◉ Sheet ○ Slides

number : 2

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The Autonomic Nervous System

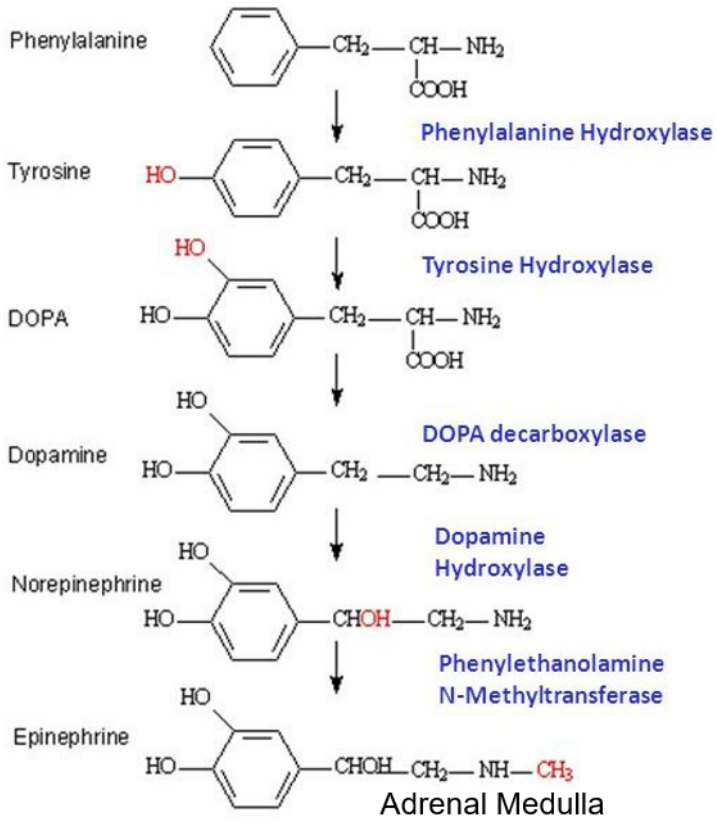
The last thing we covered in the previous lecture was adrenergic transmission. In this sheet, we will go through the synthesis and release of norepinephrine (NE), cholinoceptors, adrenergic receptors….

Synthesis of Norepinephrine

Tyrosine uptake by NET
Tyrosine Hydroxylase is
The rate-limiting enzyme
Subject to end product inhibition

DA is transported into Storage vesicle by VMAT (vesicular monoamine transporter)
and converted to NE

Reserpine inhibits VMAT causing Depletion of CA
Cocaine & Tricyclic antidepressants Inhibit NET.



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•Synthesis of NE start from tyrosine actually that enters ento the neuron, but sometimes it will come from phenylalanine

• tyrosine is converted to l-dopa by tyrosine hydroxylase, it is the most important step and it is the rate limiting step, and tyrosine hydroxylase is the rate limiting enzyme, which means that when it is inhibited, the whole synthesis process stops.

• l-dopa is converted into dopamine by dop decarboxylase (monoamine decarboxylase)

• the third step is hydroxylation of dopamine into norepinephrine by the enzyme dopamine β-hydroxylase that is found inside the vesicles. It add OH group to β-carbon.

• the previous step is the last one in the synthesis of norepinephrine, but in the chromaffin cells of the adrenal medulla there is one further step, which is the synthesis of epinephrine(EP) by methylation of norepinephrine(NE) by the enzyme phenylethanolamine N-methyltransferase(PNMT)

End product inhibition: Tyrosine hydroxylase is the most important enzyme in this synthetic pathway, it is the rate limiting step, so when the enzyme start to work, synthesis start, when it stops, synthesis stops. So the inhibition of this enzyme specifically has a major effect on the pathway. This enzyme is subjected to end product inhibition, so when all the vesicles are full of norepinephrine, norepinephrine inhibit this enzyme.

Storage:

NE is stored in vesicles bound to cAMP (4:1) + protein

Release:

1- Calcium dependent exocytosis.

NE + cAMP + protein + Dopamine-β- hydroxylaes are released.

Release can be blocked by guanethidine and Bretylium.

ω–Conotoxin GVIA (Toxin of marine snails) blocks Ca channels and reduce NE & Ach release.

