Faculty Comments & Author Responses

Faculty Member
Karl Herrup
Rutgers University, United States of America, Neuroscience

Comments
This paper takes a novel comprehensive approach to teasing out the interactions between amyloid-beta (Abeta) and tau in the pathogenesis of Alzheimer’s disease and the antecedent loss of synaptic function. The work contains multiple new and valuable insights.

The authors use Sindbis virus to express tau in hippocampal slices taken from postnatal day 6-7 wild-type mice and mice carrying an amyloid precursor protein (APP) transgene (to model familial Alzheimer's disease). They examine pyramidal cell spine morphology and monitor cell survival. Their findings lead to several intriguing, but non-intuitive, conclusions. The APP transgene alone (with three AD mutations) is sufficient to impair spine properties, and this effect is dependent on N-methyl-D-aspartate receptor (NMDAR) function and glycogen synthase kinase 3beta (GSK-3beta). Infection of the neurons with wild-type tau has no effect on spine properties, but does induce neuronal cell loss. As with the spine properties, the cell loss is also dependent on NMDAR and GSK-3beta. Tau phosphorylation is required for this effect, but tau aggregation appears not to be a factor. Finally, while two common disease-causing tau mutants, P301L and R406W, both can induce cell loss in this system, the pharmacology suggests that they do so through two different pathways. Overall, both the experimental elegance of the work as well as the new and valuable insights in the cell death pathways of Abeta and tau make this a 'Must Read' paper.

Competing interests: None declared
Evaluated 24 Nov 2009

How to cite this evaluation