

Part II

Autonomic Receptor Functions

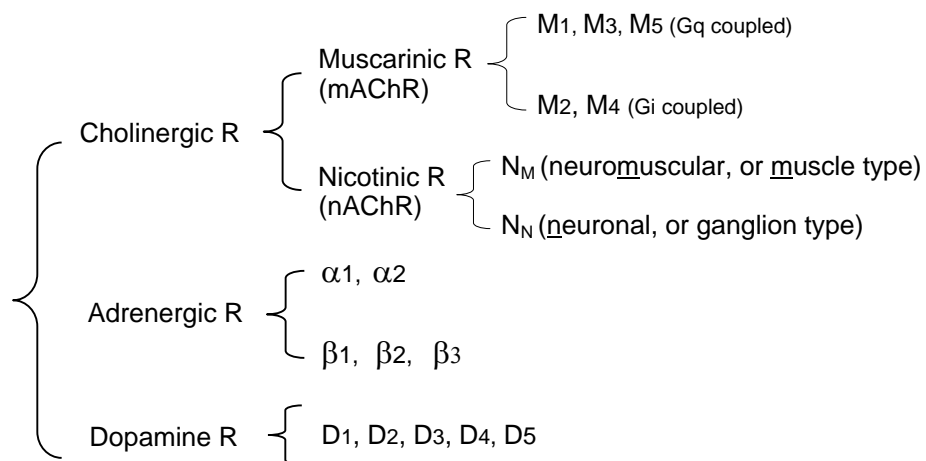
Summary of ANS overview

- Pharmacological classification of ANS is based on neurotransmitters: cholinergic, adrenergic, and dopaminergic.
- Major sites for pharmacological interventions are neurotransmitter synthesis, storage, release, action and metabolism.
- Acetylcholine synthesis is a one-step enzyme conversion. Its metabolism involves one major enzyme: cholinesterase.
- Synthesis of catecholamines (dopamine, norepinephrine, and epinephrine) requires multiple enzymes. Their metabolism requires two enzymes.
- The actions of neurotransmitters are mediated through receptors. An action on a receptor is a direct action. Indirect-acting drugs can affect receptor function through acting on a different molecule. When the net effect mimics that of a neurotransmitter, it is an agonistic effect. When the net effect negates or is opposite of the effect of a neurotransmitter, it is antagonistic.

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

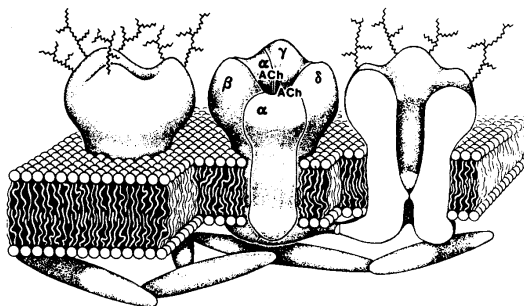
The “**Nicotinic Actions**” -- similar to those induced by nicotine

