Alzheimer's Disease: The Effects of Plaque Build Up in the Brain

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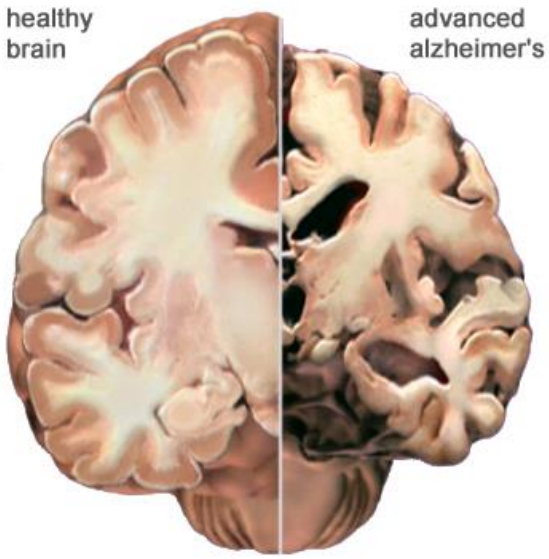
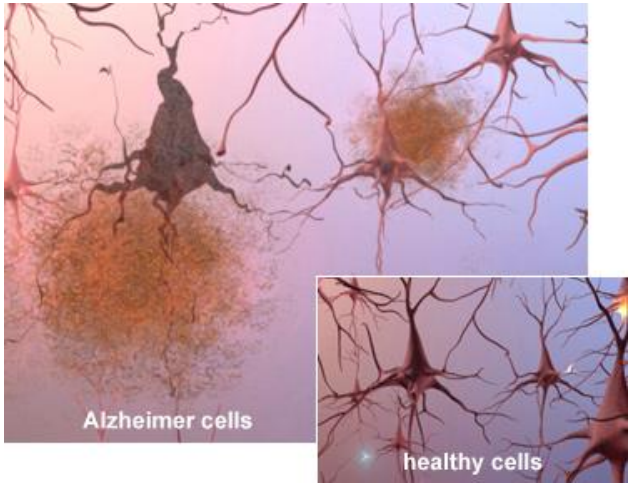
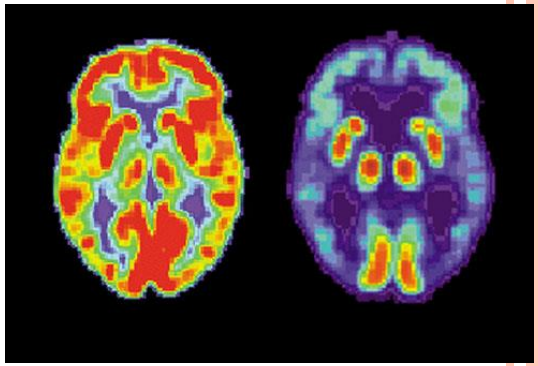


