frontiers in
AGING NEUROSCIENCE

REVIEW ARTICLE
published: 21 May 2010
doi: 10.3389/fnagi.2010.00013

Synapses, synaptic activity and intraneuronal Aβ in Alzheimer's disease

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β-Amyloid peptide accumulation plays a central role in the pathogenesis of Alzheimer's disease. Aberrant β-amyloid buildup in the brain has been shown to be present both in the extracellular space and within neurons. Synapses are important targets of β-amyloid, and alterations in synapses better correlate with cognitive impairment than amyloid plaques or neurofibrillary tangles. The link between β-amyloid and synapses became even tighter when it was discovered that β-amyloid accumulates within synapses and that synaptic activity modulates β-amyloid secretion. Currently, a central question in Alzheimer's disease research is what role synaptic activity plays in the disease process, and how specifically β-amyloid is involved in the synaptic dysfunction that characterizes the disease.

Keywords: Alzheimer disease, amyloid, amyloid precursor protein, synapse, synaptic plasticity, neprilysin, neuron, neurodegeneration

Synapses are considered the earliest site of pathology, and synaptic loss is the best pathological correlate of cognitive impairment in Alzheimer's disease (AD) (Hamos et al., 1989; DeKosky and Scheff, 1990; Terry et al., 1991; Selkoe, 2002; Coleman and Yao, 2003). Toxic effects of extracellular β-amyloid (Aβ) on synapses have been known for many years. Synapses and neurites are also frequently damaged near Aβ plaques (Dong et al., 2007; Meyer-Luehmann et al., 2009). The first direct association between Aβ peptide and synapse pathologies in the brain was provided by immunoelectron microscopy (IEM); this showed that aberrant Aβ42 accumulation within distal neurites and synapses was directly associated with pathology (Takahashi et al., 2002). Emerging studies have provided very interesting evidence that synaptic activity modulates Aβ homeostasis. Increased synaptic activation enhanced, while inhibition reduced, secretion of Aβ in cultured hippocampal slices and mouse brains (Kamenetz et al., 2003; Cirrito et al., 2005; Cirrito et al., 2008). These were important discoveries and appeared to fit the scenario that brain areas with the highest synaptic activity, including hippocampus and entorhinal cortex, are among the most vulnerable to early AD pathology (Buckner et al., 2005). Extracellular Aβ is known to reduce synaptic plasticity, and alter synaptic function, structure and protein levels in AD model systems (Selkoe, 2002; Trinchese et al., 2004a; Almeida et al., 2005; Snyder et al., 2005; Hsieh et al., 2006; Shankar et al., 2008; Deshpande et al., 2009). Therefore, increased secretion of Aβ induced by synaptic activity could lead to damage and loss of synapses and to progressive accumulation of extracellular Aβ into amyloid plaques, which are important hallmarks of AD. From this point of view, synaptic activity could be detrimental and contribute to AD pathogenesis. In fact, aberrant hyperexcitability is present in brains of AD transgenic mice (Palop et al., 2007; Busche et al., 2008), which could increase activity-induced release of Aβ and thereby aggravate pathology. Moreover, cerebral Aβ deposition is increased in human epilepsy (Mackenzie and Miller, 1994) and seizures are increased in human AD (Palop et al., 2007).

Increased cognitive activity is also able to increase Aβ secretion, since recovery of cognitive function after brain injury correlates with increased levels of extracellular Aβ in human brain (Brody et al., 2008). Levels of Aβ in the interstitial fluid have been shown to follow the circadian rhythm, being elevated when awake and reduced when asleep (Kang et al., 2009). These observations support that Aβ secretion could be a physiologic event occurring with normal brain activity. With activity-induced secretion, the concentration of extracellular Aβ remains in the picomolar range *in vitro* as well as *in vivo* (Cirrito et al., 2003; Trinchese et al., 2004b). It can be hypothesized that at this low concentration extracellular Aβ might be nontoxic. Indeed, recent studies reported that picomolar concentrations of Aβ enhanced synaptic plasticity and memory (Puzzo et al., 2008; Garcia-Osta and Alberini, 2009).

