# Physiology
Sheet **No.**


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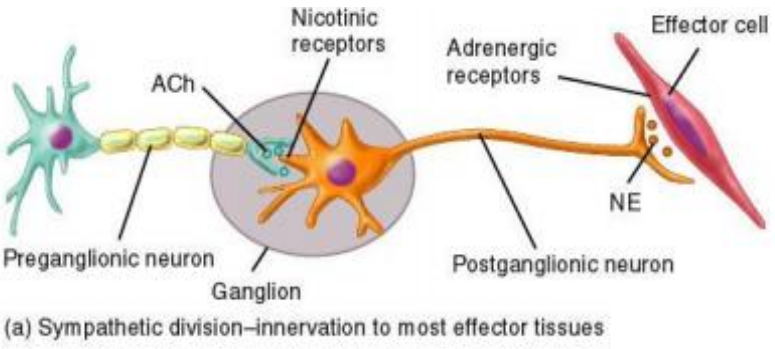
# MOLECULAR BASIS OF PHYSIOLOGICAL ACTIONS OF THE ANS:

- We know now that the preganglionic neurons synapse with the postganglionic neurons in the ganglia, and then the postganglionic neurons interact with different effectors to induce different actions in the body.

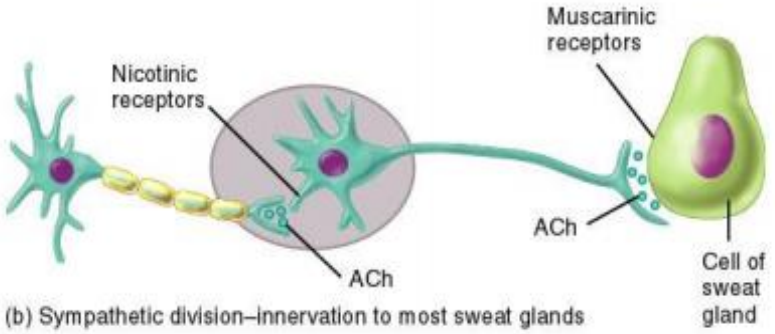
So, what type of neurotransmitters that these neurons release?

First, at ganglion:
preganglionic neurons of **both *sympathetic and parasympathetic*** release **Acetylcholine (Ach)** and causing activation of the second neuron (the postganglionic neuron).



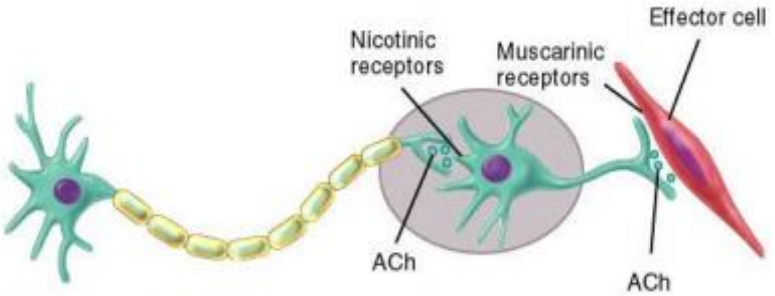
(a) Sympathetic division–innervation to most effector tissues

Now, while the second neuron is active….the ***parasympathetic postganglionic neurons*** release also **Acetylcholine** to the effector cells.



(b) Sympathetic division–innervation to most sweat glands

While the ***postganglionic neurons of sympathetic*** release **norepinephrine** to the effector cells ***except*** the postganglionic neurons that innervates sweat glands and piloerector muscles (small muscles attached to hair follicles), they release **Ach** Instead of norepinephrine.



