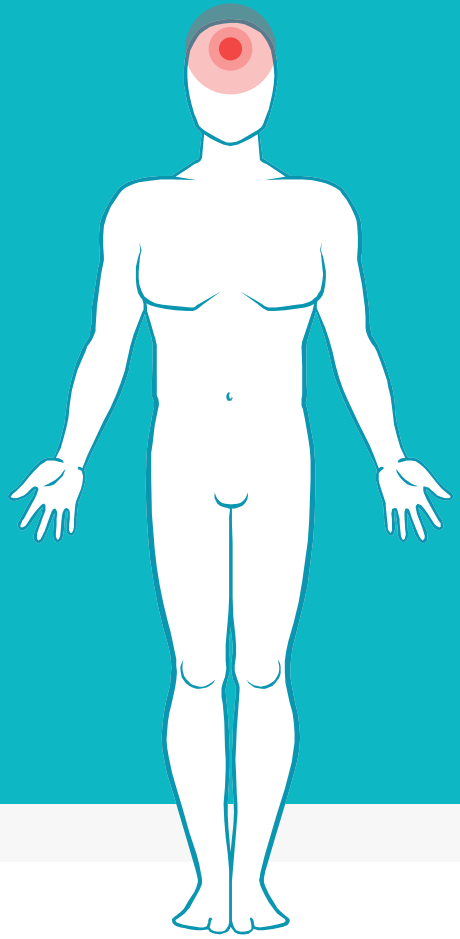
A LOOK INTO ALZHEIMER'S DISEASE



Outline of Presentation

Introduction

Etiology and Epidemiology

Diagnosis

Stages and progression

Pathophysiology

Tau protein

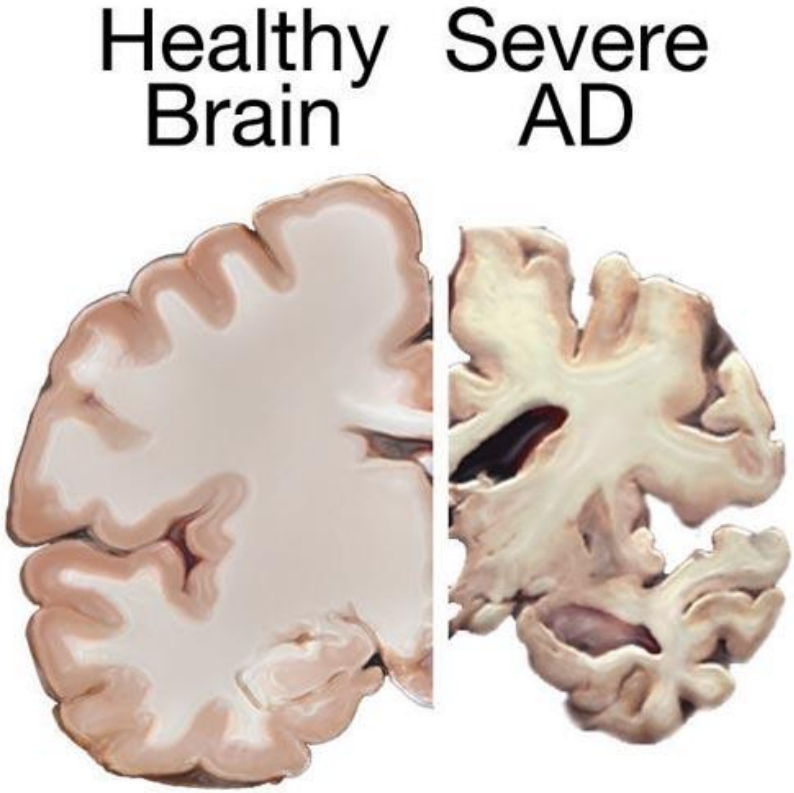
Amyloid precursor protein

Therapeutics and Future implications

Conclusion

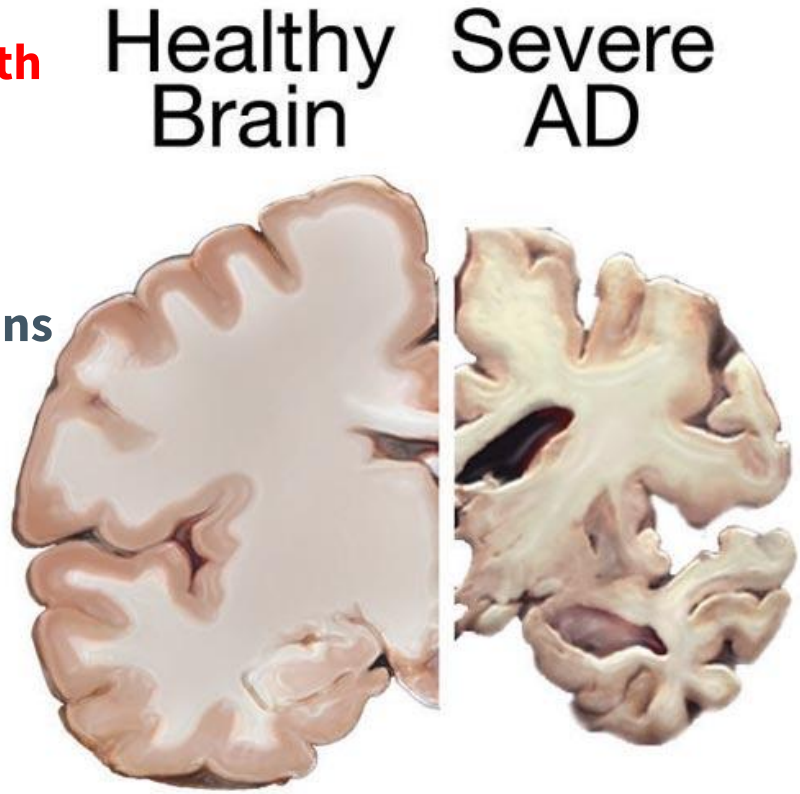
What is Alzheimer's Disease?

