NEURODEGENERATIVE DISEASES

NEURODEGENERATIVE DISEASES

- Neurodegenerative diseases
  - Alzheimer's disease (AD) and other dementias
  - Parkinson's disease (PD) and PD-related disorders
  - Prion disease
  - Motor neurone diseases (MND)
    - Amyotrophic lateral sclerosis (ALS)
  - Huntington's disease (HD)
  - Spinocerebellar ataxia (SCA)
  - Spinal muscular atrophy (SMA)

NEURODEGENERATIVE DISEASES

- Neurodegenerative diseases represent a large group of neurological disorders with heterogeneous clinical and pathological expressions affecting specific subsets of neurons in specific functional anatomic systems; they arise for unknown reasons and progress in a relentless manner

NEURODEGENERATIVE DISEASES

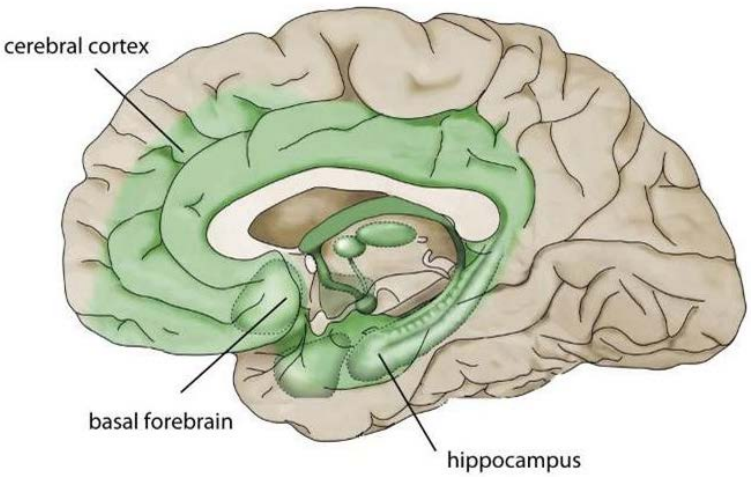
- Neurodegenerative diseases
  - Protein misfolding
  - Excitoxicity
  - Oxidative stress
    - Necrosis
    - Apoptosis

NEURODEGENERATIVE DISEASES

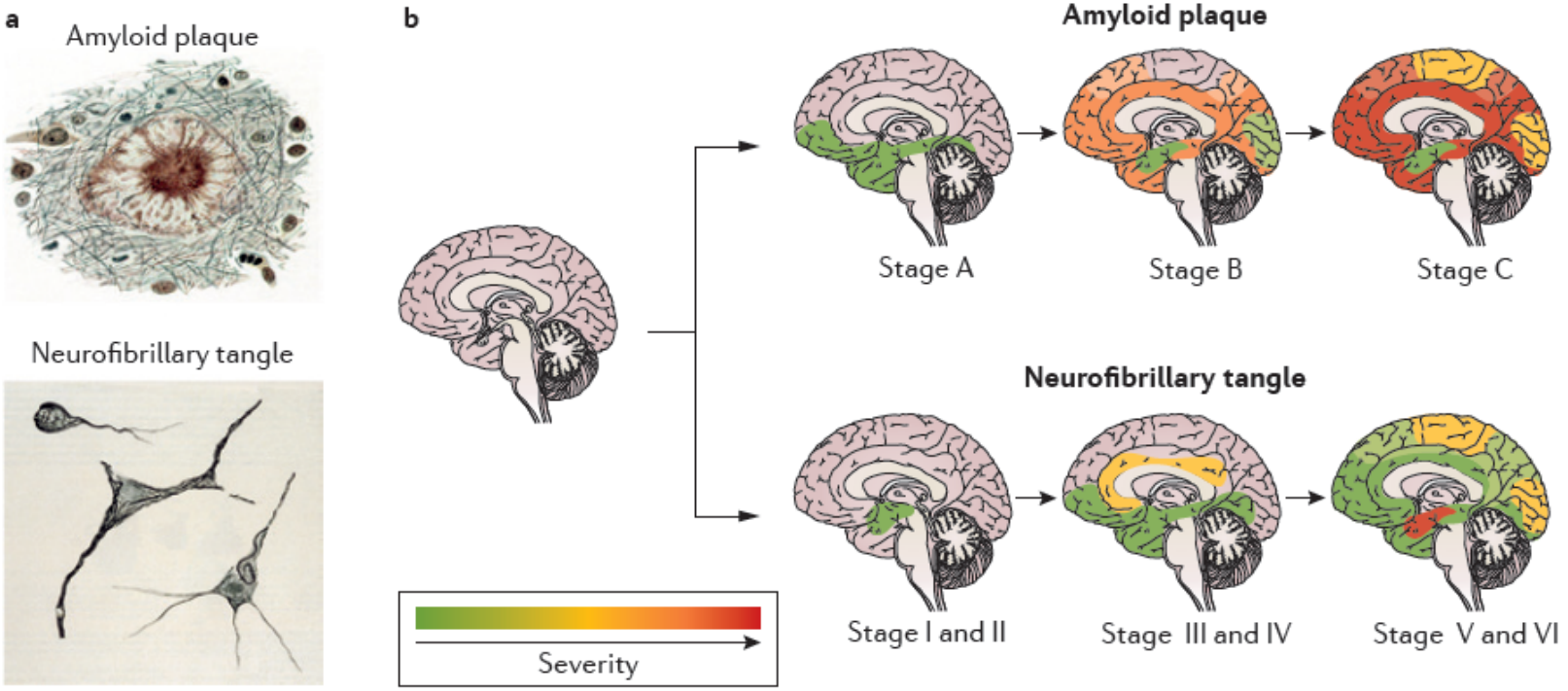
- Alzheimer’s disease
  - Alzheimer’s disease is a chronic illness with long preclinical and prodromal phases (20 years) and an average clinical duration of 8–10 years. The disease has an estimated prevalence of 10–30% in the population >65 years of age with an incidence of 1–3%
  - Most patients with Alzheimer’s disease (>95%) have the sporadic form, which is characterized by a late onset (80–90 years of age)