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

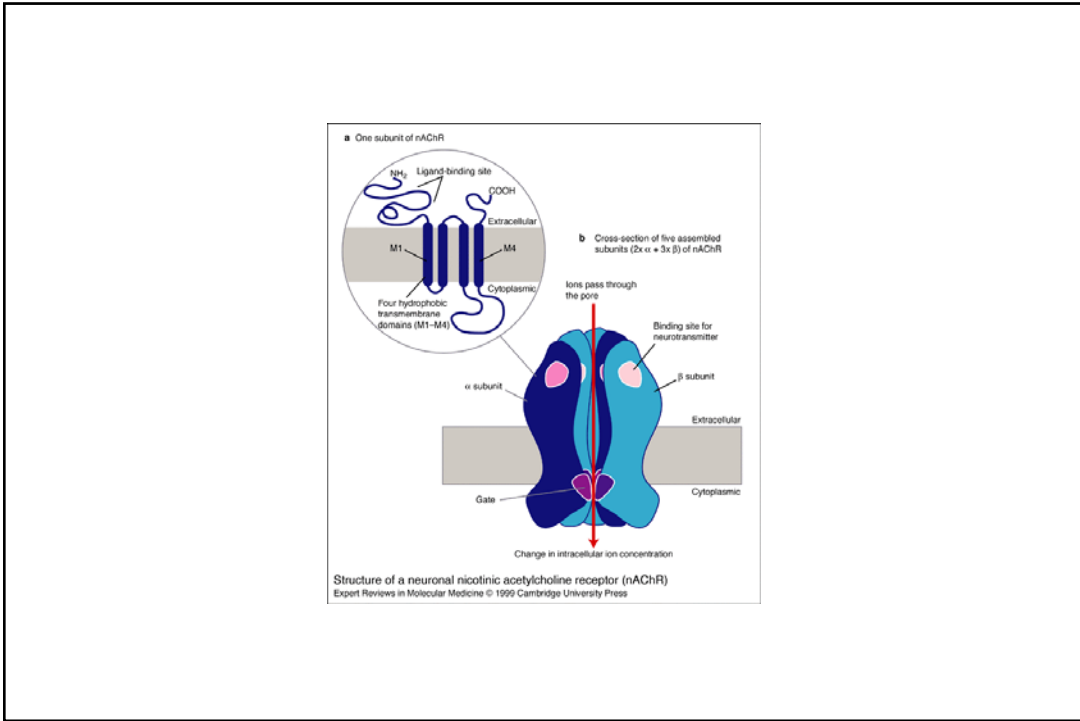
The “**Muscarinic Actions**” -- reproduced by injection of muscarine, from *Amanita muscaria*. Similar to those of parasympathetic stimulation

