Physiology | Lecture 12

Autonomic Nervous System (ANS) Pt.2

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MOLECULAR BASIS OF PHYSIOLOGICAL ACTIONS OF THE ANS

Remember that the preganglionic neurons synapse with the postganglionic neurons in the ganglia (releasing neurotransmitters) and then postganglionic neurons interact with effectors to induce actions.

Transmitters:

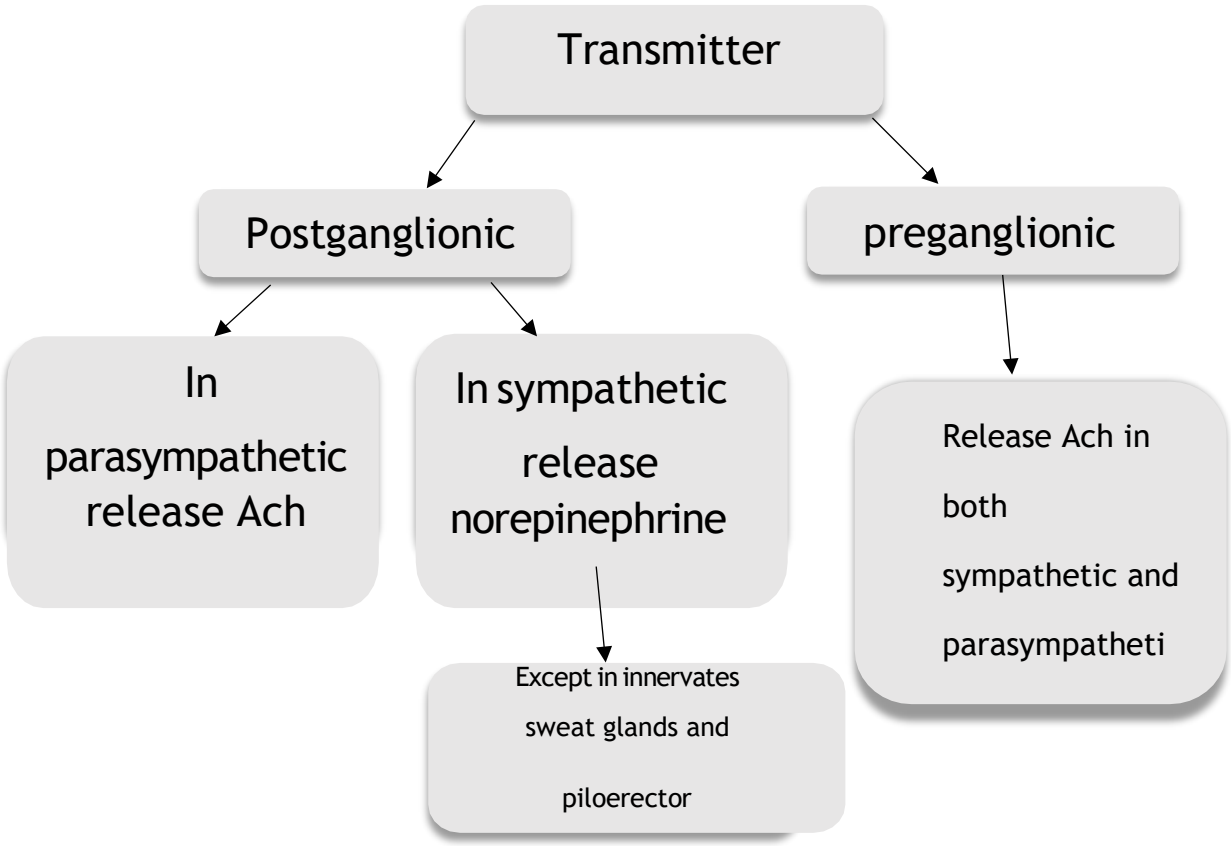
At ganglion: **pre**ganglionic neurons of both sympathetic (**SNS**) and parasympathetic (**PNS**) release **acetylcholine (Ach)** and activation of the second neuron "**postganglionic neuron**".

At effector organs: when the second neuron is activating, the **parasympathetic post**ganglionic neurons release **acetylcholine** to the effector cells, while the **post**ganglionic neurons of **sympathetic** release **norepinephrine** to the effector cells except the **post**ganglionic neurons that innervates sweat glands and piloerector muscles "**small muscles attached to hair follicles**", they release Ach Instead of norepinephrine.

