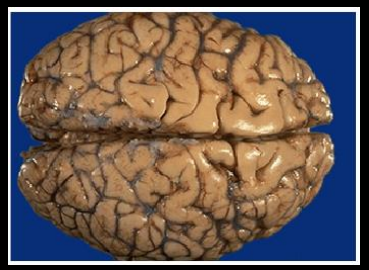
Alzheimer's Disease

CNS Block

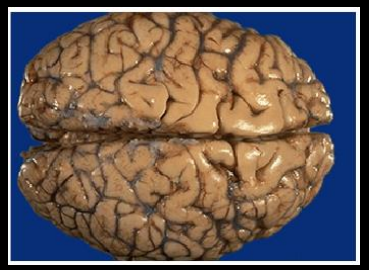
Objectives



Upon completion of this lecture, the students should be able to:

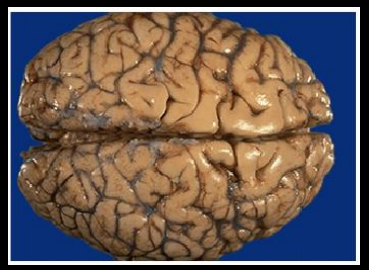
- Have an overview of neurodegenerative disorders
- Understand the role of amyloid beta 40-42 residue peptide in Alzheimer's disease
- Get an idea of the diagnosis and therapeutic approaches to treat these disorders

Neurodegenerative Diseases



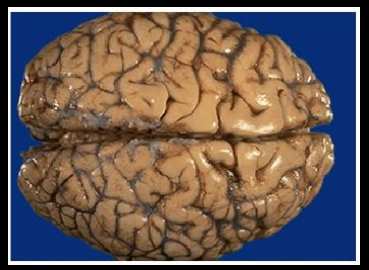
- Diseases of gray matter characterized principally by the progressive loss of neurons
- The pattern of neuronal loss is selective affecting one or more groups of neurons leaving the others intact
- The diseases arise without any clear inciting event in patients without previous neurological deficits

Neurodegenerative Diseases



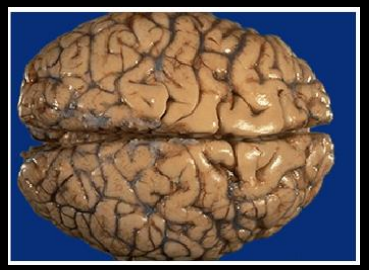
- A common theme is the development of protein aggregates that are resistant to normal cellular mechanisms of degradation
- The aggregated proteins are generally cytotoxic

Alzheimer's Disease



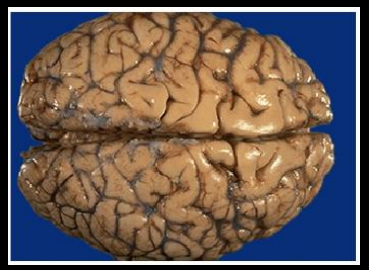
- A degenerative disease with the prominent involvement of the cerebral cortex
- Its principal clinical manifestation is dementia
  - Dementia is the progressive loss of cognitive function independent of the state of attention
- Patients rarely become symptomatic before 50 yr. of age but the incidence of disease rises with age

Alzheimer Disease



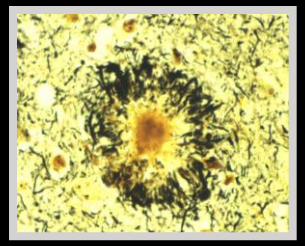
- The disease becomes apparent with:
  - Gradual impairment of higher intellectual function
  - Alterations in mood and behavior
  - Progressive disorientation
  - Memory loss
- In 5-10 yrs, the patient becomes profoundly disabled, mute and immobile
- Most cases are sporadic
- At least 5-10% are familial

Diagnosis



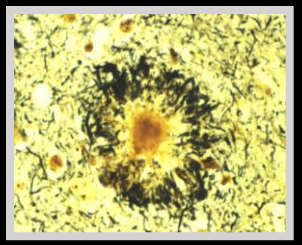
- Combination of clinical assessment and radiologic methods
- Pathologic examination of brain tissue is necessary for definitive diagnosis
- Major microscopic abnormalities include: neuritic plaques, neurofibrillary tangles and amyloid angiopathy