(c) Parasympathetic division

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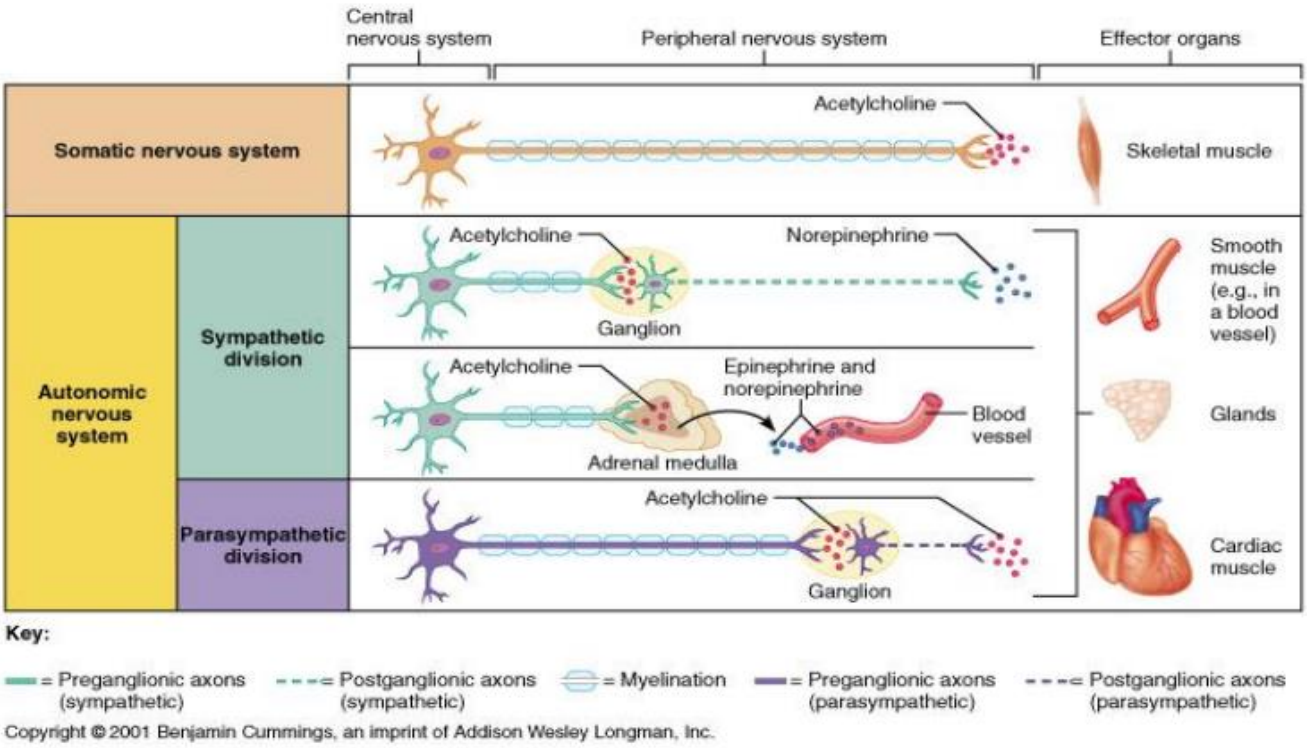




- Note from this picture that the somatic fibers also release Acetylcholine like the parasympathetic fibers, and the sympathetic fibers that innervates the suprarenal gland (adrenal gland) release Acetylcholine.

**The fibers that innervate adrenal gland don't pass throw any ganglia….so there are no postganglionic fibers).**

✓ Keep in mind that adrenal gland is an endocrine gland that releases high concentration of epinephrine and low concentration of norepinephrine to the blood stream.

Now, these neurotransmitters must have receptors located on their targets, these receptors are:

1) Receptors on the postganglionic neurons (at ganglia) are called nicotinic receptors.
2) Receptors on the parasympathetic targets are called muscarinic receptors.