Important note: the released **Ach** by **parasympathetic** system is **inactivated** by breakdown by acetylcholinesterase (**an enzyme that breaks down Ach**).

Also, **norepinephrine** is inactivated by recapture by postganglionic nerve varicosities.

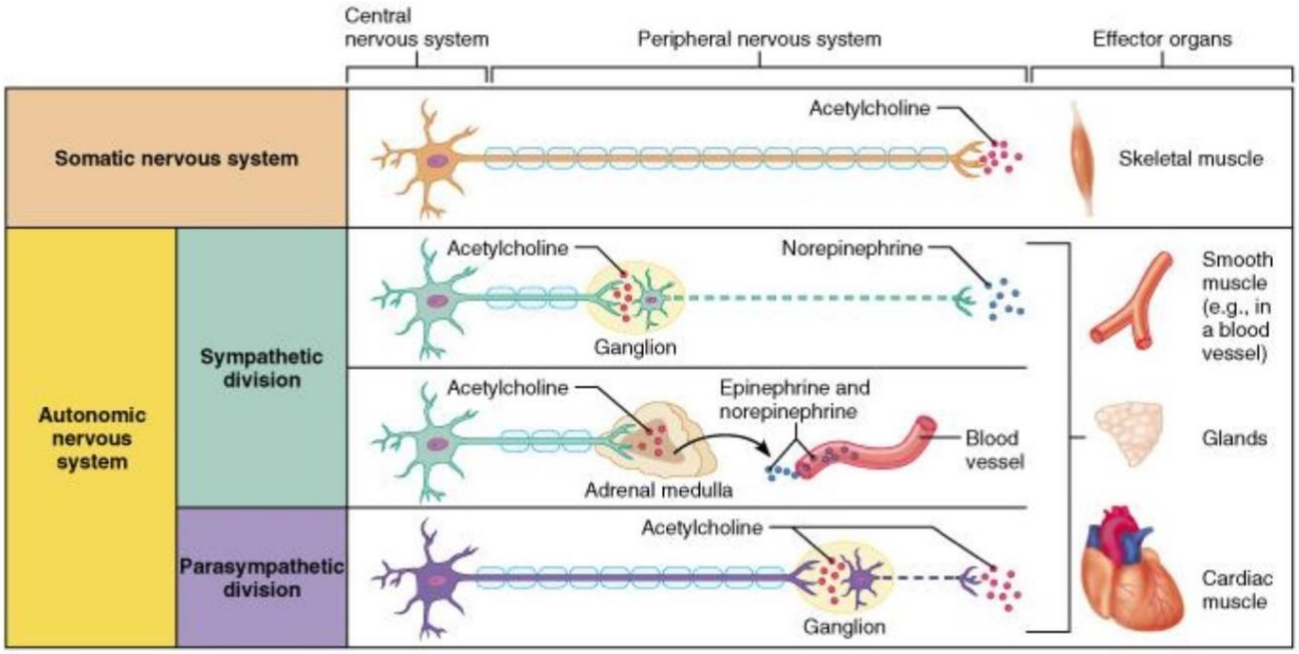
Summary:

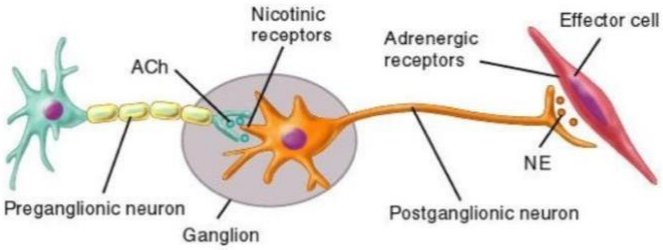


The images you will see bellow summarize the above information with some additions that we will mention now:

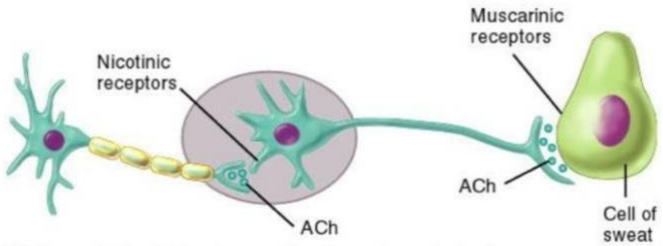
1) The **somatic** fibers release **Acetylcholine**.
2) The **sympathetic** fibers that innervate the adrenal gland release **Acetylcholine**, notice the fibers that innervate adrenal gland don't pass throw any ganglia, so there are no postganglionic fibers.

