

9- autocooids

Objectives:

To describe the synthesis, receptors and functions of histamine, eicosanoids ,nitric oxide , angiotensin, kinins & 5-HT

To study the agents which enhance or block their effects

- Titles 
- Very important 
- Extra information 
- Terms 

You can, you should, and if you're brave enough to start, you will

Angiotensin

Biosynthesis:

Renin released from the kidney converts angiotensinogen to Ag I

ACE converts Ag I to Ag II

Actions of angiotensin II

- Promotes vasoconstriction directly or indirectly by releasing NA & AD.
- Increases force of contraction of the heart by promoting calcium influx.
- Increases aldosterone release → sodium & water retention.
- Causes hypertrophy of vascular and cardiac cells and increases synthesis and deposition of collagen by cardiac fibroblasts (remodeling).

Angiotensin

is a peptide hormone that causes vasoconstriction and a subsequent increase in blood pressure. It is part of the renin-**angiotensin** system, which is a major target for drugs that lower blood pressure. **Angiotensin** also stimulates the release of aldosterone, another hormone, from the adrenal cortex.

Angiotensin inhibitors “ACE”

Those are **captopril** and **enalapril**.

Angiotensin receptor blockers “ARBs”

Those are **Isoartan** and **valsartan**.

To know the difference between ACE and ARBs, please visit this site:

<http://www.healthcentral.com/high-blood-pressure/c/question/401647/52421/>

Angiotensin inhibitors “ACE”

Those inhibitors cause a fall in the blood pressure in hypertensive patients especially those with high **renin** levels.

Renin is a hormone. **Renin's** primary function is therefore to eventually cause an increase in blood pressure, leading to restoration of perfusion pressure in the kidneys. **Renin** is secreted from juxtaglomerular kidney cells, which sense changes in renal perfusion pressure, via stretch receptors in the vascular walls.

Clinical uses of Angiotensin inhibitors “ACE”

- Treating hypertension
- In cardiac failure
- Following myocardial infarction

Angiotensin receptor blockers

- Angiotensin receptors AT I & AT II
- AT 1 receptors predominate in vascular smooth muscle, mediate most of the known actions of Ang, coupled to G proteins & DAG
- Similar uses to ACEI

RAAS = Renin angiotensin-aldosterone System (اللفهم)

How is RAAS activated?

By binding of the active form Ag2 with AT1 receptor that leads to Aldosterone secretion So Angiotensin is a hormone that stimulates Aldosterone secretion in the kidney As a result, the Sympathetic Nervous System is stimulated and following actions will take place

Blockers :

they will effect on the quantity of renin, and that will lead to decrease of activated the RAAS

Propranolol: B-blocker

Clonidine

Aliskiren (renin inhibitor)

Lisinopril (ACE inhibitor)

Omapatrilat

وهالدواء يأتى على:

Chymase endopeptidase

Candesartan (Angiotensin Receptor Blockers (ARBs))

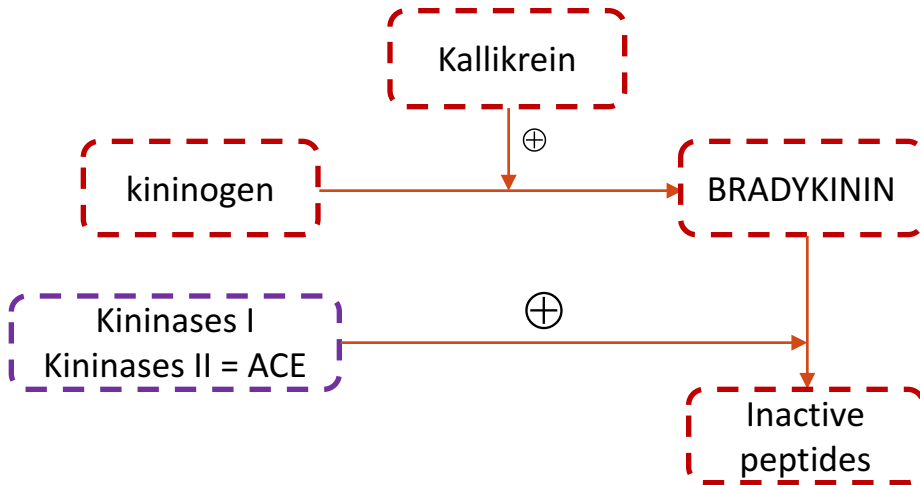
Spironolactone eplerenone (ADOSERONE Antagonists)

Kinins

Are Bradykinin & kallidin

Bradykinin is formed by proteolytic cleavage of circulating proteins (kininogens)

Bradykinin is a vasodilator



Actions of Bradykinin

1) Potent vasodilator, reduces blood pressure.

