BIOCHEMISTRY OF ALZHEIMER'S DISEASE

Color index:

- Important
- Extra explanation

"PUSH YOURSELF, BECAUSE NO ONE ELSE IS GOING TO DO IT FOR YOU"

Check this link before studying to know if there is any corrections in the teamwork

OBJECTIVES

By the end of this lecture, the students should be able to:

1-Have an overview of neurodegenerative disorders.

2-Understand the role of amyloid beta 40-42 residue peptide in Alzheimer’s disease.

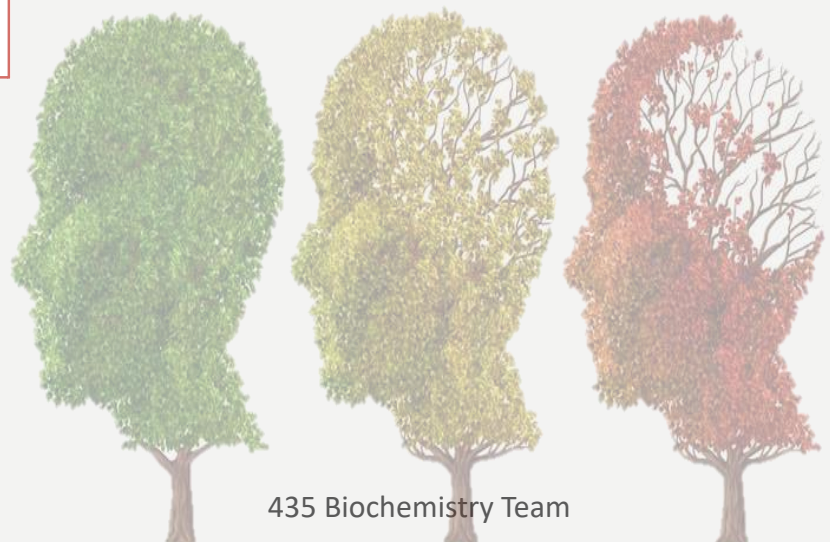
3- Get an idea of the diagnosis and therapeutic approaches to treat these disorders.

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

Misfolded proteins is degraded by Aggregated proteins is because there are too much of it or the body cannot degrade it
Dementia is not related to the aging process, it is pathologic.

Neurodegenerative diseases



Alzheimer's disease

This video is highly recommended to understand the lecture.
Dr. Othman played it in the class last year.

Biochemistry Team 435

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

Its principal clinical manifestation is dementia

Patients rarely become symptomatic before 50 yr. of age but the incidence of disease rises with age

Most cases are sporadic.
*Sporadic means it's not related to genetics

In 5-10 years, the patient becomes profoundly disabled, mute and immobile.

A degenerative disease with the prominent involvement of the cerebral cortex.

Alzheimer's Disease

At least 5-10% are familial.

Alzheimer's Disease

pathophysiology

Alzheimer's Disease

The disease becomes apparent with:

- Gradual impairment of higher intellectual functions
- Alterations in mood and behavior
- Progressive disorientation
- Memory loss

❖ **Diagnosis of Alzheimer's Disease include :**

- 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.

Major Microscopic Abnormalities

Neuritic Plaques

Spherical with 20-200 mm 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).**

Neurofibrillary tangles

- The two dominant species of Aβ, called Aβ40 and Aβ42 share an N-terminus and differ in length by two amino acids.
- Plaque is an aggregate.
- Ab: amyloid beta.
- APP: neuroprotective protein.
- A1-antichymotrypsin is protease inhibitor.
- Plaque formation is extracellular.
- People with diabetes are more prone to get Alzheimer's.

amyloid angiopathy

Other less abundant proteins in the plaque :

- Components of the compliment cascade.
- Proinflammatory cytokines.
- α1-Antichymotrypsin.
- Apolipoproteins.

Major Microscopic Abnormalities

Neuritic Plaques

Neurofibrillary tangles

amyloid angiopathy

What is it?

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).

- Tau protein maintains – stabilizes - the tubular structure of the neuron (the cytoskeleton of the cell), but in this disease the this protein are lost, which will lead to displacing of the filaments of this tubular system and it may shrink and encircle the nucleus.
- Tau protein combine to microtubule and stabilizes it
- Gsk3 (glycogen synthase kinase 3) is related to phosphorylation of tau protein
- Then tau protein will detach from microtubules causing nerve death

What is it?

Amyloid proteins build up on the walls of the arteries in the brain.

- The condition increases the risk of hemorrhagic, stroke and dementia.

-Amyloid angiopathy is An almost invariable accompaniment of Alzheimer's disease but not specific for Alzheimer's

Pathogenesis Of Alzheimer's

- The pathogenesis still being intensively studied.

(because the cause is still unknown)

- Strong correlation of number of neurofibrillary tangles with degree of dementia than neuritic plaques.

Which means : the more the neurofibril → the more the dementia.

(note: the senile plaques are not associated with the symptoms, which means the symptoms don't develop even if the plaques are found).

- However, Loss of synapses best correlates with severity of dementia.

