

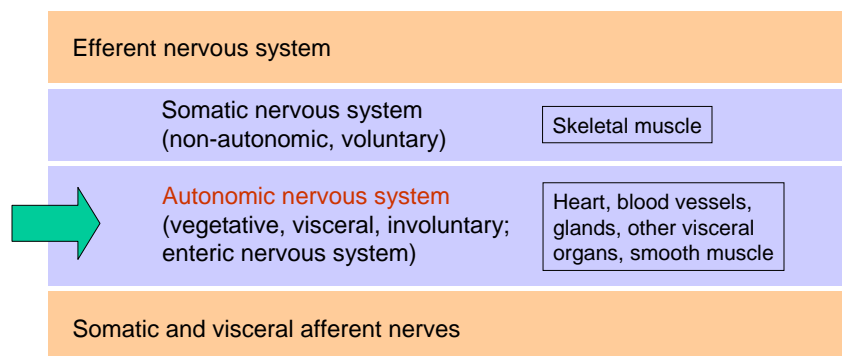
Peripheral nervous system: Overview and transmitter metabolism

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Lecture 25
PNS transmitter metabolism

Lecture 26
PNS receptor function

The Peripheral Nervous System



Anatomic classification: [sympathetic \(fight or flight\)](#)
[parasympathetic \(rest and digest\)](#)

Neurotransmitter-based classification: [adrenergic](#), [cholinergic](#), [dopaminergic](#).

Students are expected to learn through these two lectures:

What are the major neurotransmitters in the PNS?

How are they synthesized? What are the rate-limiting steps?

What are the regulatory mechanisms for neurotransmitter synthesis?

How are neurotransmitters removed after release?

What are the major sites of drug action in the PNS?

How receptors respond to adrenergic / cholinergic agonists and antagonists?



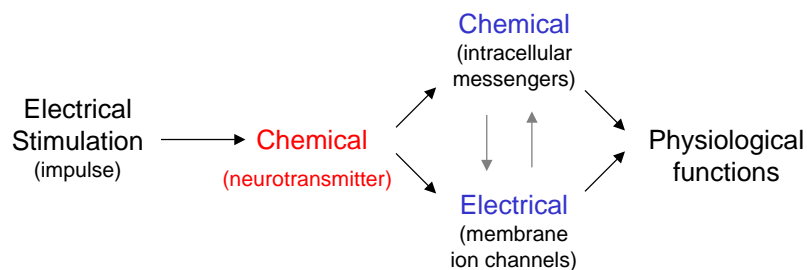
Otto Loewi (Nobel Laureate, 1936)

- He discovered that stimulation of the vagus of a frog heart causes release of a substance that, when transferred to a second heart, could slow heart rate. He called this "Vagusstoff", demonstrating the chemical basis of neurotransmission.
- He also found that atropine can prevent the inhibitory action, but not the release of the "Vagusstoff".
- Incubation of the "Vagusstoff" with frog heart homogenate inactivates it.
- Physostigmine enhances the effect of vagus stimulation on the heart, and prevents the destruction of "Vagusstoff".

On mature consideration, in the cold light of the morning, I would not have done it. After all, it was an unlikely enough assumption that the vagus should secrete an inhibitory substance; it was still more unlikely that a chemical substance that was supposed to be effective at very close range between nerve terminal and muscle be secreted in such large amounts that it would spill over and, after being diluted by the perfusion fluid, still be able to inhibit another heart. (Loewi 1921)

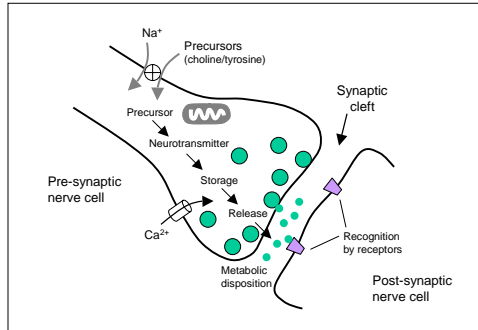
Neurotransmitter:

A chemical that transmits signals from one neuron to another or from a neuron to an effector cell.



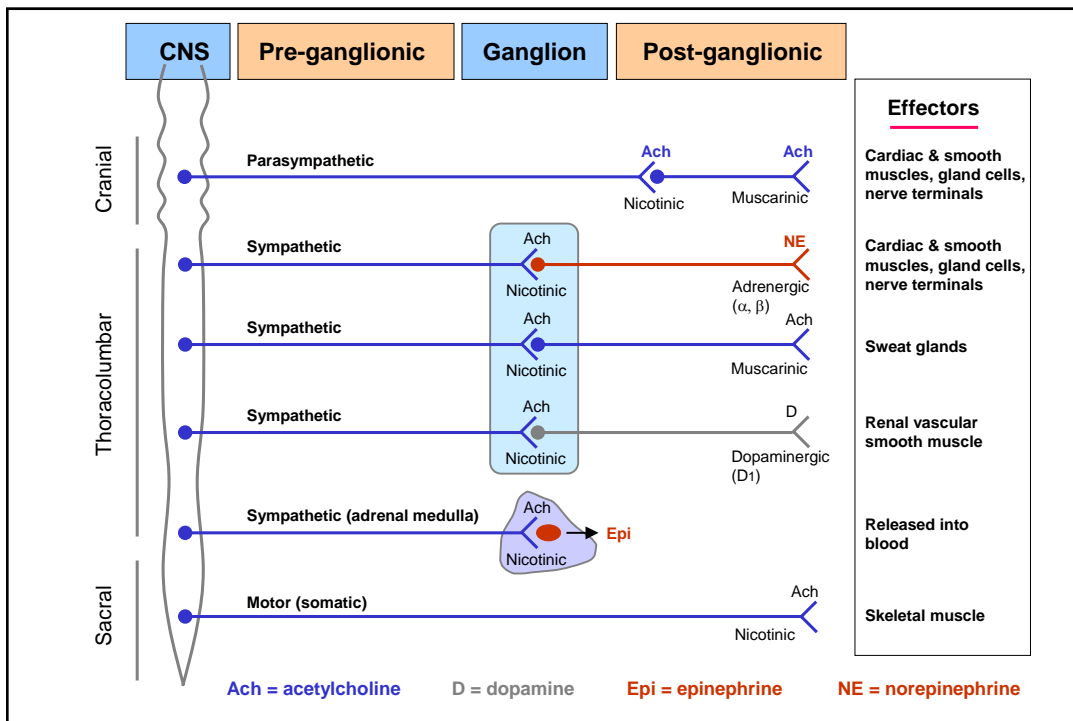
Definition of synapse:

A junctional connection between two neurons, across which a signal can pass

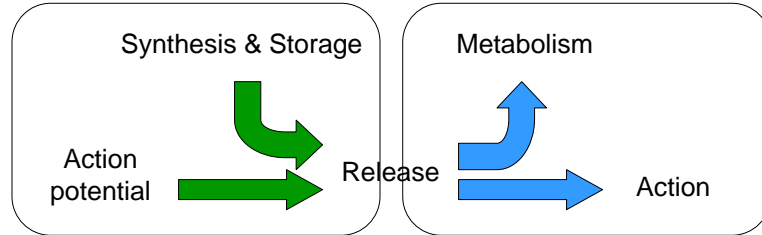


Pre-synaptic neuron: Where a neurotransmitter is synthesized, stored and released upon cell activation.

