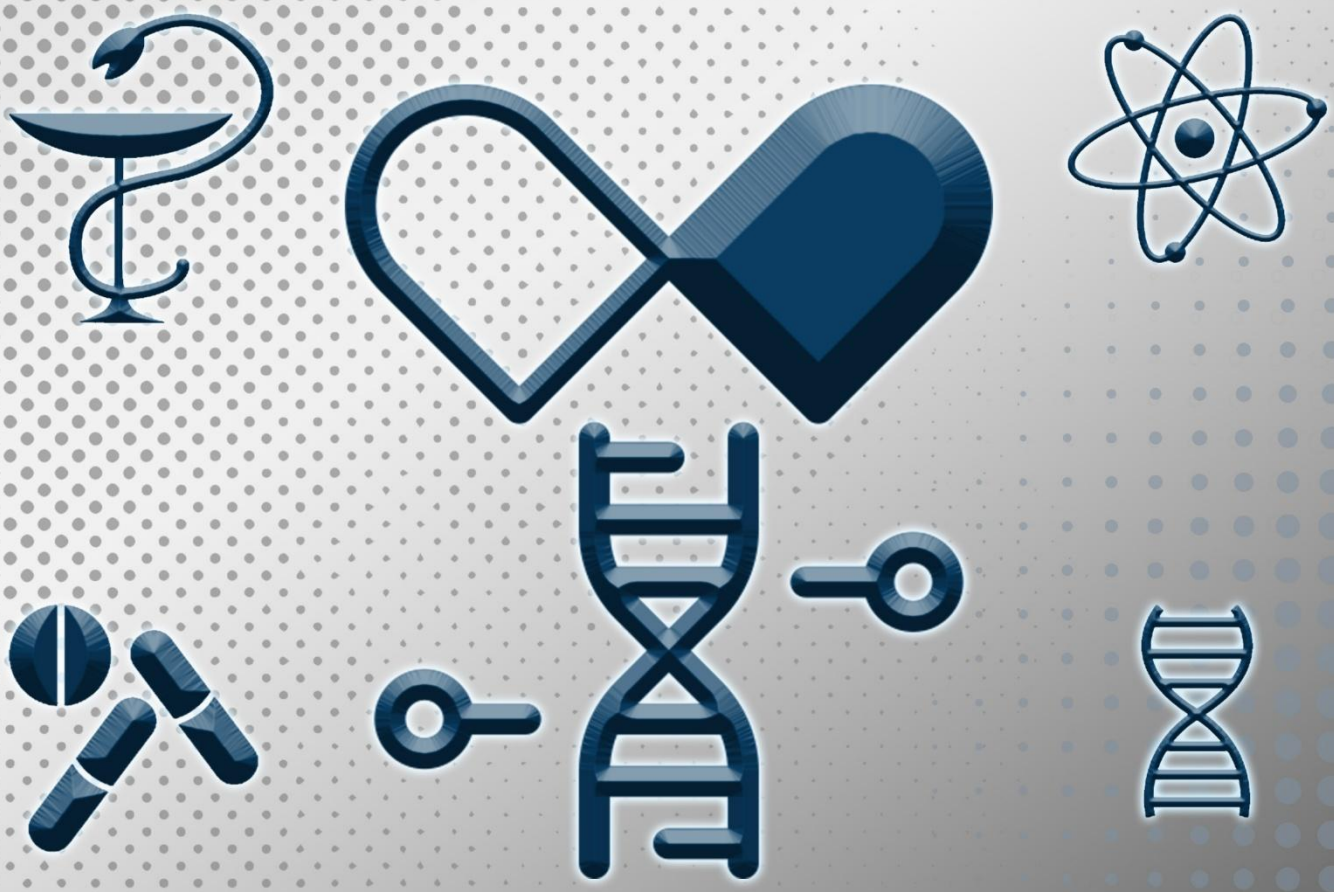
Pharmacology



Done By:

