10

Pharmacology

Doctor 2018 | Medicine | JU

◉ Sheet ○ Slides

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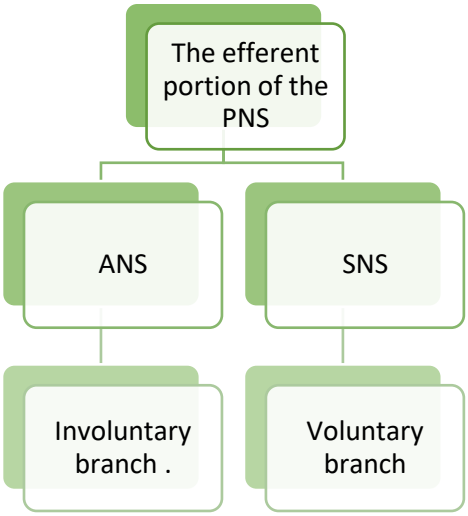
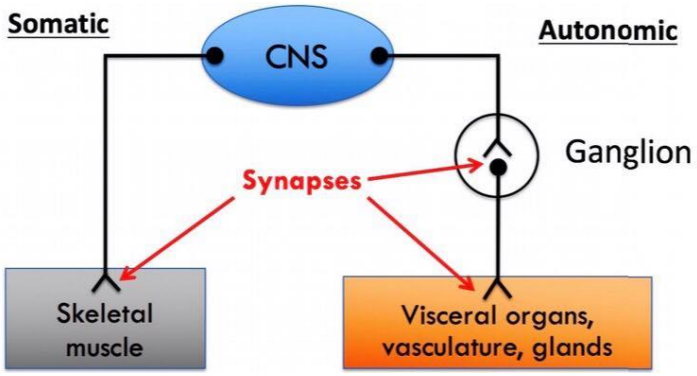
The nervous system is divided into:



- ✓ **CNS**: the brain and spinal cord
- ✓ **PNS:** The motor (efferent) portion of PNS is further divided into: Autonomic nervous system ***(ANS)*** and Somatic nervous system. The autonomic nervous system (ANS) is largely independent **(autonomous),** its activities are **NOT** under direct **conscious control**.



Autonomic nervous system has three subdivisions:

1- **Sympathetic nervous system (SANS).**
2- **Parasympathetic nervous system (PANS).**
3- **Enteric nervous system (ENS).**

- ✓ The **enteric nervous system (ENS)** is one of the main divisions of the **autonomic nervous system (ANS)** and consists of a mesh-like system of neurons that governs the function of the **gastrointestinal tract**.
- ✓ Many **transmitter** and **neuromodulator** substances have been identified in the ENS.
- ✓ The enteric nervous system functions are modulated by the **sympathetic** and **parasympathetic** systems.

- ✓ **ANS** neurons are classified as either **cholinergic** or **adrenergic** neurons based upon the **neurotransmitter released**.

✓ **An autonomic nerve pathway consists of a two-neuron chain:**

Each autonomic nerve pathway extending from the CNS to an innervated organ is a two-neuron chain (except to the adrenal medulla),the cell body of the first neuron is located in the CNS .The axon of the first neuron, the **Preganglionic neuron**, synapses with the cell body of the second neuron, which lies within a **ganglion**.(recall that a ganglion is a cluster of neuronal cell bodies outside the CNS). Whereas the axon of second neuron, the **Postganglionic neuron**, innervates the effector organ.

✓ The following table summarizes the major differences between sympathetic and parasympathetic nerve fibers of the ANS:

	SANS	PANS
Origin	**Thoracolumbar**. Sympathetic nerve fibers originate in the **thoracic** and **lumbar** regions of the spinal cord (**T1-L2**).	**Craniosacral.** Parasympathetic preganglionic fibers originate from the **cranial** and **sacral** areas of the CNS.
Preganglionic fibers	Sympathetic preganglionic fibers are **very short**, synapsing with cell bodies of postganglionic neurons within ganglia that lie in a **sympathetic ganglion chain (sympathetic trunk or paravertebral ganglia)** located along either side of the spinal cord.	**Long preganglionic** fibers, because they do not end until they reach a terminal ganglion that lies **in** or **near** the effector organs.
Postganglionic fibers	**Long postganglionic** fibers originate in the ganglion chain and end on the effector organ.	**Very short postganglionic** fibers end on the cells of an organ itself.