Post-synaptic neuron or effector cell: Where neurotransmitter is detected and its action translated into cellular activities.



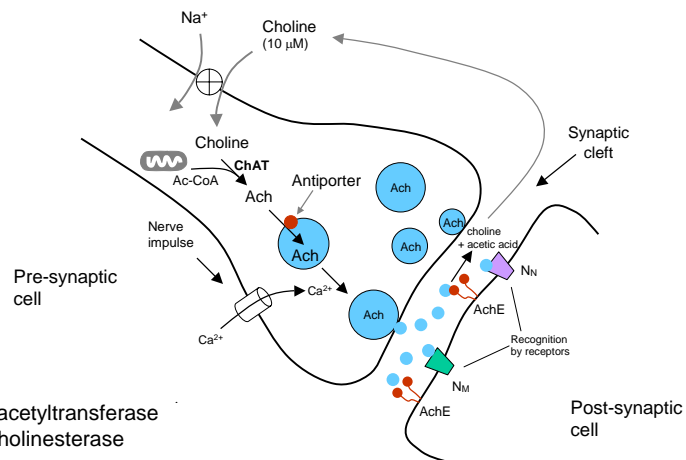
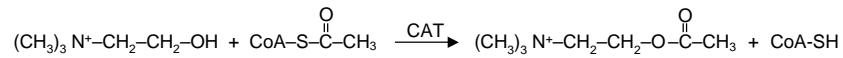
Key Steps in Neurotransmission:



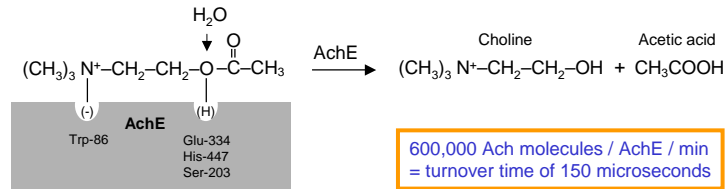
Strategies for Pharmacological Intervention:

Block synthesis and storage:	Usually rate-limiting steps; produce long-term effects
Block release:	Rapid action and effective
Interfere with metabolism:	Can be reversible or irreversible; blocking metabolism increases effective neurotransmitter concentrations
Interfere with action:	Receptor antagonists & agonists; high specificity

Synthesis, storage and release of acetylcholine:



Degradation of acetylcholine:



Steps involved in the action of acetylcholinesterase:

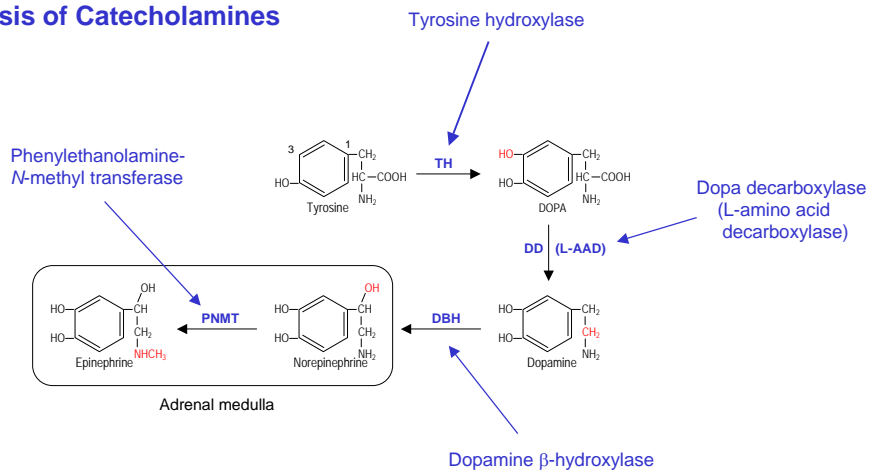
1. Binding of substrate (Ach)
2. Formation of a transient intermediate (involving -OH on Serine 203, etc.)
3. Loss of choline and formation of acetylated enzyme
4. Deacylation of AchE (regeneration of enzyme)



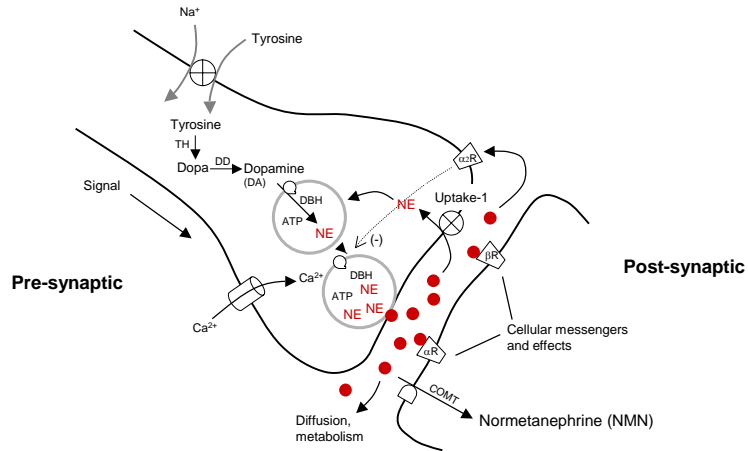
Julius Axelrod (Nobel Laureate, 1970)

His discoveries concern the mechanisms which regulate the formation of norepinephrine in the nerve cells and the mechanisms which are involved in the inactivation of this important neurotransmitter.

