Regulation of metabolic and glial changes in APP^{NL-G-F} knock-in AD mouse model

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Antibodies against β amyloid have shown promise in treatment of Alzheimer's disease (AD), demonstrating that therapy is possible and opening the opportunities of combinatorial therapies to improve efficacy, provide individualized therapies to different subsets of patient populations, and reduce side effects. Protein O-GlcNAcylation (addition of O-linked-N-acetylglucosamine) on Ser/Thr residues is carried out by O-GlcNAc transferase (OGT), and removed by O-GlcNAcase (OGA). In the current study, we aim to determine whether O-GlcNAcylation is altered in App^{NL-G-F} knock-in AD mouse model, and whether pharmacological enhancement of O-GlcNAcylation exacerbates AD-like pathology. We found increased O-GlcNAcylation in App^{NL-G-F} compared to C57BL/6J wildtype mice. To determine whether the increase of O-GlcNAcylation exacerbates or alleviates neuropathology, we performed chronic administration of Thiamet G (TG, a potent OGA inhibitor) at 3.5 month of age for 2.5 months *in vivo.* We found that OGA activities were elevated in response to chronic TG in App^{NL-G-F} mice as we previously have shown in wildtype mice. As expected, both wildtype and App^{NL-G-F} mice exhibited even higher O-GlcNAcylation after TG treatment. We found significant glial and plaque remodeling in response to elevation of protein O-GlcNAcylation. With regard to metabolism, LDH activities were decreased in App^{NL-G-F} male compared to wildtype male mice in both saline and TG treated group. Mitochondrial complex I activities were increased in App^{NL-G-F} male compared to wildtype mice, and restored to wildtype level by TG. High-resolution metabolomics analyses found significant difference of metabolomes between wildtype and App^{NL-G-F} mice, and they further diverged upon elevation of O-GlcNAcylation. Major differences between wildtype and App^{NL-G-F} mice include branched chain amino acids. Elevation of protein O-GlcNAcylation has significant impact on metabolites in the TCA cycle and fatty acids, changes of glutathione pathway in wildtype mice, while changes of carnitine shuttle in the App^{NL-G-F} mice. Taken together, this study provides significant insights into effects of protein O-GlcNAcylation on metabolism and glial homeostasis in APP^{NL-G-F} knock-in AD mouse model.

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