- Chronic neurodegenerative disease
- 60 to 80% cases of Dementia
- Targets memory, behaviour & language
- Progressive



(Alzheimer's Disease, 2016)

- Degeneration of neurons = **cell death**
- Mass of brain is **reduced**
  - Memory decline, erratic behaviors, loss of body functions
- Three stages:
  - Early
  - Mild-Moderate
  - Severe



(Alzheimer's Disease, 2016)

Epidemiology & Etiology

Epidemiology

(World Alzheimer Report, 2015)

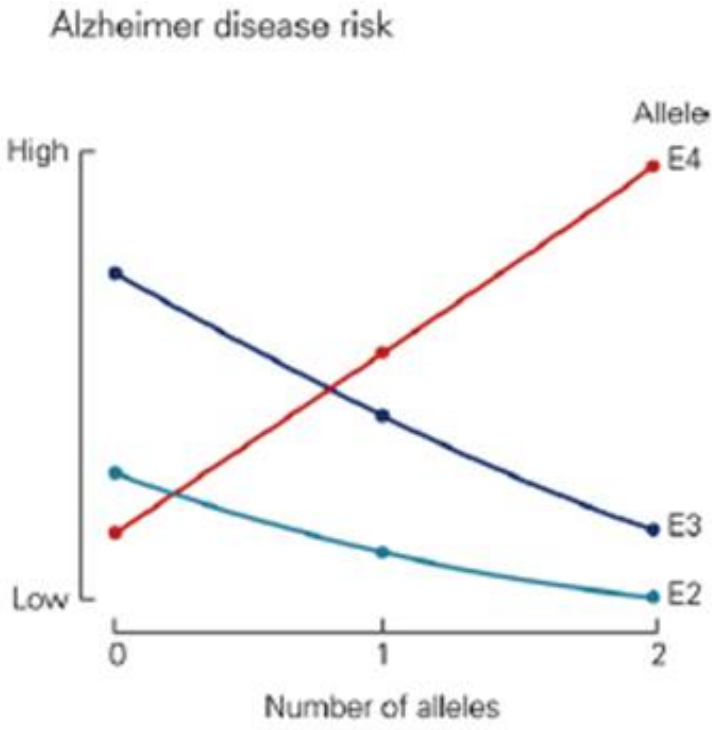
Etiology

Sporadic AD

- Late-onset AD (>60 years)
- Apolipoprotein E (ApoE)

Familial AD

- Early-onset AD (<60 years)
- Mutations in *APP*, *PSEN-1*, *PSEN-2*

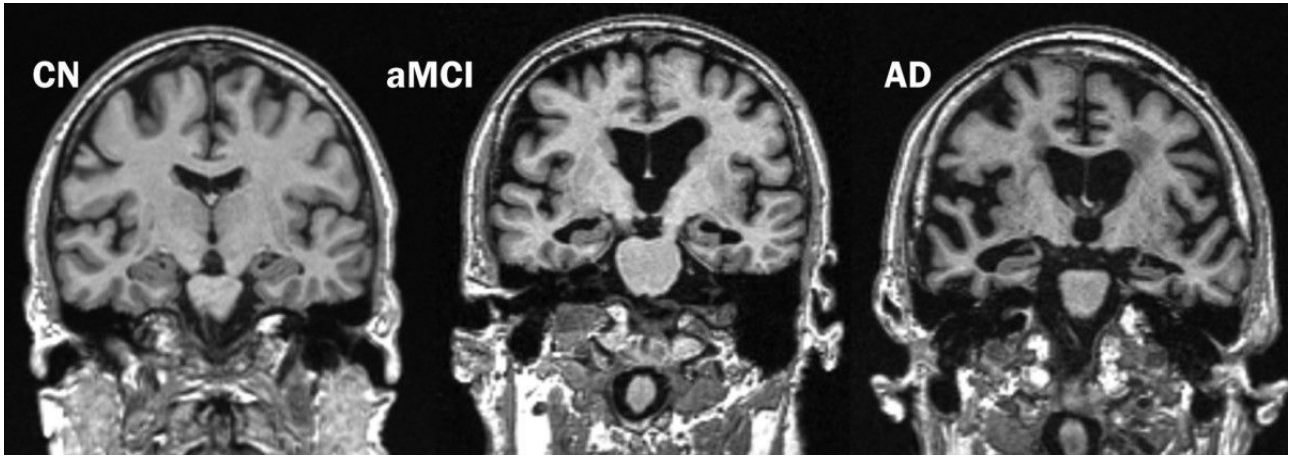


(Kandel et al., 2013)

