Alzheimer’s Disease: Neurobiology and Drug Targets

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.

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The hierarchical organization of human memory

- Explicit
- Implicit
- Short-term
- Long-term
- Semantic
- Episodic
- Classical conditioning
- Priming
- Procedural

Brain regions involved in explicit memory

- Association cortex
- Prefrontal cortex
- Parietal cortex
- Temporal cortex
- Ventral hippocampus
- Entorhinal cortex
- Parahippocampal cortex
- Dorsal and ventral striatum
- Hippocampus

Brain regions involved in implicit memory

- Association cortex
- Prefrontal cortex
- Parietal cortex
- Temporal cortex
- Ventral hippocampus
- Entorhinal cortex
- Parahippocampal cortex
- Dorsal and ventral striatum
- Hippocampus

The progression of Alzheimer’s Disease

- 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 III), 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 nuclei are lost at the mid-stage moderate stage. The final stages of the disease are associated with loss of GABAergic interneurons. The figure below is based on Braak et al. (1991), Palmer (2002) and Palmer (2011).

AD Drug Targets

The major goal for AD drug discovery is a compound that stops or slows the cascade of neurodegenerative changes that characterizes this disease. In addition to the enzyme targets shown on the adjacent diagram, a number of other AD 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 subfragment 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 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 toxic. Through its accumulation and aggregation, 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 fibers 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; FPP2A – 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 (personal experiences) categories. Implicit memory can be subdivided into classical conditioning, priming (automatic identification of objects or words) and procedural (cognitive or motor skills) memory. Semantic memory is mediated by the brain region responsible for the particular semantic task, e.g. the context 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.

Generation of Aβ and amyloid plaque formation

- Amyloid plaque deposition
- Neurofibrillary tangles

Modest AD

- Neuruphytosis
- Hyperphosphorylated tau

Moderate AD

- Neuruphytosis
- Hyperphosphorylated tau

Severe AD

- Neuruphytosis
- Hyperphosphorylated tau

References:


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