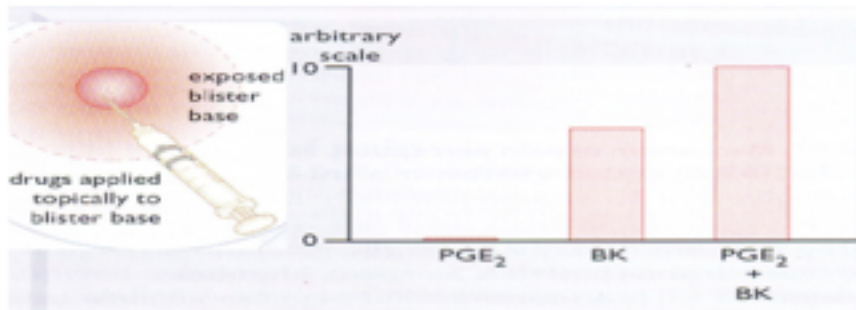
If injected locally it dilates arterioles [mediated by release of NO and generation of PGI (Prostaglandin I which is prostacyclin)] and increases permeability of post capillary venules.

2) Constricts most smooth muscles (intestines, uterus, bronchiole).

The contraction is slow and lasts for a long time. (that's why its called bradykinin: brady (slow) kinin (contraction or kinetic movement))

3) Stimulation of ion transport in epithelial cells and fluid secretion in airways and GIT.

4) Causes pain (this effect is potentiated by PG) and has a role in inflammation.



*Arbitrary scale = pain scale from 0 to 10 (0 no pain/10 severe pain)

Explanation of the picture:

Prostaglandins (PG) do not cause pain themselves but sensitize nerve endings to the action of other pain mediators. What does this mean? If I have a blister and I inject PG alone it will not cause pain. If I inject bradykinin (BK) alone it will cause pain. But if I inject both PG and BK there will be severe pain. Therefore PG potentiate or increase the effect of BK.

Bradykinin receptors & Clinical uses

There are two receptors B_1 & B_2

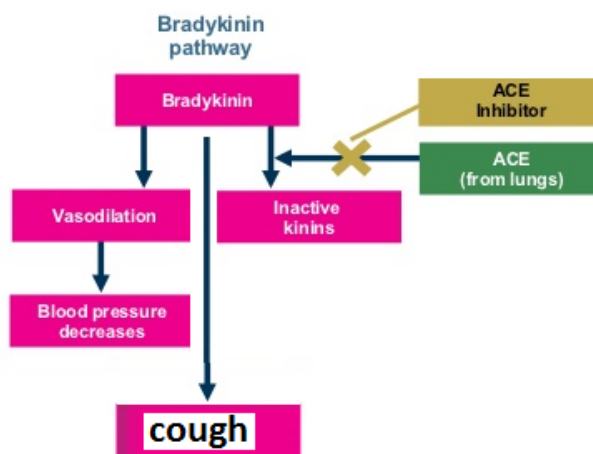
Do not confuse the B receptors for kinin and β (beta) receptors for adrenergic!!

B_1	B_2
Inducible (under conditions of inflammation)	Constitutive
Low affinity to bradykinin	High affinity to bradykinin
Significant role in inflammation and hyperalgesia	Mediates the majority of bradykinin's effects

