6.2.4

Dementia and Alzheimer's Disease

Dementia

Dementia is a general term for symptoms like memory loss and decline in reasoning and thinking skills. It is not a specific disease. Alzheimer's disease is a specific brain disease that accounts for most cases of dementia. Other types of dementia include vascular dementia (brain injury that leads to ischemic or hemorrhagic damage), frontotemporal dementia (atrophy of the frontal and anterior temporal lobes of the brain), Wernicke-Korsakoff Syndrome (caused by chronic alcoholism), and Huntington disease (a hereditary disorder characterized by chronic and progressive neurological damage and a hallmark symptom of chorea).

Before diagnosis of chronic and irreversible memory loss, it is important to rule out reversible forms of dementia or conditions that can masquerade as dementia including subdural hematoma and cerebral infarcts. The pneumonic **DEMENTIA** is helpful to remember other causes for dementia:

Drugs (especially anticholinergics)

Emotional causes (like depression)

Metabolic causes (like hypothyroidism)

Eyes & Ears (declining vision and hearing)

Normal pressure hydrocephalus

Tumors or other space occupying lesions

Infection

Anemia (can be caused by vitamin B-12 or folate deficiency)

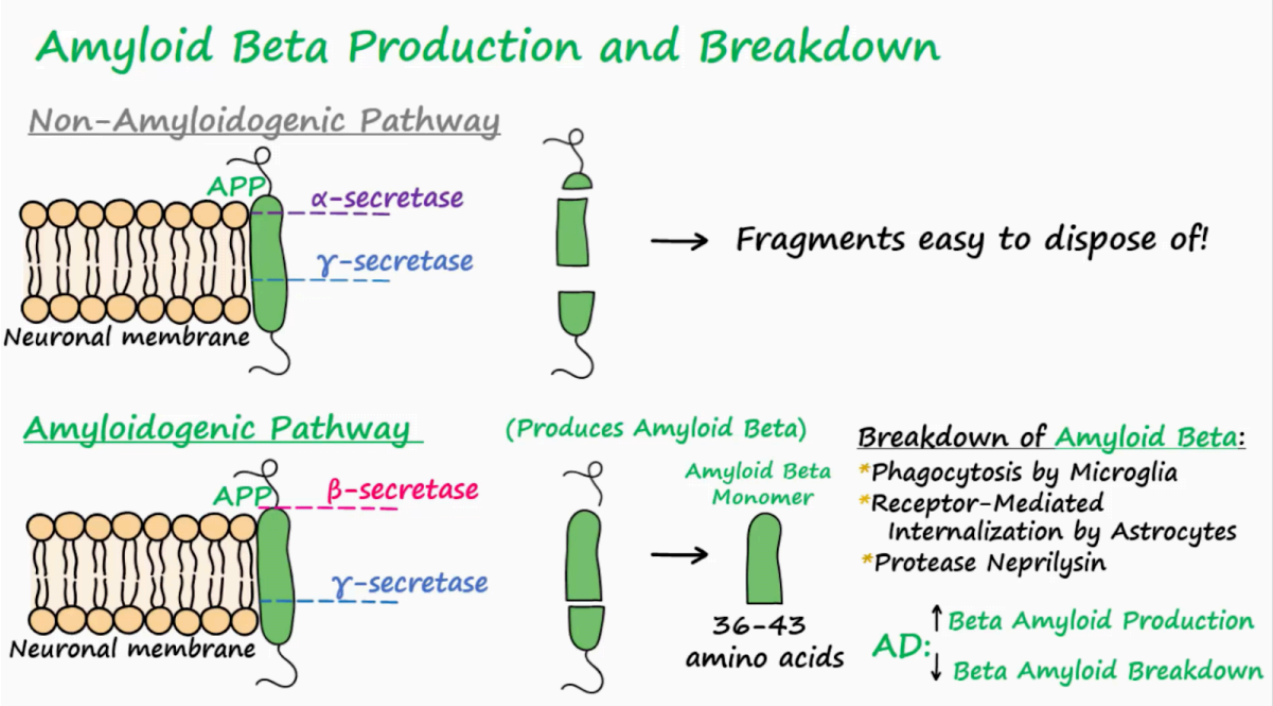
Alzheimer's Disease (AD)