Mohammad Alomari

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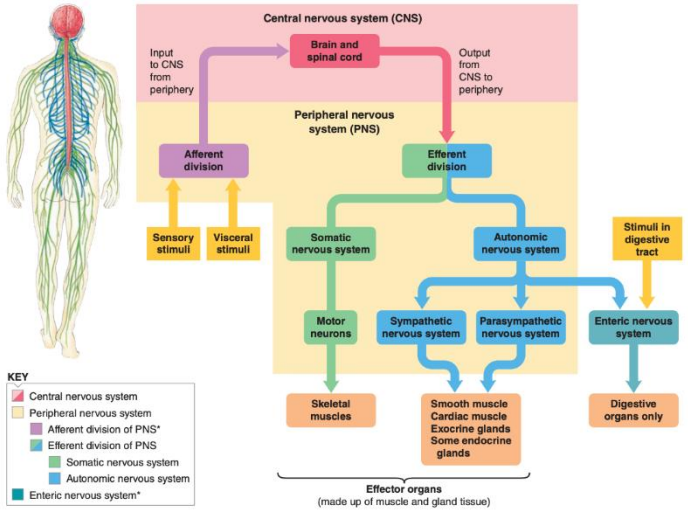
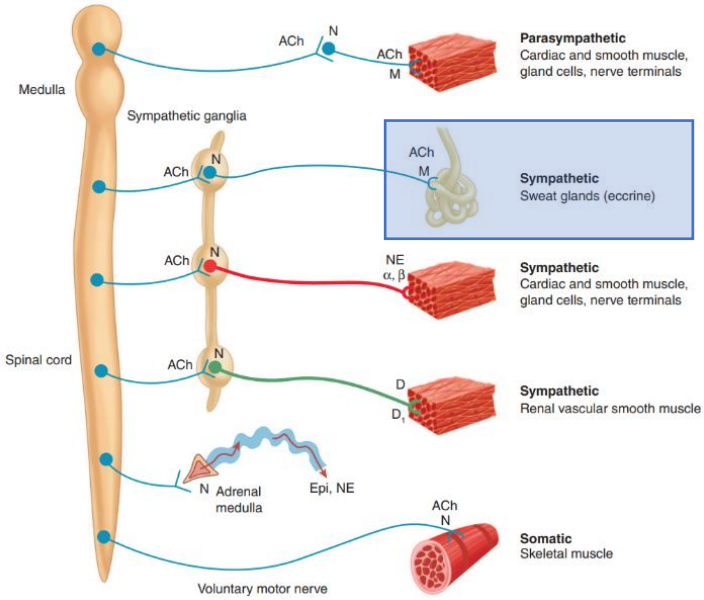
Introduction to Autonomic Pharmacology

Autonomic Nervous System



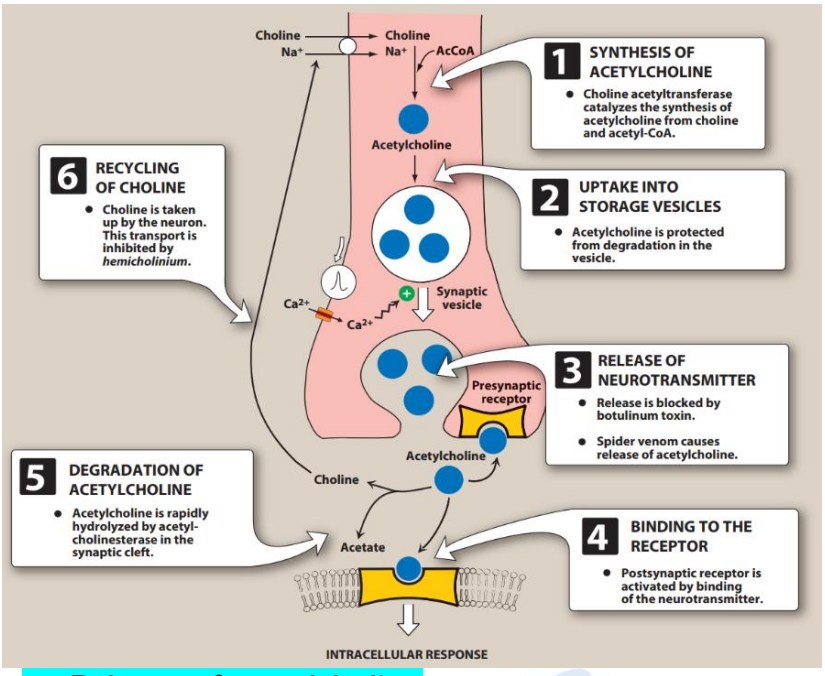


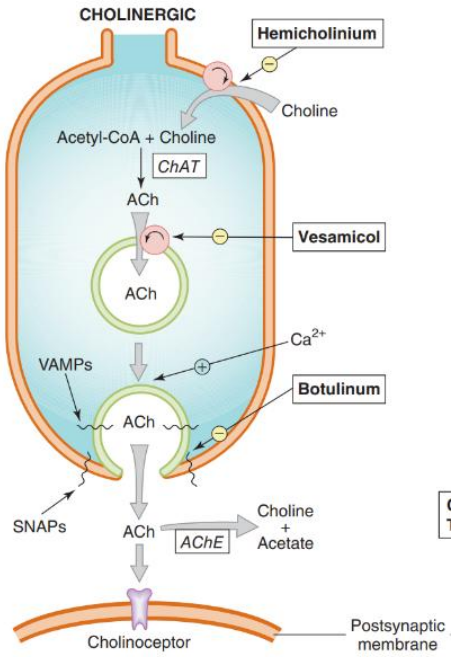
	Sympathetic	Parasympathetic
Origin	Thoracolumbar T1-L2	Craniosacral Brain stem 1973 CN X & S2, S3, S4
Ganglia location	Close to spinal cord	Within the organ (Terminal ganglia)
Activation pattern	Body-wide.	Certain organ.
Effect	Stimulatory (usually). * Fight & Flight	Inhibitory (usually). * Rest & Digest.
Preganglionic neurons	Short	Long
Postganglionic neurons	Long	Short
Preganglionic NTs	Acetylcholine "Cholinergic"	Acetylcholine "Cholinergic"
Postganglionic NTs	Norepinephrine or Adrenaline **is usually "Adrenergic".** - Except: Sweat glands, that is "Cholinergic".	Acetylcholine "Cholinergic"
Preganglionic NTs Receptors	Nicotinic found in ganglion.	Nicotinic found in ganglion.
Postganglionic NTs Receptors	Alpha & Beta & Dopamine.	Muscarinic within effector organ.