✓ Sympathetic and parasympathetic preganglionic fibers release the same neurotransmitter, **acetylcholine (Ach)**, but the postganglionic endings of these two systems release different neurotransmitters. Parasympathetic postganglionic fibers release **acetylcholine**. Accordingly, they along with all **autonomic preganglionic** fibers are called **cholinergic fibers**. In contrast, most **sympathetic postganglionic** fibers are called **adrenergic fibers** because they release **norepinephrine**. An exception to sympathetic secretions is **sweat glands**

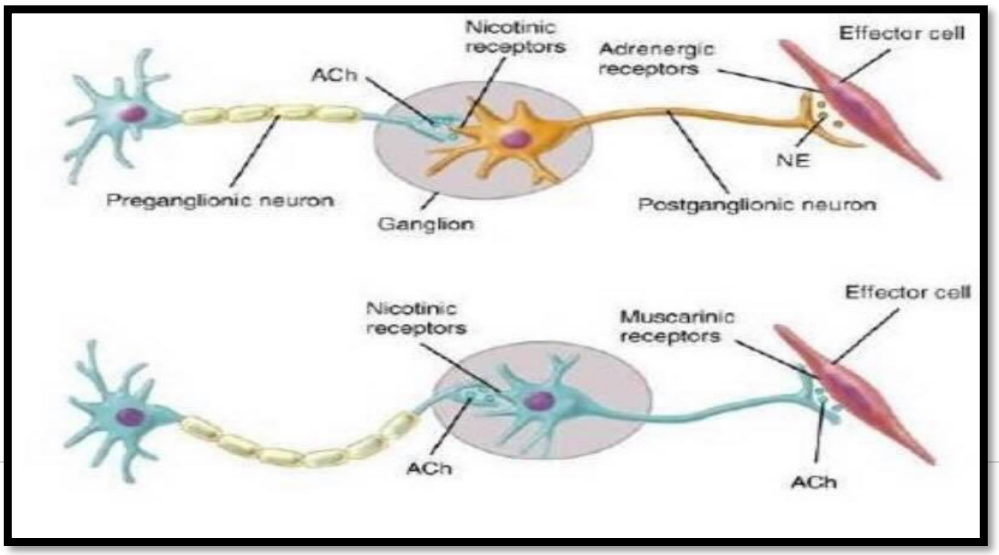
which are innervated only by sympathetic nerves, but the postganglionic fibers of these nerves are unusual because they secrete **acetyl choline** rather than **norepinephrine**.

