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Course; 322 PHL

Alzheimer's Disease

Lectures

- ✧ Alzheimer's Disease (AD) from a pharmacological prospective
- ✧ Autism Spectrum Disorder (ASD)
- ✧ Eating disorders
- ✧ Addiction
- ✧ Pain pathway and pharmacological intervention (ANALGESICs)

Learning outcomes

After lecture, student should

- Understand what is neurodegeneration.
- Understand pathophysiology behind neurodegeneration.
- Differentiate between different types of cell death (necrosis vs apoptosis).
- Know what is Alzheimer disease (AD).
- Pathophysiology and molecular etiology of AD
- Treatment approaches for AD

Neurodegeneration

- Neuronal death which lead to an irreversible consequences

Examples of neurodegenerative disease

1- Alzheimer's disease (AD)

2- Parkinson disease (PD)

→ chronic, slow development

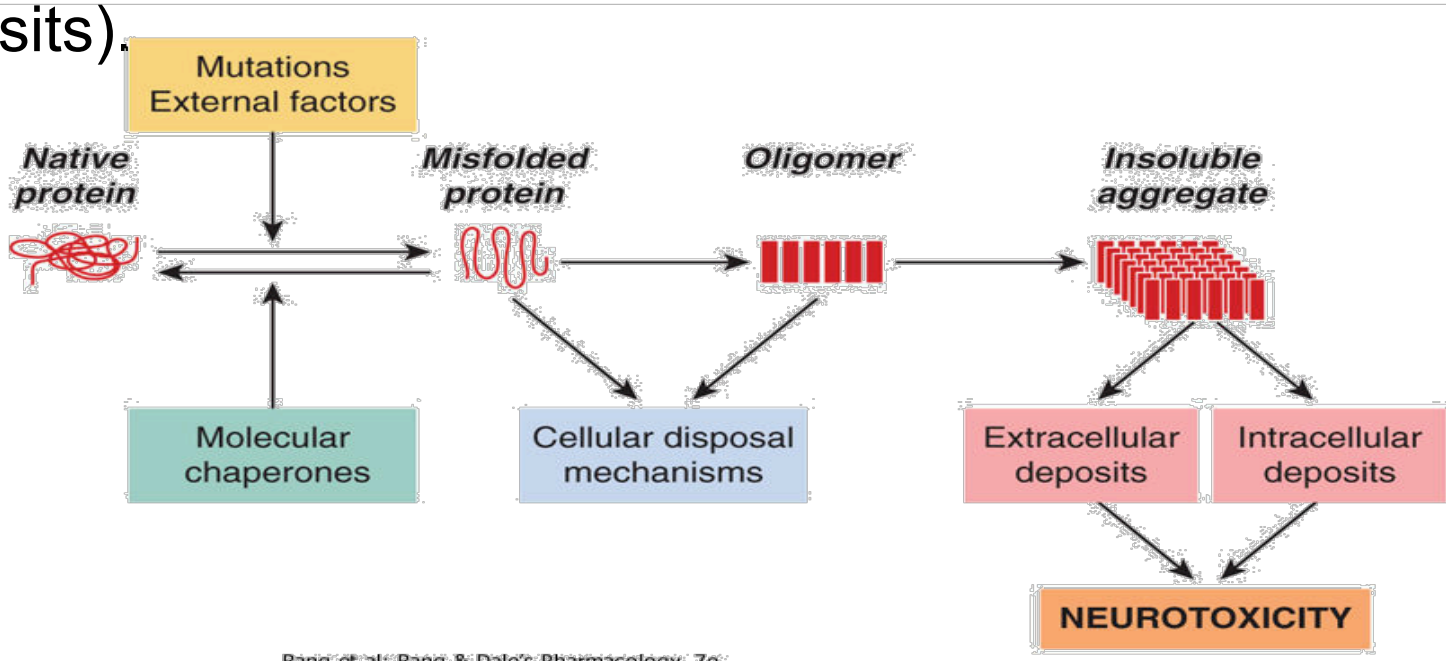
3- Ischemic brain damage (STROKE) ➔ acute ischemic brain damage

How slow, chronic neurodegeneration occur?

