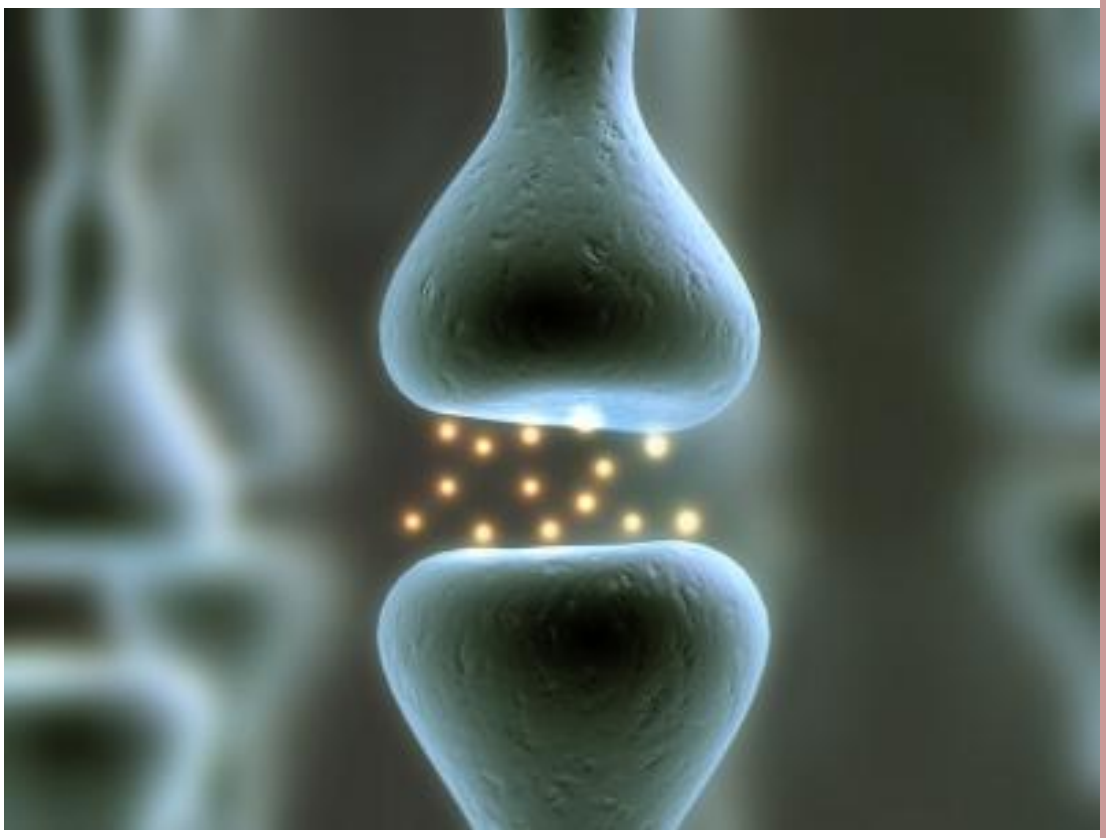
Biochemistry of the CNS



4th lecture:

Alzheimer Disease

Done by:

Mohanned Al-Essa

Aliya Al-Awaji

♣ Neurodegenerative Diseases :

- Diseases of gray matter characterized by the progressive loss of neurons and it's a continued process
- Selective neuronal loss is 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
- A common theme is the development of protein aggregates that are resistant to normal cellular mechanisms of degradation (Usually misfolded proteins ***Don't*** have normal functions and are degraded by the cell itself ***But*** sometimes the cell can't degrade all these misfolded proteins, in order to that diseases occur.
- The aggregated proteins are generally cytotoxic

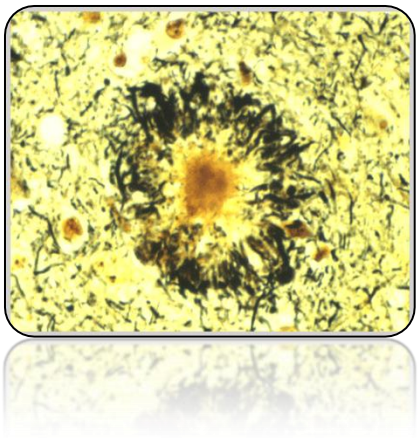
♣ Alzheimer's Disease :

- 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 50yrs of age, but the incidence of disease rises with age
- The disease becomes apparent as :
  - 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 that means it occurs at any time.
- At least 5% to 10% are familial they have genetic background.

