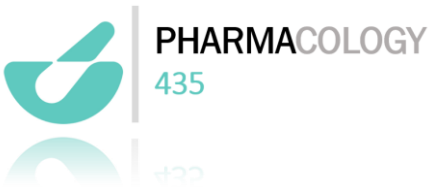
PHARMACOLOGY

Autocrine/Paracrine Mediators

OBJECTIVES:

- 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.



Cell Communications

Cell to Cell Communication

- **Endocrine system**
  - **Distance**
    - Endocrine
      - Via general routes → Blood
      - Ex: Hormones
  - **Local**
    - **Paracrine**
      - Secreted by one cell & acts upon adjacent cells or surrounding extracellular matrix [ECM]
    - **Autocrine**
      - Secreted from a cell and acts on the same cell
- **Nervous system**
  - **Nerves**

Autocrine/Paracrine Mediators:

Chemically classified into

- **MONOAMINES**
  - Histamine
  - Serotonin
- **EICOSANOIDS**
  - Prostaglandins
  - Prostacyclines
  - Thromboxane A_2
  - Leukotrienes
- **PURINES**
  - ATP / ADP
  - Adenosine
- **Nitric Oxide**
- **OTHERS**
  - Cytokines
  - Chemokine
  - Growth Factors
- **PEPTIDES**
  - ***Contractants:***
    - Angiotensin
    - Endothelin
    - NPY
    - Vasopressin
  - ***Relaxants:***
    - Kinines
    - ANP
    - Tachykinins [SP]
    - VIP

Autocrine/Paracrine Mediators

General Features of Autocrine/Paracrine Mediators:

1. **Target:** Smooth muscles (SMC), vascular or non vascular nerve endings [> non-adrenergic non-cholinergic (NANC) co-transmission], heart, exocrine glands, CNS, kidney, etc.

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

3. **Presence:**
   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)

Nitric Oxide (NO): Highly diffusible stable gas

Synthesis:

$$\text{L-arginine} + O_2 \xrightarrow[\textbf{(NOS)}]{\textbf{Nitric Oxide Synthase}} NO + \text{Citrulline} + H_2O$$

Types of NOS:

1. n-NOS: Neuronal NOS
2. i-NOS: Inducible NOS
3. e-NOS: Endothelial NOS

Nitric Oxide

	Type I N-NOS	Type II I-NOS	Type III E-NOS
Place	Cytosol of Neuronal Cells	Cytosol of macrophages, neutrophils, kuppfer cell, etc.	Bound to membrane of endothelial cells, platelets, etc.
Presence	Constitutive	Inducible	Constitutive
Function	-Neuronal Messengers -Cytoprotective	Immunocyto-toxicity	-Relaxation of VSMC -Cytoprotective

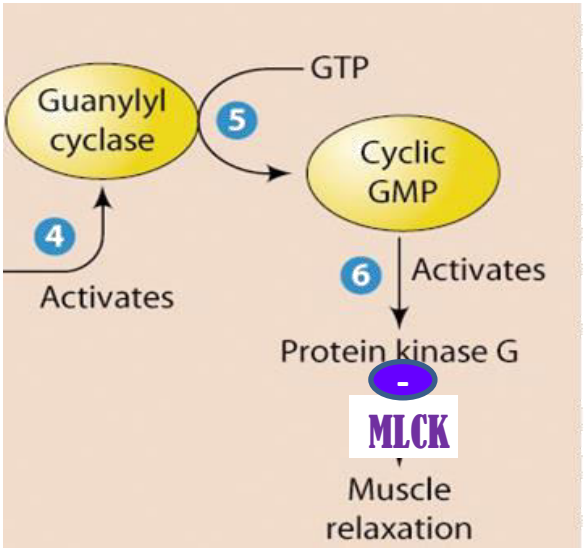
- When a Shear Stress or Agonists as; Ach, histamine, bradykinin, bind to receptors ⬆ intracellular Ca ➡ activate eNOS ➡ NO formation

Action of Nitric Oxide:

1. Vasodilation: (Paracrine)

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

Vascular Smooth Muscle [VSMC]



Nitric Oxide

2. Cytoprotection:
(Paracrine Autocrine)

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

Termination of Action:

① By Breakdown of its downstream signal (cGMP) by PDE to form GMP

② By formation of: - Stable Analogues: with proteins containing SH
- Free Radical: Peroxynitrite in oxidative stress

Drug Modulation:

Express NOS	Act as NOS Donner	Selective PDE5 Inhibitor
Statins: Used to reduce cholesterol e.g. Atorvastatin & Estrogen: CVS Cytoprotection	**Nitrates:** Venulodialator in Angina	**Sildenafil:** Erectile Dysfunction
	Na Nitroprusside: Arteriolar dilator in Hypertension	

Angiotensin

Angiotensin is a vasoconstrictor peptide

Synthesis

- **Angiotensinogen** is a plasma α-globulin synthesized from the **liver**.
- In the kidneys there's an enzyme called renin, it's secreted when there is low blood pressure and decrease in renal blood flow.
  its function is to convert **angiotensinogen** into **angiotensin 1**
- **Angiotensin 1** has to be converted to **angiotensin 2** by angiotensin-converting enzyme (ACE) that is released from the **lungs**.
- **Angiotensin 2** binds to receptors in the blood vessels to cause vasoconstriction.