Diagnosis

sMRI

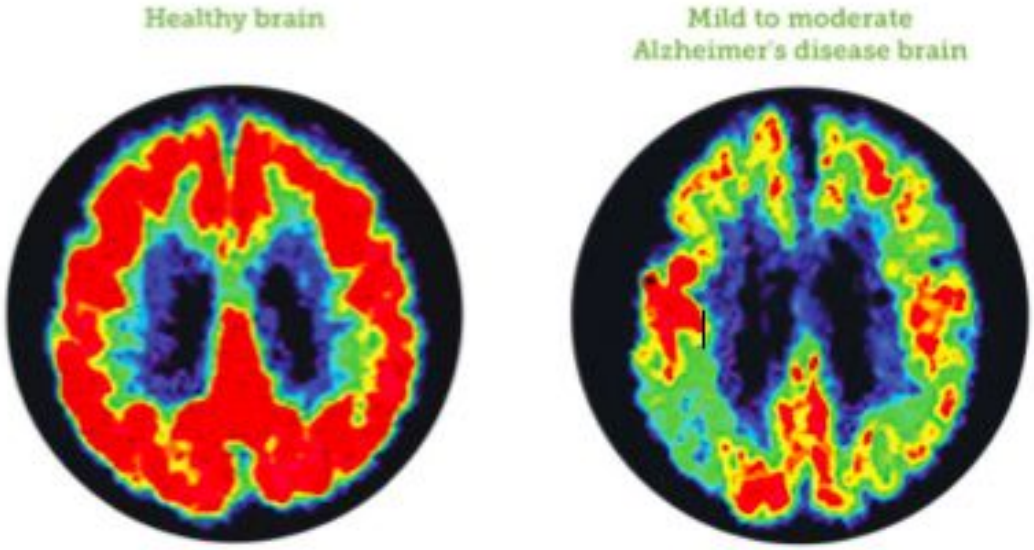
- Static anatomical information of brain
- Markers used to differentiate mild cognitive impairment stage
- Can show spread of plaque and tangles



(Vemuri & Jack, 2013)

FDG- PET Scan

- **Glucose** analog to track brain metabolic activity
  - Fluoro-deoxy-D-Glucose (FDG)
- AD patients show decreased metabolism *versus* normal

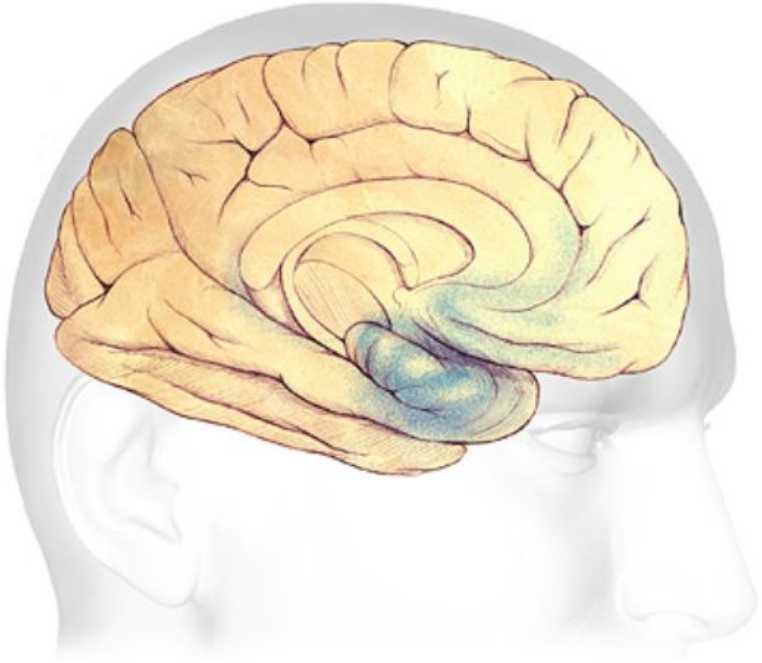


(Johnson et al., 2012)

Stages & Progression

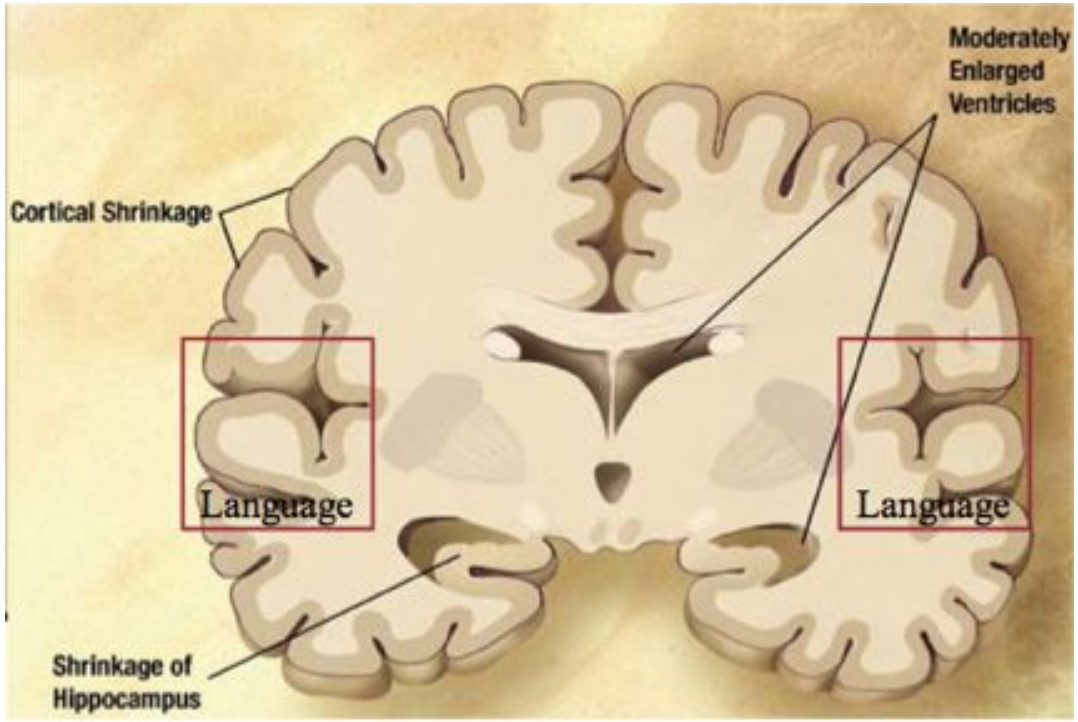
Stage 1: Early Stage

- Slow formation of plaques & tangles
  - Short-term memory loss
- Begins in entorhinal cortex, and hippocampus
- Shrinkage of amygdala
  - Emotional outbursts, changes in behaviour



(Förstl & Kurz, 1999)

