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"Neuroprotective Anti-Inflammatory Properties of Psychedelic DOI for Closed Head Traumatic Brain Injuries in *Drosophila melanogaster*"

Traumatic brain injuries (TBIs) are permanent conditions caused by an irreversible, physical pathological insult which causes multisystemic dysfunction and dysregulation leading to the development of chronic disease states, neurodegeneration, and decreased life expectancy. Current research lacks understanding of the cellular and molecular events comprising the TBI and thus prevention and recovery therapeutics are limited.

Primary features of closed head TBIs are continuous between humans and *Drosophila melanogaster* (fruit flies), suggesting underlying mechanisms are conserved. The High Impact Trauma (HIT) device delivers reproducible closed head TBIs to *D. melanogaster* through rapid acceleration and deceleration, similar to those mechanisms which cause TBIs in humans. Serotonin 2A receptor (5-HT-2AR) agonists, such as 2,5-Dimethoxy-4-iodoamphetamine (DOI), show promise as anti-inflammatory agents. Our research explores the application of *R*-DOI as a preventative anti-inflammatory treatment for closed head TBIs in *D. melanogaster*.

Flies are fed food substrate either without or with of 1 mM, 0.1 mM, or 0.01 mM (*R*)-DOI for 48 hours then subjected to TBI using the HIT device. Next, flies are placed on control food substrate (10% sucrose + 1% agarose in dH2O) for 24 hours to allow for effects of the TBI to take place. Following the recovery period, heads are removed and processed for qPCR analysis of the expression *Attacin C* (*AttC*) and *Diptericin B* (*DptB*) mRNAs. These genes encode pro-inflammatory cytokines, and thus a reduction in their presence would indicate decreased neuroinflammation.

For each gene, we performed a two-way ANOVA to graph the percent change of ΔΔCt compared to non-TBI control groups. There was a statistically significant interaction between the doses of (*R*)-DOI and the presence or absence of a TBI for both, *AttC* ($F(3, 14) = 11.92$, $p = 0.0004$) and *DptB* ($F(3, 14) = 3.656$, $p = 0.0390$) gene expression. Main effect analysis showed that *R*-DOI dose had a significant effect on *AttC* gene expression ($p = 0.0042$) across all doses, while *DptB* analysis only showed a significant change in inflammation for 0.1 mM ($p = 0.0481$) and 1 mM ($p = 0.0220$) whacked groups compared to whacked controls. Trends were observed for other relevant comparisons, and this may be due to increased variability in the *DptB* results.

Our research indicates there is a dose dependent reduction in genes marking pro-inflammatory cytotoxins in *Drosophila melanogaster* heads following TBI. of neurodegeneration caused by TBIs.