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Alzheimer's Disease: Polypeptide Hypothesis

John Cheung-yuen Chan*

An Individual Author, Kensington NSW 1465, Australia

***Corresponding author:** Mr. John Cheung-yuen Chan, An Individual Author, Kensington NSW 1465, Australia, E-mail: chantrading@bigpond.com

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Abstract

Alzheimer's Disease (AD) has no cure yet and will approach 150 million cases in 2050. Pathologically, it is characterized by intracellular neurofibrillary tangles, extracellular amyloidal protein and brain atrophy.

The proposed AD hypothesis follows: Use four hypotheses, step by step, to conclude this AD hypothesis: "Most neurodegenerations are caused by abnormal protein (polypeptides) synthesis in neuronal cells." The rationale is the following: Memory activities require energy and protein synthesis. The Reactive Oxygen Species (ROS) could damage neuronal DNA during protein synthesis, and the most DNA damage site is the "enhancer region," which controls the activity of genes when DNA is mistakenly repaired. The mistakenly repaired DNA strand served as a template for future mRNA, which could synthesize abnormal proteins, such as amyloids or tau. The mitochondria gradually lose their functions by reducing the energy production of the ATP and creating more ROS. The "mitochondria dysfunction" increase as human age. This AD hypothesis links the mitochondria dysfunction hypothesis and the amyloid cascade hypothesis.

The Late-onset AD (LOAD) progression timeline is not linear. Instead, it is an exponential degeneration, implying the LOAD progression is a positive feedback loop (vicious cycle). A good lifestyle may slow down disease progression.

Keywords : Alzheimer's disease; Alzheimer's disease hypothesis; Neurodegeneration; Mitochondrial dysfunction; DNA repair

Introduction

Human evolution

The Central Nervous System (CNS) is the crucial organ in the human body. It has a different evolutional path. The CNS controls all body functions and evolution offers special survival privileges compared to normal cells. Such as Mechanical protection: Skull and Cerebrospinal Fluid (CSF) and Biological protections: neurons are postmitotic cells with no neuronal division and replication to avoid cancer. The Brain Blood Barrier (BBB) filters out unwanted pathogens and chemicals and the CNS has faults tolerance with multiple connections between neurons by synapses.

The skull protects the CNS from mechanical impact and blocks out ultraviolet light radiation. The CSF is a mechanical shock absorber and removes waste products from the brain.

Using cancer incidence to explain neuronal biological protections: For cancer to develop, it usually requires two incidences:

1. First incident is DNA mutation is mainly occurs during cell division. For example, the large intestine has more than 5-8 times more mutations than the small intestine. However, there is a 50-fold more cancer incidence in the large intestine than in the small intestine. Most colon cancer occurs in the large intestine and cancer incidences and cell divisions strongly correlate [1,2].
2. The other incident is infectious viruses entering the cells. For example, the absolute majority of cervical cancer can be prevented by the HPV vaccine because the HPV vaccine eradicates Human Papillomavirus (HPV) [3]. Therefore, no HPV virus is available to infect the cervical cell. Hence no cervical cancer would develop even if the cervical cell's DNA breaks.

Compared to other dividable cells, the neuron becomes terminally differentiated. The postmitotic cells are not divided, which supposedly avoids DNA mutation. However, the neuron is mutated by imperfect DNA repair, in contrast to the dividable cell mutation during the cell cycle. The Brain Blood Barrier (BBB) tight junction filters out pathogens, which prevents the pathogen from infecting the neuronal cell for cancer.

Most internet communications are mesh networks. The sending message could reach the receiving destination via different nodes if the existing node breaks down. Therefore, communication can be maintained via an alternative route. Neurons have many axons and dendrites connected to other neurons via synapses. If the existing connecting synapse breaks down, the communication between neurons could go through alternative neuronal networks. Thus, we have neuroplasticity.

Mammalian cells replicate if damaged. However, there is more of a probability of cancer developing if there is too much replication. There is a limited number of normal somatic cell replication, and the Hayflick limit is about 40-60 times division and replication, which is

related to telomere length shortening [4,5]. The telomere length is shortened after each division, with no further division possible if the telomere is too short. Therefore, the human body system shuts down with age.

