CAMD セミナー

（Center for Development of Advanced Medicine for Dementia ）

Evolution of pathological hallmarks of Alzheimer's disease in models of diabetes and obesity

Emmanuel PLANEL

Associate Professor

Université Laval, CHUL, Québec, Canada

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Hyperphosphorylated tau is the major component of paired helical filaments in neurofibrillary tangles found in Alzheimer's disease (AD) brains, and tau hyperphosphorylation is thought to be a critical event in the pathogenesis of the disease since it correlates with the degree of cognitive impairment in AD. Only a small proportion of AD is due to genetic variants, the large majority of cases is late onset and sporadic in origin. The cause of sporadic AD is likely to be multifactorial, with external factors interacting with biological or genetic susceptibilities to accelerate the manifestation of the disease.

Insulin resistance might be such factor, as there is data from epidemiological studies showing that diabetes mellitus (DM) is linked to an increased relative risk for AD. In addition, insulin has been shown to modulate tau phosphorylation *in vitro* and *in vivo*. Our results with induced (streptozotocin) or spontaneous (NOD mice) models of type 1 diabetes show that insulin deficiency can indeed modulate tau phosphorylation.

However, recent data have shown that tau hyperphosphorylation observed in type 2 diabetes mouse models might be due to obesity rather than to insulin resistance. Thus, to confirm these results, we compared the impact of obesity and insulin resistance in type 2 diabetes (T2DM) on tau pathology in mice. Therefore, we investigated tau phosphorylation and its mechanisms in two genetic mouse models of spontaneous type 2 diabetes that develop diabetes in a differential manner: ob/ob mice are characterized by mild insulin resistance and extreme obesity and db/db mice, characterized by mild obesity and severe insulin resistance. We report that diabetes induced AD-like tau hyperphosphorylation in the db/db and ob/ob mice brains. This hyperphosphorylation was not a result of central insulin resitance in both mice models. Indeed, in db/db mice tau hyperphosphorylation was due to diabetes-related hypothermia, but not in ob/ob mice. Tau hyperphosphorylation in ob/ob mice could be related to factors associated with obesity. Further studies are needed to better understand the mechanisms underlying the hyperphosphorylation of tau protein in DM. This research will help understanding the link between DM and AD, for the development of future treatments or life style strategies destined to check the advance of the disease.