Note: adrenal gland releases **high** concentration of **epinephrine** and **low** concentration of **norepinephrine** to the blood stream.

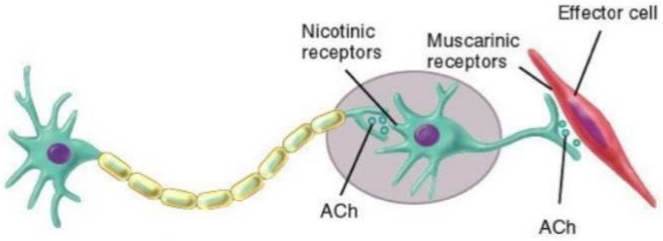




(a) Sympathetic division–innervation to most effector tissues



(b) Sympathetic division–innervation to most sweat glands



(c) Parasympathetic division

Receptors and signal transduction mechanisms

- Receptors are found at postsynaptic or post junctional membranes and they interact with transmitters released from the nerve terminals.
- These receptors function as coding system and they have **high** degree of specificity.
- The nature of response elicited in a particular tissue to a given transmitter is very precise and depends on the properties of receptor and the signaling mechanisms employed in that tissue.

Receptors on effector cells **(different type on each target):**

1) Receptors at ganglion (**parasympathetic and sympathetic**)
2) Muscarinic receptors: receptors on effector cells (**parasympathetic**)
3) Adrenergic receptors: receptors on effector cells (**sympathetic**).

Now we will talk about each one of them in detail (**FOCUS HERE**)

1) **At ganglia:** On **post synaptic (postganglionic)** membrane of sympathetic and parasympathetic there are **(nicotinic)** receptors because also nicotine can stimulate them.

- ➢ mentioned in 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 in skeletal muscles (also stimulate by Ach)
- ➢ This receptor gates ligand gated **Na^+ channel**, Activation of this receptor will cause **depolarization** on postsynaptic membrane, so when the ligand (Ach) binds to it, it opens Na^+ channels and causes depolarization of the post synaptic membrane and action potential is generated.

2) Muscarinic receptors (M1–M5):

- These **cholinergic** receptors lie on 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. Their name because mascarine can stimulate them.
- 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**, which in turn **decreases cyclic AMP** and slows the heart rate.

This Gi protein is also linked to **K^+ channels**, activation of this receptor will **slow** the rate of **depolarization**, so it **decreases** heart rate.

Once Ach binds to M2 receptor it activates a K^+ channel and inhabitation of (T-Ca^{+2}), it will slow the depolarization of the conductive tissue of the heart, that's mean we are decreasing the number of beats per minute .

Note: Other inhibitory muscarinic receptors are negatively coupled via Gi protein to adenylyl cyclase and decrease production of c-AMP.

- The excitatory receptors (**M1, M3, M5**) found on smooth muscle and glands are coupled via Gq protein to phospholipase C. This enzyme increases production of inositol-1,4,5-trisphosphate (IP3), IP3 causes release of Ca^{+2} from internal stores in muscle or glands, causing contraction (smooth muscles) or secretion (glands).

للاختصار :

Smooth muscle and glands:

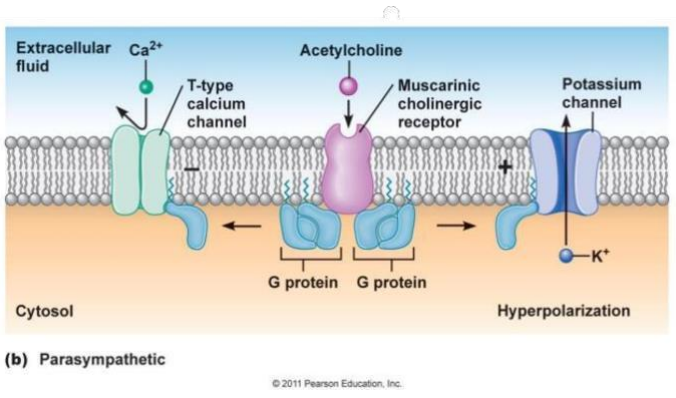
Gq protein → stimulation of phospholipase C, increase in IP3 and intracellular (Ca^{+2}).

Gq proteins: a family of G-protein that activates phospholipase C.