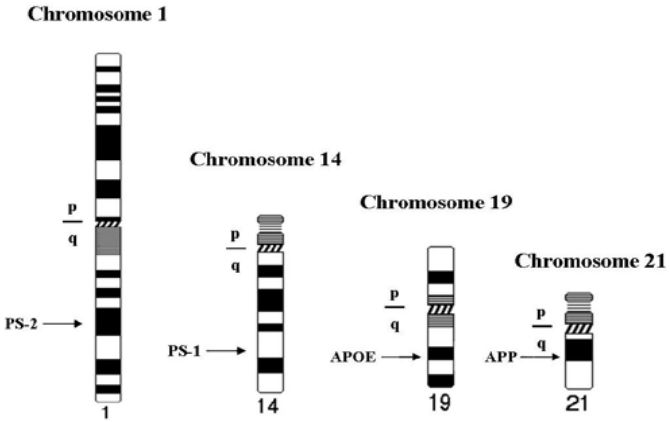
Physiology

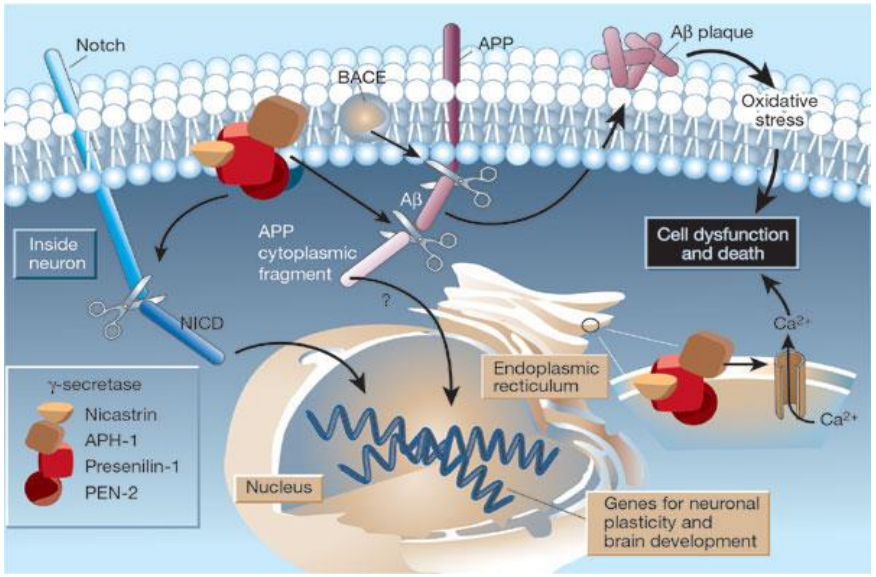




- The most common form of dementia and slowly worsens over time
- Sixth leading cause of death in America
- Affects the neurons of the brain (central nervous system)
- Late onset (65+) and early onset (30+); those already diagnosed live up to an average of 8 years
- Symptoms include forgetfulness, inability to complete every day tasks and eventually they become unresponsive to their environment, some must be watched constantly
- Plaques form in the brain – clump around neurons: prevent the transmissions of nuerotransmitters and causes cell death

Molecular Cause





- Point mutations on chromosomes 1 (PSEN2), 14 (PSEN1), 19 (APoE) and 21 (APP)
- Transmission: Autosomal dominant (age, Down's Syndrome and risk genes also affect development)
- Originally, APP is snipped to form peptides (beta-amyloid and soluble amyloid precursor protein) that aid in brain function (memory, alertness, thought, judgment, etc.)
- In Alzheimer's patients, APP is incorrectly metabolized, thus forming longer/stickier beta amyloid peptides. They lose their function and instead, the peptides clump around neurons, stopping the flow of messages between neurons.

Treatments and Limits

- Unfortunately there is no cure but treatments today include slowing down the symptoms and making life more manageable for both patients and their caretakers.
- Cholinesterase inhibitors: prevents the breakdown of acetylcholine (neurotransmitter important for alertness, thought and judgment)
- Approved for every stage of Alzheimer's: a few include Donepezil, rivastigmine, galantamine
- Limitations: Doesn't stop the breakdown of neurons and the inhibitors eventually lose effectiveness
- Memantine: regulates the activity of glutamate (chemical messenger that damages neurons in the brain when present in excessive amounts)
- Used in moderate or severe stages of Alzheimer's as currently there are no benefits in mild stages
- Limitations: Similar to the cholinesterase inhibitors they do not prevent the breakdown of neurons, only minimizing cell damage. It also begins to lose effectiveness after six to twelve months.

Proposal

- Some scientists have begun research with different types of cholinesterase inhibitors, in which their selectivity on these cholinesterase enzymes differ.
- Their different selectivity allows these new inhibitors to switch targets from chemical messengers (acetylcholine and glutamate) to the enzymes that snip the APP peptide.
- Once the enzymes are inhibited, peptides such as the beta-amyloid peptide aren't formed. Consequently, the plaques do not form and neurons do not break down.
- A few limitations include the fact that just like the current treatments, these new inhibitors will lose their function quickly, and the brain will form immunity.
- Also, there is the question of how normal peptides are to be created if the APP peptide is not snipped at all. Where will the creation of normal beta-amyloid peptide happen if the enzymes are inhibited?

References

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