

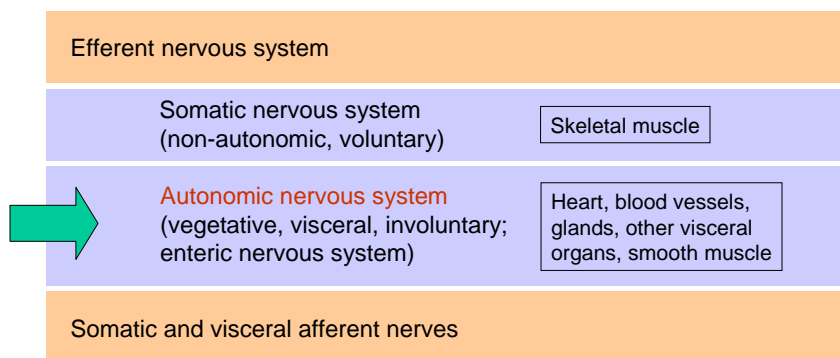
Overview: Pharmacology of the Peripheral Nervous System

Richard D. Ye
Professor of Pharmacology
College of Medicine
Tel. 996-5087
Room 4143, COMRB
E-mail: yer@uic.edu

Part I
PNS transmitter metabolism

Part II
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?

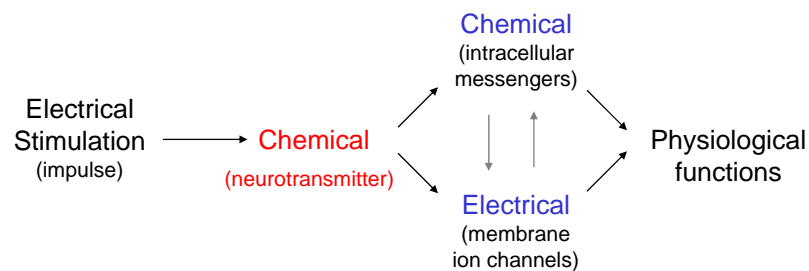


Otto Loewi (Nobel Laureate, 1936)

- He discovered that stimulation of the vagus of a frog heart causes release of a substance that, when transferred to a second heart, can have inhibitory effect. He called this "Vagusstoff".
- 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".

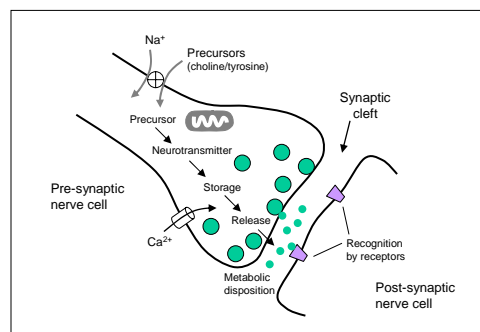
Neurotransmitter:

