Alzheimer's Disease: The Role of AICD and Aβ in Excitability

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Abstract

In the transgenic mouse models that overexpress amyloid precursor protein (APP) and/or presenilin, neuronal excitability increases at the early stage. Since the overexpression produces higher level of amyloid beta (Aβ) peptides and APP intracellular domain (AICD), the hyperexcitability could arise from AICD and/or Aβ. Their underlying mechanisms are explored in this paper. AICD has been shown to act as a transcription factor, which may regulate the expression of miR-342-5p, the microRNA that suppresses the expression of Ankyrin-G. Hence, higher AICD level is expected to reduce the production of Ankyrin-G, thereby enhancing excitability (see Paper 2). Extracellular Aβ oligomers may facilitate internalization of AMPA receptors, resulting in lower excitability, but the internalized Aβ could activate GSK-3 to enhance excitability. These findings suggest that the early hyperactivity is more likely to arise from AICD than Aβ.

Introduction

Elevated neuronal activity is an early sign of Alzheimer's disease (AD) (Dickerson et al., 2005; Putcha et al., 2011; Bakker et al., 2012; Vossel et al., 2013). Early neuronal hyperactivity has also been observed in the mouse models that overexpress amyloid precursor protein (APP) and/or presenilin with mutations found in familial AD (Busche et al., 2012; Xu et al., 2015; Bezzina et al., 2015). APP is a large transmembrane protein, containing three cleavage sites for α-, β-, and γ-secretases, respectively. Cleavage by the α-secretase produces a soluble APP fragment α (sAPPα) and a carboxy-terminal α fragment (CTFα). The β-secretase splits APP into sAPPβ and CTFβ. Subsequent cleavage of CTFβ by the γ-secretase generates the amyloid beta (Aβ) peptide and APP intracellular domain (AICD) (Figure 1).

