PHARMACOLOGY
433

King Saud University
College of Medicine
Foundation Block

Drug Acting on Autocrine, Paracrine Mediators [part 1]

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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.

KEY WORDS :

Nitric Oxide, Paracrine, Vasodilatation, Autocrine, Angiotensin (Ag), Renin, Kinins, Bradykinin.

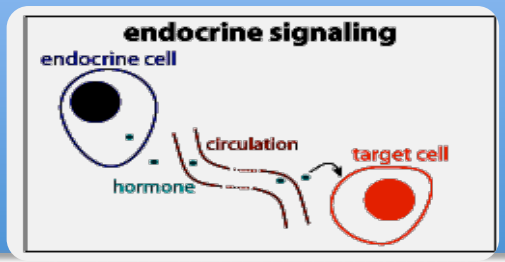
Abbreviations :

ECM : Extracellular Matrix
N-NOS : Neuronal Nitric Oxide Synthase
ECF : extracellular Fluid
SMC : Smooth Muscles Cells
NO : Nitric Oxide
MLCK : Myosin Light-Chain Kinase
E-NOS : Endothelial-Nitric Oxide Synthase
RAAS : Renin-Angiotensin-Aldosterone System
ADH : Anti-Diuretic Hormone

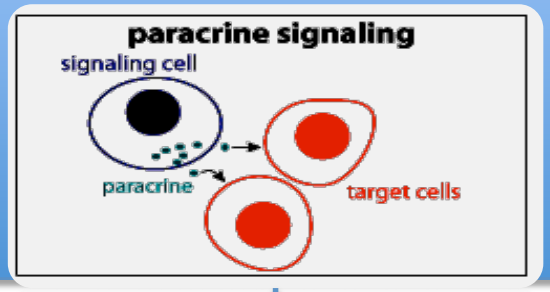
INOS : Inducible Nitric Oxide Synthase
PDE : Phosphodiestrase
VSMC : Vascular Smooth Muscle Cell
GC = Guanylate Cyclase
NANC : Non-Adrenergic Non-Cholinergic
PKG = Protein Kinase G
ACE : Angiotensin Converting Enzyme
ARB : Angiotensin Receptor Blocker
NSAIDs : Non-Steroidal Anti-Inflammatory Drugs

Cell to Cell Communication

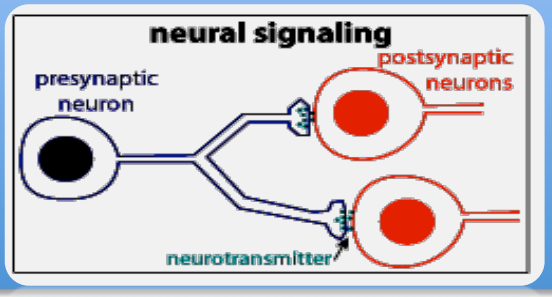
Distance: Via general routes → Blood



Local: Via → ECF, Gap junctions, ECM...



Along specified path→ Nerves



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

General Features of Paracrine Autocrine Mediators

Act mostly on

*smooth muscles (SMC) vascular, or non vascular.
*nerve endings NANC co-transmission
*heart
*exocrine glands
*CNS
*kidney

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) (in normal body functions)

Inducible:
Only present upon demand i.e. gets expressed [gene transcription, mRNA formation and ribosomal translation into protein](iNOS / COXII) (in abnormal functions of the body. E.g. inflammation)

DRUGS Acting On Paracrine Autocrine Mediators

Is a highly diffusible stable gas

Synthesis: Formed from the amino acid (arginine) with the help of (NOS)

Type	Type I [n-NOS] Neuronal NOS	Type III [E-NOS] Endothelial NOS	Type II [I-NOS] Inducible NOS
Location	Cytosol of Neuronal cells	Bound to membrane of endothelial cells, platelets	Cytosol of Macrophage, Neutrophil, Kupffer cells "in the liver"
Constitutive or Inducible	Constitutive	Constitutive	Inducible"not always existed "
Action	Neuronal messenger Cytoprotective	Relaxation of VSMC Cytoprotective	Immunocytotoxicity "toxicty for the invading organisms"

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

Action of Nitric Oxide

Role of NO in blood vessels:

Relaxation of VSMC (Vasodilatation) + Cytoprotection on ECs

Vasodilatation (Paracrine)	Cytoprotection (Paracrine and Autocrine)
Diffuse to VSMC Binds soluble GC *Change GTP to cGMP "2nd massenger" *Activate PKG &↓Ca *Inactivate MLCK *Prevent actin-myosin cross-link *No contraction RELAXATION	↓platelet aggregation. ↓inflammatory cell recruitment. ↓ Cholesterol deposition. Inhibition of Monocytes.

Termination of action

cGMP —Breaking down by PDE→ GMP

cGMP is the downstream signal of NO

GMP is not a 2nd messenger

By formation of

1. Stable analogues → with proteins containing SH
2. Free radical →Peroxynitrite → in oxidative stress

Drug Modulation of NO

Express eNOS	Act as NO donors "drugs that gives NO inside the body"	Prevent breakdown of PDE
Statins (used to reduce cholesterol) **Estrogen** → CVS cytoprotection (That's why ladies before menopause never get heart attack) because NO help in vasodilatation of their heart.	**Nitrates** → venulodilators in Angina "heart disease" **Na nitroprusside** → arteriolar dilator in hypertension "can be used in emergency situations"	Selective PDE_5 inhibitors, **Sildenafil** → erectile dysfunction Keeps the cGMP active