♣ Diagnosis :

- Combination of clinical assessment (MMSE) and radiologic methods
- For definitive diagnosis, pathologic examination of brain tissue is necessary
- The major microscopic abnormalities of Alzheimer's disease are neuritic plaques (flat deposits), neurofibrillary tangles, and amyloid angiopathy

♣ Amyloid or Neuritic Plaques :



- Are spherical and range in size from 20-200 µm in diameter
- Contain amyloid fibrils 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)
- The two dominant species of Aβ, called $\mathbf{A\beta_{40}}$ and $\mathbf{A\beta_{42}}$ share an N-terminus and differ in length by two amino acids.
- Other proteins present in the plaque in lesser abundance are
  - Components of the compliment cascade
  - Proinflammatory cytokines
  - α1-antichymotrypsin
  - apolipoproteins

♣ Neurofibrillary Tangles :

- Bundles of paired helical filaments in the cytoplasm of neurons that displace or encircle the nucleus
- A major component of filaments is abnormally hyperphosphorylated forms of the protein tau (a microtubule associated 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 association of Alzheimer's disease but not specific for Alzheimer

Neuritic Plaques (Outside the Neuron)	Neurofibrillary Tangles (Inside the Neuron)	Amyloid Angiopathy (NOT Specific for AD)
- Spherical. - The core is composeed of an abnormal protein (Aβ) peptide derived from amyloid precursor protein (APP). - Outside the core there are helical filaments, synapses and abnormal mitochondria.	- Bundles of filaments. - Abnormally hyperphosphorylated forms of the **protein tau** → associated with microtubule.	- Amyloid proteins build up on the walls of the arteries in the brain. - ↑ Hemorrhagic stroke and dementia.

♣ Pathogenesis of Alzheimer :

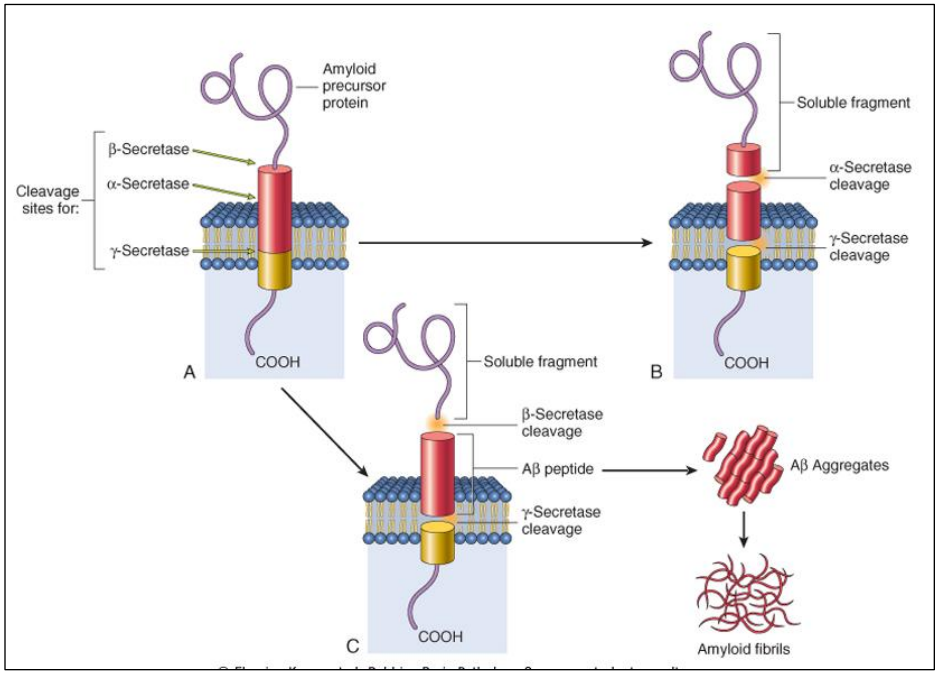
- Still being intensively studied
- The number of neurofibrillar tangles correlates better with the degree of dementia than does the number of neuritic plaques (i.e. ↑ tangles → ↑ dementia / ↓ tangles → ↓ dementia).
- Biochemical markers correlated with the degree of dementia include :
  - Loss of choline acetyl transferase because of the degeneration of the ascending cholinergic nerve fibers.
  - Synaptophysin immuno-reactivity (biochemical test to measure the synaptophysin) → major component protein of synaptic vesicles "Protein $\mathbf{P_{38}}$".
  - Amyloid burden → ↑ of Amyloid- β peptide
- The best correlation of severity of dementia appears to be with loss of synapses
- The Aβ peptide forms **β-pleated sheets**, aggregates readily and is resistant to degrdation and elicits a response from astrocytes and microglia and can be directly neurotoxic

