11

Pharmacology

Doctor 2018 | Medicine | JU

Sheet Slides

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BARORECEPTOR

Baroreceptors are sensors located in the cardio-regulatory centers in the brain stem and in Hering's nerve. They sense blood pressure and relay the information to the brain, which maintains it within normal limits.

They are activated by ANY change in BP, stimulating centers in the brain (send information to the brain) which perform reflex actions restoring homeostasis.

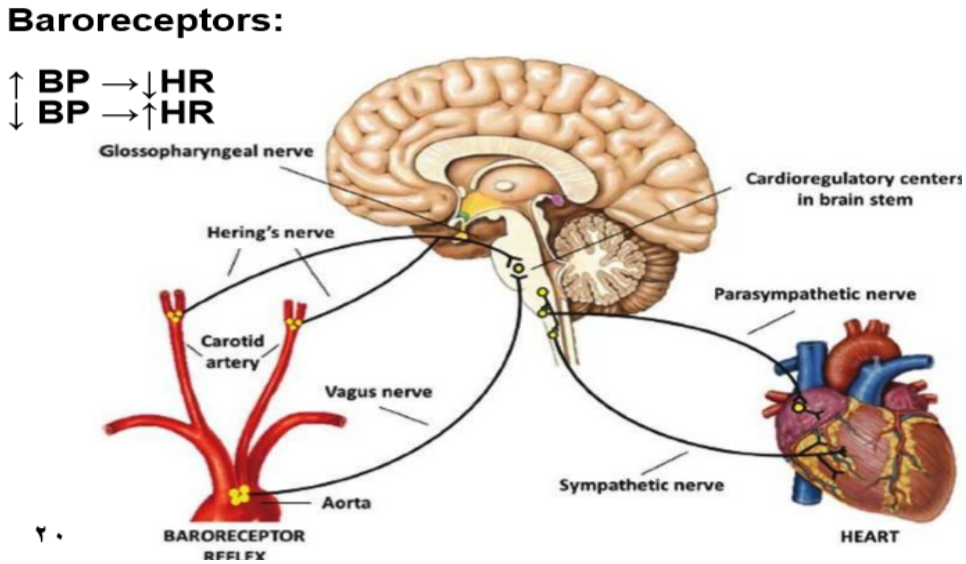
The sensory information activates autonomic reflexes, which influences the total peripheral resistance by affecting the cardiac output and vascular smooth muscle contraction.

Baroreceptors are stretch receptors, so they:

1. Detect stretching in arteries during an increase in BP
2. This results in their stimulation and so the activation of the Vagus nerve (a parasympathetic nerve)
3. Parasympathetic activity then immediately decreases the heart rate which causes the BP to decrease back to normal.

Baroreceptors also detect decreases in BP, activating the sympathetic nervous system causing the heart rate to go up.

This mechanism is very powerful and interferes with the action of drugs that cause vasoconstriction and an increase in BP. The baroreceptors immediately detect the increase in BP and reflexively stimulate the HR to decrease.



DIRECT EFFECTS OF AUTONOMIC NERVE ACTIVITY

recap of things we are familiar with, but there's no harm IN mentioning them:

Organ	Sympathetic	Receptor	Parasympathetic	Receptor
Eye				
Radial muscle + Circular muscle	Mydriasis (pupil becomes wider)	α1	Miosis (pupil becomes narrower)	M3
Ciliary muscle	No effect		Contraction (for near vision)	M3
Heart				
Sinoatrial node SA node (pacemaker of heart)	↑ in heart rate	β1	↓in heart rate	M2
Ectopic pacemakers	Accelerate	β1		
Contractility	Increases	β1	Decreases (atria)	M2
Blood vessels				
Skin, splanchnic vessels	Contract	α1		
Skeletal muscle vessels	Relax	β2	Endothelium (drug effect) releases (NO)	M3&M5
Lungs				
Bronchiolar smooth muscle	Relaxes	β2	Contracts	M3
Gastrointestinal tract				
Smooth muscle Walls	Relaxes	β2 + α2	Contracts	M3
Sphincters	Contracts	a1	Relaxes	M3
Secretion	No effect		Increases	M3
Genitourinary smooth muscle				
Bladder wall	Relaxes	β2	Contracts	M3
Sphincter	Contracts	α1	Relaxes	M3
Uterus, pregnant	Relaxes	β2	No effect	
Penis, seminal vesicles	Ejaculation	α	Erection	M
Skin				
Pilomotor smooth muscles	Contract	α		
Sweat glands	Increase	M		
Metabolic functions				
Liver	Glycogenolysis, Gluconeogenesis	β2, α β2, α		
Fat cells	Lipolysis	β3		
Kidney				
Kidney	Renin release	β1		

