ALZHEIMER DISEASE

EphB2 depletion links amyloid- β to cognitive impairment

Adapted from a figure provided by Dr Moustapha Cissé.

Depletion of the receptor tyrosine kinase EphB2 provides a link between amyloid- β (A β) accumulation and cognitive dysfunction in Alzheimer disease (AD), according to new research from the Gladstone Institutes in San Francisco.

“Past studies have found that both AD patients and mice with an AD-like condition have lower levels of *N*-methyl-D-aspartate (NMDA) receptors, which are involved in memory formation,” explains lead investigator Lennart Mucke. “Data from my laboratory and others established that A β triggers impairments of NMDA receptor function.”

Brains of patients with AD and related mouse models have decreased levels of EphB2, which is known to be a regulator of NMDA receptors. Mucke and his colleagues showed that A β oligomers bind to EphB2 *in vitro*, and that A β -induced EphB2 depletion is attributable to an increase in proteasome-mediated degradation of the latter protein.

Next, the researchers knocked down EphB2 expression in the dentate gyrus in nontransgenic mice. The animals exhibited long-term potentiation deficits similar to those seen in the human amyloid precursor protein (hAPP) mouse, a transgenic animal model of AD.

“What we were most curious about was whether normalizing EphB2 levels could fix memory problems caused by A β , and we were thrilled to discover that it did,” says Mucke. “Increasing EphB2 levels in the hippocampus of hAPP mice prevented their synaptic deficits, memory problems and behavioral abnormalities.”

Future research will address whether manipulation of EphB2 can provide a novel therapeutic approach for AD. One possibility might be to develop small molecules that block the interaction between A β and EphB2.

“Our study represents a step forward in understanding how memory loss may occur in AD, and hints at how that loss might be prevented or treated,” concludes Mucke.

Heather Wood

Original article Cissé, M. *et al.* Reversing EphB2 depletion rescues cognitive functions in Alzheimer model. *Nature* 469, 47–52 (2011)