Biochemical markers correlated to degree of dementia include:

- Loss of choline acetyltransferase.
- Synaptophysin immunoreactivity.
- Amyloid burden.

Pathogenesis Of Alzheimer's

What is APP?

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

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

Why? (in short: it's the first step)

- This Aβ peptide forms β-pleated sheets and aggregates.

It starts to appear in high numbers especially in the surface of synapses' neurons, so it blocks the signal from passing properly, and then it forms the plaques (and then turns tau protein into tangles but in an unknown way).

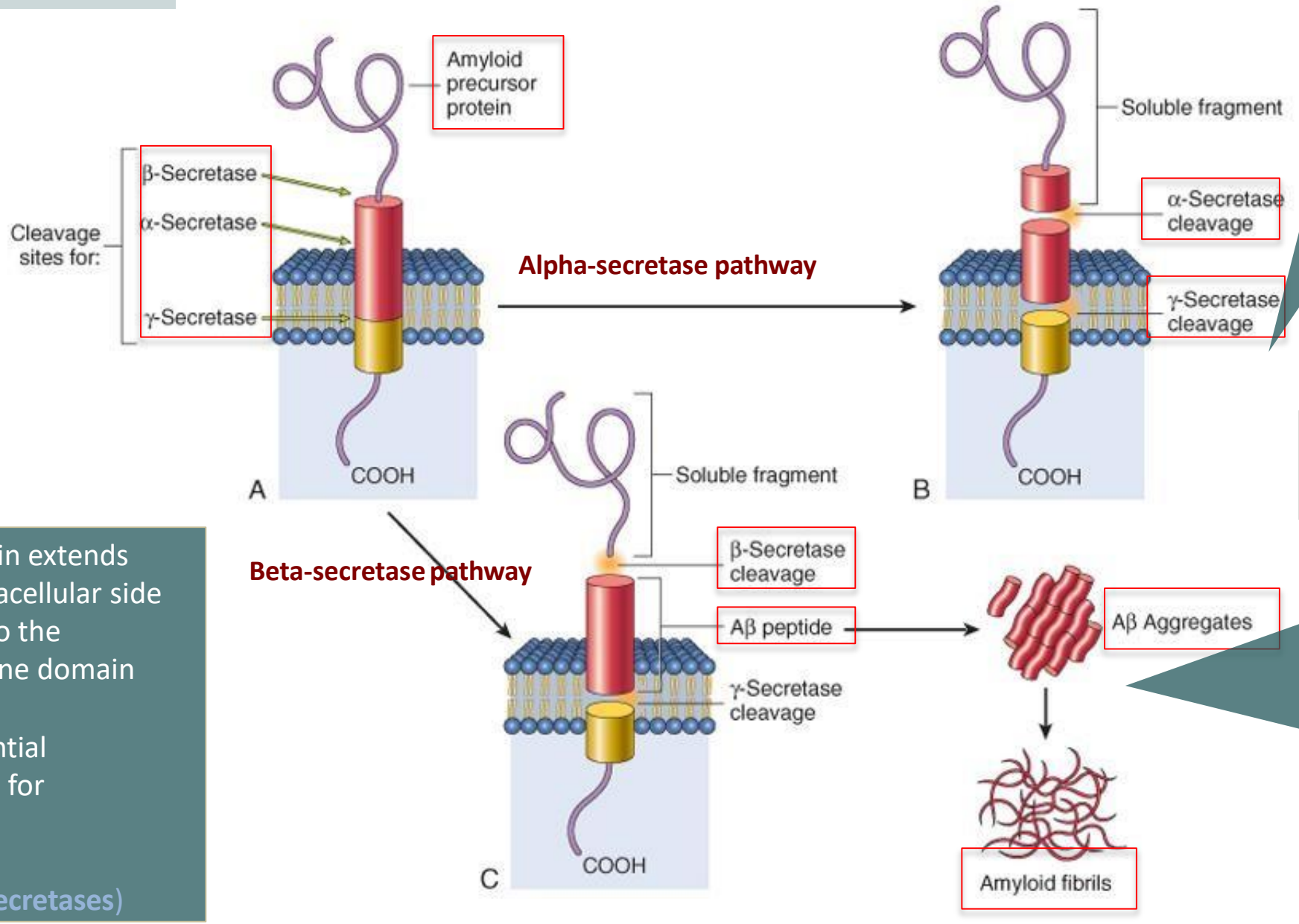
- They become Resistant to degradation, why?

Because the structure of these peptides are changed in such a way that the enzyme doesn't recognize them. (they then become beta sheets and become insoluble)

- Elicits a response from astrocytes and microglia. (for the immune response).
- These peptides Can be directly neurotoxic.

