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THE PATHOLOGICAL PATHWAY FOR THE PERSISTENCE OF AD SYMPTOMS AFTER THE REMOVAL OF AMYLOID PLAQUES

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Abstract: Amyloid plaque has been an indicative hallmark for Alzheimer's diseases (AD), however the removal of which has shown to be inefficient in altering the progression of disease; thus, the study will focus on the mechanism behind the persistence of AD. The study examines the causal relationships among Aβ, neurofibrillary tangles (NFTs), cholinergic depletion, and excitotoxicity. Using secondary data from pre-existing studies, it is evidenced that Aβ causes cholinergic depletion, NFTs, and excitotoxicity through interacting with ChaT & nAChRs, IP3-K & GSK-3β, and NR1 subunit on NMDAR respectively; NFTs causes cholinergic depletion and excitotoxicity through mitochondrial dysfunction, and interaction with vGLUT respectively; while excitotoxicity causes NFTs through interaction with cdk5 and PP2A. It is concluded that the persistence of AD after Aβ removal is due to a positive feedback loop mechanism between NFTs and excitotoxicity, which causes the persistence of NFTs, cholinergic depletion, and excitotoxicity. However, the principle causative agent of AD's progression remains undecidable.
Keywords: Cholinergic depletion; Excitotoxicity; NFTs; Amyloid plaque; Positive feedback mechanism

1 INTRODUCTION

1.1 Amyloid Plaque

AD is a type of dementia that is marked by high level of amyloid plaques in the brain. Amyloid precursor protein (APP) is a transmembrane protein, its functions in the central nervous system are not fully understood, but may be involved in facilitation of learning, neuron growth, cell adhesion, and various other neuronal activities [1]. APP undergoes proteolysis where it is cleaved into shorter fragments by protein secretases. In the amyloidogenic pathway, APP is initially cleaved by a β-secretase, to produce an intercellular APPsβ fragment. The remaining protein in the membrane is further cleaved by γ secretase, producing intercellular amyloid β protein (AβPa) and intracellular AICD [2]. In Alzheimer's disease, the concentration of Aβ in CNS is significantly higher than in healthy people. This excessive upregulation causes Aβ to aggregate and deposit in the brain, forming amyloid plaques, which has been the hallmark of Alzheimer's disease. Because of the prominent correlation between AD and plaques, a hypothesis was established in 1992, proposing that amyloid plaque is the causative agent of AD. However, 27 years later in 2019, a clinical trial reported on New England Journal of Medicine has made it clear that lowering the level of amyloid plaques does not ease AD, and in some patients the symptoms continued to get worse. This has raised a need for searching for another potential therapeutic target, as well as for a mechanism behind AD's persistence.

1.2 Pathological Processes in AD

Apart from amyloid plaques, there are various other processes associated with Alzheimer's disease, which are primarily neurofibrillary tangles (NFTs), neuroinflammation, excitotoxicity, and cholinergic depletion. NFTs are formed from tau proteins, which are proteins associated with microtubules in cytoskeleton of neuron, acting as a stabilizer maintaining the structure of microtubules. When tau proteins are hyperphosphorylated, they dissociate from microtubules and aggregate together, forming NFTs, which causes synapses loss, axonal transport impairment, and much more [3-4]. Neuroinflammation is the inflammation of nervous tissues, caused by abnormalities in astrocytes and glia cells, which secrete chemokines, cytokines, and other neuroinflammatory mediators in an irregular manner [5]. Excitotoxicity is neuronal degeneration caused by excessive stimulation of NMDA receptors [6]. Finally, cholinergic depletion is the loss of cholinergic activity, such as deficits in acetyltransferase [7]. These processes are all highly correlated with Alzheimer's disease, but the casual relationships among them remain little known.

