MECHANISTIC INTERACTION BETWEEN ALZHEIMER DISEASE AND DIABETES MELLITUS: ANALYSIS OF NOVEL MOUSE MODELS OF ALZHEIMER DISEASE WITH DIABETES

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Introduction: Recent epidemiological studies suggest that diabetes mellitus is a strong risk factor for Alzheimer disease. However, the underlying mechanisms for this association remain unknown.

Aims: In this study, to better understand the pathophysiological interaction between these diseases, we generated novel animal models which reflect the pathologic conditions of both diseases.

Methods: We crossed Alzheimer APP transgenic mice (APP23) with two types of diabetic mice (ob/ob and NSY mice), and established novel diabetic Alzheimer mouse models. We examined metabolic phenotypes and AD-like phenotypes of these animals. In some studies, mice were fed high-fat diet to induce more severe diabetic phenotypes.

Results: The onset of diabetic symptoms exacerbated Alzheimer-like cognitive dysfunction without increasing brain amyloid-beta burden. Notably, these cross-bred mice showed cerebrovascular inflammation, severe amyloid angiopathy, and impaired brain insulin signaling. On the other hand, the cross-bred mice showed more prominent diabetic phenotypes compared with original diabetic mice. We observed a significant positive correlation between brain amyloid-beta burden and severity of glucose intolerance, suggesting that amyloid pathology could aggravate diabetic conditions. In these cross-bred mice, insulin sensitivity of peripheral organs (liver and muscle) was significantly decreased.

Conclusions: Here, we created novel diabetic Alzheimer mouse models with early onset of cognitive dysfunction. Cerebrovascular changes and alteration in brain insulin signaling might play a pivotal role in this relationship. Our findings suggest the presence of mutual interaction between Alzheimer disease and diabetes, and may reveal novel insights into this intensely debated pathological association.