- **Dual reciprocal innervation of Most organs**: Eye, heart, air-passages,….

Neurotransmitter Aspects of the ANS

- Cholinergic Transmission:
  - Acetylcholine (ACh) is the primary transmitter used in:
    - ➔ Autonomic ganglia, PANS postganglionic junction, sweat glands & skeletal muscle NMJ.
  - **Synthesis and storage:**
    - ➔ Acetylcholine is synthesized in the nerve terminal as follows:
      - ❖ **Acetyl-CoA + choline** → by choline acetyltransferase → Acetylcholine.
      - ❖ Acetyl-CoA (produced in mitochondria)
      - ❖ Choline (transported across cell membrane with Na by Na/Choline symporter).
        - ⇨ The rate-limiting step is probably the transport of choline into the nerve terminal.
    - ➔ Ach is actively transported into storage vehicles by **vesicle-associated transporter, VAT**.
      - ❖ VAT: Antiport: enters Ach & exsits (Proton) H+.





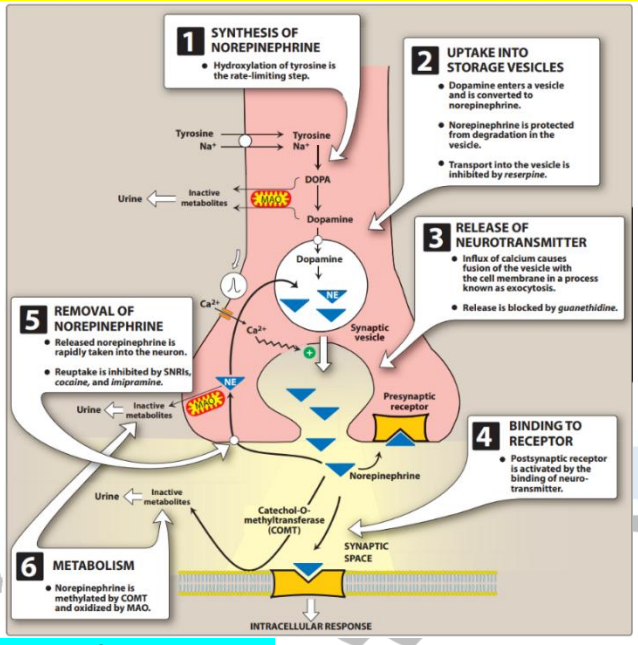
- **Release of acetylcholine**
  - ➔ When AP is arrived, this stimulates entry of calcium that will stimulates fusion of vesicle.
  - ➔ Triggering of an interaction between:
    - ❖ **SNAPs** and **VAMPs** that associated with the nerve terminal & Vesicle membranes.
    - ❖ Leading to exocytosis.
  - ➔ This results in docking of the vesicle to terminal membrane & release Ach into synaptic cleft.

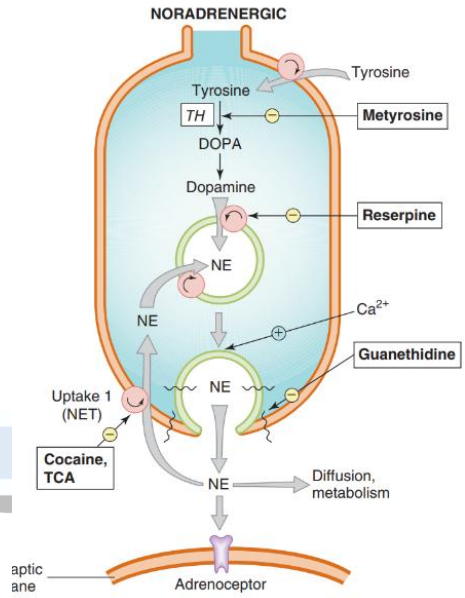
- **Termination of action of acetylcholine**
  - ➔ By removal of ACh, mainly by metabolism not ACh reuptake.
  - ➔ By metabolism to acetate & choline by **acetylcholinesterase** in the synaptic cleft.
  - ➔ **Acetate & choline are not excreted but are recycled in the body**.

- Drug effects on synthesis, storage, release, and termination of action of acetylcholine:
  - **Vesamicol:** Inhibits Ach transport into vesicles **(inhibits VAT)**.
  - **Hemicholinium:** Inhibits Na/choline symport.
  - **Botulinum toxins:** alter VAMPs to prevent Ach release.
    - ➔ Very large molecule and diffuses very slowly:
  - **Sarine gas:** Inhibition of acetylcholinesterase.
    - ➔ All of them are not very useful for systemic therapy.
      - ❖ Because their effects are not sufficiently selective (PANS & SANS & somatic).

