جامعة الملك سعود
King Saud University

"اللَّهُمَّ لا سَهْلَ إلاَّ ما جَعَلْتَهُ سَهْلاً، وأنْتَ تَجْعَلُ الحَزْنَ إذَا شِئْتَ سَهْلاً "

Biochemistry437

Alzheimer's

Biochemistry Team 437

Color index:
Doctors slides
Doctor's notes
Extra information
Highlights

Neuropsychiatry block

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Objectives:

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

Males

- Define neurodegenerative disorders.
- Identify the clinical picture and diagnostic criteria of Alzheimer's disease.
- Understand the different ways of processing of amyloid precursor protein leading to amyloid generation and accumulation.
- Differentiate between the neuritic plaques, neurofibrillary tangles and tau protein and their role in the pathogenesis of the disease.
- Understand the genetics of Alzheimer's disease.
- Discuss ongoing research and therapeutic approach to treat these disorders.

Females

- 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

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- Diseases of gray matter characterized principally by the progressive loss of neurons which leads to the loss of neuronal function leading to dementia.
- 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. (No previous infection or trauma, you can't pinpoint a cause for the symptoms)
- A common theme is the development of protein aggregates that are resistant to normal cellular mechanisms of degradation "enzymes". (these proteins aggregate in the form of plaques or tangles)
- The aggregated proteins are generally cytotoxic.

Why do proteins aggregate?

- When proteins are first translated, they are folded to a certain structure, this folded structure determines its function.
- Due to mutation or a post-transcriptional modification, the protein is folded improperly, this happens normally in the cell.
- The cell has a special mechanism to degrade these misfolded proteins called the ubiquitin system, where ubiquitin is added to the proteins so the cell can degrade them by protease enzymes.
- If the cell cannot degrade these proteins, they accumulate, become cytotoxic and cause inflammatory reactions ultimately killing the cell.
- This is the main principle of alzheimer's pathology.

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
    (the patient is conscious, but he has problems with learning, making memories, calculations and so on)
- Patients rarely become symptomatic before 50 years of age, but the **incidence** of disease **rises with age.**
- The disease becomes apparent with* :
  1. Gradual impairment of higher intellectual function
  2. Alterations in mood and behavior
  3. Progressive disorientation
  4. Memory loss
- In 5-10 yrs after the symptoms appear, the patient becomes profoundly disabled, mute and immobile, and dependant
- Most cases are sporadic (can happen to anyone). After 50
- At least 5-10% are familial. Before 50

*These are the symptoms that first appear, but pathology of the disease starts even before symptoms appear.

Diagnosis

1. The diagnosis is based on a Combination of clinical assessment [1] and radiologic methods “MRI”[2]

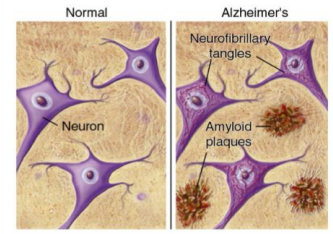
2. Pathologic examination of brain tissue is necessary for definitive diagnosis[3]

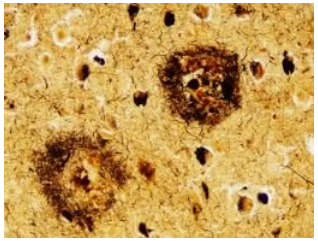
3. Major microscopic abnormalities include:
   - Neuritic plaques (senile plaques)
   - Neurofibrillary tangles
   - Amyloid angiopathy[4]

1- By asking him some questions that are related to memory mainly, or have the family members describe the changes in behavior
2- Shows atrophy
3- It is done post-mortem
4- Deposition of protein in the blood vessels and might lead to stroke

Neuritic Plaques

- Spherical with 20-200 μm in diameter
- Found extracellularly
- Contains:
  - Paired helical filaments
  - Synaptic vesicles
  - Abnormal mitochondria





- The amyloid core contains several abnormal proteins
- The dominant component of the plaque core is Aβ "Amyloid Beta", a peptide derived from a larger molecule, **amyloid precursor protein (APP)**
- The two dominant species of Aβ, called Aβ40 and Aβ42[1] share an N-terminus and differ in length by two amino acids
- Other less abundant proteins in the plaque[2]:
  1. Components of the complement cascade
  2. Proinflammatory cytokines
  3. α1 -Antichymotrypsin (Protease inhibitor)
  4. Apolipoproteins (Cholesterol transporter)