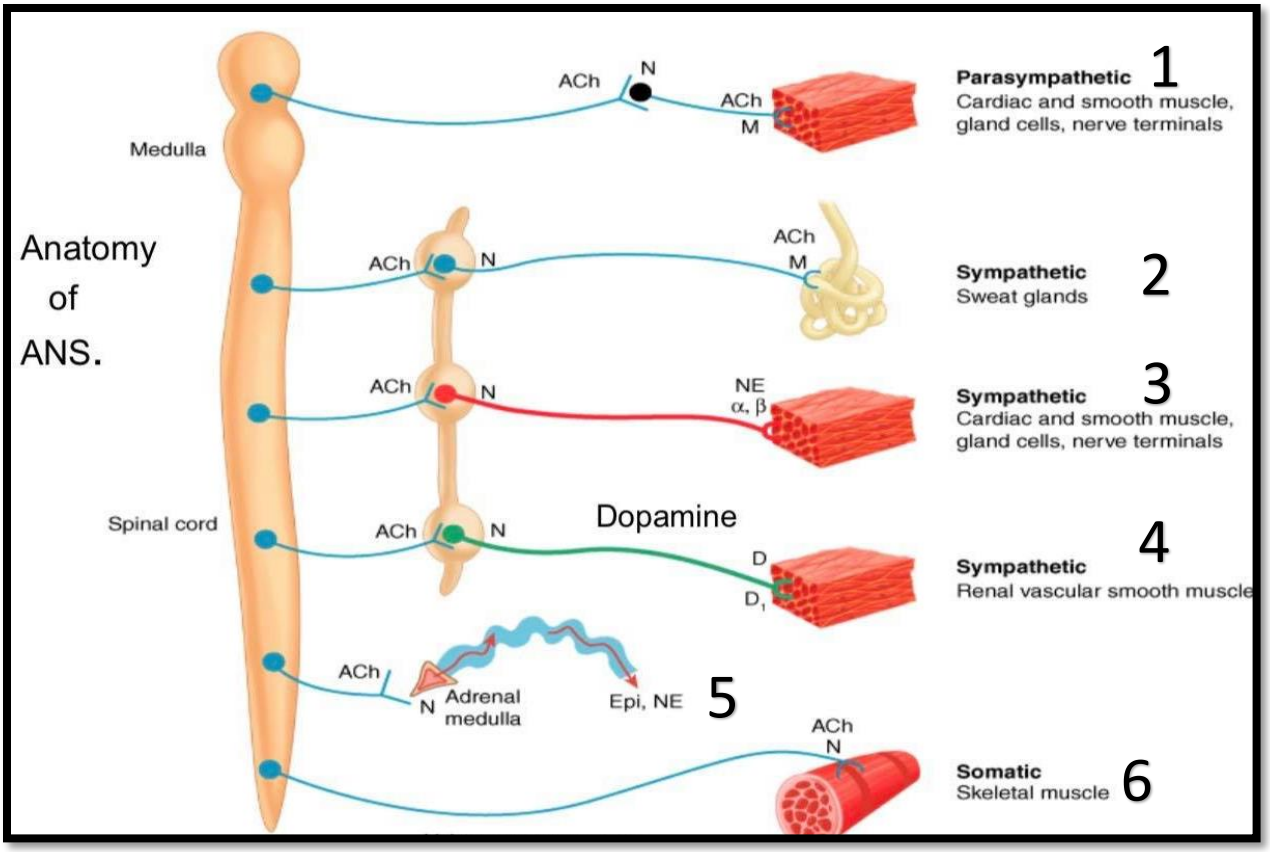
- ✓ Cholinergic and adrenergic receptors are so called based upon the **NT** that activates them.
- ✓ Cholinergic receptors are activated by the neurotransmitter Acetylcholine, two types of cholinergic receptors are identified on the basis of their response to particular drugs:

1- **Nicotinic receptors** are activated by the tobacco plant derivative nicotine.
2- **Muscarinic receptors** are activated by the mushroom poison muscarine.

Nicotinic receptors	Are found on the postganglionic cell bodies in all autonomic ganglia, these receptors respond to **Ach** released from both sympathetic and parasympathetic fibers. Muscarine has **NO** influence on these receptors (does not activate them).
Muscarinic receptors	Are found on all effector cell membranes, they bind with **Ach** released from parasympathetic postganglionic fibers. Muscarine activate these receptors, it is more active, but also more toxic than Ach.
Adrenergic receptors	The two major classes of adrenergic receptors for **norepinephrine** and **epinephrine** are **alpha (α)** and **beta (β)** receptors, which are further subclassified into **α1,α2,β1,β2**, and **β3** receptors. These various types are distinctly distributed among the effector organs

- ✓ **Adrenergic:**
- ✓ **Cholinergic:**





1. Usual parasympathetic action with nicotinic receptors at the autonomic ganglia and muscarinic receptors at the effector cells, both receptors receiving **ACh**.
2. Sweat glands innervated by sympathetic nerves but with both pre and post ganglionic fibers releasing Ach, both receptors are cholinergic, **nicotinic receptors** at the autonomic ganglia and **muscarinic receptors** at the effector cells of sweat glands.
3. Usual sympathetic action with nicotinic receptors at the autonomic ganglia and adrenergic receptors at effector cells receiving Norepinephrine (NE).
4. Unusual sympathetic innervation of the kidney, receptors found in renal vascular smooth muscles receiving Dopamine (**EXTRA:** actually, both dopamine and NE are released from adrenergic postganglionic fibers, remember that Dopamine is a precursor for NE), with **dopamine receptors** at the effector cells.