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

Nicotinic acetylcholine receptor: Structure

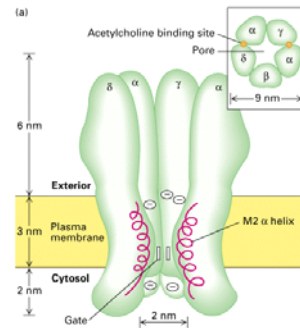


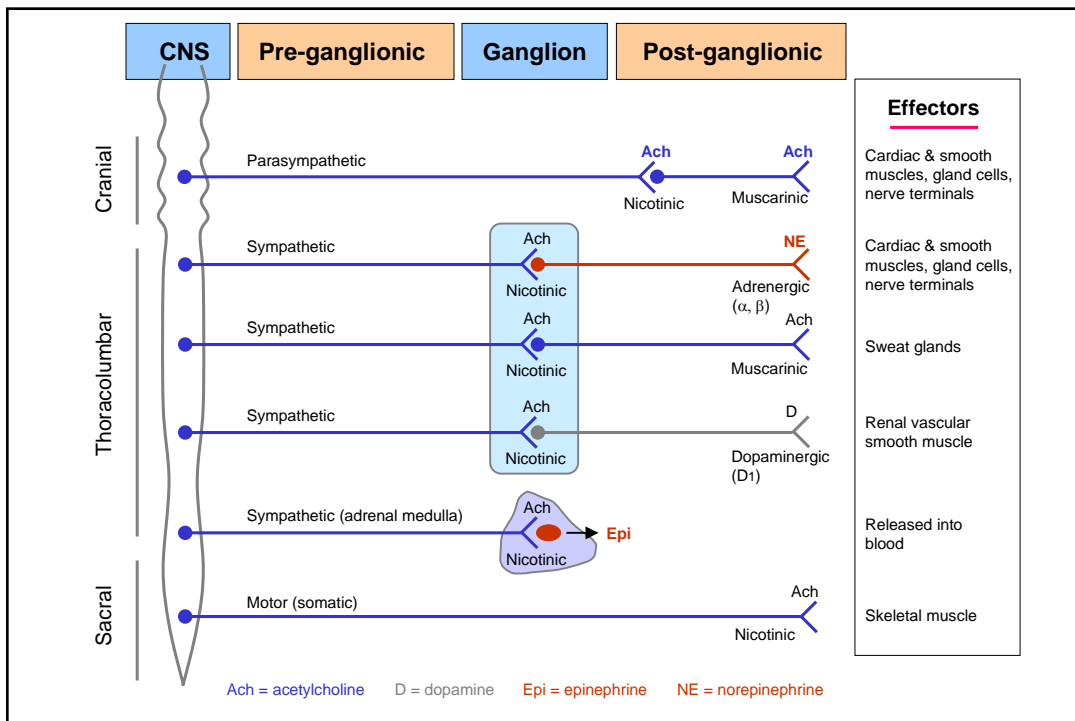
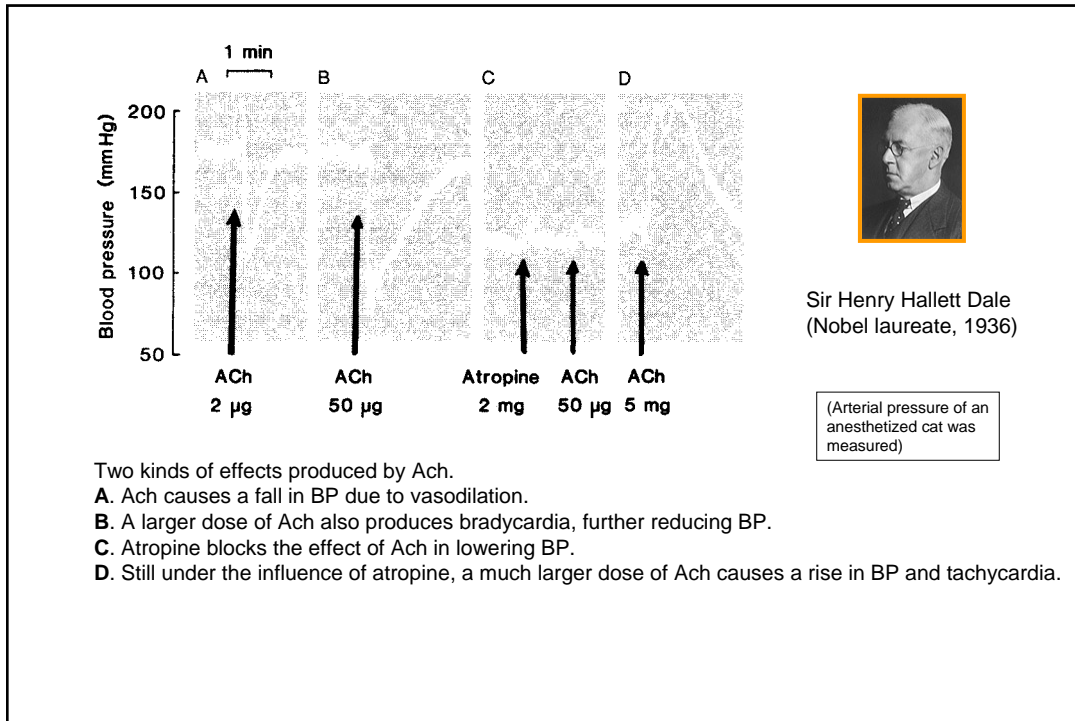
- All nAChRs have a pentameric structure, consisting of subunits in different combinations:
 - A total of 9 different α subunits and 4 different β subunits have been identified
- In skeletal muscle: $\alpha_1(2)$, β , γ , δ (γ is replaced by ϵ in adult muscle)
- In autonomic ganglion: α_3 , α_5 , α_7 , β_2 , β_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



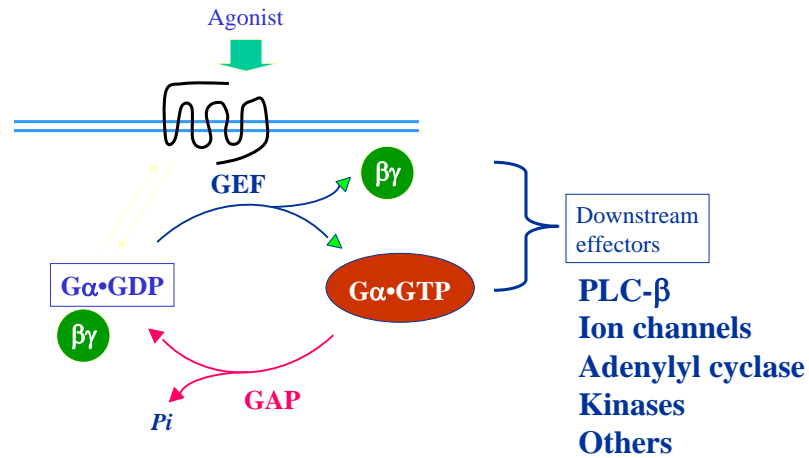
Nicotinic acetylcholine receptor: Function

- 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.