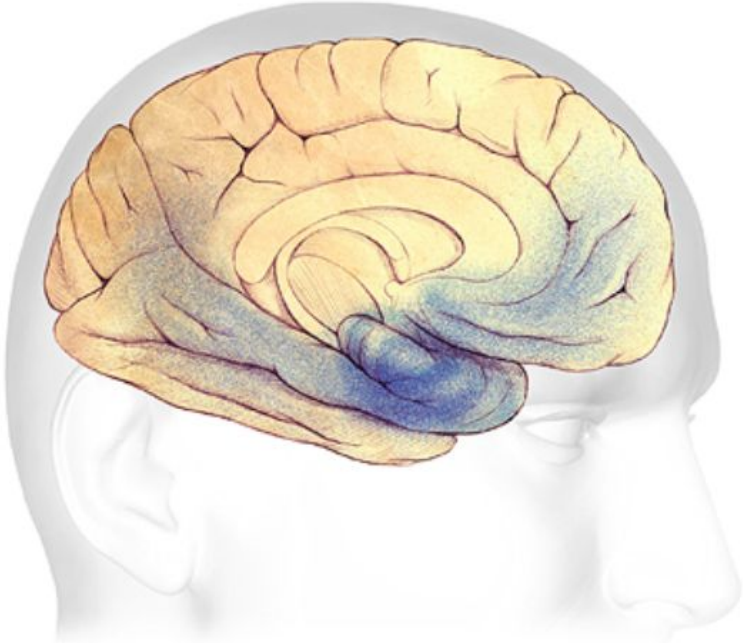
Stage 2: Mild to Moderate Stage



(Staff, 2017)

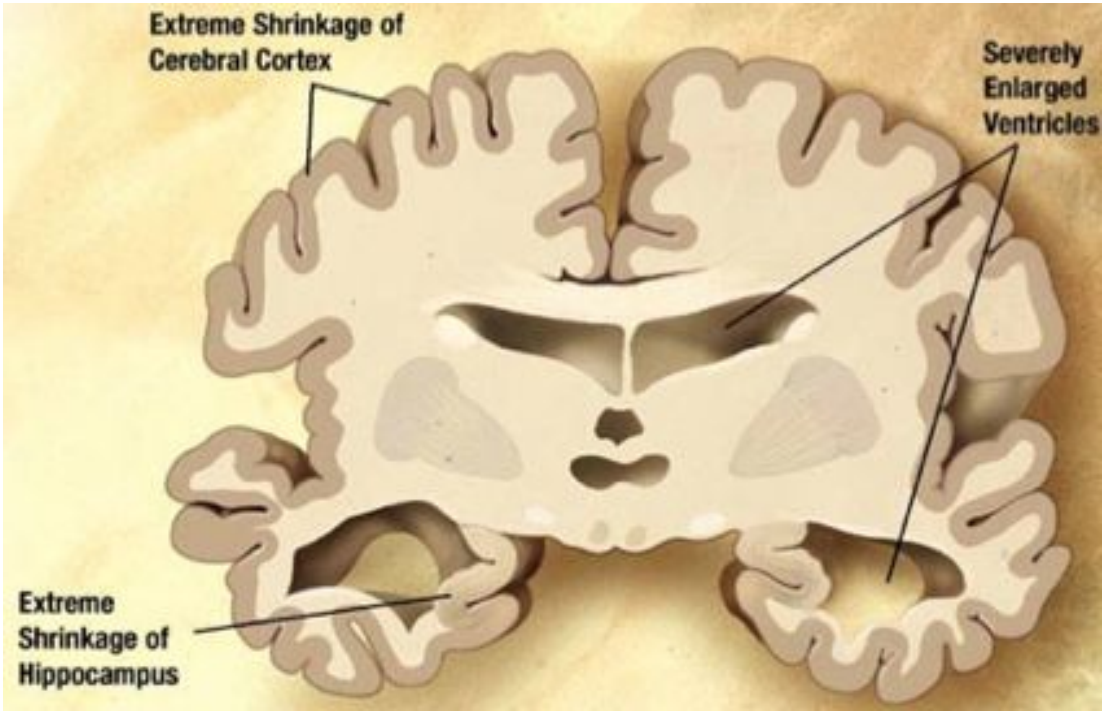
Stage 2: Mild to Moderate Stage

- Clinical diagnosis made
- Plaques & tangles continue to spread
- Memory loss continues
- Poor judgement
- Mood changes
- Increase in anxiety
- Language impairment



(Förstl & Kurz, 1999)

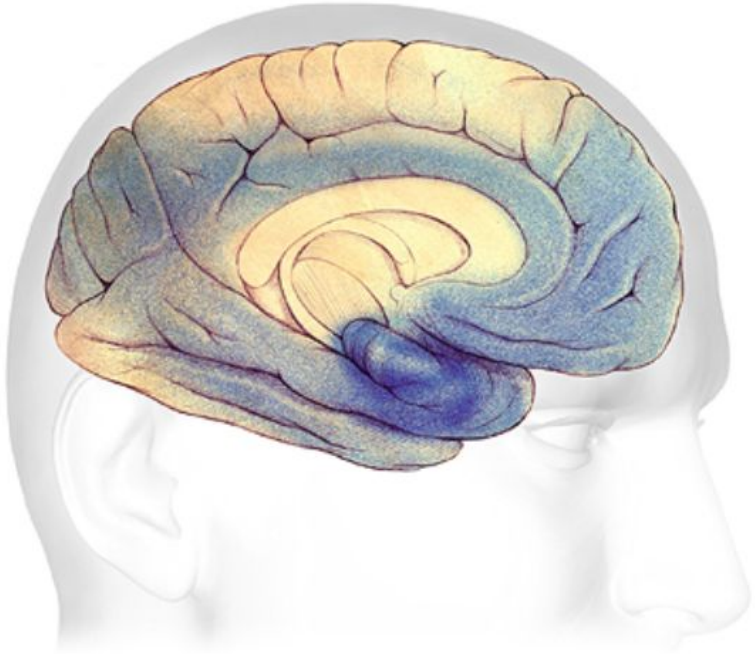
Stage 3: Severe Stage



(Staff, 2017)

