Alzheimer's Disease: Neurobiology and Drug Targets

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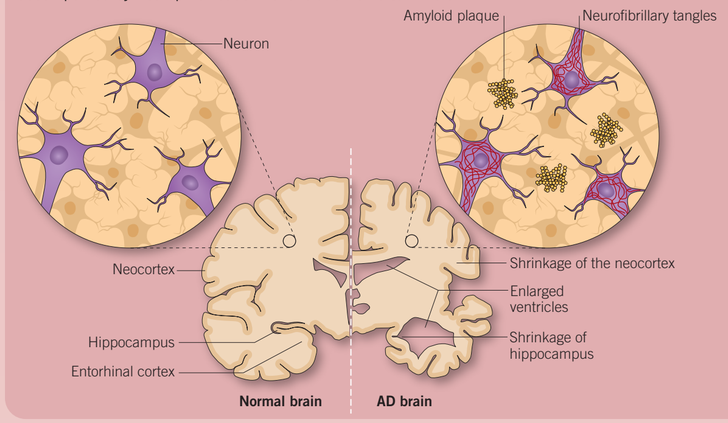
Alzheimer's disease (AD) is a degenerative brain disease and the most common type of dementia. It is characterized by a decline in memory, language, problem-solving and other cognitive skills that affect a person's ability to perform everyday activities. This decline occurs because of the loss of neurons (particularly pyramidal cells) in regions of the brain involved in cognitive function. Eventually, the disease affects parts of the brain that enable a person to carry out basic bodily functions such as walking and swallowing. People in the final stages of the disease are bed-bound and require around-the-clock care.

Alzheimer's Disease Neuropathology

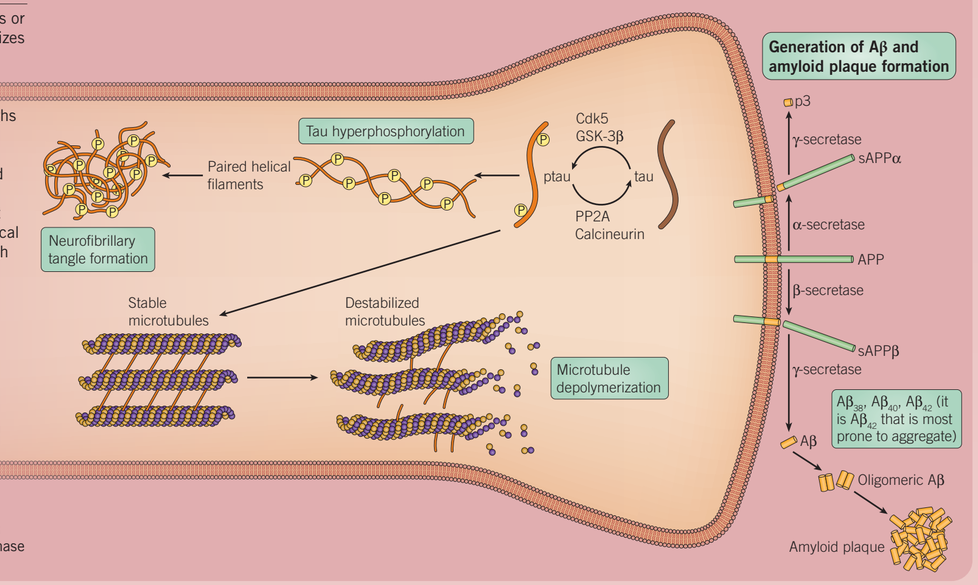
On the left is a normal healthy brain and on the right is a brain with advanced Alzheimer's disease (AD). The AD brain exhibits extreme shrinkage of the neocortex, severely enlarged ventricles and shrinkage of the hippocampus (a region that plays a critical role in memory). This atrophy reflects the loss of vulnerable neurons, principally pyramidal, cholinergic, noradrenergic and serotonergic neurons. Two key hallmarks of AD are the formation of (i) dystrophic neurites around a central core of amyloid (plaques), and (ii) abnormal filaments (neurofibrillary tangles) made up of a highly phosphorylated form of the microtubule-associated protein tau in the perikaryia of certain neurons, accompanied by neuropil threads in axons and nerve terminals.



