جامعة الملك سعود
King Saud University

Pharmacology 434

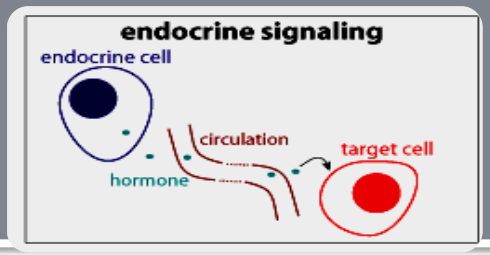
Drug Acting on Autocrine, Paracrine Mediators [part 1]

OBJECTIVES

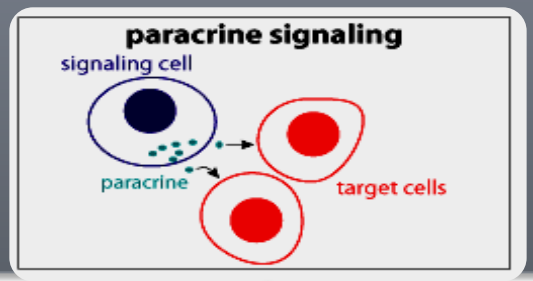
- ✓ Recognize the role of NO in cellular communication.
- ✓ Classify the different NOS available.
- ✓ Expand on its formation, actions termination and pharmacological modulation.
- ✓ Identify role of angiotensin in body homeostasis and local regulation.
- ✓ Explain its formation, target receptors, feedback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

Cell to Cell Communication

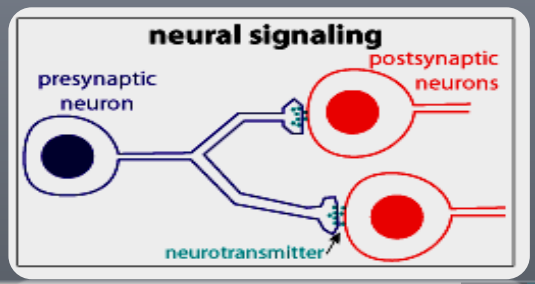
Distance: Via general routes → Blood



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

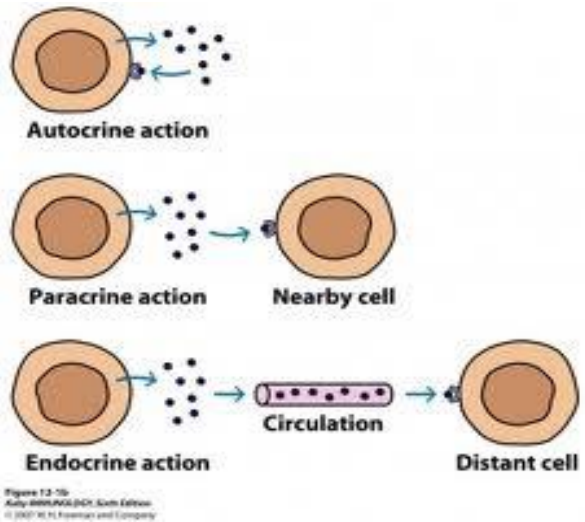


Along specified path→ Nerves



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

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)

Action of Nitric Oxide

1 Vasodilatation

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

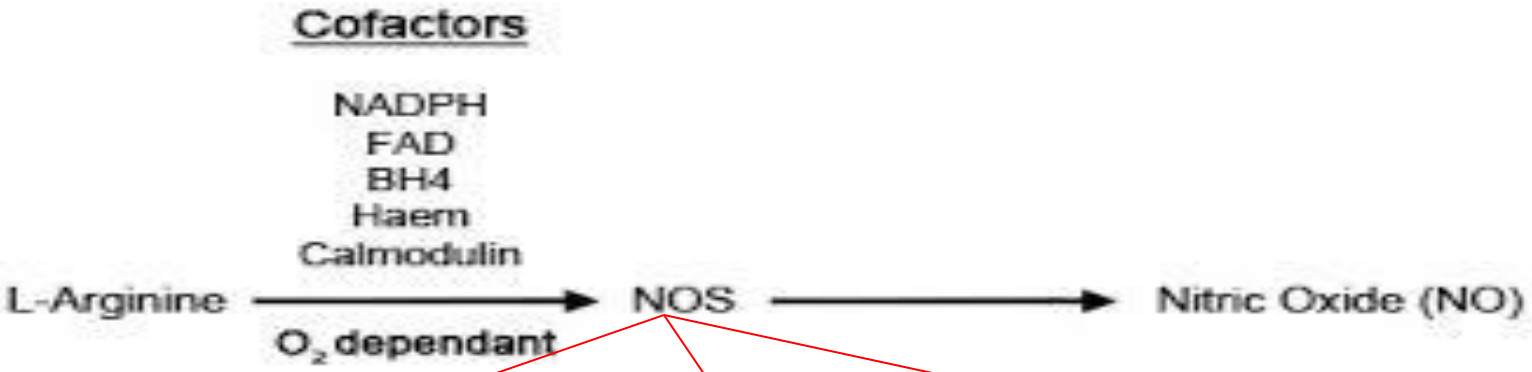
- ↓platelet aggregation
- ↓inflammatory cell recruitment
- ↓ Cholesterol deposition…etc.