This slide is taken from 433`s team

Two Pathways For APP Processing



1

When APP is cleaved by α secretase , Subsequent cleavage by γ secretase does not yield Aβ (normal)

Mechanism of amyloid generation

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

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

2

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

Accumulation of Aβ proteins

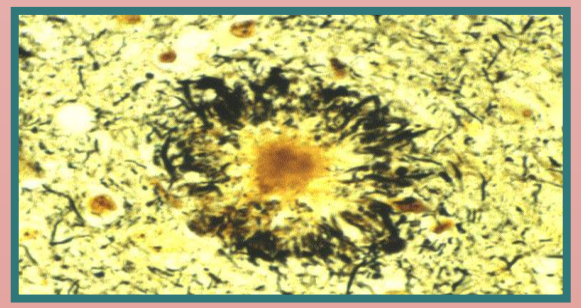
Accumulation of Aβ protein will affect neurons and neuronal function :

1- Small aggregates of Aβ alters neurotransmission

2- Aggregates can be toxic to neurons and synaptic endings

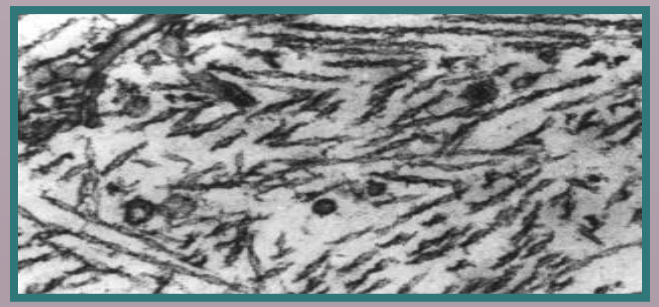
3- Larger deposits (plaques) also cause neuronal death

4- Elicit a local inflammatory response leading to further cell injury



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**



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

-Genes associated with typical, sporadic Alzheimer's disease are being identified

-This may provide new clues to pathogenesis of the disease

If it is familial the age is younger than sporadic Alzheimer

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) ApoE is present in HDL and LDL	Increased risk for development of AD Decreased age at onset of AD

Treatment

- 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.
- 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. Green tea slows down the process of the disease, Because it has polyphenols which scavenge free radicals
- 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 Alzheimer's Disease

- 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 hyper-phosphorylation of tau protein?
- All remain open questions

MCQs

1-Which one of the following is considered the dominant component of amyloid plaques :

A-Aβ40
B-Aβ42
C-ApoE
D- α1-Antichymotrypsin

2-Dementia is the progressive loss of:

A-Motor functions
B-Sensory functions
C-Cognitive functions
D-A&B

3-Which one of the following examinations is usually used to diagnose Alzheimer's:

A-Clinical assessment
B-Radiologic methods
C-Biopsy
D-A&B

4-Neurofibrillary tangles mainly contain:

A-Amyloid
B-Cytokines
C-Tau protien
D-Apolipoprotiens

5- α1-Antichymotrypsin is found in which one of the following:

A-Neuritic plaques
B-Neurofibrillary tangles
C-Blood circulation
D-A&B

1-B
2-C
3-D
4-C
5-A

MCQs

6-Degree of dementia depends mostly on:

A-Neuritic plaques

B-Neurofibrillary tangles

C-Amyloid burden

7-Which one of the following pathways would lead to deposition of Aβ:

A-α-secretase pathway

B-β-secretase pathway

C-γ-secretase pathway

8-Which one of the following medical conditions increases the risk for Alzheimer's disease:

1-Turner syndrome

2-Creutzfeldt-jakob disease

3-Down syndrome

4-Tay-sachs disease

9-Presenilin is a mutation of the catalytic subunit of which one of the following enzymes:

A-α-secretase

B-β-secretase

C-γ-secretase

10-Amyloid deposition can be seen in which of the following diseases:

A-Alzheimer

B-Parkinson

C-Huntington

D-All of the above

6-B
7-B
8-3
9-C
10-D

SAQs

❖ **Q1 :What is the principal clinical manifestation of Alzheimer's ?**

Dementia.

❖ **Q2 :What are the major microscopical findings of Alzheimer's?**

Major microscopic abnormalities include: neuritic plaques, neurofibrillary tangles and amyloid angiopathy.

❖ **Q3 :What are the neurofibrillary filaments and what are they composed of?**

Bundles of filaments in the cytoplasm of neurons that displace or encircle the nucleus.
They contain:
Hyper-phosphorylated forms of the tau protein (a protein that enhances microtubule assembly).

❖ **Q4:What are the biochemical markers correlated with the degree of dementia?**

-Loss of choline acetyltransferase.
-Synaptophysin immunoreactivity.
-Amyloid burden

❖ **Q5 :How does the accumulation of alpha beta amyloid protein accumulation play a role in the pathogenesis of Alzheimer's ?**

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

Team Members:

- لينا اسماعيل.
- سارة الخليفة.
- ربى السليمي.
- ملاك الشريف.
- مروج الحربي.
- نوف الرشيد.
- رفان هاشم.
- ثاني معافا .
- خالد النعيم.
- فارس المطيري.
- أحمد الرويلي.
- إبراهيم الشايع.
- فراس المؤمن.
- محمد الصهيل.
- عبدالله الشنيفي.

Team Leaders:

- عبدالله الغزي.
- نوف العبدالكريم.

Revised by

هشام الغفيلي & خولة العماري

* نستقبل اقتراحاتكم وملاحظاتكم على:

@435biochemteam

435biochemistryteam@gmail.com

@biochemteam435