Theories of Alzheimer’s Disease

The Scientific Search for a Cure

Theories of Alzheimer's Disease

- **Aluminum Toxicity Hypothesis**
- **Prion Hypothesis**
- **Cholinergic Hypothesis**
- **Glutamate Hypothesis**
- **Genetic Mutation Hypothesis**
- **Beta-Amyloid Protein Hypothesis**

Aluminum Toxicity Hypothesis

- Some epidemiological studies suggested that high levels of aluminum in drinking water were correlated with dementia-like diseases among Pacific Islanders
- Post-mortem studies revealed an accumulation of aluminum ions in the **senile (amyloid) plaque** of Alzheimer's disease patients
- 1965 experimental study revealed that **rabbits** exposed to high levels of aluminum developed toxic **neurofibrillary tangles**
- **Extensive follow-up research has failed to reveal a causal relationship between aluminum and dementia of any variety**
- Nonetheless, some scientists continue to study the possible toxic role of other metals such as **iron and copper**

Prion Disease Hypothesis

- Virtually all known infectious agents such as bacteria and viruses proliferate via nucleic acids (viz., DNA and RNA)
- "**scrapie**", **bovine spongiform encephalopathy** ("Mad Cow") and **Creutzfeldt-Jacob Disease** (CJD) are rare transmissible diseases that affect the brain and result in dementia-like symptoms
- **Stanley Prusiner (1982)** discovered that these forms of transmissible dementias were caused by a previously unknown type of pathogen

  1997 Nobel Prize

  viz., the **prion** – short for "proteinaceous infectious particle"

- Many researchers hypothesized and studied the possible role of prions as a cause for Alzheimer's disease

Prion Disease Hypothesis

- **Prion proteins (PrP)** are found in all humans
- When the prion protein **"mutates" into a rare conformation** (shape) it causes a "chain reaction" among other protein molecules:

  The "misfolded" protein causes other related proteins to become misfolded as well. This process (slowly) spreads from molecule to molecule

  "Misfolded" proteins can no longer participate in normal biochemical and enzymatic processes which are primarily regulated by the "lock and key" fit between interacting molecular systems

Prion Disease Hypothesis

- Research findings began to suggest that other hypothesized mechanisms appeared to be better candidates for the cause of Alzheimer's disease:

  (1) the rate of disease progression in Alzheimer's is much slower than that observed for prion diseases
  (2) No evidence for infectious transmission of Alzheimer's in humans or mouse models
  (3) Identification of the beta-amyloid protein (in senile plagues) revealed that it was much smaller than any known prion

- The prion hypothesis could no longer compete for research funding and became largely forgotten by the new generation of scientists

Prion Disease Hypothesis

Research Update:

Given the numerous disappointing results of interventions driven by the beta-amyloid protein hypothesis together with recent evidence suggesting the existence of prion forms of both the beta-amyloid and tau protein complexes, new interest in the Prion Disease Hypothesis has begun to emerge in research labs around the globe.

Cholinergic Hypothesis

- In the late 1970's, **Peter Davies** and others demonstrated that the brains of Alzheimer's disease patients suffered from a profound loss of synapses mediated by the neurotransmitter *acetylcholine* (ACh)

- Alzheimer's brains demonstrate a 90% reduction in *acetyltransferase* (a precursor of ACh) and a 50% reduction in *acetylcholine* itself

- An early casualty in the progression of Alzheimer's disease is the selective destruction of the **nucleus basalis** – a subcortical structure representing the primary site for acetylcholine production

Cholinergic Hypothesis

- The cholinergic mechanism has been the focus of much research
- Although it provides a good descriptive model of Alzheimer's disease (i.e., "what" happens) it does not explicitly provide a causative explanation (i.e., "why" it happens)
- Nonetheless, the cholinergic hypothesis has been successful in terms of generating the development of **pharmacological interventions** for the treatment of the cognitive symptoms of Alzheimer's disease

Cholinergic Hypothesis

- Acetylcholine is secreted by one neuron in order to communicate with another neuron
- Acetylcholine is quickly decomposed in the synaptic cleft by an enzyme known as *acetylcholine esterase*
- Four of the five FDA-approved medications for the treatment of Alzheimer's disease symptoms are based up the **inhibition of acetylcholine esterase** – which amplifies the effectiveness of the surviving acetylcholine-based neurons

  (Aricept; Exelon; Razadyne; Namzaric)

Cholinergic Hypothesis

- Cholinergic medications for Alzheimer's disease provide only small (and temporary) improvements in cognitive function
- The great majority of the neurons in the brain are mediated by other neurotransmitters (e.g., glutamate, GABA, etc.)
- The cholinergic hypothesis no longer plays a crucial role in generation of new research and has been replaced by other theories

