Poster
Number

68 Heparanase 1 and Heparanase 2 expression in Hippocampal Neurons

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Selective modification (weakening or strengthening) of synaptic connections between neurons within the hippocampal circuit contribute to the learning and memory processes in the brain. Enzymatic heparanase-1 (hpa1) was found expressed in hippocampus by both immunohistochemistry and in-situ hybridization. Western blot analysis of neuronal secretions however revealed the pro-form, i.e. proheparanase, which do not have enzymatic activity is secreted by hippocampal neurons. Proheparanase could trigger AMPA receptor internalization upon binding to the Heparin sulphate on the proteoglycan, therefore impact on synaptic strength and long-term potentiation of synaptic efficacy. We further found not only heparanase-1 but also heparanase-2 (hpa2) expression in hippocampal neurons. We hypothesize therefore a partnership of hpa2 with hpa1 in regulating AMPA receptor internalization at glutamatergic synapses. Immunohistochemical staining of hippocampal sections from adult rats found hpa2 expression in neurons of both the hippocampal DG, CA3 and CA1 regions. Like hpa1, hpa2 immunopositivity was found mainly in perinuclear regions of neurons. In addition to proheparanase, hpa2 was also found to be secreted by hippocampal neurons in culture. Secreted proheparanase and hpa2 remained associated with cell surface heparan sulfate. With results that support our hypothesis, we expect to pursue the partnership between proheparanase 1 and hpa2 with the respective recombinant protein.

69 Role of FE65 in neurite outgrowth

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FE65 is an adaptor protein that binds to the amyloid precursor protein (APP). As such, FE65 has been implicated in the pathogenesis of Alzheimer's disease. In addition, evidence suggests that FE65 is involved in brain development. It is generally believed that FE65 participates in these processes by recruiting various interacting partners to form functional complexes. Here, we show that via its first phosphotyrosine binding (PTB) domain, FE65 binds to the small GTPase ADP-ribosylation factor 6 (ARF6). FE65 preferentially binds to ARF6-GDP, and they colocalize in neuronal growth cones. Interestingly, FE65 stimulates the activation of both ARF6 and its downstream GTPase Rac1, a regulator of actin dynamics, and functions in growth cones to stimulate neurite outgrowth. We show that transfection of FE65 and/or ARF6 promotes whereas small interfering RNA knockdown of FE65 or ARF6 inhibits neurite outgrowth in cultured neurons as compared to the mock-transfected control cells. Moreover, knockdown of ARF6 attenuates FE65 stimulation of neurite outgrowth and defective neurite outgrowth seen in FE65-deficient neurons is partially corrected by ARF6 overexpression. Notably, the stimulatory effect of FE65 and ARF6 on neurite outgrowth is abrogated either by dominant-negative Rac1 or knockdown of Rac1. Thus, we identify FE65 as a novel regulator of neurite outgrowth via controlling ARF6-Rac1 signaling.