Aβ is a critical molecule in the pathogenesis of Alzheimer disease

It cause neurotoxicity. Aβ peptide is the reason why tau protein is hyperphosphorylated

♣ Aβ Peptides :

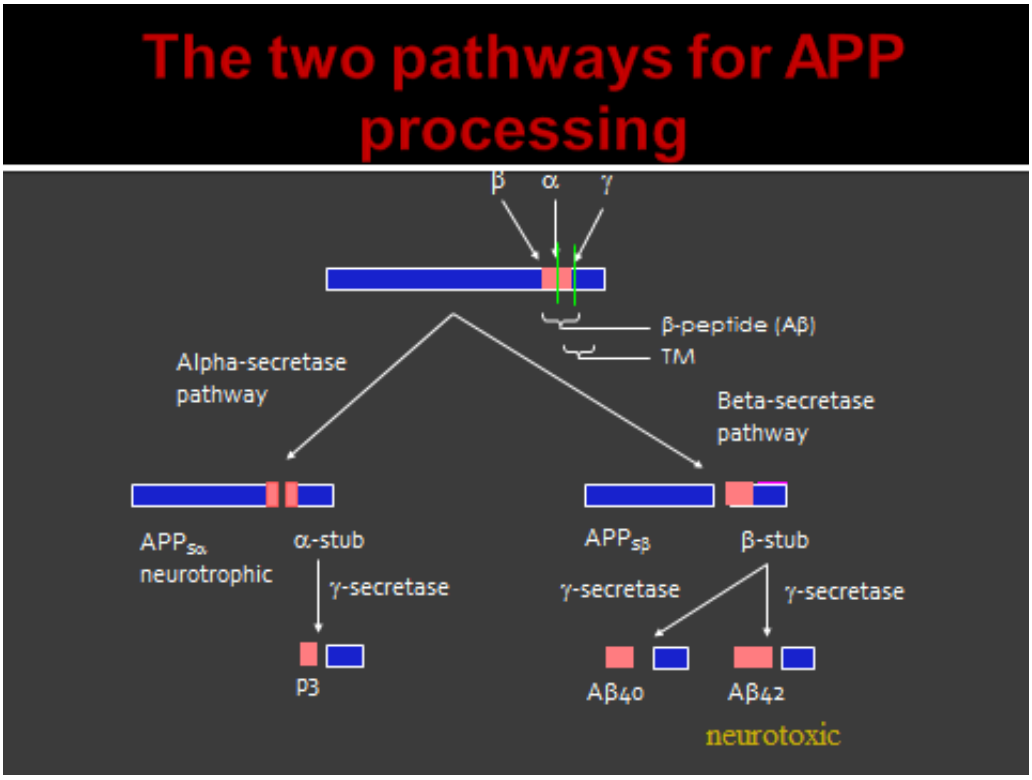
- Are derived through the processing of APP
- APP is a protein of uncertain cellular function
- It is synthesized with a single transmembrane domain and expressed on the cell surface

