Hypotheses of Alzheimer's Disease Pathogenesis

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Abstract: Alzheimer's disease (AD) is the most common cause of dementia. The two hallmarks of AD are extracellular senile plaques (SF) and intracellular neurofibrillary tangles (NFT). Numerous studies have been involved in research for AD pathogenesis, proposing different hypotheses and theories to explain the occurrence of the two hallmarks as well as AD onset. This paper will review three suppositions of AD pathogenesis, including the amyloid cascade hypothesis, the APP metabolism impairment theory, and Tau hypothesis. The amyloid cascade hypothesis is the mainstream hypothesis that suggests Aβ aggregation should predate all AD-related pathological events. Amyloid precursor protein (APP) metabolism theory considers impaired metabolism of APP to be a possible explanation for AD onset. Tau hypothesis, which is another major hypothesis for AD pathogenesis, postulates that tau aggregation and NFT play an initiating role in AD onset. Many studies have elucidated that Aβ aggregation may not cause AD; some of the AD researchers have shifted their research focus to alternative hypotheses involving other biomarkers, such as tau and APP metabolites. However, the role of Aβ should not be refuted as it interacts with so many AD pathological features. Research on Aβ should be alongside explorations of other potential pathological causes of AD.

1 INTRODUCTION

Alzheimer's disease (AD) is a progressive and irreversible neurodegenerative disease that is affecting millions of people in the world. AD is categorized into two divisions based on the onset age. Sporadic AD or late-onset AD is the most common type of AD; it usually manifests after age 65. Familial AD, also known as early-onset AD, occurs in people younger than age 60. Both types of AD together account for more than half of the dementia which is recognized as a public health priority by WHO. In the past, most of the early-staged dementia used to be deemed as one of the normal consequences of aging, overlooking AD onset. However, AD is not an inevitable consequence of aging but an abnormal neurological disorder that will cause more severe cognitive impairment as the disease progresses.

Two hallmarks of AD are extracellular senile plaques (SP) and intracellular neurofibrillary tangles (NFT) within the central nervous system. There are numerous studies on SP, NFT, and the relevant metabolic processes to investigate AD pathologies; however, different hypotheses have not yet unified to provide a clear AD pathology because of the complex nature of AD and the limitations of the hypotheses. It is of importance to summarize and compare current studies on AD pathogenesis in order to unravel the full picture of AD mechanism. This paper reviews several hypotheses of AD pathogenesis, including the amyloid cascade hypothesis, APP metabolism theory, and tau hypothesis, to serve as a concise summary of the current progress in AD mechanism research.

2 AMYLOID CASCADE HYPOTHESIS

The amyloid cascade hypothesis, also known as beta-amyloid hypothesis, posits that SPs are amyloid plaques, which are mainly composed of Aβ fibrils, contribute to NFT and other neuronal alternations associated with AD-induced dementia (Jack, Jr., et al. 2016, Bondi, Edmonds, and Salmon 2017) . For a long time, Aβ aggregation was positioned as the upstream cause of all the pathological changes in AD. Aβ is a metabolic product of amyloid-beta precursor protein (APP) which plays important role in neuronal development, neurite outgrowth, as well as intracellular trafficking in axons (Kametani, and Hasegawa 2018). APP (Figure 1) has four cleavage

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sites (i.e. α, β, and two γ sites) respectively recognized and cleaved by α-secretase, β-secretase, and γ secretase. Aβ is produced by the cleavages of APP by β-secretase and γ secretase. In accordance with the two γ cleavage sites on APP, β-γ combinatorial cleavage produces either Aβ40 or Aβ42, depending on which γ site the secretase binds. The research suggests that the elevated production level of Aβ42 rather than Aβ40 leads to aggregation of SP (Hillen 2019). Normally, Aβ is released out of the neurons and degraded; however, in pathological conditions, Aβ is accumulated to form extracellular plaques. Moreover, Aβ exists in three forms, which are soluble Aβ monomers, soluble Aβ oligomer, and insoluble Aβ fibrils. The amyloid cascade hypothesis considers amyloid plaques the aggregation of the insoluble Aβ fibrils.