Angiotensin stimulates the release of Aldosterone hormone, released by the adrenal glands of the kidney, causes sodium retention in the kidney (sodium carries water) so the sodium and water increase the volume of the blood and increase the blood pressure.

Termination of Action:

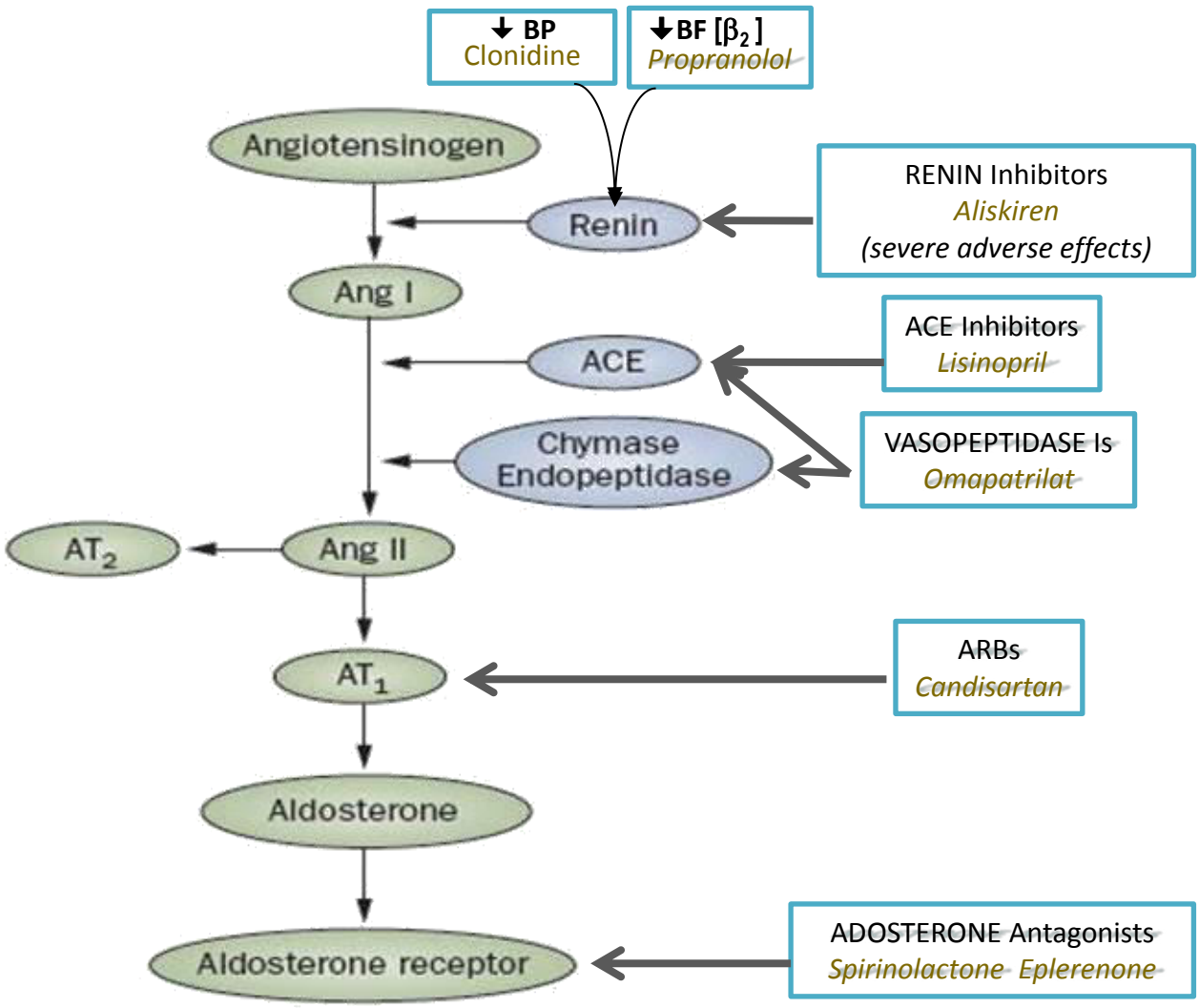
AgII acted upon by peptidases aminopeptidases (angiotensinase) to Ag III [less active] & then to fragmentation products