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



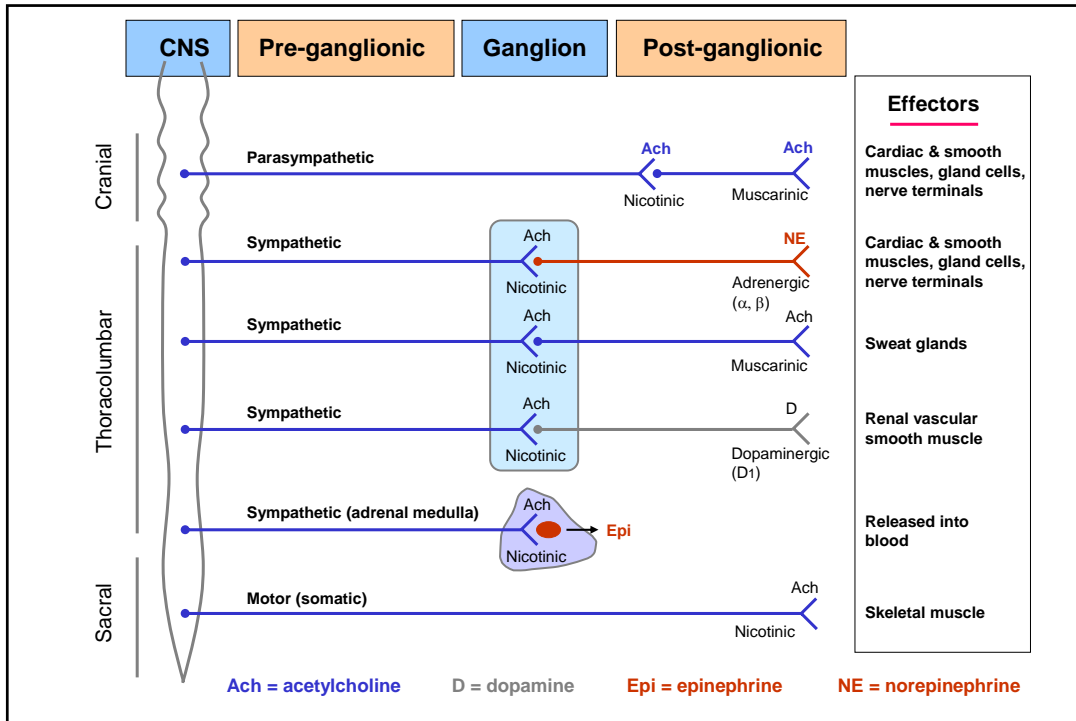
Definition of synapse:

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

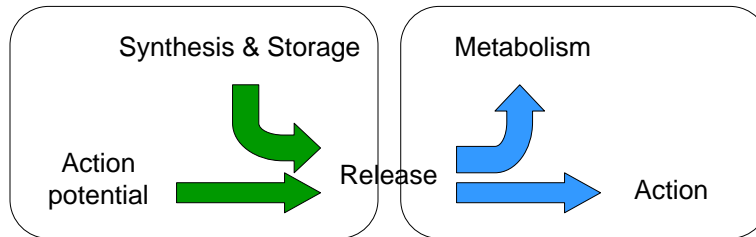


Pre-synaptic neuron: Where a neurotransmitter is synthesized, stored and released upon cell activation.

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



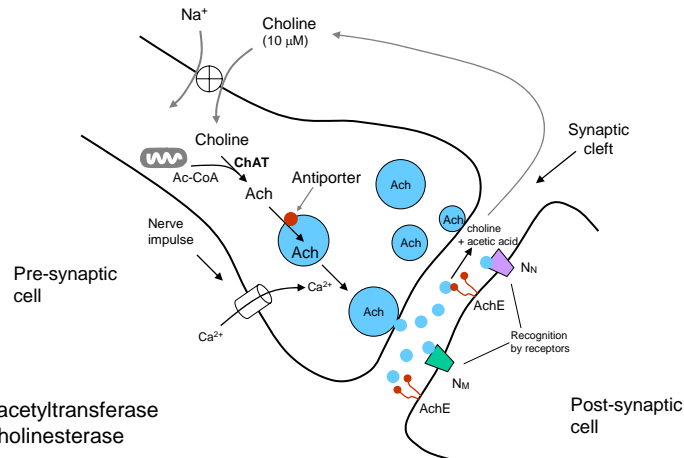
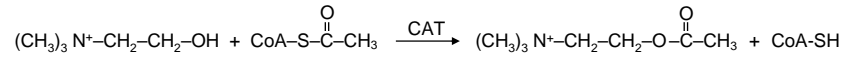
Key Steps in Neurotransmission:



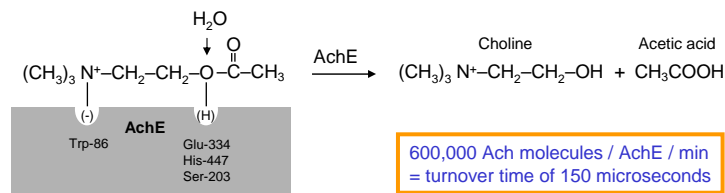
Strategies for Pharmacological Intervention:

- Blocking synthesis and storage: Usually rate-limiting steps; produce long-term effects
- Blocking 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:

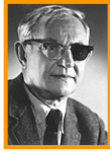


Degradation of acetylcholine:



Steps involved in the action of acetylcholinesterase:

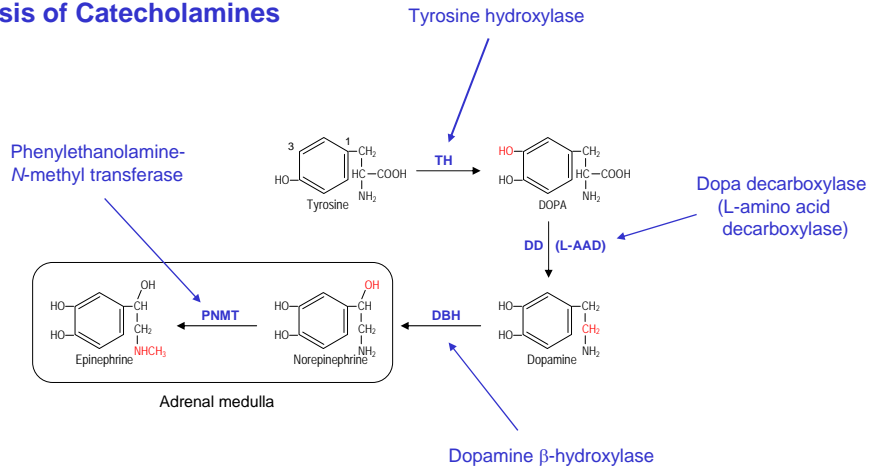
1. Binding of substrate (ACh)
2. Formation of a transient intermediate (involving -OH on Serine 203, etc.)
3. Loss of choline and formation of acetylated enzyme
4. Deacylation of AchE (regeneration of enzyme)



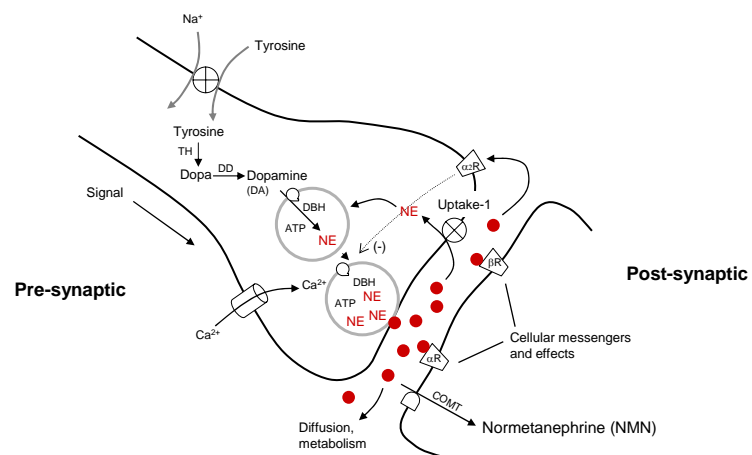
Julius Axelrod (Nobel Laureate, 1970)

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.