The first step in neurodegeneration achieved by aggregation of insoluble, misfolded protein in\out of the cell

Protein misfolding;

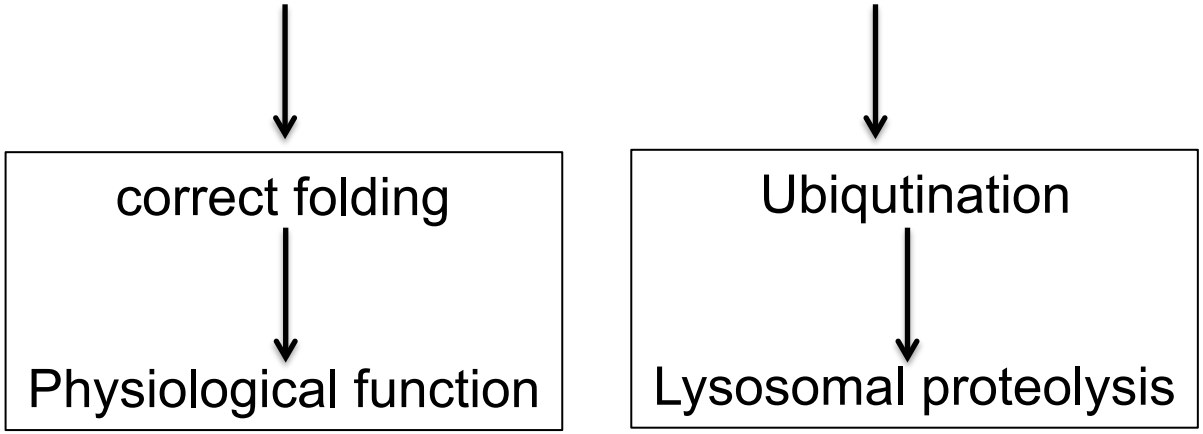
- Adoption of abnormal conformation leading to the formation of water insoluble, adhesive, oligomer aggregate.
- This aggregates then form microscopic-visible deposits (e.g. amyloid deposits).



Rang et al: Rang & Dale's Pharmacology, 7e

Defense mechanism against protein misfolding

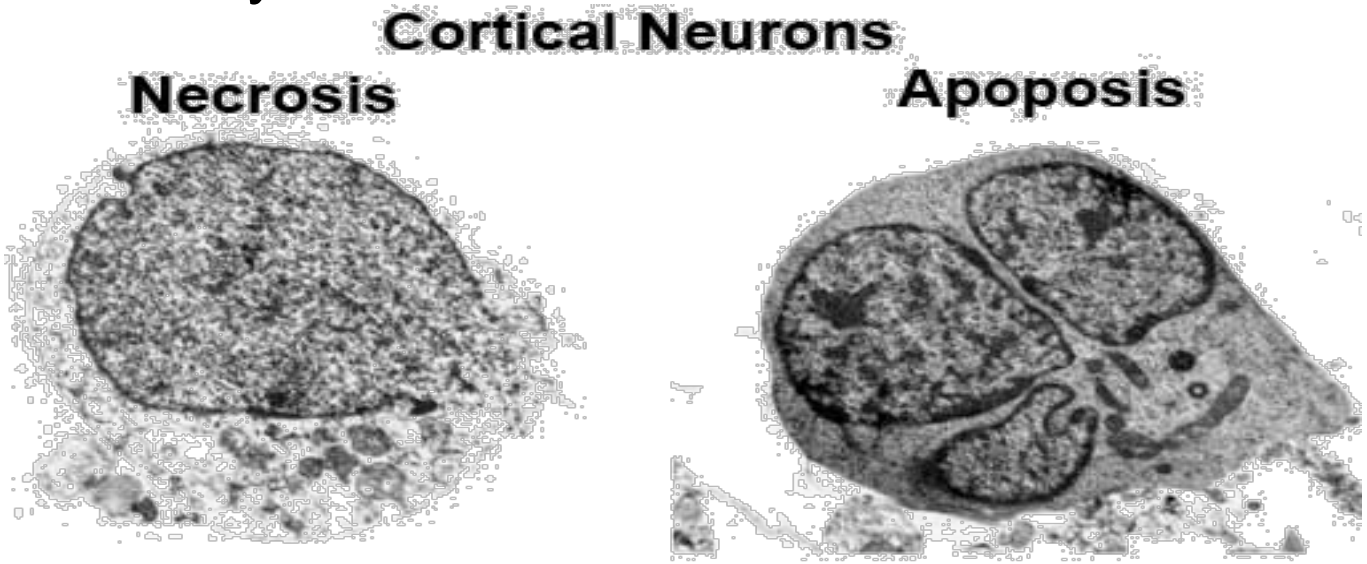
"Chaperone" binds to newly synthesized\misfolded protein



Types of cell death

1. Necrosis; Acute injury of the cell ➔ increase intracellular calcium ($[Ca^{2+}]_i$) overload ➔ cell swelling and vacuolization ➔ membrane damage ➔ cell death & lysis.

