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SH2B1 is involved in the accumulation of Aβ42 in Alzheimer's disease model

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Insulin has been identified as a modulator of the neuronal pathways involved in learning and memory, and is also implicated as a modulator of Aβ and tau metabolism toxicity. Disrupted insulin signaling pathways are evident in Alzheimer's disease (AD) patients and it is understood that type II diabetes can increase the risk of developing AD, suggesting a possible link between metabolic disorders and neurodegeneration. SH2B1 is a key protein in the insulin signaling involved in regulating the activity of the insulin receptor. To further identify the role of the insulin signaling in the pathology of AD, SH2B (*Drosophila* SH2B1 homologue) in neurons was partially knocked out or overexpressed in an AD *Drosophila* model expressing $A\beta_{42}$. Partial knockout of SH2B had a detrimental effect on mobility and neurotransmission, and increased levels and intraneuronal accumulation of $A\beta_{42}$ in the $A\beta_{42}$-expressing flies as assessed by ELISA and immunostaining, while, overexpression of SH2B produced the opposite effect. Thus, SH2B1 may be an upstream modulator of Aβ metabolism, acting to inhibit Aβ accumulation, and has a role in the pathogenesis of AD. SH2B1 may therefore have potential as a therapeutic target for this common form of dementia.

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