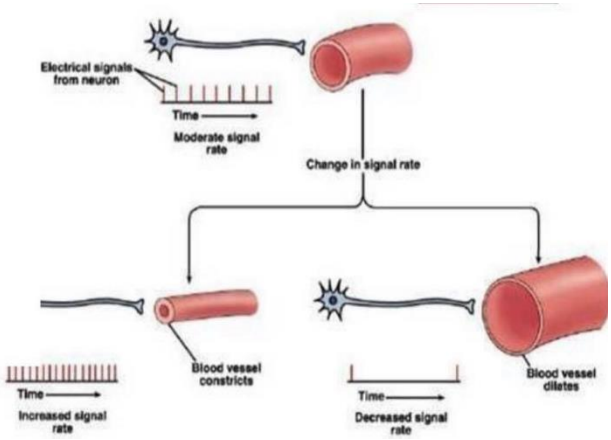
5. The adrenal medulla, a modified sympathetic ganglion, receives sympathetic preganglionic fibers and releases **epinephrine** and **norepinephrine into the blood,** adrenal medulla doesn't give rise to postganglionic neuron it secretes hormones directly into the blood stream, about 20% of the hormonal output is NE and the remaining 80% is the closely related Epinephrine.
6. Motor neurons of the SNS innervating skeletal muscles and releasing **Ach** received by Nicotinic receptors that differ from the ones present at the autonomic ganglia.

- ✓ Parasympathetic stimulation involves only one visceral effector (organ), while One sympathetic preganglionic neuron may have many branches and may synapse with 20 postganglionic neurons. Projection of divergence explains why sympathetic responses can affect many effectors at once.
- ✓ Massive **widespread** discharges take place in the sympathetic system compared to the **localized** discharges of the parasympathetic nervous system, the value of this widespread discharge is clear, considering the circumstances during which this system usually dominates.

The sympathetic and parasympathetic nervous systems dually innervate most visceral organs.

- ✓ Most visceral organs are innervated by both sympathetic and parasympathetic fibers, Innervation of the same organ by both branches of the autonomic nervous system is known as **Dual innervation**.
- ✓ The two divisions of the ANS are usually reciprocally controlled by the hypothalamus, resulting in antagonistic effects.
- ✓ **There are several exceptions to the general rule of dual innervation having only sympathetic innervation,**
    1. **Sweat glands** (as mentioned earlier).
    2. **Adrenal medulla.**
    3. **Innervated blood vessels** (the only blood vessels to receive both sympathetic and parasympathetic fibers are those supplying the penis and tongue).

- ✓ **So how is regulation accomplished?**



By regulating the **tone** of the sympathetic nervous system. Usually both systems are active and supplying a particular organ, this ongoing activity is called **sympathetic** or **parasympathetic tone** or **tonic activity**. Under given circumstances one division can dominate by firing action potentials above the tonic level, coupled with a decrease in the frequency of action potentials generated by the other system below its tonic level. But in case of organs innervated only by sympathetic fibers like blood vessels, regulation is accomplished by increasing or decreasing the firing rate (frequency) above or below the tonic level in these fibers, resulting in vasodilation (lower tone) or vasoconstriction (higher tone).

- ✓ **Hypothalamus** regulates balance (tone) between sympathetic and parasympathetic activity levels.
- ✓ **Parasympathetic nervous system** dominates in quiet, relaxed situations promoting "general housekeeping" activities such as digestion, and basic survival functions. **"REST AND DIGEST",** resulting in **Salivation**, **lacrimation**, **urination**, and **defecation**. While sympathetic nervous system dominates in emergency **"Fight or Flight"** situations, resulting in an increase in skeletal muscular activity. (Increased heart rate, blood flow, breathing) and decreased non-survival activities like food digestion.