Watch the video Pathophysiology of Alzheimer's Disease

Alzheimer's disease (AD) is a degenerative brain disease characterized by neuron cell dysfunction and death that leads to shrinkage of brain tissue. This neurodegeneration results in symptoms of progressive cognitive, behavioral, and motor impairment. A brain affected by Alzheimer's shows atrophy of the cerebral cortex, which is the brain region responsible for language and processing information. Atrophy also occurs in the hippocampus, which is the portion of the brain responsible for forming new memories. A very common early symptom due to this degeneration is an inability to remember new information.

The disease process of AD is associated with the accumulation of extracellular senile plaques and intracellular neurofibrillary tangles in the brain. To understand how and why these plaques and tangles form, it is important to know

how the protein amyloid beta is produced and broken down in the brain. There is a transmembrane protein known as **amyloid precursor protein (APP)** in the brain that helps neurons grow and repair themselves after neuronal injury. Eventually, APP wears out and the body uses two different pathways to break it down. The first is the **non-amyloidogenic pathway** and involves the cleavage of APP by the enzymes **alpha-secretase** and **gamma secretase** into smaller, soluble fragments that the brain can get rid of. The second pathway is called the **amyloidogenic pathway** and involves cleavages of APP by **beta secretase** and gamma secretase. This cleavage results in the production of an insoluble peptide called **amyloid beta (A-beta)**. Amyloid beta is broken down in several ways including phagocytosis by microglia, receptor-mediated internalization by astrocytes, and degradation by the protease neprilysin.



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In AD there is an increased production and decreased breakdown of amyloid beta. In the neurosynaptic junction, the excess amyloid beta aggregates and forms **senile plaques**. These plaques can block neurotransmitters released into the synapse and thus block neural communication. Amyloid beta can be in different forms consisting of 36-43 amino acids. The amyloid beta40 monomer is much more prevalent and easier for the brain to process compared to the amyloid beta42 monomer. Consequently, the amyloid beta42 monomer is much more likely to aggregate to form the senile plaques seen in AD.

Another protein called the Tau protein is involved with Alzheimer's disease. The Tau protein is important in stabilizing the microtubule tracks that serve to transport cellular products from the cell body of the neuron to the axon terminal and vice versa. For example: the enzyme **choline acetyltransferase (ChAT)** is produced in the soma and transported by the microtubule tracks supported by Tau to the axon terminal where it transfers an acetyl group to choline to form the neurotransmitter acetylcholine (ACh). In the pathogenesis of AD, amyloid beta activates an intracellular kinase that phosphorylates Tau proteins. In this phosphorylated state, the Tau proteins detach from the microtubules and aggregate inside the cell to form what are called **neurofibrillary tangles**. Consequently, the microtubules that lack Tau proteins destabilize and collapse and intracellular transport is disrupted.

With extracellular plaques blocking neuronal communication and intracellular tangles blocking transport, neurons become dysfunctional and begin to die. This causes the brain to shrink, resulting in the gyri thinning and the sulci widening. Areas of the neocortex and hippocampus shrink greatly. Meanwhile, the CSF-filled ventricles actually become larger. For unknown reasons, areas of the primary sensory cortex mostly remain unaffected by the process of AD.

As mentioned, the enzyme ChAT produced in the cerebral cortex and hippocampus is important in the formation of acetylcholine, a neurotransmitter essential for learning and the formation of memories. In Alzheimer's disease, a reduction of ChAT can be correlated with the number of plaques and disease severity. Dysfunctional cholinergic neurons in AD also have decreased choline uptake, decreased ACh release, and decreased nicotinic receptors. Cholinergic neurons are very important in learning and memory, so their loss or dysfunction causes learning and memory deficits.