AD Drug Targets

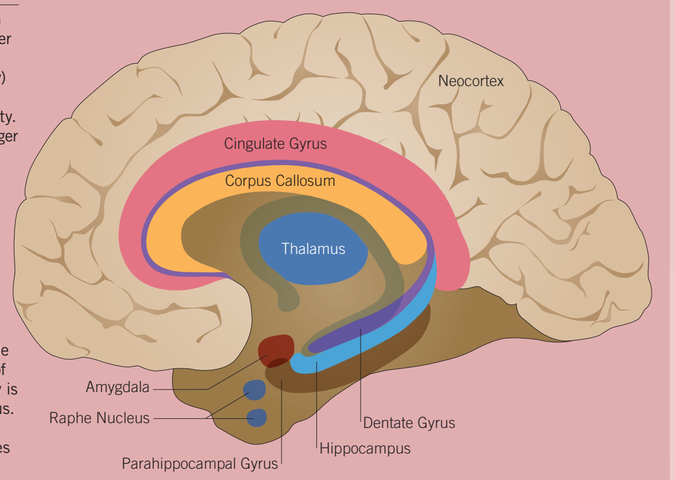
The major goal for AD drug discovery is a compound that slows or stops the cascade of neurodegenerative change that characterizes this disease. In addition to the enzyme targets shown on the adjacent diagram, anti-Aβ monoclonal antibodies have been a major focus. These efforts are critically dependent on understanding the pathogenesis of AD. Two major breakthroughs came with the discoveries that (i) deposits of Aβ, a peptide sub-fragment of APP, are present in both diffuse and neuritic plaques, and (ii), mutations in both APP and enzymes involved in its metabolism cause most cases of familial AD. This led to the formation of the amyloid hypothesis, which postulates that deposits of Aβ peptide, are responsible for the pathophysiological changes associated with AD. Aβ peptides are produced through the sequential action of two cleaving enzymes (β- and γ-secretase) on APP and can be 38, 40 or 42 amino acids in length. It is the largest form (Aβ42) that appears to be critical, through its accumulation and oligomerization. Tau, the main component of NFTs, has become an increasingly popular alternative to Aβ as a target for AD drug discovery. Hyperphosphorylated tau interacts with other tau threads and forms NFTs inside neurons, principally pyramidal cells. Hyperphosphorylated tau also destabilizes microtubules which are integral in maintaining the shape and function of neurons. Drug discovery efforts have focused on inhibitors of tau phosphorylation and tau aggregation, along with compounds to promote NFT disassembly.

Abbreviations: Aβ – amyloid beta; APP – amyloid precursor protein; Cdk5 – cyclin-dependent kinase 5; GSK-3β – glycogen synthase kinase 3β; NFT – neurofibrillary tangles; PP2A – protein phosphatase 2A.