NEURODEGENERATIVE DISEASES

- Alzheimer's disease
  - Alzheimer's disease is a progressive, unremitting, neurodegenerative disorder that affects wide areas of the cerebral cortex, basal forebrain and hippocampus. Abnormalities are usually first detected in the brain tissue that involves the frontal and temporal lobes, and then slowly progress to other areas of the neocortex at rates that vary considerably between individuals

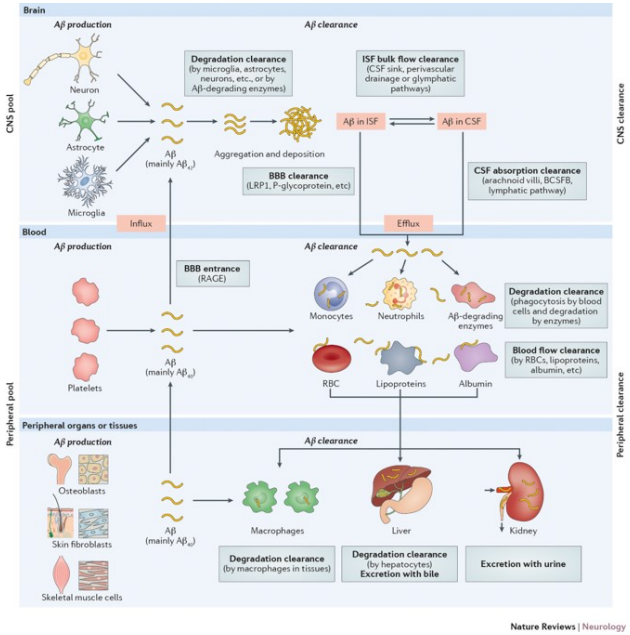


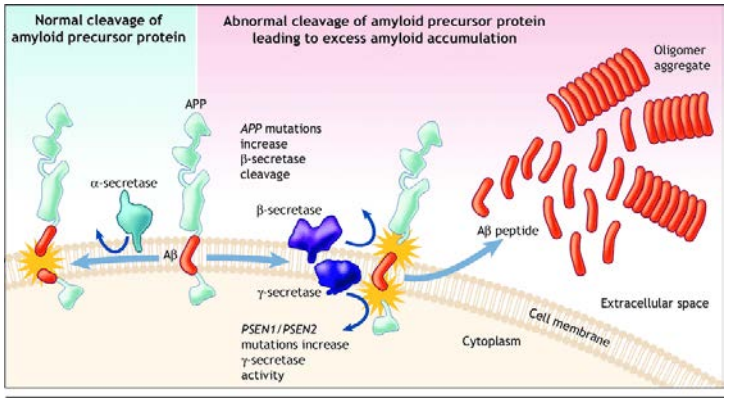
NEURODEGENERATIVE DISEASES



NEURODEGENERATIVE DISEASES

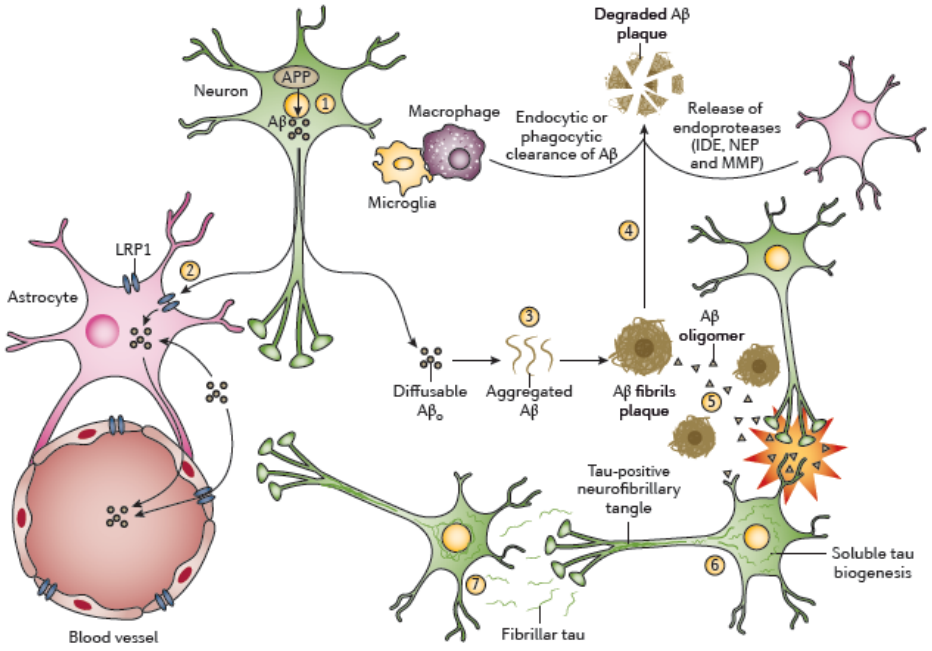
- Alzheimer's disease
  - Pathogenesis of Alzheimer's disease
    - Amyloid-β, APOE and tau are three elements that have substantial evidence as contributors of Alzheimer's disease
    - Alzheimer's disease is associated with the accumulation of insoluble forms of amyloid-β (Aβ) in plaques in extracellular spaces, as well as in the walls of blood vessels, and aggregation of the microtubule protein tau in neurofibrillary tangles in neurons
    - Altered processing of amyloid protein from its precursor (amyloid precursor protein, APP) is now recognised as the key to the pathogenesis of AD
    - It is uncertain exactly how Aβ accumulation causes neurodegeneration, and whether the damage is done by soluble Aβ monomers or oligomers or by amyloid plaques. There is evidence that the cells die by apoptosis, although an inflammatory response is also evident