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

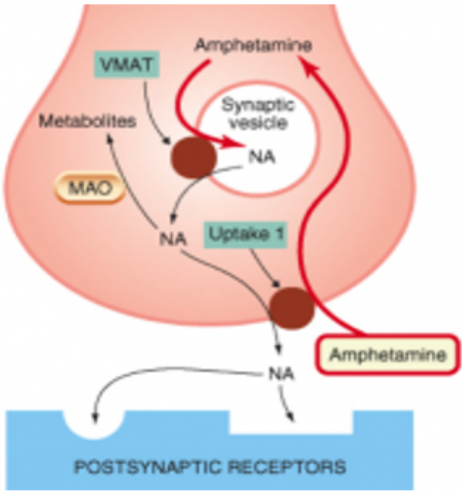
- NE is stored in vesicles bound to cAMP (4 molecules of NE for one molecule of cAMP''4:1'') and protein.
- Release can be blocked by guanethidine or bretylium.
- There are two major types of release, unlike Ach which has only one type:

1. Calcium dependent exocytosis(the major type):
   All the content of vesicle (NE,cAMP,protein,dopamine-β-hydroxylase) are released from the vesicle by exocytosis that requires Ca ions.
   • this release can be blocked by:

- Bretylium & Guanethidine
- ω-Conotoxin GVIA (this toxin is present in marine snails):this toxin can block Ca ion channels, so it reduce or inhibit the release of NE & Ach.
- α-Lactrotoxin (this toxin is present in the black window spider venom and it is 15 times more toxic than the venom of the rattlesnake): acts on vesicles causing explosive release of NE & Ach.

2- Calcium independent release.

Tyramine, amphetamine are transported by NET (NE Transporter) into the neuron then transported by VMAT into the vesicles.



They displaces 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**

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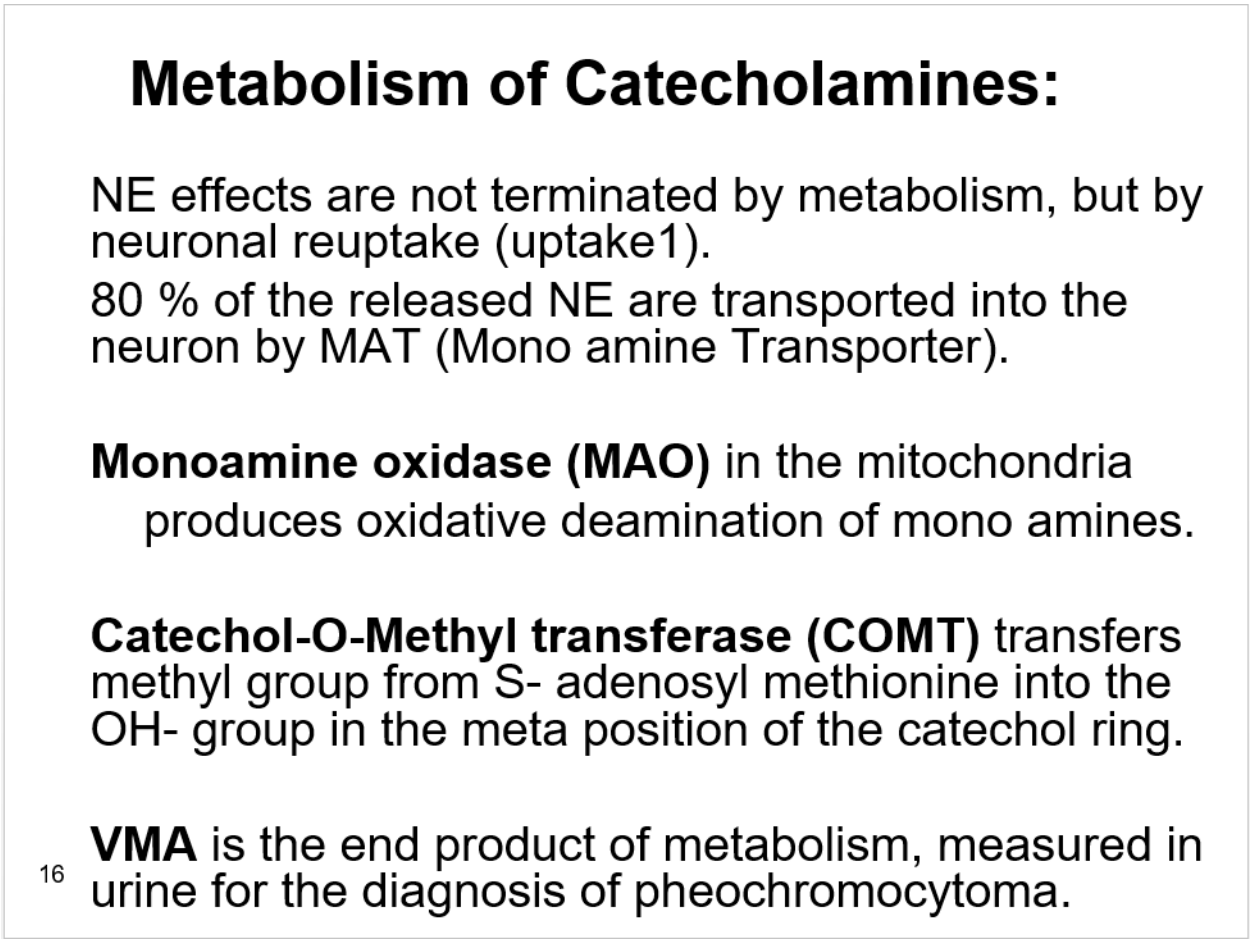
2. <u>Calcium independent release:</u>
   The second mechanism by which NE is released is independent of calcium ions. Other compounds (Tyramine, amphetamine) are responsible for its release. They use the same transporters that NE uses to enter the neuron "NET" (norepinephrine transporter), then transported by VMAT into the vesicles where they displaces NE from these vesicles into the cytoplasm. NE is transported into the synaptic cleft by reverse transport via NET (entry of tyramine to the neuron and exit of NE require the same transporter "NET"). {we said reverse because the normal way is from the outside to the inside}.

