

NCAM-associated polysialic acid promotes synaptic plasticity via inhibition of the NR2B-containing NMDA receptor - Ras-GRF1 - p38 signaling pathway

Gaga Kochlamazashvili¹, Oleg Senkov^{1,2}, Olena Bukalo¹, Benedikt Salmen¹, Meifang Xiao¹, Rita Gerardy-Schahn³, Larry Feig⁴, Melitta Schachner^{1,5}, Alexander Dityatev^{1,2} (dityatev@zmnh.uni-hamburg.de)

¹Zentrum fuer Molekulare Neurobiologie and ²Institut für Neurophysiologie und Pathophysiologie, University Medical Center Hamburg-Eppendorf, Hamburg 20246, Germany; Zellulare Chemie, Medizinische Hochschule Hannover, Hannover 30625, Germany; ⁴Departments of Biochemistry and Neuroscience, Sackler School of Graduate Biomedical Sciences, Tufts University School of Medicine, Boston, Massachusetts 02111, USA; ⁵Keck Center for Collaborative Neuroscience and Department of Cell Biology and Neuroscience, Rutgers University, Piscataway, NJ 08854, USA

The neural cell adhesion molecule NCAM, a member of the immunoglobulin superfamily of cell adhesion molecules, is the sole carrier of the unusual carbohydrate polysialic acid (PSA) in mammalian brains. Genetic ablation of NCAM, enzymatic removal of PSA and ablation of polysialyltransferase PST (the major enzyme involved in polysialylation of NCAM in mature brains) impair NMDA receptor-dependent long-term potentiation (LTP) in the CA1 region of the hippocampus. Application of recombinant polysialylated NCAM (PSA-NCAM) or PSA to acute slices of NCAM-deficient mice restores normal CA1 LTP. Since application of non-polysialylated NCAM is not effective in restoring normal LTP, the combined data indicate that PSA is both necessary and sufficient for normal induction of CA1 LTP.

Our recent experiments revealed that PSA suppresses activation of NR2B-containing NMDA receptors by low concentrations of glutamate, suggesting that PSA may restrain activity of these receptors extrasynaptically. It is noteworthy in this respect that (i) the synaptic pool of NMDA receptors activates the extracellular signal-regulated kinases (ERK), whereas the extrasynaptic pool triggers a signaling pathway that results in the inactivation of ERK; (ii) NR2B-containing NMDA receptors may signal via the Ras-guanine nucleotide-releasing factor 1 (Ras-GRF1) to the Rac effector p38 MAP kinase, which is a promoter of synaptic depression. In agreement with the idea that this pathway is hyperactive in the absence of PSA-NCAM, we found that the level of phosphorylated p38 is upregulated in NCAM deficient mice. Furthermore, we found that (i) a glutamate scavenger (reducing extrasynaptic concentration of glutamate), (ii) an inhibitor of NR2B-containing NMDA receptors, (iii) genetic ablation of Ras-GRF1, and (iv) an inhibitor of p38 normalized levels of LTP in PSA- and/or NCAM-deficient hippocampal slices to the level seen in wild-type mice. Also, intra-hippocampal injection of PSA or the inhibitor of NR2B-containing NMDA receptors normalized contextual fear conditioning of NCAM deficient mice. Thus, PSA synthesized by PST and carried by NCAM regulates synaptic plasticity and learning via inhibitory control of the NR2B - Ras-GRF1 - p38 pathway.