MLCK*=

Myosin Light Chain Kinase

Synthesis of Nitric Oxide

It is a free radical



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

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)	**Nitrates** → venulodilators in Angina "heart disease"	Selective PDE_5 inhibitors, **Sildenafil** → eractile dysfunction
Estroge → CVS cytoprotection (That's why ladies before menopause never get heart attack) because NO help in vasodilatation of their heart.	**Na nitroprusside** → arteriolar dialator in hypertention "can be used in emergency situations"	Keeps the cGMP active
		Inhibit PDE cause vasodilatation

Angiotensin [Ag] vasoconstrictor peptide

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

- **RAAS**
- **ENDOCRINE**

Termination Action

(Remember that Ag acts on G-protein receptors)
by peptidases , aminopeptidases
(angiotensinase)

AgII → AgIII
(Ag III is less active & then fragmentation products)

Action

(AgII does the action)
↑ Blood pressure
Endocrine/paracrine

- Kidney: ↑ Na retention.
- Adrenal gland: secrets aldosterone hormone.
- Heart: ↑ inotropy , ↑ chronotropy.
- Blood vessels: vasoconstriction.
- Brain: ↑ thirst , ↑ SNS activation.

Action

↑ Blood pressure
Autoctine

- Kidney: ↑ fibrosis.
- Heart: ↑ hypertophy, ↑ fibrosis.
- Blood vessels: ↑ remodeling = hypertrophy.

If Ag II was always high then it will cause diseases

Angiotensin drugs modulating

Inhibition of RAAS system
is beneficial in treatment of:

- **Hypertension (↓ hypertrophy).**
- **Heart failure (↓ hypertrophy & fibrosis)**
- **Diabetics (protect the kidney).**

Drug	Action
Clonidine	↑ SN
Propranolol	↓ BF [β_2]
Aliskiren	Inhibit renin
Lisinopril	Inhibit ACE
Omapatrilat	Vasopeptidase inhibitor
Candisartan	ARBs
Spirinolactone & Eplerenone	Aldosterone antagonists

Kinins: Bradykinin is a vasodilator peptides

Synthesis	Action	Termination of action	Drugs modulating
prekallikerin	Vasodilatation	ACE & Neutral Endopeptidase (NEP)	NSIDs: ↓Action →↓bradykinin mediated pain .
	Inflammation & exudation		
	Pain (sensory nerves)		ACE inhibitors & vasopeptides (antihypertensive drugs): ↓breakdown →↑ their concentration.
	Exocrine gland secretio		

Difference between ACE Inhibitors & ARBs action

ACE inhibitors (captopril; Ramipril): Inhibit activation of AgI to AGII + decrease degradation of bradykinin

ARBs (Ondancetran; Candisartan) : Block action of AgII on AT1 in VSMCs that is causing vasoconstriction, therefore,
The AgII acts on non-blocked AT2 on endothelial cells causing vasodilatation. However, ARBs have no effect on Bradykinin

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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 and) ▪ 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 2\ Act as NO 3\ Prevent breakdown of PDE =(Stopping the breakage of cGMP)	**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 - ACE inhibitors - Angiotensin Receptors Blockers (ARBs) - Vasopeptidase inhibitors - ADOSTERONE Antagonists	**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 act as NO donners ?
a) Sildenafil
b) Ramipril
c) Candisartian
d) Nitrates

5) Who 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 stimulate the _____ in the brain ?
a) thirst center
b) hypothalamus
c) pituitary gland
d) Both b and c

8) A drug modulator that block the angiotensin receptor (AT1) ?
*a) O*mapatrilat
b) Candisartan
c) Lisinopril
d) Non of above

9) When The Ag II act on non-blocked AT2 it cause ?
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
d) Both A and C

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

GOOD LUCK

Done by pharmacology team 434

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