- Adrenergic Transmission
  - Norepinephrine (NE) is the primary transmitter at the sympathetic postganglionic junction.
    - ➔ Important exceptions include sympathetic fibers to thermoregulatory sweat glands and probably vasodilator sympathetic fibers in skeletal muscle, which release acetylcholine.
  - Dopamine may be a vasodilator transmitter in renal blood vessels, but norepinephrine is a vasoconstrictor of these vessels.

- **Synthesis and storage**
  - ➔ The synthesis of dopamine and norepinephrine as follows:
    - ❖ Tyrosine ➔ by tyrosine hydroxylase ➔ L-DOPA ➔ Dopamine.
    - ❖ Tyrosine transported across cell membrane with Na by Na/Tyrosine symporter.
    - ❖ Tyrosine is hydroxylated by tyrosine hydroxylase to DOPA **(Rate limiting step)**.
    - ❖ DOPA is decarboxylated to dopamine.
    - ❖ Dopamine is transported into vesicles by vesicular monoamine transporter **(VMAT).**
    - ❖ Dopamine hydroxylated to norepinephrine (inside the vesicle).





- **Release of transmitter**
  - ➔ When AP is arrived, this stimulates entry of calcium that will stimulates fusion of vesicle.
  - ➔ Triggering of an interaction between:
    - ❖ **SNAPs** and **VAMPs** that associated with the nerve terminal & Vesicle membranes.
    - ❖ Leading to exocytosis.
  - ➔ This results in docking of the vesicle to terminal membrane & release Ach into synaptic cleft.

- **Termination of action**
  - ➔ By removal of the NTs, mainly by reuptake & may by metabolism.
  - ➔ Reuptake by norepinephrine or dopamine transporters, NET, DAT.
    - ❖ Reduces their concentration in the synaptic cleft and stops their action.
  - ➔ Outside the cleft, these transmitters can be metabolized by:
    - ❖ **MAO and COMT (catechol-O-methyltransferase)**
    - ❖ After the enzymatic reactions we will excrete the inactive products in urine.
      - ⇨ Metanephrine, normetanephrine, 3-methoxy-4-hydroxymandelic acid.

- Monoamine oxidase (MAO):
  - Present on mitochondria in the adrenergic nerve ending.
  - Inactivates some of dopamine and norepinephrine in the cytoplasm.

- COMT (catechol-O-methyltransferase)
  - Present in the synaptic cleft.
  - Inactivates some of norepinephrine in the synaptic cleft.

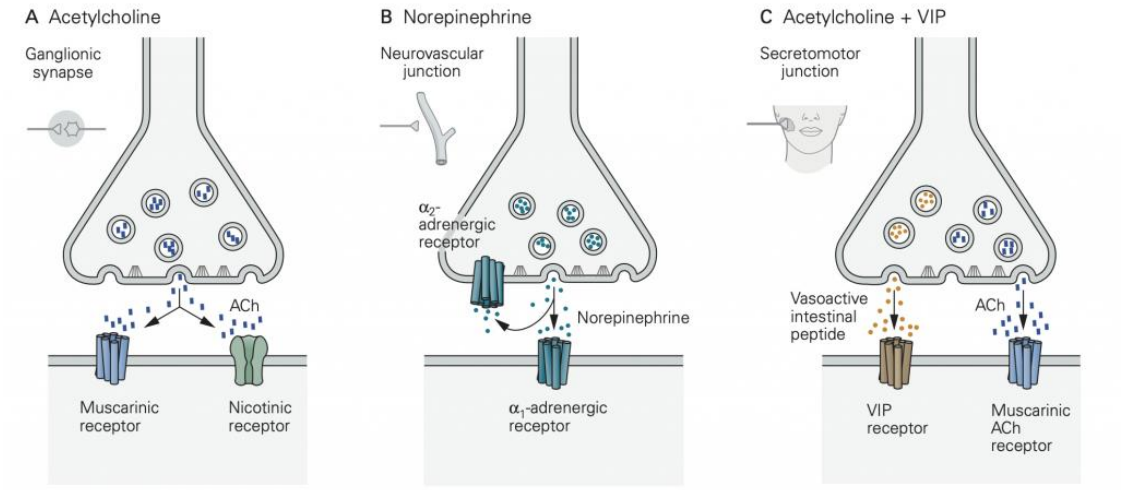
- MAO Inhibition: increases stores of catecholamines in nerve endings.
- COMT Inhibition: increases catecholamines in synaptic cleft.

In the brain is useful in Parkinson's disease.