- Amphetamine also has a tyramine-like effect: it displaces NE from the storage vesicles. NE is transported to the synapse by **reverse transport** in both cases.

- Tyramine and amphetamine produce an **indirect sympathomimetic effect**. It is *indirect* because they don't stimulate the receptors themselves but cause the release of NE which in turn stimulates the adrenoceptors.



metabolism is not the primary mechanism for termination of action of norepinephrine. Termination of noradrenergic transmission results from two processes: simple diffusion away from the receptor site (with eventual metabolism in the plasma or liver) and 80 % will be reuptaken into the nerve terminal by NET (aka Monoamine transporter "MAT'').

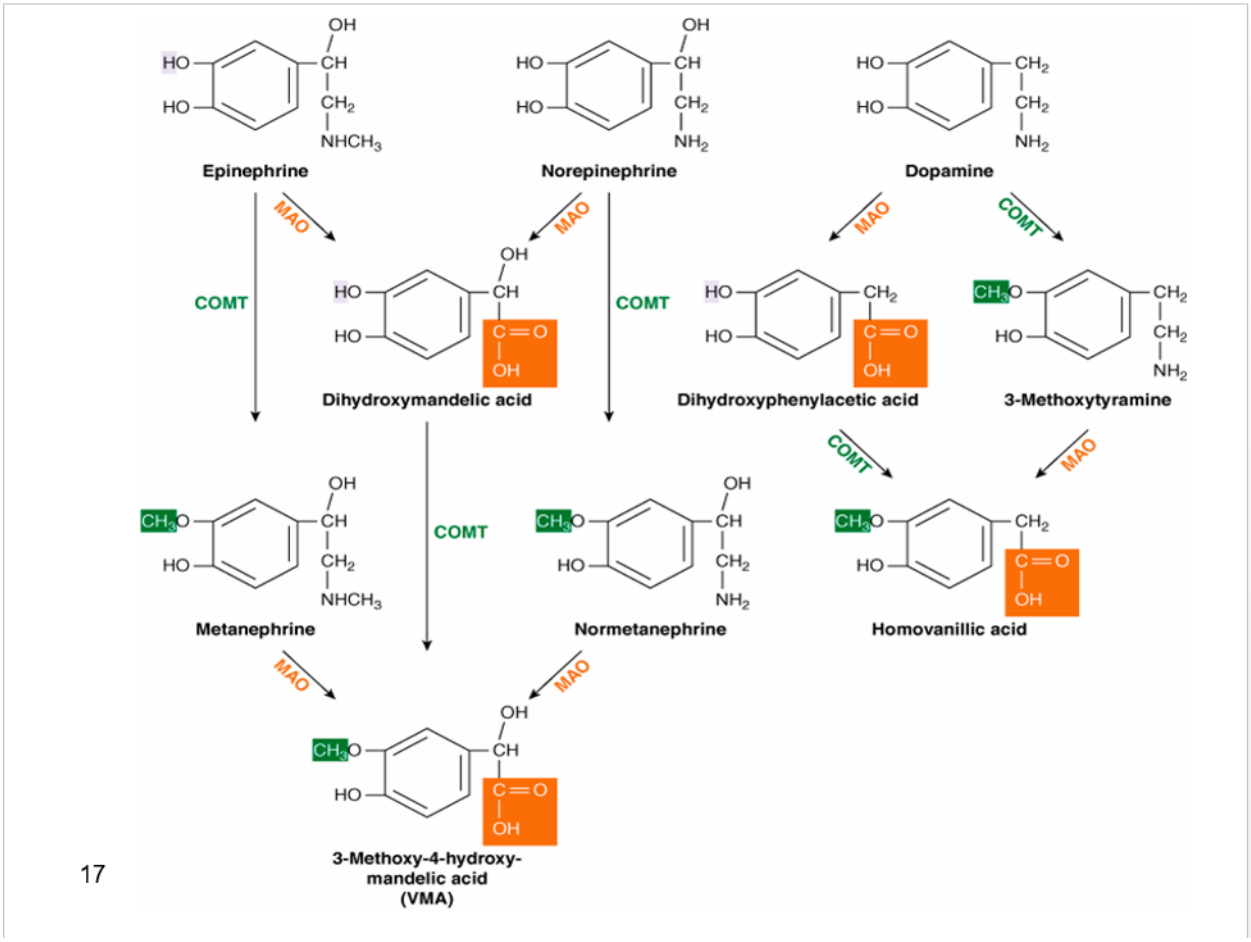
- Two enzymes required for the metabolism of catecholamines are *monoamine oxidase* (MAO) and *catechol-O-methyl transferase* (COMT).