Stage 3: Severe Stage

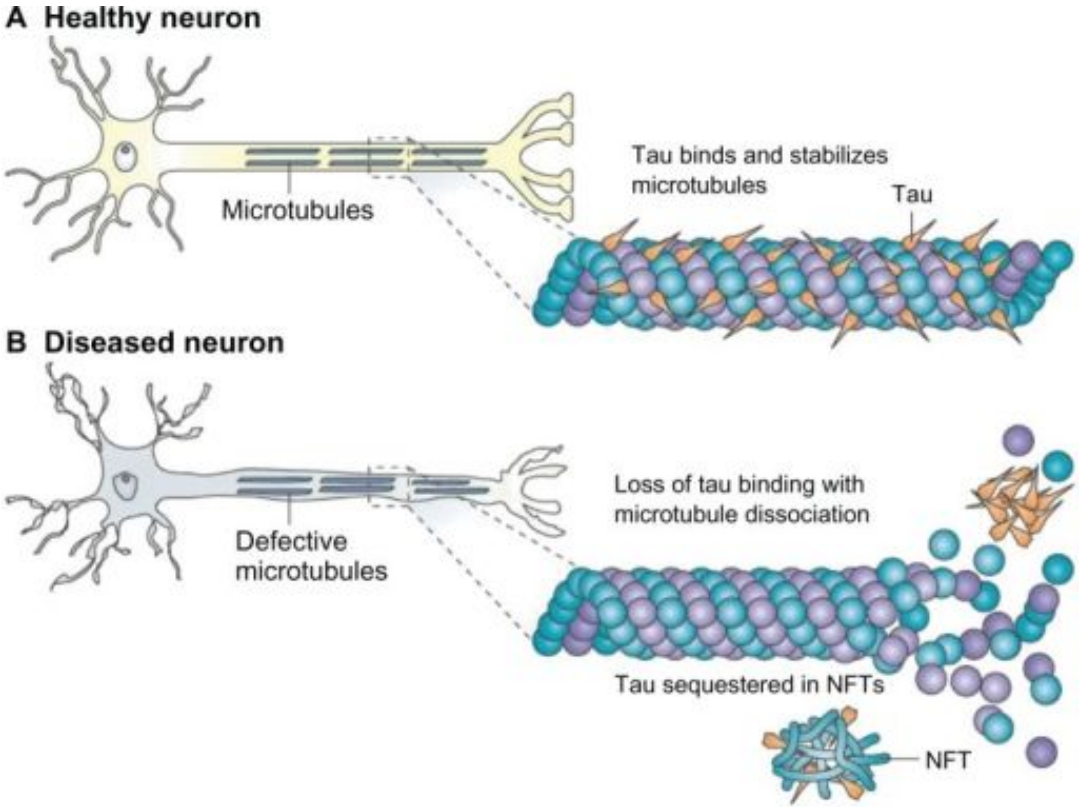
- Plaques and tangles are widespread throughout brain
- Severe dementia
- Cognitive functions are severely impaired
- Progressive loss of autonomic functions
- Complete dependence on others for care



(Förstl & Kurz, 1999)

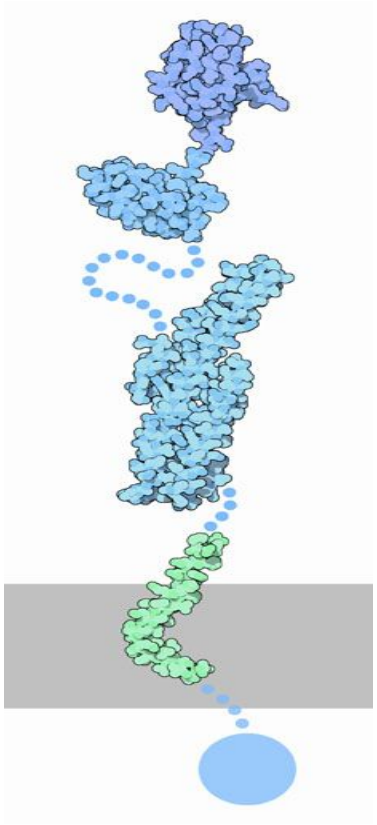
Pathophysiology

Tau Protein


A Healthy neuron
Microtubules
Tau binds and stabilizes microtubules
Tau
B Diseased neuron
Defective microtubules
Loss of tau binding with microtubule dissociation
Tau sequestered in NFTs
NFT