Neuritic Plaques

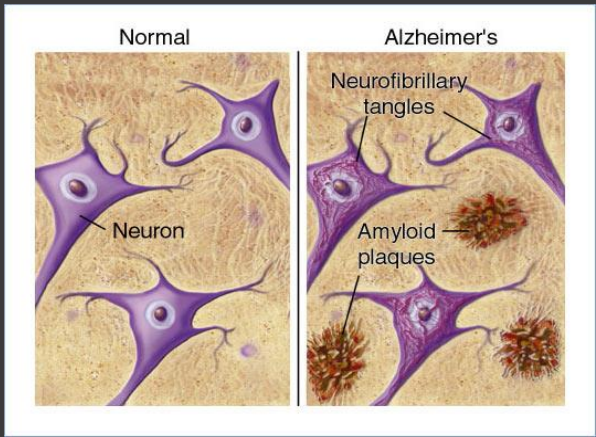


- Spherical with 20-200 μm in diameter
- Contain paired helical filaments as well as synaptic vesicles and abnormal mitochondria
- The amyloid core contains several abnormal proteins
- The dominant component of the plaque core is **Aβ**, a peptide derived from a larger molecule, **amyloid precursor protein** (APP)

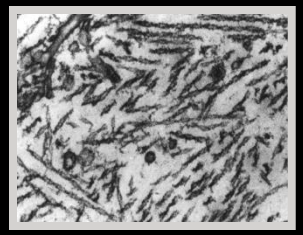
Neuritic Plaques contd..



- The two dominant species of Aβ, called **$A\beta_{40}$** and **$A\beta_{42}$** share an N-terminus and differ in length by two amino acids.
- Other less abundant proteins in the plaque:
  - Components of the compliment cascade
  - Proinflammatory cytokines
  - α_1-Antichymotrypsin
  - Apolipoproteins



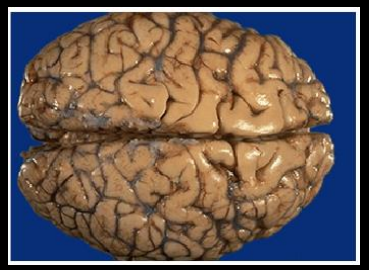
Neurofibrillary Tangles



- Bundles of filaments in the cytoplasm of neurons that displace or encircle the nucleus

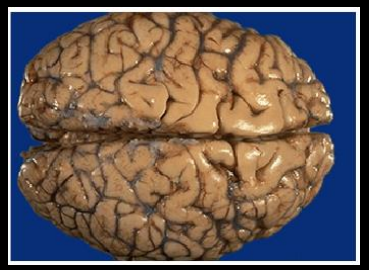
- These filaments mainly contain:
  - Hyperphosphorylated forms of the **tau protein**
  - A protein that enhances microtubule assembly

Amyloid Angiopathy



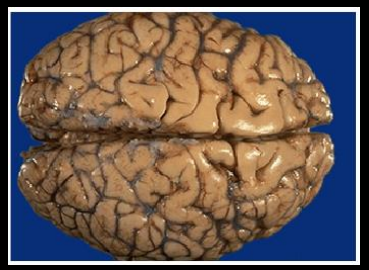
- Amyloid proteins build up on the walls of the arteries in the brain
- The condition increases the risk of hemorrhagic, stroke and dementia
- An almost invariable accompaniment of Alzheimer's disease but not specific for Alzheimer's

Pathogenesis of Alzheimer's



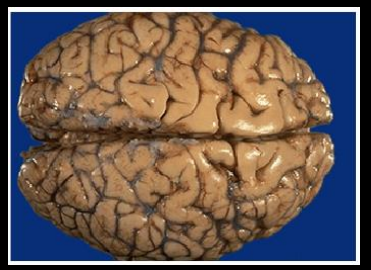
- Still being intensively studied
- Strong correlation of number of neurofibrillar tangles with degree of dementia than neuritic plaques
- Biochemical markers correlated to degree of dementia include:
  - Loss of choline acetyl transferase
  - Synaptophysin immunoreactivity
  - Amyloid burden

Pathogenesis of Alzheimer's



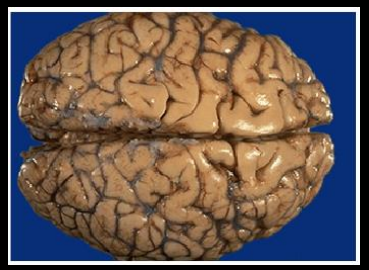
- Loss of synapses best correlates with severity of dementia

- The Aβ peptide forms β-pleated sheets and aggregates
- Resistant to degradation
- Elicits a response from astrocytes and microglia
- Can be directly neurotoxic



