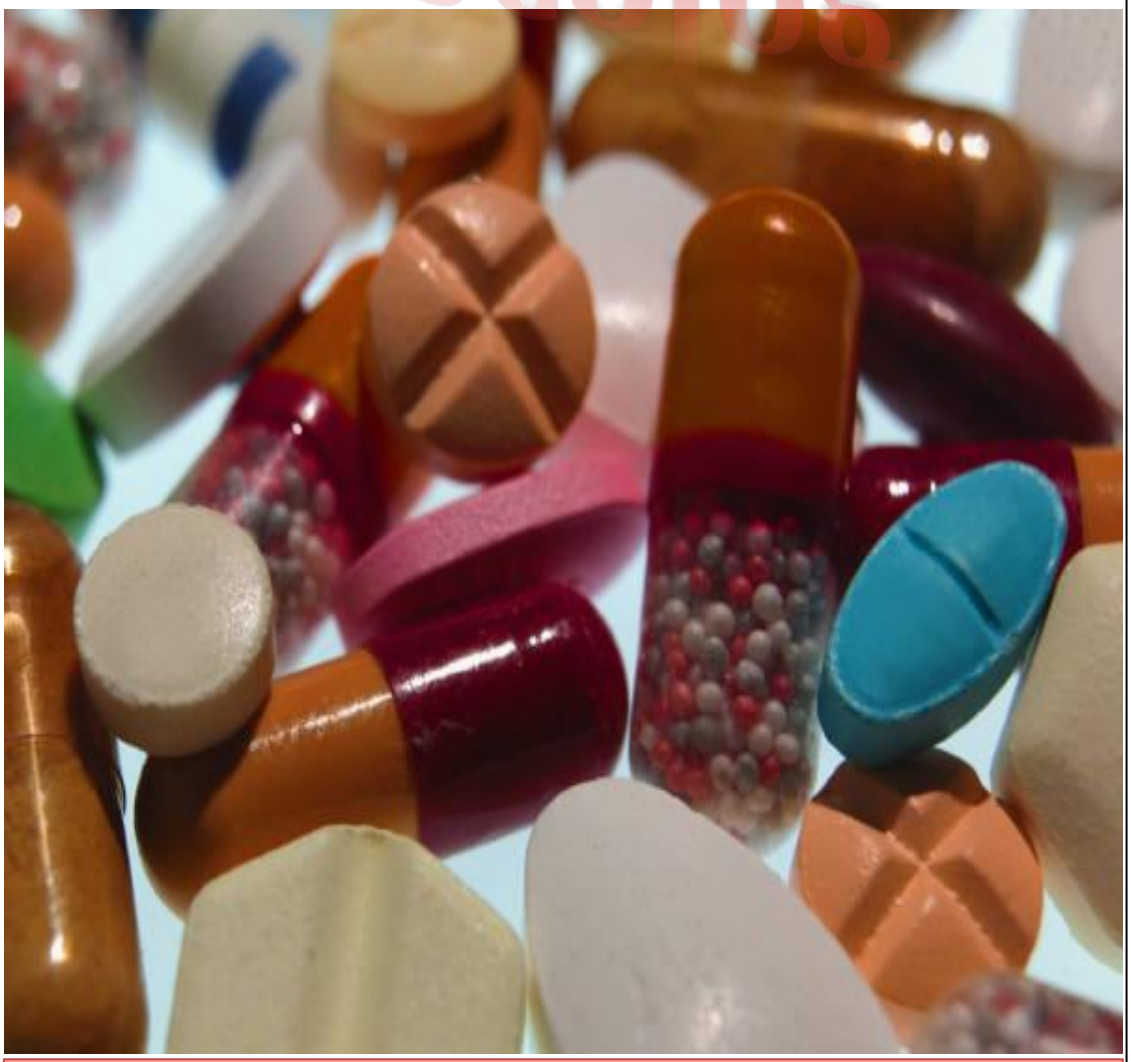
pharmacolog



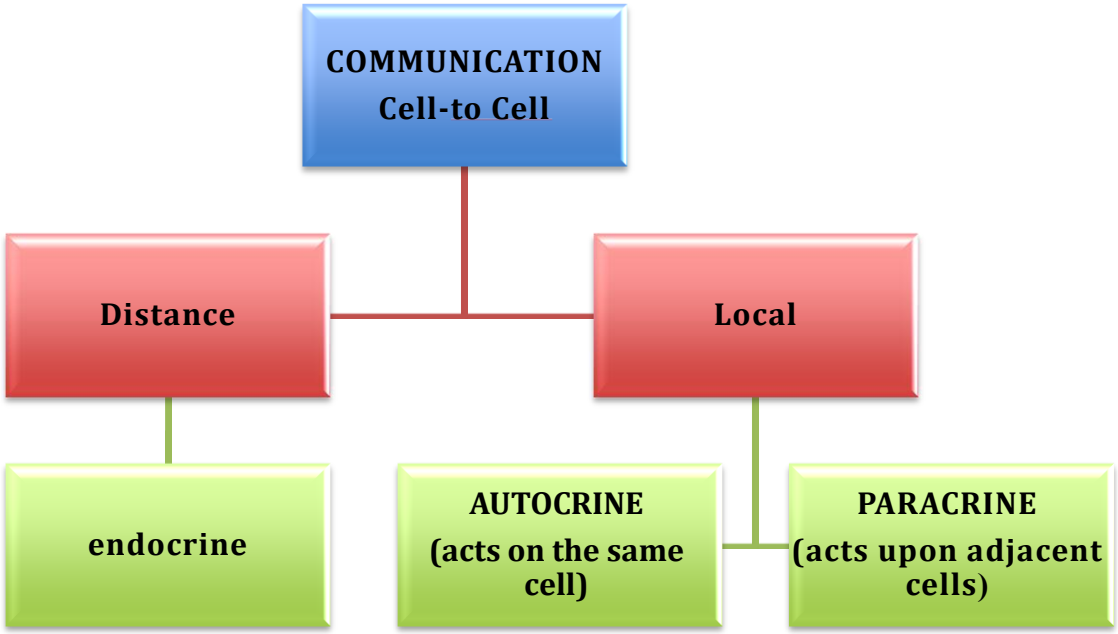
By:.

Team of pharmacology

8th pharmacology lecture "Drugs acting on paracrine and autocrine mediators part 1"

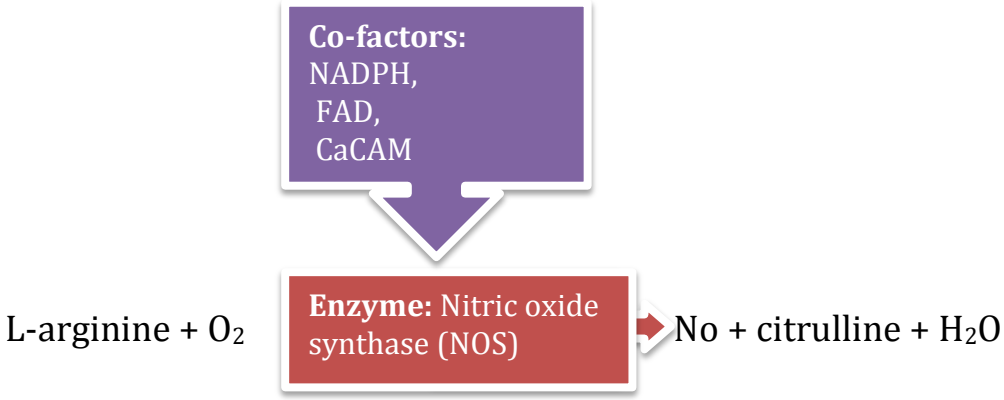
Lecture's objectives:

1. Know how to differentiate between "Nitric oxide, Angiotensin (Ag), and Bradykinin".
2. Correctly compare between the various NOS "Nitric oxide synthase" isoforms.
3. Know the synthesis, Action, Drug modulating and termination of action for: NO, Ag and bradykinin.
4. The difference between ACE and ARBs in action.
5. Make sure to differentiate CORRECTLY between the drugs names.



