Hyperhomocysteinemic Diet Promotes Amyloid Beta Accumulation in Brains of a Mouse Model of Alzheimer's Disease

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Elevated homocysteine (Hcy), i.e. hyperhomocysteinemia (HHcy), is a risk factor for Alzheimer's disease (AD). Accumulation of amyloid beta (Aβ) aggregates is a major hallmark of AD. One of the underlying mechanisms may involve modification by Hcy (N-homocysteinylation) that leads to protein damage and aggregation. Our previous ex-vivo study showed that in Hcy-treated murine cell model of AD (N2a-APPSweneuroblastoma), mTOR signaling was hyperactivated while autophagy was downregulated. Because impaired autophagy would lead to accumulation of protein aggregates, in the present study we aimed to investigate effects of dietary HHcy on autophagy and deposition of Aβ aggregates in vivo. To accomplish this aim we used a mouse model of AD (5xFAD mice harboring mutant human APP/PS1 transgenes) and a high-methionine diet to induce HHcy. Brains collected from one-year-old 5xFAD male mice fed with a high-Met diet (n=6) and a control diet (n=6) were examined. Murine brain sections were analyzed by immunohistochemical staining to quantify Aβ plaques. Levels of autophagy-related proteins in hippocampus and cortex were quantified by Western blotting. HHcy-5xFAD-mice showed significantly increased average size of Aβ plaques compared to control diet mice in primary cortex, dentate gyrus, dorsal subiculum, and basolateral amygdala , with a simi-lar percentage coverage by Aβ plaques in both groups. Moreover, the markers of mTOR signaling were upregulated while markers of autophagy were downregulated in HHcy-5xFAD-mice. Our findings indicate that chronic HHcy increases the size of Aβ plaques in brains of 5xFAD mice by impairing autophagy, which supports a mechanistic link between HHcy and neurodegeneration.