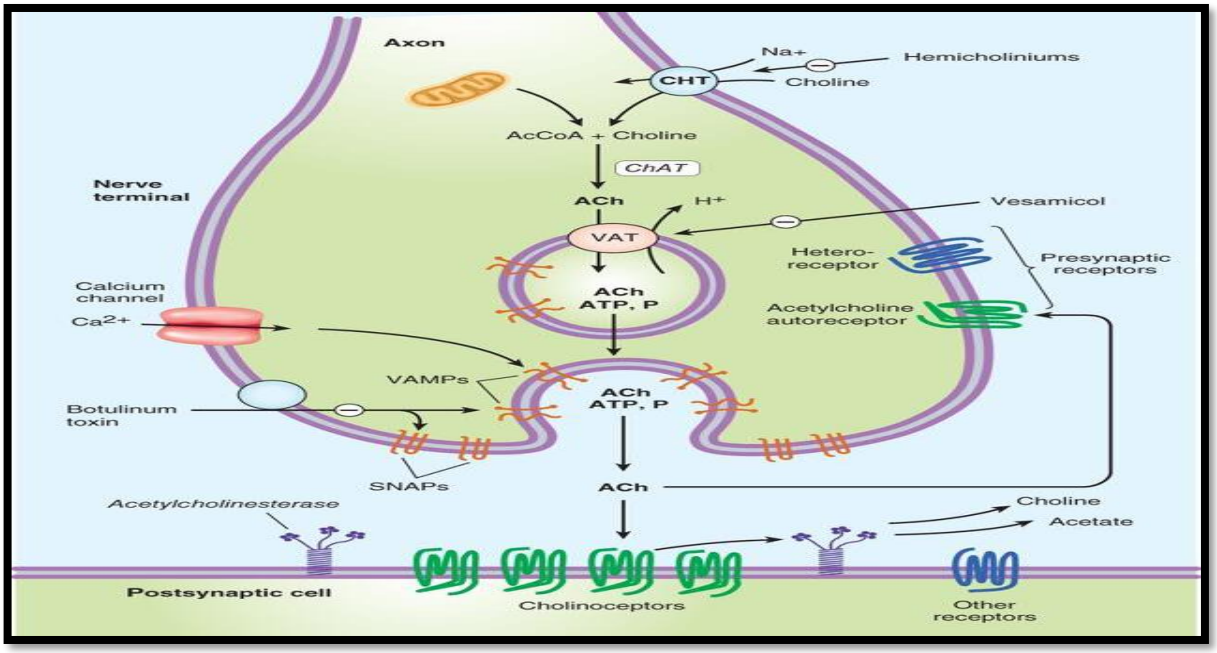
- ✓ **Example of antagonistic control:**
  An increase in sympathetic stimulation causes HR to **increase** whereas an increase in parasympathetic stimulation causes HR to **decrease**.

- **Cholinergic transmission:**
  - ✓ Transmission involves:
    1. Synthesis of Ach.
    2. Storage.
    3. Release.
    4. Interaction (binding) of Ach with post synaptic receptors.
    5. Degradation of Ach in the synaptic cleft.
    6. Recycling of Choline.
- The following table describes each single step, and the drugs that can inhibit its action:

Step	Mechanism of action	Drugs inhibiting this action
1.synthesis	Choline acetyltransferase (ChAT) catalyzes the reaction of choline with acetyl CoA to form Ach in the cytosol.	None.
2.storage	ACh is packaged and stored into presynaptic vesicles, the transporter required for this step is called vesicle associated transporter VAT, storing up to 50000 molecules of Ach along with ATP and protein (P) (cotransmission)	**Vesamicol** is a drug that inhibits the storage of Ach in vesicles causing failure of transmission, because ACh can be produced in large amounts in the cytosol and still not released without being stored in vesicles.
3.release	Releasing is a [Ca^{+2} dependent] exocytosis process, when action potential arrives the nerve ending, voltage gated calcium channels open increasing Ca+2 cytosolic concentration (influx), this promotes the fusion of synaptic vesicles with the cell membrane releasing Ach into the synaptic space.	Vesicles are provided with **vesicle-associated membrane proteins (VAMPs)** which participate in triggering the release of transmitter, the release site on the membrane contains **synaptosomal nerve-associated proteins (SNAPs)**, which interact with VAMPs. VAMPs and SNAPs are called fusion proteins. This step can be blocked by **botulinum toxin** that interferes with VAMPS and SNAPS action, vesicles cannot adhere with the right position and no exocytosis takes place.

4.interaction with receptors	Released Ach binds to **postsynaptic receptors** (either nicotinic or muscarinic) on the target cell or to **presynaptic receptors** on the membrane of the neuron that released Ach (Autoreceptors that modulate the release of ACh)	Not mentioned.
5.degradation of Ach	The signal is rapidly terminated by the enzymatic activity of **acetylcholinesterase (AChE)** that cleaves Ach to choline and acetate in the synaptic cleft.	Many drugs can inhibit this enzymatic activity but none of these drugs were mentioned during the lecture.
6.Recycling of choline	Choline is transported into the presynaptic nerve terminal by a sodium-dependent **choline transporter (CHT).**	Choline transporter can be inhibited by **hemicholinium** drugs.