1.3 Therapies for AD

Drugs have been developed for Alzheimer's disease until now, their intended therapeutic effect is one of two types; disease-controlling, meaning to suppress and stabilize the symptoms without being able to remove the root causative agent; and the other is disease-modifying, meaning to alter the progression and activity of the disease itself. However, most of them has failed to be effective, including those targeting Aβ, neuroinflammation, and tau protein. Out of all the drugs developed for AD until now, there are only four of them that are officially approved by FDA and can be prescribed to patients with mild and moderate AD. These drugs are donepezil, rivastigmine, galantamine, and

memantine, which all have a disease-controlling effect. Among these 4 drugs, donepezil, rivastigmine, and galantamine are all cholinesterase inhibitors, which lowers cholinergic depletion by inhibiting the breakdown of acetylcholine in the synaptic cleft. Memantine, on the other hand, is a NMDA receptor blocker, which lowers excitotoxicity. Furthermore, the efficacy of tau therapy has been uncertain. For example, lithium has an effect of inhibiting the protein kinase that phosphorylates tau protein, but short-term (10 weeks) lithium treatment on patients has shown no effect on improving the symptoms [8]. On the other hand, another drug called methylthioninium (MT), which is a tau aggression inhibitor, has successfully demonstrated minor beneficial effects on AD over a period of 50 weeks [9]. Since there is variation in the effect of tau protein therapy, it is uncertain whether it is the causative agent of AD, thus it bears a high potential for successful disease-modifying effect.

1.4 Hypothesis

Since the inhibition of cholinergic depletion, excitotoxicity, and sometimes the tau proteins have a disease-controlling effect on patient, there is a certain level of dependence of AD symptoms on them. Therefore, the hypothesis states that cholinergic depletion, excitotoxicity, and tau protein are responsible for the persistence of AD after the removal of amyloid plaques through a particular pathological pathway, and the removal of which will terminate the persistence.

2 ASSUMPTIONS

2.1 Assumption 1

The initial accumulation of Aβ can begin years or even decades before the onset of dementia [10]; one study has shown that amyloid plaques can even be found in people in their early 20s [11]. On the other hand, it has been controversial regarding the time of occurrence of cholinergic depletion, some studies have suggested that it occurs before the symptomatic stage like amyloid plaques [12-14], and others suggest that it only occurs after the onset of dementia [15]. However, despite the controversy, there are only two possible scenarios; that cholinergic depletion either occurs after the onset of dementia or before the onset. In this paper, we assume that cholinergic depletion occurs before the onset of dementia. This is because if it occurred after the onset of symptoms, the interaction between amyloid plaques, NFTs, and cholinergic depletion would be extremely obscure because of the extensive time interval, which is 20 to 30 years [16], between the initiation of the two events, and the research of which would extend beyond the scope of this project.

2.2 Assumption 2

Since cholinergic depletion occurs before the onset of dementia, its severity is positively correlated with that of amyloid plaque one [12]. This gives rise to three possible scenarios regarding the interaction between amyloid plaques and cholinergic depletion; the first is that cholinergic depletion is the causative agent of amyloid plaque, the second is that amyloid plaque is the causative agent of cholinergic depletion, and the last one is that their relationship is not causal, but simply a correlation. In this paper, we assume that the second scenario is true, in which amyloid plaque is the causative agent of cholinergic depletion. This is because the first scenario, cholinergic depletion causes amyloid plaque, has already been a well-established hypothesis since 1980s [17], whereas the purpose of this paper is not to verify the cholinergic hypothesis. The third scenario implies that there is no interaction between amyloid plaques and cholinergic depletion, which is highly unlikely because it does not conform with the consensus in field of research. Therefore, the second scenario is adopted in this paper.

2.3 Assumption 3

The same assumption is made about NFTs, in which it occurs before the onset of dementia and is caused by amyloid plaques. This is because although it is almost certain that it occurs before dementia as indicated by numerous papers, it is somewhat controversial regarding the causal relationship between NFTs and amyloid plaques; that is, a tau hypothesis has been established, proposing that pathological tau is the causative agent of amyloid plaques [18]. On the other hand, no assumptions are made about excitotoxicity because it is almost certain that amyloid plaques cause excitotoxicity.

3 DATA ANALYSIS

To investigate the mechanism that sustains AD after the removal of amyloid plaques, the relationships among amyloid plaques, NFTs, cholinergic depletion and excitotoxicity will be analysed. This will be done in binary sets that contain two elements at the time, for example “Aβ and cholinergic depletion”, “Aβ and NFTs”, “Aβ and excitotoxicity”, “NFTs and cholinergic depletion”, and so on. The analysis will be accomplished by using secondary data from preexisting studies done by other researchers. At last, it should be noted that amyloid plaques is used interchangeably with Aβ, and NFTs is used interchangeably with tau. This is because they are mutually inclusive; one has to present if the other is present.