1: The number "40 & 42" refers to the number of amino acids in the proteins
2: Caused by inflammation

Neurofibrillary Tangles

- Bundles of filaments in the cytoplasm of neurons that displace or encircle the nucleus.
- These filaments mainly contain:
    - Hyper-phosphorylated 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. "Can be seen in parkinson's also"

- Tau protein is a microtubule stabilizer protein.
- In case of alzheimer's, tau proteins is hyperphosphorylated, (phosphate group attaches to them) so they can no longer bind to microtubules.
- Microtubules breakdown,and the structure of the cell is unstable, leading the death of the neuron.
- Accumulation of tau filaments in neuron causes Neurofibrillary Tangles and death of neuron.
- Although plaques are thought to come first, the development of symptoms is related to tangles thus more tangles more symptoms.

Pathogenesis of Alzheimer's

Still being intensively studied

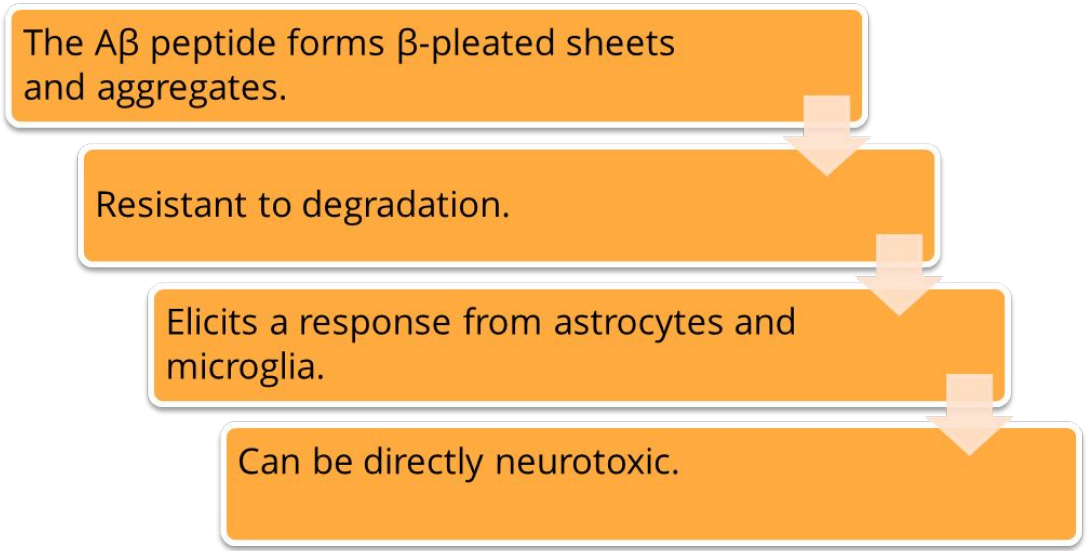
Strong correlation of number of neurofibrillary tangles with degree of dementia than neuritic plaques

Loss of synapses best correlates with severity of dementia.

- Biochemical markers correlated to degree of dementia include
  - Loss of choline acetyltransferase[1]
  - Synaptophysin[2] immunoreactivity[3]
  - Amyloid burden[4]

1- Found in synaptic vesicles, An enzyme involved in the synthesis of Ach.
2- Major protein present in the synaptic vesicles.
3- Loss of immunoreactivity test to synaptophysin.
4- Amyloid that can cross the BBB, its level go down during alzheimer's.

Cont. Pathogenesis of Alzheimer's



Overview of the process:

- Aβ peptides are derivatives of APP
- Normally they are cleaved to soluble products, in case of alzheimer's they are cleaved to hydrophobic insoluble products that are resistant to degradation
- They aggregate and cause inflammation