Hyperalgesia = increase sense of pain

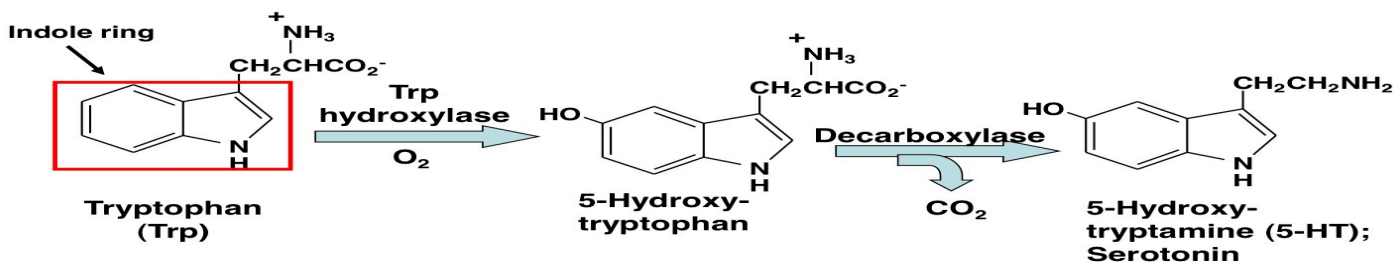
Therapeutic uses:

- No current therapeutic use of bradykinin
- Increased bradykinin is implicated in the therapeutic efficacy and cough produced by ACEIs



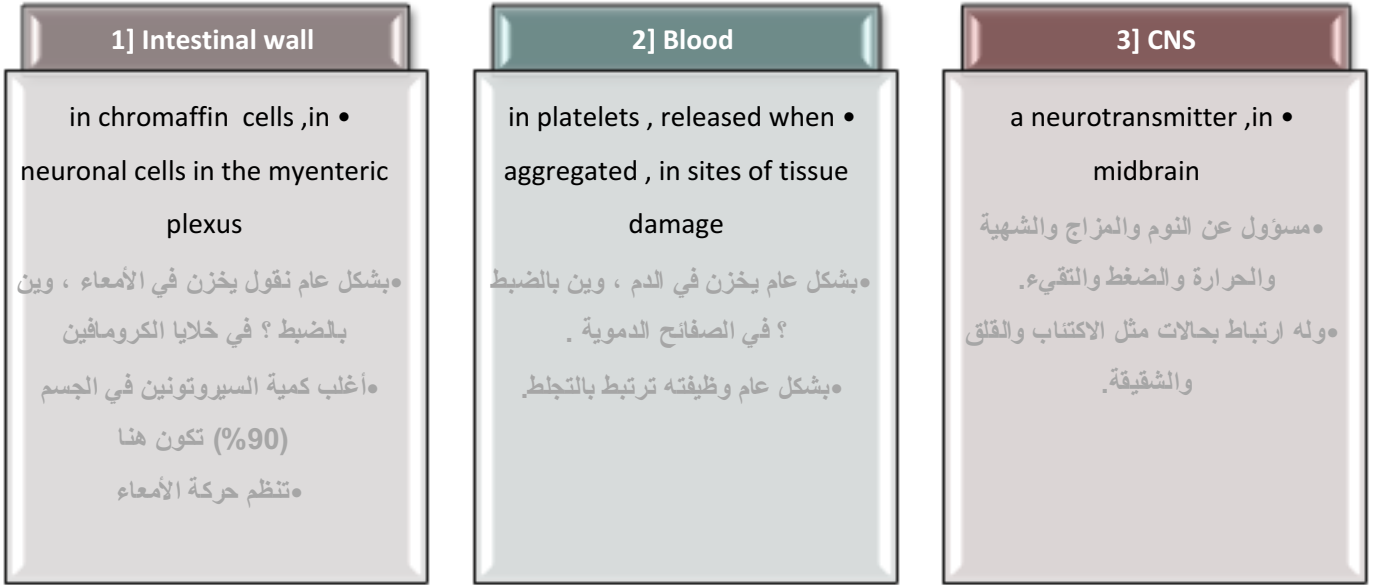
Serotonin [5ht]

