Pharmacology team

Adrenergics Depressants

Contents:

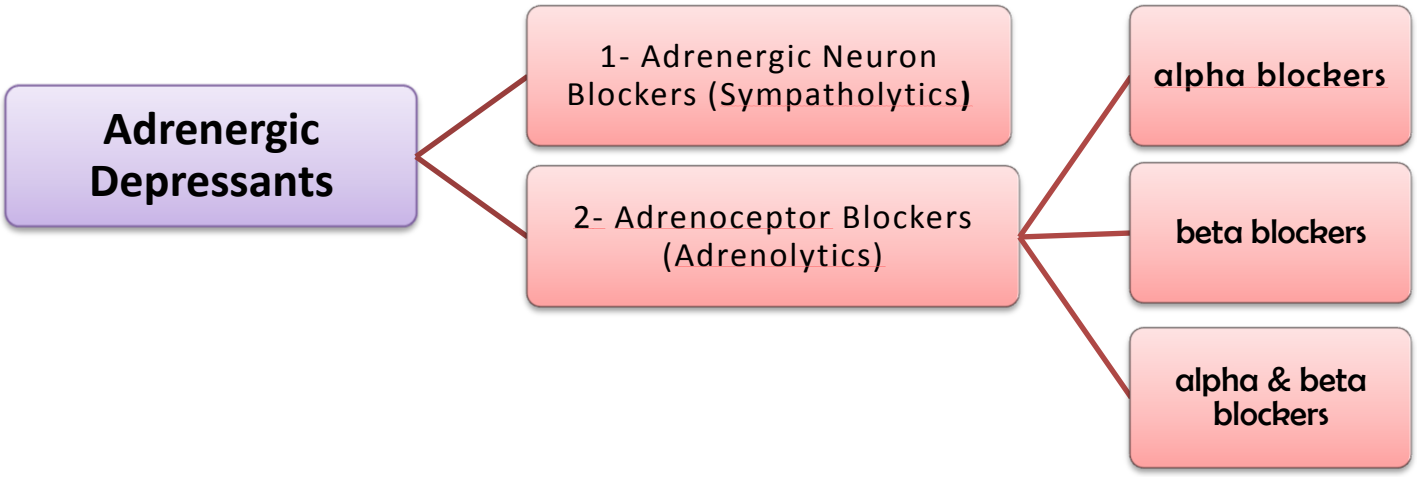
*Explanation

*Summary

*Questions

* underlined & Red = important

دعوة بظهر الغيب تكفي عن جزيل كلمات الشكر



α_2 adrenoceptor antagonist : its name is "antagonist" BUT it functions as an "agonist", because a2 is a pre-synaptic receptor. It increases sympathetic activity. E.G. Yohimbine.

Releases NE & ADH. Aphrodisiac (increases sexual instinct)

Its action is mostly localized in the pelvic plexus (and brain), it increases adrenergic activity → increase sexual activity. However, doctors don't prescribe it as a therapeutic drug. They prescribe other drugs such as Viagra to treat impotence and such conditions.

First : Adrenergic neuron blockers (sympatholytics)

1- Methyldopa : has 2 mechanisms of action:
- 1) Forms false transmitter that is released instead of NE (it takes the pathway of NE)
- 2) Acts as a_2 receptor agonist to inhibit NE release
- Used as Antihypertensive drug of choice in PREGNANCY

