SAMPLE PREVIEW

BPS3011

Disease-Focused Pharmacology

Comprehensive Study Notes

HD 83 • Monash University

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Alzheimer's Disease

Background

- Dementia-related disorder
    - Characterised by personality changes, confusion, deterioration of intellectual capacity and cognitive function, reduced impulse control
- Neurogenerative
    - Progressive neuronal loss (apoptosis)
    - Increased susceptibility to ischemia, excitotoxicity, and oxidative stress
- Features (Hallmark pathological signs):
    - Extracellular amyloid plaques
    - Intraneuronal neurofibrillary tangles
    - Microglial activation, inflammation (reactive gliosis), generation of free radicals
- 50-60% of dementia cases are due to Alzheimer's disease
- Prevalence
    - 1:15 at 65 years, 1:4 above 85 years
- Primary risk factor = advanced age
- Genetic predisposition in few patients
    - Early onset AD is linked with mutations in genes encoding:
        - amyloid precursor protein (APP)
        - Presenilin 1 and 4 (component of secretases)
    - Late onset AD associated with mutations in gene encoding apolipoprotein E4
- Most cases of AD are idiopathic
- AD may result from:
    - Exposure to a slow virus or infection
    - Genetic predisposition
    - Chronic inflammation
    - Autoimmune disorder
    - Aluminum or zinc toxicity
- Initiation factors include:
    - Down's syndrome
    - Head trauma
    - Genetic factors
    - Promoting factors:
        - Age
        - Depression
        - Stress
        - Toxins
        - Illness

- Hypothyroidism
- Illiteracy

Brain plasticity

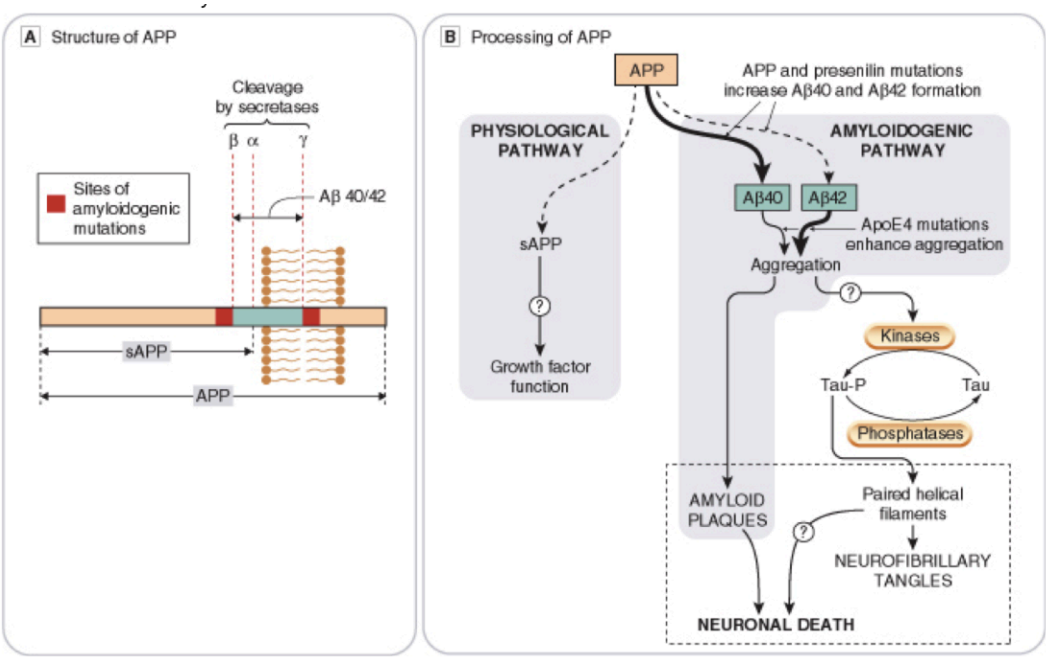
- Modified by:
  - Modifying the firing of neurons (synaptic plasticity)
  - Eliciting growth of new or pruning of existing synapses (structural plasticity)

Amyloid plaques

- Classified as diffuse or neuritic (associated with neurites)
- Amorphous extracellular deposits of beta-amyloid protein caused by increased production or insufficient removal of the aggregating amyloid protein A-beta39-43
  - This occurs due to the action of imprecise secretases/dysfunctional clearance mechanisms

Mechanism

- Toxic A-beta species aggregate into oligomers
- A-beta oligomers interfere with LTP, synaptic signalling and plasticity
  - Therefore impacting learning and memory
- A-beta stimulates the modification of Tau and activates kinases
  - Resulting in pathology correlated with degree of cell death and impairment
- Amyloid precursor protein → amyloid beta → A-beta intermediate → oligomers → fibrils or dendrites → fibrils forms plaque