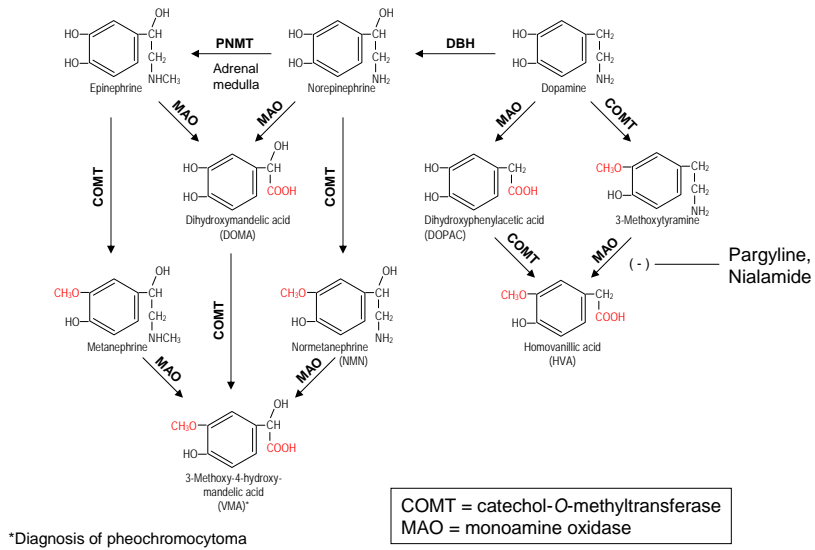
Synthesis of Catecholamines



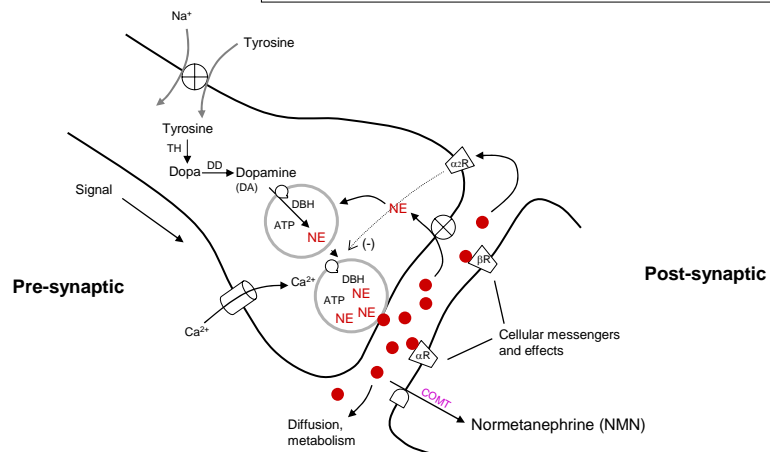
Regulation of Norepinephrine Synthesis and Metabolism:



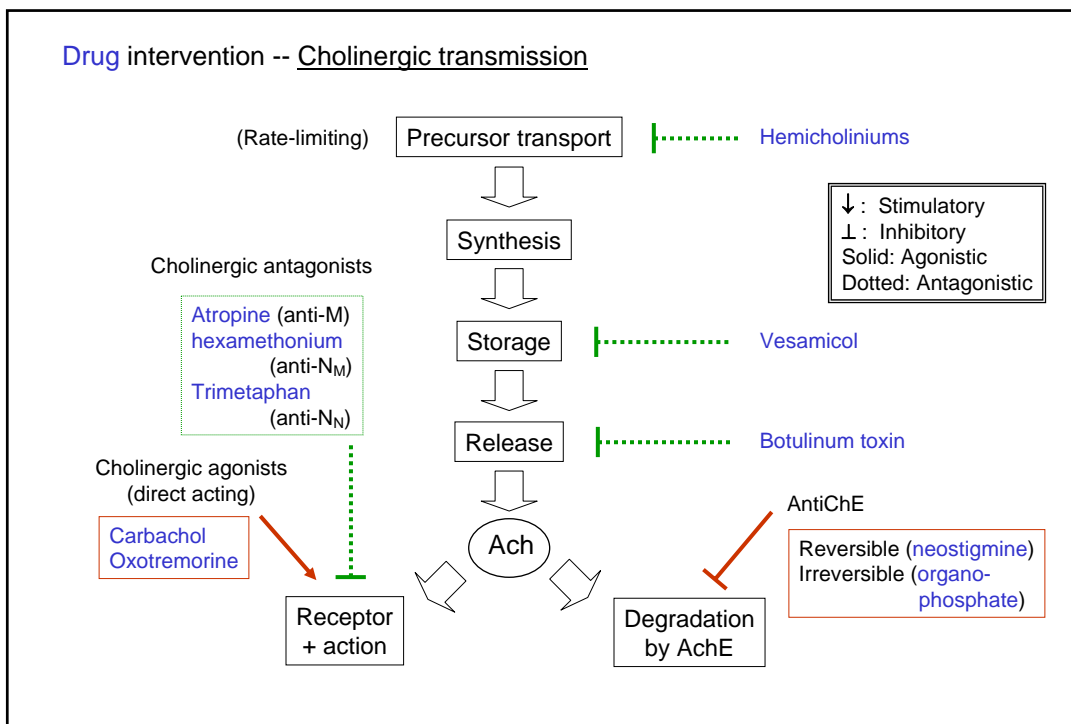
Degradation of Catecholamines:



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: A structural analog that is capable of stimulating a biological response like a natural ligand (by occupying the same receptor).

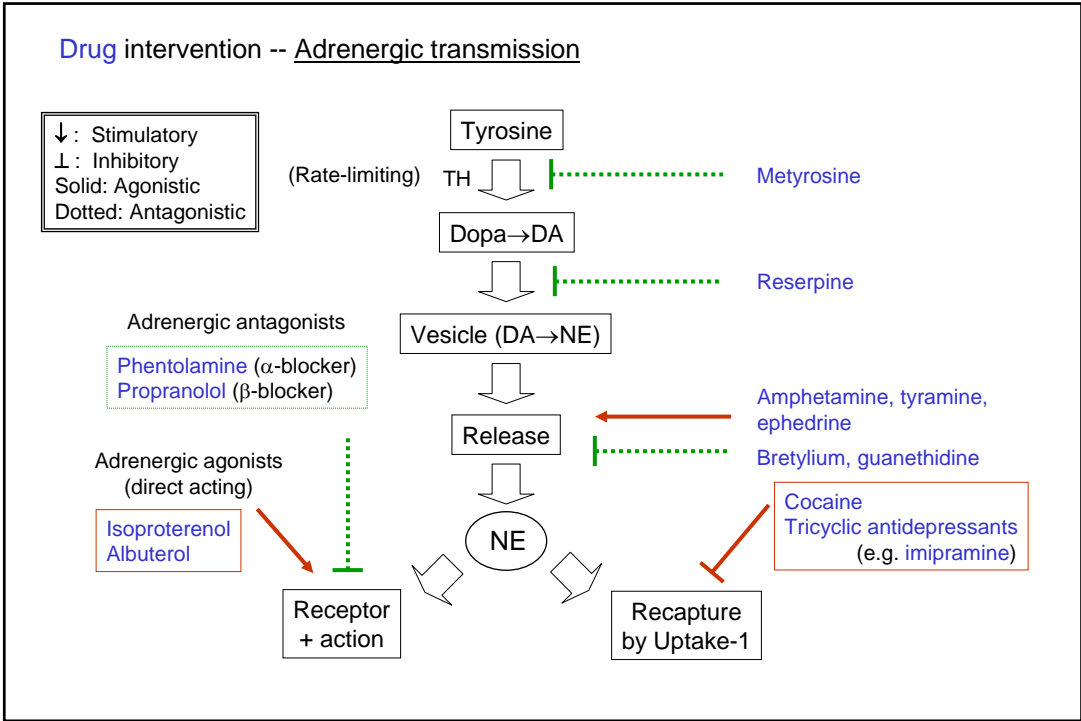
Antagonist: (1) A receptor-specific blocker. (2) A molecule, such as a drug (e.g., enzyme inhibitor) or a physiologic agent (e.g., hormone), that diminishes or prevents the action of another molecule.

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.

