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 (Aβ) 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 Aβ 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 Aβ 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 Aβ levels. Elucidating how Aβ 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.

1. Introduction

Alzheimer’s disease (AD) is the most common form of dementia, accounting for 50%–60% of all cases (Blinnlow 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 (Aβ) generation, while ApoE4 results in altered clearance and transport of Aβ, 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 (Khlistunova et al., 2006), which also mediates Aβ 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 Aβ as a critical component of AD pathogenesis (Hardy and Selkoe, 2002; Shankar et al., 2008; Walsh et al., 2005), which is derived from excessive Aβ generation and reduced Aβ clearance (Hardy and Selkoe, 2002). Thus, studies begin to focus on the factors that influence Aβ generation or clearance. It has been demonstrated that synaptic activity is one of the most important factors that regulate Aβ 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 Aβ levels in the interstitial fluid (ISF) (Johnson et al., 2010; Mackenzie and Miller, 1994; Roh et al., 2012).
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 Aβ 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 Aβ levels with the aim of preventing excessive Aβ production, and the exploration of this phenomenon is of great significance.

In this review, we will firstly present the process of Aβ generation and Aβ toxicity in AD pathogenesis. Then we summarize the synaptic activity-modulated ISF Aβ 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 Aβ levels will be described in detail. Clathrin-mediated endocytosis of APP is necessary for the activity-regulated ISF Aβ 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 Aβ generation and Aβ 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 Aβ 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 Aβ, or re-internalized in clathrin-coated pits into early and late endosomes that contain the proteases β-secretase and γ-secretase, which produces Aβ (Fig. 1) (Frielle et al., 1987). The former is called non-amyloidogenic pathway, as α-secretase cuts APP within the Aβ region, Aβ generation is precluded. APP is firstly cleaved by α-secretase, yielding 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 Aβ 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
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