NEURODEGENERATIVE DISEASES

- Alzheimer's disease
  - Pathogenesis of Alzheimer's disease
    - The other main player on the biochemical stage is Tau, the protein of which the neurofibrillary tangles are composed
    - Tau is a normal constituent of neurons, being associated with the intracellular microtubules that serve as tracks for transporting materials along nerve axons. In AD Tau is abnormally phosphorylated and dissociates from microtubules to be deposited intracellularly as paired helical filaments with a characteristic microscopic appearance
    - Tau phosphorylation is enhanced by the presence of Aβ, possibly by activation of kinases. Conversely, hyperphosphorylated Tau favours the formation of amyloid deposits

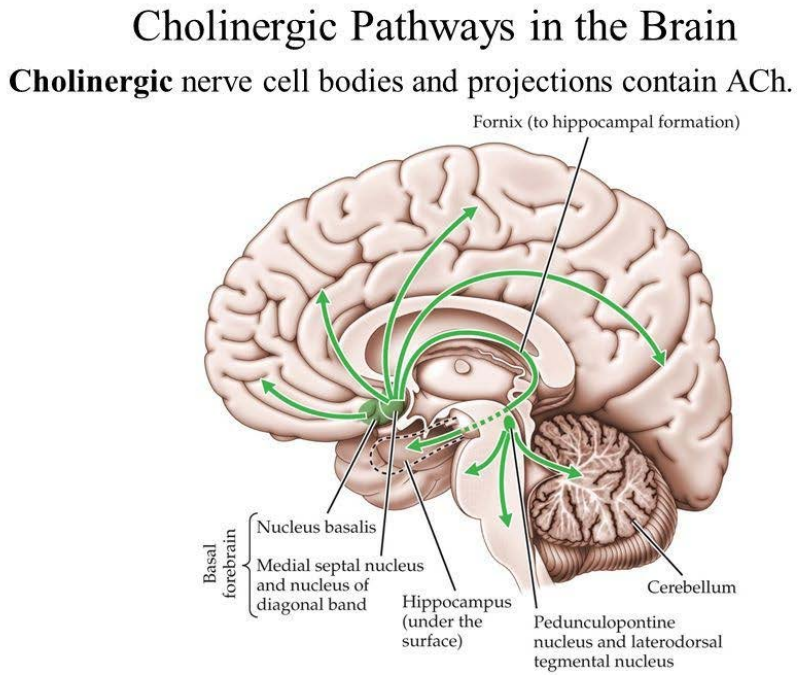


NEURODEGENERATIVE DISEASES

- Alzheimer’s disease
  - Loss of cholinergic neurons
    - Although changes in many transmitter systems have been observed a relatively selective loss of cholinergic neurons in the basal forebrain nuclei is characteristic
    - Choline acetyl transferase activity, acetylcholine content and acetylcholinesterase and choline transport in the cortex and hippocampus are all reduced considerably in AD
    - Muscarinic receptor density is not affected, but nicotinic receptors, particularly in the cortex, are reduced