- ✓ Heteroreceptors respond to neurotransmitters released from adjacent neurons or cells; they are opposite to autoreceptors, which are sensitive only to neurotransmitters or hormones released by the cell in whose membrane they are embedded, Ach in the above-mentioned case.



Adrenergic transmission:

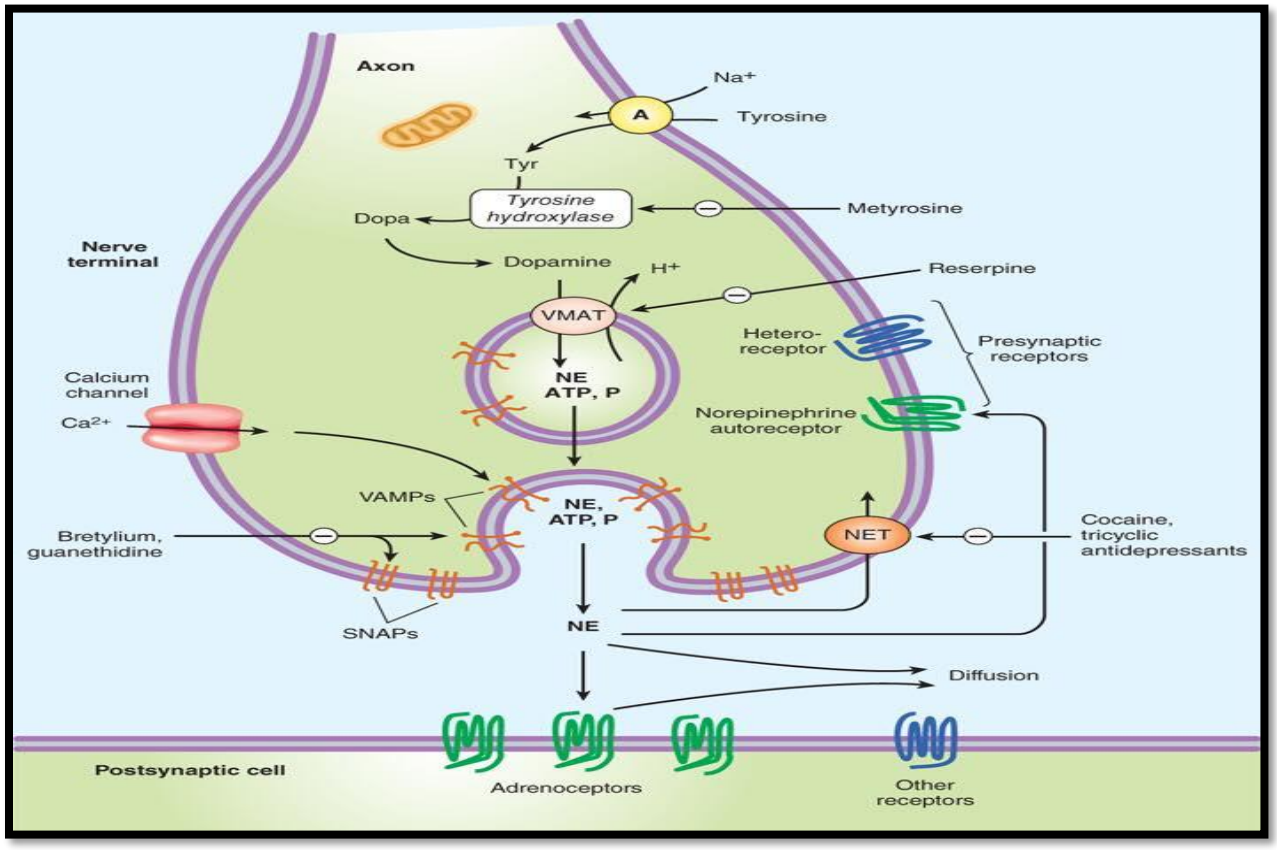
Adrenergic transmission is quite similar to the cholinergic transmission but a bit more complicated, involving the following steps:

1. Synthesis of NE.
2. Storage.
3. Release.
4. Receptor binding.
5. Removal of NE from the synaptic cleft.

✓ The following table summarizes the whole process, and drugs associated with inhibition:

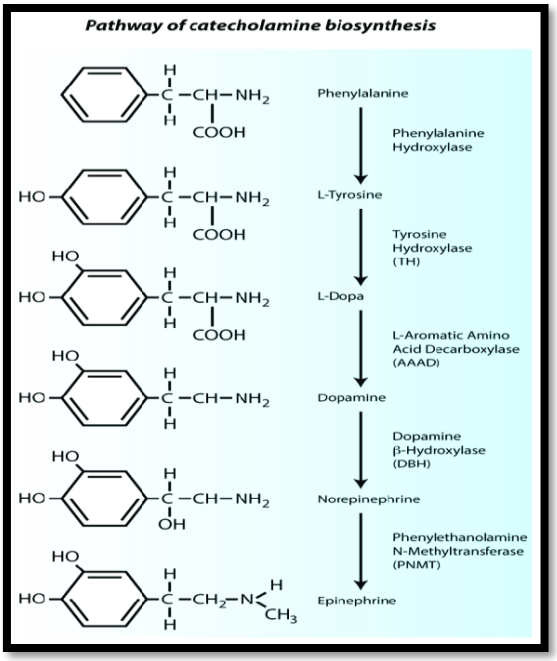
Step	Mechanism of action	Drugs inhibiting this action
1.Synthesis	**Tyrosine** is transported by a carrier into the adrenergic neuron, where it is hydroxylated and converted to **DOPA** by **tyrosine hydroxylase**, this is the **RDS** in the formation of **NE**, DOPA is then decarboxylated by **DOPA Decarboxylase** to form **Dopamine**.	**Metyrosine** inhibits the enzymatic activity of **tyrosine hydroxylase.**
2.Storage	Dopamine is then transported into synaptic vesicles by an amine transporter **(vesicular monoamine transporter, VMAT),** next dopamine is hydroxylated to form norepinephrine by the enzyme **Dopamine hydroxylase**, ATP and protein (P) are stored along with NE	VMAT carrier system is blocked by **Reserpine**.
3.release	Releasing is again a [Ca^{+2} dependent] exocytosis process, when action potential arrives to the nerve ending, voltage gated calcium channels open increasing Ca^{+2} cytosolic concentration (influx), this promotes the fusion of synaptic vesicles with the cell membrane releasing NE into the synaptic space.	Release can be blocked by drugs such as **guanethidine** and **bretylium**.

4.receptor binding	NE binds to postsynaptic adrenergic receptors or to presynaptic receptors (autoreceptors that modulate the release of NE).	Drugs are not mentioned during the lecture, but many adrenergic antagonists do exist.
5.removal	NE may: 1. Diffuse out of the synaptic cleft. 2. Be metabolized by enzymes (will be mentioned later on). 3. Undergo reuptake back into the neuron by **norepinephrine transporter (NET).**	norepinephrine transporter (NET) can be blocked by **cocaine** and certain **antidepressants**.



✓ **Synthesis of Norepinephrine (brief summary):**

1. Tyrosine uptake by a carrier.
2. Tyrosine Hydroxylase is the rate-limiting enzyme, Subject to end product inhibition, this enzyme adds a hydroxyl group to tyrosine (phenol) converting it to DOPA (Catechol).
3. Dopa is decarboxylated by DOPA decarboxylase producing Dopamine.
4. Dopamine is transported into Storage vesicle by VMAT (vesicular monoamine transporter) and converted to NE.



✓ Methylation of NE produces epinephrine in the adrenal medulla, this reaction is catalyzed by the enzyme phenylethanolamine **N-methyltransferase** (PNMT) which utilizes S-adenosyl methionine (SAMe) as the methyl donor.

NOTES:

✓ NE is stored in vesicles bound to ATP (4:1) + protein.