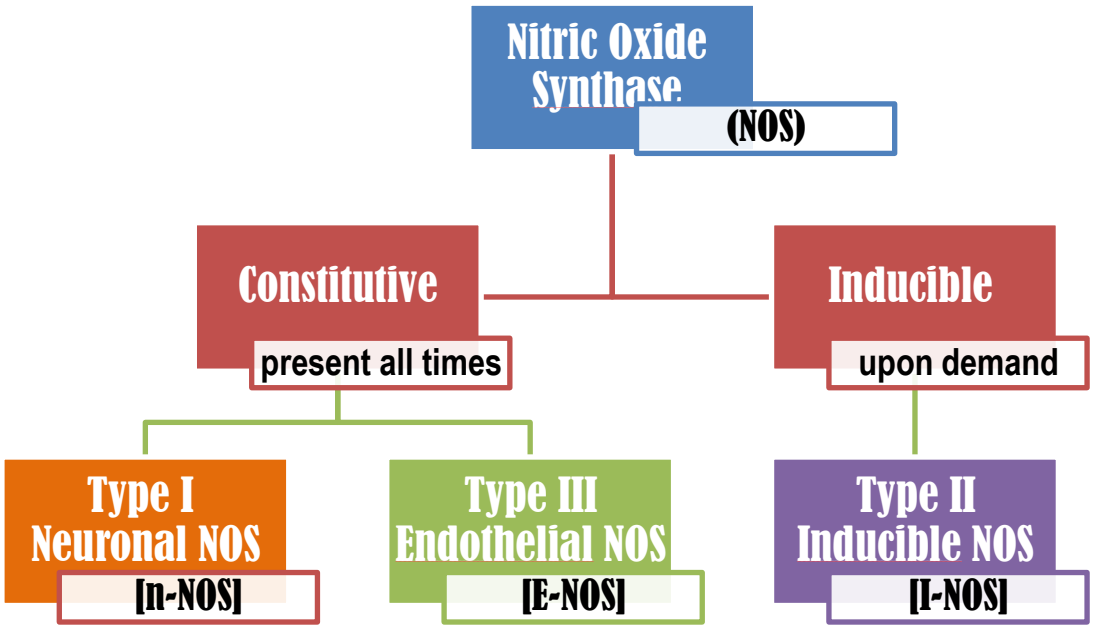
1. Nitric oxide (NO)

A-Synthesis



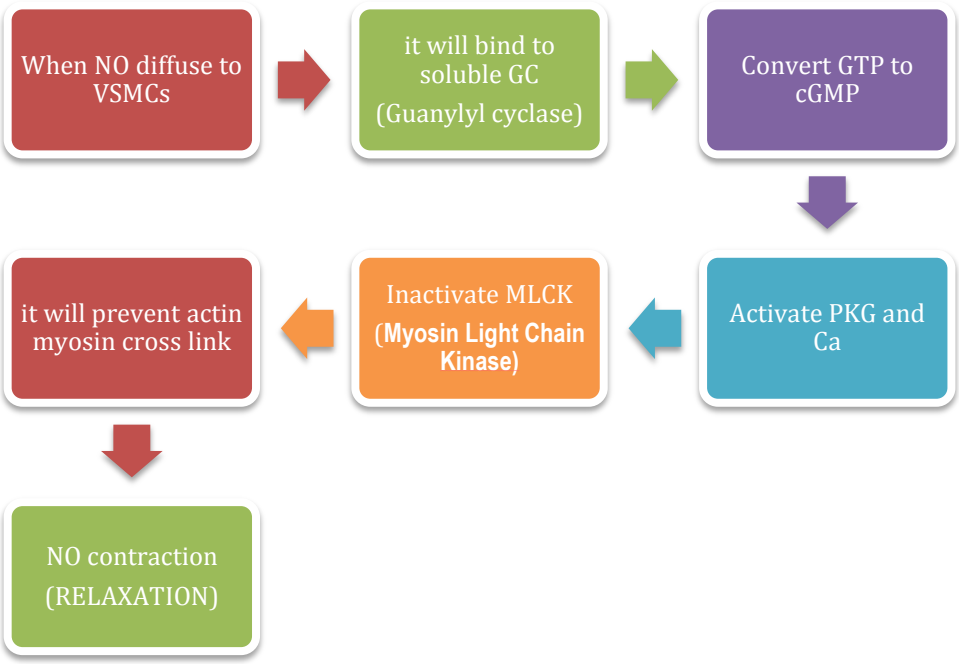
Notes:

- ✓ Shear stress or agonists as: Ach, Histamine, Bradykinin (All of these are signals) when it binds to receptors the range of intracellular Ca will increase and activates **eNOS**, which will stimulate the formation of NO.
- ✓ For example: During running the blood flow will increase then the shear stress will increase so more activation of eNOS will occur then more vasodilatation will happen.