2. Apoptosis; programed cell death initiated by specific stimuli (death receptors or mitochondrial pathway) ➔ activation of caspaces pathway (3, 8, 9) ➔ cell death



Ueda H, etal., J Cell Biol. 2007 Mar 12;176(6):853-62 PMID: 17353361

Continued types of cell death

- Apoptosis is essential for several physiological processes including embryogenesis, development, immune regulation and tissue remodeling.
- Neuronal apoptosis is antagonized by growth factors (nerve growth factor and brain-derived neurotropic factor).
- Both types occur in acute as will as chronic neurodegenerative disease.
- Current efforts directed against necrosis and compensation of neuronal loss.

ALZHEIMER'S DISEASE (AD)

- 1906, First described by german pathologist (Alois Alzheimer).
- AD is a neurodegenerative disorder that mostly affects the *ELDERLY*.
- Defined as type of dementia *("de" without "ment" mind)* that have no earlier cause (e.g. stroke, brain trauma, alcohol).
- Dementia means loss of cognitive ability (mental process) such as memory, attention, solving problems, understanding language and making decisions.
- 5% of AD cases at age of 65 yrs and ≥ 90% at 95 yrs

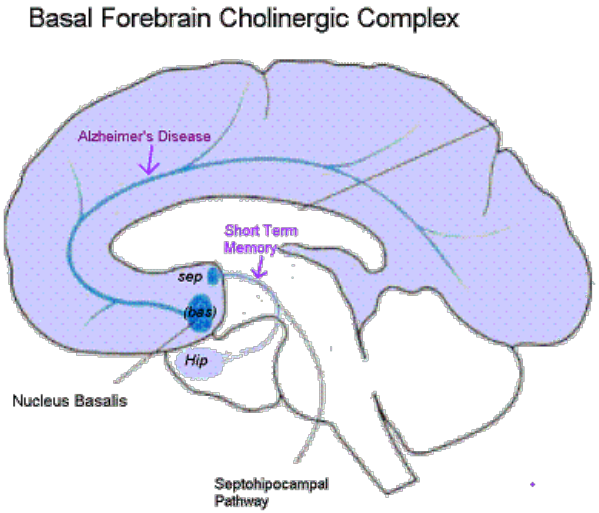
Incidence rates after age 65[204]

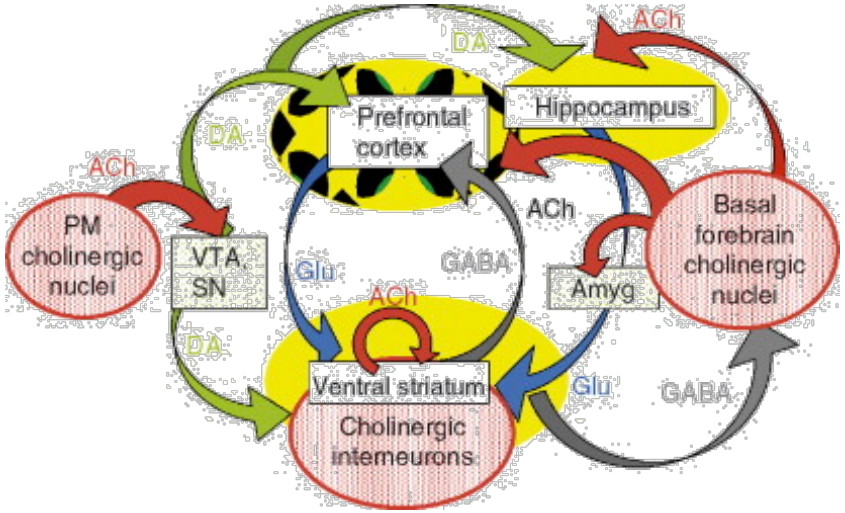
Age	New affected per thousand person–years
65–69	3
70–74	6
75–79	9
80–84	23
85–89	40
90–	69