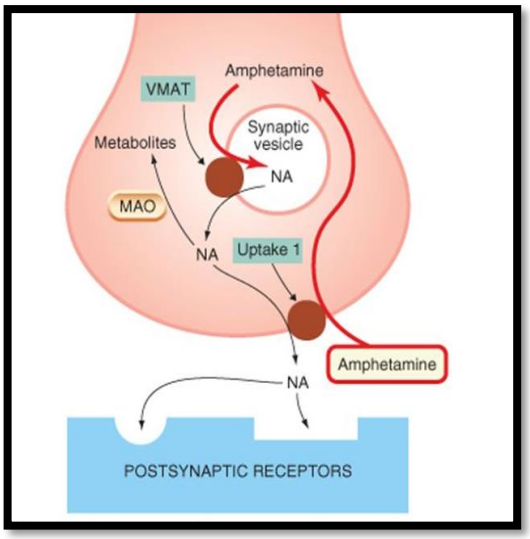
✓ In addition to norepinephrine, (ATP), dopamine-β-hydroxylase, and peptide cotransmitters are simultaneously released from the same vesicles.

✓ ω–Conotoxin GVIA, Toxin of marine snails blocks Ca^{+2} channels and reduce NE and Ach release.

✓ α–Latrotoxin (Black widow spider venom) acts on vesicles causing explosive release of NE & Ach.

✓ It is mentioned in the slides that Tyrosine is up taken by NET receptor.

Calcium independent release:



- ✓ tyramine, amphetamines, and ephedrine are capable of releasing stored transmitters from noradrenergic nerve endings by a calcium-independent process.
- ✓ Tyramine and amphetamine are transported by NET (NE Transporter) into the neuron then transported by VMAT into the vesicles. They displace NE from the vesicular stores, into the cytoplasm. Ne is transported into the synaptic cleft by reverse transport via NET, they produce an indirect **sympathomimetic effect**.

Metabolism of Catecholamines:

- ✓ NE effects are terminated by neuronal reuptake. 80% of the released NE are transported into the neuron by **MAT (Mono amine Transporter)**.
- ✓ NE is metabolized into inactive metabolites by **Catechol-O-Methyl transferase (COMT)** in the synaptic space, this enzyme transfers methyl group from **S- adenosyl methionine** into the OH group in the meta position of the catechol ring.
- ✓ **Monoamine oxidase (MAO)** in mitochondria produces oxidative deamination of mono amines.
- ✓ **VMA** vanillylmandelic acid is the end product of metabolism, measured in urine for the diagnosis of pheochromocytoma.

Pheochromocytoma is a tumor condition that arise from chromaffin cells of the adrenal glands, overproduction of catecholamines by these tumor cells is observed, excessive catecholamines and their metabolites (VMA) in urine is essential for diagnosis of pheochromocytoma

- **Cholinoceptors:**

  Muscarinic M1: CNS neurons, sympathetic postganglionic neurons, some presynaptic sites.

  Muscarinic M2: Myocardium, smooth muscle, some presynaptic sites; CNS

  Muscarinic M3: Exocrine glands, vessels (smooth muscle and endothelium), CNS.

  Muscarinic M4: CNS neurons.

  Muscarinic M5: CNS neurons.

  Nicotinic NN: Postganglionic neurons, some presynaptic cholinergic terminals.

  Nicotinic NM: Skeletal muscle neuromuscular end plates.

- **Adrenoceptors:**

  Alpha1 (α)1 Postsynaptic, especially smooth muscle. Formation of IP3 and DAG, increased intracellular Ca^{+2} producing smooth muscle contraction.

  Alpha2 (α) Presynaptic adrenergic nerve terminals, platelets, lipocytes, smooth muscle. Inhibits NE release. Inhibition of adenylyl cyclase, decreased cAMP.

  Beta1 (β1) heart, lipocytes, brain, juxtaglomerular apparatus of renal tubules. Stimulation of adenylyl cyclase, increased cAMP.

  Beta2 (β2) smooth muscle & cardiac muscle. Stimulation of adenylyl cyclase and increased cAMP.

  Beta3 (β3) lipocytes; Stimulation of adenylyl cyclase & increased cAMP.

- **Dopamine receptors:**

  D1 (DA 1, D5) Brain, especially smooth muscle of the renal vascular bed. Stimulation of adenylyl cyclase and increased cAMP.

  D2 (DA 2, D3, D4) Brain, especially smooth muscle, presynaptic nerve terminals (D2). Inhibition of adenylyl cyclase, increased potassium conductance.

The end…Good Luck ♥