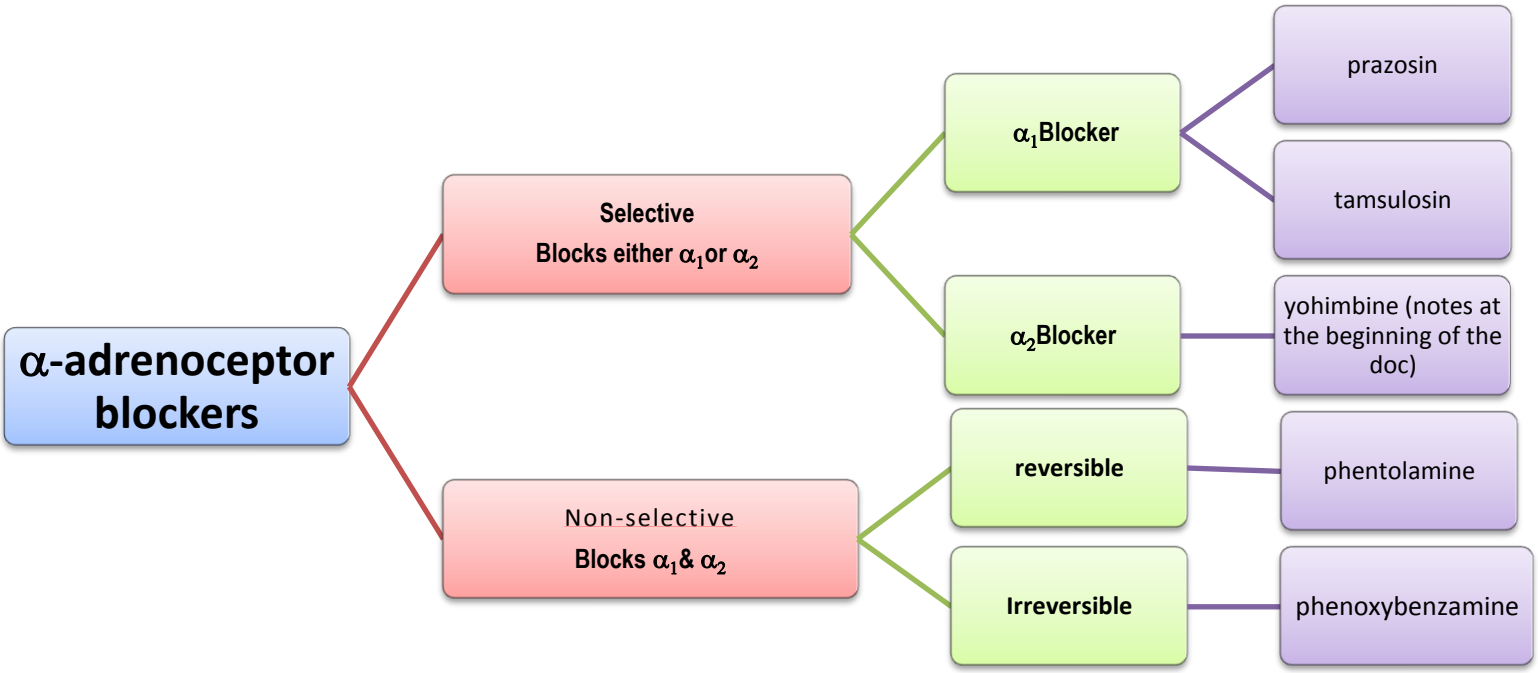
2- Guanethidine :
- Block the release (and uptake) of stored NE

3- Reserpine :
- Block the transport of NE, dopamine, and serotonin from the cytoplasm to into the vesicles (depletion), The vesicles will be empty=depleted

4- Clonidine :
- Acts directly as a_2 receptor agonist to inhibit NE release
- Little Used as Antihypertensive agent due to rebound hypertension upon abrupt withdrawal

P.S. Guanethidine and Reserpine can be used to treat hypertension but because they have many side effects, they are rarely used nowadays.

Sudden discontinuation can cause rebound hypertension in which the receptors become more sensitive to the neurotransmitter because of up regulation



Second : α- Adrenoceptor blockers :

Hypertensive crisis is when the BP is so elevated that it becomes a medical emergency. It is controlled by phentolamine

A) Non-selective α - Blockers : They both have the same effects, but Phentolamine has a shorter duration of action

- **Phenoxybenzamine** (12 hrs t ½) *:* acts 3 days, in irreversible shock , ↑microcirculation , **↓ADH**
  (In irreversible shock, the perfusion of O2 and nutrients to tissues decreases tremendously, so we need to treat the shock and increase the perfusion. The drug will block a1 receptors causing vasodilation, which will increase the perfusion i.e. improve microcirculation.)