Aβ Peptides

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

- 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

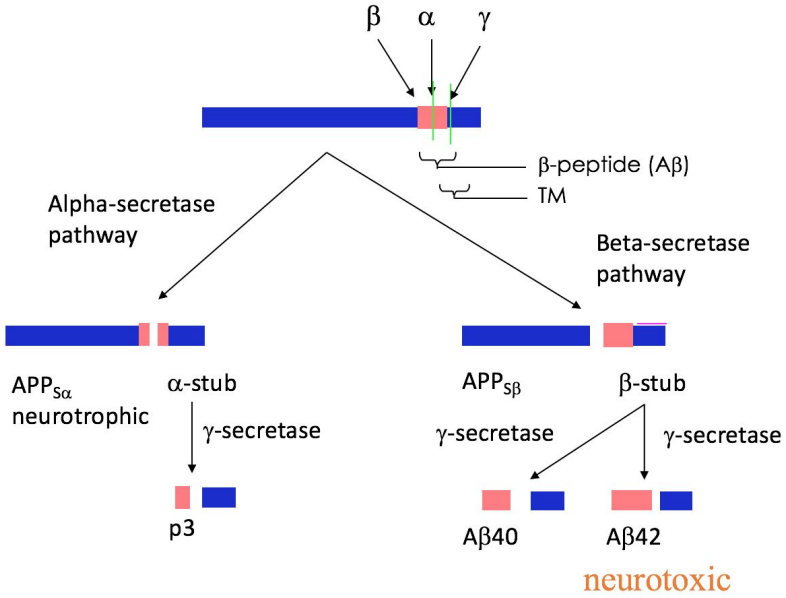
Two Pathways for APP Processing

How is Amyloid precursor protein cleaved?

- Amyloid precursor protein has 3 cleaving sites for 3 different enzymes : (α, β, and γ-secretases)
- APP can enter through one of two pathways:

The alpha secretase pathway

- First cleavage is done by α-secretase.
- This cleavage leads to the formation of a soluble alpha fragment.
- The second cleavage is always done by gamma secretase "γ-secretases" , which gives us another 2 soluble fragments.



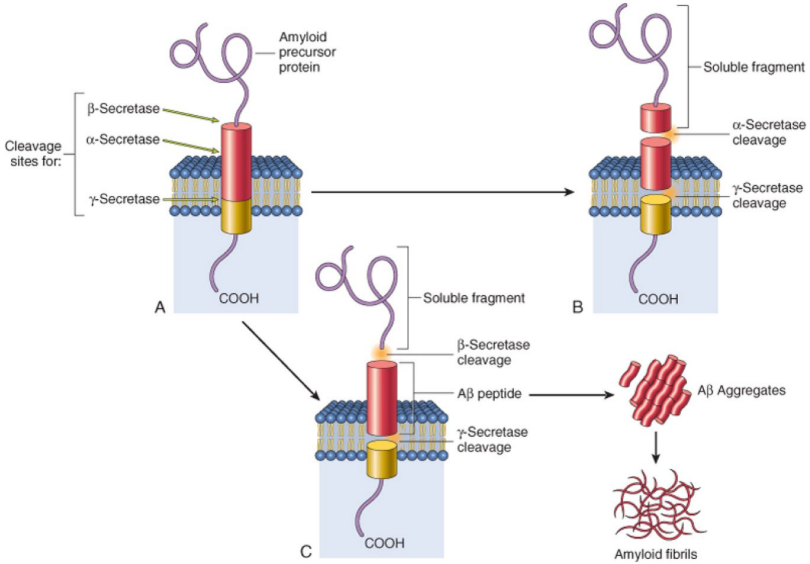
The beta secretase pathway

- The first cleavage is done by β-secretase, which gives us an insoluble beta fragment.
- The second cleavage is always done by γ-secretases.
- The second cleavage gives us two insoluble fragments Aβ40 and Aβ42.
- Aβ42 is more hydrophobic because of its shape as a beta pleated sheet.

This is the most prominent pathway in alzheimer's

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



Accumulation of Aβ protein

- Accumulation of Aβ protein affects neurons and neuronal function:
  - Small aggregates of Aβ alters neurotransmission by sitting between neurons and preventing transmission
  - 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

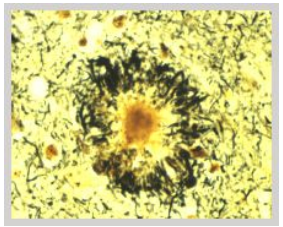
The Tau Protein

- Presence of Aβ causes hyperphosphorylation 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

- Tau protein normally stabilize the microtubules in neurons
- Hyperphosphorylated tau protein aggregates from the microtubules and make knots
- Symptoms of the disease are associated mainly with the number of neurofibrillary tangles

Aβ and tau may both contribute to the pathogenesis Of the Alzheimer's disease

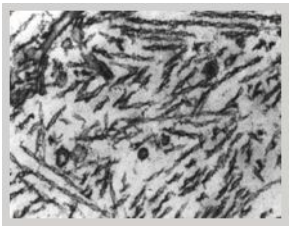
Factors that elevate **Aβ** (idiopathic)



Aβ

Fibril assembly

Nerve cell mis-function and death?