- monoamine oxidase (MAO) : (it is present inside neurons in the mitochondria):when NE is taken up by the neuron, only some of it will be deaminated by MAO(oxidative deamination).

- Catechol-O-methyl transferase (COMT): (it is present outside the neuron): It transfers methyl group from S- adenosyl methionine into the OH- group in the meta position of the catechol ring. So epinephrine (adrenaline) become metanephrine & norepinephrine become normetanephrine.

- Both the previous enzymes produce the same product, which is VAM (Vanillyl mandelic acid), and it is secreted in the urine.
- VMA is viable to diagnose pheochromocytoma which is a cancer (tumor) in the chromaffin cells of adrenal gland causes the production of large amount of epinephrine and norepinephrine resulting in different symptoms, like sudden increase in blood pressure. The diagnosis takes place by testing the urine of a whole day for VMA :{3-5 mg/ day is normal, 15-20 mg/day is a sign of pheochromocytoma}

- Dopamine: the same enzymes act on it, but the difference is in the final product, which is Homovanillic acid instead of VAM



- The slide inserted above shows the pathways involved in the metabolism catecholamines. *It is not to be memorized.*
- <u>Recall:</u> the common product of metabolism of both EP and NE is VMA.
- For dopamine, the final product is homovanillic acid. This is because dopamine doesn't have an –OH group on the meta carbon like EPI and NE.

Cholinergic receptors

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; possibly vagal nerve endings.

Muscarinic M5: Vascular endothelium, especially cerebral vessels; CNS neurons.

Nicotinic NN: Postganglionic neurons, some presynaptic cholinergic terminals.

Nicotinic NM: Skeletal muscle neuromuscular end plates.

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- There are two types of cholinoceptors (cholinergic receptors): muscarinic and nicotinic receptors.

- Muscarinic receptors are so-called because *muscarine* is a selective agonist for these receptors, and nicotinic receptors are so-called because *nicotine* is a selective agonist for them.
- There are 5 subtypes of muscarinic receptors, designated M1-M5. All of them are present in the CNS. However, only M1, M2 and M3 are present in the PNS.
- The M2 muscarinic receptors are located in the heart, where they act to <u>slow</u> the heart rate down to normal sinus rhythm after positive stimulatory actions of the sympathetic nervous system, by slowing the speed of depolarization. They also reduce contractile forces of the atrial cardiac muscle, and reduce conduction velocity of the atrioventricular node (AV node). However, they have no effect on the contractile forces of the ventricular muscle.

- M3 receptors are present in the glands and GI tract and When stimulated, it increases peristalsis (increases the motility of the GI tract).
- M1 receptors are present in presynaptic neurons → modulation of release (autoreceptors). They are also present in the autonomic ganglia in the sympathetic postganglionic neurons(autonomic ganglia is the ganglia between the two neurons of ANS).

  - There are two subtypes of nicotinic receptors: NN (nicotinic neural) receptors and NM (nicotinic muscular) receptors.

- NN receptors are present in the autonomic ganglia.
- NM receptors are present at neuromuscular (motor) end plates. *This type of receptors is only present in skeletal muscles.*

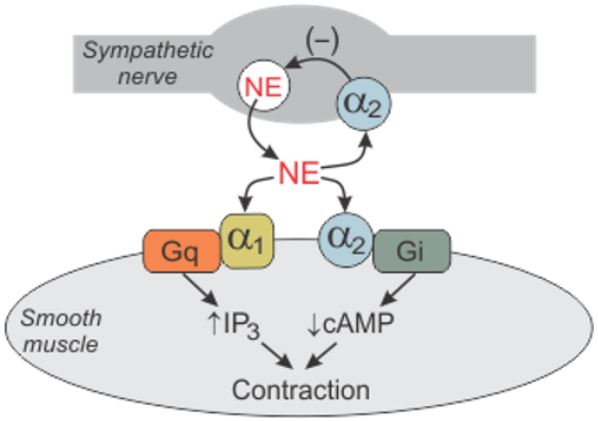
Sympathetic receptors(adrenoceptors)

Adrenoceptors

Alpha1 (α)1

Postsynaptic, especially smooth muscle.