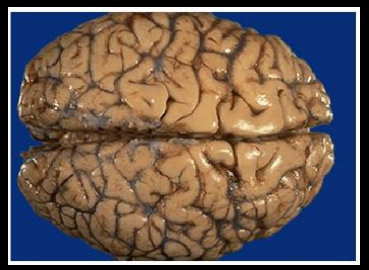
Aβ is a critical molecule in the pathogenesis of Alzheimer's disease

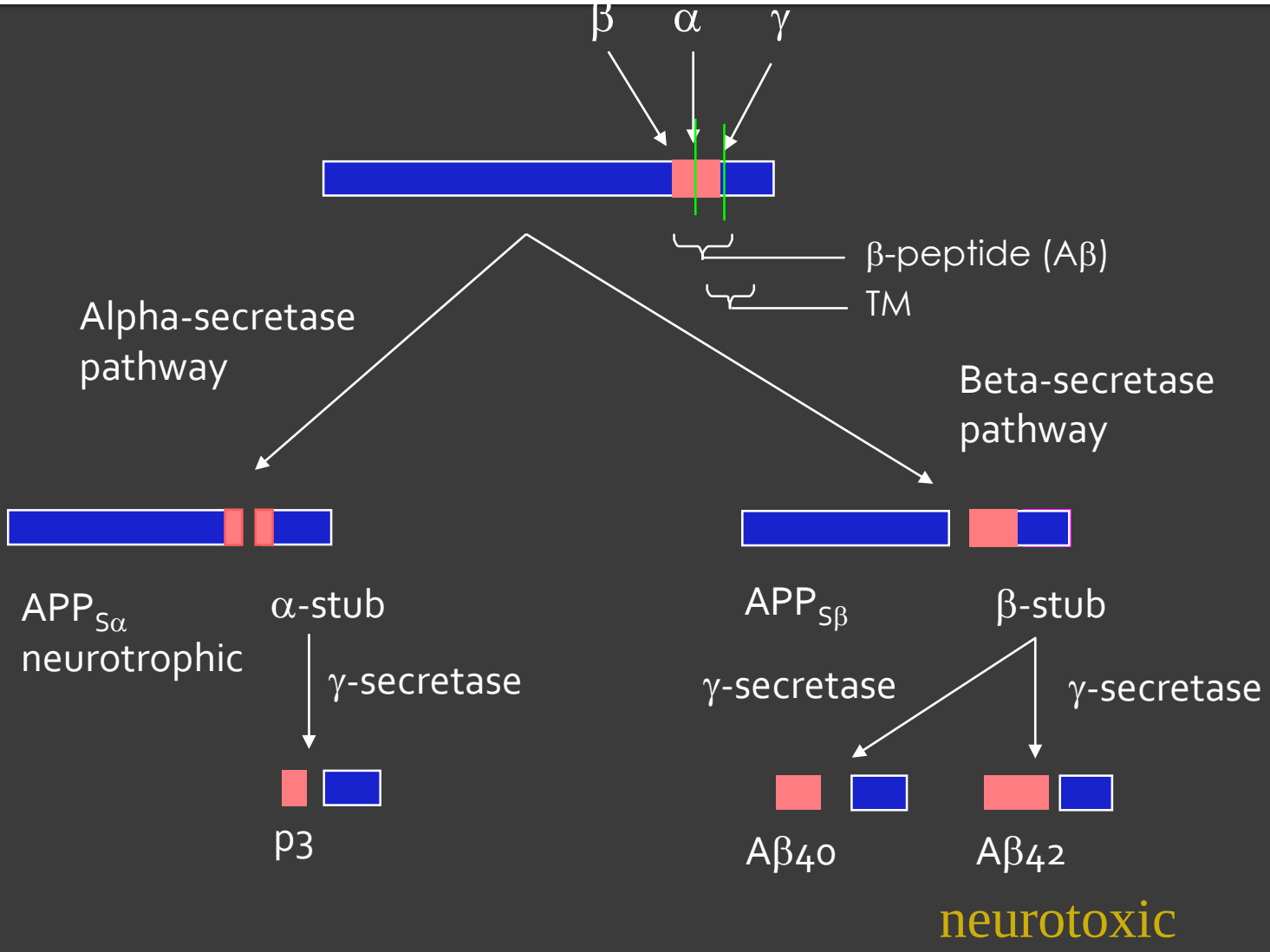
Aβ Peptides



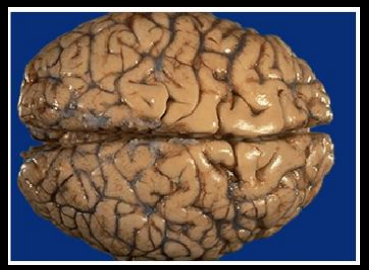
- Derived from the processing of APP
- APP is a protein of uncertain cellular function
- It is synthesized with a single transmembrane domain and expressed on the cell surface

