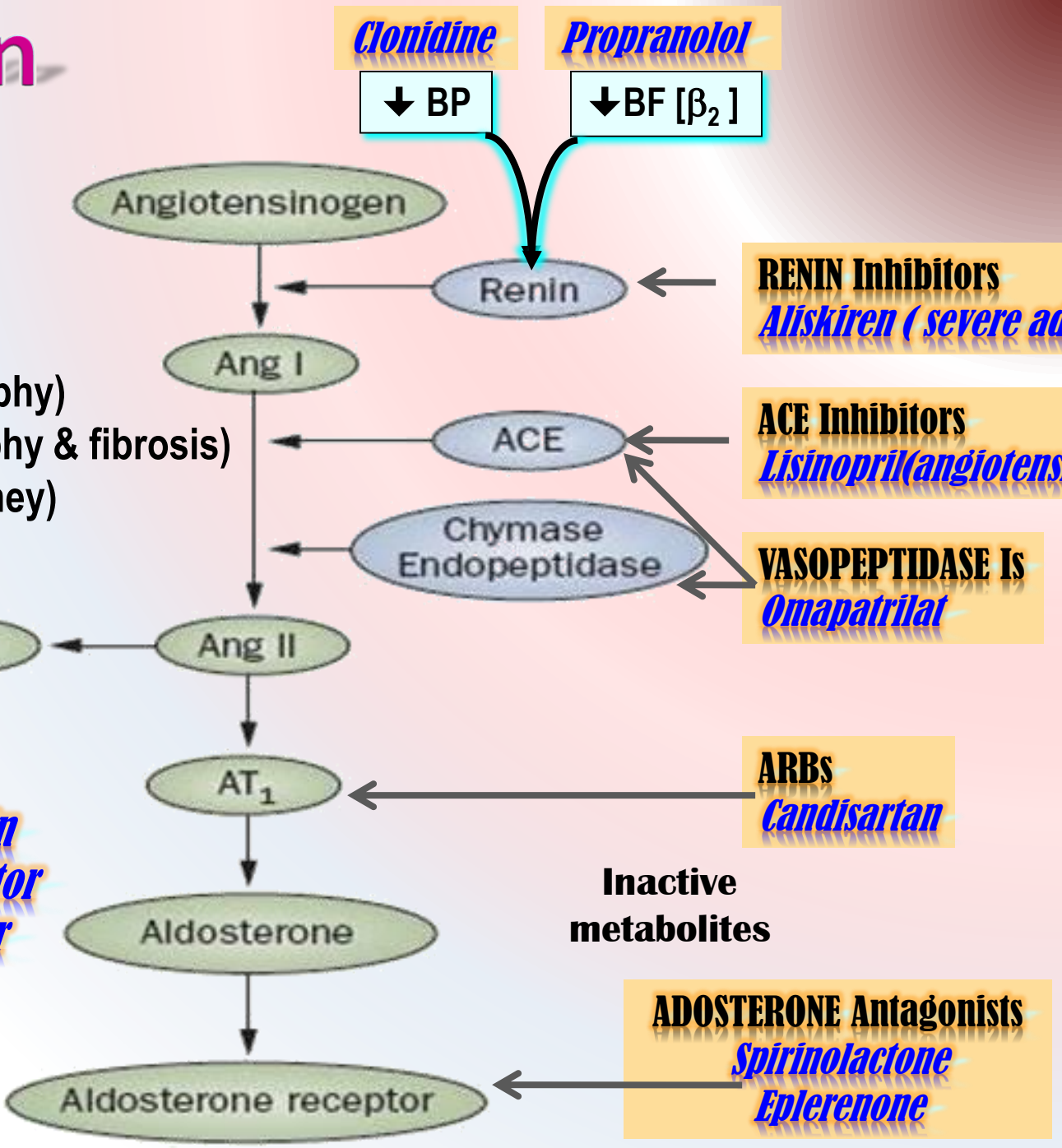
Angiotensin

Drugs modulating

INHIBITION OF RAAS SYSTEM

is beneficial in treatment of:

