Activation of PERK in Controlled Cortical Impact Model of Traumatic Brain Injury

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Shelby Meier[1] • Dealla Samadi[1] • Joe Abisambra, PhD[1]

[1]*Sanders Brown Center on Aging, University of Kentucky*

Background: Traumatic brain injury (TBI) is defined as an injury that causes intereferene in normal brain function. TBI affects an average of 1.4 million Americans each year, with at least 50,000 reported injuries resulting in death. Long-term effects of TBI include headaches, cognitive decline, seizures, mood swings, motor skill impairment, increased fatigue, and sleep disturbances. TBI is also indicated as a prominent risk factor for neurodegenerative disorders like Alzheimer's disease (AD) and Parkinson's disease (PD). There are currently no treatments for TBI, only precautionary steps to avoid future injury.

Methods: Mice were injured using the controlled cortical impact (CCI) model of TBI. Proteins of interest were measured using immunohistochemical staining. Overall protein synthesis was measured using a non-radioactive technique known as SUnSET.

Results: We recently found that PERK, a protein kinase involved in the unfolded protein response (UPR), was chronically activated in brains following TBI. We show here that PERK activation following injury is time dependent and region specific. We also show increase in overall protein synthesis (as measured by a novel, non-radioactive technique called SUnSET) following injury.

Conclusions: Our data provide novel insight into the physiological mechanisms of TBI, and suggest that PERK plays an important role in injury progression. These data also support the exploration of PERK inhibition as a therapeutic option for traumatic brain injury

IL-1β levels after TBI can be inhibited with the therapeutic MW151, without affecting microglial physiological responses

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Claudia Späni, PhD[1] • Adam D. Bachstetter, PhD[2] • Zhengqiu Zhou[1] • Danielle S. Goulding[1] • Alyssa N. Conley[1] • Linda J. Van Eldik, PhD[1]

[1]*Sanders Brown Center on Aging, University of Kentucky* • [2]*Spinal Cord and Brain Injury Research Center, University of Kentucky*

Background: Neuroinflammation, an inflammatory response in the brain, occurs in many disorders of the central nervous system (CNS) including traumatic brain injury (TBI). Dysregulated neuroinflammatory responses after TBI are thought to contribute to neurological damage and cognitive deficits in part through an increased production of proinflammatory cytokines such as interleukin-1 beta (IL-1β). These damaging proinflammatory processes thus provide an interesting potential target for intervention if endogenous recovery responses can be spared.

Methods: MW151, a CNS-penetrant, small molecule experimental therapeutic, has been shown in previous studies to restore overproduction of proinflammatory cytokines towards homeostasis without general immunosuppression in multiple TBI models. In this study we investigated the use of MW151 in a midline fluid percussion model of diffuse brain injury in mice and its effects in vitro on microglial cells.

Results: Administration of a low dose (0.5-5.0 mg/kg) of MW151 in our TBI mouse model significantly suppressed IL-1β levels in the cortex without affecting reactive astrocyte or microglial morphological responses. In vitro treatment of the BV-2 microglial cell line with MW151 demonstrated no effect on phagocytosis, proliferation or migration.

Conclusions: The results of this study show feasibility of selective therapeutic modulators to target the increase of the proinflammatory cytokine IL-1β without interfering with physiological responses of glial cell populations.