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Untangling Alzheimer's disease

RIKEN scientists have released findings that challenge common views underlying Alzheimer's disease, pointing the way for new therapeutic approaches.

A century after plaques and neurofibrillary tangles (NFTs) were first described as emblematic markers of Alzheimer's disease, scientists remain divided over which marker is more important in causing the disease. Now, in the latest issue of *The EMBO Journal*, scientists from RIKEN's Brain Science Institute led by Akihiko Takashima have stoked the debate by reporting that processes occurring before NFTs manifest themselves cause memory loss in mice.

Alzheimer's disease is often characterized as a protein misfolding disease, with the aggregation of aberrant forms of two protein players, amyloid beta (in senile plaques) and tau protein (in NFTs) suspected to be central to the process. Normal tau is a highly soluble protein expressed, in humans, mostly in the brain, where it binds to microtubules, structural proteins important in cells' cytoskeleton. The cytoskeleton is essential for normal cell function, providing cells with shape, support and the underlying machinery for intracellular transport. Tau regulates, orientates and stabilizes this critical network.

Tau's biological activity is intimately linked to its phosphorylation status, the overall number of phosphate groups enzymatically added or removed. Phosphorylation often causes proteins to change their structural conformation, and when tau is modified in this way, it becomes less soluble, starts assembling the masses of paired helical filaments constituting NFTs, and loses its ability to bind to microtubules. These abnormal, phosphorylated tau forms-which may derail cellular traffic, leading to cell function loss and neurodegeneration-are associated with diseases like Alzheimer's disease, collectively called tauopathies. Tau's role in neurodegenerative processes has gained more prominence with the recent discovery of a link between several types of dementia and mutations in the gene encoding the protein.

Frustratingly, studies utilizing mice genetically modified to express various mutant forms of human tau have failed to clarify the relationships between aging, memory impairment, neuronal loss and NFT formation. Indeed, some data suggest that deviant behavior can

occur independently of both NFTs and neuronal loss and that NFTs may not, on their own, be toxic. Moreover, Alzheimer's and other age-related neurodegenerative diseases do not involve genetic tau mutations. Therefore, Takashima's group chose to examine processes 'upstream' of NFT formation and neuronal death, using mice genetically engineered (Wtau-Tg) to express normal human tau protein.

To understand where and how tau-induced changes in behavior affect neuronal activity, the researchers first checked the performance of 'wild-type' and Wtau-Tg mice in a standard 'place-memory' test in which animals swimming in a water bath must remember the location of a flagged platform that provides escape from the water. These mice were then subjected to an enhanced MRI technique to identify active brain regions. As expected, the specific region in the brain essential for place-learning, the entorhinal-hippocampal circuit, was activated in all mice - wild-type adult and aged, as well as adult Wtau-Tg - showing normal learning performance. In contrast, only aged Wtau-Tg mice, which exhibited clear learning and memory impairments, displayed significant reductions in entorhinal cortex region activity.

Intriguingly, although these memory-deficient mice suffered loss of synapses (the junctions between connected neurons), there were no signs of neuronal loss, and the dysfunctional brain regions contained an intermediate aggregate form of hyperphosphorylated tau but no evidence of insoluble tau or amyloid beta aggregates. Takashima and colleagues hypothesize that this toxic intermediate tau aggregate induces neuronal dysfunction-and thus memory impairment-via synapse loss, in a process independent of neuronal loss and NFT formation.

Because the patterns of hyperphosphorylated tau accumulation in aged Wtau-tg mice parallel those in aged humans, the RIKEN group believes that these mice accurately model what happens in human age-related memory impairment and that future studies may lead to effective treatments for Alzheimer's disease and other tauopathies.

Original work:

Kimura, T., Yamashita, S., Fukuda, T., Park, J., Murayama, M., Mizoroki, T., Yoshiike, Y., Sahara, N. and Takashima, A. Hyperphosphorylated tau in parahippocampal cortex impairs place learning in aged mice expressing wild-type human tau. *The EMBO Journal*, published online on Nov. 14, (2007).



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