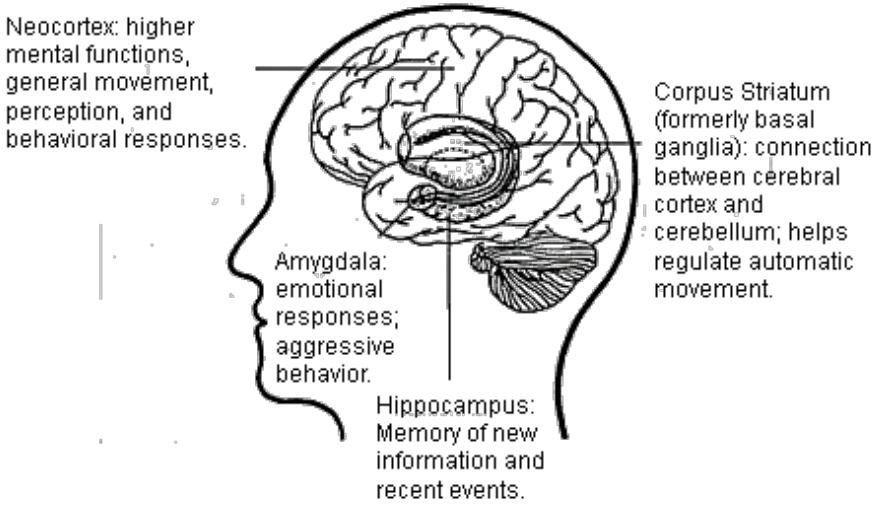
Bermejo-Pareja F *et al* J. *Neurol. Sci.*. 2008;264(1–2):63–72

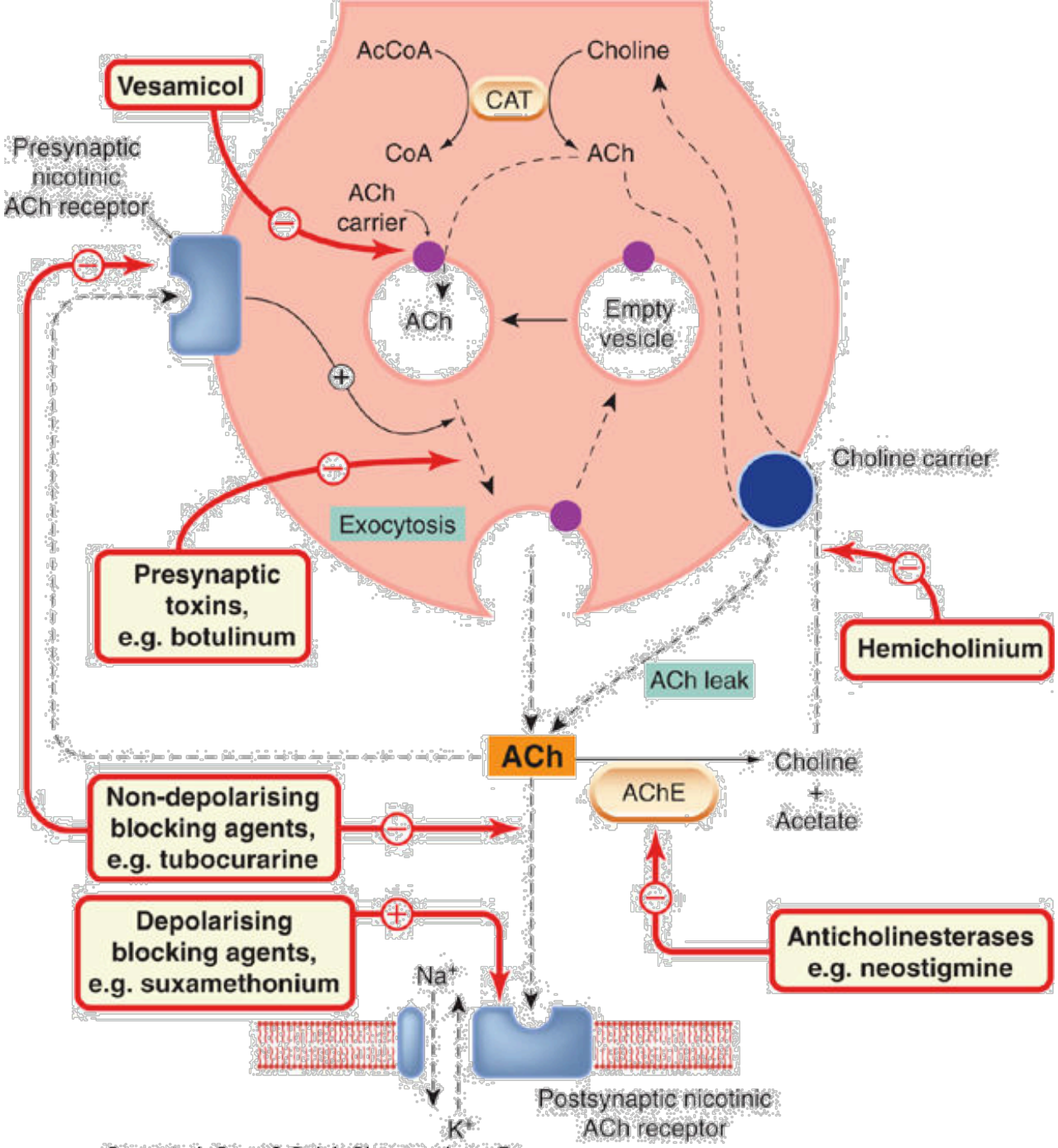
Pathophysiology of AD

- Loss of cholinergic neurons begins mainly in hippocampus and basal forebrain ➔ loss of cognitive ability and short-term memory