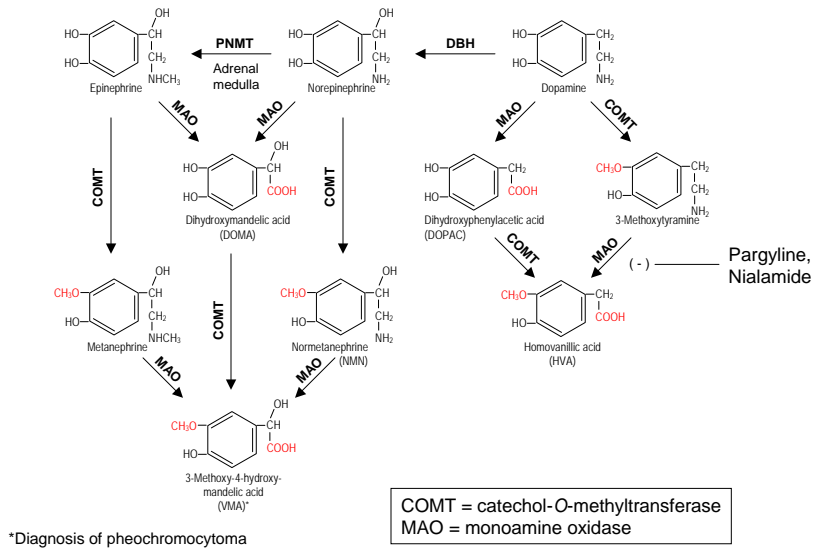
Synthesis of Catecholamines



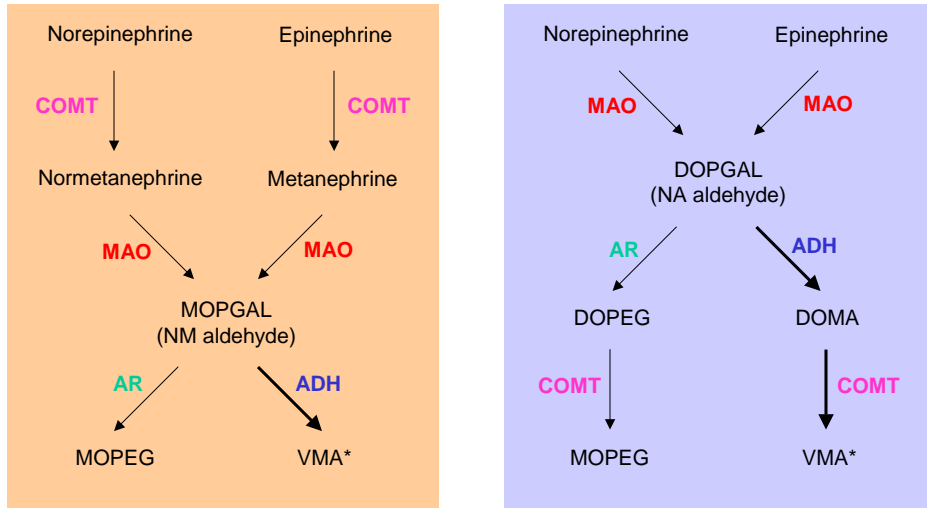
Regulation of Norepinephrine Synthesis and Metabolism:



Degradation of Catecholamines:



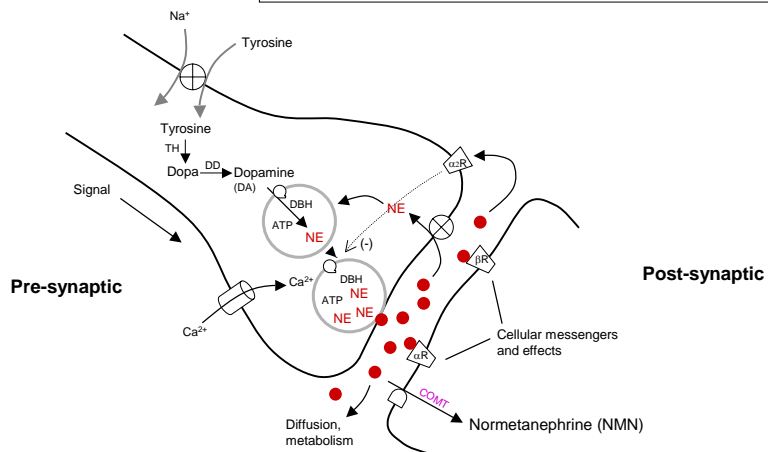
Degradation of Epi and NE (with oxidative and reductive branches shown):



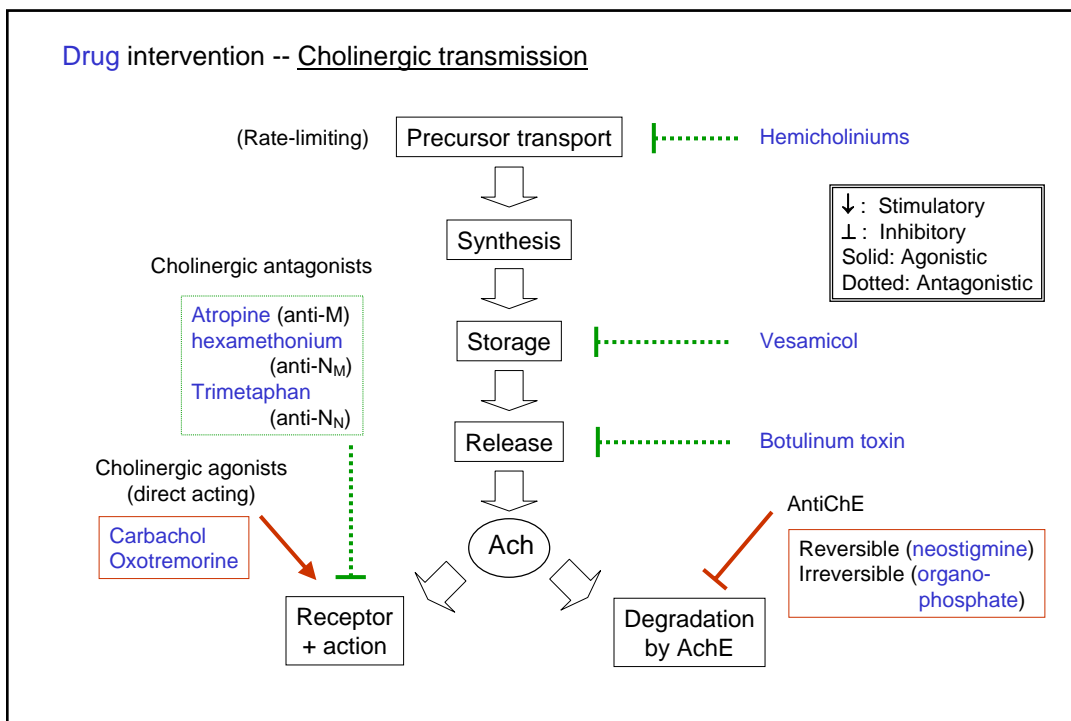
COMT = catechol-O-methyltransferase
 MAO = monoamine oxidase
 AR = aldehyde reductase
 ADH = aldehyde dehydrogenase

*VMA: vanillylmandelic acid (3-Methoxy-4-hydroxymandelic acid), a major degradation product of adrenergic transmitters in PNS. Its urine content is used for diagnosis of pheochromocytoma.