- **Drug effects on adrenergic transmission.**
  - ➔ **Me-tyrosine:** Inhibits Tyrosine hydroxylase.
  - ➔ **Reserpine:** Inhibits VMAT resulting in depletion of transmitter stores.
  - ➔ **Guanethidine**: alter VAMPs to prevent NE release (like Botulinum toxins).
    - ❖ They ↓monoamines thus block sympathetic functions.
      - ⇨ Thus, Used in past in treatment of hypertension, due block of α 1.
  - ➔ **Amphetamines**: inhibit MAO thus promote catecholamine release & SNS Effects.
  - ➔ **TCA & Cocaine:** inhibit NET thus promote catecholamine release & SNS Effects.

- **Regulation of NE release**
  - Negative feedback mechanism.
    - ➔ Presynaptic receptors **(α2 Auto-receptors)**
      - ❖ Norepinephrine that released from adrenergic nerve.
      - ❖ Stimulates the **α**2R to ↓NE release by negative feedback.

- Cotransmitters
  - They are transmitter molecules in vesicles other than Ach & NE.
  - May be localized in the same vesicles or separate vesicles.
  - Examples:
    - ➔ ATP, Vasoactive Intestinal Peptide (VIP), Enkephalin (endogenous opioids).
    - ➔ Neuropeptide Y, substance P, Neurotensin, Somatostatin, GABA.
  - Their main role in autonomic function appears to involve modulation of synaptic transmission.
    - ➔ By affecting their receptors.
  - The same substances function as primary transmitters in other synapses.



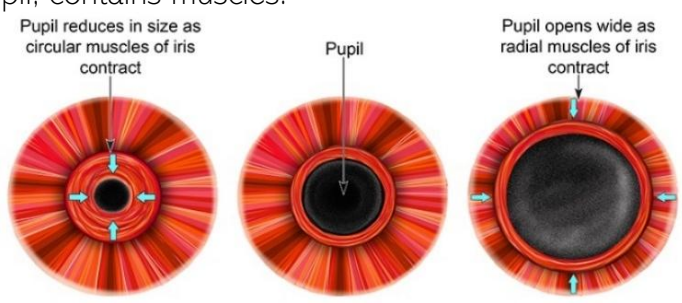
SITES OF AUTONOMIC DRUG ACTION

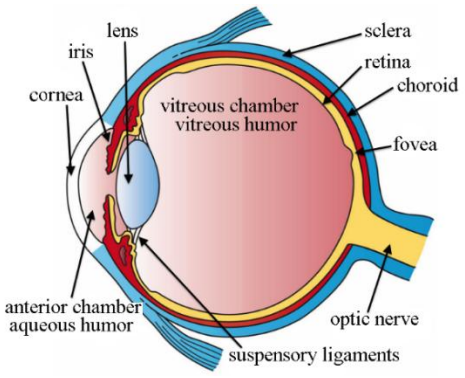
Organ	SNS	PSNS
Eye - Pupils - Ciliary muscle - Aqueous humor	 α1: Radial (pupillary dilator) m. contract. {**Mydriasis**} β: Ciliary muscle [Relaxes] β: Ciliary muscle Relaxes = **↑Aqueous**	M3: Circular (pupillary constrictor) m. Con. {**Miosis**} Ciliary muscle [Contracts] Ciliary muscle Relaxes = **↓Aqueous**
Heart	Affect β1 (Mainly): ↑ Automaticity (HR) ↑ Conduction velocity ↑ Contractility	Affect M2 (Mainly): ↓↓↓ Automaticity (HR) ↓ Conduction velocity ↓ Contractility??? Not very effective
Blood vessels	α1: Skin & GIT vessels [**Vasoconstriction**] β2: Skeletal m. vessels [**Vasodilation**]	M3: Causing release of NO [**Vasodilation**]
Lungs	Affect β2: Bronchodilation ↓ Bronchial secretion	Affect M3: Bronchoconstriction ↑ Bronchial secretion
GIT	β2: ↓ Motility.	M3: ↑ Motility
Sphincters	α1: Contracts	M3: Relaxes
Urinary Bladder	β2: Relaxation of bladder detrusor m. {**Urine retention**}	M3: Contraction of bladder detrusor m. {**↑Urination**}
Metabolic functions	Liver: 1. Gluconeogenesis: β2 2. Glycogenolysis: β2 Fat cells: Lipolysis: β3 Kidney: ↑Renin release: β1	Normal level Kidney: ↓Renin release: α1
Secretions	α2: Inhibits	M3: Increases
Thermoregulatory sweat glands	M: Increases	---
Pilomotor smooth m.	α1: Contracts	---
Uterus	β2: Relaxation of Uterus	---
Penis	α: Ejaculation	M: Erection

Receptor type, Effect, important to know.

