Alzheimer's Disease: The Effects of APP, Presenilin and ApoE4

Frank Lee
eMail: frank@geon.us
Website: http://www.geon.us

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Abstract

Down syndrome is a genetic disorder caused by the presence of three copies of chromosome 21 where the *APP* gene (encoding amyloid precursor protein) is located. Down patients are prone to develop Alzheimer's disease (AD). Apolipoprotein E (ApoE) is the principal cholesterol carrier in the brain. It can have three major variants: ApoE2, ApoE3 and ApoE4. ApoE4 has been found to increase the risk for AD. Presenilin mutations are the major cause of familial AD. Earlier experimental findings appear to support the Amyloid Cascade Hypothesis which posits that AD is initiated by amyloid beta peptide (Aβ). However, recent studies have revealed new roles of APP, presenilin and ApoE4. APP plays a crucial role in normal synaptic functions. Its expression is regulated by its own intracellular domain, AICD. The extra *APP* gene, and thus excess AICD, in Down patients may result in neuronal hyperexcitability (Paper 7), thereby increasing the risk for AD. ApoE4 has been demonstrated to reduce the level of brain-derived neurotrophic factor (BDNF) and presenilin mutants can aggravate Ca^{2+} overload by stimulating IP_3 receptors. These observations are consistent with the BDNF Cascade Hypothesis presented in Paper 4 and Paper 6.

Introduction

In rare cases (< 5%), Alzheimer's disease (AD) is caused by genetic mutations in one of three genes: *APP*, *PSEN1* and *PSEN2*, encoding amyloid precursor protein (APP), presenilin 1 (PS1) and presenilin 2 (PS2), respectively. Individuals with these inherited mutations may develop AD early in life; often in their 50s for APP mutations, and 40s for presenilin mutations (Selkoe, 2001). This type of AD is called **familial AD** or **early-onset AD**. In most cases, AD is not associated with these mutations and usually begins after 60. This type of AD is referred to as **sporadic AD** or **late-onset AD**.

Apolipoprotein E (ApoE) is the principal cholesterol carrier in the brain. It can have three major variants: ApoE2, ApoE3 and ApoE4. ApoE4 has been found to increase the risk for

AD. How ApoE4 and the mutations in APP and presenilin predispose to AD is a subject of intensive research. The Amyloid Cascade Hypothesis (Hardy and Higgins, 1992; Selkoe and Hardy, 2016) centers on their relationship with the amyloid beta peptide (Aβ). This hypothesis appears to gain support from earlier experimental findings. However, recent studies have revealed new roles of APP, presenilin and ApoE4. This paper will focus on Aβ-independent mechanisms.

Amyloid Precursor Protein

AD patients with APP mutations are very rare. Only about two dozen cases have been reported (Selkoe, 2001). These mutations are located around the cleavage sites for α-, β-, and γ-secretases (Paper 7), suggesting that the APP fragments resulting from proteolytic processing at these sites may play a role in AD. It has been found that most of the mutations lead to higher $A\beta_{42}$ level (Weggen and Beher, 2012). This finding serves as important basis for the Amyloid Cascade Hypothesis.

The pathogenic APP mutations also change the level of APP intracellular domain (AICD) (Kim et al., 2003; Wiley et al., 2005; Weggen and Beher, 2012). As discussed in Paper 7, AICD may enhance excitability via Ankyrin-G and GSK-3. In addition, AICD regulates the expression of APP (von Rotz et al., 2004), which has been demonstrated to play a crucial role in synaptic functions (Klevanski et al., 2015; Ludewig and Korte, 2017). Therefore, either higher or lower level of AICD may have detrimental effects on synaptic functions.

Down syndrome is a genetic disorder caused by the presence of three copies of chromosome 21 where the *APP* gene is located. The extra copy of *APP* gene will produce larger amount of APP, and through proteolytic processing, higher level of Aβ. Down patients are prone to develop AD. This fact has inspired the Amyloid Cascade Hypothesis (Selkoe and Hardy, 2016). However, the proteolytic processing of extra APP also results in elevated AICD which may cause AD-like features (Ghosal et al., 2009), as well as seizures (Vogt et al., 2011). Incidentally, Down syndrome is known to associate with seizures (Lott et al., 2012).

Presenilin

Presenilin is the catalytic subunit of the γ-secretase complex involved in the production of Aβ and AICD from APP (Paper 7). Earlier studies found that the pathogenic mutations in presenilin increased Aβ (Selkoe, 2001). However, in a recent study which analyzed the effects of 138 pathogenic mutations on the catalytic ability of presenilin to produce Aβ,

only 13 mutations increased Aβ while all others decreased both $A\beta_{42}$ and $A\beta_{40}$. Furthermore, the $A\beta_{42}/A\beta_{40}$ ratios show no statistically significant correlation with the mean age at onset for the corresponding mutations (Sun et al., 2017). This raises the possibility that the presenilin mutations may predispose to AD via a mechanism independent of γ-secretase function.

