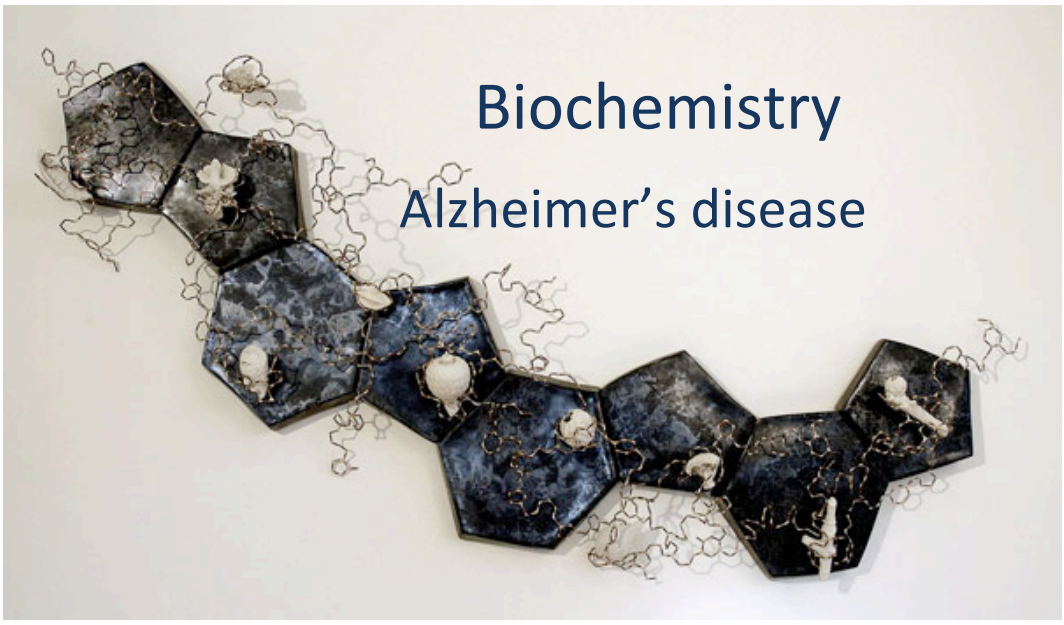

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Biochemistry
Alzheimer's disease

Objectives:

Upon completion of this lecture, 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 approach to treat these disorders

Introduction to Neurodegenerative diseases:

A group of diseases of gray matter characterized principally by the progressive loss of neurons with a selective pattern, affecting one or more groups of neurons leaving the others intact.

The diseases arise without any clear inciting event, even in patients without previous neurological deficits.

A common theme is the development of misfolded or abnormal protein aggregates that are resistant to normal cellular mechanisms of degradation. (Normally: abnormal proteins are degraded)

These aggregated proteins are generally cytotoxic .

Alzheimer's disease:

A progressive neurodegenerative disease with the prominent involvement of the cerebral cortex. It begins at one area, spreading over the years to most of the cortex.

Its principal clinical manifestation is defined as dementia

➔ Dementia is the progressive loss of cognitive function independent of the state of attention.

Alzheimer's is not used *interchangeably* with dementia as other causes (vascular..etc.) can lead to the similar manifestations.

However, Alzheimer's disease is the most common cause of dementia.

Patients rarely become symptomatic before 50yrs of age, but after 50 the incidence of disease rises with age.

Clinical Picture:

-gradual impairment of higher intellectual function
-alterations in mood and behavior
-Progressive disorientation
-memory loss

Course:

5-10 yrs, in which the patient becomes profoundly disabled, mute and immobile.

Most cases are sporadic (no family history). But at least 5% to 10% are familial.

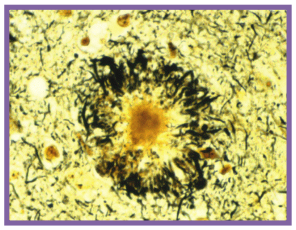
Diagnosis:

Via a combination of clinical assessment and radiologic methods (MRI shows changes in hippocampus)

For definitive diagnosis, pathologic examination of brain tissue is necessary

The major **microscopic abnormalities** of Alzheimer's disease are neuritic plaques, neurofibrillary tangles, and in most cases amyloid angiopathy (amyloid angiopathy is not specific for AD- also found in other diseases)

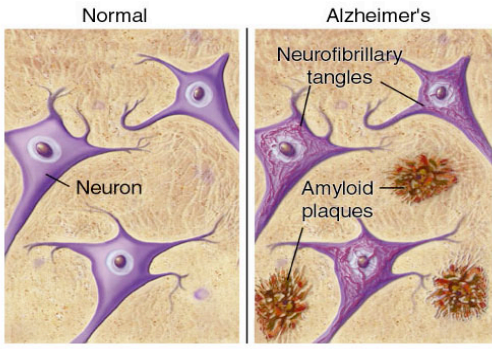
1. Neuritic (beta amyloid) plaques:



Are **extracellular** spherical structures (20-200um in diameter)

Contain paired helical filaments as well as synaptic vesicles and abnormal mitochondria (of the dying neuron) and an amyloid core made up of several abnormal proteins.