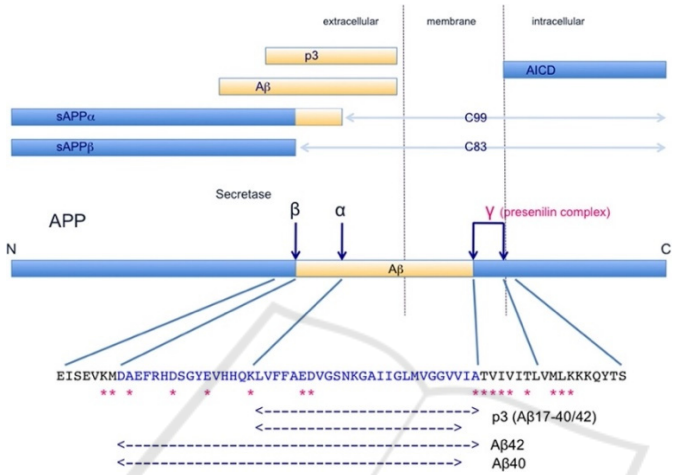

Figure 1. APP metabolism and the metabolic products. Four dark blue arrows are secretase recognition sites on APP; α, β, and γ sites correspond to α-, β-, and γ-secretases respectively. P3 is produced by cleavage by α and γ secretase. Aβ is produced by β and γ secretase. sAPPα and sAPPβ are produced by α-secretase and β-secretase cleavage respectively. AICD (APP intracellular Domain) are C-terminal fragments that result from cleavage of γ secretase. Adapted from Kametani, F., & Hasegawa, M. (2018). Reconsideration of Amyloid Hypothesis and Tau Hypothesis in Alzheimer's Disease. Front Neurosci, 12, 25. https://doi.org/10.3389/fnins.2018.00025.

The Amyloid cascade hypothesis initially proposes a clear temporal order in the AD pathogenesis, in which high-level aggregation of Aβ is the causative agent of other pathological events including NFT occurrence (Bondi, Edmonds, and Salmon 2017, Hillen 2019). Cytotoxicity of Aβ aggregation can directly cause neurodegeneration and neuron loss (Kametani, and Hasegawa, Ohshima, et al. 2018). Also, amyloid plaques can activate microglia and astrocytes to release inflammatory factors, causing neuron inflammation (Zhang, and Zheng 2019). The activated microglia are phagocytic towards synapses, resulting in synaptic impairment. Combining the clinical examples that relate AD onset to Aβ aggregation, β amyloid hypothesis is long believed to primarily account for AD onset. However, along with AD research advancing, amyloid cascade hypothesis is challenged and disapproved by many recent studies.

A lot of research, ranging from investigating Aβ neurotoxicity to exploring the relationship between AD and amyloid plaques, has validated that the temporal ordering proposed in the amyloid cascade hypothesis is wrong ((Kametani, and Hasegawa 2018, Hillen 2019). Jack et al. have acknowledged that temporal ordering of amyloid cascade hypothesis is problematic. In terms of Aβ toxicity, several lines of evidence have rejected that Aβ cytotoxicity causes synapse loss or neurodegeneration (Bondi, Edmonds, and Salmon 2017). Braak et al. directly refute the temporal ordering of amyloid cascade hypothesis by reporting that NFT is not a downstream event led by amyloid plaques, and that tau aggregation, components of NFT, precedes formation of amyloid plaques. In addition, amyloid plaques are not always related to AD as normal people could have more extensive amyloid aggregation and same-aged AD patients and normal people could have amyloid plaques of the same density (Edison, et al. 2007). It comes to a conclusion that amyloid plaque or senile plaque aggregation is related to aging but may be irrelevant to AD onset. Furthermore, the most convincing evidence refusing amyloid cascade hypothesis might be the devastating failure of all

clinical trials on AD therapeutics aiming to stop or delay AD progress by eliminating or preventing Aβ aggregation. β-secretase inhibitors that block the cleavage of Aβ from APP should have reduced Aβ production and aggregation; on the contrary, groups treated with the β-secretase inhibitors show more severe cognitive impairment than the control (Knopman 2019). In conclusion, it is unlikely that amyloid cascade hypothesis is a correct AD pathogenic mechanism. Yet rejecting the amyloid cascade hypothesis should not discontinue the research on Aβ, Aβ aggregation might still be one of the pathological events of AD onset.

3 APP METABOLISM IMPAIRMENT THEORY

Amyloid-beta precursor protein (APP) metabolism, also known as APP processing, generates several downstream peptides that are found to be important for neuron functionality. Some research suggest that AD pathogenesis should be related to the impairment of APP metabolism, where all the major APP metabolites should be considered beside Aβ aggregation (Bondi, Edmonds, and Salmon 2017, Kametani, and Hasegawa 2018). APP gene locates on chromosome 21 of which the trisomy form causes the famous Down's Syndrome. Patients of Down's Syndrome also exhibit AD-like symptoms such as cognitive ability impairment, which could be caused by the excess copies of APP gene and high amount of APP metabolites including Aβ (Wilson, et al. 2019).