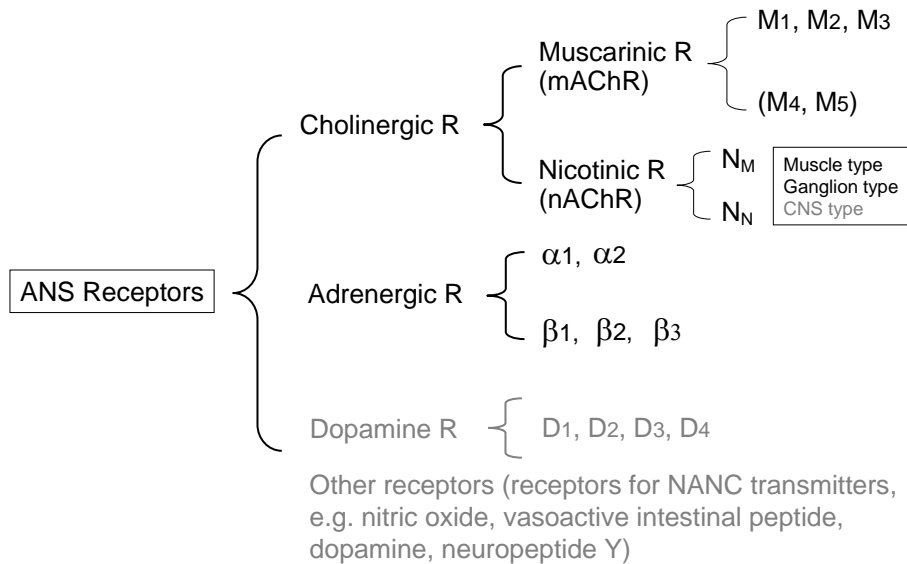
Mode of action and agonism/antagonism are different concepts. For example, a direct acting molecule can be either agonistic or antagonistic.



Part II

Autonomic Receptor Functions

ANS Receptor Classification:



The “**Nicotinic Actions**” -- similar to those induced by nicotine

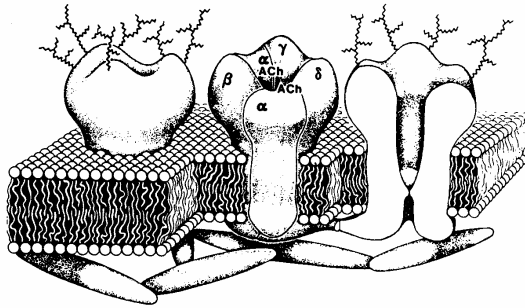
- stimulation of all autonomic ganglia (N_N)
- stimulation of voluntary muscle (N_M)
- secretion of epinephrine from the adrenal medulla (N_N)

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

- Neural (M_1): CNS, PNS, gastric parietal cells (excitatory; Gq)
- Cardiac (M_2): atria & conducting tissue; presynaptic (inhibitory; Gi)
- Glandular (M_3): exocrine glands; smooth muscle (excitatory; Gq)

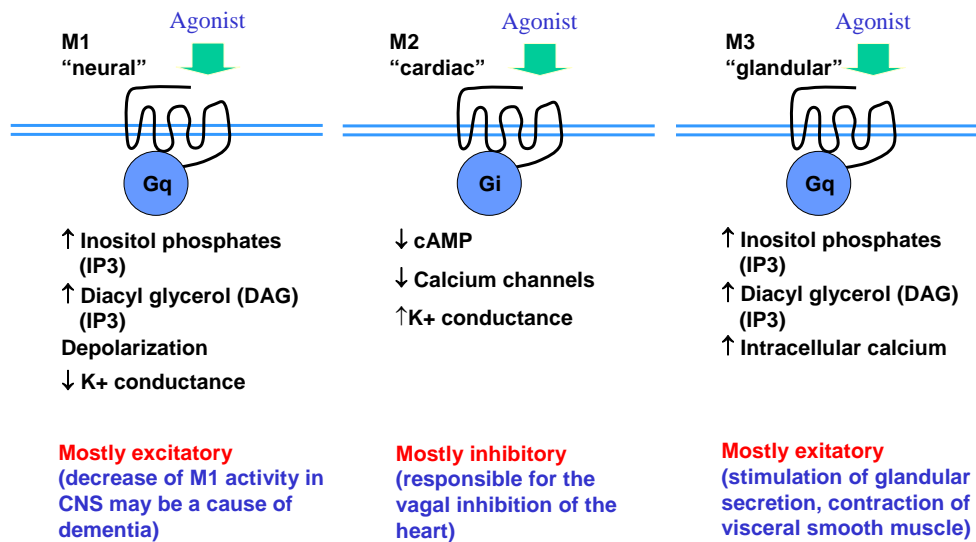
Nicotinic acetylcholine receptor (nAChR)