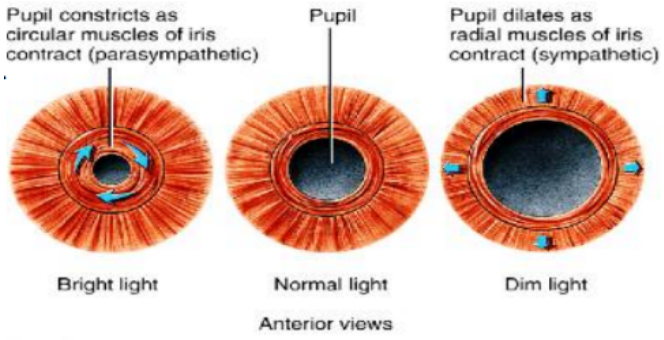
Additional information about the table:

Eye:

Has radial muscles (dilators), circular muscles (sphincters) and ciliary muscles.

Under parasympathetic stimulation, the **circular muscles** contract whilst the **radial muscles** relax, this causes the pupil to constrict and less light enters the eye. The opposite happens under sympathetic stimulation.

Ciliary muscles have ligaments attached to the eye lenses and **are affected parasympathetically only.** When they are stimulated, they contract, pulling the ligaments, which causes the shape of lenses to change. In this case the lenses focus on near objects enabling the vision of near objects like when reading.



Heart:

An ectopic pacemaker is an excitable group of cells that causes a premature heart beat outside the normally functioning SA node of the heart. In a normal heartbeat rhythm, the SA node usually suppresses the ectopic pacemaker activity due to the higher impulse rate of the SA node. However, in the instance of an ectopic focus bearing an intrinsic rate superior to SA node rate, ectopic pacemaker activity may take over the natural heart rhythm. They reach the AP at a higher frequency than the SA node, causing the heart to pump at a higher rate. β1 receptors increase the activity of these ectopic pacemakers.

The contractility is the contractile force of the target cardiac muscles. This is increased by β1 stimulation.

The ventricles have no parasympathetic innervation, so the parasympathetic effect is only on the atria, BUT the sympathetic effect is on both the ventricles and atria.

Ventricular contraction is very important because it is for ejection of the blood, so M2 receptors only decrease atrial contraction.

Blood Vessels:

Skin and splanchnic (organs in the abdominal cavity) blood vessels have α1 receptors. During the fight-or-flight response they vasoconstrict resulting in decreased blood flow to these organs. This is why your skin's color becomes white/yellow when you become scared.

Extra Information (doctor didn't explain it clearly):

Skeletal muscle blood vessels have both β2 and α1 receptors, β2 stimulation causes vasodilation and α1 stimulation causes vasoconstriction. β2 receptors are less sensitive than α1 receptors which means that at lower concentrations α1 receptors are stimulated without activating β2 receptors. During the fight-or-flight response, epinephrine is released into blood in high concentrations stimulating the β2 receptors which cause vasodilation of the skeletal muscle blood vessels.

Almost all blood vessels (99%) don't have parasympathetic innervation. However, they still have M3 receptors, which are found on endothelial cells adjacent to the smooth muscles of the blood vessel. When an exogenous parasympathetic drug (injected) binds to them, they release NO (nitric oxide), which causes the vessel smooth muscles to relax, resulting in vasodilation.

Bronchiolar Smooth Muscle:

Sympathetic stimulation of β2 receptors causes bronchodilation, hence β2 agonists are used to treat bronchial asthma. However parasympathetic stimulation of M3 receptors causes bronchoconstriction and increases bronchial secretions. These effects resemble a bronchial asthma attack.

