Alzheimer's Disease

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Physiology

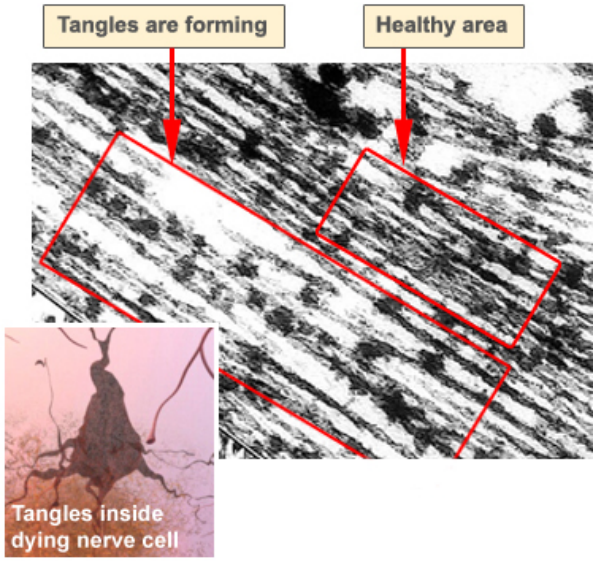


Fig 1

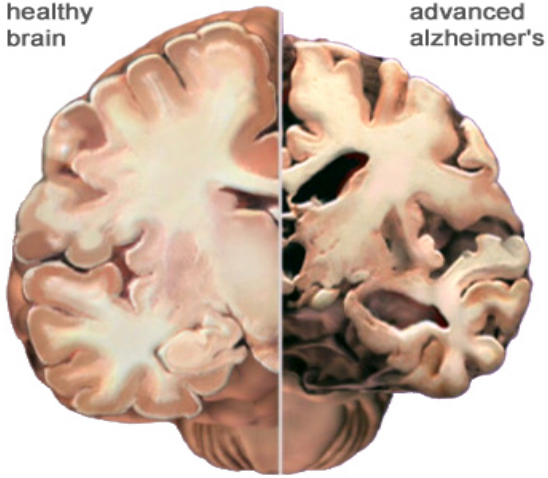


Fig 2

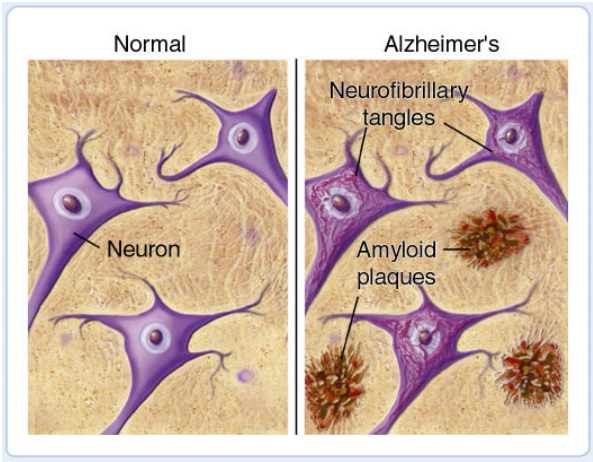
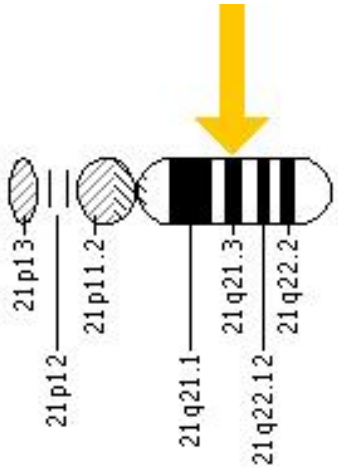
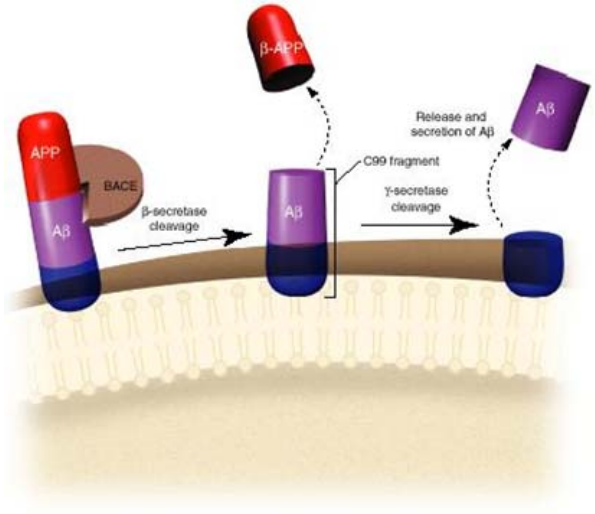