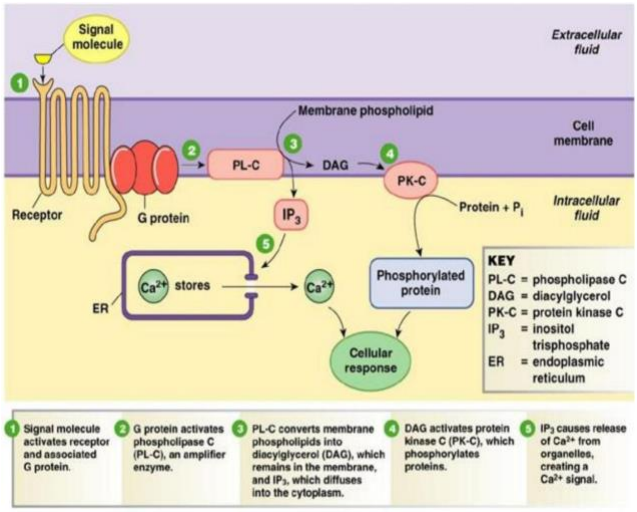
Phospholipase C: membrane associated enzyme responsible for the cleavage of phospholipids and convert it to DAG and IP3.

The increase of Ca^{+2} causes various response.

Gi→adenylate Cyclase→ reduces cAMP



(b) Parasympathetic



Note: Nicotinic receptors are stimulated by Nicotine, muscarinic receptors are activated by muscarine which is found in a type of toxic mushroom, if someone has been ingested with it, all muscarinic receptors will be activated. So heart rate and GI activity will increased and high secretion, salivation and sweating and the pupils became constriction (miosis)

"Muscarinic receptors" are activated by muscarine and inhibited by atropine.

Agonist: is a chemical substance that binds to a receptor and activates it to produce a biological response (**muscarine and nicotine are agonists for Acetylcholine, but for different receptors**), so when someone gets ingested with muscarine the receptors will be activated and he will develop obvious symptoms.

- The targets of muscarinic receptors' stimulation are illustrated by **muscarine** poisoning.

These effects include (**activation of muscarinic receptors**):

1) Stimulation of secretory activity: salivation, tearing, sweating (because the type of the receptors at the sweat glands are excitatory muscarine receptors) , nasal and bronchial secretion.
2) Increase gastrointestinal tract motility: vomiting and diarrhea.
3) Contraction of urinary bladder: urination.
4) Slowing of the heart: Bradycardia.

- These receptors are blocked by **atropine** from a plant. Atropa belladonna which induces reversal effects of muscarinic poisoning.

Effects of atropine include: (even if it high amount of atropine)

1) Inhibition of glandular secretions: dry mouth, dry eyes, and dry nasal passages.

2) Tachycardia (increase heart rate).

3) Loss of pupillary light reflex. (dilation)

4) Loss of ability to focus the lens for near vision.

Summery :

- Muscarine is an agonist for muscarinic receptors and leads to parasympathetic effects like slowing the heart rate and stimulating glands.

- Nicotine is an agonist for nicotinic receptors and leads to stimulating effects such as increased heart rate, blood pressure, and dopamine release, contributing to its addictive properties. Both muscarine and nicotine mimic acetylcholine's actions, but they affect different types of receptors and produce opposite physiological outcomes.

3) Adrenergic receptors: These receptors respond to catecholamines (epinephrine "EP" and norepinephrine "NE").

- Two types of receptors are known: alpha (α) and beta (β) receptors.

Alpha receptors:

The alpha receptors are subdivided into α_1 and α_2 receptors.

➢ **The alpha 1 (α_1) receptor**:

is widely distributed on **smooth muscles** with the exception of **bronchial muscle**. NE and EPI are about equally effective on these receptors .Stimulation of this receptor produces **excitation** → This effect involves IP3 production and release of Ca^{+2} from intracellular stores. Some (**α_1 are coupled to Ca^{+2} gated channels**) .

- **The alpha 1 (α_1):**
Excitatory: PLC → IP3

- **Alpha2 receptors:**
Nerve Adrenergic terminals →

reduce NE release.

- **Alpha 2 Heteroreceptors:**

Non Adrenergic-Gi → Adenylyl

- **Alpha2 receptors**:

  found on **sympathetic postganglionic nerve adrenergic** terminals. These receptors are important for self-inhibition of NE release, similar receptors are found on non-adrenergic (neurons that not release of NE)terminals we call it **“Alpha2 heteroreceptors”**.

- These receptors are negatively coupled to adenylyl cyclase via Gi protein and decrease c-AMP production.

- High releasing of EP and NE => inhibiting some pathways such as the pathway that transmits the pain sensation to the CNS .