MAO: associated with outer surface of mitochondria, including those within the terminals of adrenergic fibers.
COMT: located mostly in cytoplasm. Rich in liver, kidney; not found in adrenergic neurons.



VMA: vanillylmandelic acid (3-Methoxy-4-hydroxymandelic acid)



Definition of Agonist and Antagonist:

Agonist: (1) A natural ligand that activates a receptor. (2) A drug that has properties similar to a natural ligand in activating the same receptor.

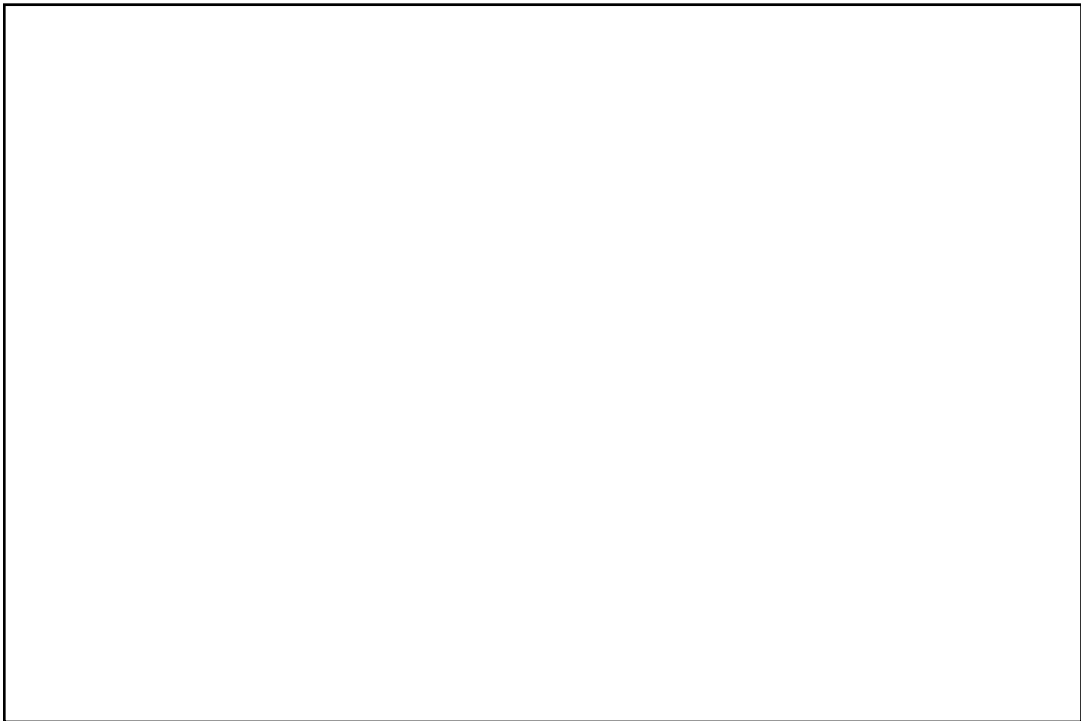
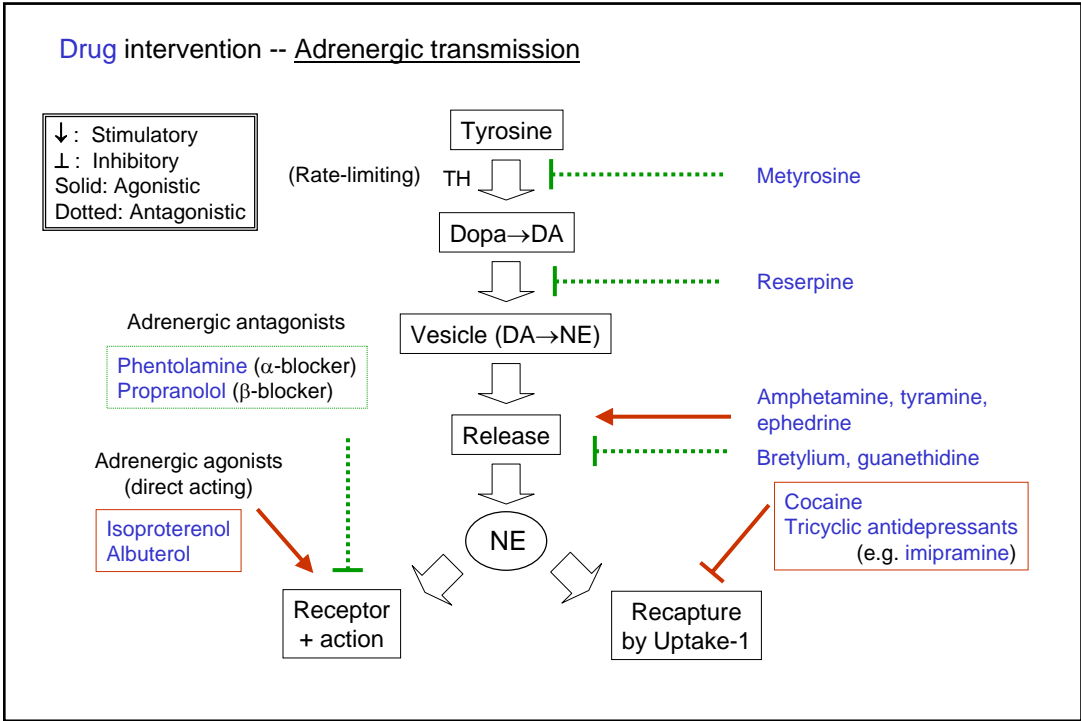
Antagonist: (1) A receptor-specific blocker. (2) A molecule, such as a drug (e.g., enzyme inhibitor) or a physiologic agent (e.g., hormone), that diminishes or prevents the action of another molecule.

Mode of Action:

Direct-acting: Molecule that physically binds to the target for its effect.
Example: carbachol activates cholinergic receptors.

Indirect-acting: Molecule that exerts effect on the target by interacting with another molecule.
Example: neostigmine blocks AchE, causing Ach accumulation.

Mode of action and agonism are different concepts. For example, a direct-acting molecule can be either agonistic or antagonistic.