3.1 Aβ and Cholinergic Depletion

The mechanism by which Aβ causes cholinergic depletion is uncertain and has not reached a consensus. For example, a study using rat hippocampal slice has found that Aβ can reversibly inhibit the nicotinic acetylcholine receptor, blocking acetylcholine from opening the channel [19]. This suggests that high concentration of amyloid plaque in people with AD may cause chronic inhibition of nicotinic receptor. Another study using rat septal neuron culture has found that Aβ treatments reduce acetyltransferase activity, which is the enzyme responsible for the synthesis of acetylcholine [20]. Although the exact underlying mechanism is unknown, these studies provide two possibilities.

3.2 Aβ and NFTs

There are many proposed mechanisms regarding how Aβ causes NFTs, for example Aβ-IP3K-GSK-3β pathway acts as a possibility. NFTs are formed from tau proteins that are abnormally hyperphosphorylated. There are various proteins that are responsible for the phosphorylation of tau, among them glycogen synthase kinase-3β (GSK-3β) is extensively studied, which could potentially act as a link between Aβ and NFTs. Another protein called phosphoinositide-3 kinase (PI-3K) acts as an inhibitory protein for GSK-3β. This is concluded from a study using in vitro rat hippocampal neurons, where it is found that the inactivation of PI-3 by wortmannin treatments induces GSK-3β activation [21]. The same study also showed that Aβ exposure inhibits PI-3 kinase activity just like wortmannin [21]. This suggests that abnormally high level of Aβ in AD patient can cause overactivation of GSK-3β by chronically inhibiting IP3K kinase, which leads to hyperphosphorylation of tau proteins. Although this mechanism is proposed based on in vitro rat neurons, its validity in human is supported by another study that found significant increase in the level of GSK-3β activity in AD patients [22]. Fundamentally, this serves as a possible mechanism underlying Aβ-NFTs relationship.

3.3 Aβ and Excitotoxicity

Excitotoxicity is defined as the overstimulation of NMDA receptors on the postsynaptic neuron, which causes damage to the neuron and is accompanied with excessive influx of calcium ions.

There are many studies shows that Aβ can bind directly to NMDA receptors to induce excitotoxicity. For example, a study using hippocampal neuron culture has found that amyloid oligomer can act as an agonist that binds NMDA receptors possibly at the extracellular Nterminal domain on the NR1 subunit and causes excessive influx of calcium ions [23]. The reason behind this idea is that in the experiment, an addition of 300 nM of amyloid oligomers to the cell culture induced a transient increase, about 3.5 folds, in the intracellular calcium level compared with the control. When an antibody that specifically blocks the N-terminal on NR1 is added to the culture in the presence of amyloid oligomer, the effect of amyloid oligomer is significantly reduced [23].

3.4 NFTs and Cholinergic Depletion

The action of tau oligomers has been demonstrated by numerous studies, and prominently, one of them is mitochondrial dysfunction. Mitochondria constantly undergo a cycle of fusion and fission in any given cell, where fission results fragments of mitochondria, and fusion results elongated mitochondria through the merging of fragments. These processes are collectively known as mitochondria dynamic, which is responsible for the size, morphology, function, and distribution of mitochondria [24]. DRP1 is a cytoplasmic protein that activates mitochondrial fission when it is translocated and incorporated to mitochondrial surface via mitochondrial receptors [24]; mitochondrial fission is inhibited when DRP1 activity is disrupted, resulting abnormally elongated mitochondria. Filamentous actin (F-actin) has a major role in mitochondrial dynamic. Although F-actin is commonly found in muscle cells, it also takes place in dendrites, where it acts as an important cytoskeletal component [25]. Study using fruit flies has found that increased F-actin stabilization (the increase in polymerization, bundling, and crosslinking of F-actin, resulting enlarged dendritic spine structure [26]) could cause mitochondrial elongation, where the DRP1 proteins failed to bind with mitochondrial surface [27-29]. Another study using fruit flies have shown that increasing the amount of tau could increase actin stabilization both in vitro and in vivo, and when tau are removed through immunodepletion, no actin stabilization was observed [30]. Combining the two experiments, since F-actin stabilization causes abnormal mitochondrial elongation, and tau proteins cause the stabilization of F-actin, therefore tau protein could indirectly cause abnormal mitochondrial elongation. To link mitochondrial elongation with cholinergic depletion, it should be noted that elongated mitochondria is a dysfunction [27]. Several studies have reported that mitochondrial dysfunction caused by tau could lead to reduction in mitochondria-dependent proteins, including pyruvate dehydrogenase [31]. Pyruvate dehydrogenase is an enzyme found inside the matrix of mitochondria; its primary function is to convert pyruvate into acetyl-coA. Acetyl-coA is needed in cytoplasm for the synthesis of acetylcholine, catalysed by acetyltransferase. In sum, it can be concluded that hyperphosphorylated tau proteins cause F-actin stabilization, which causes abnormally elongated mitochondria by disrupting the activity of DRP1, the dysfunctional mitochondria in turn produces less acetylcholine, causing cholinergic depletion. This pathway could act as a potential mechanism for the causal relationship between tau protein and cholinergic depletion.