Note : Hormone and Neurotransmitter can act over the same receptor

Beta receptors:

These receptors are subdivided into beta1 (β1) and beta 2 (β2) receptors. Both of them are more sensitive to catecholamines than alpha receptors.

- Catecholamines stimulate these receptors at much lower concentration than stimulation of alpha receptors.

- **Beta 1 (β_1) receptors**: found on heart and produces **excitation** in the heart.
- **Beta 2 (β_2) receptors**: found on tracheal and bronchial smooth muscle, in the gastrointestinal tract, and on smooth muscles of blood vessels supplying skeletal muscles (**occurs along with alpha 1 receptors**). (Inhibitory = relaxation of smooth muscles)

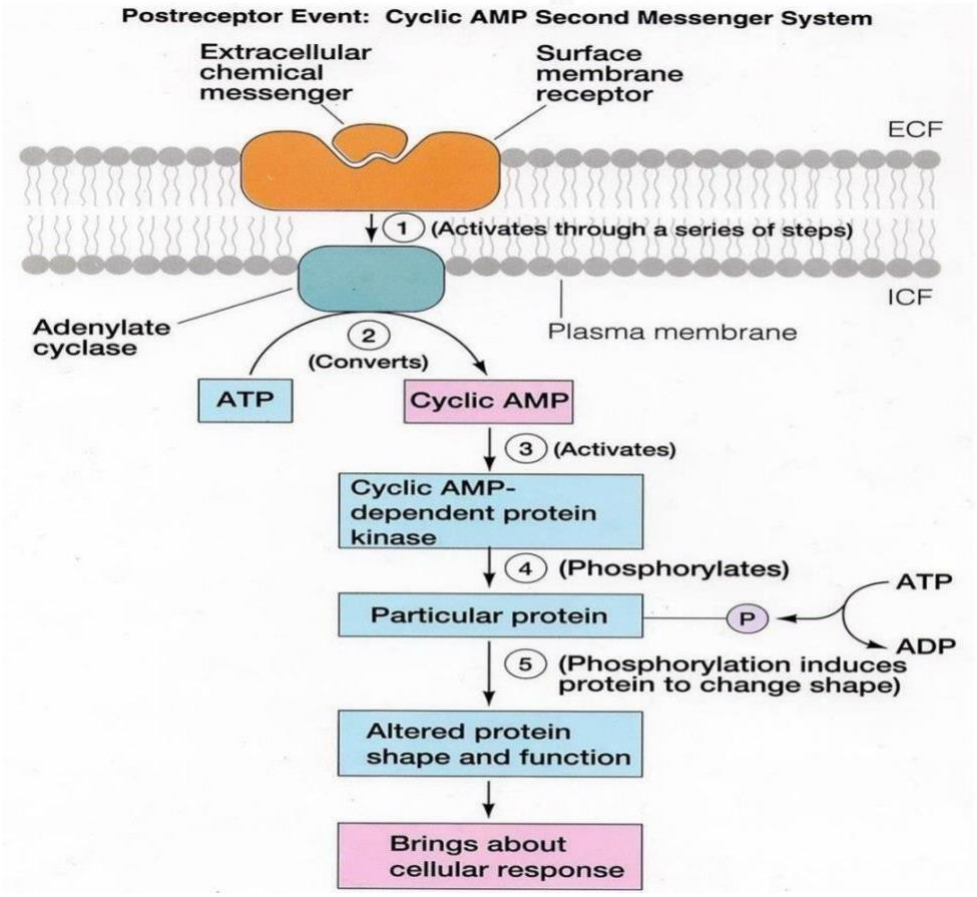
- The β_2 receptors are preferentially activated by EP rather than NE and β_1 receptors are preferentially activated by NE rather than EP .

