



Review

The role of synaptic activity in the regulation of amyloid beta levels in Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is the most common form of dementia. Accumulation of amyloid-beta (A β) peptides is regarded as the critical component associated with AD pathogenesis, which is derived from the amyloid precursor protein (APP) cleavage. Recent studies suggest that synaptic activity is one of the most important factors that regulate A β levels. It has been found that synaptic activity facilitates APP internalization and influences APP cleavage. Glutamatergic, cholinergic, serotonergic, leptin, adrenergic, orexin, and gamma-amino butyric acid receptors, as well as the activity-regulated cytoskeleton-associated protein (Arc) are all involved in these processes. The present review summarizes the evidence for synaptic activity-modulated A β levels and the mechanisms underlying this regulation. Interestingly, the immediate early gene product Arc may also be the downstream signaling molecule of several receptors in the synaptic activity-modulated A β levels. Elucidating how A β levels are regulated by synaptic activity may provide new insights in both the understanding of the pathogenesis of AD and in the development of therapies to slow down the progression of AD.

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1. Introduction

Alzheimer's disease (AD) is the most common form of dementia, accounting for 50%–60% of all cases (Blennow et al., 2006). It affects approximately 35 million people worldwide (Selkoe, 2012), and the number of cases is expected to grow dramatically (Brookmeyer et al., 2011). The projected rate of rise is even greater in the developing world than in high-income countries, and the economic burden of AD is massive. Extracellular amyloid plaques in brain are the major pathologic features of AD patients, which are composed of misfolded amyloid peptides. The mutations in genes that affect metabolism of amyloid peptides are demonstrated to contribute to AD pathogenesis, including amyloid precursor protein (APP) (Goate et al., 1991) and presenilin (PS) genes (Sherrington et al., 1995) as well as apolipoprotein E (ApoE) genotype (Corder et al., 1993). Mutations in APP and PS genes lead to excessive amyloid-beta (A β) generation, while ApoE4 results in altered clearance and transport of A β , which may contribute to amyloid plaque deposit (Fryer et al., 2005; Rhinn et al., 2013) and also account for the vast majority of sporadic AD risk (Ashford,

2004; Raber et al., 2004). In addition, intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated microtubule-associated protein tau are the other pathologic features of AD. Intermediate aggregates of abnormal tau molecules are cytotoxic (Khlitunova et al., 2006), which also mediates A β toxicity in AD (Ittner et al., 2010) and may impair cognition (Oddo et al., 2006). Studies reported that blocking tau hyperphosphorylation may be sufficient to prevent the progression to dementia (Roberson et al., 2011). Moreover, all genetic causes and risk factors of AD can lead to the failure of neuroplasticity (Teter and Ashford, 2002), which may ultimately unleash the onset of clinical AD symptomology by disrupting the balance between degenerative and regenerative processes (Arendt, 2001; Mesulam, 2000).

Much evidence suggests accumulation of A β as a critical component of AD pathogenesis (Hardy and Selkoe, 2002; Shankar et al., 2008; Walsh et al., 2005), which is derived from excessive A β generation and reduced A β clearance (Hardy and Selkoe, 2002). Thus, studies begin to focus on the factors that influence A β generation or clearance. It has been demonstrated that synaptic activity is one of the most important factors that regulate A β levels, and increasing researches continue to elucidate this regulation (Brody et al., 2008; Cirrito et al., 2005; Kang et al., 2009). Cerebral trauma, sleep deprivation, epilepsy, and other factors have been demonstrated to influence A β levels in the interstitial fluid (ISF) (Johnson et al., 2010; Mackenzie and Miller, 1994; Roh et al., 2012).

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And all these factors are associated with changes in synaptic activity and possibly neuronal activity. Moreover, synaptic activity has been demonstrated to influence the proteolysis of APP and then regulate A β levels in AD brain (Brody et al., 2008; Cirrito et al., 2005; Tampellini and Gouras, 2010). Based on this, synaptic activity may be an available target for controlling A β levels with the aim of preventing excessive A β production, and the exploration of this phenomenon is of great significance.

In this review, we will firstly present the process of A β generation and A β toxicity in AD pathogenesis. Then we summarize the synaptic activity-modulated ISF A β levels under physiological or pathologic conditions. Evidence of in vitro and in vivo as well as human data will be presented. And the mechanisms involved in the synaptic activity-regulated ISF A β levels will be described in detail. Clathrin-mediated endocytosis of APP is necessary for the activity-regulated ISF A β levels (Carey et al., 2005). Additionally, glutamatergic, cholinergic, serotonergic, leptin, adrenergic, orexin, and GABAergic receptors play major roles in this regulation, and the immediate early gene product activity-regulated cytoskeleton-associated protein (Arc) will also be discussed.