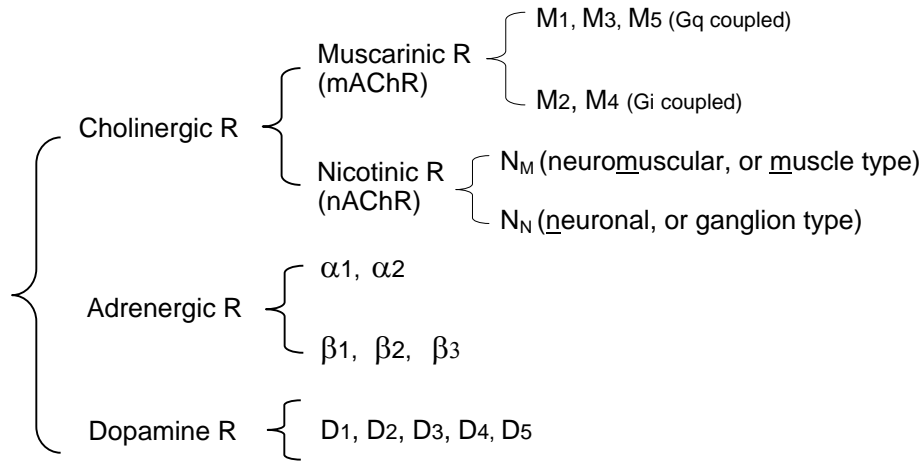
Lecture 26

PNS Receptor Functions

An example of indirect-acting pharmacological agents:

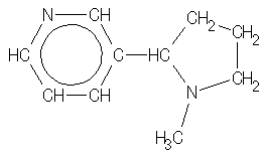
Physostigmine's effect on acetylcholine receptor is indirect. This effect is mediated through the inhibition of cholinesterase, which causes an increase in the local concentration of acetylcholine. The net effect is agonistic on acetylcholine receptor.

Autonomic Receptor Classification:



Other receptors (receptors for NANC transmitters, e.g. nitric oxide, vasoactive intestinal peptide, neuropeptide Y)

Cholinergic receptors: Nicotinic vs. Muscarinic

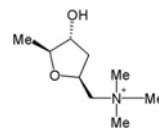


The **"Nicotinic actions"** -- similar to those induced by nicotine; action mediated by **nicotinic cholinergic receptors**:

- stimulation of all autonomic ganglia (N_N)
- stimulation of voluntary muscle (N_M)
- secretion of epinephrine from the adrenal medulla (N_N)

Cholinergic receptors: Nicotinic vs. Muscarinic

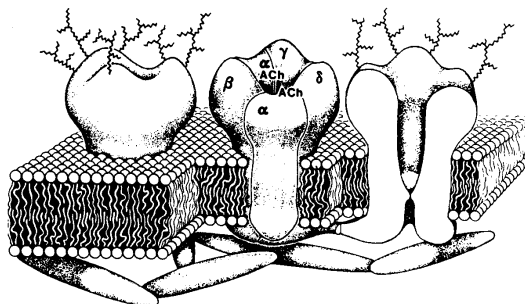
The “**Muscarinic actions**” -- reproduced by injection of muscarine, from *Amanita muscaria*. Similar to those of parasympathetic stimulation



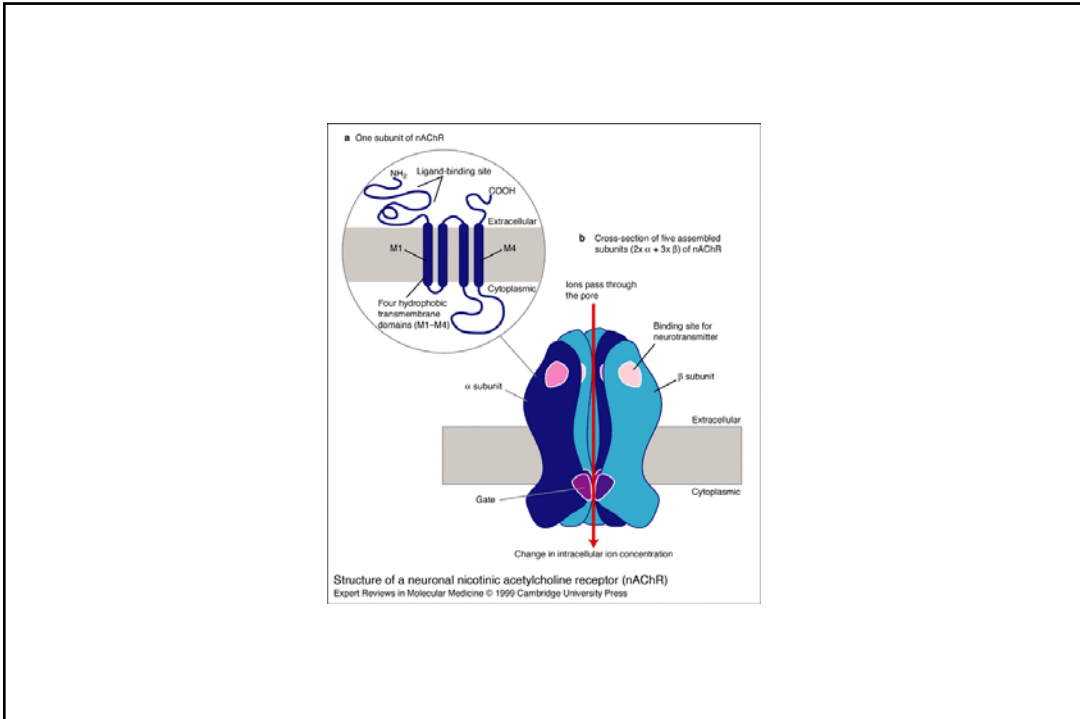
Multiple **muscarinic cholinergic receptors** distributed in different tissues:

- Neural (M₁): CNS, PNS, gastric parietal cells (excitatory; G_q)
- Cardiac (M₂): atria & conducting tissue; presynaptic (inhibitory; G_i)
- Glandular (M₃): exocrine glands; smooth muscle (excitatory; G_q)

Nicotinic acetylcholine receptor: Structure

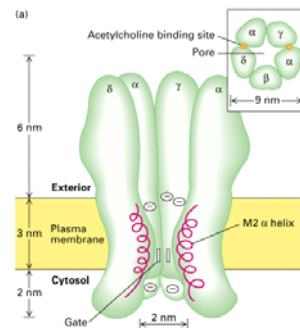


- All nAChRs have a pentameric structure, consisting of subunits in different combinations:
 - A total of 9 different α subunits and 4 different β subunits have been identified
- In skeletal muscle: $\alpha 1(2)$, β , γ , δ (γ is replaced by ϵ in adult muscle)
- In autonomic ganglion: $\alpha 3$, $\alpha 5$, $\alpha 7$, $\beta 2$, $\beta 4$
- Other combinations of α and β subunits are found among the nAChRs in CNS
- nAChRs with different composition have different affinities for some ligands. For example, α -bungarotoxin binds to nAChR in motor end plate with high affinity