Gastrointestinal Tract:

Stimulation β2 and α2 receptors of the GIT smooth muscle wall causes relaxation, whereas M3 stimulation causes contraction. The sphincter muscle has α1 receptors which are stimulated causing it to close. When the intestinal muscles are relaxed, and the sphincter is closed, nothing passes to the intestine so peristatic activity is inhibited. However, under parasympathetic stimulation the sphincter opens and the GIT smooth muscles contract, so peristatic activity is fast. The person in this case will suffer from diarrhea, colic…, etc.
Secretions are only affected by the parasympathetic system. M1 receptors in the stomach increase gastric (acid) secretions while M3 in the intestine increase intestinal secretions.

Genitourinary Smooth Muscles:

Sympathetic stimulation causes the bladder wall to relax due to β2 receptors, and the sphincter to contract (close) due to α1 receptors, this makes urination difficult. Parasympathetic stimulation on the other hand causes the opposite effect, contracting the bladder wall and relaxing the sphincter, making urination easy.

The uterus is stimulated by the sympathetic system (depends on hormonal balance) but not by the parasympathetic system. Sympathetic stimulation of β2 receptors causes uterus muscle relaxation. Therefore, premature contractions of the uterus in pregnancy are treated by giving β2 agonists to relax the uterus and hence save the pregnancy.

Skin:

Sweat glands are innervated by cholinergic sympathetic nerves. Specifically, they have muscarinic receptors which increase sweating upon stimulation.

Metabolic Function:

The liver has α2 and **β2 receptors** (more important). Under sympathetic stimulation, these promote glycogenolysis (breaking down of glycogen) and gluconeogenesis (synthesis of glucose from non-carbohydrate carbon sources like proteins), because in fight or flight conditions, your body needs energy and blood glucose. Diabetic patients and patients with anxiety, have high blood sugar because epinephrine stimulates β2 receptors to increase gluconeogenesis and glycogenolysis.

Fat cells have β3 receptors that promote lipolysis which is the breakdown of lipids to form free fatty acid that are used for energy production in the body.

Kidney:

Have sympathetic β1 receptors which upon stimulation cause:

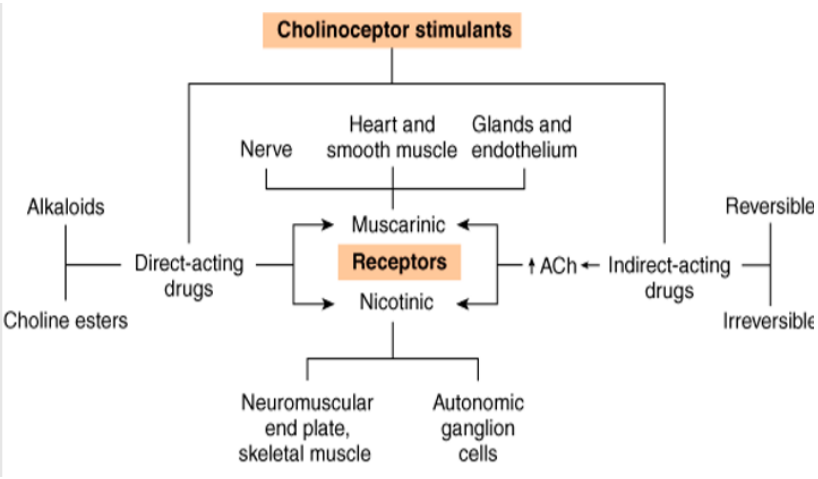
1. The release of Renin which is an enzyme that acts on a large protein in blood called angiotensinogen
2. Renin breaks down angiotensinogen into angiotensin I
3. Angiotensin I is converted into angiotensin II which is a potent vasoconstrictor
4. Angiotensin II stimulates the release of the hormone aldosterone
5. Aldosterone causes the retention of sodium and water.

CHOLINOCEPTOR ACTIVATING & CHOLINESTERASE INHIBITING DRUGS

There are two types of drugs that are cholinoceptor stimulants:

1-Direct acting drugs.

2-Indirect acting drugs



INDIRECT ACTING DRUGS

They perform their job by inhibiting Acetylcholinesterase (ACE), which is a very powerful enzyme; it hydrolyzes Acetylcholine (Ach) within milliseconds of its release. Inhibiting this enzyme increases the con. of ACh at the receptor site thus prolonging its effect (high effect). The drugs don't act directly on the receptor but they inhibit ACE therefore producing an effect similar to the activation of the cholinergic receptors directly.