2. An overview of the process of A β generation and A β toxicity

APP belongs to a protein family that includes APP-like protein 1 and 2 in mammals (Coulson et al., 2000; Wasco et al., 1992,

1993), all of which are type-I transmembrane proteins, and the A β domain is unique to the APP protein. On the cell surface, APP can be proteolyzed directly by α -secretase and then γ -secretase, a process that does not generate A β , or re-internalized in clathrin-coated pits into early and late endosomes that contain the proteases β -secretase and γ -secretase, which produces A β (Fig. 1) (Friele et al., 1987). The former is called non-amyloidogenic pathway, as α -secretase cuts APP within the A β region, A β generation is precluded. APP is firstly cleaved by α -secretase, yields the α -secretase-generated C-terminal APP fragment (C83; α -CTF) and N-terminal portion of APP (soluble APP- α ; sAPP- α) (Postina et al., 2004). Subsequently, α -CTF (C83) is further processed by the γ -secretase complex to generate APP intracellular domain (AICD) and p3 peptides (Mattson et al., 1993). The latter is called the amyloidogenic pathway, which is initiated by β -secretase, releasing a shortened β -secretase-generated C-terminal APP fragment (C99; β -CTF). The retained β -CTF (C99) is also a γ -secretase complex substrate, generating A β and AICD. The alpha and beta pathways are parts of 2 distinct normal, highly-active systems. The non-amyloidogenic pathway is found to be neurotrophic and neuroprotective (Mattson et al., 1993), while the amyloidogenic pathway may lead to synaptic loss (Grabrucker et al., 2011), as a complementary or balancing pathway, serving to destroy unneeded synapses. Moreover, a recent finding demonstrates that the AICD predominantly derives from β -CTF, which may contribute to early pathophysiological mechanisms of AD by

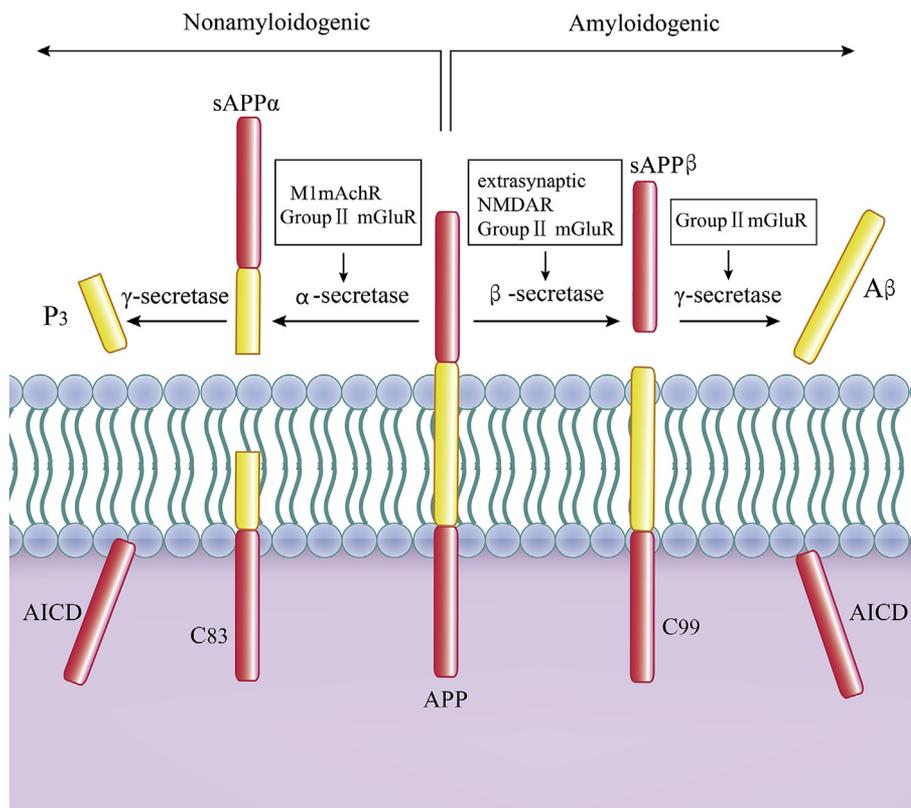


Fig. 1. Modulation of amyloid precursor protein (APP) processing by glutamatergic and cholinergic receptors. Cleavage of APP by α -secretase, which initiates nonamyloidogenic processing, generates the soluble amino-terminal ectodomain of APP (sAPP α) and the carboxy-terminal fragment C83. Subsequent cleavage of C83 by the γ -secretase complex yields the APP intracellular domain (AICD) and a short fragment termed p3. M1 muscarinic cholinergic receptors (M1 mAChRs) and group II metabotropic glutamate receptors (group II mGluRs) modulate α -secretase-mediated proteolysis (Caccamo et al., 2006; Kim et al., 2010). Alternatively, amyloidogenic processing is initiated by β -secretase, releasing a shortened sAPP β . The retained C99 is also a γ -secretase complex substrate, generating amyloid-beta (A β) and AICD. Extrasynaptic NMDA receptors (NMDARs) and the group II mGluRs have been shown to modulate β -secretase-mediated cleavage of APP (Bordji et al., 2010; Kim et al., 2010). Additionally, the group II mGluRs have also been shown to modulate γ -secretase-mediated cleavage of C99 but not C83 (Kim et al., 2010). Abbreviations: A β , amyloid-beta; AICD, APP intracellular domain; APP, amyloid precursor protein; mAChRs, muscarinic cholinergic receptors; mGluRs, metabotropic glutamate receptors; NMDARs, N-methyl-d-aspartate receptors; sAPP α , soluble amino-terminal ectodomain of APP.

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