Another set of studies supports the idea that cognitive activity may be protective against AD. Higher educational level or involvement in mentally stimulating activities correlated with a lower probability of developing AD (Stern, 2006). Experiments on environmental enrichment in AD transgenic mice demonstrated reduced plaque deposition and up-regulation of genes involved in memory formation and Aβ degradation (Lazarov et al., 2005). Moreover, recent cell biological studies provided evidence that synaptic activation reduces levels of intraneuronal Aβ and protects synapses in models of AD, despite a concomitant increase in Aβ secretion (Tampellini et al., 2009). Next to the well known presence of extracellular Aβ as plaques, AD pathology also includes a pool of Aβ accumulating within neurons (Gouras et al., 2000; D'Andrea et al., 2001; Gyure et al., 2001; Wirths et al., 2001; Mori et al., 2002; Oddo et al., 2003; Cataldo et al., 2004), which is increasingly considered to play a

critical role in the disease (Gouras et al., 2005; LaFerla et al., 2007; Bayer and Wirths, 2010). Accumulation and oligomerization of Aβ42, the most pathologic Aβ isoform, occurs progressively within distal neurites and synaptic compartments, and is directly associated with subcellular pathology (Takahashi et al., 2002, 2004) and with alterations of synaptic proteins (Almeida et al., 2005). Furthermore, intraneuronal Aβ accumulation is associated with the pre-plaque onset of physiological and behavioral abnormalities in AD transgenic models (Oddo et al., 2003; Echeverria et al., 2004; Billings et al., 2005; Cruz et al., 2006; Knobloch et al., 2007; Lord et al., 2009). Clearance of intraneuronal Aβ by treatment with Aβ antibodies protected synapses (Tampellini et al., 2007) and correlated with memory improvement (Billings et al., 2005). Overall, cumulative evidence support a scenario where progressive accumulation of intraneuronal Aβ42 becomes extracellular not by secretion but rather following degeneration of neurites and synapses. Release of this intraneuronal Aβ42 into the extracellular space may then result in an abnormally high concentration of extracellular Aβ42, potentially leading to toxic spread of Aβ pathology to surrounding synapses (**Figure 1**). Given the emerging evidence of declining extracellular Aβ42 levels in cerebrospinal fluid (CSF) in patients as the earliest harbinger for the subsequent development of AD (Fagan et al., 2009), one can now even hypothesize that AD is characterized by decreased Aβ42 secretion as Aβ42 accumulates inside neurons.

It is important to note that the extra- and intracellular pools of Aβ are related, although their relationship is complex and they can influence each other (Yang et al., 1999; Oddo et al., 2006; Tampellini et al., 2009). Intraneuronal Aβ accumulation begins before plaques (Gouras et al., 2000; Wirths et al., 2001; Mori et al., 2002; Oddo et al., 2003), and, after clearance by Aβ immunotherapy, reappears prior to plaques (Oddo et al., 2004). How specifically extracellular Aβ is toxic to neurons and synapses remains poorly understood, but appears to occur via APP and potentially intraneuronal Aβ. Addition of extracellular Aβ1–42 markedly increased intracellular Aβ (Yang et al., 1999; Tampellini et al., 2009). The role and extent of Aβ internalization from the extracellular space remain less clear (Yang et al., 1999; Saavedra et al., 2007; Kandimalla et al., 2009). Yang et al. (1999) showed minimal internalization of labeled Aβ1–42, whereas adding of unlabeled Aβ1–42 lead to a marked up-regulation of newly generated intracellular Aβ42. Extracellular Aβ1–42 was shown to induce cell death in wild type neurons but not in neurons lacking APP (Lorenzo et al., 2000) or in cells where the NPXY motif of APP was mutated (Shaked et al., 2006). Moreover, extracellular Aβ1–42 is unable to reduce levels of synaptic proteins in APP knockout neurons or when it is applied together with a γ-secretase inhibitor (Tampellini et al., 2009). Overall, these data suggest that extracellular Aβ1–42 synapto-toxicity requires γ-secretase cleavage of APP and also intraneuronal Aβ42 accumulation.