- Pentameric receptor comprised of different subunits:
 $\alpha 2, \beta, \gamma, \delta$ (muscle type)
 $\alpha 2, \beta 3$ (ganglion and CNS type)
 $\alpha 5$ (CNS type)
 There are 9 different α subunits and 4 different β subunits



- Ligand-gated ion (Na^+) channel
- ACh binds to the α subunits
- Channel opening requires binding of 2 ACh molecules
- Blocking ganglionic nAChR blocks all autonomic outflow. These agents lack selectivity and are used mostly for research purpose today
- These blocking agents include: Hexamethonium, tetraethylammonium, mecamylamine, and trimethaphan
- Nicotine initially stimulates and then blocks nAChR

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)

Classification of adrenergic receptors by agonist potency

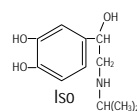
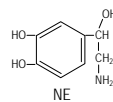
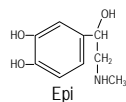
α -- NE > Epi > Iso

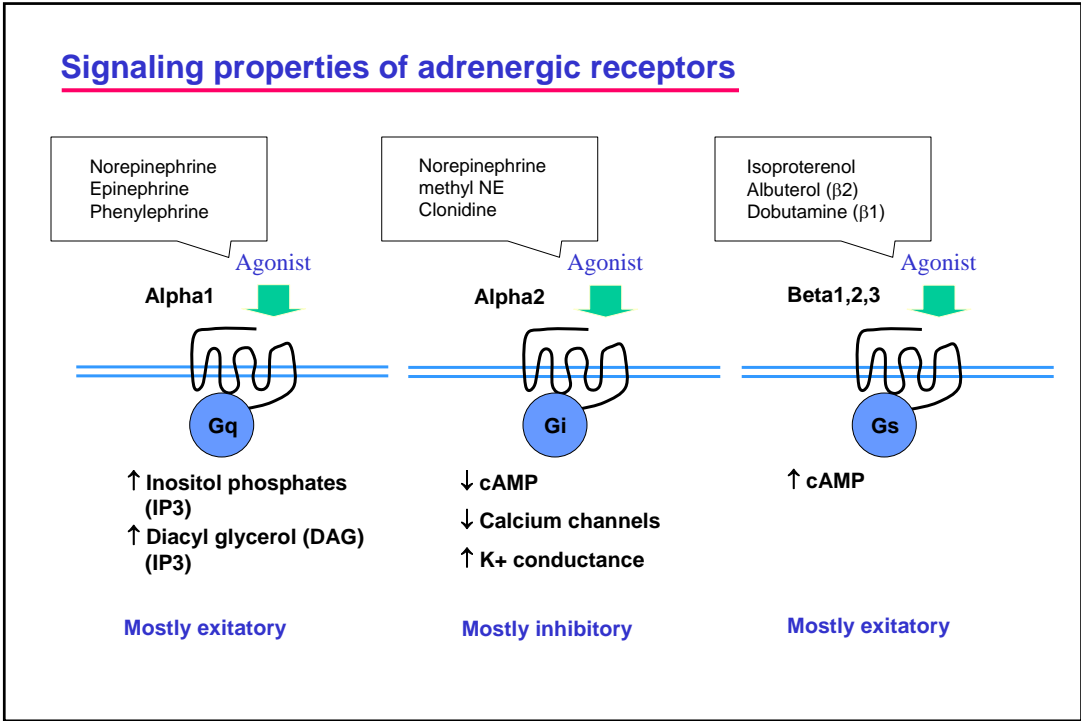
β -- Iso > Epi > NE

NE = norepinephrine

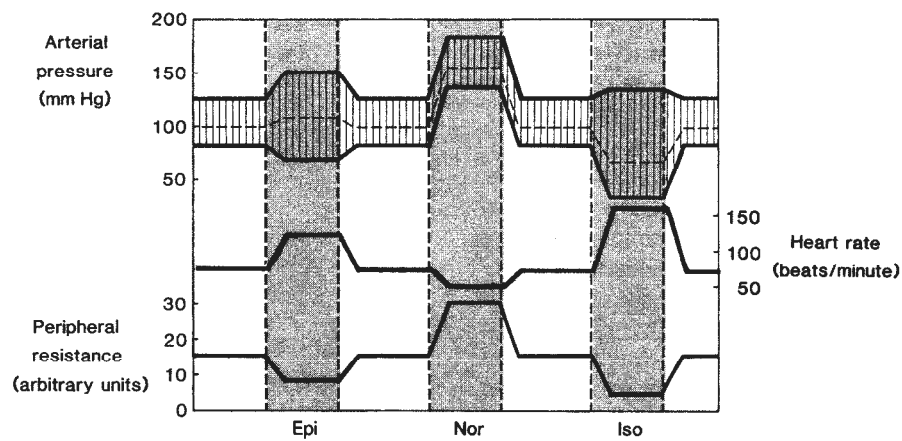
Epi = epinephrine

Iso = isoproterenol





