The Endocrine System

PHARMACOLOGY

☑ Sheet ☐ Slide ☐ Handout

Number:	3
Subject:	Autacoids/ Serotonin+ Melatonin
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(section 2 record , slides)

In this lecture we will continue talking about Autacoids ; serotonin and Melatonin, by this we conclude the autacoids, then we will move to real endocrine pharmacology in the upcoming lectures.

Tissue and organ system effects

Nervous System

1. Serotonin is a neurotransmitter
   In CNS pharmacology we will hear a lot about serotonin as it has been used to treat depression, Schizophrenia and many other CNS-related diseases.
2. It is the precursor of Melatonin (the sleepy hormone- details later)
3. Serotonin is an analgesic ,ie : have antinociceptive action (reducing sensitivity to painful stimuli).

   “Sertonin may change the Future of Pain treating “

   there is a promising serotonin agonist drug called Repinotan , to be more specific it is a 5-HT1A agonist , it is under investigations to be used to treat pain without the risk of developing respiratory depression.as some patients do develop respiratory depression when Opioids (ex. Morphine) are used as analgesics.
   it also would be used to reverse opioid-induced respiratory

depression.

so Repinotan will be used as :

- ✓ analgestic without respiratory depression risk
- ✓ if you used opioids as analgesics they can reverse the respiratory depression –if occurred-.

4. Peripherally , if you stimulate 5-HT3 receptors (present at GI nerve terminals and Vomiting receptors) these receptors induce vomiting by a chemo-sensitive reflex (not a neural reflex) ,recall from GI pharmacology [the Chemoreceptor trigger zone]
   what are those?
   a nucleus in the medulla/ Brain that detects chemical stimulants (changes) in the body and sends massages to the vomiting centers to induce vomiting.
   why the involvement of GI tract nerve terminals?
   to reverse the movement of GI tract , ie : vomit.

   so to vomit a cooperative action of 5-HT3 receptors of GI nerve terminals and Vomiting receptors in the brain work along with Chemoreceptor trigger zone.
   these data are particularly used to treat vomiting induced by chemical triggers such as cancer chemotherapy (as this is the exact mechanism of how these people vomit)
5. Similar to histamine, serotonin induces Pain and Itching at sensory nerve endings when someone get a plant or insect sting.
   a Question must be raised here:
   How come serotonin is analgesic (point 3) and it induces PAIN ?
   simply the mechanism is different AND the location of each actions are different (central or peripheral). After all its all about the

RECEPTORS, serotonin have several types of receptors (and subtypes), in fact they give serotonin this diversity of effects.

6. In coronary vascular bed, there are 5-HT3 receptors these work to induce bradycardia and hypotension.
   why bradycardia?
   a chemoreceptor reflex , stimulate vegal nerve , this increase Ach and produce bradycardia.
   So serotonin mediate the RELEASE of Ach unlike histamine, Recall in sheet 1 we said Hetero/auto H3 receptors INHIBIT the release of histamine itself or other NTs (Ach) from neurons.
   Note : this effect can be blocked by atropine (slides only)

   why hypotension?
   a chemoreceptor reflex induce hypotension , but how?
   to understand that enter this box :)

   Blood pressure (BP)= Systolic BP / diastolic BP
   diastolic BP depends on peripheral cardiac resistance , while systolic depends on cardiac output ,NOW:
   cardiac output = Heart rate * Stroke volume
   now as serotonin induced bradycardia , it decreased the heart rate >>as a result decrease cardiac output >> decrease systolic BP >> decrease BP.

   Note : Stroke volume is The amount of blood pumped by the left ventricle of the heart in one contraction.

so after exiting this box , you now know that
"hypotension is a consequence of the decrease in cardiac output that results from bradycardia."