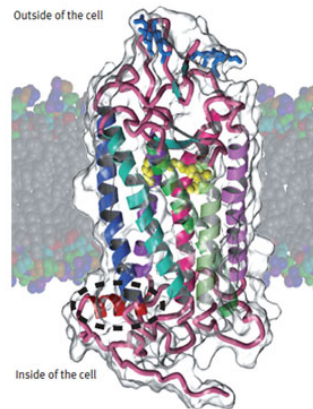
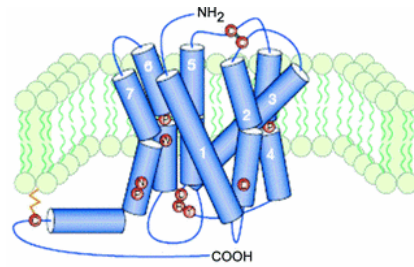
Nicotinic acetylcholine receptor: Function

- Ligand-gated ion (Na^+) channel
- Acetylcholine binds to the α subunits at the boundary of α and γ , and α and δ subunits.
- Channel opening requires binding of 2 acetylcholine molecules, with positive cooperativity.
- Structurally and functionally similar to the sodium channel, which can be blocked by local anesthetics
- Acetylcholine binds to the α -subunits of the receptor making the membrane more permeable to cations (sodium) and causing a local depolarization. The local depolarization spreads to an action potential, or leads to muscle contraction when summed with the action of other receptors. The ion channel is open during the active state.
- Nicotine in small doses stimulates autonomic ganglia and adrenal medulla. When large doses are applied, the stimulatory effect is quickly followed by a blockade of transmission.
- In addition to α -bungarotoxin, there are other blocking agents for autonomic ganglia that include hexamethonium, tetraethylammonium, mecamylamine, and trimethaphan. Blocking at this level stops all autonomic outflow and produces a broad effect.

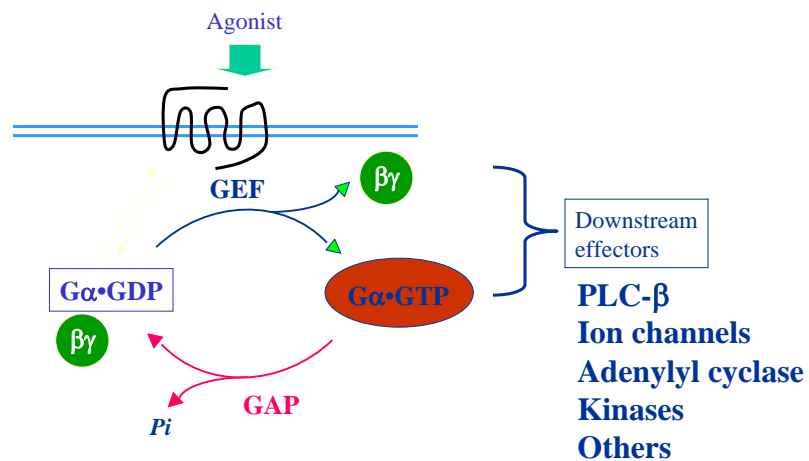


Muscarinic receptors are GPCRs

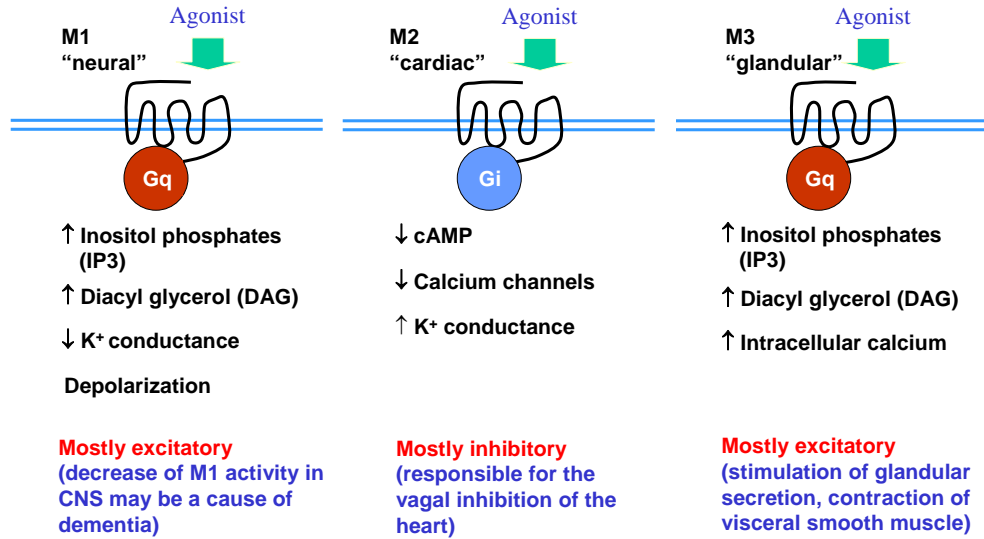
G protein-coupled receptors with 7 transmembrane domains, like the structure of rhodopsin (right)



The G protein (GTPase) activation cycle



Muscarinic acetylcholine receptors (mAChR)

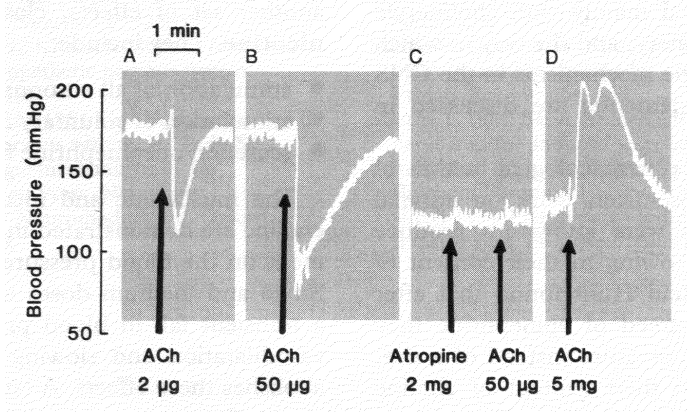


Muscarinic agonists

Drug	Receptor specificity		Hydrolysis by AchE
	mAChR	nAChR	
Acetylcholine	+++	+++	+++
Carbachol	++	+++	(-)
Methacholine	+++	+	++
Bethanechol	+++	(-)	(-)
Muscarine	+++	(-)	(-)
Pilocarpine	++	(-)	(-)

Muscarinic antagonists

Atropine, scopolamine, and pirenzepine (relatively selective for M1 mAChR)