There are two types of indirect acting drugs:

1. **Reversible:** Inhibit ACE for a short period of time (mins to hours).
2. **Irreversible**: **Very** toxic, they permanently inactivate the enzyme, e.g nerve gases.

Nicotinic receptors exist in two places:

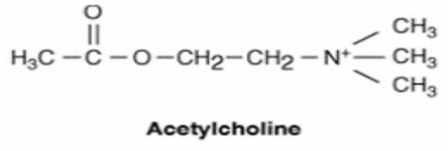
1. Neuromuscular end plates of skeletal muscles
2. Autonomic ganglia cells

DIRECT ACTING DRUGS

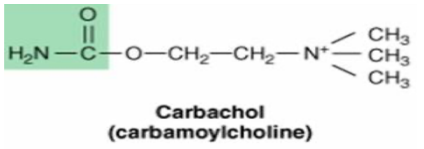
a- **Choline esters**

The most popular example is endogenous **acetylcholine**. ACh is not clinically useful, you can't use it as a drug because it'll be degraded the moment it's injected as it has a very short lifetime. If you want to see the effect of Ach you have to give it by infusion (administration directly into a vein). The response obtained depends on the infusion rate.

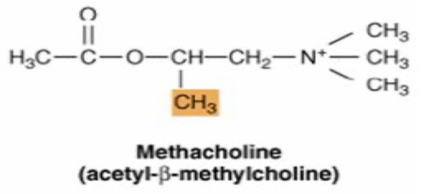
Acetylcholine's structure can be modified to produce new drugs that function better clinically. Examples:



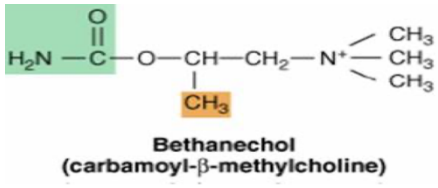
1. **Carbachol**: acetyl group is substituted with an amide group.
   a. Dangerous so it can't be used for systemic actions.



2. **Methacholine**: methyl group is added.
   a. Dangerous so it can't be used for systemic actions.
   b. Very dangerous as it can cause the heart to stop within seconds.
   c. Has an increased sensitivity for the cardiovascular system.



3. **Bethanechol:** a combination of the drugs above; A methyl group is added, and the acetyl group is substituted with an amide group.
   a. Can be used for systemic actions.
   b. Bethanechol's muscarinic effect is more in the GI tract and urinary tract than in the cardiovascular system (unlike Methacholine); so it has a less chance of causing bradycardia
   c. Best drug.



* Here we're talking about cholinoceptor activating drugs, so 99% of their effect is **parasympathetic**.

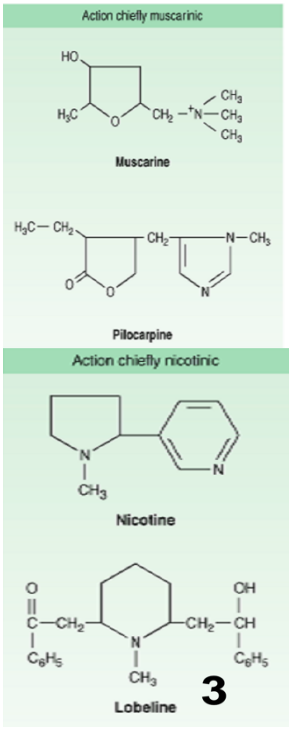
The effect of ACE on the drugs, and the effect of the drugs on muscarinic and nicotinic receptors:

Choline Ester	Degree of effect		
	by ACE	Muscarinic Receptors	Nicotinic Receptors
Acetylcholine	Extremely affected	Highly affects	Highly affects
	++++	+++	+++
Methacholine	Slightly affected	Extremely affects	No effect
	+	++++	
Carbachol	Not affected	Moderately affects	Highly affects
		++	+++
Benthanechol	Not affected	Moderately affects	No effect
		++	

NOTE that the drugs that target nicotinic receptors have more like sympathomimetic effect which is not our point here.

b-**Alkaloids**

1. **Muscarine**:
    a. Most well-known one
    b. Natural
    c. Has a stronger effect than ACh on muscarinic receptors
2. **Pilocarpine** (muscarinic agent):
    a. Direct acting
    b. Natural alkaloid that comes from plants.
3. **Nicotine**
    a. Only stimulates nicotinic receptors
4. **Lobeline**
    a. Very similar to nicotine (acts on nicotinic receptors)
    b. Natural alkaloid that comes from plants.



