GALECTIN-8 Is a Neuroprotective Factor in the Brain that Can Be Neutralized by Human Autoantibodies

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Abstract

Galectin-8 (Gal-8) is a glycan-binding protein that modulates a variety of cellular processes interacting with cell surface glycoproteins. Neutralizing anti-Gal-8 antibodies that block Gal-8 functions have been described in autoimmune and inflammatory disorders, likely playing pathogenic roles. In the brain, Gal-8 is highly expressed in the choroid plexus and accordingly has been detected in human cerebrospinal fluid. It protects against central nervous system autoimmune damage through its immune-suppressive potential. Whether Gal-8 plays a direct role upon neurons remains unknown. Here, we show that Gal-8 protects hippocampal neurons in primary culture against damaging conditions such as nutrient deprivation, glutamate-induced excitotoxicity, hydrogen peroxide (H2O2)-induced oxidative stress, and β-amyloid oligomers (Aβo). This protective action is manifested even after 2 h of exposure to the harmful condition. Pull-down assays demonstrate binding of Gal-8 to selected β1-integrins, including α3 and α5β1. Furthermore, Gal-8 activates β1-integrins, ERK1/2, and PI3K/AKT signaling pathways that mediate neuroprotection. Hippocampal neurons in primary culture produce and secrete Gal-8, and their survival decreases upon incubation with human function-blocking Gal-8 autoantibodies obtained from lupus patients. Despite the low levels of Gal-8 expression detected by real-time PCR in hippocampus, compared with other brain regions, the complete lack of Gal-8 in Gal-8 KO mice determines higher levels of apoptosis upon H2O2 stereotaxic injection in this region. Therefore, endogenous Gal-8 likely contributes to generate a neuroprotective environment in the brain, which might be eventually counteracted by human function-blocking autoantibodies..

Keywords

Galectins, Neuroprotection, Integrins, ERK1/2, PI3K/AKT, Hippocampal neurons.