Tau

Filament assembly

Nerve cell mis-function and death?

We think that the plaques form first and they lead to the formation of neurofibrillary tangles and that both might lead to 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 syndrome (trisomy 21) beyond 45 years of age
- The gene encoding APP is located in chromosome 21
- Due to APP gene dosage effects[1]

- Genes associated with typical,sporadic Alzheimer disease are being identified[2]
- This may provide new clues to 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

1: - Familial Alzheimer's disease
- Since there is an extra gene in down syndrome, there will be extra production of APP

2: We only know about APO E4

Treatment of AD

- Currently no effective treatment for AD.
- Regulating neurotransmitter activity (eg.enhancing cholinergic function improves symptoms).
- Epidemiological studies show NSAIDs decrease the risk for developing AD, unfortunately Clinical trials of NSAIDs in AD patients are not very fruitful.
- Polyphenols "antioxidants" such as flavonoids (found in fruit) reduce proinflammatory responses.
- Flavonoid supplements may be a new therapeutic approach for AD
- Stem cell therapy offers:
    - Cellular replacement and/or provide environmental enrichment to attenuate neurodegeneration "by grafting a certain type of neurons in an affected area"
    - Neurotrophic support to remaining cells Prevent the production or accumulation of toxic factors that harm neurons

All of these are being researched

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

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Summary

Alzheimer's Disease

General Information	• prominent involvement of the cerebral cortex , Its principal clinical manifestation is dementia , Most cases are sporadic. • Becomes symptomatic before 50 years of age but the incidence of disease rises with age. • becomes profoundly disabled, mute and immobile In 5-10 years, At least 5-10% are familial		
Diagnosis	• Combination of clinical assessment and radiologic methods "MRI" • Pathologic examination of brain tissue is necessary for definitive diagnosis • Major microscopic abnormalities include: neuritic plaques , neurofibrillary tangles and amyloid angiopathy		
Microscopic findings	1. Neuritic Plaques	2. Neurofibrillary Tangles	3. Amyloid Angiopathy
	• Spherical : 20-200 mm in diameter. • Contain paired helical filaments and abnormal mitochondria • The amyloid core contains several abnormal proteins • The dominant component of the plaque core is Aβ from (APP) • The two dominant species of Aβ, called Aβ40 and Aβ42	• Bundles of filaments in the cytoplasm of neurons that displace or encircle the nucleus • These filaments mainly contain : 1- Hyperphosphorylated forms of the tau protein 2- A protein that enhances microtubules assembly • There is strong correlation of number of neurofibrillary tangles with degree of dementia than neuritic plaques	• Amyloid proteins build up on the walls of the arteries in the brain • The condition increases the risk of hemorrhagic, stroke and dementia • not specific for Alzheimer's
Genetics of Alzheimer's	1- Mutations in APP gene in Chromosome 21 2- Mutations in γ-secretase (presenilin-1 in Chromosome 14) or (presenilin-2 in Chromosome 1) 3- Apolipoprotein E (ApoE) in Chromosome 19		
Treatment	• Currently, no effective treatment for AD • we can regulate neurotransmitter activity e.g., Enhancing cholinergic function improves AD • Cellular therapies using stem cells offer great promise for the treatment of AD by : 1- Cellular replacement and/or provide environmental enrichment to attenuate neurodegeneration. 2- Neurotrophic support to remaining cells. • Pro-inflammatory responses may be countered through polyphenol(flavonoids) Supplementation of these natural compounds may provide a new therapeutic line of approach to this brain disorder.		

Take Home Messages

- 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's disease is. amyloid β42(Aβ42) peptide

MCQs:

Q1: Neurofibrillary tangle are composed of:

A- Amyloid beta
B- Tau protein
C- APP

Q2: Most of conditions of alzheimer disease are due to:

A- Familial
B- Sporadic
C- MS

Q3: Alzheimer disease usually associated with which condition?

A- Spina bifida
B- Down syndrome
C- MS

3-B
2-B
1-B

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