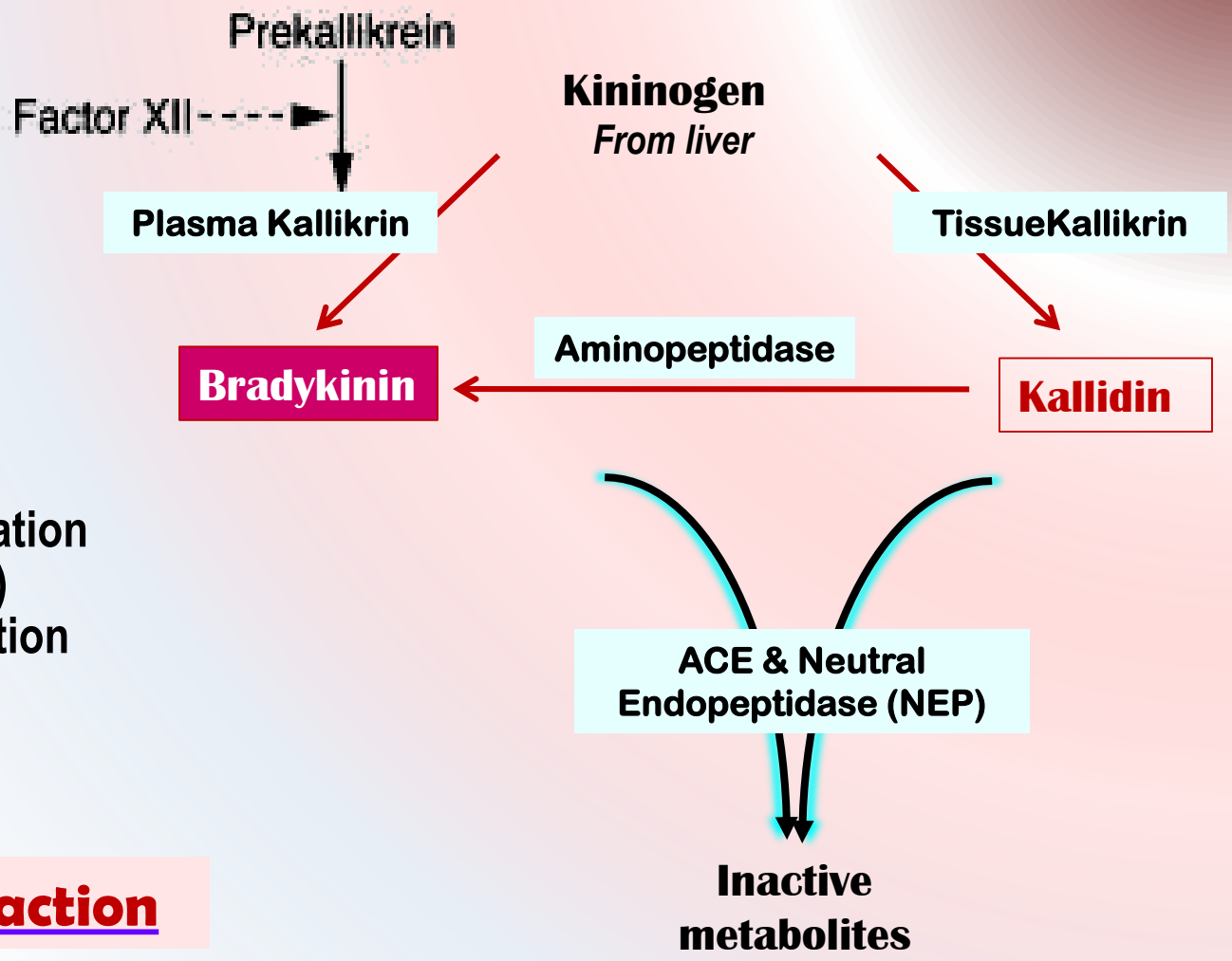
- Hypertension (↓hypertrophy)
- Heart Failure (↓hypertrophy & fibrosis)
- Diabetics (Protect the kidney)