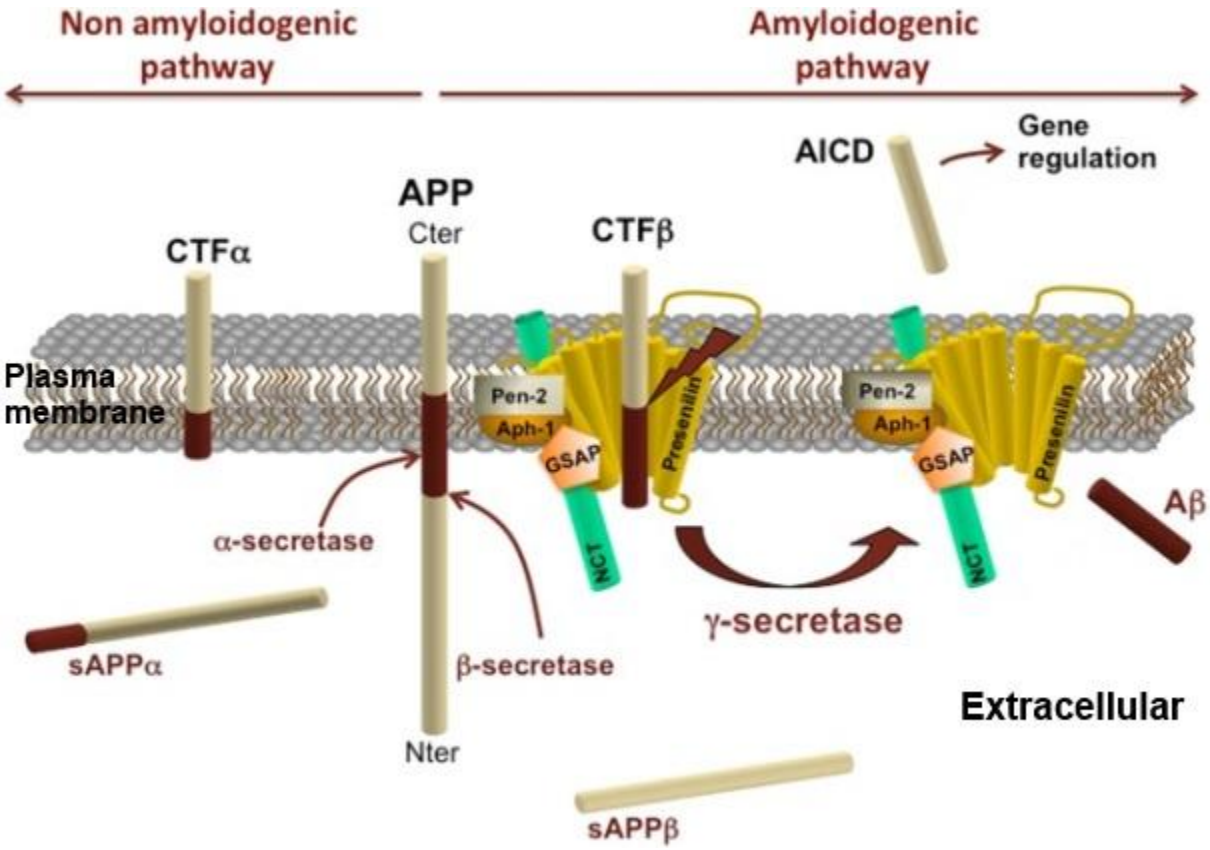

Figure 1. Schematic representation of APP processing by α-, β-, and γ-secretases. Presenilin is the catalytic subunit of the γ-secretase complex, which also includes nicastrin (NCT), γ-secretase activating protein (GSAP), pen-2, and aph-1. [Source: Vingtdeux et al., 2012]

The γ-secretase lacks sequence specificity. Its cleavage site may shift slightly, resulting in different lenghth of the Aβ peptide, which may vary between 40 and 42 amino acid residues. According to the Amyloid Cascade Hypothesis (Hardy and Higgins, 1992; Selkoe and Hardy, 2016), Aβ, especially $A\beta_{42}$, is crucial for the initiation of AD. However, recent studies suggest that AICD could make an important contribution to the onset of AD by enhancing neuronal excitability and Tau phosphorylation (Ghosal et al., 2009; Vogt et al., 2011; Ghosal et al., 2016).

AICD May Enhance Excitability Via Ankyrin-G and GSK-3

Over the last two decades, many studies has revealed an important function of AICD in the cell: regulation of gene transcription (Nhan et al., 2015; Multhaup et al., 2015). This function requires the protein Fe65 to stabilize AICD within the nucleus (Cao and Südhof, 2001). More than a dozen target genes have been discovered, including *APP* and *BACE1* (β-secretase) (Pardossi-Piquard and Checler, 2012). Recently, it has

been shown that AICD also regulates microRNA transcription (Shu et al., 2015). The following evidence suggests that AICD could regulate miR-342-5p, which in turn targets Ankyrin-G (Figure 2).

In the transgenic mouse models that overexpress APP and/or mutant presenilin, the microRNA miR-342-5p was upregulated (Sun et al., 2014). The major function of a microRNA is to suppress the translation of its target mRNA. It was found that the increased miR-342-5p downregulates the expression of Ankyrin-G. Very interestingly, Ankyrin-G has been proposed to play a critical role in excitability by anchoring microtubules to the plasma membrane at the axon initial segment. Downregulation of Ankyrin-G should reduce the number of anchoring points, thereby increasing excitability (Paper 2). This may contribute to the hyperexcitability observed in APP/presenilin transgenic mice (Busche et al., 2012; Xu et al., 2015; Bezzina et al., 2015).