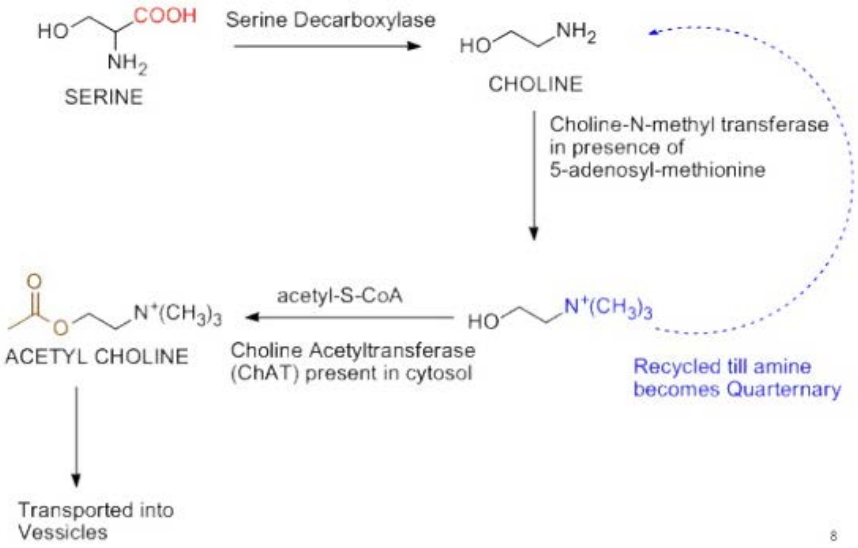
CHOLINERGIC TRANSMISSION

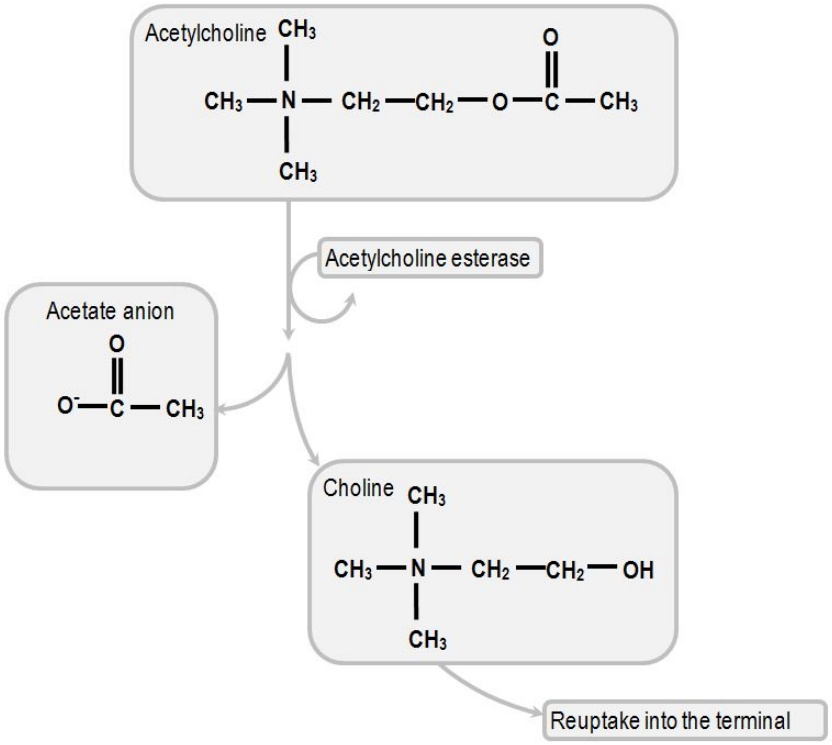
CHOLINERGIC PATHWAY



- Degeneration of the forebrain cholinergic neurons is a pathogenetic feature of Alzheimer’s disease and alcoholic and pugilistic dementia, conditions in which loss of attention and memory deficits represent the first and the most important symptoms

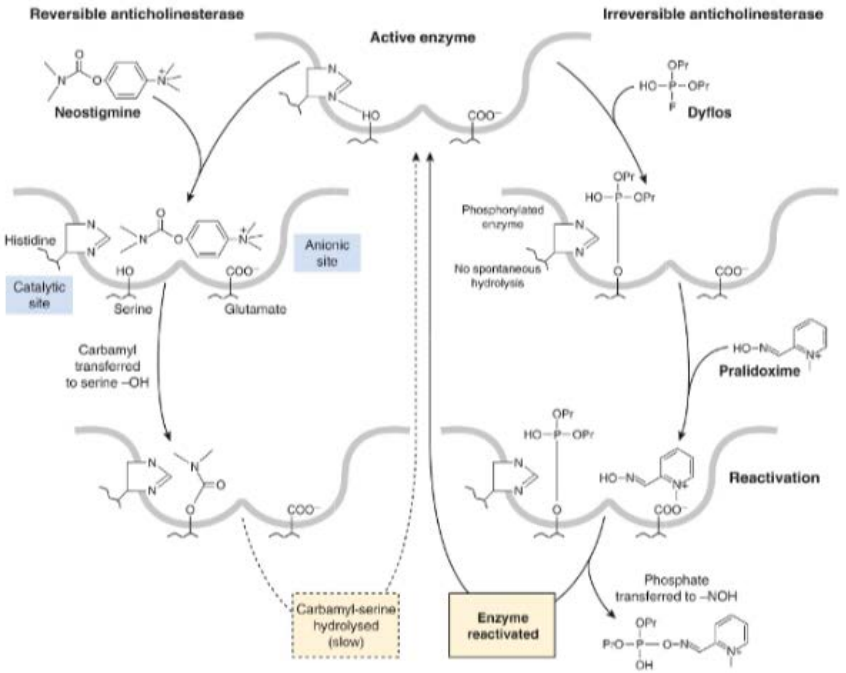
SYNTHESIS AND METABOLISM OF ACETYLCHOLINE