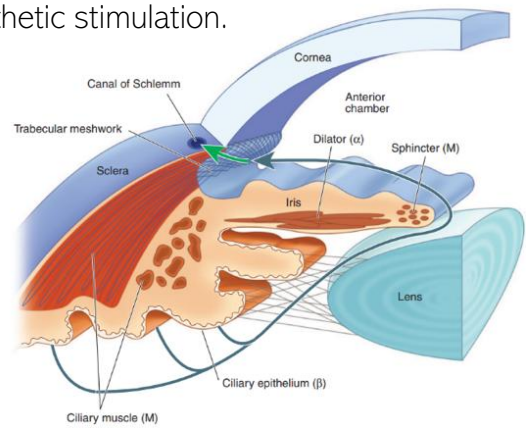
☒ **Notes:**

- The Sympathetic is the main drive of changing blood diameter; due to absence of PSNS innervation
- Eye anatomy:
  - The pupil, contains muscles:





- The ciliary body:
  - ➔ The ciliary muscle: Controls accommodation.
  - ➔ The ciliary epithelium: Aqueous humor secretion.
    - ❖ Aqueous humor:
      - ⇨ Maintains the eye shape & integrity & IOP: 15-20mmHg.
      - ⇨ IOP ↑ in Sympathetic stimulation & ↓ in Parasympathetic stimulation.
      - ⇨ Secreted from: ciliary epithelium.
      - ⇨ Drained by: canal of Schlemm.



- Glaucoma (**المي الزرقاء في العين**):
  - Definition: increase in IOP.
  - Pathophysiology:
    - ➔ ↑ Synthesis of Aqueous humor.
    - ➔ ↓ Drainage of Aqueous humor.
  - Complications: Blindness.
  - Treatment: by ↓ IOP.
    - ➔ Drug groups used: Parasympathomimetic & Sympatholytic.

ANS receptors

- The ANS receptors include: [1]cholinoceptors, [2]adrenoceptors, and [3]dopamine receptors,
- **Cholinoceptors (Cholinergic receptors).**
  - These receptors respond to acetylcholine and its analogs.
  - All types of cholinergic receptors have the same affinity toward Ach.
  - They are subdivided into:
    - ➔ Muscarinic receptors
      - ❖ G-protein coupled receptors.
      - ❖ They respond to muscarine (an alkaloid) as well as to acetylcholine.
      - ❖ The effect of their activation equals parasympathetic nerve stimulation.
      - ❖ They are located primarily on the [1]heart, [2]vascular endothelium, [3]smooth muscle, [4]presynaptic nerve terminals, and [5]exocrine glands.
      - ❖ M1,3,5 their receptors are Gq-Coupled & M2,4 their receptors are Gi-Coupled.

Receptor	Location	Mechanism	Major Functions
M_1	Nerve endings	G_q-coupled	↑ IP_3, DAG cascade
M_2	Heart, some nerve endings	G_i-coupled	↓ cAMP, activates K^+ channels
M_3	Effector cells: smooth muscle, glands, endothelium	G_q-coupled	↑ IP_3, DAG cascade
N_N	ANS ganglia	Na^+-K^+ ion channel	Depolarizes, evokes action potential
N_M	Neuromuscular end plate	Na^+-K^+ ion channel	Depolarizes, evokes action potential
M_4	———	G_i-coupled	
M_5	———	G_q-coupled	

(Not in Ganglia)

    - ➔ Nicotinic receptors
      - ❖ Found in ganglia (N_n) and in skeletal muscle end plates (N_m).
      - ❖ These receptors are located on Na+-K+ ion channels.
      - ❖ Respond to acetylcholine and nicotine, by opening the channel.

- **Adrenoceptors (adrenergic receptors).**
  - G-protein coupled receptors.
  - Adrenoceptors are divided into:
    - ➔ Alpha receptors
      - ❖ Located on vascular smooth muscle, presynaptic nerve terminals, blood platelets, fat cells (lipocytes), and neurons in the brain.
      - ❖ Further divided into: α1 and α2.
      - ❖ These 2 subtypes constitute different families and use different G-coupling proteins.

Receptor	Location	G Protein	Second Messenger	Major Functions
Alpha$_1$ (α_1)	Effector tissues: smooth muscle, glands	G_q	↑ IP_3, DAG	↑ Ca^{2+}, causes contraction, secretion
Alpha$_2$ (α_2)	Nerve endings, some smooth muscle Platlets → Aggregation	G_i	↓ cAMP	↓ Transmitter release (nerves), causes contraction (muscle)
Beta$_1$ (β_1)	Cardiac muscle, juxtaglomerular apparatus	G_s	↑ cAMP	↑ Heart rate, ↑ force; ↑ renin release
Beta$_2$ (β_2)	Smooth muscle, liver, heart	G_s	↑ cAMP	Relax smooth muscle; ↑ glycogenolysis; ↑ heart rate, force
Beta$_3$ (β_3)	Adipose cells	G_s	↑ cAMP	↑ Lipolysis
Dopamine$_1$ (D_1)	Smooth muscle	G_s	↑ cAMP	Relax renal vascular smooth muscle

    - ➔ Beta receptors:
      - ❖ Located on most types of smooth muscle, cardiac muscle, some presynaptic nerve terminals, and lipocytes.
      - ❖ Divided into 3 major subtypes, β1, β2, and β3.
      - ❖ These subtypes are rather similar and use the same G-coupling protein.