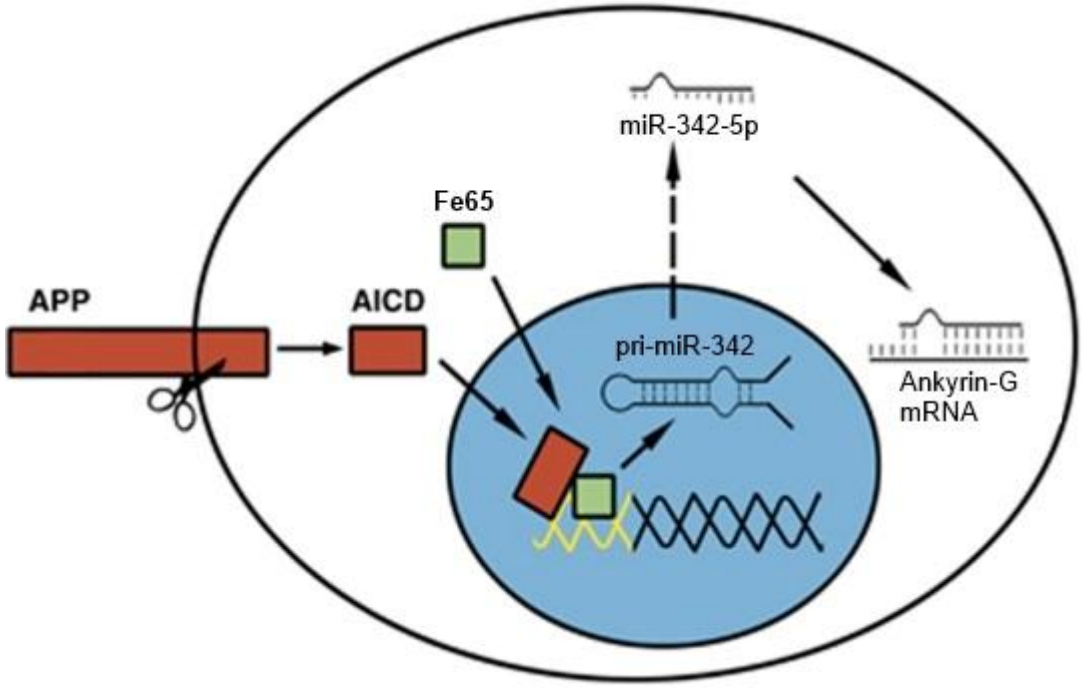

Figure 2. The proposed function of AICD as a transcription factor regulating the expression of miR-342-5p, which may suppress the translation of Ankyrin-G. [Adapted from: Shu et al., 2015]

Hyperexcitability may induce excess Ca^{2+} influx through various voltage-gated calcium channels. The elevated intracellular Ca^{2+} level could impair mitochondrial function, resulting in oxidative stress (Peng and Jou, 2010). Numerous studies have

revealed that oxidative stress may augment the production and aggregation of Aβ (Zhao and Zhao, 2013; Arimon et al., 2015). Therefore, hyperexcitability can cause not only the Tau pathology described in Paper 6, but also Aβ pathology. In agreement with the notion that Ankyrin-G could modulate excitability, active vaccination with Ankyrin-G has been demonstrated to reduce the Aβ pathology in APP transgenic mice (Santuccione et al., 2013).

Ca^{2+} overload could also activate calpain to promote GSK-3 activity (Paper 6), which is likely to enhance excitability (see GSK-3, Valproic Acid and Epilepsy). In addition to this indirect mechanism, AICD may associate with GSK-3 and directly promote its activity (Zhou et al., 2012). Hence, elevated AICD level should enhance excitability, in line with the observations from AICD transgenic mice (Ghosal et al., 2016).

Modulation of Excitability by Aβ

It has been well established that elevated Aβ level may cause internalization of AMPA receptors (AMPARs), resulting in long-term depression (Hsieh et al., 2006; Tu et al., 2014; Guntupalli et al., 2016), which is a manifestation of reduced excitability (Yun et al., 2006). However, there are also reports that Aβ increases excitability (Ren et al., 2014; Tamagnini et al., 2015; Scala et al., 2015; Wang et al., 2016). To make things more complex, another study found that low and high doses of $Aβ_{42}$ have different effects on excitability: low dose(1 nM) attenuates excitability whereas high dose (500 nM) initially reduced excitability but later enhanced excitability (Wang et al., 2009). These apparently conflicting reports could be reconciled by the following Aβ-induced pathways.