- **Phentolamine** (shorter t ½) :in **pheochromocytoma** used 1-2 weeks before surgical removal -> -ve **hypertensive crisis** (important) this effet also produce by **Phenoxybenzamine**

A neuroendocrine tumor of the medulla of the adrenal glands in which excess amount of catecholamines is being secreted. Surgical option requires prior treatment with phentolamine.

B) Selective α_1 Blockers :

- **Prazosin** *: doxazosin, terazosin & trimazosin (* long t ½*) :*
  - **Peripheral vasodilatation** (arteries and veins)
  - minimal changes in CO (cardiac output)& renal blood flow
  - **used** in **Raynaud's disease** **(** in which the peripheral arteries become suddenly narrowed. Characterized by bilateral; ischemia of the fingers, toes, and sometimes ears and nose. It is usually brought on by cold **)**
  - Can be used (Rarely, due to their side effects) in hypertension, Heart Failure
  - **Adverse effects**: **Tachyphylaxis** , **hypotension syncope** , nasal stuffiness**, ↓ ejaculation** & impotence.
- **Tamsulosin** :
  - Is a **Uroselective** α_{1A}
  - It causes contraction of bladder wall and relaxation of bladder neck & sphincter.
  - Used in **Benign Prostatic Hypertrophy** (BPH) (it doesn't treat the tumor itself, but only the urine problem)

Third : β- Adrenoceptor blockers (classification) :

1- According to extent of blockade :

Non-selective	Selective (BEAM)
Block β_1& β_2 Propranolol, Sotalol, Timolol (Eye) Labetalol, Carvedilol (β & α_1)	Block β_1>> β_2 Bisoprolol, Esmolol, Atenolol, Metoprolol

2- According to presence of agonist/antagonist action (intrinsic sympathommetic activity) :

ISA is not a pure antagonist, but it is a **partial agonist** that bind and block – **antagonize** - the receptor but has some agonistic affects.

Without ISA	With ISA
Propranolol, Atenolol, Sotalol, Bisoprolol, Timolol, Metoprolol; carvedilol It's block the sympathetic very strongly. So the adaptive mechanism of the body is Up-regulation of β-receptors. For that it has rebound effect.	Labetalol ,Acebutalol There is little sympathetic effect so no rebound effect after stop taking it. It good for elderly people.
In case you forgot : (No ISA = more than one "o") **except** carvedilol	(ISA = only one " o ")

3- According to membrane Stabilizing effect (i.e. block Na channels "quinidine-like") :

- **L**abetalol, **A**cebutalol, **P**ropranolol (**SLAP** ☺)

4- According to presence of CNS depressant effect (i.e. sadative drugs) :

[Propranolol, Metoprolol, Labetalol > Carvedilol] = ↓ Anxiety

5- According to Lipid solubility (Pharmacokinetic classification) :

	Lipophylic	Hydrophilic
Oral absorption	Complete	Irregular
Liver metabolism	Yes	No
$t_{1/2}$	Short	Long
CNS side effects	High	low
	Propranolol, Metoprolol, Timolol, Labetalol > Carvedilol	Atenolol, Nadolol, Sotalol, Acebutalol, Bisprolol, Esmolol

Nadolol = longest $T_{1/2}$, Esmolol = shortest $T_{1/2}$

β- Adrenoceptor blockers : Propranolol

- It's the prototype, non-selective competitive blocker of β1 & β2
- Has quinidine-like & sedative action but no ISA
- Lipophilic, completely absorbed,70% destroyed during 1st pass hepatic metabolism, 90-95% protein bound, cross BBB and excreted in urine