MECHANISM OF ACTION

MUSCARINIC TRANSMISSION IN THE HEART

The M2 receptor is the most abundant receptor on the heart while the M3 receptor is present in the stomach and most other tissues

Mechanism:

Ach activates M2 receptors which release **Gi proteins:**

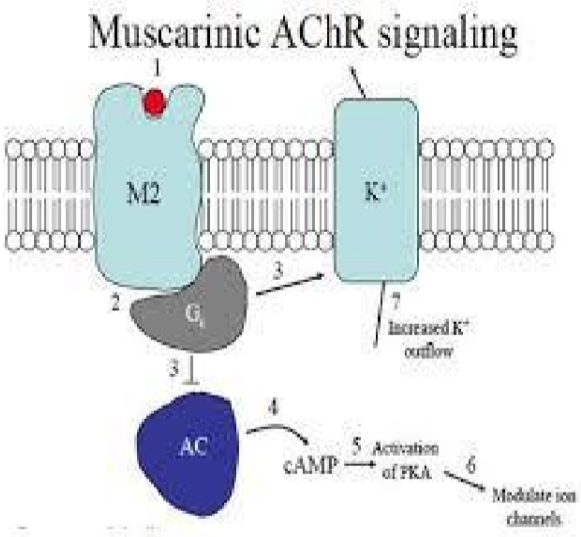
A. Gi protein stimulates K^+ channels to open:
    a. This results in an outflux of K^+ ions causing hyperpolarization; the inside of the cell becomes more negative, so a greater AP is needed to produce an effect.
    b. In the case of the cardiac pacemaker, the voltage-dependent opening of pacemaker Na+ channels is shifted to more negative potentials making them harder to open. Thus, we get less action potentials per unit time and so less contractility and heart rate.

B. Gi protein also inhibits adenylyl cyclase AC:

1. This decreases cAMP production inside the cell
2. Which results in a decrease in phosphorylation of L-type Ca^{+2} channels which are responsible for the excitation-contraction coupling of the cardiac muscle. Phosphorylation of these channels increases their permeability to Ca+ and increases the contractility of their respective cardiac myocyte.
3. So less phosphorylation = less contraction of the myocytes which results in a lower heart rate and force of contraction

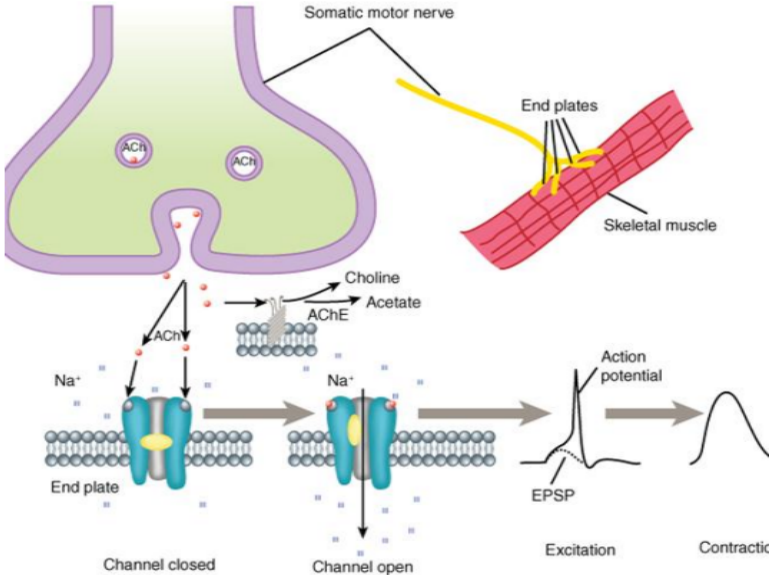
Summary:

- M2R stimulates Gi protein → Open K^+ channel → Hyperpolarization → ↓HR & ↓ force of contraction.
- M2R stimulates Gi protein →↓adenylyl cyclase → ↓cAMP formation→ ↓HR & ↓ force of contraction.