Fig 3

- Most common type of dementia (50-80% of dementia cases), progressive
- Late adulthood onset (~ 60), 5% early onset cases, risk increases with age
- Targets the central nervous system and eventually the digestive system and neuromuscular system
- Brain: abnormal deposits beta-amyloid between nerve cells, plaques, tangles (tau) → RESULT: death of nerve cells, ventricles expand, brain shrinks
- Memory loss, difficulty with speech/understanding, loss of bladder control, weight loss, seizures, skin infections, impaired swallowing, rigid muscles

Molecular Cause





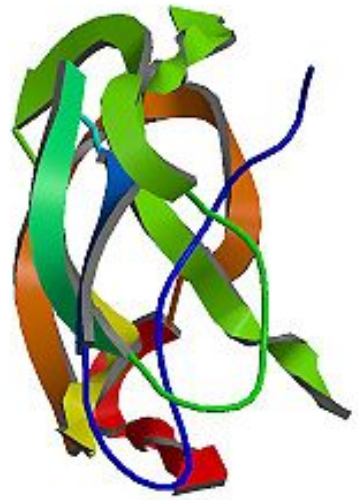


fig4 **fig 5** **fig 6**

- APP (amyloid precursor protein) gene on chromosome 21, location 21q21.3
- Provides instructions for making amyloid precursor protein which helps direct movement of nerve cells in the brain during early development
- Transmission: Autosomal Dominant, one mutated APP gene will result in manifestation of disease, 25% of cases are hereditary (15% APP gene) mutation, 75% of cases are random mutations
- Point mutation replaces the amino acid valine with the amino acid isoleucine at protein position 717
- Amyloid precursor protein is cut by 3 enzymes (alpha, beta and gamma-secretase); gamma-secretase cleavage results in formation of beta-amyloid peptide. Mutation in the APP gene alters the amyloid precursor protein resulting in an increased amount of a slightly longer and stickier form of the beta-amyloid peptide (plaques)
- Patients with Down syndrome (trisomy 21) have an increased risk of developing Alzheimer's disease, three copies of the APP gene

Treatments/Risks and Limits

- There is currently no cure to Alzheimer's Disease
- 5 FDA approved drugs
- Cholinesterase inhibitors (Aricept, Cognex, Exelon, and Razadyne): Alzheimer's destroys cells that use acetylcholine (neurotransmitter), reducing amounts available to carry messages. Cholinesterase inhibitors block the activity of acetylcholinesterase, a chemical that break acetylcholine down; increased concentrations of acetylcholine; increase communication between nerve cells
- Namenda: regulates the amount of chemical messenger in the brain called glutamate which plays a role in learning and memory. Brain cells of patients with Alzheimer's release too much of this neurotransmitter.
- Limits: slow progression of symptoms temporarily (6-12 months), side effects (diarrhea, vomiting, nausea, fatigue, loss of appetite, and weight loss), Cognex may also cause liver damage
- Cures on the horizon:
  - CLR01 ("molecular tweezer"): reported to prevent toxic proteins from binding together and killing the brain's neurons in Parkinson's disease, tested in mouse model (crossed the mouse's blood-brain barrier and effective in clearing the brain of amyloid-beta and tau aggregates), next step: confirm that the tweezers improve memory
  - beta-secretase inhibitors aimed to reduce the production of beta-amyloid peptide by binding to beta-secretase to prevent the cleaving of APP into beta-amyloid peptide (CTS-21166 phase 2)