Continued Pathophysiology of AD

Evidence for the loss of cholinergic neurons

- Choline acetyltransferase (CAT) activity, Ach content in cortex and hippocampus is significantly reduced in AD but not other disorders including PD and schizophrenia.
- Number of muscarinic receptors (mAchR) in these area is not affected, however nicotinic receptors (nAchR) is reduced.

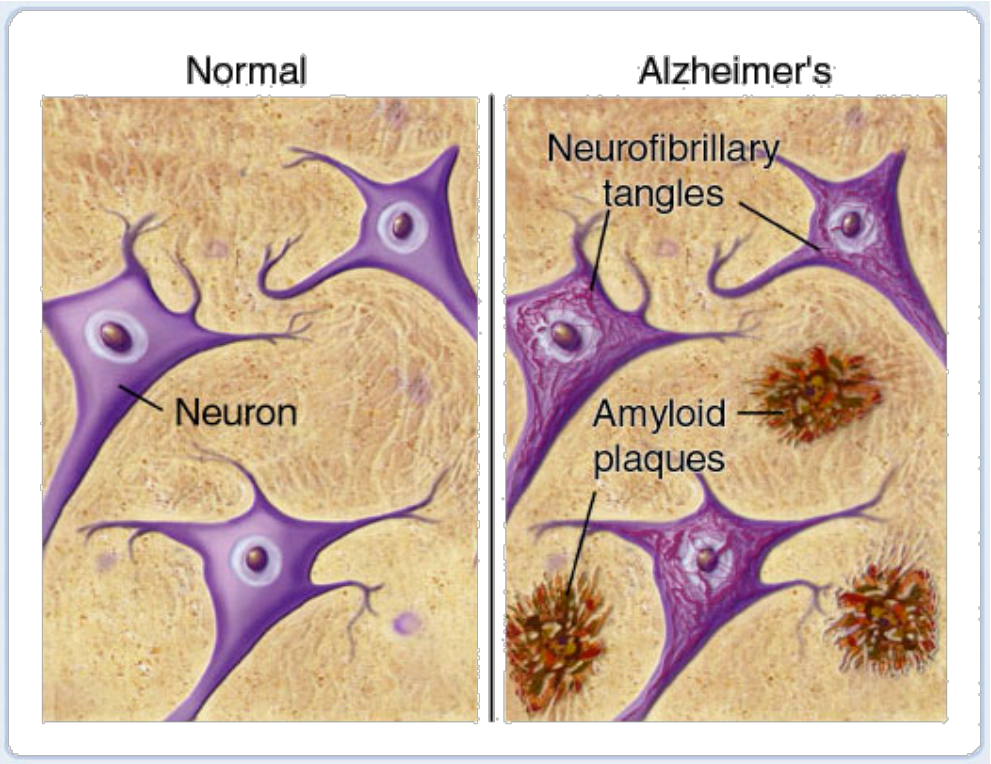
N.B. Reason behind the selective loss of cholinergic neurons is UKNOWN