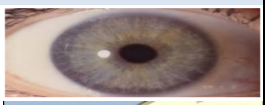
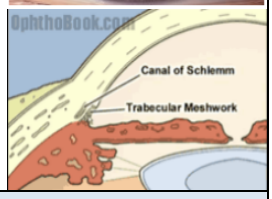
NICOTINIC TRANSMISSION AT NEUROMUSCULAR JUNCTIONS:

1. Released Ach binds to and opens the Na^+ nicotinic receptors
2. This allows Na^+ to flow into the cell, producing an excitatory postsynaptic potential (EPSP).
3. The EPSP depolarizes the muscle membrane, generating an action potential, and triggering contraction.
4. After Ach dissociates, it is metabolized into choline and acetate by the extracellular Acetylcholinesterase (ACE).



EFFECTS OF DIRECT-ACTING CHOLINOCEPTOR STIMULANTS:

MOST OF THESE EFFECTS ARE PARASYMPATHETIC HENCE 99% OF THE CHOLINOCEPTORS ARE PARASYMPATHETIC.

Organ	Response
Eye	
Sphincter muscle of iris (circular muscle)	Contraction – stimulation of miosis 
Ciliary muscle	• Contraction (for near vision) • Facilitation of Aqueous humor outflow into the canal of Schlemm. 
Heart	
SA node	Decrease in rate (negative chronotropy)
Atria	Decrease in contractile strength (negative inotropy)
Atrioventricular node	• Decrease in conduction velocity (negative dromotropy) • Increase in refractory period.
Ventricles	Small decrease in contractile strength (because it is only sympathetic)
Blood vessels	
Arteries + Veins	Dilation via **Nitric Oxide**
Lung	
Bronchial muscle	Contraction (Bronchoconstriction) 
Bronchial glands	Stimulation - increase bronchial secretion
GI tract	
Motility	Increase
Sphincter	Relaxation
Secretion	Stimulation
Urinary bladder	
Detrusor	Contraction
Trigone and sphincter	Relaxation (voiding of urine)
Glands	
Sweat, salivary, lacrimal, nasopharyngeal	↑ Secretion

Glaucoma

In a normal eye, a liquid called the **aqueous humor** is continuously produced and drained, maintaining the shape of eye. In **glaucoma** (eye condition), **aqueous humor** builds up and increases pressure within the eye. Such increased pressure can damage the optic nerve directly or restrict blood flow, thus damaging the optic nerve indirectly.

If a patient has **glaucoma**, we give him **pilocarpine** which is a **parasympathetic drug** that causes the opening of the **canal of Schlemm** thus facilitating the drainage of **aqueous humor** to decrease intraocular pressure.

Atrioventricular node

The **AV node** is a part of the electrical conduction system of the heart that electrically connects the atria and ventricles by conducting the normal electrical impulse from the atria to the ventricles. It has a **refractory period** which is the minimum interval between two ventricular impulses propagated from the atria.

Parasympathetic activation here **decreases** the **conduction velocity** (The speed of impulses (AP) passing from the atrium to the ventricle) and **increases** the **refractory period**, so less impulses (AP) pass. If parasympathetic activation increase drastically, **heart block** occurs (no impulses can pass from the AV node).

ORGAN SYSTEM EFFECTS

The effect of these drugs on the system as a whole:

Cardiovascular system (M2)

Intravenous (IV) infusions of **low doses** of **Ach** cause:

1. Vasodilation
2. This causes a reduction in blood pressure (Hypotension)
3. Which evokes the baroreceptor reflex
4. Resulting in an increase in heart rate to restore blood pressure to normal levels

Intravenous (IV) infusions of **larger doses** of **Ach** produce:

- Bradycardia (↓HR):
    - The direct effect of Ach on the M2 receptors overrides the Baroreceptor reflex thus reducing the heart rate
- Decreases in the AV node conduction velocity
- Hypotension due to vasodilation of blood vessels

Decrease the contractility of atrial & ventricular cells:

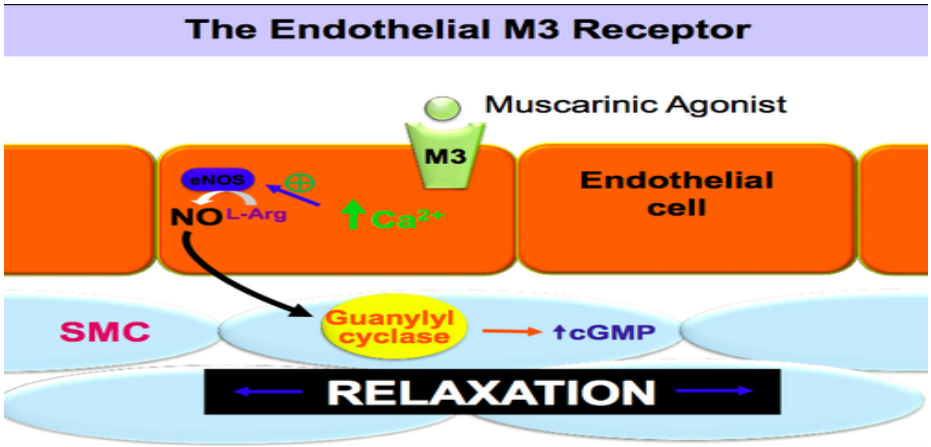
- The sympathetic nerve innervating the ventricles has muscarinic receptors. When these are stimulated, the release of norepinephrine is reduced, hence decreasing ventricular contractility.
- On the other hand, atria have parasympathetic receptors and the effect observed is due to their direct stimulation.

The direct slowing of sinoatrial rate & atrioventricular conduction is often opposed by reflex sympathetic discharge, elicited by the decrease in blood pressure.

Mechanism of Muscarinic stimulation (M3 receptors)

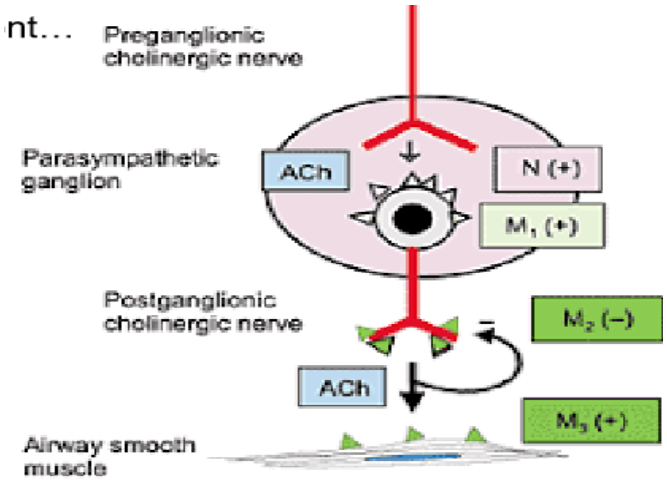
IV injection of muscarinic agonists produces marked vasodilation:

1. Muscarinic agonists bind to their receptors (M3)
2. This stimulates the release of nitric oxide (NO) from the endothelial cells.
3. NO diffuses to adjacent vascular smooth muscle activating guanylyl cyclase
4. Guanylyl cyclase increases intercellular cGMP concentration resulting in muscle relaxation



Pilocarpine:

Natural alkaloid that may produce **hypertension (vasoconstriction) after a brief initial hypotension (vasodilation).** The longer-lasting hypertensive Effect is due to sympathetic ganglionic activation caused by activation of ganglionic M1 receptors, which elicit slow excitatory postsynaptic potentials. This effect, like the hypotensive effect, can be blocked by atropine, an antimuscarinic drug.



The **Initial hypotension** is due to stimulation of **M3 receptors on endothelial cells**, followed by **prolonged hypertension** due to stimulation **of M1 receptors on the postsynaptic sympathetic fibers** innervating the BVs, inducing them to release epinephrine & norepinephrine thus increasing the BP and a total result of **hypertension**.

Pilocarpine is used to induce chronic epilepsy in rats, to examine different treatments (M1 effect).

Respiratory System:

Bronchoconstriction and increase in bronchial secretion.