In a seminal work, Cheung et al. (2008) demonstrated that presenilin mutants could bind with the inositol trisphosphate receptor (IP_3R), thereby enhancing Ca^{2+} release from the endoplasmic reticulum. This discovery was substantiated by a follow-up study (Cheung et al., 2010), and corroborated by the finding that reduced IP_3R expression rescued aberrant hippocampal long-term potentiation in PS1M146V knock-in mice (Shilling et al., 2014). Hence, presenilin mutations may exacerbate AD by elevating cytosolic Ca^{2+} concentration. This mechanism supports the hypothesis that AD is fundamentally caused by Ca^{2+} overload (Paper 6).

ApoE4

The ability of ApoE4 to clear Aβ from the brain appears to be less than other isoforms (Castellano et al., 2011). This report was used to support the Amyloid Cascade Hypothesis. On the other hand, several lines of evidence suggest that ApoE4 may reduce the level of brain-derived neurotrophic factor (BDNF), thereby enhancing excitability and Ca^{2+} overload.

- ApoE4 carriers have significantly lower serum BDNF levels than non-ApoE4 carriers (Liu et al., 2015).
- Physical exercise normally upregulate BDNF, but this capacity is impaired in elderly African Americans with ApoE4 (Allard et al., 2017).
- Combination of ApoE4 and high carbohydrate diet reduces hippocampal BDNF (Maioli et al., 2012).
- ApoE4, together with Aβ oligomers, reduce BDNF expression (Sen et al., 2015).
- In AD patients, apathy and ApoE4 are associated with reduced BDNF level (Alvarez et al., 2014).
- ApoE4 is linked to epilepsy (Aboud et al., 2013).
- Neurotoxic effects of ApoE4 are mediated via dysregulation of calcium homeostasis (Veinbergs et al., 2002).

These observations are consistent with the BDNF Cascade Hypothesis presented in Paper 4 and Paper 6. The following section is a brief summary highlighting the effects of genetic disorders.

