NEURODEGENERATIVE DISEASE

Insights into synaptotoxicity in AD

Synapse loss is thought to be one of the main pathogenic events leading to dementia in Alzheimer disease (AD), but the mechanisms underlying this process are unclear. Two recent studies, published in *Brain*, provide new insights into the role of apolipoprotein E (Apo-E) and the synaptic adhesion molecule N-cadherin in synaptotoxicity mediated by amyloid- β (A β).

Tara Spires-Jones and colleagues previously demonstrated the presence of soluble A β in plaques, and showed its synaptotoxic effects, in mouse models of AD. “No one had conclusively proven whether there is soluble A β at synapses in the intact human brain,” she explains. “In this study, we used the same techniques in human AD and further asked if the isoforms of Apo-E are involved in A β -mediated synapse loss.”

Using an array tomography technique on brain sections immunostained for A β , synaptic proteins and Apo-E, the researchers identified oligomeric A β at synapses in patients with AD. “We observed synapse loss around plaques, which was exacerbated in patients with one or two copies of the *APOE* ϵ 4 allele,” says Spires-Jones. Colocalization of Apo-E and A β at the synapses was more common with the ϵ 4 protein isoform (Apo-E4) than with the ϵ 3 isoform (Apo-E3). *In vitro* studies indicated that Apo-E targets A β to the synapse in an isoform-graded manner (E4>E3). “For over two decades, we have not known why Apo-E4 increases the risk of developing AD,” states Spires-Jones. “This study links Apo-E4 with exacerbated synapse loss.”

In the second study, Kurt Gottmann and colleagues investigated the effects of synaptic instability in A β -mediated synapse destruction. “Synaptic cell adhesion molecules, such as N-cadherin, are well-known molecular players in the stabilization of synapses,” explains Gottmann. “However, the role of these molecules in synapse destabilization during progression of neurodegenerative diseases has hardly been addressed experimentally.”

Under physiological conditions, presynaptic and postsynaptic N-cadherin interact to maintain synaptic stability. The transmembrane N-cadherin protein is proteolytically cleaved to an ectodomain and C-terminal domain, known as NcadCTF1, which is processed by γ -secretase. AD-associated mutations in the presenilin gene are known to generate a hypofunctional form of γ -secretase, which causes accumulation of both A β and NcadCTF1. The researchers hypothesized that synapse destabilization via inhibition of N-cadherin might enhance, or accelerate, A β -mediated synaptic damage.

Using *in vitro* cultures, the team found that blockade of N-cadherin function by use of molecular inhibitors or dominant-negative N-cadherin accelerated the synaptotoxic effect of A β , observed as a reduction in postsynaptic signalling events. Overexpression of NcadCTF1 caused a similar enhancement of A β synaptotoxicity. Linking this process to human disease, examination of postmortem brain tissue revealed increased expression of NcadCTF1 in patients with AD compared with healthy controls.

“Our findings indicate that the enhanced presence of NcadCTF1 is not only an indicator of γ -secretase dysfunction, but also seems to be important in accelerating the synapse-damaging effect of A β ,” says Gottmann. This synergistic link between A β and N-cadherin also has implications for therapy in AD: the authors suggest that γ -secretase-based therapies that reduce A β ₄₂ production but retain the capacity to break down NcadCTF1 would be desirable.

These two studies provide insights into the mechanistic basis of A β -mediated synaptotoxicity in AD, but much work remains to be done. “In the near future, we will address whether C-terminal fragments that are generated by the processing of other synaptic adhesion molecules also have destabilizing effects, or whether this mechanism is specific for N-cadherin,” says Gottmann. Spires-Jones and colleagues aim to determine which synapses are vulnerable to loss in AD. “We are also examining if Apo-E2 can be protective against A β -induced synapse loss,” she says.

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Original articles Koffie, R. M. *et al.* Apolipoprotein E4 effects in Alzheimer's disease are mediated by synaptotoxic oligomeric amyloid- β . *Brain* doi:10.1093/brain/aww127 | Andreyeva, A. *et al.* C-terminal fragment of N-cadherin accelerates synapse destabilization by amyloid- β . *Brain* doi:10.1093/brain/aww120