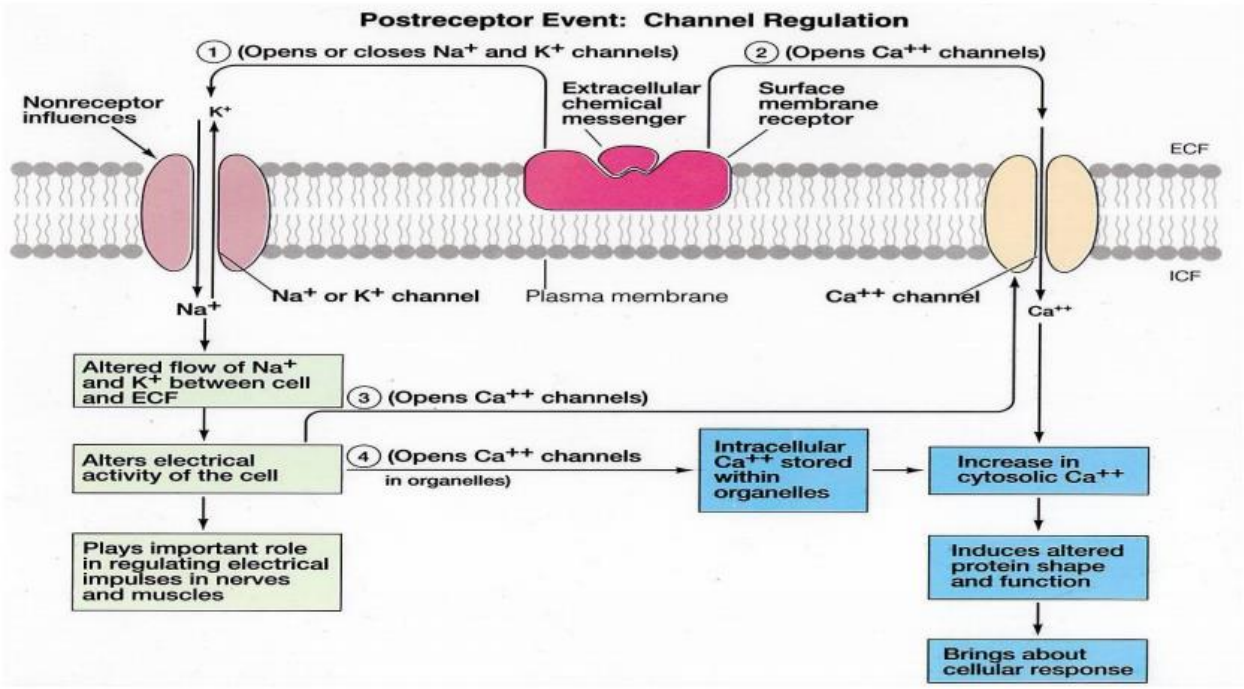
3) Receptors on the sympathetic targets are called adrenergic receptors.

# *Receptors and signal transduction mechanism:

## 1) Receptors at ganglion (nicotinic receptor)

- On **postganglionic** membrane of **sympathetic and parasympathetic** there are **nicotinic** receptors. These receptors are excited by Acetylcholine. The drug nicotine can also stimulate these receptors.
- This receptor is similar but not identical (they have different subunit structures) to nicotinic receptor of the neuromuscular junction.

- This receptor binds to ligand gated Na+ channel. Activation of this receptor will cause depolarization on **postganglionic** membrane.



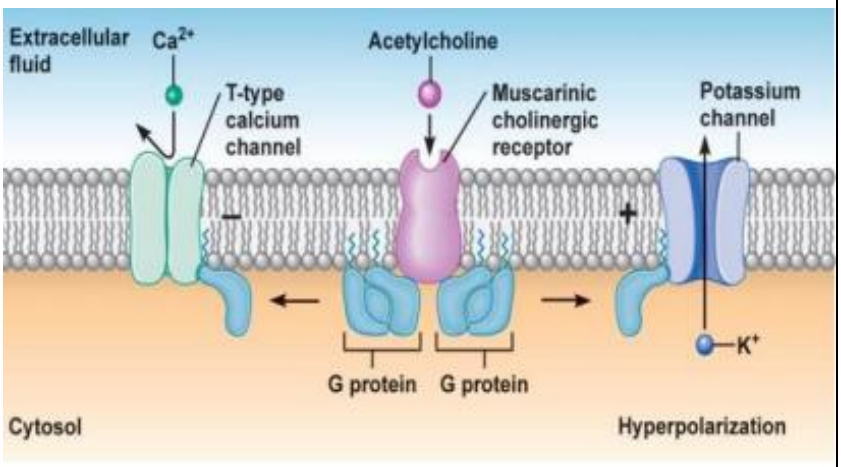

In the ganglion, the nicotinic receptors are linked -via G-proteins- to the sodium channels. So the signal transduction mechanism here:

Activation of nicotinic receptors → activation of the Na+ channels → Depolarization of the postsynaptic membrane → Action potential

## 2) muscarinic receptors

- These cholinergic receptors lie on the effector cells of **parasympathetic** neuro-effector junctions. They differ from nicotinic receptors found on ganglia and neuromuscular junction.
  - ✓ Many muscarinic receptors have been known (M1-M5) at these junctions, all these receptors are coupled to G protein.
- For example, The inhibitory receptor that is found in the heart (M2) is coupled to Gi protein, which inhibits adenylyl cyclase activity so decreasing cyclic AMP and slowing the heart rate (we will talk about the mechanism of that later on ) this Gi protein is also linked to K+ channels, activation of this receptor will slow the rate of depolarization.