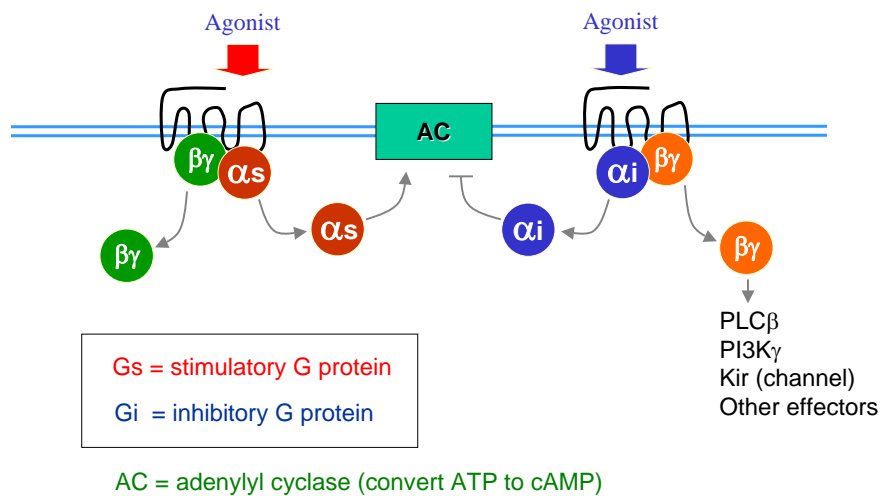




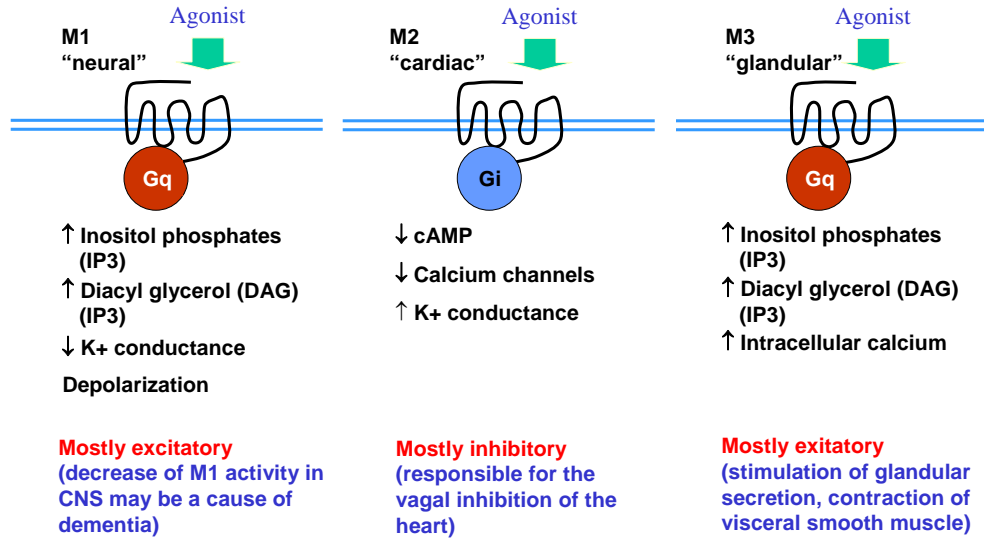
G-proteins are activated by muscarinic receptors



Gs and Gi proteins have different functions



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

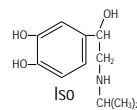
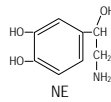
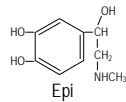
α -- NE > Epi > Iso

β -- Iso > Epi > NE

NE = norepinephrine

Epi = epinephrine

Iso = isoproterenol

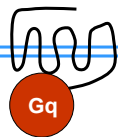


Signaling properties of adrenergic receptors

Norepinephrine
Epinephrine
Phenylephrine

Agonist

$\alpha 1$



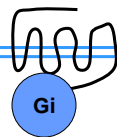
↑ Inositol phosphates (IP3)
↑ Diacyl glycerol (DAG) (IP3)

Mostly excitatory

Norepinephrine
Methyl NE
Clonidine

Agonist

$\alpha 2$



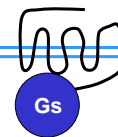
↓ cAMP
↓ Calcium channels
↑ K⁺ conductance

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 ad./ ch nerve term.