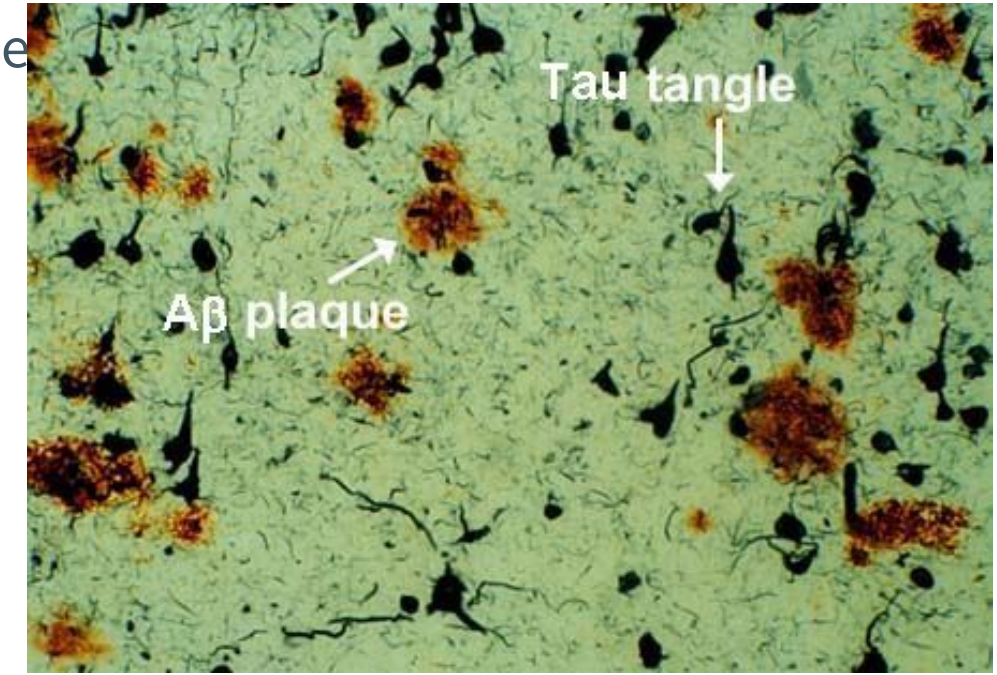
Amyloid Precursor Protein (APP)

- Large membrane protein found on cell surface
- Four domains
  - Three extend cell surface
  - One peptide expanding the membrane
- Acts as a G protein receptor
  - Heparin and laminin
- Can break down via proteases



Histopathological Features of APP

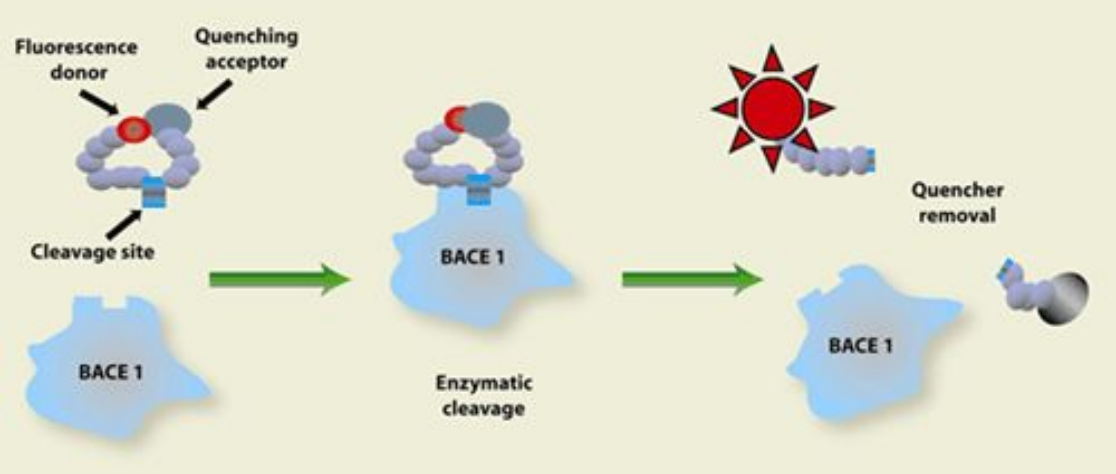
- Formation of plaques via proteolytic cleavage of the APP protein
- 40-42 amino acid b-amyloid (AB) peptide chains
- Concentrations of AB plaque in cerebrospinal fluid
  - 500-900ng/ml



(Seeman, 2011)

APP Mutation in Familial Case

- APP plaque formation is implicated with early onset of Alzheimer's
- APP cleavage occurs via beta and gamma secretase enzymes
- Secretase enzymes are produced via (Beta site APP cleaving enzyme) BACE
- Cerebral deposition of amyloid peptides



(Vassar et al., 1999)