B-Action

1. Vasodilatation (paracrine action)



2. Cytoprotection (autocrine paracrine action):
protect the endothelial cells by:

- ↓platelet aggregation
- ↓inflammation cell recruitment
- ↓cholesterol deposition.

C-Termination of action

By formation of:

1. Stable analogues
2. Free radical

By break down of:

1. cGMP

(NO increase the blood flow and cause vasodilatation so long as cCMP is formed and exists acting. If cGMP is broken down by PDE into GMP then the vasodilatation produced by NO stops. Remember that one way to keep NO induced vasodilatation is to inhibit PDE, so cGMP does not change to GMP.)

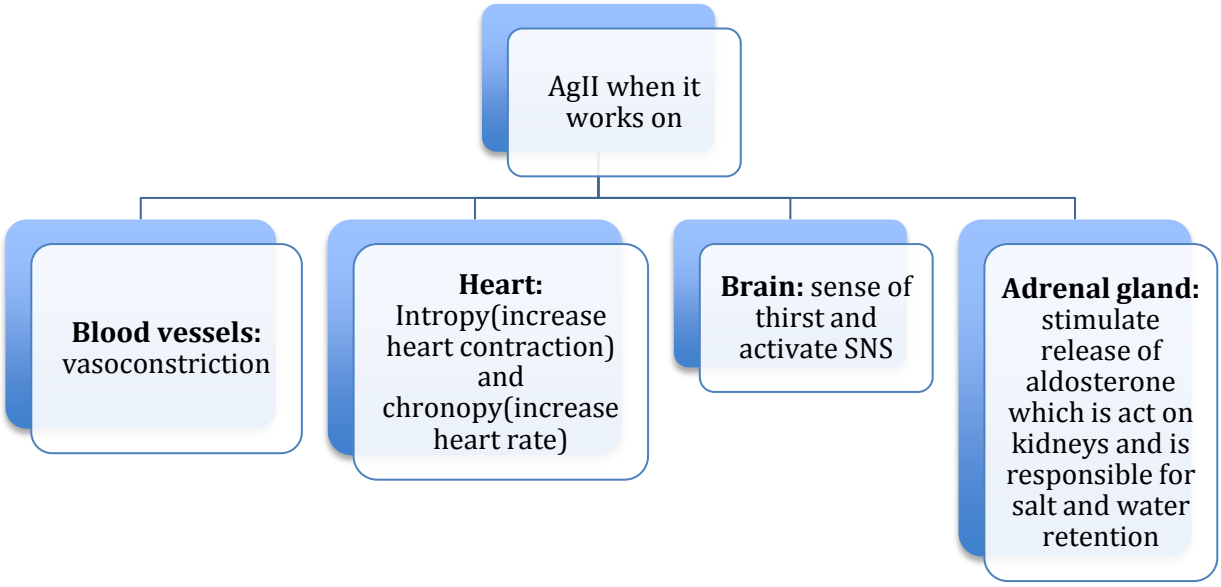
2. Angiotensin (Ag): a Vasoconstrictor peptide

A-Synthesis

Angiotensinogen is released from the liver in an INACTIVE form, to be active it should be convert to **AgI** By **Renin (released from the kidneys by the renal juxtaglomerular apparatus)**, then it should be convert to **AgII** by **ACE (Angiotensin Converting enzyme)**

