COMMENTARY

Toward a unified therapeutics approach targeting putative amyloid-β oligomer receptors

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Cognitive decline in Alzheimer's disease (AD) is associated with synaptic loss (1) and network dysfunction (2). The mechanisms involved are not fully understood; however, recent evidence indicate that the neurotoxicity of amyloid-β (Aβ) oligomers is mediated by interactions with synaptic receptors (3). In PNAS, Fu et al. demonstrate that soluble Aβ oligomers trigger synaptic loss and dysfunction via activation of erythropoietin-producing hepatocellular A4 receptor (EphA4) (4). Remarkably, blockade of EphA4 reversed the functional deficits in the hippocampus in animal models of AD. Moreover, based on molecular docking studies, they identify rhynchophylline as a novel EphA4 inhibitor that, following oral administration, rescued the Aβ oligomer-induced deficits in neurotransmission in amyloid precursor protein (APP)/presenilin 1 (PS1) transgenic mice. In agreement with these findings, a recent study by Vargas et al. showed that Eph4 activation via c-Abl mediates the synaptic damage triggered by Aβ oligomers (5). Together, these studies point to EphA4 as a novel mediator of AD-associated synaptic dysfunction and support the notion that Aβ oligomer receptors might be viable therapeutic targets for this disease.

In recent years, several surface proteins were identified as putative Aβ oligomer receptors, including among others prion protein (PrP) (6), metabotropic glutamate receptor 5 (mGluR5) (7, 8), NMDA (9), α7-nicotinic acetylcholine receptor, insulin receptor, NGF receptor, Frizzled, and Wnt-3a (10) (Fig. 1). In the CNS, the Eph family of tyrosine kinase receptors has an important role in axonal guidance, synaptogenesis, and synaptic transmission (11). To date, 10 different subtypes of the EphA and 6 subtypes of EphB receptors have been identified.

Genome-wide association studies of late-onset AD showed increased susceptibility associated with SNPs at the EphA1 loci (12). Moreover, in AD patients, EphB2 is down-regulated, and rescue of the network dysfunction phenotype in AD-like tg mice was achieved by overexpression of this receptor in the hippocampus (13). In contrast, in AD and APP/Ps1 mice (4) EphA4 is up-regulated, and blocking this receptor genetically or pharmacologically ameliorated the synaptic alterations in AD-like tg mice.

The Eph family has been explored as a therapeutic target for cancer, nerve injury, Parkinson disease (PD), motor neuron disease (MND), arthritis, and reperfusion injury (11). EphA4 inhibitors are currently under consideration for the treatment of spinal cord injury because this promotes axonal outgrowth (14). Interestingly, EphA4, probably through interaction with EphB2 and EphB3, appears to have a role in blocking axonal regeneration after injury, and pharmacological inhibition of these interactions might promote functional recovery (11). For example, in models of spinal cord injury, blocking EphA4–ephrin interactions with antibodies (14) or small peptides (15) resulted in significant functional recovery.

The study by Fu et al. advances the field by identifying a novel EphA4 inhibitor, rhynchophylline, that reverses the synaptic deficits in AD-like models (4). It is of interest to consider that the beneficial effects of rhynchophylline might involve both Aβ-dependent and Aβ-independent mechanisms. Rhynchophylline's therapeutic mechanisms might be related to its ability to directly block the interaction between Aβ and EphA4, attenuate the activity of glutamate receptors and calcium channels (16), block downstream toxic signaling pathways such as c-Abl, or promote neurite outgrowth by coregulating EphB2 and EphB3 (11) (Fig. 1). The study by Fu et al. also underscores the potential therapeutic usefulness of rhynchophylline and related Eph4A inhibitors in the treatment of other neurological disorders such as PD, motor neuron disease, and nerve injury.

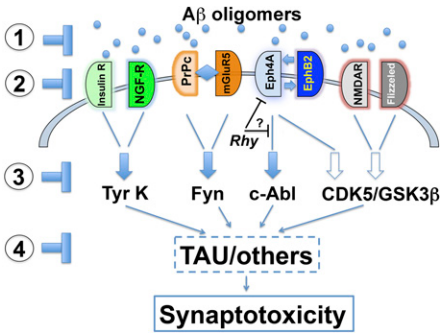

Fig. 1. Putative Aβ oligomer receptors, signaling pathways, and therapeutic targets. A number of potential cell surface molecules (insulin receptor, NGF receptor, PrPc, mGluR5, EphA4, EphB2, NMDA, and Flizzled) that mediate the synaptotoxic effects of Aβ oligomers have been identified. In general terms, they can be divided into those that signal via tyrosine kinase (tyr k, fyn, and c-Abl) and those that hyperactivate CDK5/glycogen synthase kinase (GSK)3β. Therapeutics for AD might involve (*1*) directly clearing Aβ oligomers, (*2*) blocking the surface receptors, (*3*) interfering with signaling pathways, or (*4*) decreasing downstream effectors such as Tau. The study by Fu et al. identifies rhynchophylline (Rhy) as an antagonist of EphA4. The mechanisms as to how this compound protects neurons from the toxic effects of Aβ are unclear; however, Rhy might directly block EphA4 or interfere with signaling.

In addition to EphA4, and because of the involvement of other surface molecules as putative Aβ oligomer receptors, recent studies have explored developing inhibitors to PrP (17), mGluR5, NMDA (9), α7-nicotinic acetylcholine receptor, p75, insulin receptor, and others (18) for the treatment of AD. The results of the study by Fu et al. might suggest that blocking just one of the putative receptors might be sufficient, at least in experimental models (4). However, it is likely that several of these receptors cross-talk, interact, and/or have a role at different stages during the progression of AD (Fig. 1). This suggests that a combined therapeutic approach targeting

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families of these potential oligomer receptors may be needed.

Given that blocking all of the oligomer receptors might be counterproductive, this raises an important, albeit difficult, question to answer: which groups of receptors to target simultaneously and/or in which sequence? One intriguing possibility is to consider compounds with multiple receptor tyrosine kinase inhibitory activity (Fig. 1). Here it is worth noting that several of the mediators of Aβ oligomer synaptotoxicity involve tyrosine kinase signaling; for example, EphA4 engages c-Abl (5), Prp/mGluR5 triggers Fyn (6), and the insulin and NGF receptors are well known to involve tyrosine kinase activation (Fig. 1). The other signaling pathways aberrantly stimulated by Aβ oligomers include cyclin-dependent kinase 5 (CDK5) and GSK3β (19) (Fig. 1). Interestingly, some tyrosine kinase inhibitors were shown to have multiple kinase modulatory activity that includes members of the CDK family (20). Because both tyrosine kinases and CDK5 are deregulated in AD, therapeutic strategies using compounds with dual activity targeting these pathways might be particularly advantageous. The papers by Fu et al. (4) and Vargas et al. (5) identify that one such target, EphA4, which is within the receptor tyrosine kinase family, might have downstream effects on CDK5, and when inhibited, ameliorated the deleterious effects of Aβ in various in vitro and in vivo models of AD (4).

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