- **Dopamine Receptors**
  - A subclass of adrenoceptors but with rather different distribution and function.
  - They are important in the renal and splanchnic vessels and in the brain.
  - Although at least 5 subtypes exist:
    - ➔ D1 subtype appears to be the most important one on peripheral effector cells.
    - ➔ D2 receptors are found on presynaptic nerve terminals.
    - ➔ D1, D2, and other types of dopamine receptors also occur in the CNS.

- **NONADRENERGIC, NONCHOLINERGIC (NANC) TRANSMISSION**
  - Some nerve fibers don't has any feature of either cholinergic or adrenergic fibers.

Neurotransmitter	
ATP	From motor fibers in bronchi, gastrointestinal tract, and urinary tract
Nitric oxide (NO)	Not stored but is synthesized on demand.
Substance P from Sensory fibers	Stored in and released from the fiber terminals.

Peptidergic (peptides).

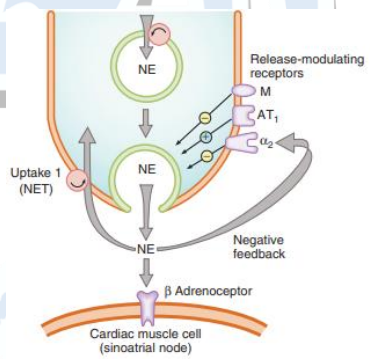
INTEGRATION OF AUTONOMIC FUNCTION

- Central integration: by CNS.

- Systemic Reflexes: The control of blood pressure as example.
  - To maintain mean arterial blood pressure at normal level, baroreceptor reflex & RAAS work.
    - ➔ Any deviation from this "set point" causes a change in ANS activity and RAAS.
      - ❖ Decrease in blood pressure results in:
        - ⇨ Increased SNS discharge:
          - ■ Increase of peripheral vascular resistance, venous tone, heart rate, cardiac force.
          - ■ This response can be blocked with ganglion-blocking drugs (hexamethonium).
        - ⇨ Increased renin release:
          - ■ Increase Aldosterone → retention of salt and water.
          - ■ Increase Angiotensin II → Increase of peripheral vascular resistance.

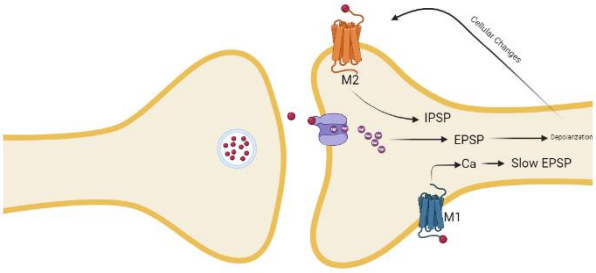
  - These compensatory responses may overcome some of the actions of drugs.
    - ➔ Chronic treatment of hypertension with a vasodilator (hydralazine):
      - ❖ It will be unsuccessful if compensatory mechanisms are not prevented; the body will adapt.

- Local integration:
  - Negative feedback mechanism.
    - ➔ Presynaptic receptors **(Auto-receptors)**
      - ❖ Found on presynaptic neuronal membrane.
      - ❖ Inhibits the NTs release by negative feedback.
      - ❖ Types: **α**2 (adrenergic control), M2 (cholinergic control)



  - Heteroreceptors:
    - ➔ At Adrenergic nerve terminals for: acetylcholine, histamine, serotonin, prostaglandins, peptides, and others.
    - ➔ AT1R: Angiotensin I Receptors,
      - ❖ Stimulates NE release thus increase vasoconstriction,
      - ❖ Thus, Angiotensin is a potent vasoconstrictor.

  - Postsynaptic modulatory receptors:
    - ➔ M1 and M2 muscarinic receptors, that found in ganglionic synapses, where nicotinic transmission is primary.
    - ➔ These receptors may facilitate or inhibit transmission by evoking:
      - ❖ Slow excitatory or inhibitory postsynaptic potentials (EPSPs or IPSPs)



QUESTIONS

1. A 3-year-old child has been admitted to the emergency department having swallowed the contents of 2 bottles of a nasal decongestant. The active ingredient of the medication is a potent, selective **α**-adrenoceptor agonist drug. Which of the following is a sign of **α**-receptor activation that may occur in this patient?
   (A) Bronchodilation
   (B) Cardiac acceleration (tachycardia)
   (C) Pupillary dilation (mydriasis)
   (D) Renin release from the kidneys
   (E) Vasodilation of the blood vessels of the skin