USA life expectancy was 39 years in 1883 [6]. Based on available records, the Chinese Emperor's average life was 39 years in the last 2,000 years. The USA's life expectancy increased after the industrial revolution and is now 78 years. Besides infection, the prevalent diseases that have impacted human life are neurodegeneration, cancer, and cardiovascular diseases. All these diseases have no significant impact on humans if the life expectancy is less than 40 years. However, those diseases have substantial implications on modern society because human lives longer. The percentage of people with Alzheimer's dementia increases by 32% of people aged 85 and older who have AD [7]. There is no known cure for AD. Human evolution has not caught up with the current biological requirements.

Literature Review

Hypothesis for neuron DNA breakage and reparation

Four proposed hypotheses regarding neurodegeneration

Memory storage retrieval and memory consolidation require protein synthesis: In an animal model, ongoing protein synthesis is needed to enable memory consolidation and reconsolidation. Long-term memory formation requires new protein synthesis [8-15].

We could look at the analogy of computer memory, where Random Access Memory (RAM) needs to change capacitance or hard disc storage requires altering the magnetic property. It requires some energy and activity to access or store information. In biology, it requires energy, ATP and protein synthesis. One of the neuron's functions is synthesizing necessary proteins for memory activities.

Free radicals could cause neuronal DNA breakage during the synthesis of protein: Free radicals are chemical species containing one or more unpaired electrons in their outer orbitals that are toxic by-products of aerobic metabolism, causing oxidative damage. The fidelity of the genomes in all aerobic cells is continuously challenged by Reactive Oxygen Species (ROS). ROS can attack the cell's vital components like DNA and proteins. DNA damage is mostly generated by mitochondrial respiration. Oxidative stress accumulates in the DNA of the human brain, especially in the mitochondrial DNA. Many neurodegenerative disorders are strongly associated with the accumulation of oxidative damage [16-21].

In the Suberbielle study, mice explored a new environment filled with unfamiliar sights, smells, and textures for two hours. After exploring the new environment, the group increased Double-strand Breaks (DSBs) in multiple regions involved in learning and memory. It was most abundant in the dentate gyrus. More specifically, the neuronal activity by stimulation increased the DSBs in relevant but not in irrelevant networks. DNA repair is late with a delay. The marker is γH2A.X to identify DSBs [22]. This study shows that DNA breaks after access and retrieves memory.

Neuron DNA mutation is due to faulty DNA repairment during protein synthesis, in contrast to typical cell DNA mutation by cell division during the cell cycle:

Acetylation of histone tails neutralizes their positive charge resulting in the loosening of histones and the associated DNA, and the loose chromatin structure promotes transcriptional activation [23]. The binding of histones to the DNA and its organization into higher-order chromatin structures dramatically protects the DNA against strand breaks and the cellular defense against the induction of oxidative DNA damage [24]. Most dividable cell DNA breaks when the DNA unzips by splitting the DNA into separate strands during cell replication or partially unwound non-dividable DNA (transcription bubble) while copying DNA into mRNA for protein synthesis. In the pre-mRNAs, these splicing sequences make splicing susceptible to mutations [25].

The neuron either apoptosis or mutates if the neuronal DNA repair processes fail. The damaged neurons were often found within "enhancers," which control the activity of nearby genes. Implying mutation occurs during protein synthesis rather than cell division during the cell cycle. It also implies that defects in the repair process, not the DNA damage itself, DSBs may result from gene transcription. DNA DSBs capable of translocating are enriched around active gene Transcription Start Sites (TSSs). Neuronal DNA is continuously broken and repaired in a non-random fashion [26-28].

Alzheimer's disease

Free Radicals: Free radicals could destroy invading pathogenic microbes as a body defense mechanism [16]. Antioxidants neutralize free radicals by giving up some of their own electrons. The bulk of neuronal DNA damage is acquired by oxidative DNA damage [20]. Most organic radicals possess short lifetimes and quickly undergo oxidation [29]. The studies on the effectiveness of antioxidant supplementation therapy showed conflicting results [30]. The most promising AD treatment antioxidants were Vitamin E, coenzyme Q10 (CoQ10), melatonin, polyphenols, curcumin, and selenium [31]. Beydoun's study analyzed levels of antioxidants and carotenoids in the blood rather than carried out generally by analyzing dietary intake levels. The Serum antioxidant vitamins and carotenoids may protect against neurodegeneration [32]. When introducing the catalyst (TH10785) into the enzyme (OGG1), the enzyme becomes ten times more effective at repairing oxidative DNA damage [33].

