
Beta-amyloid and the amyloid hypothesis

In Alzheimer's disease, brain cells that process, store and retrieve information degenerate and die. Although scientists do not yet know the underlying cause of this destruction, they have identified several possible culprits.

One prime suspect is a microscopic brain protein fragment called beta-amyloid, a sticky compound that accumulates in the brain, disrupting communication between brain cells and eventually killing them. Some researchers believe that flaws in the processes governing production, accumulation or disposal of beta-amyloid are the primary cause of Alzheimer's. This theory is called "the amyloid hypothesis."

Although early studies suggested that amyloid plaques — large accumulations of beta-amyloid — were the cause of nerve cell toxicity in Alzheimer's, researchers now believe that small, soluble aggregates of beta-amyloid may be more toxic.

What is beta-amyloid?

Beta-amyloid is a small piece of a larger protein called "amyloid precursor protein" (APP). Although scientists have not yet determined APP's normal function, they know a great deal about how it appears to work. In its complete form, APP extends from the inside of brain cells to the outside by passing through the fatty membrane around the cell. When APP is "activated" to do its normal job, it is cut by other proteins into separate, smaller sections that stay inside and outside cells. There are several different ways APP can be cut; under some circumstances, one of the pieces produced is beta-amyloid.

Why is beta-amyloid a prime suspect in Alzheimer's disease?

Some versions of beta-amyloid are chemically "stickier" than other fragments produced when APP is cut, so the type of beta-amyloid fragment produced may affect how much it accumulates in the brain. It accumulates in stages into microscopic amyloid plaques that are considered a hallmark of a brain affected by Alzheimer's. The pieces first form small clusters called oligomers, then chains of clusters called fibrils, then "mats" of fibrils called beta-sheets. The final stage is plaques, which contain clumps of beta-sheets and other substances.

According to the amyloid hypothesis, these stages of beta-amyloid aggregation disrupt cell-to-cell communication and activate immune cells. These immune cells trigger inflammation. Ultimately, the brain cells are destroyed.

What evidence implicates beta-amyloid?

Supporters of the amyloid hypothesis cite three main lines of evidence:

- In a few hundred extended families worldwide, scientists have identified rare genetic mutations that virtually guarantee an individual will develop Alzheimer's. These mutations occur in any of three genes. Each of these genes is involved in biological processes associated with beta-amyloid production or accumulation. Only an estimated 1% of people living with Alzheimer's disease have one of these mutations.
- Scientists have developed mice genetically engineered to carry some of these genetic mutations. The mice develop amyloid plaques, have difficulty remembering their way through mazes and develop other symptoms that mimic human Alzheimer's.
- Another gene related to the risk of Alzheimer's disease is APOE. The e4 version of APOE increases the risk of the disease. Recently, it has been shown that the e4 version impairs the ability of the brain to remove beta-amyloid, leading to amyloid plaques and disease.
- In contrast, individuals with the e2 version of the APOE gene have a reduced risk of Alzheimer's. These individuals appear to produce lower amounts of beta-amyloid.
- Several other genetic variations that have been linked to increased risk of Alzheimer's disease have been identified. Further research on the functions of these genes has tied many of them to some aspect of beta-amyloid activity or clearance, further strengthening the idea that beta-amyloid is a key player in the Alzheimer's disease process.
- Individuals with Down syndrome, who have three copies of the chromosome carrying the APP gene instead of the normal two, almost invariably develop amyloid plaques by age 40. Not all people with Down syndrome develop Alzheimer's disease, but studies suggest that about 75% of those older than age 65 are living with Alzheimer's.