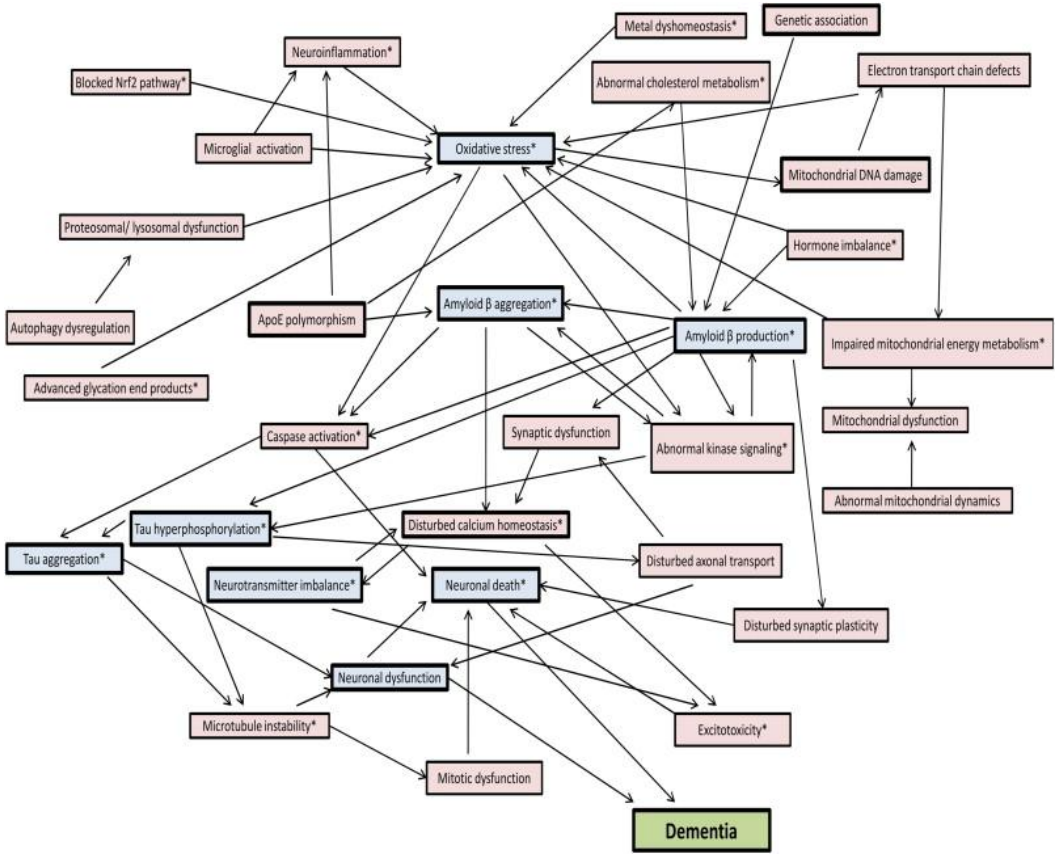
Treatments

Treatments

- Numerous mechanisms → Pathogenesis + Pathophysiology of AD
- Current therapeutics based on cholinergic hypothesis:
  - Loss of cholinergic neurons → loss of cholinergic activity
  - Confirmation studies: used monkeys to show effect of anticholinergics on memory deficits seen in AD
- Therapeutics developed focus on augmentation of cholinesterase activity
  - Cholinesterase inhibitors (CIs):
    - Enhance cholinergic transmission

(Lleo, 2007)

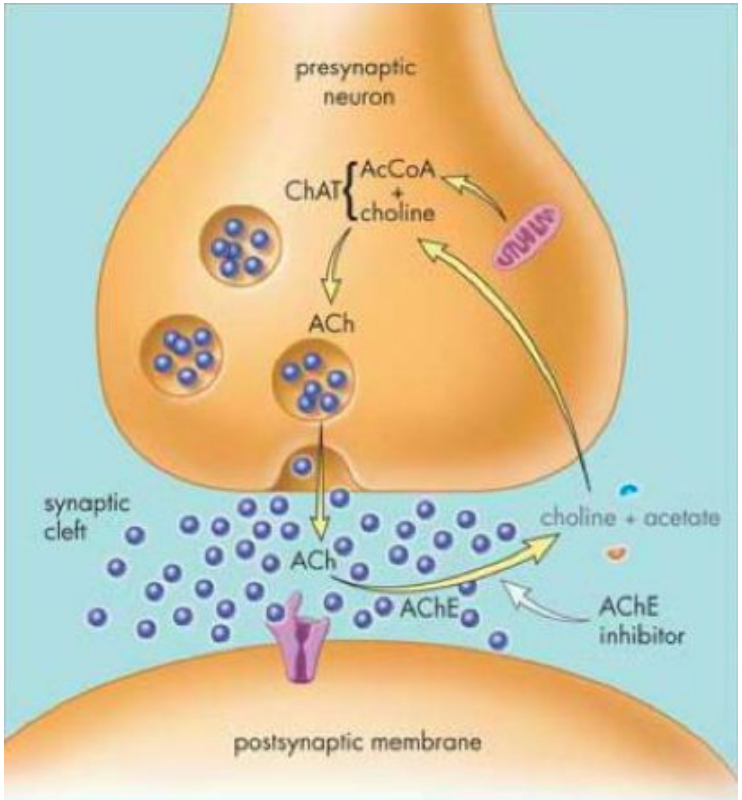
Mechanisms Involved in The Pathogenesis and Pathophysiology of AD



(Anand, 2014)

Cholinesterase Inhibitors (CIs)

- Four cholinesterase inhibitors:
  - Donepezil, rivastigmine, galantamine, tacrine
  - For mild and moderate cases
- Study by Hansen et al. shows donepezil, rivastigmine, galantamine providing benefits
  - Cognition, function, and behavior
- Side effects:
  - Nausea, vomiting, diarrhea, bradycardia, muscle cramps, and insomnia



(Stahl, 2000)

Additional Therapeutics: Memantine

- Memantine: N-methyl D-aspartate (NMDA) receptor agonist
  - For moderate and severe cases
- Prevents excessive release of glutamate → excitotoxicity
- Study McShane et al. shows benefit of memantine
  - Cognition, activities of daily living, behavior
- **Side effects:**
  - Dizziness, constipation, confusion, headaches, hypertension, and visual hallucinations

(Yiannopoulou, 2013)

Future Research & Implications

Future Therapeutics: AB Peptide Immunization

Study: Immunization of AB peptides in murine models of Alzheimer's disease

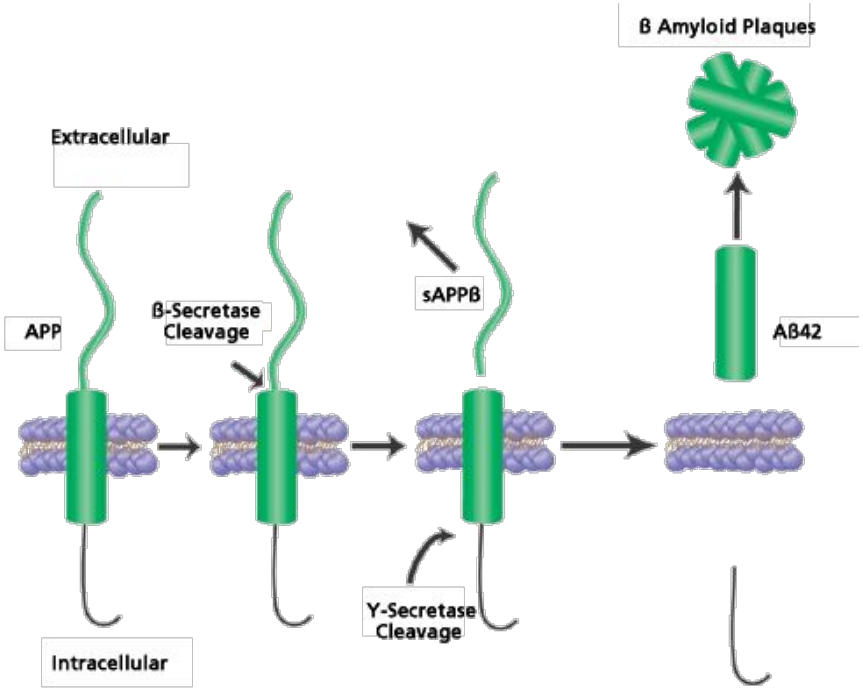
Methods: injecting a mutated APP transgene in the vaccinated (AB42 or IAPP) and control murine models followed with memory recall test

