ALTERED NR2A/NR2B RATIO IN HIPPOCAMPUS OF SPATIAL LEARNING-IMPAIRED AGED RATS

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Introduction. The activation of the N-methyl-D-aspartate receptor (NMDAR) is critical for the induction of synaptic plasticity in the hippocampus. Aging can alter glutamatergic synaptic transmission in the hippocampus, and cognitive impairments in aged animals are accompanied by reduced NMDAR-mediated plasticity at Schaffer collateral—CA1 synapses. However, the specific contribution of NMDAR subunits to NMDAR-mediated synaptic responses in aged tissue has not yet been fully understood. The main purpose of present study was to examine whether there is an impact of aging on NMDAR subunit expression and whether synaptic plasticity may depend on NMDAR subunit composition in the aged hippocampus.

Materials and methods. Male young (3-5 months) and aged (22-26 months) rats were subjected to Morris water maze hidden platform task to evaluate spatial learning and memory ability of animals and field excitatory postsynaptic potentials (fEPSPs) were measured in hippocampal slices (400 thick) to evaluate synaptic plasticity via long-term potentiation. Finally, the intracellular recording techniques were used to assess the NMDAR subunit expression in NMDAR-mediated EPSPs (excitatory postsynaptic potentials) in CA1 pyramidal cells.

Results. We observed that aged rats learnt to find the hidden platform significantly more slowly than young rats. Consistent with behavioral data, we found a decline of synaptic plasticity at Schaffer collateral-CA1 synapses in aged rats (LTP: 132.2±10.6% of baseline, n=9) as compared to young ones (LTP: 163.0±11.9% of baseline, n=12). These electrophysiological data also indicate that, although the aged hippocampus was still capable of producing LTP, the magnitude of which was significantly less than that in young hippocampus ($P < 0.01$). The NMDAR-EPSP after application of the specific NR2A blocker NVP-AAM077 was 50.7±1% in the young group versus 31.9±4% in the aged group ($P < 0.01$), but after application of the specific NR2B blocker Ro25-6981 the NMDAR-EPSP was reduced to 55.4±3% in the young group versus 66.8±9% in old one ($P > 0.05$). The calculated EPSP response ratio of NR2A/NR2B was 1.1 in young rats and 2.1 in aged rats, suggesting an age-related alteration of NMDAR composition in the hippocampus.

Conclusions. We have investigated the impact of aging on learning and memory function (in *vivo* and *in vitro)* in correlation with the NMDAR subunit composition in the hippocampus of young and aged rats, and demonstrated that age-related impairment of learning and memory function is associated with an increase of NR2B/NR2A ratio in the rat hippocampus. Our results suggest that NR2B subunits are downregulated during aging, while NR2A subunits are unaffected by this process.