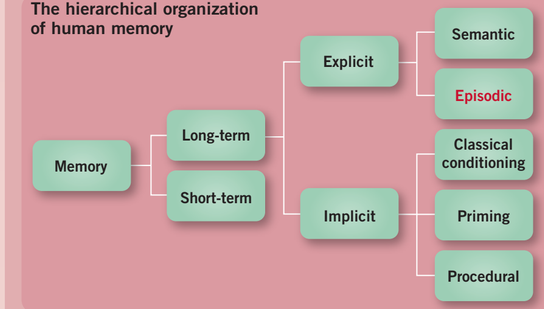


Normal Memory Processing

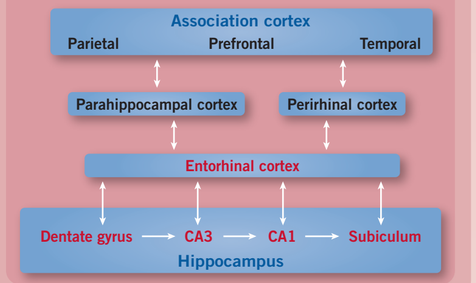
In a normal brain, memory is the process by which knowledge of the world is encoded, stored, and later retrieved. It can be divided into short-term and long-term memory. Short-term (or working memory) allows recall for a period of several seconds to a minute without rehearsal, and has a limited capacity. By contrast, long-term memory can store much larger quantities of information for a period that can be as long as a lifetime. Long-term memory can be subdivided into explicit (conscious) and implicit (unconscious) memory. Explicit memory can be subdivided into semantic (facts and general knowledge) and episodic (personally experienced events). Implicit memory can be subdivided into classical conditioning, priming (enhanced identification of objects or words) and procedural (cognitive and motor skills) memory. Semantic memory is mediated by the brain region responsible for the particular semantic task, e.g. the concept of tools resides in the motor cortex. Episodic memory is mediated by the entorhinal cortex and hippocampus. Both episodic and semantic memory are affected early in the course of AD. As the disease progresses these deficits become progressively worse and are accompanied by impairments in implicit (unconscious) conceptual memory; implicit perceptual memory seems to be preserved.



The hierarchical organization of human memory



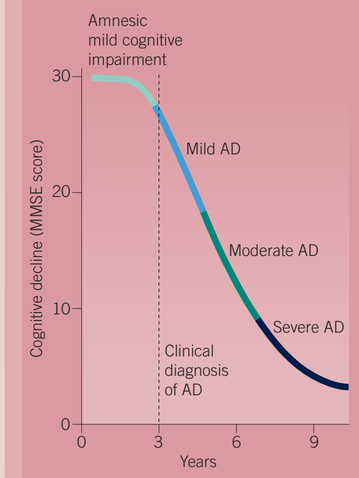
Brain regions involved in explicit memory



Progression of Alzheimer's Disease

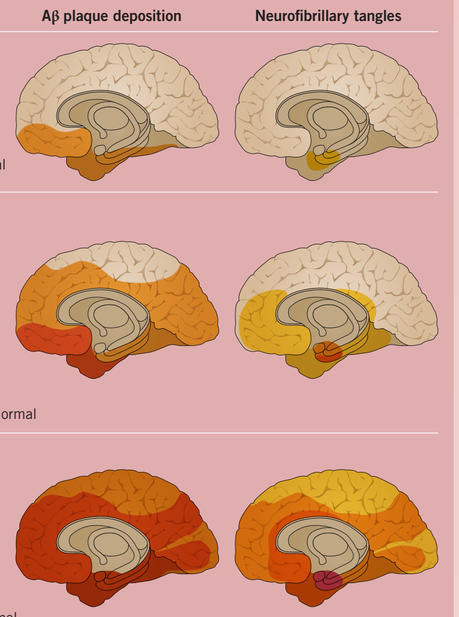
Currently, a definitive diagnosis of AD can only be made on the basis of a postmortem examination of the brain. The disease begins about 15 years before symptoms appear and starts to emerge in a prodromal form (amnesic mild cognitive impairment). It then evolves through six stages based on the presence of neurofibrillary tangles in distinct brain regions. The entorhinal cortex is affected first, leading to impairments in episodic memory. With the disease spreading to other areas of the neocortex, additional domains of cognitive function become impaired and the syndrome of dementia becomes evident.

The progression of cognitive decline in Alzheimer's disease



MMSE = mini mental state examination

Braak and Braak have divided the progression of AD into six stages (I to VI) on the basis of the pattern and severity of Aβ deposition (depicted in the brains on the left) and neurofibrillary changes (depicted in the brains on the right), which are indicated as mild (stages I to II), moderate (stages III to IV), and severe (stages V to VI). The disease begins in excitatory amino acid releasing pyramidal neurons in the entorhinal cortex and spreads from the hippocampus and other limbic structures to affect pyramidal neurons in the neocortex and ascending cholinergic, noradrenergic, and serotonergic neurons. Degeneration of the pathways connecting the entorhinal cortex and the hippocampus is an early change in the disease process. Projections from the nucleus basalis of Meynert, the locus coeruleus, and the raphe nucleus are lost at the mild/moderate stage. The final stages of the disease are associated with loss of GABAergic interneurons. The figure below is based on Braak *et al.* (1998), Palmer (2002) and Palmer (2011).



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Nrf2
CDDO Im, NK 252, TAT 14

JNK
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PERK
GSK 2606414

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