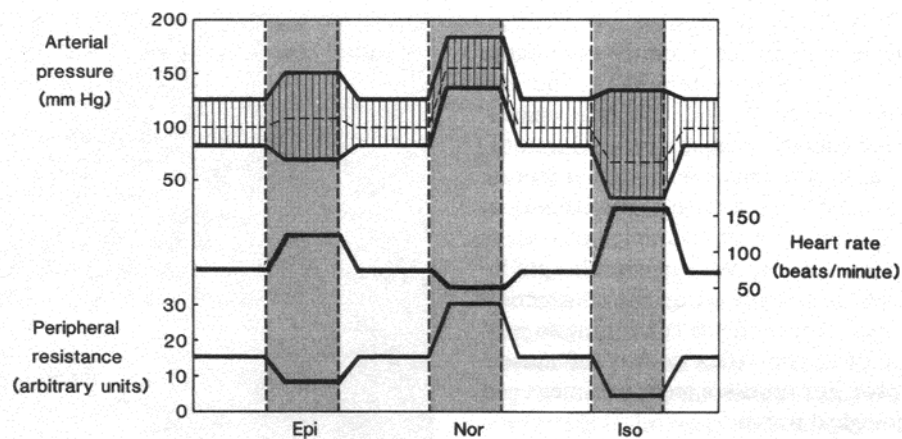
Increased cardiac rate & force, relaxation of gastrointestinal smooth muscle

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, \uparrow outflow of aqueous humor

Adrenergic effects:

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

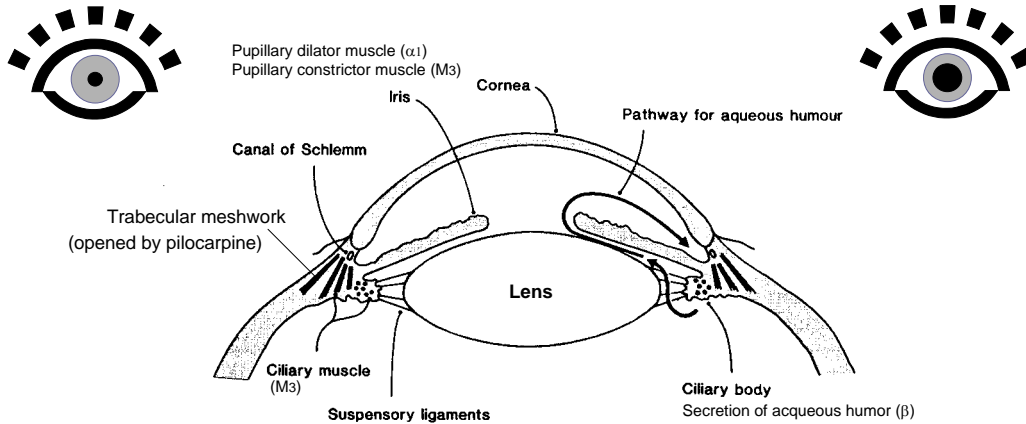


Fig. 6.5 The anterior chamber of the eye, showing the pathway for secretion and drainage of the aqueous humor.

Dopamine and Dopamine Receptors

- Important neurotransmitter in CNS – accounts for more than half of the total catecholamines made in CNS. Related to Parkinson's, schizophrenia, etc.
- Effects in peripheral is mainly mediated through the type 1 receptor (D1), dilating renal arterial vasculature and improving glomerular blood flow. When injected *i.v.*, dopamine stimulates NE release and thereby increases β AR activation in heart.
- The 5 dopamine receptors are all G protein-coupled receptors, and can be classified into two groups:
 - D1 and D5: Gs-coupled; when activated, cause increase in intracellular cAMP.
 - D2, 3, 4: Gi-coupled; when activated, cause decrease in intracellular cAMP and increase in inositol (3,4,5)-trisphosphate.