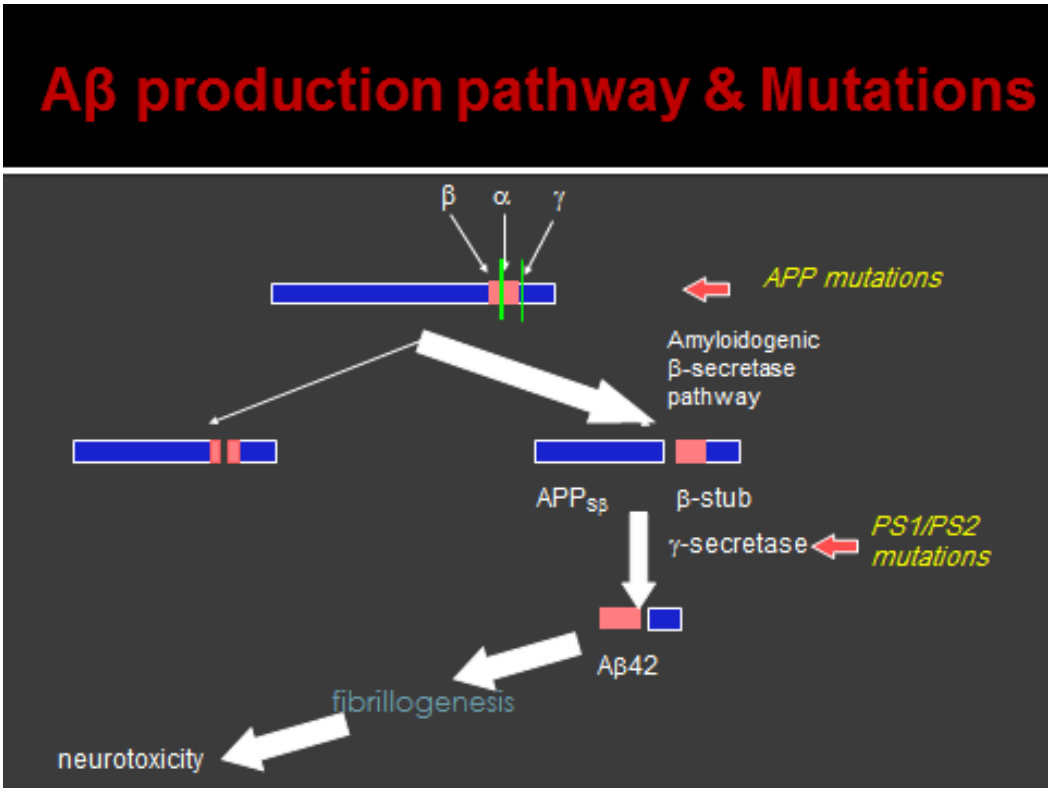


♣ Mechanism of Amyloid Generation :

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

Two Pathways for APP Processing





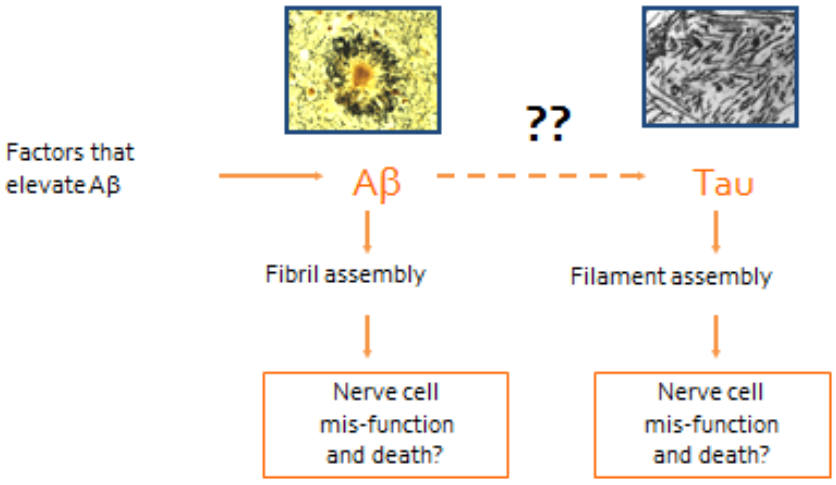
♣ Accumulation of Aβ :

- Accumulation of Aβ has several effects on neurons and neuronal function:
  - Small aggregates of Aβ can alter neurotransmission, and can be toxic to neurons and synaptic endings
  - Larger deposits, in the form of plaques, also lead to neuronal death and elicit a local inflammatory response that can result in further cell injury.

♣ Tau Protein :

- The presence of Aβ also leads neurons to hyperphosphorylate the microtubule binding protein "tau"
- With this increased level of phosphorylation, tau redistributes within the neuron and aggregates into neurofibrillary tangles
- This process also results in neuronal dysfunction and cell death

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



♣ Genetics of Alzheimer Disease :

- Mutations in APP or in components of γ-secretase (presenilin-1 or presenilin-2) lead to early onset familial Alzheimer disease by increasing the rate at which Aβ accumulates
- Alzheimer disease occurs in almost all patients with trisomy 21 (Down syndrome)-where the gene encoding APP is located-who survive beyond 45 years (due to APP gene dosage effects)
- The search for genes associated with typical, sporadic Alzheimer disease is beginning to identify genetic associations that may provide new clues about the pathogenesis of the disease

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 Late onset of AD

♣ Continued Research of Alzheimer Disease :

- The small aggregates of Aβ as well as larger fibrils are directly neurotoxic
- They can elicit oxidative damage and alterations in calcium homeostasis
- But how Aβ is related to neurodegenration of AD and how it is linked to tangles and hyperphosphorylation of tau all remain open questions

♣ Take Home Message :

- Neurodegeneration is the progressive loss of structure or function of neurons, including death of neurons.
- Extracellular deposition of normally soluble proteins in certain tissues in the form of insoluble fibrous aggregates known as amyloid.
- The deposition of amyloid interferes with normal cellular function, resulting in cell death and eventual organ failure.
- The dominant component of amyloid plaque that accumulates in Alzheimer disease is amyloid β 42(Aβ42) Peptide.