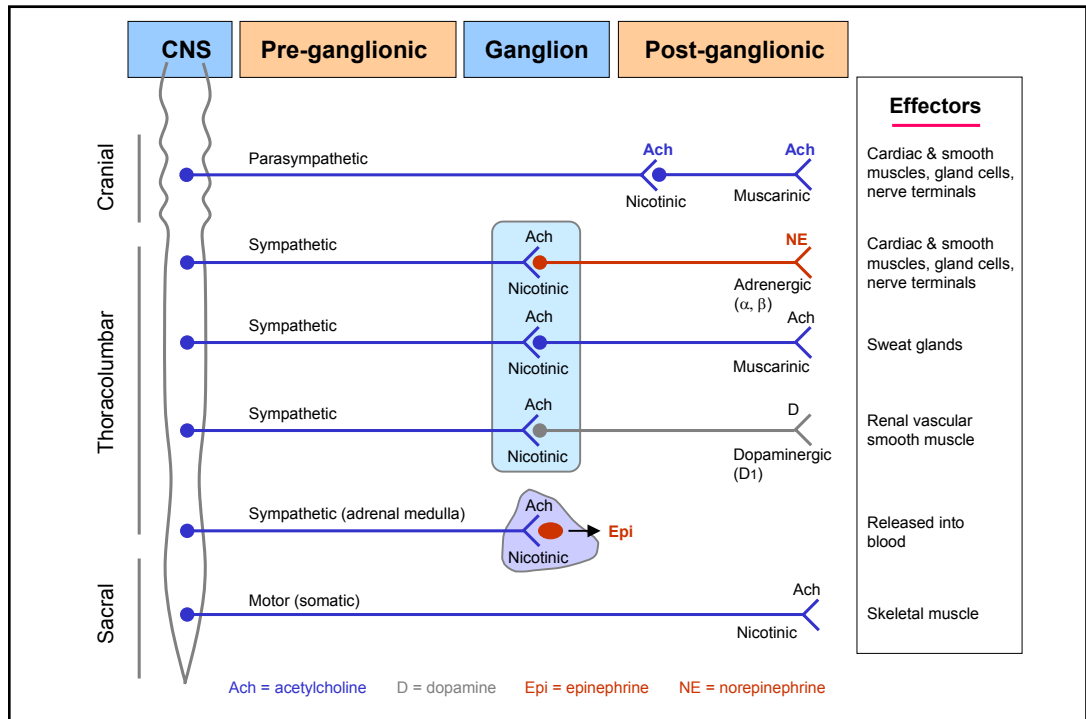


Sir Henry Hallett Dale
(Nobel laureate, 1936)

(Arterial pressure of an anesthetized cat was measured)

Two kinds of effects produced by Ach.
A. Ach causes a fall in BP due to vasodilation.
B. A larger dose of Ach also produces bradycardia, further reducing BP.
C. Atropine blocks the effect of Ach in lowering BP.
D. Still under the influence of atropine, a much larger dose of Ach causes a rise in BP and tachycardia.

A, B: Muscarinic effects of Ach (M)
 C: Muscarinic antagonistic effect (M)
 D: Stimulation of sympathetic ganglia (N_N)



Classification of adrenergic receptors by agonist potency

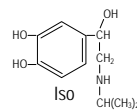
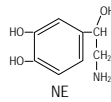
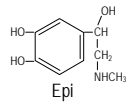
α -- NE > Epi > Iso

β -- Iso > Epi > NE

NE = norepinephrine

Epi = epinephrine

Iso = isoproterenol

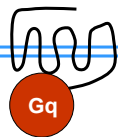


Signaling properties of adrenergic receptors

Norepinephrine
Epinephrine
Phenylephrine

Agonist

$\alpha 1$



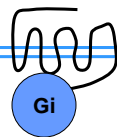
↑ Inositol phosphates (IP3)
↑ Diacyl glycerol (DAG)

Mostly excitatory

Norepinephrine
Methyl NE
Clonidine

Agonist

$\alpha 2$



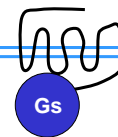
↓ cAMP
↓ Calcium channels
↑ K⁺ conductance

Mostly inhibitory

Isoproterenol
Albuterol ($\beta 2$)
Dobutamine ($\beta 1$)

Agonist

$\beta 1, 2, 3$



↑ cAMP

Mostly excitatory

Distribution and functions of adrenergic receptors:

α 1: postsynaptic effector cells, especially smooth muscle

Vasoconstriction, relaxation of gastrointestinal smooth muscle, hepatic glycogenolysis

α 2 presynaptic adrenergic nerve terminals (autoreceptor), platelets, lipocytes, smooth muscle

Inhibition of transmitter release, platelet aggregation, contraction of smooth muscle

β 1 postsynaptic effector cells: heart, lipocytes, brain, presynaptic adrenergic / cholinergic terminals

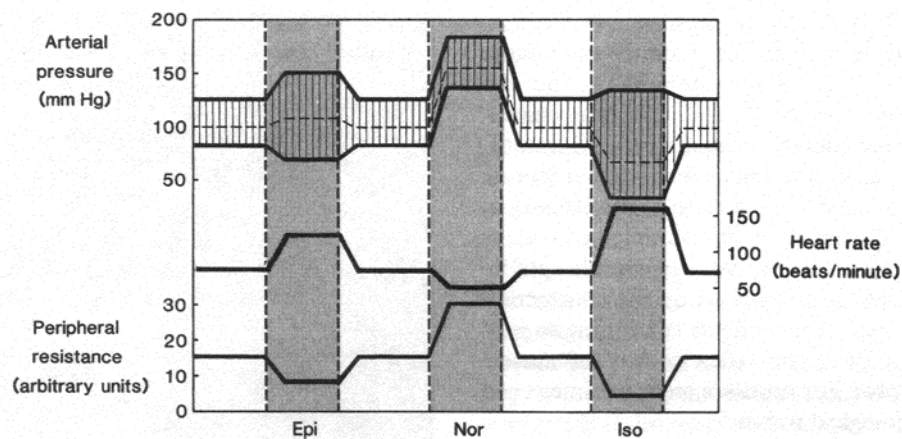
Increased cardiac rate & force, relaxation of gastrointestinal smooth muscle

β 2 postsynaptic effector cells: smooth muscle, cardiac muscle

Bronchodilation, vasodilation, relaxation of visceral smooth muscle, hepatic glycogenolysis

β 3 postsynaptic effector cells: lipocytes

Lipolysis



Cardiovascular effects of intravenous infusion of epinephrine, norepinephrine, and isoproterenol in man. Norepinephrine (predominantly α -agonist) causes vasoconstriction and increased systolic and diastolic BP, with a reflex bradycardia. Isoproterenol (β -agonist) is a vasodilator, but strongly increases cardiac force and rate. Mean arterial pressure falls. Epinephrine combines both actions.