The beta-amyloid hypothesis has been the subject of debate because, until recently, several drugs that effectively prevent or remove beta-amyloid accumulation did not affect cognition in clinical trials. There are several possible explanations. One is that some trial participants diagnosed as having Alzheimer's disease based on their symptoms didn't actually have the amyloid plaques characteristic of Alzheimer's disease. That is, they did not have Alzheimer's disease but instead had another cause of dementia. If an individual doesn't have amyloid plaques, but receives a drug that removes them, it's reasonable to expect the drug will not be effective. Current clinical

trials targeting beta-amyloid aim to recruit only volunteers whose brain scans show they have beta-amyloid.

Another possible explanation is that, to be most effective, anti-amyloid drugs need to be given earlier in the disease process. Alzheimer's brain changes are believed to begin up to 20 years before symptoms like memory loss appear. Receiving anti-amyloid drugs during the preclinical or mild cognitive impairment phases of Alzheimer's instead of the dementia phase could be very important.

Not all scientists are convinced that beta-amyloid is the primary cause of Alzheimer's. Researchers worldwide are investigating a variety of other possible triggers for the destructive series of events that eventually kill brain cells.

If beta-amyloid does play an important role, how could treatments block its effects?

In June 2021, the U.S. Food & Drug Administration (FDA) granted accelerated approval of aducanumab (Aduhelm™), an anti-amyloid therapy to treat Alzheimer's disease. The FDA's historic decision marks the first new Alzheimer's treatment available in almost 20 years and the first-ever drug approved to target the underlying biology of the disease. While not a cure, aducanumab is the only FDA-approved treatment that is expected to lead to a reduction in the clinical decline of Alzheimer's in some people rather than just temporarily address disease symptoms.

Later in June, the FDA granted "Breakthrough Therapy" designation to two other anti-amyloid drugs for Alzheimer's: donanemab and lecanemab. This action is meant to speed the development and review of drugs that are intended to treat a serious condition. It acknowledges that preliminary evidence indicates the drug "may demonstrate substantial improvement over available therapy."

Additionally, scientists are testing a number of strategies to block the effects of beta-amyloid. These include decreasing the production of the beta-amyloid protein, preventing its aggregation and increasing its removal from the brain:

Decreasing beta-amyloid production

To decrease beta-amyloid production, experimental drugs change the behavior of proteins that cut APP into beta-amyloid. Scientists have identified several of these proteins, called secretases, involved in cutting APP into beta-amyloid. Those that have received the most attention are beta-secretase (also known as

BACE1) and gamma-secretase. Changing the behavior of these proteins could prevent or reduce beta-amyloid production. Drugs called “secretase inhibitors” block the clipping action of secretases.

Another approach reduces beta-amyloid by changing the way secretases work or encouraging secretases, such as alpha-secretase, to cut APP into fragments other than beta-amyloid.

Preventing beta-amyloid aggregation

Because Alzheimer's is characterized by amyloid plaques, scientists have explored drugs that prevent beta-amyloid aggregation as a potential treatment for the disease. Some studies suggest that the toxic effects of beta-amyloid occur before the formation of plaques and oligomers, so researchers are looking for ways to prevent the initial interactions between beta-amyloid and nerve cells that lead to toxicity.

Increasing beta-amyloid removal

Methods to increase removal of beta-amyloid from the brain include mobilizing the immune system to produce antibodies to attack beta-amyloid, administering laboratory-produced antibodies to beta-amyloid and administering natural agents with anti-amyloid effects.

Immune system-generated antibodies to beta-amyloid

Experimental agents in this category are called “active vaccines.” These vaccines incorporate a beta-amyloid fragment that is attached to a carrier protein. When injected, the body should produce antibodies to attack beta-amyloid and reduce levels of beta-amyloid in the brain.

Laboratory-produced antibodies to beta-amyloid

Experimental drugs in this category are called “passive vaccines.” These vaccines may be safer because they can be given in predetermined doses and do not stay in the body after dosing ends.

Natural agents with anti-amyloid effects

Intravenous immunoglobulin (IVIg) contains a broad array of natural antibodies that may reduce beta-amyloid levels. IVIg is obtained from the plasma of human blood donors.

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