Serotonin is synthesized from the amino acid L-tryptophan



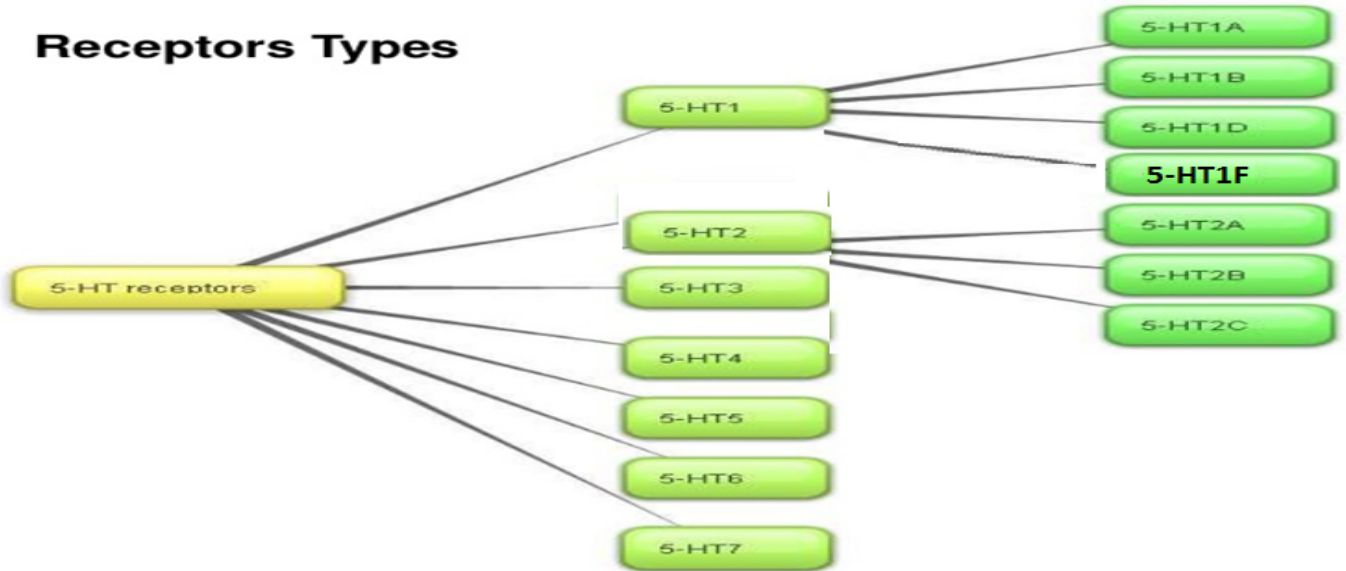
Distribution of Serotonin [5-ht]

بعد تصنيعه اما انه يخزن (في 3 أماكن) أو يحصل له تثبيط سريع (له تفصيل لكن غير مطالبين به الآن) :



Serotonin receptors

Receptors Types



* أهم شيء تعرفون أن مستقبلاته **7** أنواع وأن النوع الأول والثاني يتفرعون لأنواع بعد

* مما يدل على أهمية السيروتونين أن له الكثير من المستقبلات وكل مستقبل يقوم بوظيفة مختلفة وموجود في مكان مختلف عن الآخر , فالسيروتونين يقوم بوظائف كثيرة تختلف باختلاف المستقبل الذي يرتبط معه.

* كل المستقبلات من نوع (المعتمد على البروتين جي) إلا المستقبل رقم 3 فهو من نوع (المعتمد على قناة أيون)

Actions of 5-ht:

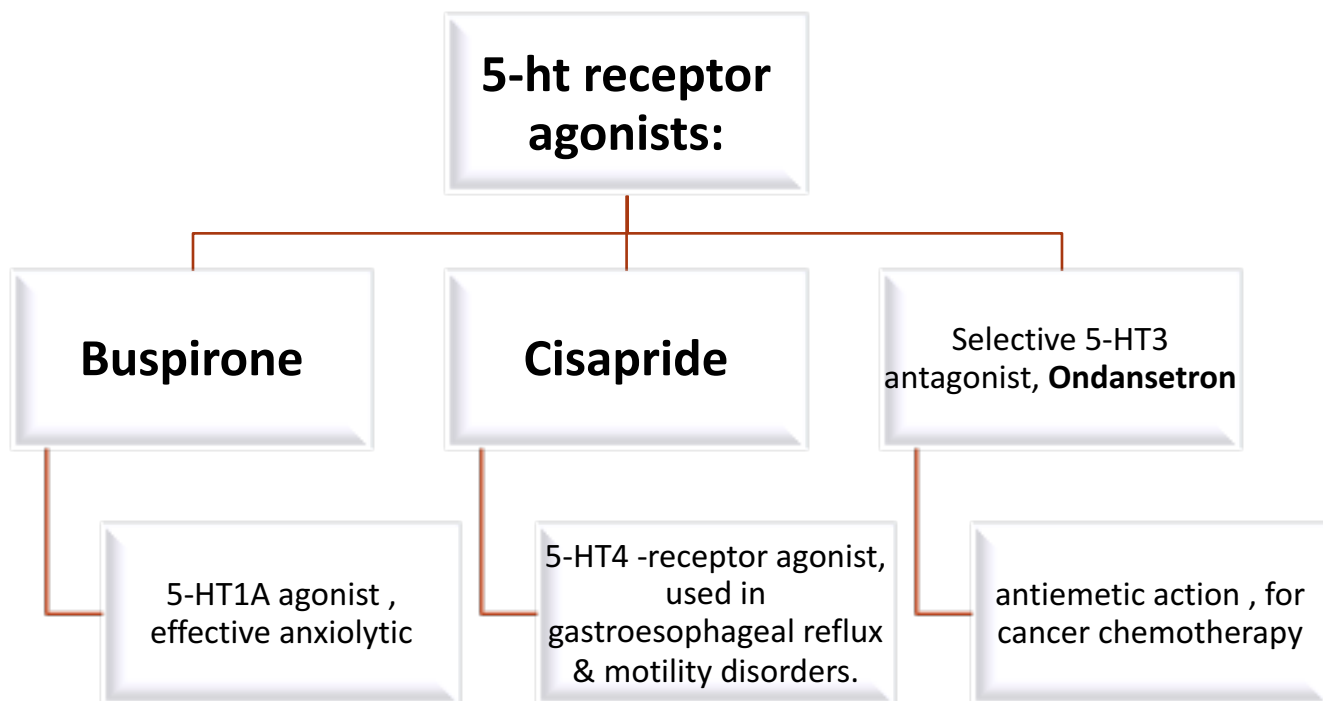
- GIT:-5-HT increases motility
- Contracts uterus bronchiole ,other smooth muscles