Dynamics of Propranolol

1- Blocking effects :

- On heart β1 :
  - Negative inotropic, chronotropic, dromotropic → ↓ CO

Given To decrease cardiac work, as a result the need for O2 for the heart will decrease. Used in **ischemic coronary** cases. It treats by the above mechanism through the **blocking of B1** effects, **not by coronary dilatation which is produced by B2 agonists.**

- Used as Anti-anginal ,anti-arrhythmic
- On blood vessels β2 :
  - Causes vasoconstriction so↑PR & blood flow to the organs except brain, so it is contraindicated in Raynaud's disease
- On bronchi β2 :
  - Causes bronchospasm. It's better to use selective beta blocker in asthmatic patients
- On Blood Pressure (BP) :
  - Antihypertensive. it decreases cardiac output , renin & aldosterone secretions, sympathetic outflow , NE from β2 presynaptic .. all of them are decreased -> **↓ BP**
- On metabolism :
  - It decreases glycogenolysis in liver & glucagon secretions in pancreas (β2) -> hypoglycemia
  - It decreases lipolysis in adipocytes (β3)
  - It causes Na retention 2ndry to decrease in blood pressure
  - It causes hyperkalemia

2. CNS effect:

- ↓ tremors & anxiety → protect against social anxiety
- → combat performance anxiety → performance enhancement
- Block Na channels → direct depressant to myocardium → local anesthetic effect

When we block Na channels we inhibit the action potential from being propagated, so it has anesthetic effect.

Indication

1- Hypertension
2- Arrhythmias
3- Angina (*Its anti-anxiety adds to the antianginal effect It does not cause coronary dilatation*)

4- **Myocardial infarction :**
   - ↓ myocardial O_2 demand.
   - ↑ Redistribution of blood flow in the myocardium → { decrease infarct size }
   - ↓ free fatty acids.
   - Anti-arrhythmic action →↓ incidence of sudden death
5- **Pheochromocytoma:** used with α-blocker (never alone), β-blockers protect the heart from NE & α-blocker **↓ BP**
6- **Hyperthyroidism :**
   - Controls symptoms; *tachycardia, tremors, sweating*
   - Protects the heart against the sympathetic over-stimulation.
   - Lowers the conversion rate of T_4 into T_3 (the active form)
7- **Migraine (Prophylactic);** ↓ catecholamine-induced vaso-dilatation in the brain vasculature.
8- **Chronic glaucoma:** ↓ IOP by ↓secretion of aqueous humor by ciliary body (Timolol is given this case)
9- **Familial tremors and anxiety (especially social & performance type)**

Adverse effects

It would decrease pt's awareness of hypoglycemia and can potentially be fatal

1- **Due to cardiac β1-receptor block:**
   - A) Bradycardia → by -ve chrontropic → treated by atropine. B) Hypotension
2- **Due to blockade of β2- receptor:**
   - Asthma, emphysema, chronic bronchitis → by bronchospasm
   - Cold extremities & intermittent claudication → by vasoconstriction
   - Coronary spasm → in variant angina patients (not a coronary dilators)
   - Erectile dysfunction & impotence
   - Hypoglycemia → But all b-blockers mask hypoglycaemic manifestations (i.e. tachycardia → COMA)
   - ↑ TG & ↓ HDL
3- **CNS effects** Depression, nightmares, vivid dreams and hallucinations
4- **Sodium retention** → can add diuretic
5- **Hyperkalemia** → due to β_2 blockade
   - **Sudden stoppage** will give rise to a withdrawal syndrome:
     - Rebound angina, arrhythmia, myocardial infarction & hypertension
     - WHY ? → Up-regulation of β-receptors
     - N.B. Occurs more with β-blockers, that do not possess ISA.