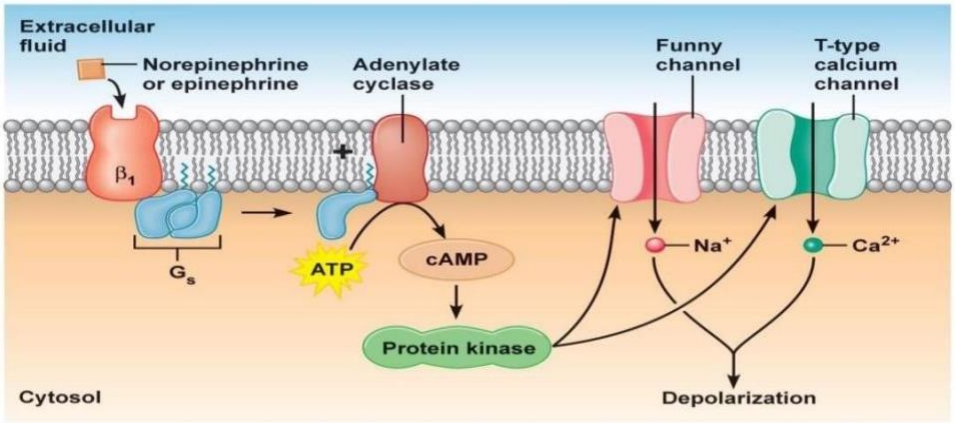
Important note 1: Both receptors are positively coupled to adenylyl cyclase via Gs protein and **increase c-AMP**, this will result in subsequent activation of protein kinase and phosphorylation of one or more proteins. The response elicited depends on the role of phosphorylated proteins. (the effect is different)

Important note 2: All subclasses of adrenergic receptors can be **blocked** by specific blocking agents (**antagonists**).

- β_1 blockers are useful as antiarrhythmic drugs.
- β_2 selective agonist (**produce activation of β2 receptor**) will dilate bronchi, this agonist is useful in asthma.

Asthma: a chronic lung disease that causes constriction of the bronchi, high secretion and difficulty in air flow. When you give an asthmatic patient a β blocker, it will kill the patient. So we give the patient a β_1 selective blocker not general if the patient has tachycardia.





(a) Sympathetic

Activation of Na+ and Ca+2 channels => increase the rate of the slow depolarization (increase heart rate)

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Transmitters:

At ganglion: preganglionic neurons of both sympathetic and parasympathetic release **acetylcholine** (Ach).

At effector organs:

- Post ganglionic terminals of parasympathetic fibers release **acetylcholine**.

- Post ganglionic terminals of sympathetic fibers release **norepinephrine**. An exception for sympathetic nerves to sweat
- glands, which release **acetylcholine** (Ach).

- The released Ach by parasympathetic system is inactivated by breakdown by *acetylcholinesterase*. Epinephrine is inactivated by recapture by postganglionic nerve varicosities.

Receptors and signal transduction mechanisms:

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Receptors at ganglion:

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Receptors on effector cells:

- Muscarinic receptors:

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Many muscarinic receptors have been known (M1-M5) at these junctions. All these receptors are coupled to G protein.

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Other inhibitory muscarinic receptors are negatively coupled via Gi protein to adenylyl cyclase and decrease production of c-AMP.

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- Inhibition of glandular secretions→ dry mouth, dry eyes, and dry nasal passages.
- Tachycardia. (increase heart rate).
- Loss of pupillary light reflex.
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The **alpha 1 (α_1)** receptor is widely distributed on smooth muscles with the exception of bronchial muscle. NE and EPI are about equally effective on these receptors.

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Alpha2 receptors: are found on sympathetic postganglionic nerve terminals. These receptors are important for self inhibition of NE release.

Similar receptors are found on nonadrenergic terminals are called Alpha2 heteroreceptors.

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Test yourself

Quiz

Additional Resources

رسالة من الفريق العلمي:

Reference Used:

1. Dr. MK's lecture
2. Dr. MK's handout

أيامٌ اختصّها الله بالفضل ،ورفع فيها الأجر ،وجعلها موسمًا للطاعة والرجوع إليه.

إنها العشر الأوائل من ذي الحجة؛ الأيام التي أقسم الله بها في كتابه الكريم
قال تعالى :
﴿وَالفجرِ ۝ وليالٍ عشر ﴾
وقال رسول الله ﷺ:
(ما من أيامٍ العملُ الصالحُ فيها أحبُ إلى الله من هذه الأيام)

فما أجمل أن نستقبلها بقلوبٍ صادقة ،وتوبةٍ خالصة ،وعزيمةٍ جديدة على القرب من الله.
أكثروا فيها من:

- الصلاة والذكر
- قراءة القرآن
- الصدقة وصلة الرحم
- التكبير والاستغفار
- الدعاء وإصلاح القلوب

لا تنسونا ووالدينا والأمة الإسلامية من صالح دُعائكم ،ولا تنسوا أهلنا في غزة والمستضعفين من المسلمين في كل بقاع الأرض في هذه الأيام الفضيلة 💙 .

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Versions		Slide #	Before	After
V0 → V1				
V1 → V2				