Insulin-like growth factor-1 overexpression enhances neurogenesis and activates the mTOR pathway after moderate TBI

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Nearly 5 million people in the United States are living with TBI related disabilities, in part because of the brain's limited capacity to replace lost and damaged neurons. Immature neurons in the hippocampus are highly vulnerable to trauma, but can be replaced through proliferation and differentiation of neural stem cells in the subgranular zone. The extent of injury-induced neurogenesis, however, may be injury severity dependent. Insulin-like Growth Factor 1 (IGF1) modulates basal and injury-induced hippocampal neurogenesis. Using a transgenic mouse model with IGF1 overexpression restricted to astrocytes (IGF Tg) to raise brain levels of IGF1 by means of injury-induced astrogliosis, we previously showed that IGF1 enhances recovery of the immature neuron population and morphology after severe TBI. Mammalian target of rapamycin (mTOR), a signaling molecule downstream of IGF1, has been identified as a potential target for TBI interventions because of its regulatory role in plasticity and cell survival. We hypothesized that increased IGF1 would stimulate mTOR activity following moderate injury, resulting in improved neurogenesis. To this end three cohorts of IGF Tg and wild-type (WT) mice received moderate controlled cortical impact and survived 1, 3 or 10d or received sham injury at 1 and 3d following moderate injury. Immunohistochemical labeling of pS6, a well characterized downstream effector of mTOR, was quantified in the granule cell layer, molecular layer, and the hilus of the dentate gyrus. Analysis of pS6 at the injury epicenter (3 sections/animal) suggests that IGF1 stimulates activity of the mTOR pathway following moderate TBI in a region-specific manner. At 10d after moderate injury, IGF1 overexpression enhances recovery of immature neurons.