The precise molecular and cellular mechanism(s) whereby synaptic activity modulates Aβ and then Aβ first alters synapses are of major interest. The reduction of intracellular Aβ with synaptic activation is partially due to secretion of intracellular Aβ to the extracellular space (Tampellini et al., 2009). Aβ degradation is also involved in the reduction of the intraneuronal pool during activity. Synaptic activity failed to reduce the intraneuronal pool of Aβ42 in the presence of the neprilysin inhibitor thiorphan or in neprilysin knockout neurons. These data implicate neprilysin in the degradation of the most disease-linked Aβ isoform with activity. In contrast, levels of intraneuronal Aβ40 were still decreased, although to a lesser extent, with thiorphan treatment or in neprilysin knockout neurons, during synaptic activity (Tampellini et al., 2009). This might be explained by Aβ40 being more soluble and more abundantly secreted than Aβ42 (Kamenetz et al., 2003). The reduction of intraneuronal Aβ with synaptic activity, which correlated with synaptic improvement, supports the hypothesis that synaptic activity may also be protective in AD pathogenesis. Currently, AD patients are encouraged to increase their mental and social activities. We hypothesize that under physiological conditions of synaptic activity both extra- and intracellular pools of Aβ are efficiently cleared, but then with aging and other AD risk factors (e.g. apolipoprotein Eε4), Aβ clearance mechanisms become impaired. It is of considerable interest that levels of neprilysin have been reported to decrease with aging (Iwata et al., 2002; Apelt et al., 2003). Because nepri-

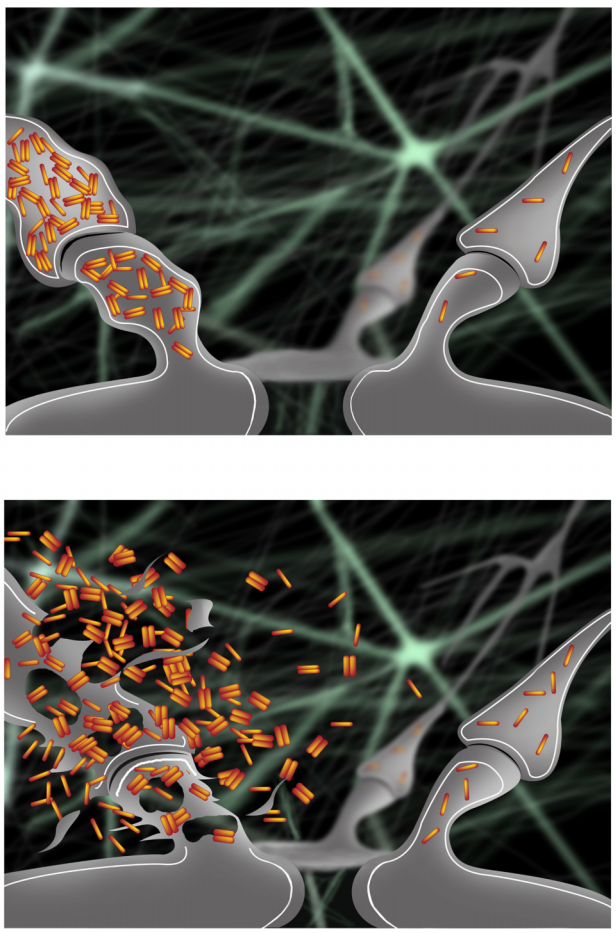

FIGURE 1 | (A) Accumulation of intraneuronal Aβ42 at early stages of AD occurs progressively in a synapse (left) and is associated with pathological alterations compared to a normal synapse (right). **(B)** Intraneuronal Aβ42 is released in the extracellular space following degeneration of the synapse (left). Release of intraneuronal Aβ42 into the extracellular space may contribute to the toxic spread of Aβ pathology to a nearby synapse (right).

lysin localizes to synapses (Fukami et al., 2002), its age-dependent decline could explain the progressive synaptic accumulation of Aβ42 (Takahashi et al., 2002, 2004, 2008).