Blood vessels:-

Contracts large vessels by a direct action & relaxes other vessels by releasing **NO**
Increases capillary pressure & permeability

5-ht actions:

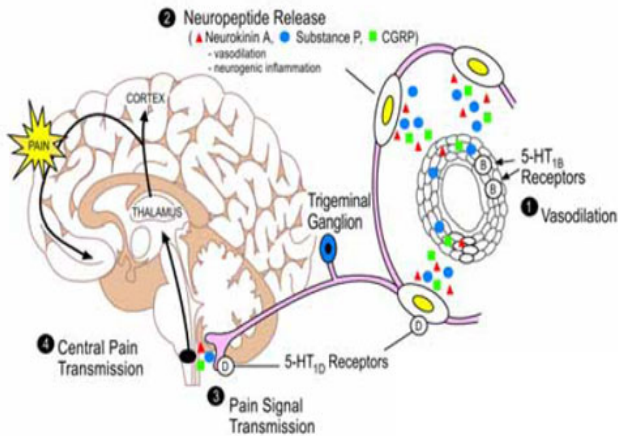
	The effect
Platelets	causes aggregation ,aggregated platelets release 5-HT
Neuronal terminals	5-HT stimulates nociceptive neuron endings → pain
CNS	stimulates some neurons & inhibits others , inhibits release of other neurotransmitters



Clinical conditions in which 5-ht is implicated:

1-migraine:

Activation of trigeminal system leads to peptides release promoting an inflammatory reaction. This increases flow of sensory traffic through the brain stem, the thalamus & the cortex



Sumatriptan

- 5-HT_{1D}, 1B & 1F-receptor agonist , effective in acute migraine attack
- It binds to 5HT_{1B} , in cranial blood vessels causing vasoconstriction & 1D & 1F in presynaptic trigeminal nerve causing inhibition of pro inflammatory neuropeptide release

2- Carcinoid syndrome:

- A malignant tumor of intestinal chromaffin cells
- The tumor releases 5-HT, SP, PGs, kinins & histamine causing flushing ,diarrhea, bronchoconstriction & hypotension
- Serotonin antagonists (**cyproheptadine**, 5HT₂ antagonist) could be administered to control diarrhea ,flushing & malabsorption

Quick Quiz

[https://www.onlineexambuilder.com/
pharmacology-l9/exam-110846](https://www.onlineexambuilder.com/pharmacology-l9/exam-110846)

Helpful video

[https://www.youtube.com/watch?v=f
jDgKSVspoU&t=8s](https://www.youtube.com/watch?v=fjDgKSVspoU&t=8s)

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jDgKSVspoU&t=8s](https://www.youtube.com/watch?v=fjDgKSVspoU&t=8s)

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