Epigenetic Suppression of Neuroligin 1 Underlies Amyloid-Induced Memory Deficiency

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Abstract: Modification of histone acetylation modulates hippocampal synaptic plasticity, learning and memory in rodent models of amyloid-induced memory deficiency. Upregulated HDAC2 activity is associated with reduced expression of several genes important for learning and memory and is linked to memory deficiency in a rodent model of Alzheimer's disease. Neuroligin 1 (NLGN1), a postsynaptic protein found in central excitatory synapses, governs excitatory synaptic efficacy and plasticity in the brain. In the present study we explored the HDAC2-mediated modulation of NLGN1 and its functional significance in the rodent model of amyloid-induced memory deficiency. All animal procedures were approved by the Institutional Animal Care and Use Committee. The Morris water maze test was employed to determine memory function in rats. We found significant increase of HDAC2 in hippocampal CA1 in the rats with bilateral microinjecting of $A\beta_{1\text{-}40}$ fibrils (10 μg per side) (**Fig. 1a**). In rats injected with $A\beta_{1\text{–}40}$ fibrils, compared to the administration of scrambled RNA (scRNA), microinjection of *Hdac*2 siRNA (5 nmol per side) (i) attenuated the upregulation of HDAC2 (**Fig.1b-d**); (ii) ameliorated the NLGN1 suppression (**Fig.1e,f**); (iii) recovered the number of hippocampal synapses (**Fig.1g**) and synaptic plasticity (**Fig.1h-i**); and (iv) mitigated the memory deficiency induced by $A\beta_{1\text{–}40}$ fibrils (**Fig.1j,k**). Our findings suggest that HDAC2-mediated epigenetic suppression of NLGN1 may underlie amyloid-induced hippocampal synaptic dysfunction and memory deficiency.

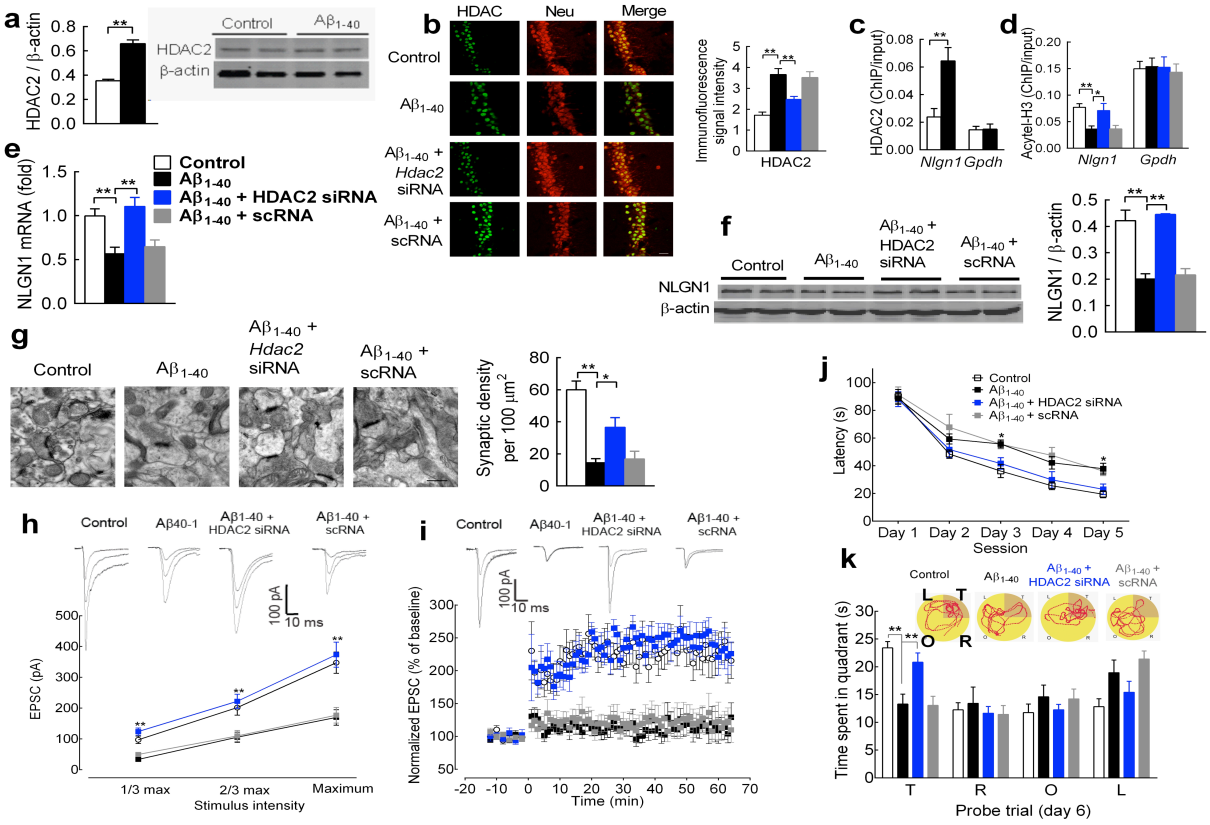

Figure. 1. Administration of HDAC2 siRNA significantly attenuated the upregulation of HDAC2, recovered the NLGN1 expression, hippocampal synaptic plasticity and memory deficiency in the

modeled rats. Synaptic ultrastructure was examined by transmission electron microscopy and hippocampal synaptic density per 100 μm^2 of neuropil is shown (g). Representative path tracings (k) in each quadrant during the probe trial of the Morris water Maze test on day 6 (T, target quadrant; R, right quadrant; O, opposite quadrant; L, left quadrant). Data represent mean ± SEM (n = 8-10 per group). Scale bar = 25 μm, (b) and 0.5 μm (g). *P<0.05, **P<0.01 (ANOVA followed by Student-Newman-Keuls multiple range test).