***The receptors (G-protein coupled) are:**
At1 (vasoconstriction) and At2 (Vasodilatation)

B-Action

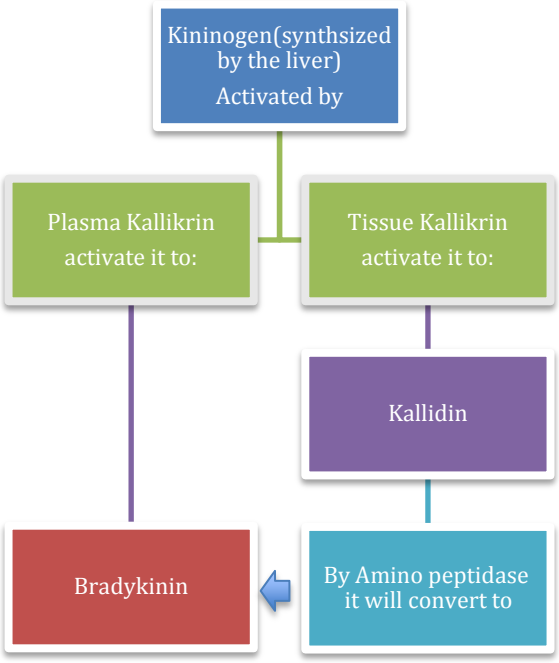


C-Termination of action

AgII acted upon by peptidases amino peptidases (Angiotensinase) to **AgIII (Less active)**

3.Kinin: Bradykinin is a vasodilator peptide

A-Synthesis



B-Action

1. Vasodilatation **(by working on its receptors to activate NO synthase) (Indirect vasodilator)**

2.Inflammation **(Kinin can produce all the symptoms of inflammation)**

3.Pain **(Stimulate nociceptive nerve afferent fibers)**

4.Responsible for exocrine gland secretion.

C-Termination of action

By breaking down to inactive metabolites by **(ACE and Neutral Endopeptidase (NEP))**

Drug modulating: Decrease breakdown of bradykinin by increase concentration of ACEIs and vasopeptidase inhibitors.

Difference between ACEIs and ARBs action:

ACEI; Inhibit activation of AgI to AGII+decrease degradation of bradykinin.

ARBs; Block action of AgII on AT1 in VSMCs that is causing vasoconstriction. The AgII act on non-blocked AT2 on endothelial cells causing vasodilatation.

Drug modulating:

Name	Description
Statins **Estrogen**	Express or active eNOS (CVS cytoprotection)
Nintrates	Acts as NO donner (venulodilators in angina (الذبحة الصدرية))
Na nitroprusside	Acts as NO donner (Arteriolar dilator in hypertension)
Sildenafil	Selective PDE_5 inhibitor prevent breakdown of cGMP (Erectile dysfunction)
Propranolol	Beta1 blocker (reducing Renin)
Clonidine	Works as anti-hypertension
Aliskiren (very important).	Renin inhibitor
Lisinopril **Captopril (very important).** **Ramipril**	ACE inhibitor
Omapatrilat	Vasopeptidase inhibitor (inhibits ACE and kinase)
Candesartan **Valsartan**	Angiotensin receptor blocker (ARB)
Spironolactone **Eplerenone**	Adosterone antagonists
NSAIDS	Inhibit pain sensation by decreasing bradykinin

General Notes:

❖ Types of cell to cell communication:

- Along specific path: the signal is transmit it from the CNS to any organ throughout a nerve
- Distance: transmit it throughout the blood vessels like the thyroid gland which has many function that act upon different organs
- Local: two adjacent cell communicate with each other throughout the ECF, GAP JUNCTION, ECM (extra cellular matrix)

❖ NO and some PEPTIDE are involved in the regulation of the CVS.
❖ NVSMC: like the GIT and urinary bladder.
❖ VSMC: blood vessels.
❖ De novo: produced when need it.
❖ NO: vasodilatation.
❖ Bradykinin: vasodilatation.
❖ Angiotensin: vasoconstrictor.

❖ NO: is a gas mediator (secreted from certain place and go to another place to do its work then disappear).
❖ NO reaction produce free radicals.
❖ Shear stress; is a place in the endothelium that secrete the E NOS.
❖ NO bind to GC then change GIP to CGMP (second messenger) which active the PKG (inhibit the cross linking between the actin and MLCK.
❖ Angiotensin found in the blood produced by the liver but in inactive form (Ag).
❖ Inotropy; increase the heart contraction.
❖ Chronotropy; increase the heart rate.