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Biochemistry of Alzheimer's disease

The **biochemistry of Alzheimer's disease** (AD), one of the most common causes of adult dementia, is as yet not well understood. It has been identified as a protein misfolding disease due to the accumulation of abnormally folded amyloid beta protein in the brains of AD patients.[1] Amyloid beta, also written Aβ, is a short peptide that is an abnormal proteolytic byproduct of the transmembrane protein amyloid precursor protein (APP), whose function is unclear but thought to be involved in neuronal development.[2] The presenilins are components of proteolytic complex involved in APP processing and degradation.[3]

Amyloid beta monomers are soluble and contain short regions of beta sheet and polyproline II helix secondary structures in solution,[4] though they are largely alpha helical in membranes;[5] however, at sufficiently high concentration, they undergo a dramatic conformational change to form a beta sheet-rich tertiary structure that aggregates to form amyloid fibrils.[6] These fibrils deposit outside neurons in dense formations known as *senile plaques* or *neuritic plaques*, in less dense aggregates as *diffuse plaques*, and sometimes in the walls of small blood vessels in the brain in a process called amyloid angiopathy or congophilic angiopathy.

AD is also considered a tauopathy due to abnormal aggregation of the tau protein, a microtubule-associated protein expressed in neurons that normally acts to stabilize microtubules in the cell cytoskeleton. Like most microtubule-associated proteins, tau is normally regulated by phosphorylation; however, in AD patients, hyperphosphorylated tau accumulates as paired helical filaments[7] that in turn aggregate into masses inside nerve cell bodies known as neurofibrillary tangles and as dystrophic neurites associated with amyloid plaques. Although little is known about the process of filament assembly, it has recently been shown that a depletion of a prolyl isomerase protein in the parvulin family accelerates the accumulation of abnormal tau.[8][9]

Neuropathology

At a macroscopic level, AD is characterized by loss of neurons and synapses in the cerebral cortex and certain subcortical regions. This results in gross atrophy of the affected regions, including degeneration in the temporal lobe and parietal lobe, and parts of the frontal cortex and cingulate gyrus.[10]

Both amyloid plaques and neurofibrillary tangles are clearly visible by microscopy in AD brains.[11] Plaques are dense, mostly insoluble deposits of protein and cellular material outside and around neurons. Tangles are insoluble twisted fibers that build up inside the nerve cell. Though many older people develop some plaques and tangles, the brains of AD patients have them to a much greater extent and in different brain location.[12]

Biochemical characteristics

Alzheimer's disease has been identified as a protein misfolding disease, or proteopathy, due to the accumulation of abnormally folded A-beta proteins in the brains of AD patients.[1] A-beta, also written Aβ, is a short peptide that is a proteolytic byproduct of the transmembrane protein amyloid precursor protein (APP), whose function is unclear but thought to be involved in neuronal development. The presenilins are components of a proteolytic complex involved in

APP processing and degradation.[3] Although amyloid beta monomers are soluble and harmless, they undergo a dramatic conformational change at sufficiently high concentration to form a beta sheet-rich tertiary structure that aggregates to form amyloid fibrils[6] that deposit outside neurons in dense formations known as *senile plaques* or *neuritic plaques*, in less dense aggregates as *diffuse plaques*, and sometimes in the walls of small blood vessels in the brain in a process called amyloid angiopathy or congophilic angiopathy.

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Levels of the neurotransmitter acetylcholine are reduced. Levels of the neurotransmitters serotonin, norepinephrine, and somatostatin are also often reduced. Glutamate levels are usually elevated.[13]

Disease mechanism

Although the gross histological features of AD in the brain are well characterized, three major hypotheses have been advanced regarding the primary cause. The oldest hypothesis suggests that deficiency in cholinergic signaling initiates the progression of the disease. Two alternative misfolding hypotheses instead suggest that either tau protein or amyloid beta initiates the cascade. While researchers have not identified a clear causative pathway originating from any of the three molecular hypotheses to explain the gross anatomical changes observed in advanced AD, variants of the amyloid beta hypothesis of molecular initiation have become dominant among the three possibilities.

