LEUKEMIA INHIBITORY FACTOR (LIF) REDUCES INJURY AND AIDS NEUROLOGIC RECOVERY AFTER CONCUSSIVE HEAD INJURY

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Introduction

• Traumatic Brain Injuries (TBI) affect more than 500,000 children every year.
• About 75% of pediatric TBI are diffuse, closed-head injuries.
• LIF is a potent, vital signaling molecule for development and injury response.
• Our lab recently established that mice haplodeficient for LIF sustain significantly more damage after a closed-head injury (CHI).
• We hypothesize that intranasally administered LIF will reduce brain injury when provided after a closed-head injury.
Methods

• Juvenile wild-type CD1 mice were administered blunt, closed-head injuries. A pneumatically driven piston impacted the skull at the midline between Lambda and Bregma at 4 m/s at a depth of 1mm.

• The mice were split into three groups (sham, vehicle, and experimental) and were intranasally administered either H$_2$O or LIF (2ug/mL) acutely (4 hours post-surgery) or subacutely (3 days post-surgery).

• An 11 point neurological exam was administered that included beam walking and balance tests followed by histological evaluations using cresyl violet, Fluoro-Jade C and immunofluorescence for GFAP, Iba-1, Olig-2, CC1, SMI-32, and MBP.
Intranasal Leukemia Inhibitory Factor enters the brain and activates the canonical Jak-Stat pathway. Phosphorylated Stat3 (pSTAT3) levels were evaluated at 30 minutes after intranasal administration of water or 2 µg/mL LIF by immunofluorescence. pSTAT3 immunoreactivity in vehicle (A) and LIF (B) mice. (C) pStat3+ cells quantification. Vehicle (n=4) and LIF (n=4). ***p<0.001 by Student’s t test vs. vehicle.
Intranasal LIF reduces neurological deficits after CHI. mNSS is an 11 point neurological exam. Acute: Sham (n=4), vehicle (n=4), LIF (n=4). Subacute: Sham (n=5), vehicle (n=6), LIF (n=7). **p<0.01 by Student’s t-test vs. vehicle.
Intranasal LIF reduces neurodegeneration after CHI. LIF was administered starting 72 h after CHI and tissue examined 4 days after injury. (A) Fluoro Jade C staining in the corpus callosum (B) Quantification of Fluoro Jade C staining. *p<0.05 by Student’s t-test vs. Sham animals.
Subacute administration of intranasal LIF increases oligodendrocyte maturation. Sham (n=2), vehicle (n=3), and LIF (n=3). Values are expressed as the means ± SEM. *p<0.05 by Student’s t-test vs. vehicle.
Discussion

• Approximately half of all TBI cases sustain white matter injury.
• Approved therapeutics to prevent secondary brain injury and to promote white matter repair are lacking.
• A new model of pediatric concussive brain injury was designed to acutely and subacutely (several days after injury) administer iN LIF.
• Prior to this study, iN LIF had not been evaluated for its regenerative potential in any model of neurological disorder.
• Our data demonstrates LIF can reduce neurodegeneration and axonal damage as well as aid in oligodendrocyte maturation and SVZ cell expansion.
• LIFs therapeutic potential is especially important in a time of increasing demand for neurodegenerative treatments.
Summary Points

• Concussions are a growing concern esp. among the adolescent population.

• LIF is a potent cytokine, which is both neuroprotective and neuroregenerative.

• Administration of iN LIF penetrates deep into the brain and activates the JAK-Stat pathway.

• Both histological and behavioral studies demonstrate neurological recovery after iN LIF administration.

• LIF has the potential to be used as a therapeutic agent after concussive brain injury.