  - ✓ This is a **muscarinic** receptor(**M2**), once ACH bind to the receptor, it can cause activation of ***potassium channels*** and *inhibition* of the ***T-type calcium*** channels, so the slow depolarization of the heart conducive tissue becomes even slower (we have less number of beats per minute), which leads to decrease in the heart rate.



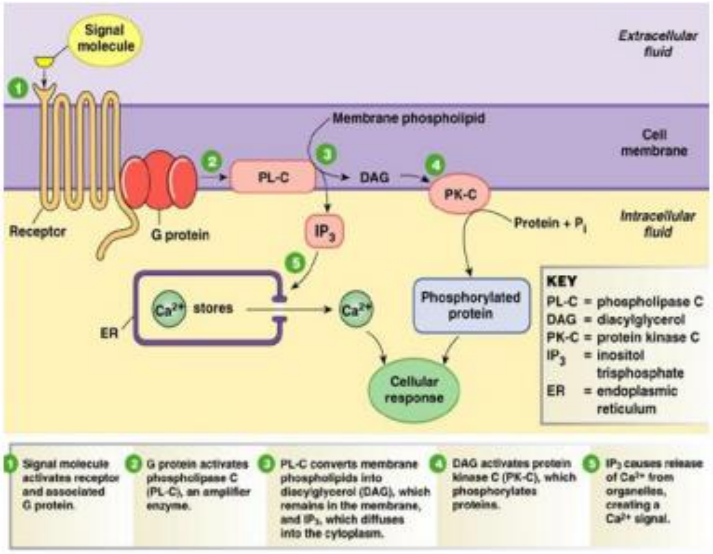

- While we have **M2** receptor that is considered as **inhibitory** receptors, we have also another sub-types that are **excitatory** receptors which are (**M1,M3,M5**) receptors that are found on smooth muscle cells and glands, these receptors are linked to **Gq** proteins to activate phospholipase C.

  - ☒ **Phospholipase C**: membrane associated enzyme responsible for the cleavage of phospholipids and convert it to DAG and IP3.

  - ☒ **Gq proteins**: a family of the heterotrimeric G-protein alpha subunits.

- Due to the activation of phospholipase C, the concentration of the IP3 in the cytosol **increases**, which causes the release of $Ca^{2+}$ from its stores and the ER.

- The increase in $Ca^{+2}$ causes various responses, like *muscle contraction*.




☒ So……Why are they called nicotinic and muscarinic?

- **Nicotinic** receptors are stimulated by **Nicotine**, and **muscarinic** receptors are activated by **muscarine** which is found in a type of toxic mushroom, so if someone has been ingested it, all muscarinic receptors will be activated.

- This type of toxic mushroom is rich in **muscarine**, and ingesting it causes activation of all muscarinic receptors, and patients will develop a lot of obvious *signs and symptoms* like:

**Remember: Agonist is a chemical that binds to a receptor and activates the receptor to produce a biological response. (muscarine and nicotine are agonists for Acetylcholine but for different receptors)**

1) Stimulation of **secretory activity**, e.g.→ salivation, tearing, sweating nasal and bronchial secretions, pupil constriction [**Miosis**].
2) **Contraction** of urinary bladder → urination
3) **Increase in the gastrointestinal tract motility**, which causes vomiting and diarrhea.
4) **Slowing of the heart**, which is called ***Bradycardia***.

**Always remember that muscarine is an agonist for Acetylcholine that is responsible for the parasympathetic activity, so when muscarine is ingested in the body… we expect to see the same signs of parasympathetic activity + the activity of sweat glands even if they are sympathetic because they are activated by ACH (look at the signs above)**

☒ ***So how to reverse the effects of intoxication by muscarine?***

- we use a drug (antagonist) to **block** the muscarinic receptors which is called **Atropine** [from a plant (*Atropa Belladonna*)]. The doses (الجرعات) are given to the patient until we notice a change reversing of the intoxication effects by – mainly- following the patient's **heart rate** and **pupillary light reflex** [change in the pupil diameter as a response to light].