3.5 NFTs and Excitotoxicity

Tau has been widely reported as the causative agent of excitotoxicity in AD, but the exact mechanism remains uncertain [32-35].

Several studies have been done demonstrating that pathological tau can cause excitotoxicity mediated by extrasynaptic NMDA receptors (NMDAR). One study using mice has shown that genetically induced pathological tau can cause overactivation of extrasynaptic NR2B-containing NMDAR. In the study, different receptor inhibitors were given to in vitro neuron cultures where NFTs are present, which are nifedipine (blocking L-type voltage-gated calcium channel), tetrodotoxin (blocking sodium channels), and so on. Out of all the drugs, only ifenprodil (blocking NR2B unit on NMDAR) has significantly reduced calcium influx. Since tau causes excess calcium influx, and only blocking extrasynaptic NR2B-containing NMDAR decreases the influx, it is concluded that the excitotoxicity by tau is mediated by extrasynaptic NR2B-containing NMDAR [32]; that the source of excess calcium influx is NR2B-containing NMDAR. The mechanism by which tau causes NR2B-containing NMDAR to be overactivated is through excessive glutamate. NR2B-containing NMDAR is activated by excess glutamate [36]. The same study has found that the there is a significant increase in the level of extracellular glutamate (~45% relatively to control) when missorted tau is present in the slice culture [32]. In addition, another study using mouse model showed that missorted tau is correlated with a significant increase in vGLUT and a decrease in GLT-1 [37]. vGLUT is a transporter located on presynaptic neuron membrane that transports glutamate into neuron, while GLT-1 is located on nearby glia that removes glutamate from the extracellular space once glutamate is used [37]. In conclusion, pathological tau may cause excitotoxicity by increasing vGLUT and decreasing GLT-1, which increases extracellular glutamate level by decreasing its clearance; the excessive glutamate then overactivates extrasynaptic NR2B-containing NMDAR, causing excess influx of calcium.

3.6 Excitotoxicity and NFTs

The causal relationship between NFTs and excitotoxicity is likely to be bidirectional, where excitotoxicity can in turn cause the formation NFTs, forming a positive feedback loop. The study using kainic acid (KA) injection on mouse has demonstrated that glutamate-induced excitotoxicity can cause hyperphosphorylation of tau [38]. KA is an agonist that binds to kainite receptor, which is a glutamatergic receptor like NMDA and AMPA receptors. The KA injection in the experiment directly induces excitotoxicity [38]. The effect of KD injection on tau has two phases; the first phase (0-6 hours after KA injection) is marked with a short-term decrease in hyperphosphorylation of tau, and the second phase (6-10 hours after KA injection) involves rapid rephosphorylation of tau, where the phosphorylation level significantly exceeds the control [38]. The activities of protein kinase and phosphatase were monitored during the experiment, and it was concluded that the dephosphorylation of tau in the first phase is due to activation of PP2A (a phosphatase that dephosphorylates tau [39]), while the hyperphosphorylation in the second phase is due to activation of cdk5 (a kinase that phosphorylates tau [40]) and inhibition of PP2A [38]. On the other hand, the other kinases such as GSK-3β, PKA, and CaMKII do not have much contribution to the two-phase changes of tau phosphorylation [38]. In summary, excitotoxicity mediated by glutamatergic receptor may cause the formation of NFTs by first activating PP2A to induce dephosphorylation of tau, and then activates cdk5 and inhibits PP2A to cause hyperphosphorylation of tau, which forms NFTs.