Results: Mice vaccinated with the AB42 or IAPP vaccine show better memory recall on the Morris model maze test and reduction in AB plaques

(Janus et al., 2000)

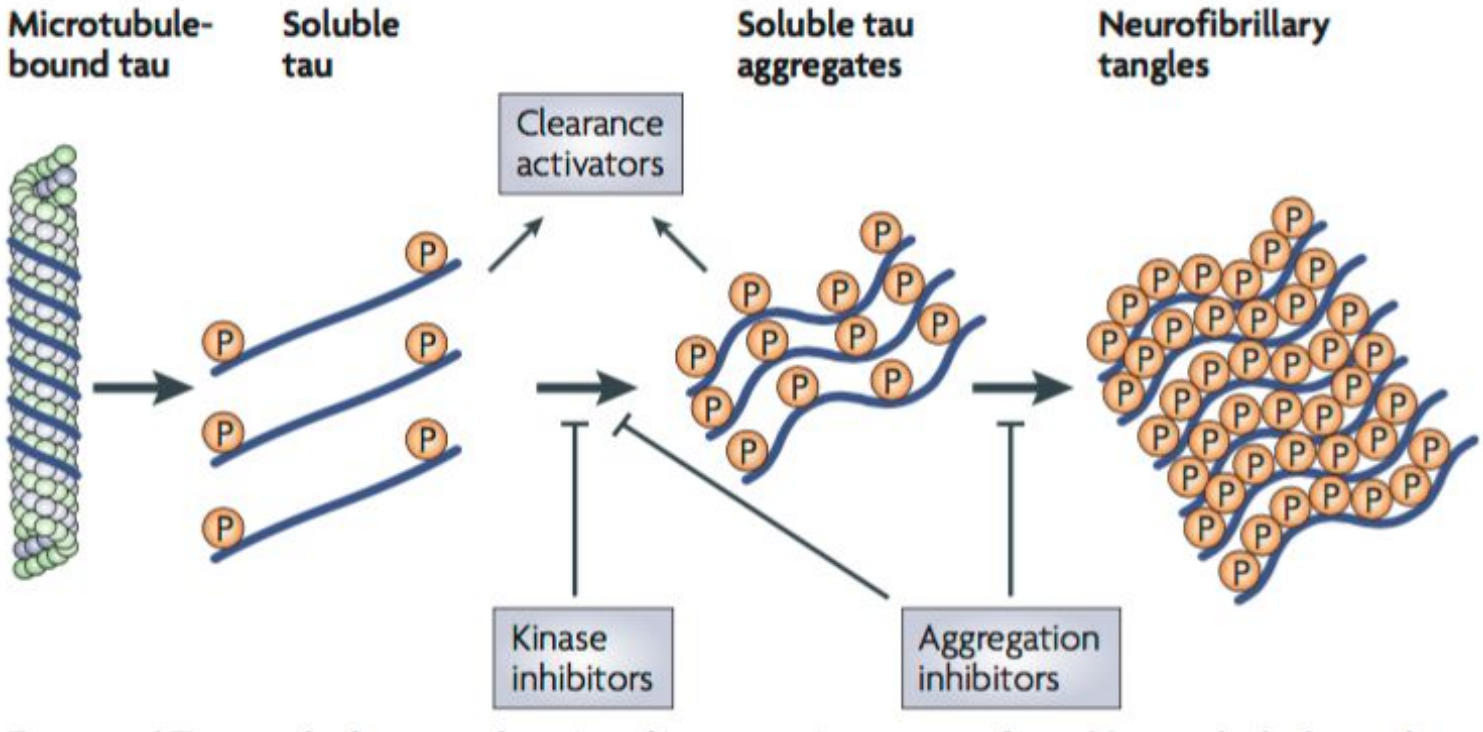
Future Therapeutics: BACE Inhibition

- Inhibiting the production of BACE is seen to reduce the levels of beta secretase
- BACE knockout studies in mice show a reduction in beta amylase production



(Roberds et al., 2001)

Future Therapeutics: Targeting Tau Aggregates



(Citron, 2010)

Conclusion

Questions

1. **Which gene is not linked to familial cases of Alzheimer's Disease?**
   a. **Apolipoprotein E**
   b. **Amyloid Precursor Protein**
   c. **PSEN-1**
   d. **PSEN-2**

Questions

1. Which gene is not linked to familial cases of Alzheimer's Disease?
   a. Apolipoprotein E
   b. Amyloid Precursor Protein
   c. PSEN-1
   d. PSEN-2

Questions

2. Which proteins are being targeted in immunotherapy to treat Alzheimer's Disease?

a. Amyloid plaques
b. Glycoproteins
c. Tau proteins
d. A and B
e. A and C

Questions

2. Which proteins are being targeted in immunotherapy to treat Alzheimer's Disease?

a. Amyloid plaques
b. Glycoproteins
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