Formation of IP3 and DAG, increased intracellular Ca producing smooth muscle contraction.



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

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❖ **Adrenoceptors(α,β)**

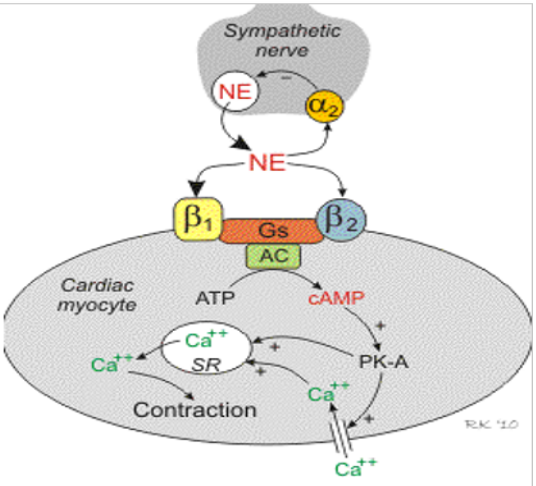
There are two types of α adrenergic receptors(α1,α2) and thre types of β adrenergic receptors(β1,β2,β3)

- α1

- it is postsynaptic (on the tissue not the neuron), especially found on smooth muscles in the walls of blood vessels, where their stimulation causes vasoconstriction. Contraction of smooth muscle is caused by the action of IP_3 (inositol triphosphate) and DAG → increase in cytosolic Ca^{+2} → contraction.

- α2
  - it is present in presynaptic adrenergic nerve terminals.
    **Remember when we talked about autoreceptors that inhibit further release of NE when there is excess amount of NE in the synaptic cleft, they are α2 receptors.
  - it found in: platelets, lipocytes, smooth muscle.
  - it may be found postsynaptic but it doesn't play a major role.
  - inhibits adenylyl cyclase and decreases cAMP "the second messenger.

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

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  - I

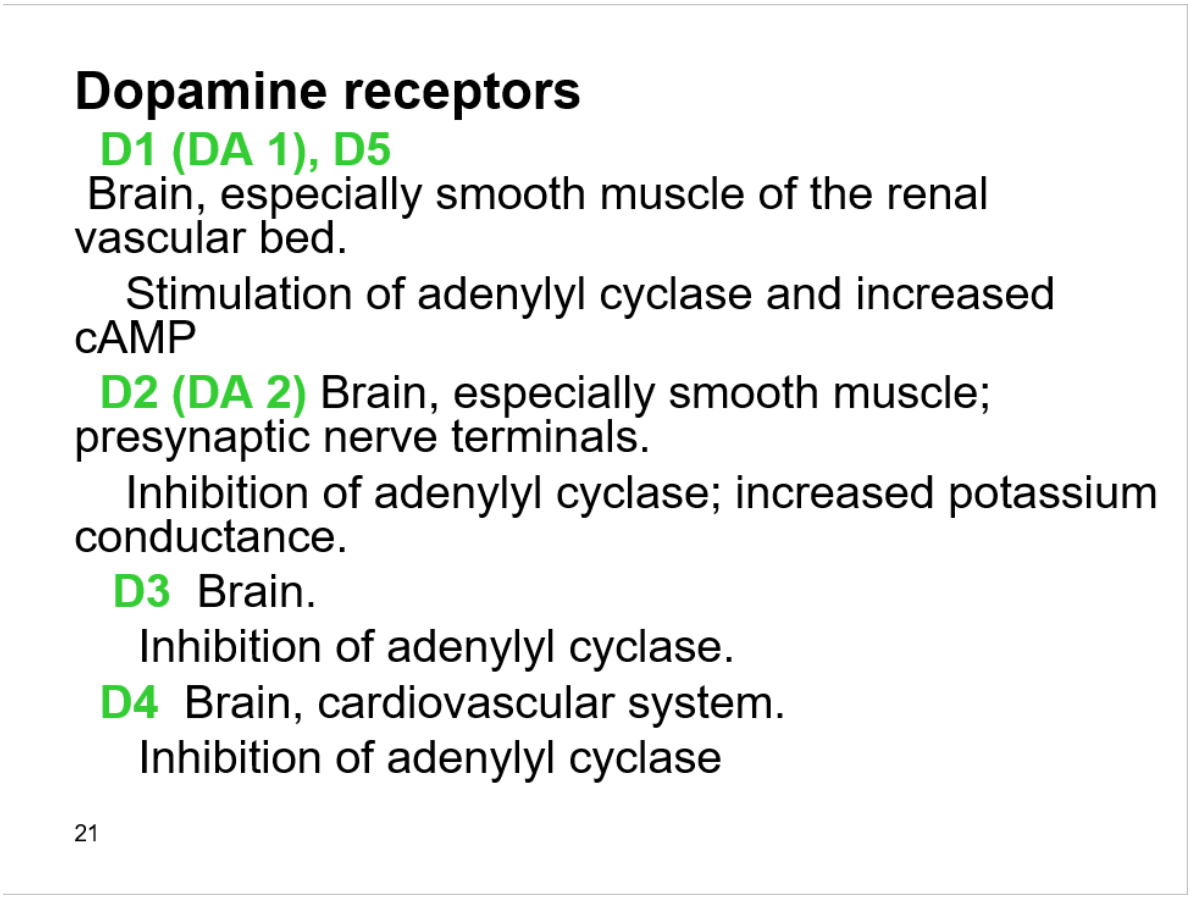
    t is present in the heart and in the kidney
  - When β1 receptors are stimulated in the kidneys, the enzyme *renin* is released. Renin hydrolyses angiotensinogen into