       To prevent withdrawal manifestations → drug withdrawn gradually
   - **Selective b1-blocker is safer in :**
     - COPD , Raynaud's phenomenon & PVD , and Diabetes/Dyslipidemias

Contraindications

1- Uncompensated Heart Failure.
2- Massive Myocardial Infarction.
3- Heart Block.
4- Bronchial Asthma (not with cardio-selective β-blockers).
5- Peripheral vascular disease (not with cardio-selective β-blockers).
6- Diabetic patients. (Type I) (On Insulin or oral hypoglycaemic) ➔ Masking of hypoglycaemia
7- Hypotension
8- Alone in pheochromocytoma (must be with an α-blocker).

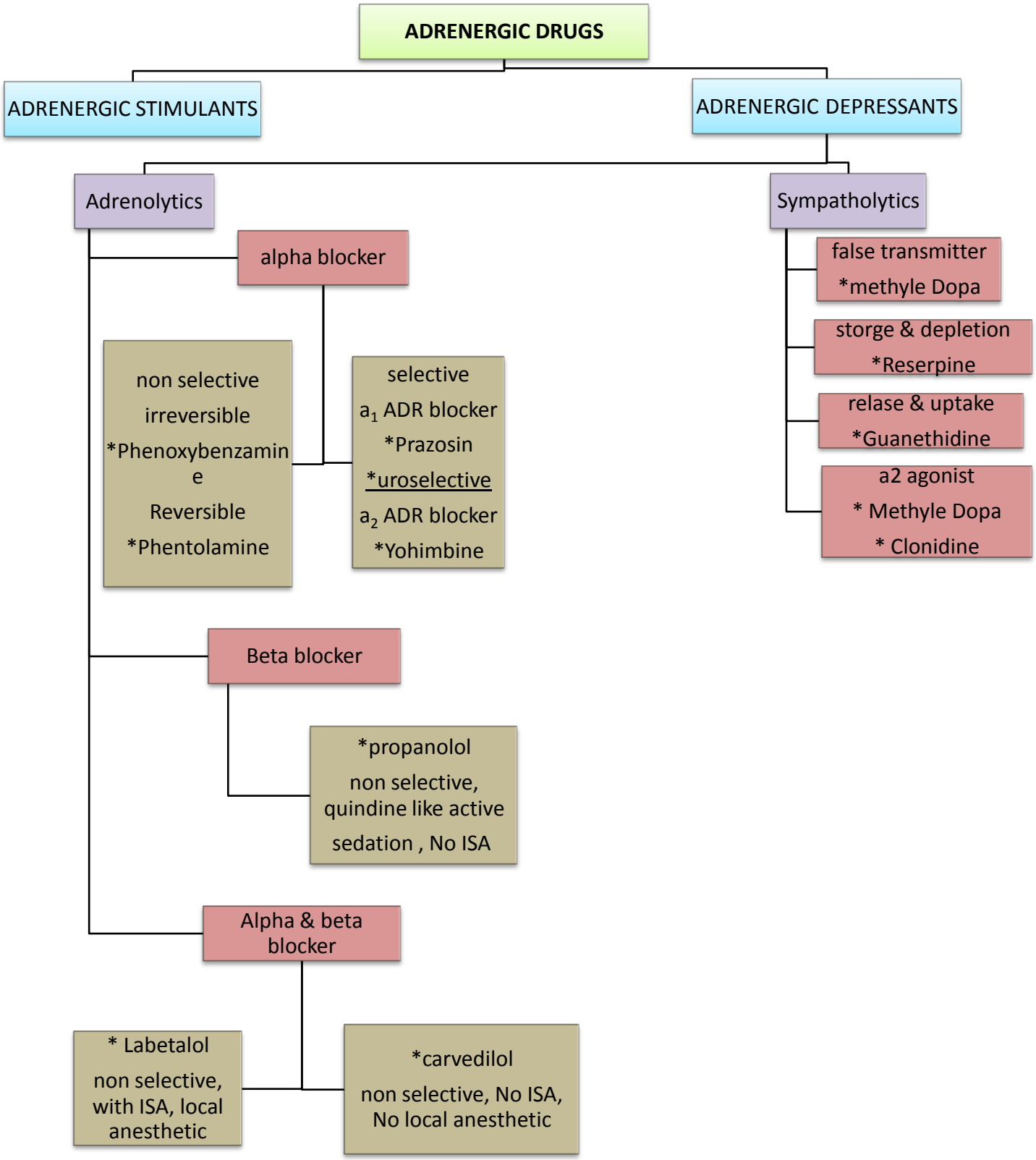
Interaction

1- Bradycardia / heart block ➔ with verapamil ➔both induce A.V block ➔-ve dromotropism
2- Attenuation of hypertensive effect ➔ with NSAIDs ➔ because they ↓ vasodilating prostaglandins.
3- Claudications, parasthesia, …etc ➔with ergot alkaloids in migraine. Not important
4- Enhanced neuromuscular blockade ➔ Tubocurarine. Not important
5- Hypoglycaemia ➔ with anti-diabetic drugs (insulin > sulfonylureas) > Non selective β-blockers

Non-Selective α and β- Adrenoceptor blockers :

Labetalol (**Blocks β & α_1**)	Carvedilol (**Blocks β > α_1**)
Rapid acting, non-selective with ISA & local anesthetic effect	Non-selective with no ISA & no local anesthetic effect
Do not alter serum lipids or blood glucose	Favorable metabolic profile.
Used in Severe hypertension in pheochromocytoma & hypertensive crisis during abrupt withdraw of clonidine	ANTIOXIDANT (*protect our cells from damage caused by free radicals)*
Used in pregnancy-induced hypertension instead of methyldopa	Used effective in ➔ CONGESTIVE HEART FAILURE ➔ reverses its patho- physiological changes
ADR; Orthostatic hypotension, sedation & dizziness	ADR; Edema