- Distribution and functions of adrenergic receptors:
- α1:** postsynaptic effector cells, especially smooth muscle
 Vasoconstriction, relaxation of gastrointestinal smooth muscle, hepatic glycogenolysis
 - α2** presynaptic adrenergic nerve terminals (autoreceptor), platelets, lipocytes, smooth muscle
 Inhibition of transmitter release, platelet aggregation, contraction of smooth muscle
 - β1** postsynaptic effector cells: heart, lipocytes, brain, presynaptic ad./ ch nerve term.
 Increased cardiac rate & force, relaxation of gastrointestinal smooth muscle
 - β2** postsynaptic effector cells: smooth muscle, cardiac muscle
 Bronchodilation, vasodilation, relaxation of visceral smooth muscle, hepatic glycogenolysis
 - β3** 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, \uparrow outflow of aqueous humor

Adrenergic effects:

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

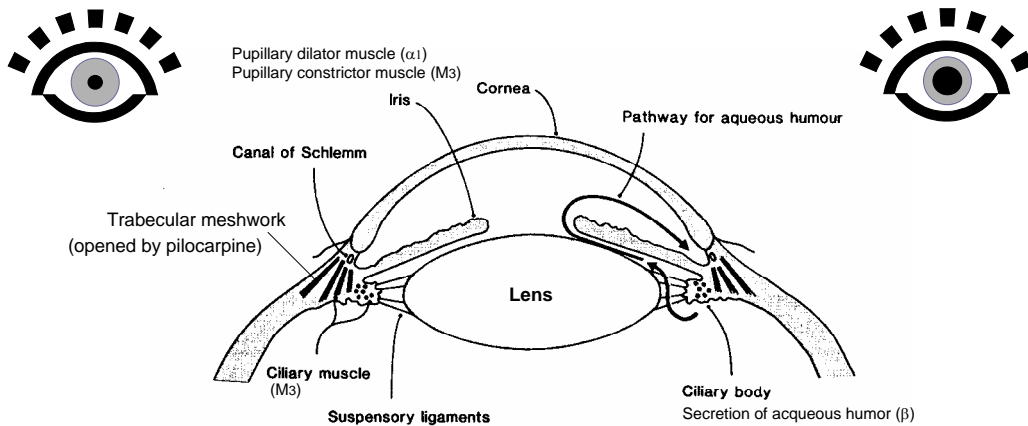


Fig. 6.5 The anterior chamber of the eye, showing the pathway for secretion and drainage of the aqueous humor.