The extracellular Aβ oligomer has been shown to bind with α7 nicotinic acetylcholine receptors (α7-AChR) in the presynaptic axon terminal, resulting in the release of glutamate, which may activate synaptic NMDA receptors (sNMDARs) in the postsynaptic neuron, leading to increased Ca^{2+} concentration. Alternatively, the Aβ oligomer may also bind with α7-AChR in the glial cell (astrocyte and microglia), which then release glutamate to activate extrasynaptic NMDA receptors (eNMDARs). This pathway also increases Ca^{2+} concentration (Tu et al., 2014). Ca^{2+} elevation via the NMDA receptors is known to induce either long-term potentiation (LTP) or long-term depression (LTD), depending on stimulation patterns (Dudek and Bear, 1992). As noted above, stimulation by Aβ has been demonstrated to cause LTD. This could be due to the activation of calcineurin and/or protein

phosphatase 1 (PP1) (Knobloch et al., 2007), resulting in dephosphorylation of AMPARs at Ser-845, which facilitates AMPAR endocytosis (Ehlers, 2000).

In principle, calcineurin and/or PP1 could dephosphorylate and activate GSK-3. However, in the study of Zempel et al. (2010), the Aβ-induced Ca^{2+} elevation did not activate GSK-3. Rather, other kinase activities (e.g., MARK) were enhanced. MARK may phosphorylate the Tau protein at Ser-262, -293, -324, and -356, resulting in Tau missorting to dendrites and microtubule disruption (Drewes et al., 1997). It is important to note that the enhanced kinase activities by extracellular Aβ oligomers do not phosphorylate Tau at Ser-396 (Zempel et al., 2010), which is critical for AMPAR internalization (Regan et al., 2015) and subsequent degradation. The AMPARs which are internalized through a process dependent on Ca^{2+} and protein phosphatases (e.g., calcineurin and PP1) can readily be re-inserted into the membrane, but the process independent of Ca^{2+} and phosphatases will lead to AMPAR degradation (Ehlers, 2000). Therefore, the aforementioned pathway toward AMPAR endocytosis simply facilitates LTD and reduces excitability. It has minimal toxicity to the neuron. By contrast, the pathway discussed below may cause AMPAR degradation because it does not involve Ca^{2+} or phosphatases.

Extracellular Aβ could be internalized through a number of mechanisms (Mohamed and Posse de Chaves, 2011). The intracellular Aβ may activate caspase-3 to cleave Akt (Scala et al., 2015; Jo et al., 2011; Lee et al., 2009), which is a major negative regulator of GSK-3. Cleavage of Akt will activate GSK-3, leading to higher excitability via decreased potassium currents (Wildburger and Laezza, 2012), increased sodium currents (Shavkunov et al., 2013; Paul et al., 2016), or membrane insertion of AMPARs (Wei et al., 2010). The latter pathway is mediated by Rab5, a small GTPase controlling the transport from plasma membrane to early endosomes. On the other hand, GSK-3 can efficiently phosphorylate Tau at Ser-396 (Cavallini et al., 2013), which facilitates AMPAR internalization by enhancing the interaction between the GluA2 subunits of AMPARs with the protein interacting with C-kinase 1 (PICK1) (Regan et al., 2015). This Ca^{2+}- and phosphatase-independent internalization should lead to AMPAR degradation (Ehlers, 2000).