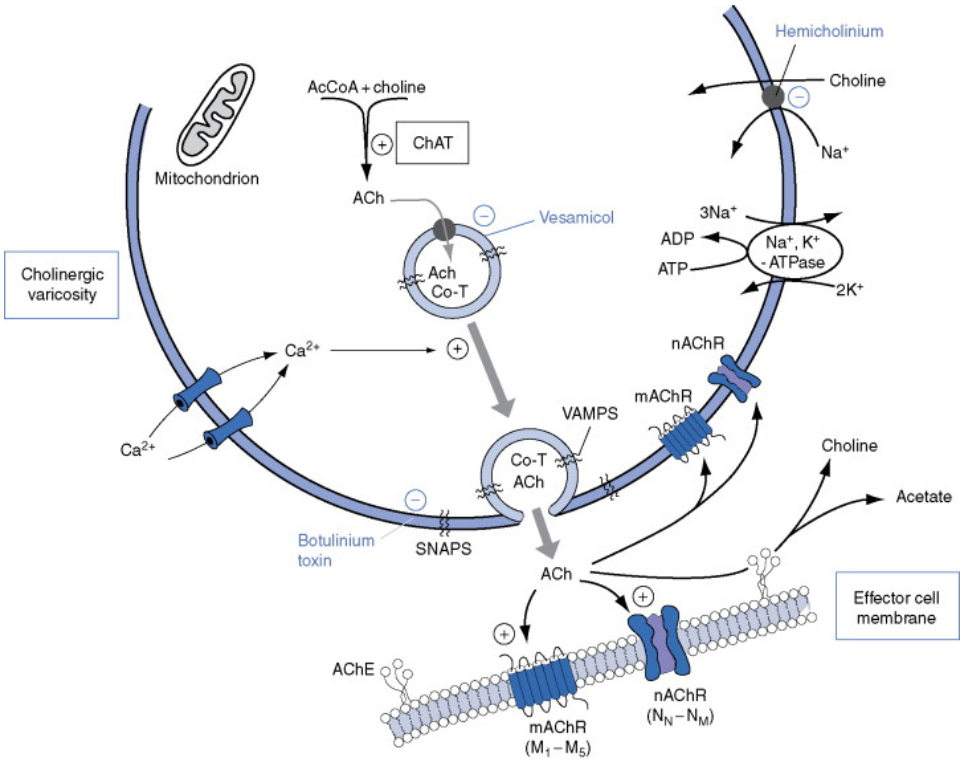


NEURODEGENERATIVE DISEASES

- Cholinergic transmission
  - Cholinesterases
    - There are two cholinesterases (ChE)
      - Acetylcholinesterase (AChE), whose function is the rapid hydrolysis of the Ach released in the synaptic cleft
      - Butyrylcholinesterase (BChE), whose physiological function has not yet been fully understood
      - Both consist of globular catalytic subunits, which constitute the soluble and bound BChe and AChE
    - AChE and BChE belong to the class of serine hydrolases



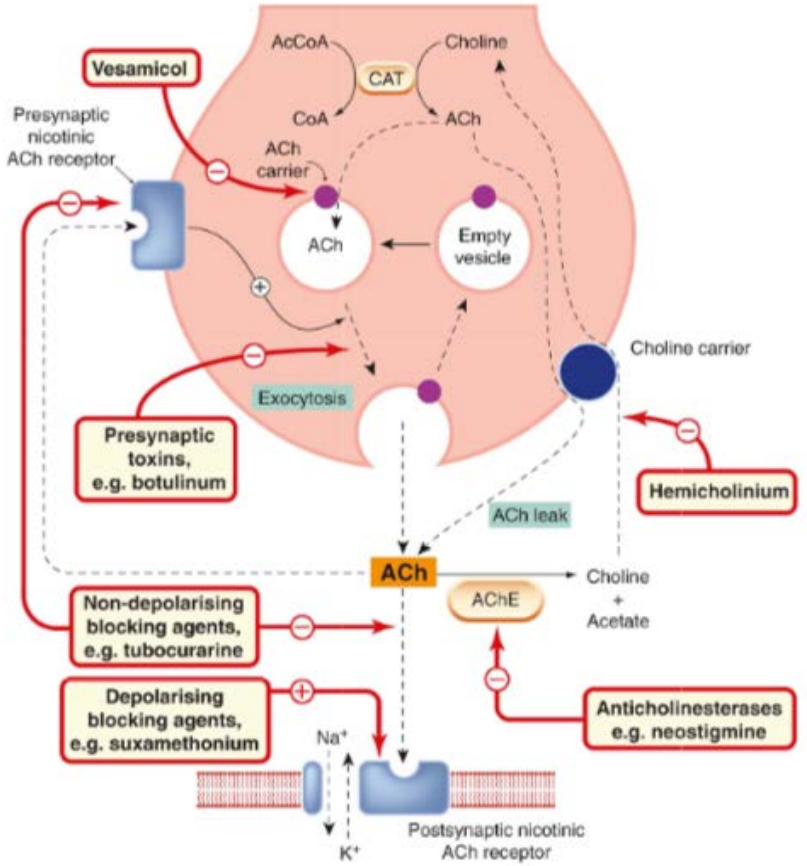
ACETYLCHOLINE STORAGE-RELEASE-REUPTAKE-INACTIVATION



- The synthesis of ACh in the varicosity depends on the uptake of choline via a sodium-dependent carrier. This uptake can be blocked by hemicholinium. Choline and the acetyl moiety of acetyl coenzyme A (AcCoA), derived from mitochrondria, form ACh, a process catalyzed by the enzyme choline acetyltransferase (ChAT). ACh is transported into the storage vesicle by another carrier that can be inhibited by vesamicol. ACh is stored in vesicles along with other potential cotransmitters (Co-T) such as adenosine triphosphate (ATP) and vasoactive intestinal polypeptide at certain neuroeffector junctions. Release of ACh and the Co-T occurs on depolarization of the varicosity, which allows the entry of Ca^{2+} through voltage-dependent Ca^{2+} channels. Elevated $[Ca^{2+}]$in promotes fusion of the vesicular membrane with the cell membrane, and exocytosis of the transmitters occurs. This fusion process involves the interaction of specialized proteins associated with the vesicular membrane, called vesicle-associated membrane proteins (VAMPs) and the membrane of the varicosity, called synaptosome-associated proteins (SNAPs). The exocytotic release of ACh can be blocked by botulinum toxin. Once released, ACh can interact with the muscarinic receptors (mAChRs), which are G-protein-coupled receptors, or nicotinic receptors (nAChRs), which are ligand-gated ion channels, to produce the characteristic response of the effector. ACh can also act on presynaptic mAChR or nAChR to modify its own release. The action of ACh is terminated by metabolism to choline and acetate by the enzyme acetylcholinesterase (AChE), which is associated with synaptic membranes