Respiratory system

Induce bronchoconstriction , this produce difficulty in breathing (as histamine) the receptors responsible for this are 5-HT2A receptors.
this effect is dual :can be induced directly by serotonin or indirectly by releasing Ach (a Bronchoconstrictor too)
Now to compensate this "Narrowing effect " caused by serotonin , Hyperventilation will occur (as a result of a chemoreceptor reflex or stimulation of bronchial sensory nerve endings.)
Note: this compensation is protective against respiratory difficulty , it can compensate to a certain limit , then an intervention must be made.
so two actions of serotonin upon respiratory system :

- ✓ Bronchoconstriction
- ✓ Hyperventilation

Cardiovascular system

1. generally speaking serotonin contracts smooth muscles everywhere (blood vessels , GI , Urinary ..) exept of two places: blood vessels of cardiac and skeletal muscles >> as it acts as vasodilators.
   [Note : vasodilation here means atrial- dilation not venous]
   Why serotonin constrict SMCs everywhere but not in cardiac and skeletal muscles?

because

“Vasodilation requires intact endothelium”

Explanation (refer to figure 1)

endothelium cells of heart and skeletal muscles arteries have serotonin receptors (5-HT2 receptors) , when stimulated a release of Endothelium-derived relaxing factors (EDRF) [like nitric oxide “NO”] will occur . Nitric oxide will go to SMCs of these arteries and dilate them.

so we can conclude that serotonin is an indirect vasodilator; it doesn’t have receptors on SMCs (smooth muscle cells) but on the surrounded endothelium that will release NO upon stimulation that will target SMCs to dilate.

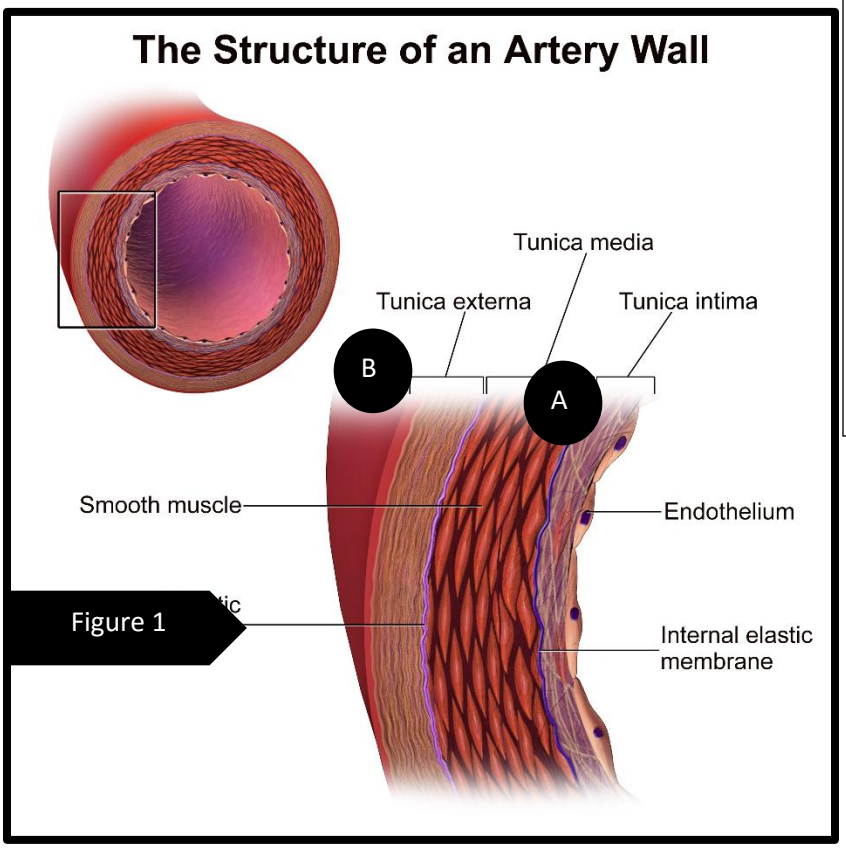

Figure 1 : serotonin is an indirect vasodilator.

1. Serotonin target the endothelium indicated as “A”
2. Endothelium release NO
3. NO target smooth muscles , indicated as B
4. Vasodilation occur.

