

POSTER PRESENTATION

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Abeta is prerequisite, but insufficient to cause tau phosphorylation *in vivo*: tau phosphorylation in APP mice by diabetes

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Background

Epidemiological studies suggest that diabetes mellitus increases the risk of onset of Alzheimer disease (AD). However, the underlying mechanisms have not been fully understood. Retrospective studies indicate that diabetes does not increase senile plaques. On the other hand, a Japanese cohort, Hisayama study suggested that insulin resistance in midlife increased the risk of development of senile plaques. Therefore, the aim of this study is to understand the mechanisms by which diabetes increase the risk of AD by dividing them into two phases; 1) before and 2) after the development of senile plaques.

Methods

1) To test whether insulin resistance increases Abeta accumulation in the brain, we fed wild-type mice with a high-fat diet and measured the levels of Abeta in the brain. 2) To investigate the effects of diabetes on AD, we further analyzed the phenotypes of APP+*ob/ob* mice [1], which showed the increased cerebral amyloid angiopathy and impaired insulin signaling, especially focusing on tau phosphorylation.

Results

1) Six months on a high fat diet increased Abeta40 in B6C mice brain. 2) 18 month old APP+*ob/ob* mice showed highly increased level of tau phosphorylation in the brain. Furthermore, a high fat diet increased plasma Abeta levels in APP/PS1 mice, but not in wild type mice.

Conclusion

Tau phosphorylation is increased by diabetes in APP mice, suggesting that Abeta is prerequisite, but insufficient to cause tau phosphorylation *in vivo*. Abeta accumulation, insulin signaling and tau phosphorylation might play essential roles in the pathological interaction between AD and diabetes [2]. Of note, a vicious cycle likely underlies the interaction between AD and diabetes. High fat diet-induced elevation of plasma Abeta level might be involved in this mutual pathological interaction between the diseases [3,4]. These results suggest that diabetes disrupts homeostasis against AD.

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