angiotensin I. Angiotensin I is further cleaved by another enzyme into angiotensin II. Angiotensin II has 2 important effects: 1. the constriction of blood vessels (vasoconstriction) and 2. the release of aldosterone from the kidneys. Aldosterone causes the retention of salts and water → elevated blood pressure.

- B1 receptors in the heart: when stimulated → increased heart rate, increased contractility of the ventricles and increased cardiac output.
- β1 receptors are G protein-coupled receptors. They act by stimulating adenylyl cyclase → more cAMP (*second messenger*) → activation of a protein kinase or liberation of Ca^{++} → response.
- Recall: the neurotransmitter is the *first messenger*. It is sent by the brain.

- β2
  - postsynaptic, lungs (bronchi relax to carry more oxygen),blood vessels of the skeletal muscles (dilate to deliver more blood to the muscles in order to contract),smooth muscles of the lungs.
    **Notice that we need more O2 and blood because we are in a fight-or-flight situation.
  - acts by stimulation of adenylyl cyclase, increasing CAMP.
- β3
  - it is present in the lipocytes
  - stimulate the breakdown of lipids into free fatty acids by stimulation of adenylyl cyclase and increased cAMP.

Dopamine receptors



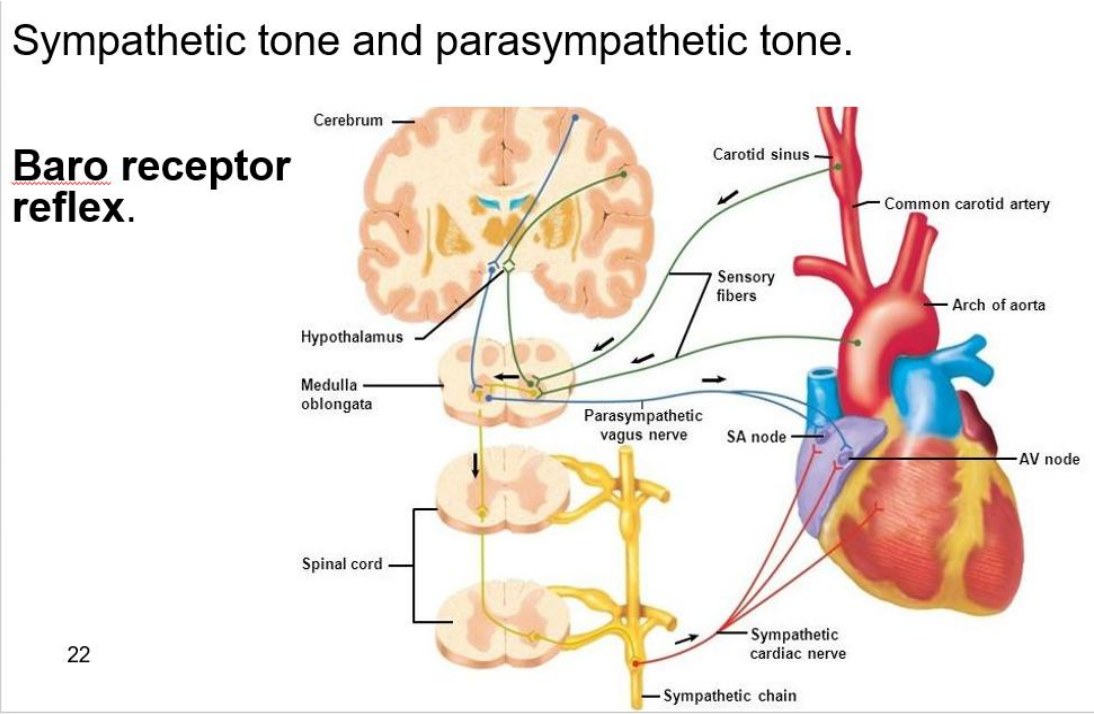
- There are two *main* receptors: D1 and D2 receptors, in addition to D3, D4 and D5 receptors.
- Dopamine is involved in many things in the brain. It is associated with psychosis, schizophrenia, addiction…etc.
- D1 and D5 are actually the same receptors. They are designated different numbers because D5 receptors are more sensitive than D1 receptors → a lower concentration of dopamine is capable of stimulating the D5 receptor. Besides, there is a particular blocker that blocks one receptor but not the other but the function is the same. The function of the D5 receptor is more concerned with the CNS.
- D2 receptor is a presynaptic receptor
- D4 receptor is related to schizophrenia
- D2, D3 and D4 receptors have the same function but their distribution is different within the CNS.