2. Bradycardia (discussed before)
3. Veno-constriction , the consequences of this effect is increased capillary filling , this will lead to flushing.(figure 2)

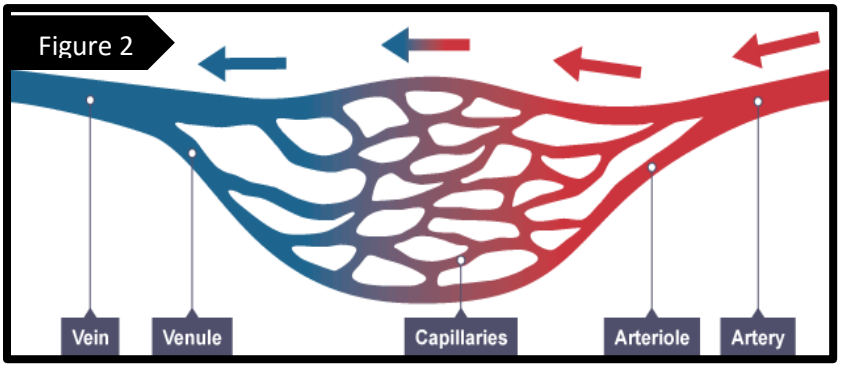

Figure 2 : venoconstriction caused flushing .
when the vein is constricted , the blood is collected in capillaries >>capillaries increase in size >> flush blood out.

4. In case of carcinoid tumors (prolonged high level of serotonin) will induce subendocardial fibroplasia (fibrosis under the endothelium of heart) this will affect the conductor (electrical)function and valvular function of the heart.

5. Platelet aggregation by activating surface 5HT2 receptors.

Gastrointestinal tract

1. serotonin facilitating peristalsis by stimulating SMCs of GI .
   Note: in case of carcinoid tumors>> excessive serotonin >> excessive peristalsis >> diarrhea.
   (diahrea is one of the manifestations of carcinoid tumors)

You do remember what a carcinoid tumor is , Right? ;)

a carcinoid tumor : Carcinoids are tumors of the **neuroendocrine system**. They are also called neuroendocrine tumors (NETs). rare tumors which tend to be slow growing. They may not cause any symptoms for several years. They can develop at any age, but the average age of diagnosis is around 60

mechanism (slides only)
by stimulating 5-HT2 smooth muscle receptors and stimulation of ganglion cells in the enteric nervous system). 5-HT1A and 5-HT7 receptors may also be involved.

2. prokinetic effect , Recall: this term was discussed in GI pharma as prokinatics were used to treat Gastroesophageal reflux disease GERD [قِرد :P] prokinetic effect means enhancing GI movement in the right direction (not-vomiting-wise-direction)
   Mechanism
   serotonin increases acetylcholine release by activation of 5-HT4 receptors in enteric nervous system.

3. Diarrhea (discussed)

Syndromes

Serotonin Syndrome

Like in carcinoid tumors, there is an incensement of serotonin in this syndrome.
it is important to know that this syndrome occur centrally
caused by certain drugs:

1. **Serotonin selective reuptake inhibitors (SSRIs).**
   used to treat depression, they increase serotonin at the synaptic space as they inhibit its reuptake by neurons. this enhance the action of serotonin.
2. **Second generation antidepressants.**
   these are non-selective Serotonin reuptake inhibitors. They also

increase serotonin in the synaptic space this enhance the action of serotonin.
Note: these inhibit many “reuptakers=transporters” like those related to epinephrine and norepinephrine, they were listed here as they also inhibit serotonin **reuptake.**

3. **Monoamine oxidase inhibitors (MAOIs).**
   we said that Monoamine oxidase is used to metabolize serotonin.
   in case of inhibiting this enzyme serotonin will accumulate.

This syndrome is Manifested within hours by hypertension, hyperreflexia, tremor, clonus *, hyperthermia, hyperactive bowel sounds, diarrhea, mydriasis, agitation (irritability), coma and may be DEATH (it is a fetal syndrome).

***clonus** is a series of involuntary, rhythmic, muscular contractions and relaxations it is thought to be caused by calcium abnormalities.

there is something else that cause such like symptoms , which is

Malignant hyperthermia

occur when giving a genetically susceptible patient succinylcholine and halothane during a surgery ,characterized by elevated ,it will elevate so severely (that’s why they called it Malignant-not cancer).
Malignant hyperthermia is similar to serotonin syndrome but still distinctive from it.

Neuroleptic Malignant hyperthermia

this will be discussed in CNS.

the doctor showed us this table. Notice how these syndroms are similar but not identical. Make sure that you “read” it. Focus on Bolds.

TABLE 16–4 Characteristics of serotonin syndrome and other hyperthermic syndromes.