NEURODEGENERATIVE DISEASES

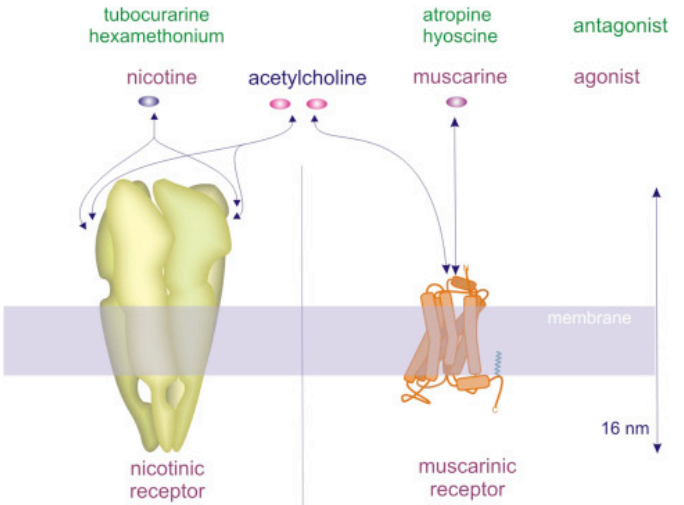
- Cholinergic transmission



NEURODEGENERATIVE DISEASES

- Cholinergic transmission
  - Acetylcholine (ACh) synthesis:
    - requires choline, which enters the neuron via carrier-mediated transport
    - choline is acetylated to form ACh by choline acetyl transferase, a cytosolic enzyme found only in cholinergic neurons. Acetyl coenzyme A is the source of acetyl groups
  - ACh is packaged into synaptic vesicles at high concentration by carrier-mediated transport
  - ACh release occurs by Ca^{2+}-mediated exocytosis. At the neuromuscular junction, one presynaptic nerve impulse releases 100–500 vesicles
  - At the neuromuscular junction, ACh acts on nicotinic receptors to open cation channels, producing a rapid depolarisation (endplate potential), which normally initiates an action potential in the muscle fibre. Transmission at other ‘fast’ cholinergic synapses (e.g. ganglionic) is similar
  - At ‘fast’ cholinergic synapses, ACh is hydrolysed within about 1 ms by acetylcholinesterase, so a presynaptic action potential produces only one postsynaptic action potential
  - Transmission mediated by muscarinic receptors is much slower in its time course, and synaptic structures are less clearly defined. In many situations, ACh functions as a modulator rather than as a direct transmitter
  - Main mechanisms of pharmacological block: inhibition of choline uptake, inhibition of ACh release, block of postsynaptic receptors or ion channels, persistent postsynaptic depolarisation

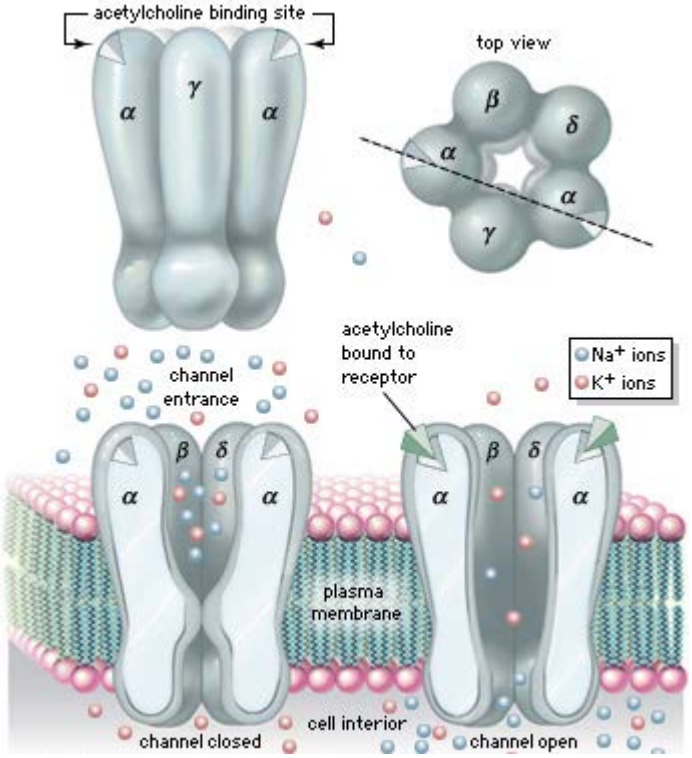
ACETYLCHOLINE RECEPTORS



membrane depolarization (or Ca^{2+} entry) "ionotropic"	G-protein regulated effectors "metabotropic"	
Nmuscular -neuromuscular junction	M1	-brain, -autonomic ganglia -glands
Nneuron -brain -peripheral nervous system -chromaffin cells (adrenal medulla)	M2	-heart -brain
	M3	-smooth muscle (airway, gut, bladder, eye) -glands (salivary, gastric, sweat, airway submucosal) -endothelium -brain
	M4	-brain
	M5	-brain (substantia nigra -salivary gland -smooth muscle eye