Receptor	Action on adenylyl cyclase

D1 and D5	Stimulation (↑ cAMP)
D2, D3 and D4	Inhibition (↓ cAMP)

Dual innervations of most organs by sympathetic & parasympathetic systems

Remember that any organ that have dual innervations (Parasympathetic and sympathetic), the balance between their tones is what regulates the function.



Our body is constantly trying to maintain homeostasis by resisting changes in the internal environment.

- If a person is taking a drug that works by inhibiting β receptors (β blocker), his body will respond by producing more β receptors → upregulation. After a while, you'll find a huge number of β receptors.
- In the case of a person suffering from asthma using a β2 agonist → downregulation of receptors so that the effect is reduced (to restore normal conditions).

- ***Baroreceptor reflex***:
  Baroreceptors are stretch-sensitive receptors. They are present in the carotid sinus and the aortic arch. They sense small changes that occur in the *elastic* walls of arteries (as blood is pumped to the aorta → stretching and recoiling of the arteries (felt as pulse)).

CASE 1: If, for any reason, blood pressure is elevated, these baroreceptors detect the change and directly send signals to the hypothalamus. The hypothalamus responds by sending signals to the *vasomotor center* in the medulla oblongata → **increased parasympathetic vagal tone of the heart**. This causes *bradycardia* (heart rate decreases to balance the increase in blood pressure).

Blood pressure increases as peripheral resistance increases.
Peripheral resistance: the resistance to the flow of blood through arteries.

CASE 2: Again, changes in peripheral resistance are detected by baroreceptors.
Suppose ↑ peripheral resistance: they send impulses to the hypothalamus which in turn sends impulses to the vasomotor center in the medulla oblongata → stimulation of the vagus nerve → sympathetic tone is decreased and parasympathetic is increased → increase in heart rate is balanced by the decrease in heart rate and cardiac output.
CASE 3: Any decrease in blood pressure is sensed by the baroreceptors → signals to hypothalamus → signals to vasomotor center in medulla oblongata → stimulation of sympathetic neurons → increased heart rate to balance the decreased blood pressure

If we want to test the effect of a drug on the body, we have to take the effect of baroreceptors into account.
NE is a β1 and α1 stimulant. If NE is injected intravenously, it causes constriction of all blood vessels (vasoconstriction) because it is an α1 stimulant → total peripheral resistance will increase. Besides, NE stimulates β1 receptors in the heart → increased heart rate.
What actually happens is that the total peripheral resistance increases but the heart rate *goes down*. Why? **The very strong vagal stimulation overrides the direct stimulatory action of NE on the β1 receptors in the heart.**

Bronchiolar smooth muscle	Relaxes	β2	Contracts	M3
Gastrointestinal tract				
Smooth muscle Walls	Relaxes	β2, α2	Contracts	M3
Sphincters	Contracts	α1	Relaxes	M3
Secretion			Increases	M3
Genitourinary smooth muscle				
Bladder wall	Relaxes	β2	Contracts	M3
Sphincter	Contracts	α1	Relaxes	M3
Uterus, pregnant	Relaxes	β2		
	Contracts	α	Contracts	M3
Penis, seminal vesicles	Ejaculation	α	Erection	M
Skin				
Pilomotor smooth muscle	Contracts	α		
Sweat glands	Increase	M		
Metabolic functions				
Liver	Glycogenolysis,		β2 α	
	Glyconeogenolysis		β2 α	
Fat cells	Lipolysis		β3	
Kidney	Renin release		β1	

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Now we need to memorize the above two slides well ☹ so let's summarize them

	Sympathetic activity		parasympathetic activity	
Eye	action	Receptor	action	receptor
Iris radial muscle (dilator muscles)	contracts →Mydriasis	α1	_____	_____
Iris circular muscle	_____	_____	Contracts → miosis	M3
Ciliary muscle	_____	_____	contracts→near vision	M3

- Radial muscles of the eye (dilator muscles) have α1 receptors. When stimulated, they contract → widening of the pupil "*mydriasis*".
- Circular muscles of the eye have M3 receptors. When stimulated, they contract → narrowing of the pupil "*miosis*".

