Insulin-like growth factor-1 overexpression mediates regional alterations to the mTOR signaling pathway in the hippocampus following TBI

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Although IGF1 is known to enhance adult neurogenesis, the intricate signaling mechanisms through which it modulates neurogenesis and subsequent plasticity events remain unclear, especially in the setting of TBI. In the nervous system PI3-K/Akt signaling predominates in mediating many of IGF1 functions, including precursor proliferation and differentiation and neuronal survival. In a transgenic mouse model with IGF1 overexpression restricted to astrocytes, we show that increased IGF1 levels in the hippocampus by means of injury-induced astrogliosis leads to increased activation of Akt. Akt activation results in the phosphorylation of multiple downstream signaling molecules including mammalian target of rapamycin (mTOR). In developing neurons, mTOR signaling is known to regulate brain plasticity events including dendritic sprouting . Following brain injury, mTOR is transiently activated in the hippocampus. We hypothesized that increased brain levels of IGF1 would potentiate posttraumatic activation of the mTOR signaling pathway, a pathway associated with growth and differentiation. To this end, astrocyte-specific IGF1 conditionally overexpressing mice (IGF1-TG) and wild-type (WT) mice received controlled cortical impact (CCI, n=8/genotype) or sham (n= 3/genotype) injuries. At 72hrs following 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 TBI.

mTOR Inhibition After Controlled Cortical Impact Alters Hilar Interneuron Excitability

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Traumatic brain injury (TBI) is among the most common causes of acquired temporal lobe epilepsy (TLE). The latent period after injury and prior to expression of seizures includes plasticity events that support epileptogenesis, including cell loss and synaptic reorganization in the dentate gyrus. A murine model of TBI using controlled cortical impact (CCI) injury was used to examine the effect of daily rapamycin treatment (3 mg/kg) on excitability of surviving GABAergic hilar interneurons in mice that express GFP in a subset of inhibitory neurons (FVB-Tg(GadGFP) 4570Swn/J; i.e., GIN mice). GFP-labeled hilar interneurons ipsilateral to CCI injury were reduced in number relative to controls, and rapamycin treatment did not inhibit this cell loss. Whole-cell patch-clamp and on-cell recordings in vitro were used to examine spontaneous EPSC frequency and action potential firing rates of surviving GFP-labeled hilar interneurons in GIN mice that were treated with rapamycin for 8-12 weeks after CCI injury. An increase in spontaneous EPSC frequency and action potential firing rate of GFP-labeled hilar interneurons ipsilateral to CCI injury was detected, relative to cells contralateral to the injury. Relative to CCI injury alone, daily rapamycin treatment resulted in a reduction in the increase in sEPSC frequency and spontaneous firing rate of GFP-labeled hilar interneurons and reduced mossy fiber sprouting ipsilateral to the injury. Although reduced relative to CCI injury, these measures were not normalized to control levels; analysis of the effects of high- dose rapamycin treatment (10 mg/kg) is underway. Rapamycin treatment therefore reduces the enhanced synaptic excitation of hilar interneurons after CCI injury in a manner consistent with suppression of reactive plasticity in granule cells. Ongoing experiments utilizing glutamate photolysis to activate granule cells and CA3 pyramids will test the hypothesis that effects of rapamycin treatment are mainly due to selective effects on mossy fiber sprouting.