Answer: C

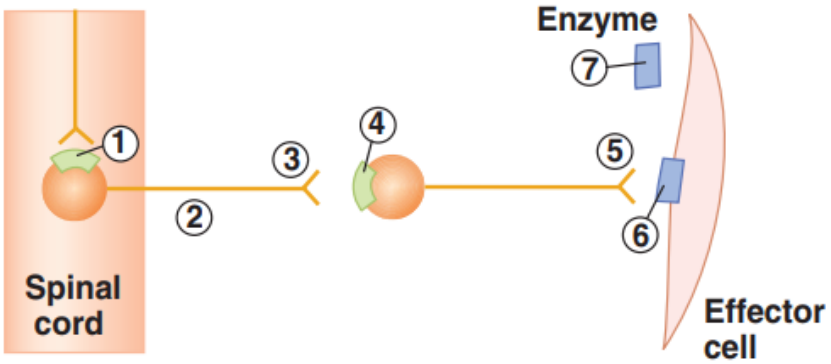
2. Mr Green is a 60-year-old man with poorly controlled hypertension of 170/110 mm Hg. He is to receive minoxidil. Minoxidil is a powerful arteriolar vasodilator that does not act on autonomic receptors. Which of the following effects will be observed if no other drugs are used?
   (A) Tachycardia and increased cardiac contractility
   (B) Tachycardia and decreased cardiac output
   (C) Decreased mean arterial pressure and decreased cardiac contractility
   (D) Decreased mean arterial pressure and increased salt and water excretion by the kidney
   (E) No change in mean arterial pressure and decreased cardiac contractility.

Answer: A

3. Full activation of the parasympathetic nervous system is likely to produce which of the following effects?
   (A) Bronchodilation
   (B) Decreased intestinal motility
   (C) Increased thermoregulatory sweating
   (D) Increased pupillary constrictor tone (miosis)
   (E) Increased heart rate (tachycardia)

Answer: D

For these questions, use the accompanying diagram. Assume that the diagram can represent either the sympathetic or the parasympathetic system.



Answer: C

Answer: C

4. Assuming the structure is part of the thoracolumbar system, norepinephrine acts at which of the following sites in the diagram?
   (A) Sites 1 and 2
   (B) Sites 3 and 4
   (C) Sites 5 and 6

5. If the effector cell in the diagram is a pupillary constrictor smooth muscle cell, which of the following receptor types is denoted by structure 6?
   (A) Alpha1 adrenoceptor
   (B) Beta2 adrenoceptor
   (C) M3 cholinoceptor
   (D) Ng cholinoceptor

6. Nicotinic receptor sites do not include which one of the following sites?
   (A) Bronchial smooth muscle
   (B) Adrenal medullary cells
   (C) Parasympathetic ganglia
   (D) Skeletal muscle end plates
   (E) Sympathetic ganglia

Answer: A

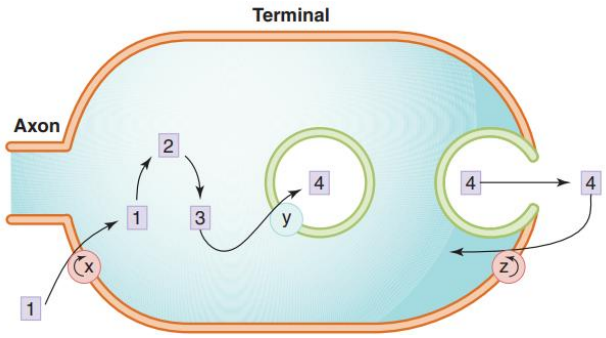
7. Several children at a summer camp were hospitalized with symptoms thought to be due to ingestion of food containing botulinum toxin. Which one of the following signs or symptoms is consistent with the diagnosis of botulinum poisoning?
   (A) Bronchospasm
   (B) Cycloplegia
   (C) Diarrhea
   (D) Skeletal muscle spasms
   (E) Hyperventilation

Answer: B

8. Which one of the following is the primary neurotransmitter agent normally released in the sinoatrial node of the heart in response to a blood pressure increase?
   (A) Acetylcholine
   (B) Dopamine
   (C) Epinephrine
   (D) Glutamate
   (E) Norepinephrine

Answer: A

Assume that the diagram below represents a sympathetic postganglionic nerve ending.



9. Which of the following blocks the carrier represented by "z" in the diagram?
   (A) Amphetamine
   (B) Botulinum toxin
   (C) Cocaine
   (D) Hemicholinium
   (E) Reserpine

Answer: C

10. Which of the following inhibits the carrier denoted "y" in the diagram?
   (A) Cocaine
   (B) Dopamine
   (C) Hemicholinium
   (D) Reserpine
   (E) Vesamicol

Answer: D

When you complete this chapter, you should be able to:

- Describe the steps in the synthesis, storage, release, and termination of action of the major NTs.
- Name drugs affect the previous steps.
- Name 2 co-transmitter substances.
- Name the major types & subtypes of autonomic receptors and the tissues in which they are found.
- Describe the organ system effects of stimulation of the parasympathetic and sympathetic systems.
- List the determinants of blood pressure and describe the baroreceptor reflex response for the following perturbations:
  - Blood loss, administration of a vasodilator or vasoconstrictor, cardiac stimulant & depressant.

حبُّ السلامةِ يُثني همَّ صاحبِه
عن المعالي ويُغري المرءَ بالكَسَلِ