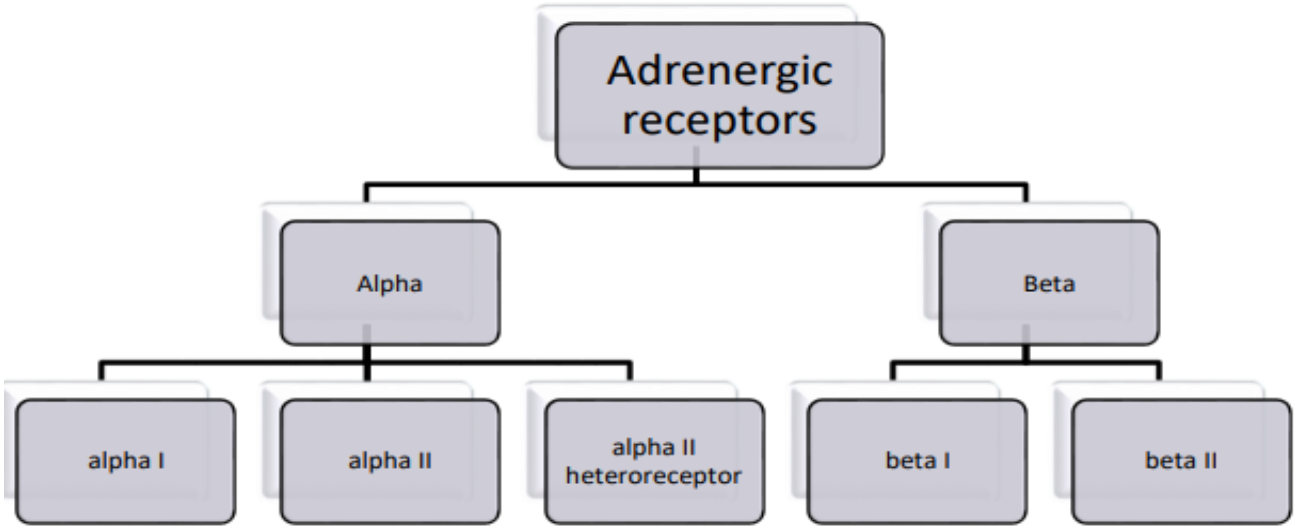
**Again…. when we give the patient Atropine which blocks the receptors for ACH, we expect to see decreasing of the parasympathetic activity.**

☒ ***What happens if the patient was given an overdose of Atropine?***

1. **Inhibition of glandular secretions** → causes dry mouth, eyes and nasal passage.
2. **Increase in heart rate** → which is called ***Tachycardia.***
3. Loss of pupillary light flex, pupil dilation [**Mydriasis**] and loss of ability to focus lens for near vision.

# 3) Adrenergic receptors

- The stimulation of the sympathetic NS causes the release of **norepinephrine** and **epinephrine** [which are also called catecholamines], and in our bodies we have a type of receptors called adrenergic receptors that response to these neurotransmitters.



## *Alpha receptors:

1) **Alpha I → Excitatory**, found in smooth muscle cells of vessels and arteries.

    - Here there is an Activation of phospholipase C which cause Vasoconstriction [constriction of blood vessels → raise the blood pressure], this effect involves IP3 production and Ca2+ release since alpha I is coupled with Ca2+ gated channels.

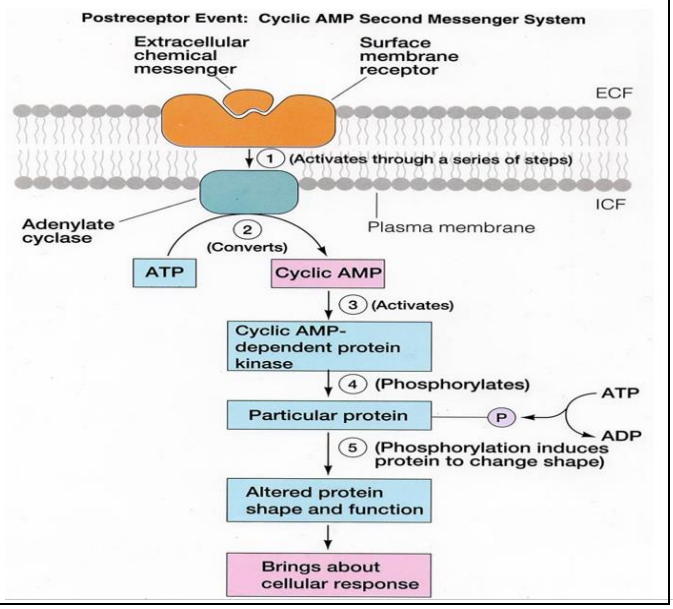
2) **Alpha II** → are found on **sympathetic postganglionic** nerve terminals. These receptors are important for self-inhibition of NE release (negative feedback) .
3) **Alpha II heteroreceptor** → found in **non-adrenergic** neurons Work through Gi proteins, reduce the synthesis of c-AMP and inactivate these neurons.