Syndrome	Precipitating Drugs	Clinical Presentation	Therapy[1]
Serotonin syndrome	SSRIs, second-generation antidepressants, MAOIs, linezolid, tramadol, meperidine, fentanyl, ondansetron, sumatriptan, MDMA, LSD, St. John's wort, ginseng	Hypertension, hyperreflexia, tremor, clonus, hyperthermia, hyperactive bowel sounds, diarrhea, mydriasis, agitation, coma; onset within hours	**Sedation (benzodiazepines), paralysis, intubation, and ventilation;** consider 5-HT_2 block with cyproheptadine or chlorpromazine
Neuroleptic malignant syndrome	D_2-blocking antipsychotics	Acute severe parkinsonism; hypertension, hyperthermia, normal or reduced bowel sounds, onset over 1–3 days	**Diphenhydramine** (parenteral), cooling if temperature is very high, sedation with benzodiazepines
Malignant hyperthermia	Volatile anesthetics, succinylcholine	Hyperthermia, muscle rigidity, hypertension, tachycardia; onset within minutes	**Dantrolene**, cooling

[1]Precipitating drugs should be discontinued immediately. First-line therapy is in **bold** font.

MAOIs, monoamine oxidase inhibitors; MDMA, methylenedioxy-methamphetamine (ecstasy); SSRIs, selective serotonin reuptake inhibitors.

however the doctor did mention this:
to treat serotonin syndrome we Paralyze muscles –temporally- , as the respiratory muscles will be paralyzed so we will also intubate the patient. So we will use a sedative agent to treat serotonin syndrome (like benzoDIAZEPINES)
we can also use anti-serotonins with anti-histamines (cyproheptadine/ chlorpromazine) but this is not the first line therapy.

Serotonin Agonists

Why do we use serotonin agonists rather than serotonin itself?

→Serotonin has no clinical applications as a drug, because it has very quick elimination rate, so by the injection it will disappear "like histamine and prostaglands, by the injection the will disappear". (The adverse effects are not the main reasons).

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Some agonists are of value:
(you should know each drug acts at which receptor, and the action produced by that).

[1]- Buspirone ($5\text{-}HT_{1A}$) → for Anxiolytic.

[2]-Dexfenfluramine ($5\text{-}HT_{2c}$)→for Appetite suppression, it is used to treat obesity, because it is very toxic and causes cardiac valvulopathy, it was withdrawn from the pharmacies.

This drug induces fibrosis at therapeutic concentration, unlike serotonin, which produce fibrosis at high concentration, may be it is more potent than serotonin, but the doctor didn't know the real cause.

It is very bad to treat a disease and replace the patient with another disease, valvulopathy is more dangerous than obesity.

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An advice from Dr. Yacoub ❤

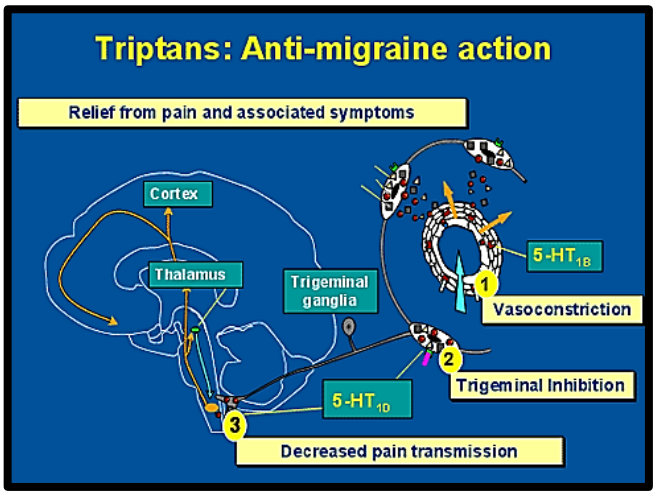
"Body weight cannot be reduced by any drug safely,

it can be reduced but not safely, reducing body weight→stop eating, change your habits,,,, tremendous work".

[3]-Lorcaserin(5-HT_{2C}) agonist, has recently been approved by the FDA for use as a weight-loss medication.