Radial and circular muscles contract and relax to adjust the size of the pupil as a response to changes in brightness.

- Ciliary muscles of the eye have ligaments attached to the lens. When they contract, the lens bulges → enable near vision.

Contraction and relaxation of ciliary muscles control accommodation (to view objects at different distances).

	Sympathetic activity		parasympathetic activity	
Heart	action	receptor	action	receptor

Sinoatrial node	Accelerates	β1	Decelerates	M2
Ectopic pacemakers	Accelerates	β1	_____	_____
Contractility	increases	β1	Decrease(atria)	M2

- Sinoatrial node of the heart (SA node) has β1 receptors that when stimulated, accelerates heart rate . However, stimulation of M2 receptors (parasympathetic) decelerates the heart rate.
- Contractility of the ventricles: β1 receptors increase the contractility and M2 receptors have no effect on ventricles because they are not innervated by the vagus nerve. However, M2 receptors decrease atrial contractility.

	Sympathetic activity		parasympathetic activity	
Blood vessels	action	receptor	action	receptor
Skin, splanchnic vessels	contracts	α1	_____	_____
Skeletal muscle vessels	relaxes	β2	_____	_____
Endothelium of vessels (drug effect)	_____	_____	Releases EDRF*	M3,M5

EDRF= Endothelium-derived relaxing factor

- α1 receptors in blood vessels mediate vasoconstriction.
- β2 receptors in blood vessels supplying skeletal muscles mediate vasodilation.
- In the endothelium → parasympathetic activity only. **Endothelium-derived relaxing factor (EDRF)** is produced and released by the endothelium to promote smooth muscle relaxation. The best-characterized is nitric oxide (NO).

	Sympathetic activity		parasympathetic activity	
Organ	action	receptor	action	receptor
Bronchiolar smooth muscle	Relaxes	β2	Contracts	M3

- Bronchial smooth muscles have β2 and M3 receptors, where the stimulation of β2 receptors causes relaxation (sympathetic activity) whereas the stimulation of M3 receptors causes constriction(parasympathetic activity).

	Sympathetic activity		parasympathetic activity	
GI tract	action	receptor	action	receptor
Smooth muscle walls	Relaxes	α2,β2	Contracts	M3
Sphincters	Contracts	α1	Relaxes	M3
Secretion	_____	_____	Increases	M3

- The smooth muscles in the walls of the GIT have α2 and β2 receptors, which both, when stimulated, cause relaxation. On the contrary, M3 receptors (parasympathetic) cause contraction of the smooth muscles.

	Sympathetic activity		parasympathetic activity	
Genitourinary smooth muscle	Action	Receptor	Action	Receptor
Bladder wall	Relaxes	β2	Contracts	M3
Sphincter	Contracts	α1	Relaxes	M3
Uterus, pregnant	Relaxes	β2	_____	_____
Penis, seminal vesicles	Ejaculation	α	Erection	M

- The bladder wall has β2 receptors → relaxation of bladder
- Sphincter muscle in genitourinary tract has α1 receptors → contraction → inhibition of urination.

*For urination to occur, the bladder must contract and the sphincter muscles must relax(*parasympathetic activity)

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- The uterus of a pregnant woman: β2 stimulation produces relaxation of the uterus. If strong contractions of the uterus occur before full-term, there is a

high risk of abortion. The pregnant woman is given a β2 agonist to save her pregnancy.

	Sympathetic activity		parasympathetic activity	
Skin	Action	Receptor	Action	Receptor
Pilomotor smooth muscle	Contracts	α	_____	_____
Sweet gland	Increase	M	_____	_____

	Sympathetic activity		parasympathetic activity	
Metabolic functions	Action	Receptor	action	receptor
Liver	Glycogenolysis	β2,α	_____	_____
Liver	Glyconeogenolysis	β2,α	_____	_____
Fat cells	Lipolysis	β3	_____	_____
Kidney	Renin release	β1	_____	_____

- Glycogenolysis is the breakdown of glycogen to produce blood glucose. If β2 receptors are stimulated in diabetic patients (if they are upset, frightened….etc.)→ glycogenolysis is stimulated so blood glucose will rise.

لاتنسونا من دعواتكم

Good luck! ☺