Gastrointestinal Tract:

Effects:

- Increases the secretory and motor activity of the gut
- Salivary and gastric glands are strongly stimulated
- Peristaltic activity is increased
- Most sphincters are relaxed

M3 receptors work through DAG and IP3, increasing calcium ion concentration, which increases contractility in the intestine. So M3 receptors are required for the direct activation of smooth muscle contraction.

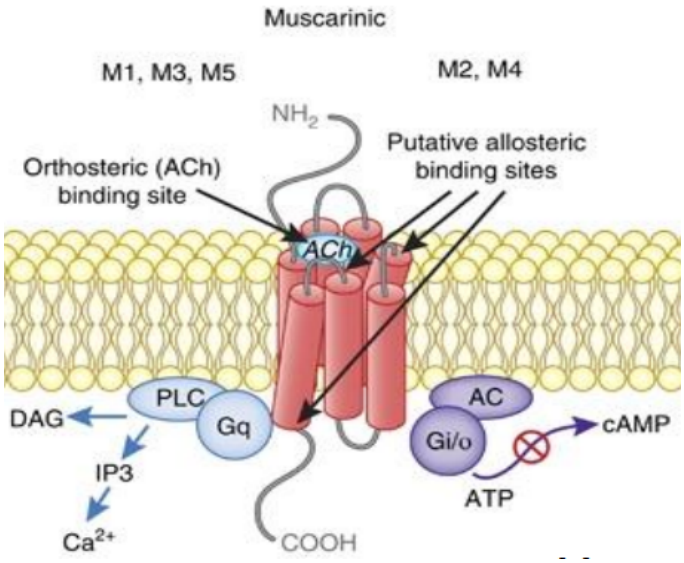
β2 receptors of the sympathetic nervous system cause relaxation by stimulating cAMP production. M2 receptors cause inhibition of cAMP formation. Therefore, M2 receptors reduce cAMP formation & relaxation caused by sympathomimetic drugs.

M4 + M2 have similar effects

M1 + M3 + M5 have similar effects

All of them exist in brain:

- M5 + M4 mostly in the brain
- M1 + M2 + M3 exist peripherally.



Genitourinary Tract:

Stimulate the detrusor muscle and relax the trigone and sphincter muscles of the bladder, thus promoting voiding.

The function of M2 and M3 receptors in the urinary bladder is the same as in intestinal smooth muscle:

- M3 receptors are required for the direct activation of smooth muscle contraction
- M2 receptors reduce cAMP formation & relaxation caused by sympathomimetic drugs

The human uterus is not sensitive to muscarinic agonists.

Miscellaneous Secretory Glands:

Muscarinic agonists stimulate secretion of sweat, lacrimal, and nasopharyngeal glands.

NICOTINIC EFFECTS OF NICOTINE INTAKE:

Central Nervous System:

The CNS contains both **muscarinic** and **nicotinic** receptors. The brain is richer in **muscarinic** receptors while the spinal cord contains more **nicotinic** receptors.

Presynaptic **nicotinic receptors** regulate the release of several neurotransmitters (in physiological concentrations).
In high concentrations nicotine induces tremor, emesis, and stimulation of the respiratory center. At even higher levels, nicotine causes convulsions & fatal coma.

Autonomic ganglia:

In the CVS, the effects of nicotine are chiefly sympathomimetic.

Nicotine causes:

- Hypertension
- Tachycardia which may alternate with a bradycardia mediated by vagal discharge (due to baroreceptors).

GIT and urinary tracts:

The effects are parasympathomimetic: nausea, vomiting, diarrhea, and voiding of urine.

Prolonged exposure to nicotine may result in depolarizing **blockade** of the ganglia.

Neuromuscular Junction:

Nicotine stimulates nicotinic receptors producing contractile responses that vary from disorganized fasciculations to strong contraction of entire muscles.

Nicotine is a stimulant in low concentrations and inhibitor (blocker) at high concentrations

Under high concentrations, nicotine causes rapid development of depolarization blockade. This happens when the motor end plate is depolarized for a long period, desensitizing it by blocking the generation of new action potentials for some time. Transmission blockade persists even when the membrane has repolarized.

This latter phase of block is manifested as flaccid paralysis of skeletal muscle.