Two pathways for APP processing



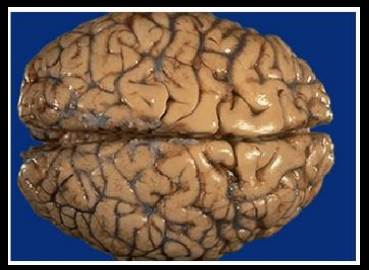


Mechanism of amyloid generation

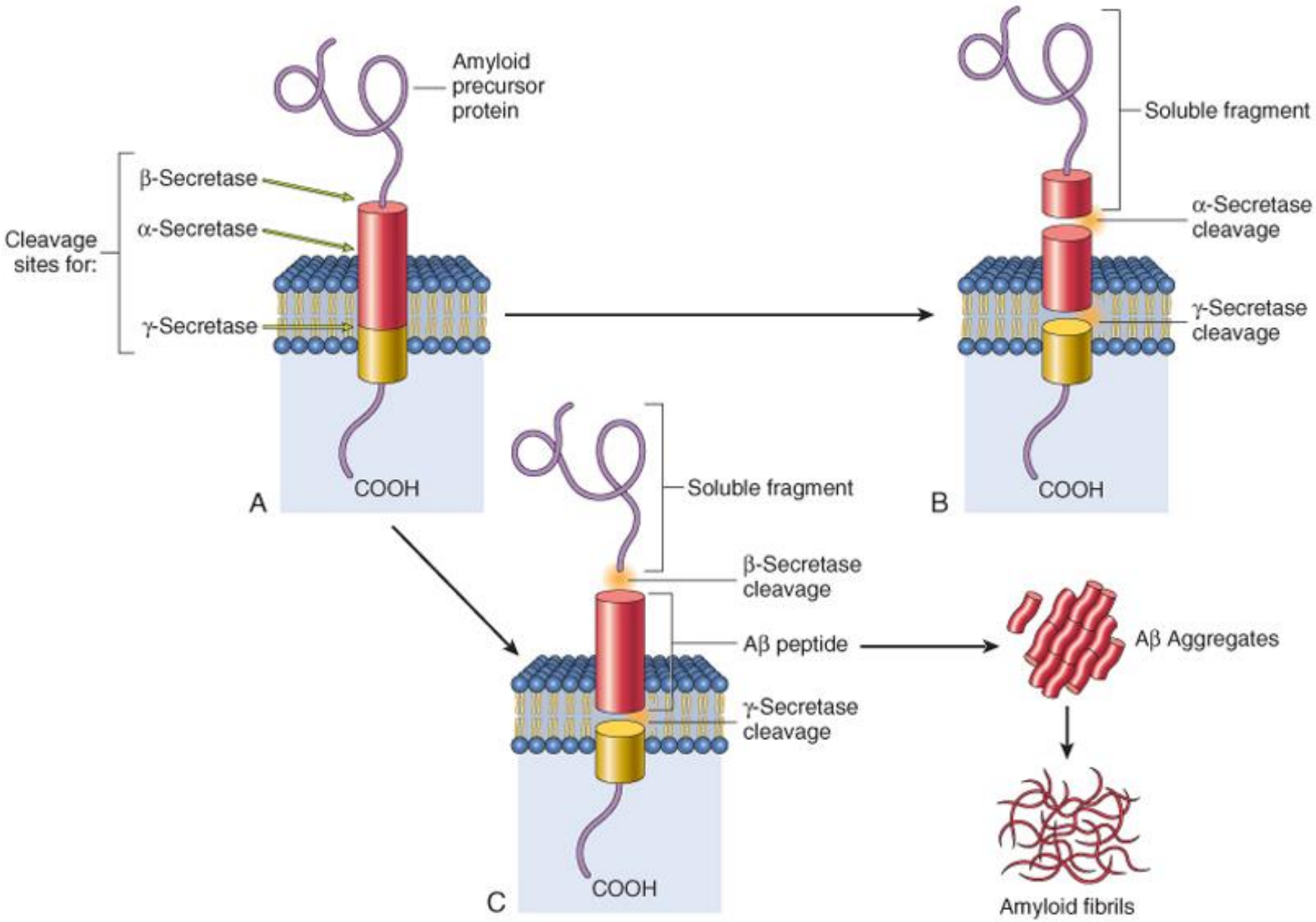


- APP has potential cleavage sites for three distinct enzymes (**α, β, and γ-secretases**)
- The Aβ domain extends from the extracellular side of protein into the transmembrane domain
- When APP is cleaved by α-secretase , subsequent cleavage by γ-secretase does not yield Aβ