Kinins

Bradykinin is a vasodilator peptides

Synthesis



Action

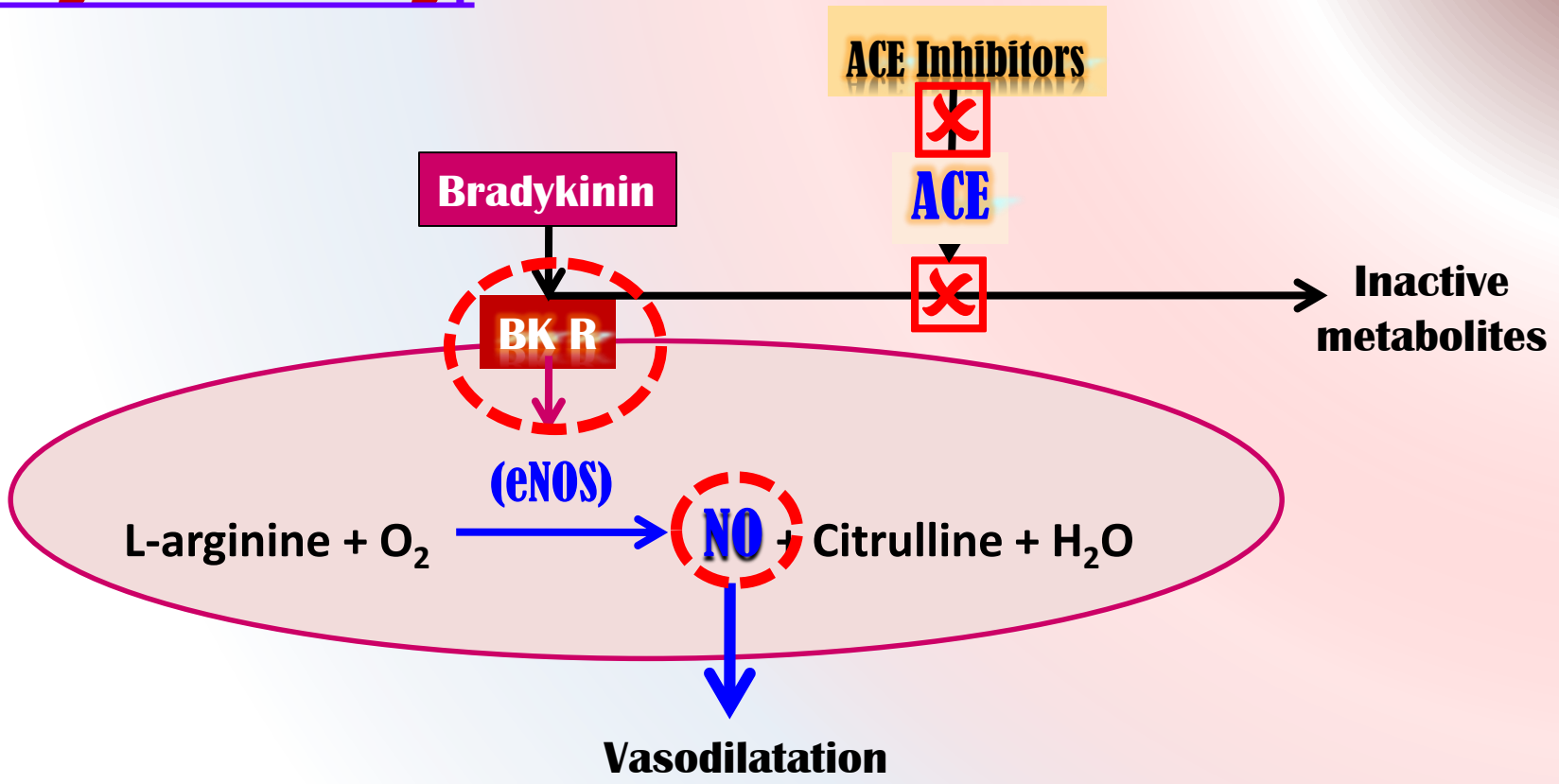
- Vasodilatation
- Inflammation & Exudation
- Pain (sensory nerves)
- Exocrine gland secretion

Termination of action

Kinins

Drugs modulating :