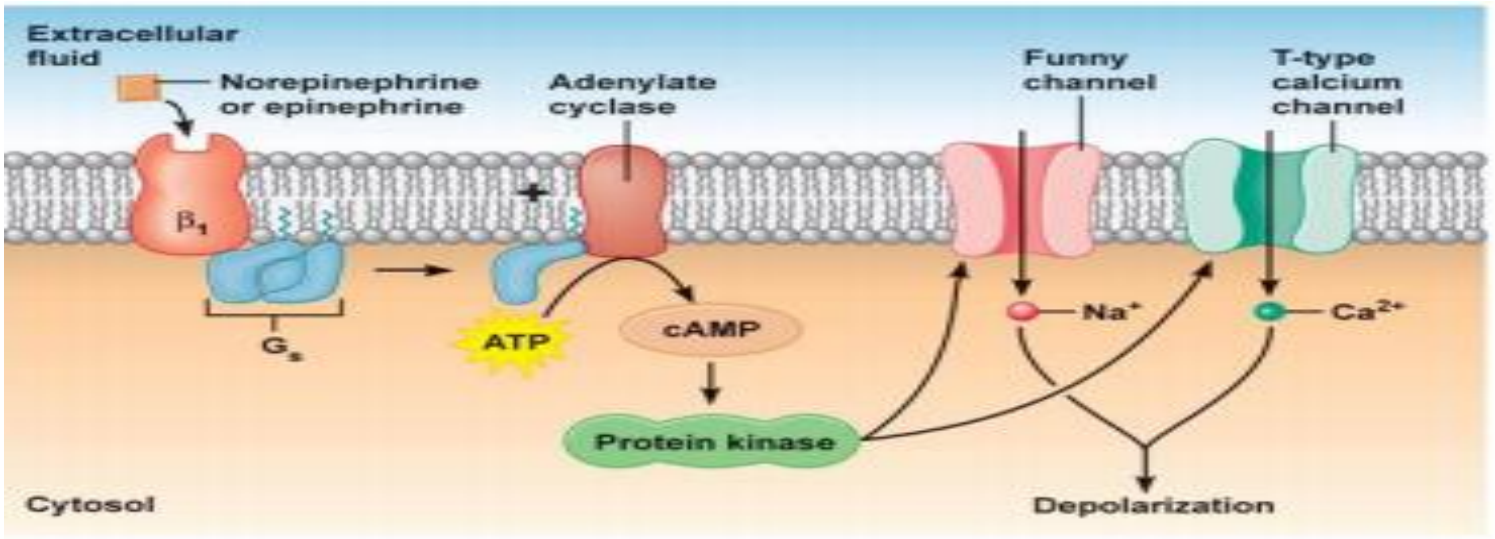
## *Beta receptors:

- These receptor are more sensitive to EP& NE than alpha, (lesser concentration needed for a response to occur)

1. **Beta I** → an **excitatory receptor in the heart**.
2. **Beta II** → an **inhibitory receptors found in smooth muscle** cells like in the bronchial muscle cells, the gastrointestinal tract,blood vessels supplying skeletal muscles.

- The activation of the receptors increases cAMP concentration which will act in an either **excitatory** or **inhibitory** way, depending on <u>beta receptors</u> location [the type of cells they are found in], for example, **increasing the cAMP in the smooth muscle cells will lead to relaxation of these muscles, while in the heart increasing the cAMP will increase the heart rate.**






This is what really happens in the conductive tissue of the heart due to increase in cAMP :

Activation of adenylyl cyclase → Increase in cAMP concentration → Activation of Na+ & T-type Ca2+ channels → Increase the heart rate

- some points that the doctor didn't talk about in the lecture, but written in the sheet :

- The released Ach by parasympathetic system is inactivated by breakdown by acetylcholinesterase. Epinephrine is inactivated by recapture by postganglionic nerve varicosities.
- All subclasses of adrenergic receptors can be blocked by specific blocking agents (antagonists). β1 blockers are useful as antiarythmic drugs. β2 selective agonist (produce activation of β2 receptor) will dilate bronchi. This agonist is useful in asthma.

**BEST OF LUCK~~**