Continued Pathophysiology of AD

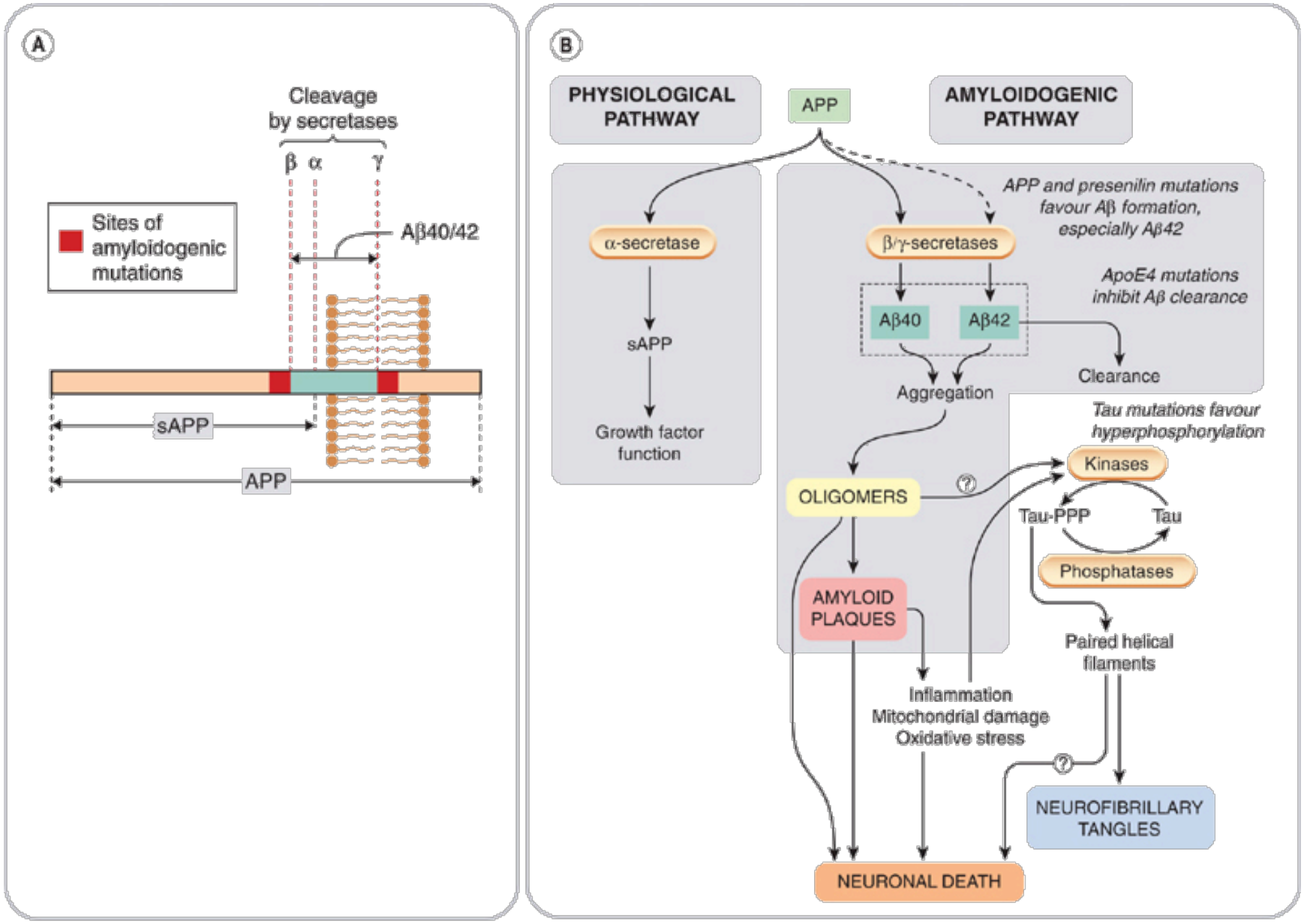
Microscopic features of AD

1. Depositions of extracellular amyloid plaques β-Amyloid (Aβ)
2. Intraneuronal neurofibrillary tangles (Phosphorylated form of microtubules-associated protein called "tau")

- Both are aggregates of misfolded protein.
- Symptoms appear several years after appearance of these markers.
- Altered processing of Aβ from amyloid protein precursor (APP) is the key of AD pathogenesis!!!



processing of Aβ from amyloid protein precursor (APP)



Treatment approach of AD

- Compensatory rather than preventing or reversing loss of neurons.
- 1967, pharmaceutical applications that restoring cholinergic function using cholinesterase (AchE) inhibitors might be beneficial for AD patients.
- Research experiments ➔ AchE inhibitors can also reduce neurotoxicity of Aβ (clinical trials could not prove it!)

✧ Cholinesterase inhibitors (AChE)

1. Tacrine (Cognex)

- 1st drug approved
- Cause improvement of cognitive ability in 40% of AD patients
- Enhance cholinergic transmission
- Not CNS selective
- Also act on buteryl cholineesterase (BuChE)
- Duration approximately 6h (taken 4x)
- Side effects (Cholinergic side effects including abdominal pain, nausea and diarrhea), hepatotoxicity

2. Donepezil (Aricept)

- CNS, AChE selective
- Duration ~24 h (Once-daily oral dosage)
- Side effects; slighter cholinergic side effects than Tacrine

3. Rivastigmine (Exelon)

- CNS selective
- Duration ~8 h (Twice-daily oral dosage)
- Cholinergic side effects that tend to subside with continuing treatment

4. Galantamine (Razadyne or Reminyl)

- Affects both AChE and BuChE
- enhances nicotinic ACh receptor activation by allosteric action
- Duration ~8 h (Twice-daily oral dosage)
- Side effects; slighter cholinergic side effects than Tacrine

