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Perspectives on Treatment of Alzheimer's Disease: A Closer Look into EphB2 Depletion

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Review of Shi et al.

Alzheimer's disease (AD) is characterized by massive synaptic loss, leading to dementia. This loss is thought to be caused primarily by small, soluble oligomers of amyloid β (Aβ), a protein that aggregates and forms large plaques in the AD brain. These oligomers, called Aβ-derived diffusible ligands (ADDLs), attach to dendritic spines of excitatory synapses, alter spine morphology, and decrease spine density (Lacor et al., 2007). ADDLs rapidly reduce surface expression of NMDA receptors (NMDARs) and ephrin type-B receptor 2 (EphB2), both of which are involved in synaptic plasticity and long-term potentiation (LTP). Several studies indicate that an ADDL-mediated EphB2 depletion may be the basis of cognitive dysfunction in AD. For example, in APP transgenic mice, overexpressing EphB2 can restore its levels in the synapse as well as rescue cognitive deficits (Cissé et al., 2011).

ADDLs bind directly to the fibronectin binding domain (FN) of EphB2, which leads to a decrease in EphB2 levels through proteasomal degradation (Cissé et al., 2011). In a recent publication in *The Journal of Neuroscience*, Shi et al. (2016) first confirmed that treating cultured hippocampal neurons with synthetic ADDLs reduced the surface expression of the NMDAR subunit GluN2B, as well as the surface and total expression of EphB2. Shi et al. (2016) then identified four peptide sequences of the FN domain that ADDLs interacted with. Finally, they synthesized peptides corresponding to these domains and tested the ability of these peptides to interfere with binding between ADDLs and EphB2. Pep63 was the most effective in blocking this interaction.

Next, Shi et al. (2016) examined the ability of Pep63 to block the effects of ADDLs on hippocampal neurons. In cell culture, the ADDL-induced decrease in surface expression of GluN2B and EphB2 were rescued by Pep63. In addition, *in vivo* expression of GluN2B and Eph2B were rescued by Pep63 treatment of APP/PS1 transgenic mice, which express mutated AD-linked proteins and normally develop cognitive impairment. Finally, Pep63 rescued cognitive deficits in APP/PS1.

Shi et al. (2016) show that EphB2 is an ADDL receptor. How ADDLs cause NMDAR internalization still remains unclear, but it has been found that EphB2 colocalizes with NMDARs (Calò et al., 2006; Cissé et al., 2011). Moreover, it has been found that EphB2 increases Ca^{2+} influx through clustering of NMDARs and thus influences the activation of downstream transcription factors involved in LTP formation (Takasu et al., 2002). Shi et al. (2016) found that ADDLs induced the depletion of GluN2B-containing NMDARs while GluN2A-containing NMDARs were unaffected. Although GluN2B subunits are expressed throughout life starting at embryonic development, they are slowly but progressively replaced by GluN2A with age. GluN2B-containing NMDARs specifically keep playing an important role in memory, synaptic plasticity, and LTP induction (Yashiro and Philpot, 2008). The depletion of this NMDAR subtype due to ADDLs may contribute to the mechanism behind memory impairment seen in AD (Yashiro and Philpot, 2008).

In addition to impairing synaptic function by causing internalization of NMDARs, EphB2 depletion may provide a connection between Aβ and hyperphosphorylated tau, another protein that characteristically accumulates in AD. The amount of tau aggregates are correlated to some extent with neuronal loss in AD (Gómez-Isla et al., 1997). It has recently been shown that EphB2 stimulation can attenuate tau phosphorylation via a Pi3K/Akt-mediated inhibition of GSK-3β, a kinase implicated in tau hyperphosphorylation (Jiang et al., 2015). Because EphB2 has been shown to mediate dephosphorylation of tau, EphB2 depletion may increase hyperphosphorylation of tau, subsequent tangle formation, and thus the microtubule instability seen in individuals with AD.

ADDL-interfering peptides like Pep63 may prove to be a promising strategy for

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AD treatment. Indeed, many research groups are attempting to identify treatments for AD by looking for short synthetic peptides designed to bind to specific Aβ regions and neutralize or interfere with the pathological properties of oligomeric Aβ species. Some time ago, Granic et al. (2010) showed that an anti-amyloid peptide (LPYFDa) can preserve memory by reverting Aβ oligomer-induced learning deficits in mice. More recently, Suzuki et al. (2016) screened drugs approved for clinical use in humans for compounds that selectively inhibit the binding of Aβ oligomers to EphB2. They have found four compounds that may be safe and effective drugs for the treatment of AD, therefore offering a potential therapeutic strategy for AD.

While the findings of the study by Shi et al. (2016) are promising, it must be remembered that the effect of the small peptide Pep63 was evaluated using transgenic mice. While these mice display cognitive deficits at an early stage, humans do not show cognitive decline until there is a large amount of Aβ accumulation in the brain (Serrano-Pozo et al., 2011). In addition, clinicopathological correlation studies have shown that the confirmation of AD diagnosis occurs when patients already have substantial and widespread synaptic and neuronal loss (Serrano-Pozo et al., 2011). Although Pep63 might be effective at preventing or treating the early stages of AD pathology, it might be ineffective in patients in whom there is already a large quantity of neuronal loss. Therefore, for this kind of peptide-based therapy to work, very early diagnosis is crucial.

Finally, issues that must be addressed in developing any drug for treating AD are administration and delivery. One promising approach, reported by Gregori et al. (2017), is the use of nanoliposomes decorated with small peptides that inhibit the formation of Aβ oligomers and fibrils. These nanosystems can cross an *in vitro* blood–brain barrier. Therefore, liposomes might successfully act as carriers for new inhibitor peptides. The effectiveness of these treatments might be increased by using multi-ligand-decorated nanoliposomes, which may more effectively recognize their molecular targets, like Aβ oligomers. An alternative strategy for delivery, reported by Born et al. (2002), is intranasal administration, which can deliver neuropeptides to the brain without uptake into the circulation.

In summary, Shi et al. (2016) have identified a potentially promising strategy for AD treatment. Blocking the interaction between EphB2 and ADDLs with Pep63, a small interfering peptide, can inhibit the mechanisms that underlie cognitive decline in AD. These mechanisms include reduced function of NMDAR and EphB2, which contribute to the impairment of LTP. EphB2 depletion may also increase tau hyperphosphorylation and accumulation, although further work is required to determine whether inhibiting ADDL-mediated EphB2 depletion affects tau phosphorylation state (Jiang et al., 2015). Despite the promise of this and similar treatments, an efficient means of administering these inhibitory peptides and advances in early diagnostics will be needed before they can become an effective treatment for AD patients.

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