The dominant component is **Aβ (Amyloid beta)**, a resistant peptide abnormally derived from a larger molecule called **amyloid precursor protein** (APP) that has an unknown function.



Other proteins present in the plaque in lesser abundance are:

- Components of the compliment cascade
- Proinflammatory cytokines
- α1-antichymotrypsin
- apolipoproteins

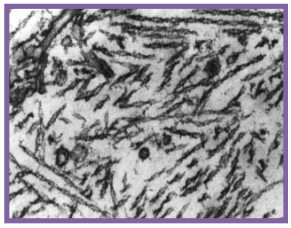
Note that there are two dominant species of Aβ, called;

$A\beta_{40}$: which is soluble and does not initiate the plaque formation

$A\beta_{42}$: the more hydrophobic form **in charge of plaque formation**
The two share an N-terminus and differ only in length by two amino acids.

The number indicates the number of amino acid residues

2. Neurofibrillary tangles:



Intracellular bundles of filaments in the cytoplasm of neurons that displace and/or encircle the nucleus

A major component of filaments is abnormally hyperphosphorylated forms of the **protein tau** (a microtubule associated protein that normally enhances microtubule assembly in neuronal axons)

Hydrophosphorylation causes the protein tau to make knots, dissociating from the microtubule. The microtubules are left fragmented and degraded, forming tangles in the neuron. The loss of structure causes shrinking of the axon emptying its components into the cell body. This leads to the separation of synapses and loss of communication between adjacent neurons.

3. Amyloid Angiopathy:

Amyloid proteins build up on the walls of the arteries in the brain increasing 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 disease:

Research is still being intensively studied.

Findings:

The number of neurofibrillary tangles correlates better with the degree of dementia than does the number of neuritic plaques.

The best correlation of severity of dementia appears to be with loss of synapses.

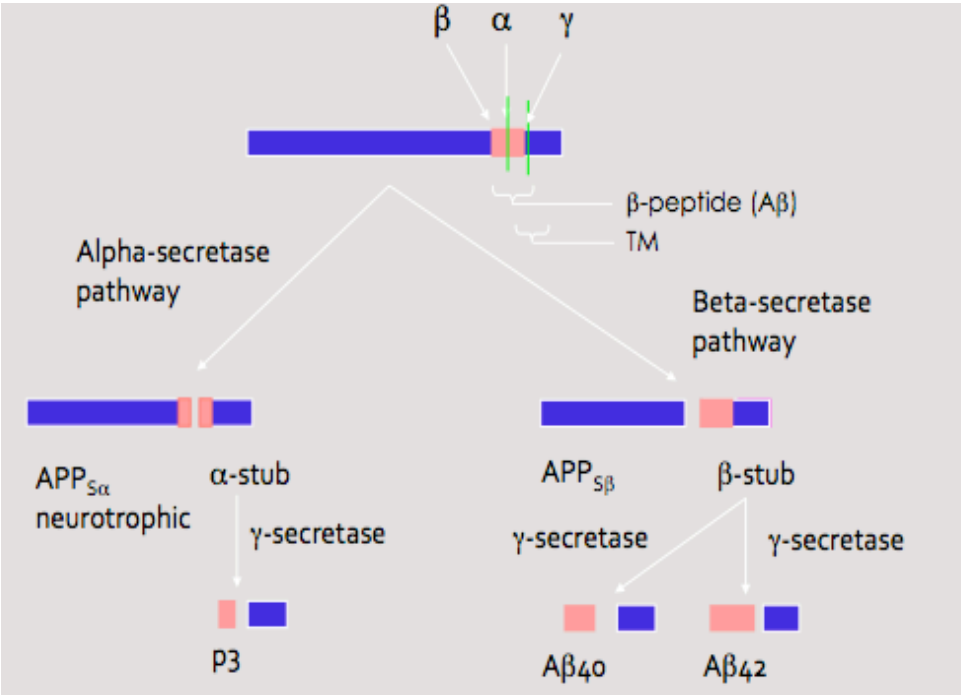
Aβ is a critical molecule in the pathogenesis of Alzheimer disease

- The Aβ peptide forms β-pleated sheets, aggregates readily and is resistant to degradation
- It elicits an inflammatory response from astrocytes and microglia which can be directly neurotoxic (via proinflammatory cytokines that lead to the death of neurons)
- 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

Two pathways for APP processing:

APP has 3 potential cleavage sites for three distinct enzymes (**α, β, and γ-secretases**)