Mitochondria

One of the main mitochondrial functions is energy production, ATP. Mitochondrial DNA is a double-stranded supercoiled ring molecule that does not contain histones [34-37]. In healthy organisms, the production of free radicals is low. The antioxidant defense systems quickly remove ROS before they cause damage to the cell [16]. The mitochondrial function and cognitive function may be maintained if protected from ROS [21].

Mitochondrial DNA generally has more damage than nuclear DNA due partly to its proximity to sources of ROS production and without histone protection [35,36]. Damaged mitochondrial results in energy metabolism dysfunction, leading to decreased ATP production and increased ROS [37]. Oxidative stress accumulates the mitochondrial DNA and plays a critical role in neurological disorders, including Alzheimer's disease [20].

DNA breaks and repairs: If DNA repair is compromised; it will impact the nervous system. The types of causative DNA damage are associated with transcription or oxidative metabolism [38]. In Wu's study, neurons accumulate high levels of DNA SSBs located within enhancers at or near CpG dinucleotides and sites of DNA demethylation. They suggest in patients with defective SSBs repair [26].

Abnormal protein: The Amyloid-β (Aβ) is a fragment of the amyloid precursor protein (APP) produced by brain neurons. Two subsequent proteolytic cleavages of APP by β-secretase and γ-secretase generate Aβ [39].

In the Chang study, another polypeptide source is misfolding and aggregation of disease-specific proteins. The amyloid fibril composed of a 135 amino acid C-terminal fragment of TMEM106B is common in distinct human neurodegenerative diseases, including abnormal aggregation of TDP-43, tau, or α-synuclein protein [40].

ROS can damage virtually any cellular component and protein synthesis. Results in the production of aberrant protein molecules or the generation of sub-optimal protein.

Mutations in both the APP and the PSEN genes cause Familial Alzheimer's disease (FAD) with autosomal dominant inheritance and early onset of disease. The analysis of the disease features in FAD and Sporadic AD (SAD) populations indicates that FAD and SAD share the same pathophysiology and progression [41-45].

In Lee's study, Neuronal damage characteristic of Alzheimer's disease takes root inside cells and well before these thread-like amyloid plaques fully form and clump together in the brain [46]. They observed almost-fully formed plaques inside some damaged neurons of AD. They also explain why many experimental therapies designed to remove amyloid plaques have failed to stop disease progression. The brain cells are already crippled before the plaques fully form outside the cell. In this study, the source of amyloids inside neurons is most likely synthesized by neuronal DNA directly.

The hypothesis for another source of polypeptide in the CNS is that:

The neuron DNA may mutate due to faulty DNA repair, and it could produce abnormal mRNA code for polypeptides if genes are mutated and consequently produce an alternative polypeptide sequence:

The mutated DNA has the following consequences:

Once such repaired mistakes are established, unfortunately, the incorrectly sequenced DNA strand serves as a template for future mRNA [47]

A single mRNA could produce multiple copies of the corresponding polypeptides [48]

The deposition of Aβ in Alzheimer's disease eventually leads to Tau tangles and neurodegeneration. Düzel suggests that the tau load in the brain impairs memory function only when the amyloid accumulation is also high [49,50].

CNS inflammation: Acute inflammation in the brain is a well-established defense against infection, toxins, and injury. Innate immune activation and inflammatory response are driven by microglial cells. Aβ species can trigger an inflammatory response in microglial cells. Oxidative stress can lead to chronic inflammation. The inflammatory process induces oxidative stress and reduces cellular antioxidant capacity. Late-onset AD is associated with strong innate immune system activation [51-57].

Central nervous system

Hippocampus: The hippocampus is essential in forming, organizing, storing new memories, and connecting to other memories. The hippocampal atrophy rate is a reliable biomarker of disease stage and progression [58,59]. Hippocampal atrophy on Magnetic Resonance Imaging (MRI) is an early characteristic of Alzheimer's disease [60]. The hippocampus is critical for creating new memories; it's one of the first regions of the brain to deteriorate as we get older and much more severely in Alzheimer's disease [61].

