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The role of proheparanase in synaptic plasticity of the hippocampus

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Perineuronal heparan sulfate (HS) moieties are implicated in the modulation of neurotransmission by controlling the functional properties of AMPA-type glutamate receptors. We hypothesize that neuronal mechanisms modulate peri-synaptic HS level, thereby regulating synaptic strength and plasticity. To address this, basal synaptic strength and long-term changes in synaptic efficacy in the Schaffer collateral pathway of the rat hippocampus were assessed in relation to strategies that perturb peri-synaptic HS. In hippocampal slices, heparitinase treatment led to dose-dependent attenuation of long-term potentiation (LTP) in correlation with loss of perineuronal HS moieties. As heparanase expression was found at the CA1 hippocampal neurons, we further tested if heparanase is the mammalian counterpart of heparitinase in the regulation of synaptic strength/plasticity. We asked therefore if neuronal heparanase is secreted as the pro-form or the active form. Following phorbol ester stimulation of hippocampal neurons in culture, pericellular proheparanase accompanied by increase in enzymatically active heparanase in the cytoplasmic fraction was revealed by Western blot analysis of both the pericellular and cytoplasmic fractions. In addition, treatment of the cultures with exogenous proheparanase triggered co-internalization of both cell-surface HS and AMPA receptors. With use of calcium-imaging technique, proheparanase treatment was found to reduce glutamate-induced calcium influx of the hippocampal neurons in culture. Consistent with these findings, treatment of hippocampal slices with exogenous proheparanase resulted in declines in both basal synaptic strength and LTP. Taken together, our findings indicate neuronal secretion of proheparanase to peri-synaptic HS-sites as a novel mechanism that contributes to synaptic plasticity by regulating AMPA receptor level at the synapse.