↓ Action → ↓ bradykinin mediated pain → **NSAIDs**



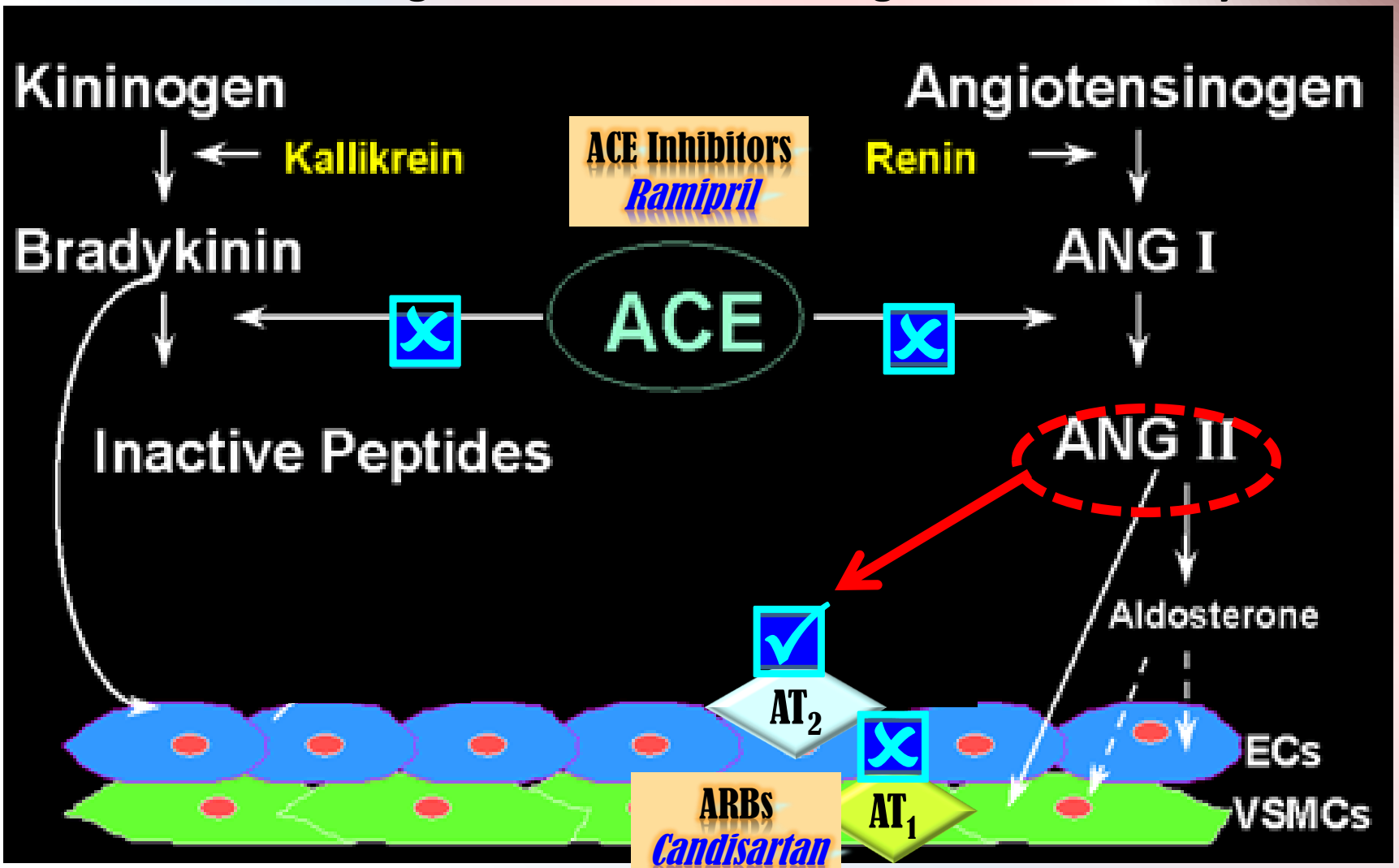
↓Breakdown → ↑their concentration → **ACE Inhibitors**

VASOPEPTIDASE Is

Antihypertensive drugs

Difference between ACE Is & ARBs action

Inhibit activation of AgI to AGII + decrease degradation of bradykinin



Block action of AgII on AT1 in VSMCs that is causing vasoconstriction

The AgII act on non-blocked AT2 on endothelial cells causing vasodilatation

DRUGS Acting OnParacrine Autocrine Mediators

GOOD LUCK