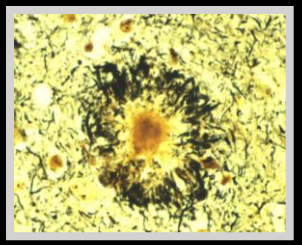
Mechanism of amyloid generation



- Cleavege by β-secretase followed by γ-secretase results in production of Aβ
- Aβ can then aggregate and form fibrils

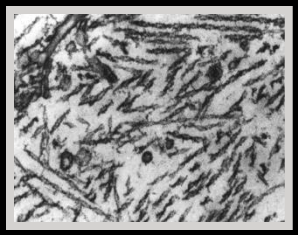

Amyloid precursor protein
β-Secretase
α-Secretase
γ-Secretase
Cleavage sites for:
COOH
A
Soluble fragment
α-Secretase cleavage
γ-Secretase cleavage
COOH
B
Soluble fragment
β-Secretase cleavage
Aβ peptide
γ-Secretase cleavage
COOH
C
Aβ Aggregates
Amyloid fibrils

Accumulation of Aβ protein



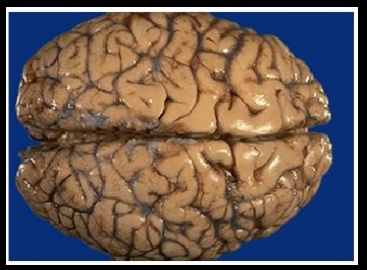
- Accumulation of Aβ protein affects neurons and neuronal function:
  - Small aggregates of Aβ alters neurotransmission
  - Aggregates can be toxic to neurons and synaptic endings
  - Larger deposits (plaques) also cause neuronal death
  - Elicit a local inflammatory response leading to further cell injury

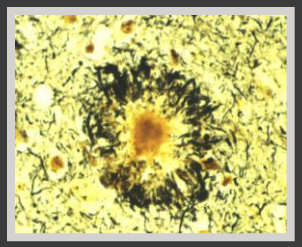
The Tau Protein



- Presence of Aβ causes hyper-phosphorylation of tau protein in neurons
- This leads to redistribution and aggregation of tau protein into tangles in neurons (from axon into dendrites and cell body)
- The process results in neuronal dysfunction and cell death

Aβ and Tau may both contribute to the pathogenesis of Alzheimer's Disease



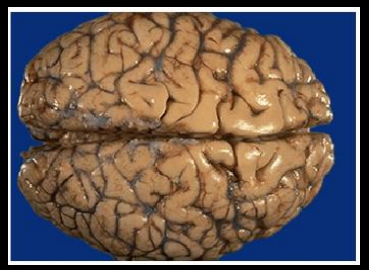


Factors that elevate Aβ → Aβ — ?? → Tau

Aβ → Fibril assembly → Nerve cell mis-function and death?

Tau → Filament assembly → Nerve cell mis-function and death?

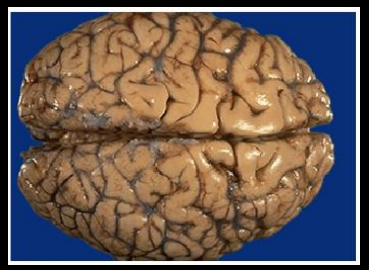
Genetics of Alzheimer's



- Mutations in APP gene
- Mutations in γ-secretase (presenilin-1 or presenilin-2)
- Both lead to early onset of familial Alzheimer's disease due to high rate of Aβ accumulation

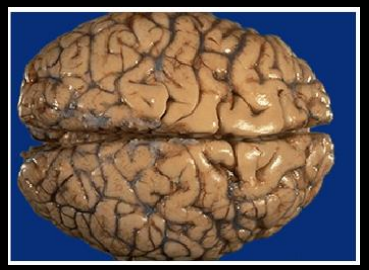
- Alzheimer's occurs in most patients with Down's syndrome (trisomy 21) beyond 45 years of age
- The gene encoding APP is located in chromosome 21
- Due to APP gene dosage effects