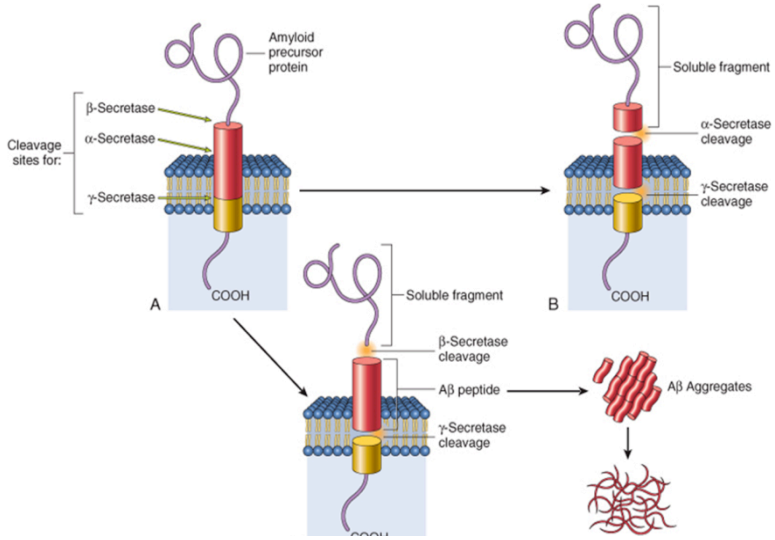
The Aβ domain extends from the extracellular side of protein into the transmembrane domain



When APP is cleaved by α-secretase, subsequent cleavage by γ-secretase does not yield Aβ, but instead it yields peptides that are soluble and don't cause damage.

Cleavage by β -secretase, followed by γ-secretase results in production of Aβ:
- $Aβ_{40}$ in a non-toxic form
- $Aβ_{42}$ can then aggregate and form fibrils

Amyloid protein:



Accumulation of Aβ:

Accumulation of Aβ has several effects on neurons and neuronal function:

➔ Small aggregates of Aβ can alter neurotransmission and have a toxic effect on neurons and synaptic endings

➔ Larger deposits in the form of plaques, lead to neuronal death. They elicit a local inflammatory response that results in further cell injury

Tau Protein:

Hyperphosphorylation of the microtubule binding protein "tau"

With this increased level of phosphorylation, tau redistributes within the neuron from the axon into dendrites and cell body and aggregates into tangles which also results in neuronal dysfunction and cell death

Genetics of Alzheimer's Disease:

Mutations in APP or in components of γ-secretase (presenilin-1 or presenilin-2) leads to early onset of familial Alzheimer disease (5-10% of cases) by increasing the rate at which Aβ accumulates.

The gene encoding APP is located on **chromosome 21**

Alzheimer disease occurs in almost all patients with trisomy 21 (Down syndrome) who survive beyond 45 years (due to APP gene dosage effects) since they have three chromosomes 21 they are at higher risk.

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 Decreased age at onset of AD

FAD: Familial Alzheimer's disease

a lipid carrier typically found in HDL
the one related to AD is ApoE4, while ApoE 2&3 are neuroprotective

Secondary risk factors for Alzheimer's disease:

- Head injury
- Low education or mental inactivity
- High fat diet

Treatment of Alzheimer's Disease:

Currently, there is no effective treatment for AD

Regulating neurotransmitter activity, for example enhancing cholinergic function, improves AD

Epidemiological studies showed that treatment with NSAIDs decreases the risk for developing AD. Unfortunately, clinical trials of NSAIDs in Alzheimer's patients have not been very fruitful because of the side effects and lack of response of patients.

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.

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.

(Neurotrophic: protein factors that are responsible for the growth and survival of developing neurons and maintenance of mature neurons)

Continued Research of Alzheimer's 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 in AD and how it is linked to tangles and hyperphosphorylation of tau protein all remain open questions.

Take home messages:

-Neurodegeneration is the progressive loss of structure or function of neurons, including death of neurons.

-Extracellular deposition of insoluble fibrous aggregates known as amyloid in certain areas of neural tissue.

-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.

Questions:

1. Which is not true about amyloid plaques?

    a) It is extracellular

    b) It is spherical

    c) It is initiated by Aβ40

2. Which microscopic abnormality is not specific for Alzheimer disease?

    a) neuritic plaques

    b) amyloid angiopathy

    c) neurofibrillary tangles

3. Which pathway will give Aβ and cause damage?

    a) Cleavage by alpha secretase then gamma secretase

    b) Cleavage by beta secretase then gamma secretase

    c) both A and B

4. Which chromosome has the gene that encodes for APP?

    a) 21

    b) 19

    c) 1

    d) 14

Done by

Hadeel Helmi and Noha Khalil

Revised by

Alanood Asiri

Answers: 1 C 2 B

3 B 4 A