ANGIOTENSIN

vasoconstrictor peptide

Synthesis

***Precursor is Angiotensinogen**

"a plasma α-globulin synthesized in the liver"

***RAAS**

***ENDOCRINE**

Termination of Action

(Remember that Ag acts on G-protein receptors)

Ag II —(by peptidases, aminopeptidases (angiotensinase))→ Ag III

Ag III is less active]

Fragmentation products

Action

(Ag II does the actions)

↑Blood Pressure

Endocrine/paracrine

*In Kidney : ↑ Na retention

*Adrenal Gland : Secrets Aldosterone hormone

*Heart : ↑inotropy (heart contractility), ↑chronotropy (heart rate)

*Blood Vessels : vasoconstriction

*Brain : ↑Thirst, ADH "water retention"

Action

↑Blood Pressure

Autocrine

*In Kidney : ↑ fibrosis

*Heart : ↑ hypertrophy, ↑ fibrosis

*Blood Vessels : ↑ remodeling = hypertrophy

Angiotensin modulating drugs

Inhibition of RAAS treats :
***Hypertension (↓hypertrophy)**
***Heart Failure (↓hypertrophy & fibrosis)**
***Diabetics (Protect the kidney)**

Drug	Action
Clonidine	Decrease BP
Propranolol	Decrease BF (β_2)
Aliskiren	Inhibit Renin
Lisinopril & ramipril	Inhibit ACE
Omapatrilat	Vasopeptidase inhibitor
Candisartan	ARBs
Spirinolactone and Eplerenone	Aldosterone receptor antagonists

Kinins e.g. **Bradykinin**

synthesis	Action	Termination of action	Drugs modulation
prekallikerin	Vasodilatation	ACE & Neutral Endopeptidase (NEP) to decrease the BP	**NSAIDs:** Decrease action →decrease bradykinin-mediated pain
	Inflammation & exudation		
	Pain (sensory nerves)		**ACE inhibitors & vasopeptidase inhibitors (antihypertensive drugs):** Decrease breakdown of bradykinin → increase their concentration
	Exocrine gland secretion e.g. “Salivary, sweat glands..etc.”		

Difference between ACE Inhibitors & ARBs action

Inhibit activation of AgI to AGII + decrease degradation of bradykinin
➔ Vasodilation

Block action of AgII on AT1 in VSMCs that is causing vasoconstriction and make AgII act on non-blocked AT2 on endothelial cells
➔Vasodilation

SUMMARY

*Recognize the role of NO in cellular communication.
*Classify the different NOS available.
*Expand on its formation, actions termination and pharmacological modulation.

Is a highly diffusible stable gas	**NO**
L-arginine + O_2 -> NO + Citrulline + H_2O	**Formation**
▪ Type1: N-NOS (In the nervous tissue) ▪ Type2: I-NOS (Cytosol of Macrophages) ▪ Type3: E-NOS (Endothelial cells)	**Classification**
Role of NO in blood vessels: Vasodilatation + Cytoprotection	**Role**
1- Formation of stable compounds. 2- Formation of free radical. 3- By break down of its downstream signal cGMP by Phosphodiesterase to form GMP	**Termination**
1\ eNOS activation : statins, estrogen 2\ Act as NO: nitrates, Na nitroprusside 3\ Prevent breakdown of PDE =(Stopping the breakage of cGMP) : sildenafil	**Drugs Modulating**

*Identify role of angiotensin in body homeostasis and local regulation.

A vasoconstrictor peptide	**Angiotensin**
▪ Angiotensin Receptor I ▪ Angiotensin Receptor II	**Receptors**
AgII is converted to AgIII by certain enzymes (AgIII is less active)	**Termination**
Inhibition of the RAAS system - Renin inhibitors: Aliskiren - ACE inhibitors: Rampril - Angiotensin Receptors Blockers (ARBs): Candesartan - Vasopeptidase inhibitors: Omapatrilat - Aldosterone receptor antagonists: spirinolactone	**Drugs Modulating**

MCQS

1) What is the action of nitric oxide NO ?
a) Vasodilatation
b) Exocrine gland secretion
c) Cytoprotection
d) Both a and c

2) What is the name of enzyme that convert Ag1 to Ag2 ?
a) ACE
b) NOS
c) Renin
d) PDE

3) What is the name of enzyme that convert cGMP to GMP ?
a) ACE
b) Renin
c) PDE
d) NOS

4) Which of these is a drug that acts as NO donners ?
a) Sildenafil
b) Ramipril
c) Candisartian
d) Nitrates

5) Which is responsible for activation of angiotensinogen to angiotensin I ?
a) Renin
b) ACE
c) ARB
d) Kallikrein

6) Renin is released from the kidney when:
a) the BP is low and the renal flow is high
b) the BP is high and the renal flow is low
c) the BP is low and the renal flow is low
d) Non of above

1-D ,2-A , 3-C , 4-D, 5-A 6-C

MCQS

7) AG II stimulates the _____ in the brain

a) thirst center
b) hypothalamus
c) pituitary gland
d) Both b and c

8) A drug modulator that blocks the angiotensin receptor (AT1) ?

a) Omapatrilat
b) Candesartan
c) Lisinopril
d) None of above

9) When The Ag II acts on non-blocked AT2 it causes ?

a) Vasodilation.
b) Vasoconstriction.
c) termination of action.
d) Nothing happen

10) One way to terminate Nitric Oxide action is by the formation of?

a) Chymase
b) Stable analogues
c) Aldosterone

7-A , 8-B ,9-A , 10-B

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We hope that we made this lecture easier for you
Good Luck !