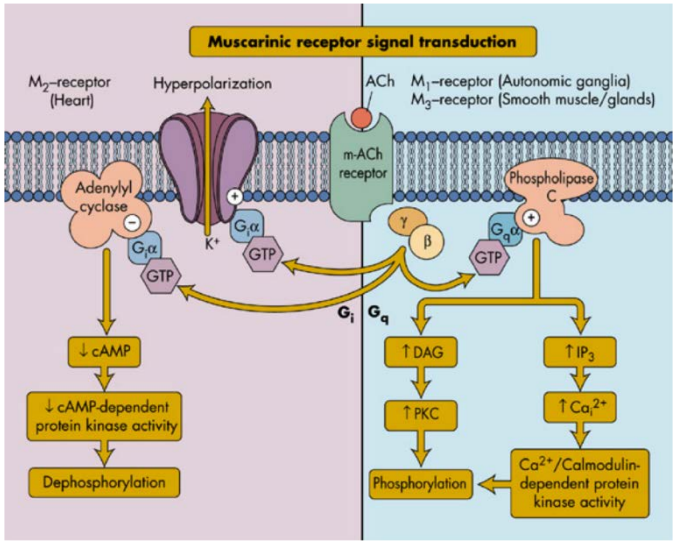
NEURODEGENERATIVE DISEASES

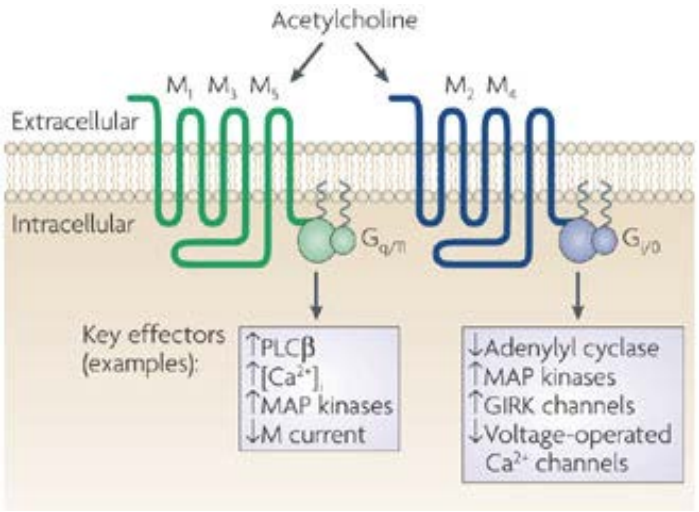
- Cholinergic transmission
  - Acetylcholine receptors
    - Nicotinic receptor (nAChR)
      - nAChRs are directly coupled to cation channels, and mediate fast excitatory synaptic transmission at the neuromuscular junction, autonomic ganglia and various sites in the central nervous system (CNS). Muscle and neuronal nAChRs differ in their molecular structure and pharmacology



NEURODEGENERATIVE DISEASES

- Cholinergic transmission
  - Acetylcholine receptors
    - Muscarinc repetor (mAChR)
      - mAChRs are G protein-coupled receptors causing:
        - activation of phospholipase C (hence formation of inositol trisphosphate and diacylglycerol as second messengers)
        - inhibition of adenylyl cyclase
        - activation of potassium channels or inhibition of calcium channels
      - mAChRs mediate acetylcholine effects at postganglionic parasympathetic synapses (mainly heart, smooth muscle and glands), and contribute to ganglionic excitation. They occur in many parts of the CNS
      - Three main types of mAChR occur:
        - M_1 receptors ('neural') producing slow excitation of ganglia
        - M_2 receptors ('cardiac') causing decrease in cardiac rate and force of contraction (mainly of atria). M2 receptors also mediate presynaptic inhibition
        - M_3 receptors ('glandular') causing secretion, contraction of visceral smooth muscle, vascular relaxation





NEURODEGENERATIVE DISEASES

- Cholinergic transmission
  - Effects of drugs on cholinergic transmission
    - Drugs can influence cholinergic transmission either by acting on postsynaptic ACh receptors as agonists or antagonists, or by affecting the release or destruction of endogenous Ach
      - Muscarinic agonists
      - Muscarinic antagonists
      - Ganglion-stimulating drugs
      - Ganglion-blocking drugs
      - Neuromuscular-blocking drugs
      - Anticholinesterases and other drugs that enhance cholinergic transmission

NEURODEGENERATIVE DISEASES

- Alzheimer’s disease
  - Cholinesterase inhibitors
    - There is some evidence from laboratory studies that cholinesterase inhibitors may act somehow to reduce the formation or neurotoxicity of Aβ, and therefore retard the progression of AD as well as producing symptomatic benefit. Clinical trials, however, have shown only a small improvement in cognitive function, with no effect on disease progression
      - Tacrine
      - Donepezil
      - Rivastigmine
      - Galantamine