Proposal Cure/Limits

- Regulating the production of beta-amyloid peptide by targeting beta-secretase and gamma-secretase with feedback inhibitors
- Buildup of beta-amyloid peptide→ the inhibitors will bind to its corresponding enzyme to prevent APP cleavage. Low level of beta-amyloid peptide→the inhibitors will dissociate with the enzymes, allowing the cleavage of APP and the production of beta-amyloid peptide
- Extracellular beta-secretase cleavage of APP: a clinically effective beta-secretase inhibitor must be able to penetrate the blood-brain barrier and the neuronal membranes.
- Mouse model for drug development - *Mus musculus* is genetically similar to humans and mutation of APP gene demonstrates similar phenotype (reduced brain weight, disruption in locomotive activity)
- Propose to deliver both inhibitors of beta and gamma-secretase to three mouse models (normal -control, heterozygous mutant, mutant)
- Scientists have found ways for drugs to go through the blood-brain barrier using vasoacative substances such as bradykinin (increase vascular permeability)
- Separate studies being done for beta-secretase inhibitors and gamma-secretase inhibitors (limits: interference with processing of other proteins such as Notch-signaling pathway between cells, removal of Notch is lethal in mice, short life span of inhibitors)
- If successful (normal levels of beta-amyloid peptide, improved brain functioning), submit for clinical trials; mass production of inhibitors delivered by needle in spinal canal

References

Physiology Slide:

Content:

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→*Alzheimer's Disease Fact Sheet: National Institute on Aging*. U.S. Department of Health and Human Services, Sept. 2012. Web. 8 Mar. 2013. <http://www.nia.nih.gov/alzheimers/publication/alzheimers-disease-fact-sheet>

→ *Genetics Home Reference: Your Guide to Understand Genetic Conditions*. U.S. National Library of Medicine, 4 Mar. 2013. Web. 8 Mar. 2013. <http://ghr.nlm.nih.gov/>

→ Andrews, Tina. "What Body Systems are Affected by Alzheimer's Disease." *Livestrong.com The Limitless Potential of You. Web. 30 Mar. 2011. 18 May. 2013.* <http://www.livestrong.com/article/177220-what-body-systems-are-affected-by-alzheimers-disease/>

Images:

Healthy vs. Alzheimer's Brain (figure 2)
http://www.alz.org/braintour/healthy_vs_alzheimers.asp

Tangles vs healthy areas (figure 1)
http://www.alz.org/braintour/tangles.asp

Plaques and tangles (figure 3)
http://www.prlog.org/12056983-vitamin-b12-may-curb-risk-for-alzheimers-disease.html

Treatments/Risks and Limits Slide:

Content:

→ *Alzheimer's Disease and Dementia*. Alzheimer's Association (n.d.). Web. 8 Mar. 2013. <http://www.alz.org/alzheimers_disease_what_is_alzheimers.asp>

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Molecular Cause Slide:

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Images:

Amyloid beta precursor protein (figure 6)
http://en.wikipedia.org/wiki/Amyloid_precursor_protein

APP Gene Location (figure 4)
http://ghr.nlm.nih.gov/dynamicImages/chromomap/APP.jpeg

APP processing (figure 5)
http://www.rndsystems.com/cb_detail_objectname_WI00_BaceAlzheimers.aspx

Proposal Cure/Limits Slide:

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→ "APP Gene Detail." *Mouse Genome Informatics*. N.d. Web. 18 May 2013. <www.informatics.jax.org/marker/MGI:88059>

→ "Blood-brain barrier." *Wikipedia*. 4 May 2013. Web. 18 May 2013. <http://en.wikipedia.org/wiki/Blood-brain_barrier>

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→ "Notch1 loss of heterozygosity causes vascular tumors and lethal hemmorrhage in mice." *JCI: The Jounral of Clinical Investigation*. 25 Jan. 2011. Web. 18 May 2013. <http://www.jci.org/articles/view/43114>