With synaptic activation, APP is anterogradely transported to synapses, followed by internalization and amyloidogenic processing at active synapses (Tampellini et al., 2009). The effect of synaptic activity on transport in neurites of protein cargoes is not uniform (Perestenko and Henley, 2003; Bingol and Schuman, 2006; Cai et al., 2007; Kang et al., 2008). The synaptic activity-dependent increase of APP anterograde transport and β-cleavage support that Aβ production is locally enhanced at activated synapses (Cirrito et al., 2008; Tampellini et al., 2009). How Aβ starts to accumulate at synapses and contributes to pathogenesis remains unclear. The role of aging should not be underestimated in promoting AD pathogenesis. Mitochondrial dysfunction and oxidative stress, as well as reduced cellular degradation, appear to be important contributors to the neurobiology of aging. In fact, it was reported that elevated oxidative stress promoted Aβ pathology in AD transgenic mice (Li et al., 2004). On the other hand, once Aβ accumulation begins with aging, it is unclear how Aβ then contributes to progression of synaptic dysfunction. Cumulative data over the past two decades support that APP is trafficked via the Golgi apparatus to the plasma membrane where α-secretase cleavage can occur and thereby preclude Aβ formation. An additional pool of APP is re-internalized from the plasma membrane and then processed to Aβ peptides in endosomes (Rajendran et al., 2008; Thinakaran and Koo, 2008), followed by secretion of predominantly Aβ40 peptides. Evidence supports that relatively higher amounts of the more hydrophobic, aggregation-prone and AD-linked Aβ42 is retained within endosomes. It is this pool of Aβ42 that prominently accumulates and then oligomerizes with aging in distal neurites and synapses in the brain with AD pathogenesis (Takahashi et al., 2002, 2004). At a basic level it would appear that aberrant Aβ42 accumulation in endosomes near synapses might be central to early synaptic dysfunction in AD. Indeed, Aβ accumulating primary neurons derived from APP-transgenic mice compared to wild type neurons were shown to have Aβ-dependent endocytic abnormalities specifically in the multivesicular body (MVB) sorting pathway but not in the internalization or recycling pathways (Almeida et al., 2006). Recent work has shown that intraneuronal Aβ can also be pathogenic to mitochondria. Because of the critical role that mitochondria play in cells in general, and particularly at active synapses where they are abundant, Aβ effects on mitochondria may be critical for the pathogenesis of AD (Lin and Beal, 2006; Chen and Yan, 2007; Reddy, 2009). The pathogenic pathway from aberrant Aβ accumulation to synaptic damage likely includes altered signaling pathways, cellular ionic imbalance, and emerging apoptosis pathways at synapses that remain to be determined.

Elucidating the molecular and cellular mechanisms by which synaptic activity and Aβ homeostasis affect each other may provide new insights both in understanding the pathogenesis of AD and for the development of new therapies.

ACKNOWLEDGMENTS

The support of an Alzheimer's Association New Investigator Award (D. Tampellini) and Zenith Award (G.K. Gouras), and National Institute of Health grants AG027140 and AG028174 (G.K. Gouras). We thank Mr. Matteo Tampellini for the preparation of the schematic figures.

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Conflict of Interest Statement: The authors declare that they have no commercial or financial relationship that could be construed as a potential conflict of interest.

Received: 08 January 2010; paper pending published: 16 February 2010; accepted: 12 March 2010; published online: 21 May 2010.

Citation: Tampellini D and Gouras GK (2010) Synapses, synaptic activity and intraneuronal Aβ in Alzheimer's disease. Front. Ag. Neurosci. ***2****:13. doi: 10.3389/fnagi.2010.00013*