NEURODEGENERATIVE DISEASES

- Alzheimer's disease
  - Cholinesterase inhibitors

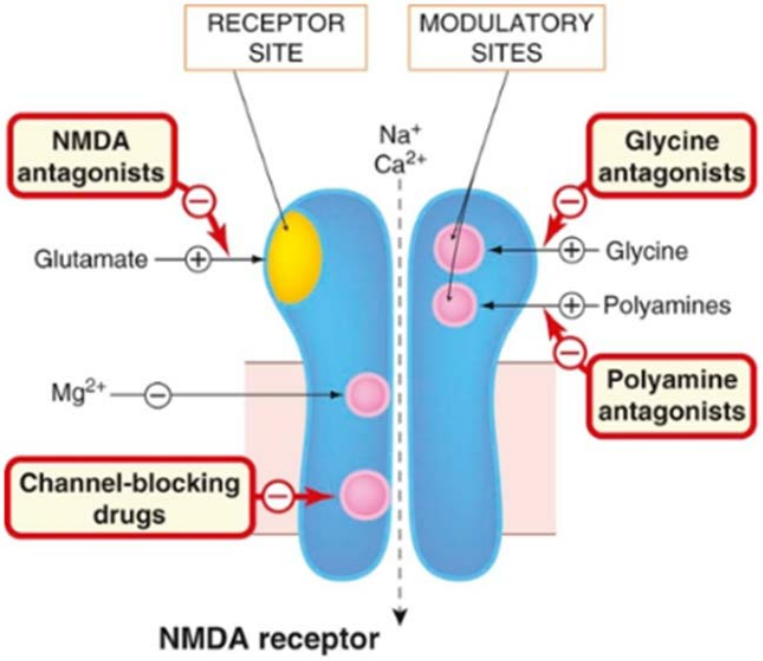
Drug	Tipe of inhibiion	Duration of action and dosage	Main saide effects	Notes
Tacrine	Affects both AChE and BuChE Not CNS selective	~6 h 2–3 times daily oral dosage	Cholinergic side effects (abdominal pain, nausea, diarrhoea), hepatotoxicity	The first anticholinesterase shown to be efficacious in AD Monitoring for hepatotoxicity needed
Donezepil	CNS, AChE selective	~6 h 2–3 times daily oral dosage	Slight cholinergic side effects	
Rivastigmine	CNS selective	~8 h Twice-daily oral dosage	Cholinergic side effects that tend to subside with continuing treatment	Gradual dose escalation to minimise side effects
Galantamine	Affects both AChE and BuChE Also enhances nicotinic ACh receptor activation by allosteric action	~8 h Twice-daily oral dosage	Slight cholinergic side effects	

NEURODEGENERATIVE DISEASES

- Glutamate receptor
  - Glutamate and related excitatory amino acids activate both ionotropic (ligand-gated cation channels) and metabotropic (G protein-coupled) receptors
    - Ionotropic Glutamate Receptors
      - NMDA
      - AMPA
      - kainate

NEURODEGENERATIVE DISEASES

- Glutamate receptor
  - NMDA
    - NMDA receptors are assembled from seven types of subunit (GluN1, GluN2A, GluN2B, GluN2C, GluN2D, GluN3A, GluN3B)
    - They are highly permeable to $Ca^{2+,}$ as well as to other cations, so activation of NMDA receptors is particularly effective in promoting Ca^{2+} entry
    - They are readily blocked by $Mg^{2+,}$ and this block shows marked voltage dependence. It occurs at physiological Mg^{2+} concentrations when the cell is normally polarised, but disappears if the cell is depolarised
    - Activation of NMDA receptors requires glycine as well as glutamate. The binding site for glycine is distinct from the glutamate binding site, i.e. glycine is an allosteric modulator, and both have to be occupied for the channel to open



NEURODEGENERATIVE DISEASES

- Glutamate receptor
  - Metabotropic Glutamate Receptors (mGlu)
    - There are eight different metabotropic glutamate receptors (mGlu1–8)
    - They can be divided into three groups on the basis of their sequence homology, G protein coupling and pharmacology
      - Neuronal group 1 mGlu receptors are located postsynaptically and are largely excitatory
      - Group 2 and 3 mGlu receptors are mostly presynaptic receptors and their activation tends to reduce synaptic transmission and neuronal excitability
      - They can be autoreceptors, involved in reducing glutamate release
    - mGlu receptors are widely distributed throughout the central nervous system on neurons, where they regulate cell excitability and synaptic transmission, and on glia

NEURODEGENERATIVE DISEASES

- Glutamate receptor
  - In general, it appears that NMDA and mGlu receptors play a particular role in long-term adaptive and pathological changes in the brain, and are of particular interest as potential drug targets

NEURODEGENERATIVE DISEASES

- Alzheimer’s disease
  - NMDA receptor antagonists
    - Memantine
      - An orally active weak antagonist at NMDA receptors. It produces – surprisingly – a modest cognitive improvement in moderate or severe AD, but does not appear to be neuroprotective. It may work by selectively inhibiting excessive, pathological NMDA receptor activation while preserving more physiological activation. It has a long plasma half-life, and its adverse effects include headache, dizziness, drowsiness, constipation, shortness of breath and hypertension as well as a raft of less common problems

NEURODEGENERATIVE DISEASES

- Alzheimer's disease
  - Inhibiting neurodegeneration
    - Inhibitors of β- and γ-secretase
      - Though they are effective in reducing Aβ formation, they appear to make cognition impairment worse. Several proved toxic to the immune system and gastrointestinal tract, and development has been halted
    - Kinase inhibitors aimed at preventing Tau phosphorylation
      - The large number of phosphorylation sites and different kinases make this a difficult approach
    - Monoclonal Aβ antibodies
    - NSAIDs
    - Aβ plaques bind copper and zinc, and removal of these metal ions promotes dissolution of the plaques
      - The amoebicidal drug clioquinol is a metal-chelating agent that causes regression of amyloid deposits in animal models of AD, and showed some benefit in initial clinical trials. Clioquinol itself has known toxic effects in humans, which preclude its routine clinical use, but less toxic metal-chelating agents are under investigation

NEURODEGENERATIVE DISEASES

- Alzheimer's disease
  - Other approaches
    - New potent and selective histamine H_3 antagonists may improve cognition in AD
    - Levetiracetam, an anticonvulsant with a novel mechanism of action, may slow the development of AD
    - Caprylidene (caprylic triglyceride)
      - It may be useful in mild to moderate AD to improve memory and cognitive function but it does not reverse neuronal degeneration
    - Latrepirdine
    - Statins