Angiotensin

Drug Modulation

INHIBITION OF RAAS SYSTEM is beneficial in treatment of:

1. Hypertension (↓hypertrophy)
2. Heart Failure (↓hypertrophy & fibrosis)
3. Diabetics (Protect the kidney)

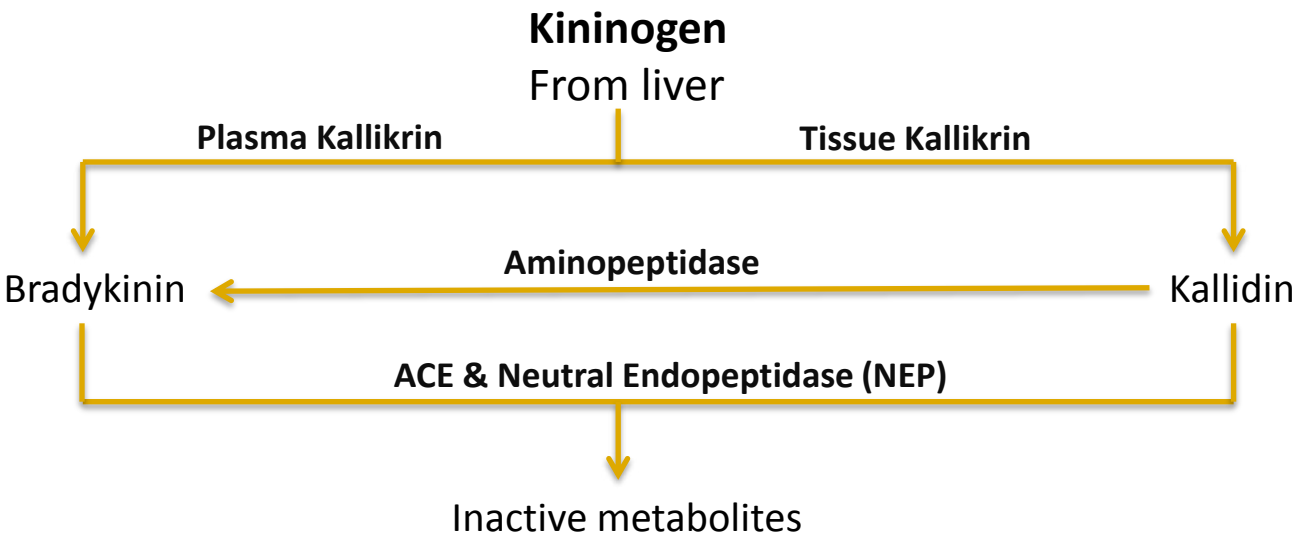


ACEI: Angiotensin Converting Enzyme Inhibitor
ARB: Angiotensin Receptor Blockers

Kinins

Bradykinin is a vasodilator peptides

Synthesis:



Action:

① Vasodilatation
② Inflammation & Exudation
③ Pain (sensory nerves)
④ Exocrine gland secretion

Drug Modulation

1. ↓ Action will ↓ bradykinin mediated pain → NSAIDs (Non Steroidal Anti Inflammatory Drugs)
2. ↓ Breakdown will ↑ their concentration → ACE Inhibitors VASOPEPTIDASE (Antihypertensive drugs)

What is the difference between ACE and ARB?

ACEI: Inhibit activation of AgI to AGII + decrease degradation of bradykinin

ARB: Block the action of AgII on AT1 in VSMCs that is causing vasoconstriction so the AgII will act on non-blocked AT2 on endothelial cells causing vasodilatation

THANK YOU FOR CHECKING OUR WORK

THE PHARMACOLOGY TEAM

مريم سعيدان
كيان كعكي
نورة الطويل
اسرار باطرفي
كوثر الموسى
نوف العبدالكريم
لمى الزامل
رفان هاشم
ديمة الفارس
ياسمين الفارسي

ساره الخليفه
رنيم الدبيخي
منيرة الحسن
ديمه الراجحي
هديل الغرير
ريم العقيل
سارا الحسين
نوف الرشيد
نورة العقيل

عبدالرحمن السياري
خالد الزهراني
عبدالله الجنيدل
أحمد المصعبي
مهند الزيد
عبدالرحمن الشمري
معاذ باعشن
عبدالعزيز الشعلان

For any correction, suggestion or any useful information do not hesitate to contact us: Pharmacology.med435@gmail.com