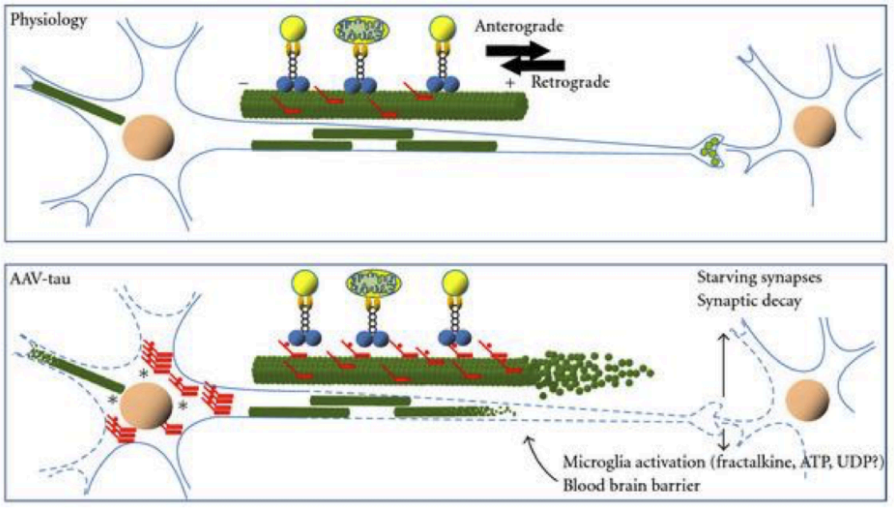


Neurofibrillary triangles

- Tau (microtubule-associated protein) stabilizes microtubules
- Filaments of hyperphosphorylated Tau protein clump and de-stabilize the microtubule network
- Tau and neurofibrillary tangles correlate with the degree of neuronal loss and cognitive impairment

Neurodegenerative triggers

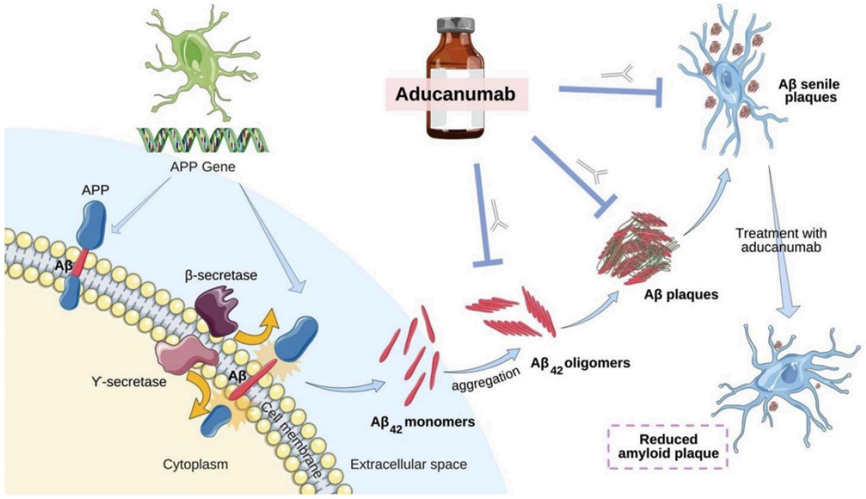
- Degeneration of neuronal processes seen when overproduced or hyperphosphorylated Tau interferes with transport processes



- **Normal conditions:**
  - Tau is regulated tightly at different levels to ensure normal transport along microtubules in axons and dendrites
    - Includes isoform expression, phosphorylation, microtubule binding, turnover
- **Pathophysiology**
  - Increased expression of Tau (geneticallty or pathologically) increases the amount of Tau bound to microtubules which competes for and blocks the binding sites needed for the motor proteins that carry out transport
  - Results in impairment in transport of cargo from synaptic vesicles/mitochondria to proteins will impair transport and energy-dependent processes at the synapse
  - This extends and evolves into degenerating neuronal processes and leads to neuronal death
  - Defective synaptic transmission is expected = early symptom of AD
  - Small and loose aggregate or oligomers of protein Tau collect into the microtubules
  - This causes the oligomers to disintegrate or collapse
  - Injured neuronal processes also releases proteins and factors that activate microglia and astroglia

- Activation of microglia and astroglia (inflammatory cells) secrete factors that affect neurons and cells that compose the blood-brain barrier allowing for higher permeability which negatively affects neurons

Aduhelm; Aducanumab MOA



Symptoms

- Progressive deterioration of intellectual and cognitive function
- Impaired memory (retrograde amnesia; loss of previously formed memories and anterograde amnesia; inability to form new memories)
- Aphasia; impairments in language
- apraxia; impairments in performing purposeful movements
- agnosia; impairments in recognition
- Reduced ability to learn, solve problems, perform mathematical equations, think abstractly, make appropriate decisions
- Profound alterations in personality
- Reduced impulse control, hyper-excitability, loss of insight, confusion
- Gait disturbances
- Amnesia - memory loss

Clinical staging of Alzheimer's disease

- Clinical phase = Symptoms
- Normal = No change in cognition
- Very mild = Forgets object location, word finding deficits
- Mild (early confusion) = Early cognitive deficits, memory loss, decreased ability to work, name-finding deficits, decreased social functioning, loss of recall, anxiety
- Moderate = Unable to perform complex tasks, loss of concentration, loss of knowledge of current events
- Moderately severe (early dementia) = Needs assistance for survival and daily functions, disoriented as to time and recent events, maybe tearful

PREVIEW

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The full set is 98 pages, covering every topic with all diagrams and a clickable table of contents.

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