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How do soluble oligomers of amyloid β-protein impair hippocampal synaptic plasticity?

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A commentary on

Soluble oligomers of amyloid β-protein facilitate hippocampal long-term depression by disrupting neuronal glutamate uptake
by Li, S., Hong, S., Shepardson, N.E., Walsh, D.M., Shankar, G.M., Selkoe, D. Neuron 2009; 62, 788–801.

Alzheimer's disease (AD), the most common neurodegenerative disorder, is characterized by progressive memory and cognitive impairment and the cerebral accumulation of extracellular amyloid plaques and intraneuronal neurofibrillary tangles. A principal neuropathological finding in AD subjects is cortical atrophy associated with degeneration of neurites, decreased dendritic spine density and frank neuronal loss (Terry et al., 1991; Knobloch and Mansuy, 2008). Although the specific molecular initiators of the AD process remain unknown in most patients, biochemical studies indicate that the severity of cognitive impairment in AD correlates more strongly with the cortical levels of soluble amyloid β-protein (Aβ assemblies than with the burden of insoluble amyloid plaques (Lue et al., 1999; McLean et al., 1999; Shankar et al., 2008). Extensive experimental work on hippocampal plasticity has indicated that the induction of long-term synaptic depression (LTD) results in decreased dendritic spine volume or outright elimination of spines (Matsuzaki et al., 2004; Nägerl et al., 2004; Zhou et al., 2004), changes which may parallel molecular and structural aspects of synaptic failure in AD. Therefore, understanding how Aβ impairs hippocampal synaptic function at the molecular level could enable the development of specific neuroprotective therapies for AD.

Studies from numerous laboratories have now established that soluble Aβ oligomers can inhibit long-term potentiation (LTP), or the strengthening of synapses, in the hippocampus. But heretofore, only a few studies have examined the effects of Aβ on the induction of LTD, and those few have yielded inconsistent results. For example, synthetic Aβ peptides were reported to potently enable the induction of LTD in CA1 in an NMDAR-dependent manner *in vivo* (Kim et al., 2001; Cheng et al., 2009), whereas other studies found no effect on LTD in slices (Wang et al., 2002, 2004; Raymond et al., 2003). To address this problem, we recently extracted buffer-soluble Aβ oligomers directly from the brains of typical AD patients and demonstrated that these species can facilitate LTD induction in hippocampal slices of wild-type mice (Shankar et al., 2008). While the induction of both LTP and LTD requires glutamatergic transmission, the direction in which synaptic strength is modulated by the specific class of glutamate receptor that is activated, the kinetics of cytosolic calcium concentration, and the initiation of intracellular signaling cascades. Specifically, we found that LTD induction was facilitated by pathophysiologically relevant low concentrations of soluble Aβ oligomers through activation of either NMDA receptors or metabotropic glutamate receptors (mGluRs), depending on the electrical stimulation protocol used to induce the LTD (Li et al., 2009). Given that several prior studies, including our own, have already shown that Aβ has little or no effect on presynaptic neurotransmitter release probability (e.g., Townsend et al., 2006; Shankar et al., 2008; Cheng et al., 2009), we hypothesized that the Aβ oligomers alter synaptic glutamate concentration by disrupting glutamate transport mechanisms. In the current study, we report that pharmacologically blocking glutamate uptake closely recapitulates the effects of Aβ on LTD induction, suggesting that Aβ oligomers bias towards synapse weakening in part through such a mechanism (Li et al., 2009).

A growing number of reports indicate that glutamate transporters are disturbed in AD (Masliah et al., 1996). The levels of transporters such as GLAST/EAAT1 and GLT-1/EAAT2 are reduced in postmortem AD brain tissue and in APP transgenic mice (Maragakis et al., 2004; Jacob et al., 2007). Synthetic Aβ (at supraphysiological concentrations) has been shown to inhibit glutamate uptake in cultured neurons and astrocytes (Harris et al., 1996; Harkany et al., 2000; Fernández-Tomé et al., 2004) and in oocytes (Gu et al., 2004). Although most glutamate transporters are located on astrocytes, reduced neuronal expression of EAAT1 was also suggested to be an early marker of neuronal dysfunction in AD, preceding or occurring on a similar timeline to the expression of hyper-phosphorylated tau protein in the same neurons of AD brains (Scott et al., 2002). Interestingly, it was demonstrated recently that detergent insoluble EAAC1/EAAT3 transporters accumulate aberrantly in hippocampus in AD subjects (Duerson et al., 2009). Taken together, these various reports suggest that neuronal and/or glial glutamate uptake may be interrupted in AD.

Glutamate transporters play the important role of regulating concentrations of glutamate in the extracellular space, keeping it at low levels. Without normal activity of glutamate transporters, glutamate would accumulate to cytotoxic levels and could contribute to progressive neuronal loss in AD (Pomara et al., 1992; Harkany et al., 2000). Early AD studies focused on frank Aβ-enhanced excitotoxicity mediated through glutamate receptors, especially NMDA receptors (Greenamyre and Young, 1989; Mattson et al., 1992; Hynd et al., 2004). However, the perturbations in extracellular glutamate levels resulting from altered transport kinetics could even be responsible for the more subtle ultrastructural alterations noted in AD, such as dendritic spine loss. *In vivo* microdialysis recently revealed that soluble Aβ oligomers secreted by APP-transfected cells, when microinjected into wild-type rat brain, can

significantly increase the hippocampal levels of extracellular glutamate but not GABA or aspartate (O'Shea et al., 2008). Inhibition of glutamate uptake by the pharmacological agent TBOA has been shown to increase spontaneous epileptiform discharges, and this increased excitability can be blocked by the NMDA antagonist, AP5 (Campbell and Hablitz, 2004). In our current study, we found that the effects of Aβ oligomers in facilitating LTD in hippocampal slices were very similar to those of TBOA (Li et al., 2009). Interestingly, Aβ accumulation *in vivo* has been found to significantly increase spontaneous nonconvulsive seizure activity in cortical and hippocampal networks in APP transgenic mice (Palop et al., 2007). In the context of these various studies, our new findings that soluble Aβ oligomers can facilitate the induction of LTD through both an mGluR pathway (300-pulse stimulation protocol) and a NMDAR pathway (900-pulse stimulation protocol) and that this LTD induction is mimicked by the effect of TBOA suggest that a common upstream element, the neuronal glutamate transporter, is misregulated by diffusible Aβ oligomers.

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