[4]- Sumatriptan (5-HT_{1D} and 5-HT_{1B})

There are (6-7) triptan drugs, the first one is sumatriptan→use for Acute migraine and cluster headache (vascular headaches). → vasoconstriction in cerebral and meningeal vessels. Activation of 5-HT1D/1B receptors on presynaptic trigeminal nerve endings may inhibit the release of vasodilating peptides.



[5]-Tegaserod (5-HT_4): Irritable bowel syndrome with **constipation**.

? Why we say "with constipation"?

Because there is an irritable bowel syndrome with diarrhea

Irritable bowel syndrome IBS is diagnosed by exclusion, the patient is complaining from pain in the abdomen, pain and sometimes associated with constipation or diarrhea, before you decide that the patient has IBS, you should do all investigations to exclude all other causes of that condition.

→so, IBS with constipation→the treatment is Tegaserod, if there is no constipation, you should not give the patient Tegaserod in order not to cause diarrhea.

[6]- Selection Serotonin Reuptake inhibitors "**SSRIs**" (fluoxetine): Depression.

Very important drug to treat depression, what we mean by depression here is "a depression as an illness", not "a depression as a reflex".

Ex: after a difficult exam, a student got a bad mark (من غير شرّ ☺) then he will be depressed, which is normal. In this situation, you should not give him an anti-depressant drug→ if you do that, the student will develop many problems and complications, which are not seen in a real depressed patient, because the real depressed patient has many other psychological problems overcoming such problems.

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Another advice from Dr.Yacoub.

You must know that trials participates or anyone that take drugs without need - even if the dose was small- , would develop many problems in the body and even death, this is might not be due a wrong (unsafe)pharmacological effect of the drug but may be due synergisms, reflexes …etc.

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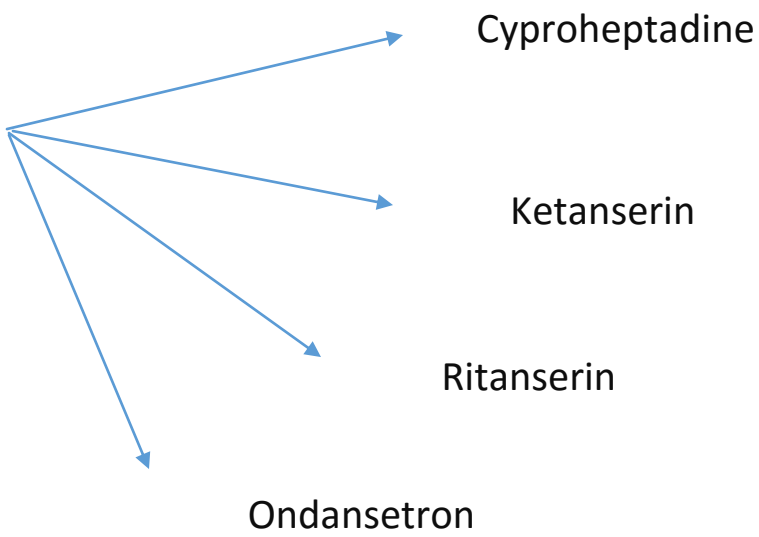
Serotonin –Receptor Antagonists



1)) Cyproheptadine:

Resembles phenothiazene antihistamines.

- Blocks histamine H1 receptors. (1^{st} generation histamine antagonist).
- Blocks 5-HT2 receptors.
- Blocks the smooth muscle effects of both amines (serotonin and histamine), **but does not block histamine induced gastric acid secretion**, why?

➔ Because gastric acid secretion is mediated by H_2 receptors.

*What about other non-histamine dependent actions?

Has significant antimuscarinic effect, α-adrenergic blocking actions and causes sedation.

Major clinical applications:

1-Treatment of the smooth muscle manifestation of **carcinoid tumor**.
2- **Allergic reaction**, ex: Cold induced urticarial.
3-(May be) useful in serotonin syndrome, as we said before serotonin syndrome is "thought" to be associated with Ca^{2+}.
4- May reduce muscle spasms following **spinal cord injury**, in which activity of 5-HT2C receptors is "thought" to be associated with increases in Ca2+ currents leading to spasms.

- When we say: "thought", that indicate there is a weak evidence to approve that, or there is two evidences; one with the approval and the other is the opposite.

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2)) Ketanserin.

Blocks 5-HT_2 receptors on smooth muscle.