Glutamate Hypothesis

- ***Glutamate* is a major neurotransmitter in the human brain** and stimulates *N-methyl-D-aspartate* (NMDA) receptor sites found on many neurons
- Glutamate→ NMDA activation cause **calcium ion (CA++) uptake** which depolarizes the neuron and causes it to “fire”
- **The glutamate hypothesis proposes that Alzheimer’s disease is associated with excessive glutamate output** from brain neurons
- Excessive glutamate release leads to **calcium ion toxicity** that gradually kills neurons throughout the brain

Glutamate Hypothesis

- The glutamate hypothesis has generated research which has led to the **development of two FDA-approved medications** for the treatment of Alzheimer's disease symptoms (Namenda and Namzaric)
- These drugs function by binding to NMDA receptor sites and preventing their neurons from being over-activated by glutamate (i.e., **NMDA-agonists**)
- Like the cholinergic class of medications, the NMDA-agonists provide **only very mild (and temporary) mitigation of cognitive symptoms**
- The glutamate hypothesis is a descriptive model ("what" happens) and remains quite limited in its ability to generate additional research

Genetic Mutation Hypothesis

- Several lines of evidence have converged to suggest that Alzheimer's disease might be the result of an inherited genetic mutation

  (1) A number of familial clusters around the world are characterized by a **highly inheritable form of early-onset Alzheimer's** disease

  (2) Persons with **Down Syndrome** develop a form of dementia resembling Alzheimer's disease before their 50th birthday

- This suggests that a search of the genome should reveal a corrupt gene associated with these dementias…Since Down syndrome is due to problems with **chromosome 21**…that would be a good place to start the search

Genetic Mutation Hypothesis

- NIH researchers **quickly discovered a genetic explanation** for these early-onset forms of Alzheimer's disease:

  a unique set of variations in the gene that expresses the **Amyloid Precursor Protein (APP)** is now known to be involved in the formation of the **senile plaques** and **neurofibrillary tangles** that are the signature of Alzheimer's disease [found on chromosome 21]

- **Importantly, however, this mutation is NOT found among individuals suffering from the more common late-onset variant of Alzheimer's disease**
  [only a weak association with APOE-e4 gene on chromosome 19]

Beta-Amyloid Protein Hypothesis

- **Amyloid Precursor Protein (APP)** is found in all human brains
- APP function is not fully understood:

  -concentrated at synaptic connections between neurons
  -perhaps involved in synapse formation and maintenance

- The gene for APP production is found on chromosome 21

  -mutation in APP gene causes early-onset Alzheimer's
  -also implicated in the development of Down syndrome dementia

Beta-Amyloid Protein Hypothesis

- New **APP** is continuously produced and old **APP** cleared-out
- Here's where things go wrong:

① excess **BACE** is produced (**B**eta-**A**myloid **C**leaving **E**nzyme)
② **BACE** cleaves **APP** into two: **beta-amyloid** & gamma-amyloid
③ beta-amyloid clumps together into "senile plaques"
which cannot be cleared from the brain
④ beta-amyloid produces toxic effects on neurons
including breakdown of **tau protein** inside neurons
which aggregate to form "neurofibrillary tangles"

Beta-Amyloid Protein Hypothesis

- **Beta-amyloid toxicity** has been the dominant theory guiding the development of Alzheimer's disease medications for two decades
- Strategies for treating Alzheimer's have focused upon:

  ① preventing new beta-amyloid accumulation
  ② reversing existing beta-amyloid clusters

- **Scores of clinical trials and many billions of dollars of investment have failed to yield a successful treatment**

Beta-Amyloid Protein Hypothesis

Has the beta-amyloid hypothesis reached the end of its usefulness?

Recent editorial in the New England Journal of Medicine:

> "…it would be foolish to ignore the continued failures of anti-amyloid approaches. In spite of a mountain of evidence supporting the primacy of (beta-amyloid) in Alzheimer's disease, researchers are coming to the realization that our preclinical models of the disease may be missing the mark"
>
> M. Paul Murphy (2018)

Beta-Amyloid Protein Hypothesis

Summary of Contrary Evidence

- Dismal performance of clinical trials
- Mouse models developed to produce excessive beta-amyloid accumulations in the brain to not reveal concomitant cognitive deficits
- Post-mortem studies of non-demented older adults often reveal massive amyloid plaque accumulations in the absence of any evidence of memory or cognitive deficits

Clearly, we seem to be missing an important piece of the puzzle…

Beta-Amyloid Protein Hypothesis
Everything Old is New Again

- Recent evidence suggests that a combination of the **beta-amyloid** and the **prion disease** hypotheses can be "combined" to yield a constructive explanation of the failed clinical trials
- Several investigators have shown that both beta-amyloid and tau proteins in the Alzheimer's brain appear to produce subspecies that **behave like the prions** in Cruetzfeldt-Jacob disease (i.e., contagious protein misfolding without DNA/RNA)
- Reconceptualizing Alzheimer's disease as a **"Dual Prion" disorder** helps explain the failed clinical trials and generates many new strategies for intervening with the progress of the disease

In the meantime, let's keep our fingers crossed…