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**Role of HDAC4 in pre- and post-synaptic protein SUMOylation imbalance in a mouse model of Alzheimer’s disease**

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**Abstract**

**Background:** Early dysfunction in Alzheimer's disease (AD) is characterized by dysmorphic neurites, decreased spine density and cognitive deficits as a result of abnormal synapse structure and function. The class II member HDAC4, which has recently been recognized as a key player in synaptic plasticity and memory, was discovered to be affected in AD, albeit it is unclear how this may contribute to AD pathogenesis. **Methods:** HDAC4 localization and function was assessed in hippocampal tissue from adult (7-month-old) control (WT) and 3×Tg mice (AD) by confocal analyses, co-immunoprecipitation and biochemical fractioning. Cultured hippocampal neurons or organotypic brain slices from WT and AD mice were transduced to overexpress a cytoplasmic mutant form of HDAC4 (HDACSD) or the empty vector and their effects on synaptic protein localization and function, synaptic transmission and spine density were investigated.

**Results:** In WT mice, HDAC4 was localized at synapses and interacted with synapsin I and several post-synaptic proteins, whereas in the AD mice it underwent nuclear import (synaptic HDAC4 in AD: 0.62±0.08 vs WT; nuclear HDAC4 in AD: 2.14±0.36 vs WT). Similar results were found in WT neuronal cultures treated with amyloid- (Aor tau (HDAC4 at synaptic fraction: A 0.75±0.05; tau 0.54±0.09 vs control; HDAC4 at nuclear fraction: A 1.43±0.11; tau 1.53±0.13 vs control). Loss of synaptic HDAC4 in AD was associated with decreased HDAC4-mediated SUMO2/3ylation of synapsin I and PSD95. Overexpression of HDAC4SD in AD hippocampal neurons recovered synapsin I SUMO2/3ylation and its clustering and interaction with actin favoring the formation of a reserve pool. At the post-synaptic domain HDAC4SD recovered PSD95 SUMO2/3ylation, dendritic length and expression of several synaptic proteins (fold change AD-HDACSD: HDAC4 5.17±0.83, NCAD 2.25±0.46, PSD95 2.19±0.18, GluA1 1.59±0.13, CaMKII 1.61±0.19 vs AD). Moreover, in AD organotypic hippocampal slices HDAC4SD rescued spine density and synaptic transmission.

**Conclusion**: These results highlight a new role of HDAC4 at both pre- and post-synaptic compartments, relying on post-translational modification (SUMOylation) of synaptic proteins and providing a scaffold for proper membrane localization and function. Furthermore, our findings suggest that controlling HDAC4 localization may be a promising strategy to prevent and/or counteract synaptic dysfunction in AD.

Keyword selection: Histone deacetylases, synapse, Alzheimer’s disease

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