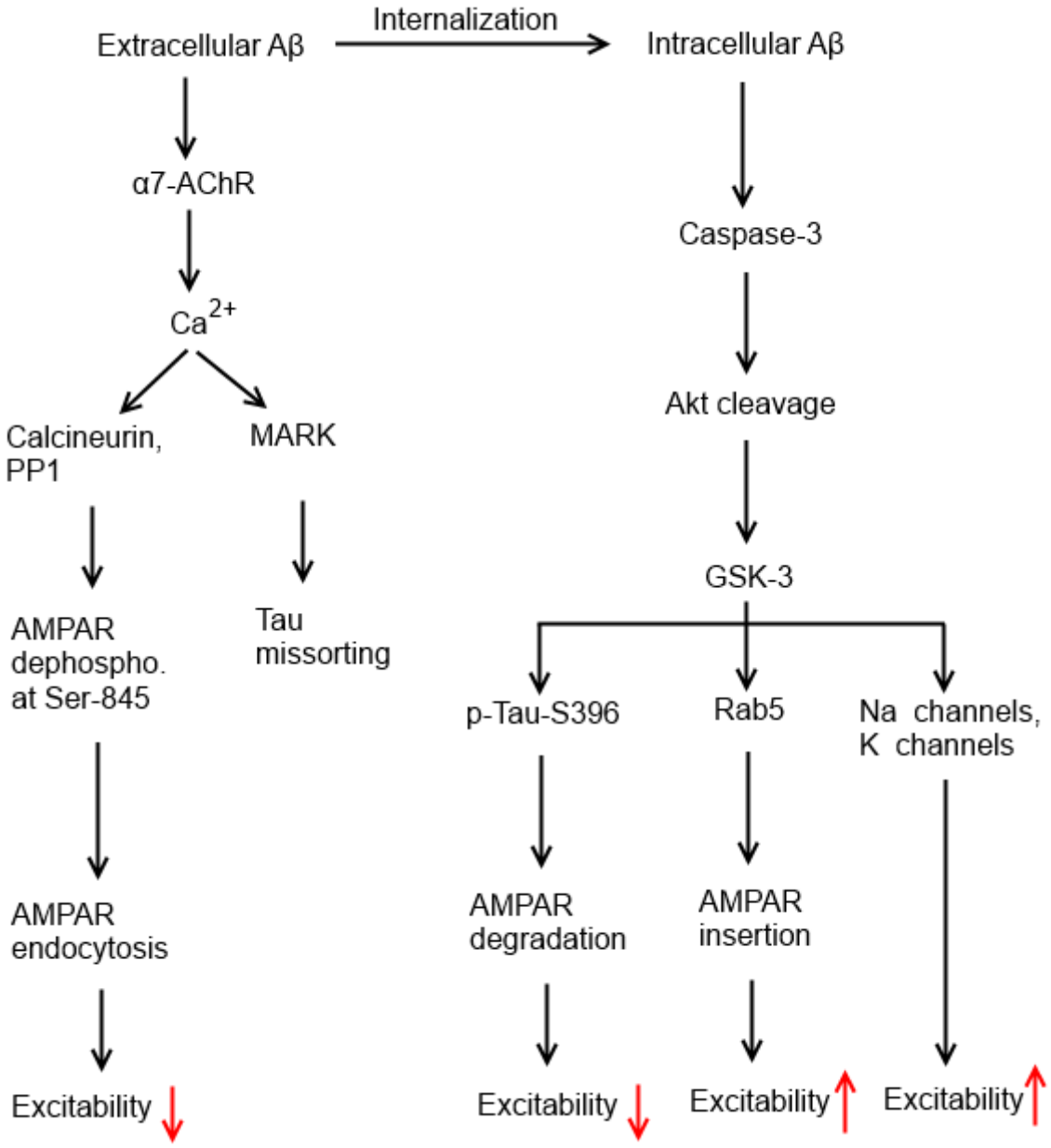

Figure 3. The proposed Aβ-induced pathways and their effects on excitability. In the pathway leading to AMPAR endocytosis, AMPARs are translocated to early endosomes where they may readily be re-inserted into the membrane. In the degradation pathway, AMPARs are targeted to late endosomes and lysosomes where they will be destroyed. Tau phosphorylation at serine 396 (p-Tau-S396) is crucial for inducing AMPAR degradation.

According to the above Aβ-induced pathways (Figure 3), low dose of extracellularly applied Aβ may not be internalized sufficiently to activate GSK-3, thus resulting in AMPAR endocytosis and reduced excitability. High extracellular

Aβ level also reduces excitability initially, until the internalized Aβ is sufficient to activate GSK-3. This could be the mechanism underlying the observations of Wang et al. (2009). In support of this mechanism, washout of Aβ has been found to reverse the effects on excitability by low dose Aβ, but not by high dose Aβ possibly because a significant portion of Aβ have been internalized.