✧Excitotoxicity inhibition

Memantine

- Oral, NMDA receptor antagonist
- Formal use as antiviral
- Modest improve in moderate-sever AD patient
- Side effects, fatigue, pain, increases in blood pressure, dizziness, headache constipation, vomiting, back pain and confusion

Inhibition of neurodegeneration (clinical trials) Phase II/ Phase III

1. Inhibitors of Aβ aggregation (Immunological approach; antibody directed against Aβ).
2. Inhibitors of β- and γ-secretase.
3. Aβ vaccination.
4. Clioquinol (amoebicidal & metal chelating agent): Aβ plaques bind cooper and zinc, thus removal of these metal ions promotes dissolution of the plaques.
5. Nerve growth factor: shortage of growth factors may contribute to the loss of forebrain cholinergic neurons in Alzheimer's disease.
6. NSAIDs (esp. ibuprofen & indomethacin) reduce Aβ42 formation by regulating γ-secretase (unrelated to COX inhibition)

Additional Treatments for AD

- the role of dietary factors (low saturated fat diets, moderate alcohol intake)
- Cholinergic stimulation: nicotine patch, varenicline (Chantix , Champix)
- Vitamin E – decrease cytotoxicity - may slow the progression of the disease
- Mild sedatives (Haldol) are helpful in reducing agitation and behavior disturbances

Autism spectrum disorders (ASDs)
Autism

- ASDs include asperger's disorder, childhood disintegrative disorder, rette's disorder, pervasive development disorder, and autistic disorder (autism).
- The most common is autistic disorder (autism)
- First described by Kanner in 1943
- Autism is neurodevelopmental disorder defined by qualitative impairment in social interaction, impaired communication, and stereotyped patterns of behavior (The Diagnostic and Statistical Manual of Mental Disorders).
- Appears during the first 3 years of life and persist throughout the lifespan
- The affected regions of the brain include the areas of social interaction and communication skills.

symptoms

1. Repetitive and stereotypic behavior

- Intensely preoccupied with a single subject, activity or gesture
- Practice strange actions like rocking or hand-flapping
- Sniff or lick toys
- Show no sensitivity to burns or bruises, and engage in self-mutilation
- Show distress over change
- Insist on routine or rituals with no purpose
- Lack of fear
- Symptom similarity exists between these phenomena in autism and patients with obsessive-compulsive disorder (OCD)
- Evidence of serotonin system dysregulation in individuals with autism.

2. Hyperactivity and inattention

- The symptoms of hyperactivity and inattention are similar to those seen in Attention-Deficit/Hyperactivity Disorder (ADHD).

3. Irritability

- Aggression.
- Self-injurious behavior (SIB).
- Severe tantrums (emotional outburst including stubbornness, crying, yelling, screaming).
- Physically attack and injure others without provocation.