Genetics of Alzheimer's



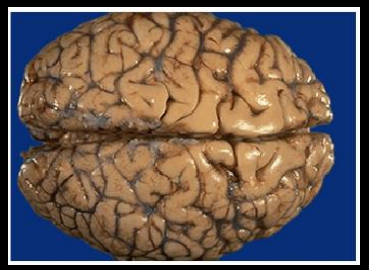
- Genes associated with typical, sporadic Alzheimer's disease are being identified
- This may provide new clues to pathogenesis of the disease

Genetics of Alzheimer's



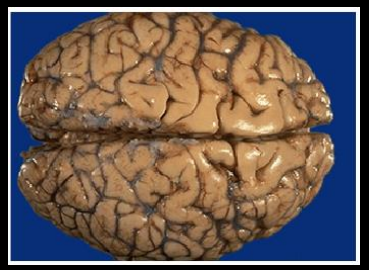
Chromosome	Gene	Consequences
21	Amyloid Precursor Protein (APP)	Early onset FAD Increased Aβ production
14	Presenilin-1 (PS1)	Early onset FAD Increased Aβ production
1	Presenilin-2 (PS2)	Early onset FAD Increased Aβ production
19	Apolipoprotein E (ApoE)	Increased risk for development of AD Decreased age at onset of AD

Treatment of AD



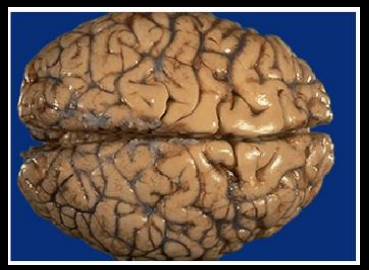
- Currently, no effective treatment for AD
- regulating neurotransmitter activity e.g., Enhancing cholinergic function improves AD
- Epidemiological studies showed that treatment with NSAIDs decreases the risk for developing AD. Unfortunately, clinical trials of NSAIDs in AD patients have not been very fruitful.

Treatment of AD contd..



- Proinflammatory responses may be countered through polyphenols (flavonoids). Supplementation of these natural compounds may provide a new therapeutic line of approach to this brain disorder.

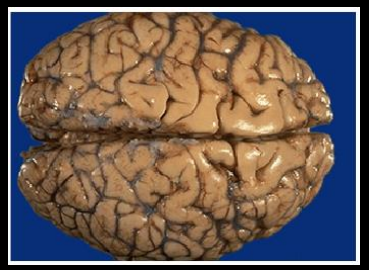
Treatment of AD contd..



- Cellular therapies using stem cells offer great promise for the treatment of AD
- Stem cells offer

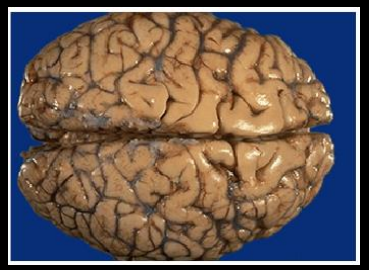
1. Cellular replacement and/or provide environmental enrichment to attenuate neurodegeneration.
2. Neurotrophic support to remaining cells or prevent the production or accumulation of toxic factors that harm neurons.

Continued Research on AD



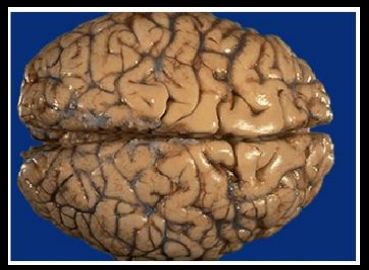
- The small aggregates of Aβ and larger fibrils are directly neurotoxic
- They can elicit oxidative damage and alterations in calcium homeostasis
- How Aβ is correlated to neurodegeneration in AD? How it is linked to tangles and hyperphosphorylation of tau protein?
- All remain open questions

Take home message



- Neurodegeneration is progressive loss of structure and function of neurons including neuronal death
- Amyloid protein forms insoluble fibrous aggregates in neurons leading to Alzheimer's disease
- Deposition of amyloid interferes with normal cellular function resulting in loss of function and cell death
- The dominant component of amyloid plaque that accumulates in Alzheimer's disease is amyloid β 42 (Aβ42) peptide

Further reading



- Illustrated Reviews of Biochemistry by Lippincott 4th edition (pp21-22).
- Fundamentals of Biochemistry by Voett and Voett (pp 170-174)