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Polysialic acid mimetics to reset the balance between synaptic and extrasynaptic NMDA receptors and rescue learning and memory in mouse models of neurodegenerative diseases

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Dysregulated cortical expression of the neural cell adhesion molecule (NCAM) and deficits of its associated polysialic acid (polySia) have been found in Alzheimer's disease and schizophrenia. However, the functional role of polySia in cortical synaptic plasticity remains poorly understood. Here, we show that acute enzymatic removal of polySia in medial prefrontal cortex (mPFC) slices leads to increased transmission mediated by the GluN1/GluN2B subtype of N-methyl-D-aspartate receptors (NMDARs), increased NMDAR-mediated extrasynaptic tonic currents, and impaired long-term potentiation (LTP). The latter could be fully rescued by pharmacological suppression of GluN1/GluN2B receptors or by application of small polySia mimetics. Furthermore, intranasal delivery of polySia mimetics could rescue performance of polySia-deficient mice, 5xFAD model of Alzheimer's disease and mice virally overexpressing human Tau[R406W] mutant in the mPFC-dependent behavioral tasks (novel object recognition, temporal order/recency recognition). Two-photon imaging of a DMB-tagged polySia mimetic confirmed its penetration through blood-brain-barrier into the neuropil. In vitro data show that different polySia mimetics either do not change or even increase cell viability measured by MTT assay. These data demonstrate the essential role of polySia-NCAM in the regulation of signaling through synaptic versus extrasynaptic NMDARs in the cortex and highlight the therapeutic potential of polySia mimetics to target extrasynaptic NMDAR signaling in neurodegenerative diseases.