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The role of polysialylated NCAM in hippocampal long-term potentiation and acquisition and late consolidation of contextual memory

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Polysialic acid (PSA), a carbohydrate attached to the neural cell adhesion molecule (NCAM), modulates its properties and is indispensable for functioning of NCAM during development and in neuroplasticity in the adult. Little is known, however, regarding individual contributions of PSA and NCAM to different phases of learning and memory consolidation. To investigate this, we injected recombinantly produced extracellular domains of NCAM and PSA-NCAM, and PSA into the dorsal hippocampi of wild-type and NCAM deficient mice at different phases of fear conditioning. We found that PSA-NCAM or PSA, but not NCAM, injected 4 h before training impaired formation of hippocampus-dependent contextual memory, as measured by the freezing response during 3 consecutive days after learning. Consolidation of contextual memory was affected only by PSA-NCAM when injected during late, but not its early phases (6 versus 2 hours after fear conditioning). None of the tested compounds disrupted extrahippocampal tone memory. Mice, lacking the polysialyltransferase ST8SialV/PST, an enzyme responsible for attachment of PSA to NCAM in the adult brain, showed a mild deficit in contextual learning, compared to NCAM deficient mice that exhibited significant abnormalities in both contextual and tone memories. These severe cognitive deficits in NCAM deficient mice were partially rescued by pre-training injection of PSA-NCAM. These data are in line with the effects of PSA-NCAM and PSA on long-term potentiation (LTP) in the CA1 region of hippocampal slices: injections of PSA and PSA-NCAM inhibited LTP in wild-type mice but restored impaired LTP in NCAM deficient mice. Thus, our data support the view that PSA is involved in synaptic plasticity with respect to formation and late consolidation of contextual memory. Recovery of LTP and memory in NCAM deficient mice by application of PSA-NCAM suggests a heterophilic binding mechanism through which PSA-NCAM may act during hippocampal learning.