EPIGENETIC SUPPRESSION OF NEUROLIGIN-1 UNDERLIES AMYLOID FIBRIL-INDUCED MEMORY DEFICIENCY.

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Summary: Accumulation of amyloid-! (A!) in the hippocampus leads to cognitive impairment and is a pathologic hallmark of Alzheimer's disease. It is well established that excitatory glutamatergic transmission in the hippocampus CA1 area is involved in memory function. Recently, it was shown that postsynaptic neuroligin-1 critically modulates glutamatergic synapse efficiency via pre- and postsynaptic mechanisms. Here, we investigated the adaptation of glutamatergic transmission and the epigenetic modulation of neuroligin-1 in the hippocampal CA1 area using a rat model of Alzheimer's disease. Infusion of A!-forming fibrils into the CA1 area (i) significantly extended the escape latencies in the rats during a water maze test, which suggests that the amyloid fibrils induced memory deficiency; (ii) significantly attenuated basal glutamatergic strength in the hippocampal CA1 neurons (Fig. 1); (iii) increased the ratio of paired-pulse evoked excitatory postsynaptic currents (EPSCs), which indicates that presynaptic glutamate release is decreased (Fig. 2); and (iv) suppressed the response of postsynaptic AMPA receptors, as evidenced by the decreased AMPA receptor-mediated component of the EPSCs and attenuated evoked current by perfusion of exogenous AMPA. These pre- and postsynaptic adaptations (Fig. 3A and 3B) may underlie the attenuated basal glutamatergic transmission (Fig. 3C and 3D) in the CA1 area of the rats with A! fibrils. Furthermore, amyloid fibril injection significantly decreased the expression of neuroligin-1 in the CA1 area. A chromatin immunoprecipitation assay revealed decreased acetylation of histone H3 across the neuroligin-1 promoter area (Fig. 4A and 4B) in the CA1 tissue from the rats with A! fibrils (Fig. 4C to 4F), indicating that an epigenetic mechanism was involved in this process. These findings may focus the synaptic adaptation and the epigenetic mechanism underlying the cognitive impairment in the rat model of Alzheimer's disease with microinjection of A! fibrils in the hippocampus.

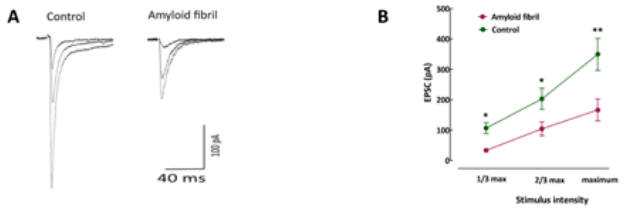

Fig. 1. Attentuated basal glutamatergic strength in the CA1 neurons of rats following microinjection of amyloid fibrils. (A) Representative traces showing the evoked EPSCs in the CA1 neurons in both groups. (B) Decreased evoked EPSCs in the CA1 neurons in rats following microinjection of amyloid fibrils. *P<0.05, **P<0.01.

Fig. 2. Decreased presynaptic glutamate release in the CA1 in the rats following microinjection of amyloid fibrils. (A) Representative traces showing the paired-pulse ratio (PPR) of evoked EPSCs in the CA1 neurons from rats in both groups. (B) Increased PPR of the evoked EPSCs in the CA1 neurons in both groups, indicating an attenuated presynaptic glutamate release. *P<0.05, **P<0.01.

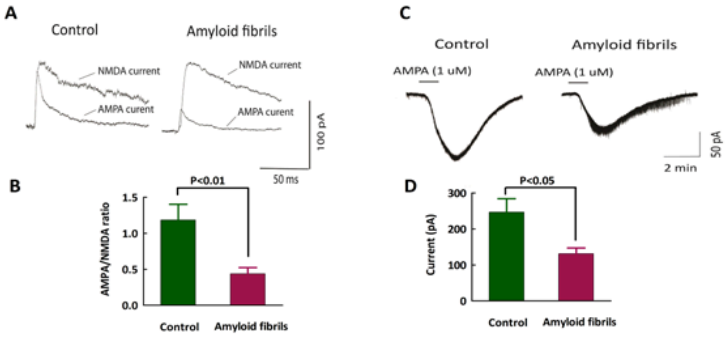

Fig. 3. Decreased AMPA receptor-mediated EPSC component in the CA1 and decreased exogenous AMPA (1 μM)-evoked current in the CA1 neurons of rats following microinjection of amyloid fibrils. (A) representative traces showing the AMPA receptor- and NMDA receptor-mediated EPSC currents in the CA1 neurons from both groups. (B) Decreased AMPA receptor-mediated EPSC component in the CA1 neurons in rats following microinjection of amyloid fibrils. (C) Representative traces showing the inward currents evoked by perfusion of exogenous AMPA (1 μM) in the CA1 neurons in both groups. (D) Decreased exogenous AMPA-evoked currents in the CA1 neurons in rats following microinjection of amyloid fibrils.

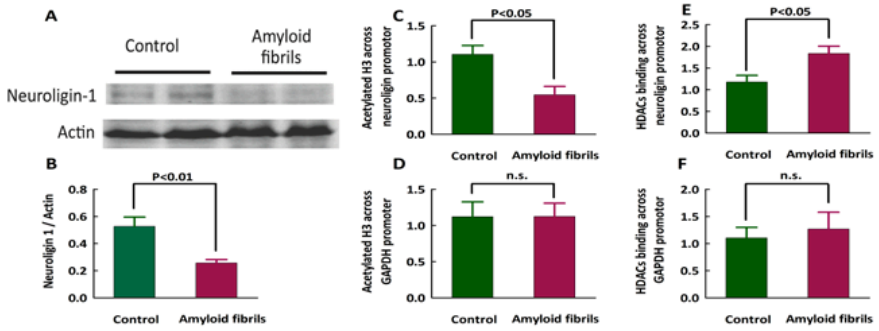

Fig. 4. Epigenetic suppression of neuroligin-1 in the CA1 area in rats following microinjection of amyloid fibrils. (A and B) Decreased expression of neuroligin-1 in the CA1 area after microinjection of amyloid fibrils (n = 6 in each groups). (C and D) Chromatin immunoprecipitation assay revealed a decreased acetylated H3 across neuroligin-1 promoter region (C) but not across the promoter region of GAPDH (D). (E and F) Chromatin immunoprecipitation assay revealed an increased HDAC1 binding across neuroligin-1 promoter region (E) but not across the promoter region of GAPDH (F).