In an analogy to a computer, the hippocampus, like Random Access Memory (RAM), the RAM is short-term memory with high traffic of information input and output. The hippocampus is busy with memory creation and retrieving. Therefore, it requires lots of protein synthesis. There is more chance of DNA breakage if ROS presents, and the possible consequence is apoptosis. Neural Stem Cells (NSC) reside in the Sub-ventricular Zone (SVZ) of the adult human brain and the dentate gyrus of the adult mammalian hippocampus [62]. The regenerative capacity of the hippocampus also subsides with age [63]. The new neural progenitor cells may not be sufficient to replenish the death of the hippocampus neuron. Therefore, the net number of neurons in the hippocampus is reduced with aging.

Individuals with AD can typically remember events in the distant past better than those in the immediate past because short-term memories rely more on the hippocampus. In contrast, familiar memory is stored in another brain region.

Microglial cells: Microglia are involved in synaptic organization, trophic neuronal support during development, phagocytosis of apoptotic cells in the developing brain, myelin turnover, control of neuronal excitability, phagocytic debris removal and brain protection and repair [52]. The advanced Late-onset AD (LOAD) eventually loses microglia's total function [64].

BBB permeability: The vascular blood-brain barrier is a highly regulated interface between the blood and brain. With inflammation, the vascular blood-brain barrier becomes more permeable to solutes and undergoes an increase in lymphocyte trafficking. Systemic inflammation impairs blood-brain barrier function [65,66].

Lifestyle-sleep: Healthy sleep habits help prevent the protein Amyloid-Beta from forming clumps and require a circadian rhythm for daily oscillation in Aβ42 clearance. AD has a bi-directional relationship with circadian disruption with sleep disturbances starting years before disease onset [67]. Deep sleep serves a role in waste clearance, an evolutionarily conserved core function of sleep [68]. In an animal model of Alzheimer's disease, restoring normal sleep by returning to normal the activity of the Thalamic Reticular Nucleus (TRN), a brain region involved in maintaining stable sleep, reduced the accumulation of Aβ plaques in the brain. The Alzheimer's mice woke up 50% more times than non-Alzheimer's mice [69]. An imbalance between Aβ neuronal production and extracellular clearance of Aβ was associated with accumulation in plaques [39,70,71]. A strong relationship occurs between several sleep disturbances and the incidence of dementia over time. [67-72].

Lifestyle-exercise: Regular physical exercise diminishes BBB permeability as it reduces oxidative stress and has anti-inflammatory effects. Stress-free mild exercise increases hippocampal neuronal activity and promotes adult neurogenesis in the hippocampus's dentate gyrus [61]. Exercise training also increases brain mitochondrial biogenesis. Aerobic exercise training reduced central arterial stiffness and increased cerebral blood flow [73-75].

In the Irimia, et al. study The Tsimane indigenous people of the Bolivian Amazon are exceptionally physically active; only about 1% suffer from dementia. In contrast, 11% of people age 65 and older

living in the United States have dementia. Their brains likely experience far less brain atrophy than Westerners as they age [76,77].

There are many hypotheses relating to AD. There are four main AD hypotheses as follows:

- The hypothesis is on the progression of AD pathologies states that Aβ plaques appear first, causing hyperphosphorylation of tau, leading to tangles and neurodegeneration [39].
- The hypothesis focuses on mitochondrial dysfunction with several mitochondrial defects in central nervous system disorders. The mitochondrial produce ROS that attacks tissue and causes oxidative damage [21].
- The hypothesis is that a pathogen (virus, bacteria, prion, etc.) is the root cause of AD [78,79]. The most likely pathogen entry to CNS is via the permeable BBB.
- The hypothesis is that AD results from external influx of free fatty acids (FFAs) and lipid-rich lipoproteins into the brain following disruption of the BBB [80].

This AD hypothesis links the mitochondrial dysfunction hypothesis and the amyloid cascade hypothesis. The infectious hypothesis and the lipid invasion hypothesis rely on the permeability of BBB.