APP can be processed by three different secretases (i.e. α-secretase, β-secretase, and γ secretase) via four recognition sites (i.e. α, β, and two γ sites) (Figure 1). In the non-amyloidogenic pathway, APP is sequentially cleaved by α-secretase and γ-secretase; in the amyloidogenic pathway, α-secretase is substituted by β-secretase, generating Aβ. In both pathways, γ-secretase cleaves to produce APP intracellular domain (AICD). Evidence suggests that α-secretase predominately cleaves more than 90% of the APP while β-secretase only accounts for less than 10% of the APP cleavage (Kametani, and Hasegawa 2018). Accordingly, the major metabolites should be sAPPα, p3, C99, and AICD while Aβ is supposed to be in a small amount (Figure 1). In pathological conditions, a large amount of Aβ is produced to form amyloid aggregation, indicating that β cleavage is more predominant than α cleavage. There is another explanation for the prevalence of β cleavage. Research on APP trafficking found that APP primarily locates intracellularly, co-residing with β-secretase whose activity is optimized by the acidic endosomal environment, causing amyloidogenic processing (Wang, et al. 2017). On the contrary, only a small fraction of APP, localizing on the cell surface where α-secretase is abundant, undergoes non-amyloidogenic pathway. Given that β-secretase is pivotal to Aβ generation, inhibiting β cleavage should have ameliorated AD symptoms by reducing Aβ production. However, experiment of β cleavage inhibition, which aims to reduce Aβ aggregation, even worsens cognitive impairment (Knopman 2019), implying that AD pathology is not limited to amyloid plaques but APP metabolism as a whole.

Besides the notorious Aβ accumulation in the amyloidogenic pathway, research has also investigated the neuronal effects of other APP metabolites (i.e. sAPPα, p3, C99, and AICD) of the non-amyloidogenic pathway (Zhang, et al. 2011). sAPPα is considered to be neurotrophic (Zhang, and Zheng 2019). P3 has long been classified as "non-amyloidogenic", so studies on APP metabolites usually omit p3 and few studies focus on its cytotoxicity. Nevertheless, Kuhn et al. and Kuhn and Raskatov have revisited the function of p3; they concluded that p3 is amyloidogenic and it may play a role in amyloid plaque formation. Firstly, p3 contains the amyloidogenic region in Aβ; secondly, p3 fibrils facilitate the formation of Aβ fibrils that later assemble to become amyloid plaques (Kuhn and Raskatov 2020). Some researchers believe that Aβ toxicity is due to the hydrophobicity of Aβ oligomers (Hardy, and Selkoe 2002). P3 is almost entirely hydrophobic, so it could have higher cytotoxicity than Aβ (Wei, et al. 2002), which might eventually contribute to neurodegeneration.

C99 and AICD are both C-terminal fragments (CTF) of APP. CFT accumulation might be closely related to AD onset. Stocking of CTF could induce synaptic failure, abnormally phosphorylated tau protein, and memory loss (Tamayev, et al. 2012) . Additionally, the accumulation of CFT interferes the normal function and morphology of mitochondria in neurons (Vaillant-Beuchot, et al. 2021, Devi, et al., 2006); specifically, CFT accumulation alters mitochondria sizes, disorganize mitochondrial cristae, and affects the mitophagy process. Mitochondria are believed to be involved in AD pathologies. Nevertheless, its role in the pathogenesis is unclear. Some research proposes a primary mitochondria hypothesis where mitochondria disruption causing neuron dysfunction predates Aβ accumulation. Meanwhile, some others studies support a secondary mitochondria hypothesis in

which mitochondrial dysfunction is downstream of Aβ aggregation (Devi, et al. 2006, Swerdlow 2018).

Summing the studies on APP metabolites, it is clear that Aβ is not the only neurotoxic APP metabolite that could potentially lead to neurodegeneration. The impairment of APP processing that alters the relative amount of various APP metabolites should be considered as a whole to explain AD onset.

4 TAU HYPOTHESIS

Tau is a microtubule-associated protein that is responsible for the regulation of tubulin assemblies and stabilization of neuronal microtubules in the central nervous system. Normally, tau is only moderately phosphorylated; hyperphosphorylated tau fibrils form NFT, which is an AD hallmark. Tau's hypothesis suggests that tau in hyperphosphorylated states form paired helical filaments and straight filaments, both of which contribute to the formation of intracellular NFT ((Kametani, and Hasegawa 2018, Muralidar, et al. 2020) . In tau hypothesis, Aβ is a tau-induced downstream event.