4. Core Social Impairment

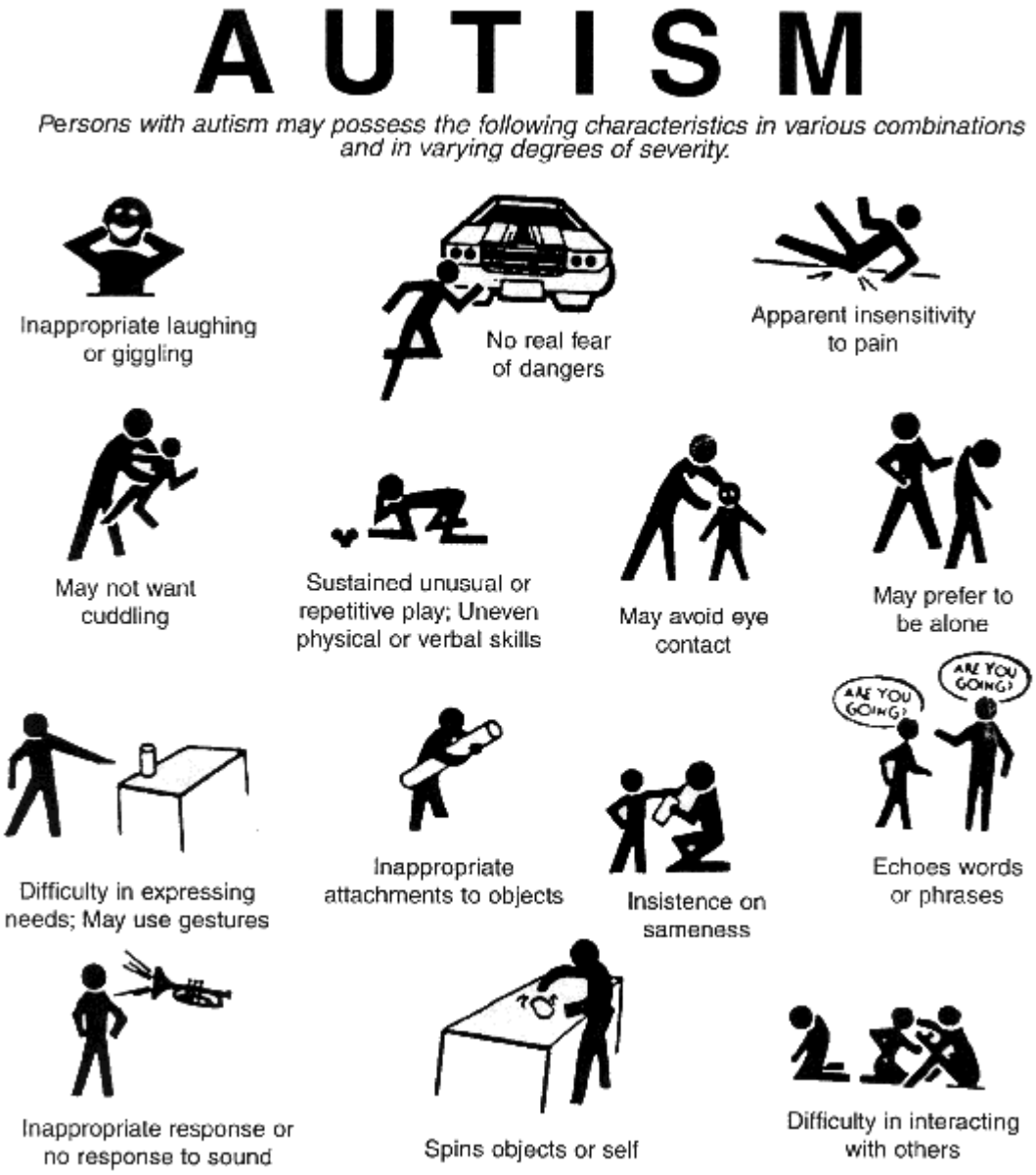
- Communication

- Avoid eye contact
- Act as if deaf
- Develop language, then abruptly stop talking
- Fail to use spoken language, without compensating by gesture

- Social relationships

- Act as if unaware of the coming and going of others
- Are inaccessible, as if in a shell
- Fail to seek comfort
- Fail to develop relationships with peers
- Have problems seeing things from another person's perspective, leaving the child unable to predict or understand other people's actions

Symptoms of children with autism



Cause of autism

- Studies of twins confirm that autism has a heritable compound but suggest that environmental influences play a role as well (teratogens)
- By examining the inheritance of the disorder, researchers have shown that autism does run in families, but not in a clear-cut way
- Several lines of evidence point to synaptic dysfunction as a cause of autism. Some rare mutations may lead to autism by disrupting some synaptic pathways, such as those involved with cell adhesion.
- MMR vaccination!, MILK?
- A specific cause is not known, but current research links autism to biological and neurological differences in the brain

Treating Autism

1. Repetitive, restrictive and stereotypic behavior

- Serotonin reuptake inhibitors (SSRI)
- SSRIs are prescribed for depression, and/or obsessive-compulsive disorder. Fluoxetine has been approved by the FDA for both OCD and depression in children age 7 and older, fluvoxamine, age 8 and older; sertraline, age 6 and older.
- TCA; Clomipramine, age 10 and older.

2. Hyperactivity and inattention

- psychostimulants; methylphenidate, amphetamine and dextroamphetamine
  - moderate response in autistic patients
  - High probability of side effects including anorexia, sleep disorder, anxiety and irritability limit their use

- Selective noradrenaline reuptake inhibitors; atomoxetine
- α-2 adreneoceptor agonists; clonidine

3. Irritability

- Atypical antipsychotic; Risperidone and Aripiprazole
  - The most common medications used clinically to target these symptoms.
  - The only pharmacologic agents approved byFDA to treat maladaptive behaviors associated with autism.

4. Core Social Impairment

- No medications are currently FDA approved for treatment of social impairment associated with autism.
- Research investigating of the role of the glutamate system in the treatment of core social impairment in autism has demonstrated promising.

Interestingly, studies of atypical antipsychotics targeting irritability in children and adolescents with autism also have shown improvement of stereotypic behavior

Treating Seizures:

- One in four people with ASD also have a seizure disorder. usually they are treated with anticonvulsants such as carbamazepine, lamictal , topiramate or divalproex . Although medication usually reduces the number of seizures, it cannot always eliminate them.