The hallmark manifestations of AD are neurological symptoms such as loss of short-term memory, denial of memory loss, disorientation, impaired and abstract thinking, apraxia (difficulty with skilled movement), and changes in personality. A patient will advance through mild, moderate, and progressed stages of Alzheimer's disease over an average 10 year period. In addition to memory loss, patients in the initial stages will start to experience mild changes in personality such as social withdrawal and loss of sense of humor. The moderate stage may last several years and patients begin to experience language deficits, lack of ability to problem solve, loss of math skills, and loss of learned motor skills. These patients are unable to live on their own and may become depressed and/or aggressive. Some patients become hostile toward family members or caregivers. In the advanced stage, patients become mute, incontinent, and bedridden. For most patients, the advanced stage lasts 1.5 to 2 years. Patients usually die from aspiration pneumonia (due to losing the ability to swallow), infection, or cardiac arrest.

Treatment for AD focuses on slowing the progression of the disease and managing symptoms. Acetylcholinesterase inhibitors are often administered to help with cholinergic dysfunction that occurs in AD. Anti-inflammatory agents and antioxidants may also be useful in the treatment of AD because they help with neuron injury. In AD, ischemia and amyloid deposition can lead to glutaminergic excitotoxicity of NMDA receptors. NMDA receptors stimulated by the NT glutamate can facilitate increased intensity and duration of nerve stimulation, however overstimulation can become toxic. Hence, NMDA receptor antagonists are used for AD to block the receptors of NMDA and prevent this excitotoxicity. Assessment using the Mini-Mental State Exam (MMSE) can assist in measuring cognitive impairment and determining if an individual may have AD. Because the only definitive diagnosis of AD is tissue examination from an autopsy, it is very important to rule out other reversible causes for dementia such as vitamin B-12 deficiency, thyroid dysfunction, electrolyte imbalance, and other brain diseases that can be detected by CT scan or MRI.

Certain genetic factors increase the risk for developing AD at a younger age:

- **Mutations in the APP gene and presenilin genes** increase the risk for AD. The genes presenilin 1 and presenilin 2 code for subunits that make up the gamma secretase enzyme. In certain familial forms of AD, mutations in these genes result in a gain of function for gamma secretase. This increased function causes it to generate increased amounts of amyloid beta, especially A-beta42 which is particularly prone to aggregate and form more amyloid plaques.
- Those with **Down syndrome** also often develop early onset AD. The gene that codes for APP is located on chromosome 21. Because those with Down syndrome have an extra copy of chromosome 21, they have an extra APP gene which results in increased expression of APP and therefore increased amyloid beta.
- **Inheritance of an APO E4 allele:** The Apo E gene codes for Apo E which is a lipoprotein involved in lipid transport. Apo E is synthesized by astrocytes and has been shown to play a role in A-beta clearance from the brain. Individuals inherit one Apo E gene from each parent. Several different versions or alleles of the Apo E gene exist including E2, E3, and E4. The E3 allele is the most common and is found in more than 50% of the general population. The Apo E2 allele is less common but may even be protective against Alzheimer's disease. Inheriting an Apo E4 gene from each parent increases the risk for developing Alzheimer disease and is correlated with amyloid deposition and neuronal damage. This is because Apolipoprotein E4 is not as effective at clearing amyloid beta.

There is no definitive evidence that any particular practice is able to prevent AD, but certain activities and environmental factors are believed to be associated with higher or lower risk for development.

- **Factors that increase risk:** cardiovascular risk factors like hypercholesterolemia, a diet high in saturated fat and simple sugars, hypertension, diabetes, and smoking.
- **Factors that lower risk:** regular participation in cognitive activities like reading, playing board games, doing crossword puzzles, and playing musical instruments. Also regular social interactions, learning a second language, regular physical activity (may release growth factors for neurons), a healthy diet (Japanese or Mediterranean diet), and long-term NSAID use (anti-inflammatory).