4. CONCLUSION AND DISCUSSION

4.1 Pathological Pathway

Summarizing the interaction between amyloid plaques, NFTs, cholinergic depletion, and excitotoxicity, a pathological pathway can be established (Figure 1); when amyloid is present, it acts as the upstream molecule whose primary role is to initiate all the downstream activities. In the downstream, it is likely that there is a positive feedback loop mechanism between the NFTs and excitotoxicity, where they amplify each other. If this was the case, even if amyloid plaques were removed from the brain, the activities of NFTs, excitotoxicity, and cholinergic depletion will still be maintained. However, it is still unknown which one of the activities is the principle causative agent; it could be any one of them or more than one.

4.2 Hypothesis Testing

To test the hypothesis, the amyloid plaques would have to be removed from the brain to isolate the downstream molecules. In other words, the procedure would have to be an extension of the clinical trial done in 2019 that falsified amyloid plaque cascade hypothesis. However, since human trials are time-consuming and costly, the removal of amyloid plaque can be done in animals. When amyloid plaques are removed, two conditions must be met in order for the pathological pathway to be true: 1. removing excitotoxicity causes subsequent elimination of both NFTs and cholinergic depletion, also accompanied by the termination of AD; 2. removing NFTs causes subsequent elimination of both excitotoxicity and cholinergic depletion, also accompanied by the termination of AD.

5. COUNTER-ARGUMENT

In the beginning, 3 assumptions were made. If either one of the assumptions is proved to be false, then the entire pathological pathway would be false. Even if the assumptions were true, the scope of this study is small, there are many other processes not taken into consideration, such as neuroinflammation, apolipoprotein gene, and so on. In addition, the molecules in the pathological pathways may have other actions which are not covered, for example there are studies

shown that GSK-3β could interact with excitotoxicity, which would alter the pathological pathway if taken into consideration. Therefore, the possibility of hypothesis being true is extremely small, but it is never zero until experiment is carried out. The pathological pathway can be seen in Figure 1.

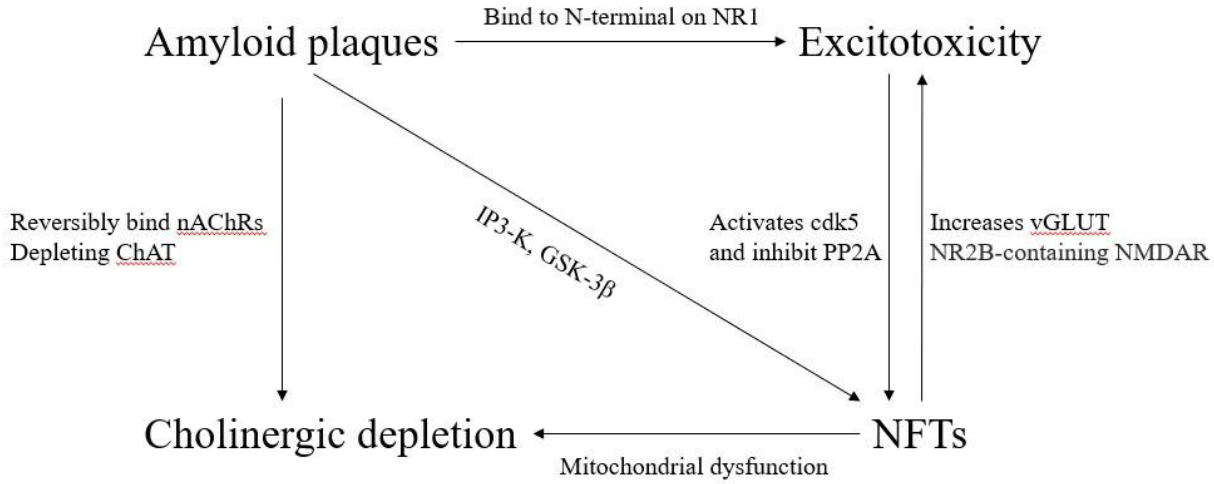

Figure 1 The Pathological Pathway

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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