Alzheimer's disease is a complex disease not caused by a single factor. However, oxidational stress is the predominant driver of AD. For dividable cells, the DNA may break after DNA is unzipped for cell replication. Cancer may develop if the DNA repairment is imperfect. For non-dividable cells, such as neurons, the DNA is unzipped partially for protein synthesis and may break. The DNA may mutate if the repair process is not perfect. The imperfect repaired DNA strand serves as a template for future mRNA, which could synthesize an abnormal protein. The relationship between compromised DNA repair and neurodegeneration was first suggested by Cleaver [18, 81]. Use four individual hypotheses, step by step, to conclude this AD hypothesis, "Most neurodegenerations are caused by abnormal protein (polypeptides) synthesis in neuronal cells."

Using the hippocampus explains this AD hypothesis: Memory activity requires protein synthesis. The ROS is a by-product of aerobic metabolism, the oxidative damage accumulated in mitochondria with age. The mitochondria gradually lose their functions by reducing ATP production and creating more ROS, the "mitochondria dysfunction." The ROS oxidative stress damaged neuronal DNA is mutated by imperfect repair. The DNA damage site is mostly in the "enhance" region during protein synthesis. The mutated DNA may be coded for abnormal protein or fragments of protein-polypeptides, which could be Aβ or tau. The accumulation of Aβ and tau would cause AD. The hippocampus has the most protein synthesis activity and therefore suffers the brunt of harm in the CNS.

The Late-onset AD (LOAD) individual loses its biological protections as humans age. The neuron is mutated or apoptotic, as a post-mitotic cell that supposedly does not divide and replicate. The BBB permeability is compromised by neuroinflammation, and the immune microglia are unable to clear the plaques or unable to eradicate invading pathogens.

In an alternative viewpoint, an AD individual is unable to slow down the positive feedback loop (vicious cycle) in neurodegeneration, such as reducing the ROS and neuroinflammation and retaining immunity. The LOAD progression timeline is not linear. Instead, it is an exponential degeneration, which implies LOAD progression is a positive feedback loop. For AD individuals, good sleep and daily walking, and eating vegetables may slow down AD progression.

The interplay within CNS is in the following interactive chains (though not a comprehensive list):

- If there is less ROS generated, then the less DNA breakage
- If there is less DNA breakage, then the less neurons would undergo apoptosis, or the less DNA mutation occurs
- If there are less DNA mutation, then the less polypeptide produced, such as Aβ and Tau
- If there are less abnormal polypeptides synthesis, then the less inflammation
- If there is less inflammation, then the less ROS and the BBB may maintain its permeability
- If the permeability of BBB is maintained, then the less pathogens and unwanted chemicals could enter to CNS and the less insult to CNS
- If there are less microbiome pathogens entering to CNS, then the less neuroinflammation.

The human brain requires energy input for memory activities. Despite comprising only 2 percent of the body, our brains consume 20 percent of the body's oxygen supply. The unfortunate side effect is ROS because of aerobic metabolism. This oxidative stress could initiate a CNS malfunction, cascading events that could lead to a positive feedback degeneration loop if not stopped early.

Using the Naked Mole Rats (NMR) as an example, in the Boughey study: NMR can live for over three decades (the average rat lifespan is two years). Despite their long lifespan, NMRs show little neurodegeneration. The exceptional neuronal preservation is the improved antioxidant response, higher fidelity translation, stringent DNA repair, and faithful proteome function [43]. The example of the NMR retaining healthier CNS throughout its whole life shows that it is possible for humans don't suffer neurodegeneration when they age. However, this potential future is still a long distance away.

Conclusions

There are four hypotheses in the following:

- Memory activity needs protein synthesis
- DNA could be damaged by ROS while synthesizing protein
- DNA mutated by imperfectly repaired during protein synthesis
- The mutated DNA strand could serve as a template for future mRNA synthesizing abnormal protein.

These four hypotheses are well known to AD scientists. However, combining them all concludes that polypeptides cause neurodegeneration and how it develops, or if under oxidative stress and imperfect DNA repairment, the neuron could synthesize abnormal protein. The abnormal protein could cause AD.

Referring to NMR, the example of the NMRs show little neurodegeneration because of

Improved antioxidant response: Therefore, less possibility of DNA being damaged by oxidative stress.

Stringent DNA repair: Therefore, less DNA mutation even when the DNA breaks.

High fidelity protein translation: Therefore, less abnormal protein synthesis if there is less oxidative stress and stringent DNA repair.

Conflict of Interest

The author has no conflict of interest to report.

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