Cholinergic hypothesis

The oldest hypothesis is the "cholinergic hypothesis". It states that Alzheimer's begins as a deficiency in the production of acetylcholine, a vital neurotransmitter. Much early therapeutic research was based on this hypothesis, including restoration of the "cholinergic nuclei". The possibility of cell-replacement therapy was investigated on the basis of this hypothesis. All of the first-generation anti-Alzheimer's medications are based on this hypothesis and work to preserve acetylcholine by inhibiting acetylcholinesterases (enzymes that break down acetylcholine). These medications, though sometimes beneficial, have not led to a cure. In all cases, they have served to only treat symptoms of the disease and have neither halted nor reversed it. These results and other research have led to the conclusion that acetylcholine deficiencies may not be directly causal, but are a result of widespread brain tissue damage, damage so widespread that cell-replacement therapies are likely to be impractical. More recently, cholinergic effects have been proposed as a potential causative agent for the formation of plaques and tangles[14] leading to generalized neuroinflammation.[15]

More recent hypotheses center on the effects of the misfolded and aggregated proteins, amyloid beta and tau. The two positions are lightheartedly described as "ba-ptist" and "tau-ist" viewpoints in scientific publications by Alzheimer's disease researchers. "Tau-ists" believe that the tau protein abnormalities initiate the disease cascade, while "ba-ptists" believe that beta amyloid deposits are the causative factor in the disease.[16]

Tau hypothesis

The hypothesis that tau is the primary causative factor has long been grounded in the observation that deposition of amyloid plaques does not correlate well with neuron loss.[17] A mechanism for neurotoxicity has been proposed based on the loss of microtubule-stabilizing tau protein that leads to the degradation of the cytoskeleton.[18] However, consensus has not been reached on whether tau hyperphosphorylation precedes or is caused by the formation of the abnormal helical filament aggregates.[16] Support for the tau hypothesis also derives from the existence of other diseases known as tauopathies in which the same protein is identifiably misfolded.[19] However, a majority of researchers support the alternative hypothesis that amyloid is the primary causative agent.[16]

Amyloid hypothesis

The amyloid hypothesis is initially compelling because the gene for the amyloid beta precursor APP is located on chromosome 21, and patients with trisomy 21 - better known as Down syndrome - who thus have an extra gene copy almost universally exhibit AD-like disorders by 40 years of age.[20][21] The traditional formulation of the amyloid hypothesis points to the cytotoxicity of mature aggregated amyloid fibrils, which are believed to be the toxic form of the protein responsible for disrupting the cell's calcium ion homeostasis and thus inducing apoptosis.[22] This hypothesis is supported by the observation that higher levels of a variant of the beta amyloid protein known to form fibrils faster *in vitro* correlate with earlier onset and greater cognitive impairment in mouse models.[23] and with AD diagnosis in humans.[24] However, mechanisms for the induced calcium influx, or proposals for alternative cytotoxic mechanisms, by mature fibrils are not obvious.

A more recent and broadly supported variation of the amyloid hypothesis identifies the cytotoxic species as an intermediate misfolded form of amyloid beta, neither a soluble monomer nor a mature aggregated polymer but an oligomeric species, possibly toroidal or star-shaped with a central channel[25] that may induce apoptosis by physically piercing the cell membrane.[26] A related alternative suggests that a globular oligomer localized to dendritic processes and axons in neurons is the cytotoxic species.[27][28]

Relevantly, the cytotoxic-fibril hypothesis presented a clear target for drug development: inhibit the fibrillization process. Much early development work on lead compounds has focused on this inhibition;[29][30][31] most are also reported to reduce neurotoxicity, but the toxic-oligomer theory would imply that prevention of oligomeric assembly is the more important process[32] or that a better target lies upstream, for example in the inhibition of APP processing to amyloid beta.[33]

Soluble intracellular (o)Aβ42

Two research papers published in 2009 have shown that oligomeric (o)Aβ42 (specific toxic species of Aβ), when in soluble intracellular form, acutely inhibit synaptic transmission, a pathophysiology that characterizes AD (specially in early stages), by activating casein kinase 2.[34][35]

Isoprenoid changes

A 1994 study [1] showed that the isoprenoid changes in Alzheimer's disease differ from those occurring during normal aging and that this disease cannot, therefore, be regarded as a result of premature aging. During aging the human brain shows a progressive increase in levels of dolichol, a reduction in levels of ubiquinone, but relatively unchanged concentrations of cholesterol and dolichyl phosphate. In a Alzheimer's disease, the situation is reversed with decreased levels of dolichol and increased levels of ubiquinone. The concentrations of dolichyl phosphate are also increased, while cholesterol remains unchanged. The increase in the sugar carrier dolichyl phosphate may reflect an increased rate of glycosylation in the diseased brain and the increase in the endogenous anti-oxidant ubiquinone an attempt to protect the brain from oxidative stress, for instance induced by lipid peroxidation. [36] These findings appear to have been supported by a trial conducted at the Brain Sciences Institute at Swinburne University in Melbourne, Australia, reported in 2006, that confirmed certain neurocognitive effects of the polyprenol preparation Ropren identified previously in Russia [2] (polyprenols are metabolised into dolichols in the body).

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