- Blocks vascular α1 - adrenoceptors (hypotension).
- Antagonizes platelet aggregation induced by serotonin (5-HT_2).

- Useful for hypertension and vaso-spastic conditions**.**

→there are so many drugs to treat hypertension, Ketanserin "serotonin antagonist" can be considered as anti-hypertensive agent, since serotonin involves in many functions, one of them is blood pressure regulation.

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3)) Ritanserin:

- ❖ Blocks 5-HT2 receptors with no α1 - adrenoceptor-blocking action.
- ❖ Reduces thromboxane formation by platelets.

Recall from GI pharmacology we also used aspirin to reduce thromboxane formation consequently it inhibit platelet aggregation and vasoconstriction (used to treat MI ..) Note: thromboxane is responsible for both vasoconstriction and platelet aggregation, this effect is clear in case of injury, as aggregated platelets will close the defect.

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4)) Ondansetron:"anti-vomitting agent".

- Blocks 5-HT3 receptors.
- Used for prevention of nausea and vomiting associated with surgery and cancer chemotherapy.

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It is N-acetyl-5-methoxytryptamine, a product of serotonin (i.e. the precursor of melatonin is serotonin).

→Produced in the pineal gland, "on X-ray, the pineal gland appears calcified; it contains a remnant of cells that produce melatonin".

→Melatonin is very important to sleep, if there is no melatonin you cannot sleep, if melatonin in your body is normal, your sleep-wake behavior is much better.

→Conversion of serotonin to melatonin:

*needs folic acid.
*happens at night or in the dark conditions even in the morning "ex: at dark room".

- Melatonin receptors in the brain, **MT1** and **MT2** , are found in membranes of neurons in the suprachiasmatic nucleus of the hypothalamus, an area associated with circadian rhythm.
- So melatonin is responsible for regulation of circadian rhythm, it must be normal, if there is any disturbance to it, you cannot sleep well and you may develop depression.
- If somebody didn't sleep well at the night, in the next day he may develop depression.
- MT1 and MT2 are Gi protein-coupled receptors. The result of receptor binding is inhibition of adenylyl cyclase.

Keep in mind:

G protein coupled receptor, is an amazing receptor, it has many diverse actions.

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A third receptor, MT_3, is an enzyme; with a poorly defined physiologic role, possibly related to intraocular pressure.

Activation of the MT1 receptor results in sleepiness, whereas the MT2 receptor may be related to synchronization of the biologic circadian clock.

If there is a lack of synchronization of the biologic circadian clock, MT2 agonist is used for treatment.

Synchronization (توازن الساعة البيولوجية) →there is certain times for sleeping and waking up, ex: somebody always sleep at 10 and wake up at 4 .

Lack of Synchronization →you cannot control your circadian rhythm, usually associated with depressive illness.

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Melatonin may also have the following actions:

1) Anti-apoptotic effects.
2) May be involved in depressive disorders, HOW?
   By excess amount.
3) It may ameliorate jet lag (السفر الطويل), if someone travels from his country to another, at the arrival time, if it was morning, but in the original country it was evening, the circadian rhythm will change →jet lag. To prevent that, melatonin agonist must be used.

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Melatonin Agonists

- ✓ **Ramelteon** is a selective MT1 and MT2 agonist – treatment of insomnia.
- ✓ **Tasimelteon** is a newer MT1 and MT2 agonist – used for the "non-24-hour sleep-wake disorder" (circadian rhythm disorder).

- ✓ **Agomelatine** is an MT1 and MT2 agonist and a 5-HT2C antagonist – used in major depression, HOW?

Remember that serotonin antagonist's causes depression, so how is Agomelatine used to treat depression?

One of depression causes is the lack of serotonin in the brain, suppose you have a receptor of serotonin that inhibit serotonin secretion, if I block it, serotonin secretion will increase. [it is just a possible mechanism, not the real cause].

May be it is associated with down regulation of serotonin, down regulation starts at the endocytosis step, and terminates at the gene regulation step or even at receptor insertion step.

If you notice that all of these drugs are working in the same receptors (MT1 and MT2), but for different therapeutic uses, it depend on the clinical studies and approval of each drug.

"نتمنى لكم في الامتحان توفيقاً، وفي كل شيء"
د. يعقوب.