D-SERINE IMPROVES LEARNING AND MEMORY IN EPILEPTIC ANIMALS

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Introduction. The N-methyl-D-aspartate receptor (NMDAR) is critical for the induction of synaptic plasticity and is essential for many forms of learning and memory. Activation of NMDAR by glutamate requires the presence of D-Serine, which is an endogenous physiological co-agonist of the receptor and plays an important role in glutamate mediated NMDAR-dependent synaptic plasticity in the brain. However, the role of D-serine in synaptic plasticity and learning in chronic epilepsy is not known.

Methods & Results. The main objective of the present study is to investigate the effect of D-serine on hippocampal synaptic long-term potentiation (LTP) in the pilocarpine-induced status epilepticus rat model. Initially we found that NMDAR-dependent LTP induced by a modified theta-burst stimulation was significantly reduced in pilocarpine-treated rats in the lateral perforant path. We demonstrate further that the application of D-serine (100 µM) significantly enhanced NMDAR-dependent LTP at lateral perforant path synapses only in epileptic rats so that similar levels of LTP were observed in both groups. The LTP rescuing effect of D-serine was blocked by CGP78608 (0.2 µM), an NMDAR antagonist at the glycine site, suggesting that it was due to D-serine binding to the NMDAR glycine site. It was also prevented by prior bath-application of Ro25-6981 (0.5 µM) and PPDA (1 µM), the antagonists of the NR2B-subunit-containing and the NR2C/D-subunit-containing NMDARs, respectively. The LTP modifying effect of D-serine was further demonstrated in D-amino-acid-oxidase overexpressing mice. In both the lateral and the medial perforant path LTP was reduced in these mice compared to controls. In addition to the LTP recordings in vitro, we tested the learning behavior in the Morris water maze. Epileptic rats showed a drastically worse performance in the hidden platform task compared to controls, but could be significantly enhanced by oral D-serine substitution which by itself had no effect on the performance of control rats. The relative D-serine level (as a percentage of total serine) in the hippocampus was measured and revealed a significant reduction in pilocarpine-treated rats. However, oral D-serine substitution could significantly enhance relative D-serine levels in both groups.

Conclusion. Our study provides direct evidence of the D-serine effect on hippocampal synaptic plasticity and spatial memory, thus underscores the importance of D-serine in synaptic plasticity and learning, especially in the epileptic animal.