Summary


ADRENERGIC DRUGS
ADRENERGIC STIMULANTS
ADRENERGIC DEPRESSANTS
Adrenolytics
Sympatholytics
alpha blocker
non selective
irreversible
*Phenoxybenzamine
Reversible
*Phentolamine
selective
a1 ADR blocker
*Prazosin
*uroselective
a2 ADR blocker
*Yohimbine
false transmitter
*methyle Dopa
storge & depletion
*Reserpine
relase & uptake
*Guanethidine
a2 agonist
* Methyle Dopa
* Clonidine
Beta blocker
*propanolol
non selective,
quindine like active
sedation , No ISA
Alpha & beta blocker
* Labetalol
non selective,
with ISA, local anesthetic
*carvedilol
non selective, No ISA,
No local anesthetic

- **Alpha2 agonist→ cause suppression of sympathetic activity by inhibiting the release of NE**
- **Alpha2 antagonist→ cause activation of the sympathetic activity by increase the release of NE**

What to do mean by Up-Regulation?

It means increase in the number and the sensitivity of receptors to neurotransmitters.

Labetalol and Carvedilol → they are both beta blockers **with alpha receptor blocking effect**

Questions:

1-Propranolol is not useful in treatment of which one of the following:

a. Angina
b. Familial tremor
c. Hypertension
d. Idiopathic hypertrophic subaortic cardiomyopathy
e. Partial atrioventicular heart block

2-Adverse effects that limit the use of adrenoceptor blockers include which one of the following:

a. Bronchoconstriction from a-blocking agent
b. Heart failure exacerbation from B-blockers
c. Impaired blood sugar response from a-blockers
d. Increased IOP with B-blockers
e. Sleep disturbance from a-blocking drugs

3- A patient receiving a B-blocker for chronic angina complains of sleep disturbance and loss of energy. She is probably receiving:

a. Atenolol
b. Esmolol
c. Labetalol
d. Nadolol
e. Propranolol

Answers :

E

B

E