The BDNF Cascade Hypothesis

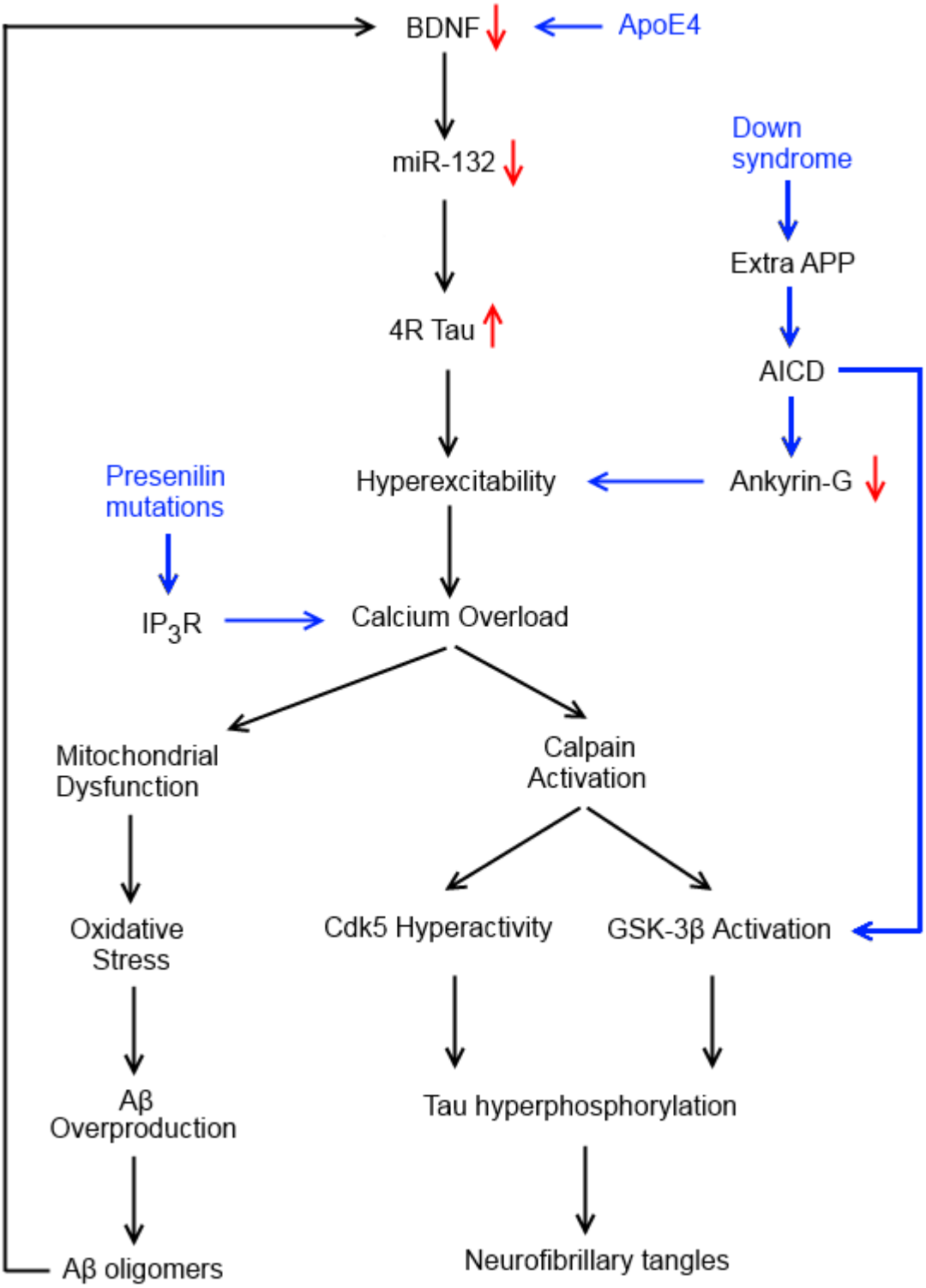

Figure 1. The BDNF Cascade Hypothesis, highlighting the effects of genetic disorders. ApoE4 reduces BDNF, Down syndrome increases excitability via AICD, and presenilin mutations aggravate Ca^{2+} overload by stimulating IP_3

receptors. Black arrows: main pathogenic cascade; blue arrows: pathways induced by genetic disorders; red arrows: up or down regulation.

According to the BDNF Cascade Hypothesis, neurodegenerative disorders are fundamentally caused by Ca^{2+} overload, which is initiated by BDNF deficiency, leading to neuronal hyperexcitability. Various neurodegenerative disorders differentiate at the neurons that exhibit hyperexcitability and Ca^{2+} overload. AD begins in the entorhinal cortex (EC) for two possible reasons. (1) The stellate cells of EC layer II are intrinsically very excitable. They regularly display subthreshold oscillations such that minimal elevation (1-3 mV) of membrane potential is sufficient to generate spikes (Alonso and Klink, 1993). (2) The expression of Tau proteins is almost twice as great in EC than elsewhere in the brain (Shukla and Bridges, 1999).

Each component in the main pathogenic cascade may be influenced by other factors. For instance, ApoE4 and Aβ oligomers may reduce BDNF level, AICD may enhance excitability and presenilin mutations can aggravate Ca^{2+} overload. The Ca^{2+} overload could lead to oxidative stress by disrupting mitochondrial functions (Peng and Jou, 2010). Numerous studies have demonstrated that oxidative stress promotes the production of Aβ (Oda et al., 2010; Zhao and Zhao, 2013; Arimon et al., 2015), which may aggregate to form Aβ oligomers and plaques.

From Figure 1, we see that there is a loop from BDNF deficiency to the production of Aβ oligomers which in turn can reduce BDNF level (Peng et al., 2009; Xia et al., 2017). Therefore, on the basis of this cascade alone, AD might originate from Aβ. However, by considering other experimental findings, this possibility can be ruled out. AD is known to begin in EC, but postmortem studies have shown that Aβ deposits appear first in neocortex (Thal et al., 2002). Recent PET studies on living people also suggest that Tau tangles, but not amyloid-β plaques, correlate with cognition and clinical symptoms (Tosun et al., 2017). In accelerated-senescence nontransgenic rats, named OXYS rats, Aβ deposits occur later than synapse loss, neuronal death, mitochondrial abnormalities, and Tau hyperphosphorylation (Stefanova et al., 2015). Moreover, Aβ oligomers are not the only factor that can cause BDNF deficiency. Other abnormalities may also reduce BDNF level, such as glucocorticoid elevation (Suri and Vaidya, 2013; Wosiski-Kuhn et al., 2014), estrogen deficiency (Carbone and Handa, 2013) and melatonin deficiency (Imbesi et al., 2008; Zhang et al., 2013; Rudnitskaya et al., 2015). Hence, drugs targeting Aβ alone will not halt disease progression via other pathogenic pathways. This explains why "clinical trials with Aβ therapies, including immunotherapy, have thus far failed to show any reduction in neurofibrillary pathology or improvement in cognitive performance of patients with AD" (Dai et al., 2017).