The Role of Aging-Dependent Metabolic Dysfunction in Traumatic Brain Injury Outcomes

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What is Traumatic Brain Injury?

Traumatic Brain Injury (TBI): a nondegenerative, noncongenital insult to the brain caused by an external mechanical force that results in damage to the brain and disrupts its normal function.

Quick Facts about TBI:
- TBI contributes to the death of ~50,000 people per year in the United States alone.
- TBI is on track to be come the leading cause of death worldwide by the year 2020.
- Effects of TBI include: Memory loss, Mood swings, Trouble with language and speech, Increased risk of seizures and stroke, Increased risk of Alzheimer’s, Parkinson’s, Partial paralysis, Coma, Death.

The Link Between TBI, Aging, and Metabolism

TBI and Aging
- Elderly individuals (ages 75+) experience the highest level of mortality from TBI (80.6-88.8%).
- The non-fatal TBI hospitalization rate doubles after age 65.
- The severity of post-TBI effects are strongly correlated with the age a person is when they receive a TBI.

Physiologic Changes Occurring Both with TBI and Normal Aging
- Innate Immune Response
- Intestinal Permeability
- Brain Atrophy
- Reactive Oxygen Species
- Insulin Sensitivity

Could TBI Cause Accelerated Aging?

Clinical studies have suggested that cellular changes occurring in the brain after TBI are similar to those seen in normal aging.

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Metabolic and Genetic Screens:
- Our lab has developed a spring-loaded device called the HIT device, to inflict blunt, closed-head TBI in flies. The HIT device is made up of a metal spring clamped to a wooden board, with the unclamped and placed over a polyethylene pad. To inflict injury, we place 60 flies in a plastic vial stoppered with cotton and slide the open end of the vial onto the free end of the spring. We lift the spring back 90° from the wooden board and when it is released, the vial rapidly hits the pad and the flies experience inertial and contact forces as they hit the vial wall.
- Following a strike, a portion of flies experience:
  - Temporary incapacitation without external damage, Ataxia, Neurodegeneration, and Death.

TBI model:
- Drosophila melanogaster (fruit fly)
- Modeling TBI in Drosophila melanogaster
- Permanent incapacitation without external damage, Ataxia, Neurodegeneration, and Death.

Glucose-6-Phosphate Dehydrogenase Expression Affects Mortality Following TBI

- Glucose-6-phosphate dehydrogenase (G6PD) is an enzyme required for the synthesis of NADPH, which is necessary for the production of ATP and for maintaining cellular homeostasis.
- Overexpression of UAS-G6PD in neuronal, glial and ubiquitous Gal4 drivers significantly decreased post-TBI mortality (P < .05). Neuronal knockdown of G6PD was semi-lethal, ubiquitous knockdown of G6PD was lethal.

TBI Causes Temporary Hyperglycemia

Average Mn2+ with SEM for 1-7 day flies with standard HIT protocol normalized to Mn2+ of controls, flies containing a UAS-G6PD overexpression construct were decreased to control flies (1.84 ± 0.06), as well as flies containing a UAS-G6PD construct: flies containing a UAS-G6PD knockdown of G6PD (w+;UAS-RNAi) were decreased to control flies, as well as flies containing neuronal, glial and ubiquitous Gal4 drivers (w+). Glial and ubiquitous overexpression of G6PD significantly decreased post-TBI mortality (P < .01, .05, respectively). Glial and ubiquitous knockdowns of G6PD increased post-TBI mortality (P < .001, .01, respectively). Glial knockdown was not lethal, ubiquitous knockdowns of G6PD were lethal.

TBI Sensitizes Flies to the Effects of ROS

- Increased TBI severity results in a decrease in median survival time.
- 0-7 day females were exposed to the HIT device and immediately placed on filter paper containing 500μL of 30mM paraquat + 5% sucrose solution (A) or 5% sucrose solution only (B). Percent survival is graphed vs the hours post-injury. Each data point is the average and SEM survival of three biological replicates.

Quick Facts about TBI:
- Temporary incapacitation without external damage,
- Ataxia, Neurodegeneration, and Death.

Aging and Diet Affect TBI Outcomes

- Shown is the Mn2+ of 30 RAL lines subjected to standard TBI protocol at younger and older ages and subsequently fed water or food. Each data point is the average of four treatments:
  - Younger flies (0-7 days old)
  - Older flies (20-27 days old)

Average Mn2+ with SEM for 1-7 day flies with standard HIT protocol normalized to Mn2+ of controls, flies containing a UAS-G6PD overexpression construct were decreased to control flies (1.84 ± 0.06), as well as flies containing a UAS-G6PD construct: flies containing a UAS-G6PD knockdown of G6PD (w+;UAS-RNAi) were decreased to control flies, as well as flies containing neuronal, glial and ubiquitous Gal4 drivers (w+). Glial and ubiquitous overexpression of G6PD significantly decreased post-TBI mortality (P < .01, .05, respectively). Glial and ubiquitous knockdowns of G6PD increased post-TBI mortality (P < .001, .01, respectively). Glial knockdown was not lethal, ubiquitous knockdowns of G6PD were lethal.

References