Cholinergic effects:

- Contraction of pupillary constrictor muscle
-- miosis
- Contraction of ciliary muscle - bulge of lens
-- near vision, ↑ outflow of aqueous humor

Adrenergic effects:

- Contraction of pupillary dilator muscle
-- mydriasis
- Stimulation of ciliary epithelium
-- ↑ production of aqueous humor

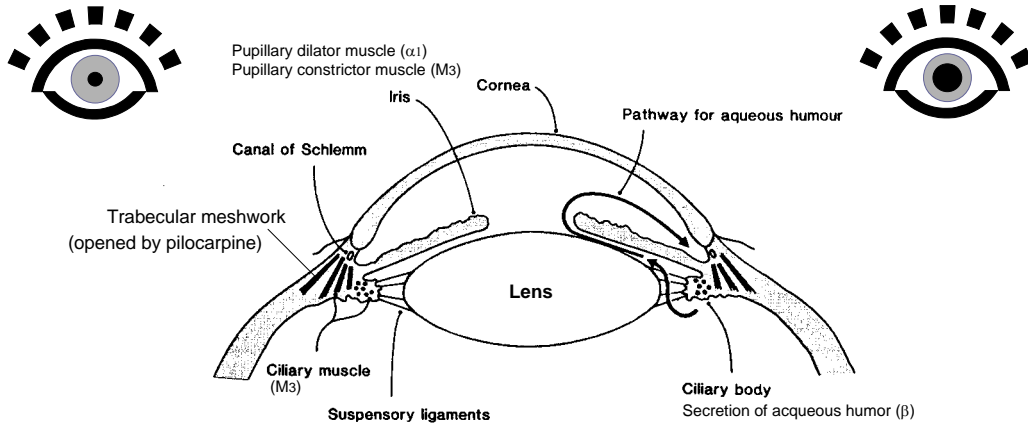
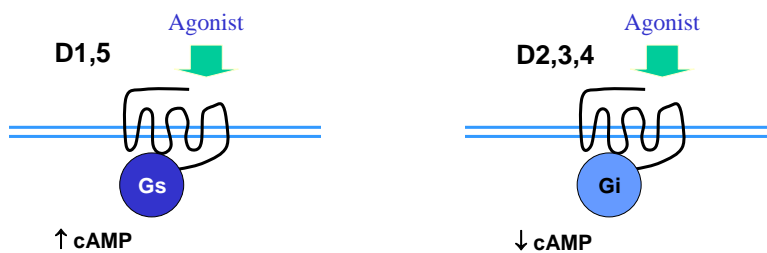


Fig. 6.5 The anterior chamber of the eye, showing the pathway for secretion and drainage of the aqueous humor.

Dopaminergic receptors in the periphery

Dopamine receptors play important roles in CNS. Notably, dopamine neurotransmission is involved in several diseases including Parkinson's disease, schizophrenia, and attention deficiency disorder.

There are 5 types dopamine receptors (D1 – D5). In periphery, D1 dopamine receptor mediates **renal vasodilation**, and **increased myocardial contractility**.



Dopaminergic receptors in the periphery

Cardiovascular and pulmonary systems:

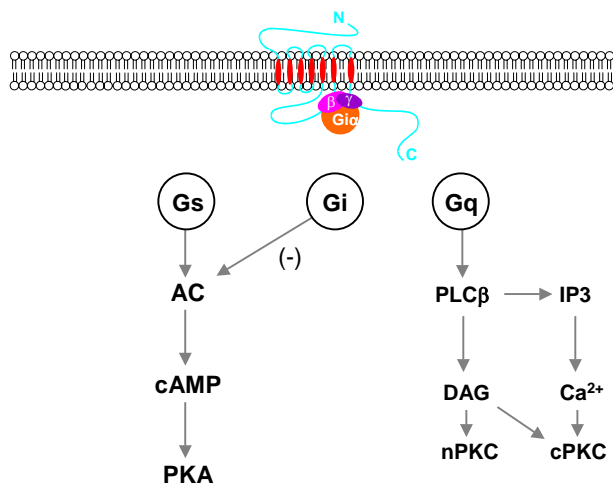
Human pulmonary artery expresses D1, D2, D4, and D5 dopamine receptors. These receptors may be responsible for **vasorelaxation effect** of dopamine in the blood.

D4 receptors have been identified in the atria, and dopamine increases myocardial contractility without changing heart rate, leading to increased cardiac output.

Renal system:

Dopamine receptors (mostly D1) exist along the nephron in the kidney, and is expressed at high level in proximal tubule epithelia cells. Dopamine can affect diuresis and natriuresis.

A part of the G protein-mediated signaling pathways



Receptor distribution and effects in the autonomic nervous system:

<u>Organ</u>	<u>Sympathetic</u>	<u>Receptor</u>	<u>Parasympathetic</u>	<u>Receptor</u>
Heart				
SA node	Rate ↑	β_1 (β_2)	Rate ↓	M2
Atrial muscle	Force ↑	β_1 (β_2)	Force ↓	M2
AV node	Automaticity ↑	β_1 (β_2)	Conduction velocity ↓	M2
Ventricular muscle	Automaticity ↑	β_1 (β_2)	AV block	
	Force ↑	β_1 (β_2)		
Blood vessels				
Arterioles				
Coronary	Contraction	α_1		
Skeletal muscle	Relaxation	β_2		M3
Viscera	Contraction	α_1		
Skin	Contraction	α_1		
Brain	Contraction	α_1		
Erectile tissue	Contraction	α_1	Relaxation	M3
Salivary gland	Contraction	α_1	Relaxation	M3
Vein	Contraction	α_1		
	Relaxation	β_2		

(Continued, next page)

<u>Organ</u>	<u>Sympathetic</u>	<u>Receptor</u>	<u>Parasympathetic</u>	<u>Receptor</u>
Viscera				
Bronchiolar SMC	Relaxation	β_2	Contraction	M3
Glands			Secretion	M3
GI track				
Smooth muscle	Motility ↓	α_2, β_2	Motility ↑	M3
Sphincters	Contraction	α_1	Relaxation	M3
Glands			Secretion	M3
			Gastric acid secretion	M1
Uterus	Contraction	α_1		
	Relaxation	β_2	Variable	
Skin				
Pilomotor SMC	Contraction (piloerection)	α		
Salivary glands	Secretion	α_1, β_1	Secretion	M3
Lacrimal glands			Secretion	M3
Kidney	Renin release	β_1		
Liver	Glycogenolysis	β_2, α_1		
	Gluconeogenesis	β_2, α_1		
Fat	Lipolysis	β_3		

From: Rang et al. Pharmacology, 6th Ed. p. 169. Also, see Katzung, Basic & Clinical Pharmacology, 10th Ed. p.86.