Tau is cytotoxic as it negatively affects neuron cytoskeletal structure, axonal transport, and mitochondrial membrane integrity. Hyperphosphorylated tau loses the ability to regulate tubulin, which is pivotal for the neuron skeletal system (Muralidar, et al. 2020). One of the most important functions of tau is stabilizing the microtubules in the axons. Normally, moderate phosphorylated tau attaches to the microtubules in the axons, allowing for the binding of motor molecules that act as cargo for intracellular trafficking (Combs, et al. 2019) (Figure 2a). Hyperphosphorylated tau detaches from the microtubules (Figure 2b), disaggregating the microtubules and thus disrupting the axonal transport (Combs, et al. 2019, Arnsten, et al. 2021); later, the detached tau assembles into NFT. Disruption of axonal transport eventually contribute to neurodegeneration. (Camilleri, Ghio) report that accumulation of tau leads to mitochondrial organelle swelling and loss of membrane potential, causing mitochondrial defects

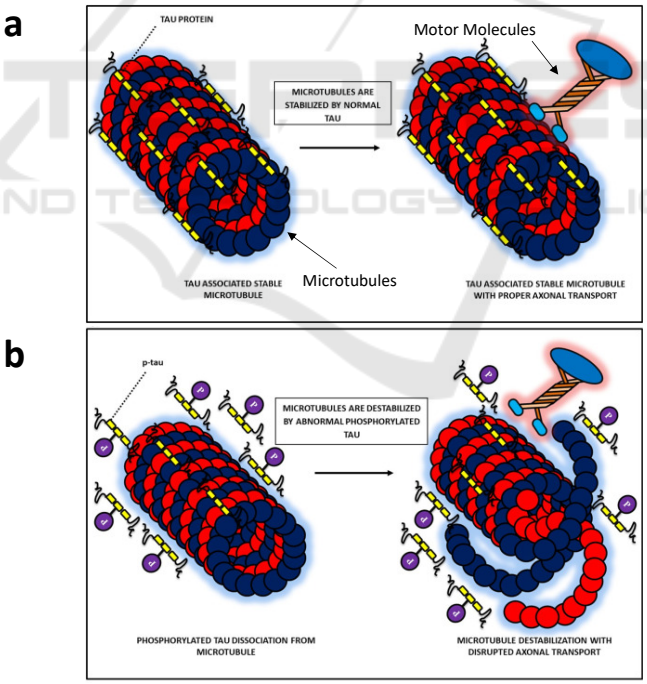

Figure 2. Stabilization of microtubules by tau protein. (a) In normal neurons, moderately phosphorylated tau (without P) proteins associate to stabilize the microtubules, allowing for the binding of motor molecules. (b). Hyperphosphorylated tau (with P) detach from microtubules, which then disaggregate microtubular structure. Motor molecules fail to bind to the microtubules. Adapted from Muralidar, S., Ambi, S. V., Sekaran, S., Thirumalai, D., & Palaniappan, B. (2020). Role of tau protein in Alzheimer's disease: The prime pathological player. Int J Biol Macromol, 163, 1599-1617.

The core proposition of tau hypothesis is that the tau is the causative agent of AD and it is upstream of Aβ plaques. Multiple studies have confirmed the upstream tole of tau and verified tau-induced NFT (Arnsten, et al. 2021) . Most importantly, the self-propagating and aggregation-promoting characteristics of tau can explain the staging and progression of AD. Abnormally hyperphosphorylated tau occurs in only a limited range of neurons, and they can convert the normal tau into the hyperphosphorylated states, increasing the total amount of hyperphosphorylated tau and propagating to a larger range of neurons (Nonaka, et al. 2010). Moreover, aggregation of hyperphosphorylated tau inhibits protein aggregation clearance, which in turn protects tau aggregation from degradation (Keller, Hanni, and Markesbery 2000), forming a viscous cycle that enables for enlargement of hyperphosphorylated tau aggregation. The nature of the viscous cycle and self-propagation of tau might explain the progression of AD clinically.

5 CONCLUSIONS

In summary, different hypotheses have not unified to provide a clear AD pathology yet. A large amount of evidence has rejected the amyloid cascade hypothesis, especially the temporal ordering. However, the role of Aβ should not be completely refuted since it interacts with so many other hypotheses for AD pathology. Some other hypotheses, such as APP metabolism theory and Tau hypothesis, seem to be valid explanations for AD. P3 and CTF, which are under-researched APP metabolites, should be revisited for their neurotoxicity, their relationship to SF and NFT, and the relevance to AD onset. Also, as evidence suggests, tau aggregation should be one of the pivotal events in AD pathology that needs further investigation. This review collates the above hypotheses of AD pathogenesis and provides a clear demonstration and comparison of the current advances in AD research, which provide a wide picture for AD mechanisms. To date, we have witnessed an explosion of research into Alzheimer's disease and the development of drugs at all levels, but much remains to be done. As mentioned above, the failure of clinical trials suggests that we should revisit the role of beta-amyloid and reconsider other factors involved in AD pathogenesis in future research.

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