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

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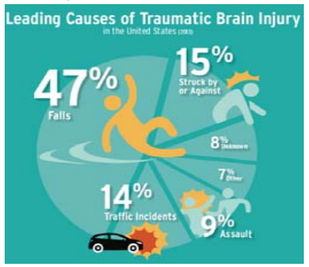
What is Traumatic Brain Injury?

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 **3rd 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

Brainline.org



The Link Between TBI, Aging, and Metabolism

TBI and Aging

- Elderly individuals (ages 75+) experience the highest level of mortality from TBI (60.9-86.6%)
- 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

TBI and Metabolism

- Hyperglycemia is an independent predictor of TBI mortality, length of time in the ICU, and Glasgow Coma Score
- Diabetics post-TBI fare worse than non-diabetic controls

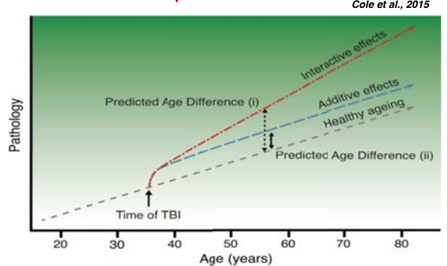
Physiologic Changes Occurring Both with TBI and Normal Aging

- ↑ Innate Immune Response
- ↑ Brain Atrophy
- ↑ Intestinal Permeability
- ↑ 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

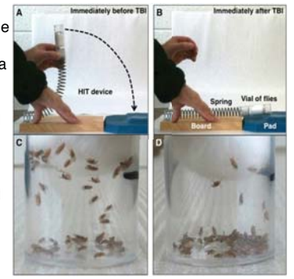
Cole et al., 2015



Modeling TBI in *Drosophila melanogaster* (fruit fly)

TBI model:

Our lab has developed a spring-loaded device called the High-Impact Trauma (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 end placed over a polyurethane 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.

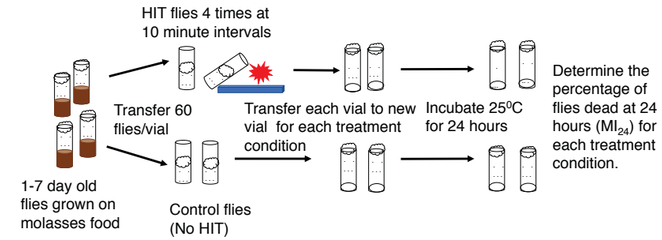


Katzenberger et al., 2013

Following a strike, a portion of flies experience:

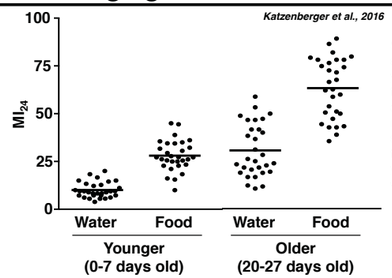
- Temporary incapacitation without external damage, Ataxia, Neurodegeneration, and Death

Metabolic and Genetic Screens:



Aging and Diet Affect TBI Outcomes

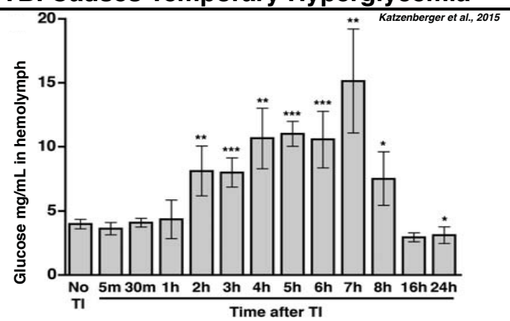
Katzenberger et al., 2016



Shown is the MI_{24} 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 at least three biological replicates. The average MI_{24} was significantly different (P<0.0001, one-tailed t-test) between younger water and younger food as well as between younger water and older water.

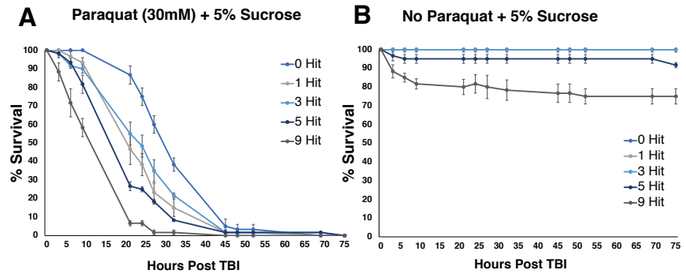
TBI Causes Temporary Hyperglycemia

Katzenberger et al., 2015



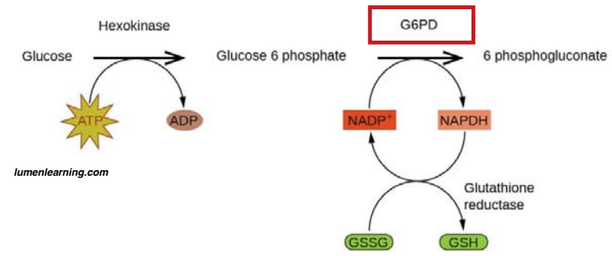
Average and SEM of glucose concentration at times after TBI. A significant increase in glucose concentration occurred between 2 and 8 hr., and a significant decrease in glucose concentration occurred at 24 hr.

TBI Sensitizes Flies to the Effects of ROS



Increased TBI severity resulted in a decrease in median survival time. 0-7 day female w^{1118} flies were exposed to the HIT device and immediately placed on filter paper containing 500uL 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.

Glucose-6-Phosphate Dehydrogenase Expression Affects Mortality Following TBI



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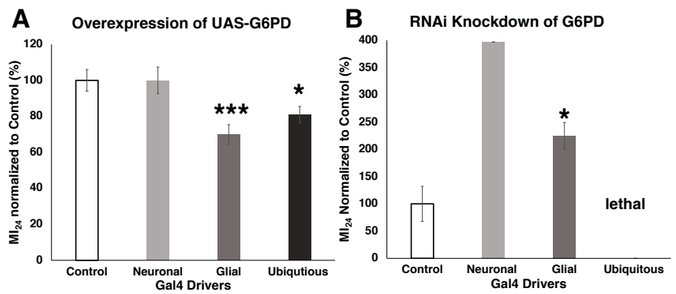

Average MI_{24} with SEM for 1-7 day flies with standard HIT protocol normalized to MI_{24} of controls. Flies containing a UAS-G6PD overexpression construct were crossed to control flies (w^{1118}), as well as flies containing neuronal, glial and ubiquitous Gal4 drivers (A) Flies containing a UAS-RNAi knockdown of G6PD (*Zw*) were crossed to control flies, as well as flies containing neuronal, glial and ubiquitous Gal4 drivers (B). Glial and ubiquitous overexpression of G6PD significantly decreased post-TBI mortality (P< .001,.05, respectively). Glial knockdown of G6PD significantly increased post-TBI mortality (P < .05). Neuronal knockdown of G6PD was semi-lethal, ubiquitous knockdown of G6P was lethal.

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