Examining Drug Intervention on optic stress responses after Traumatic Brain Injury

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Background

Traumatic Brain Injury (TBI) is a major health concern caused by major blows or trauma to the brain or skull

- Approximately 2.9 million cases yearly
- Leads to primary injuries (acute injury) and secondary injuries (Changes in cellular physiology)

Traumatic Optic Neuropathy (TON) refers to the effects of TBI on the optic nerve

- 50-60% of all TBI injuries results in visual deficits
- 2-3% of Visual deficits are caused by TON

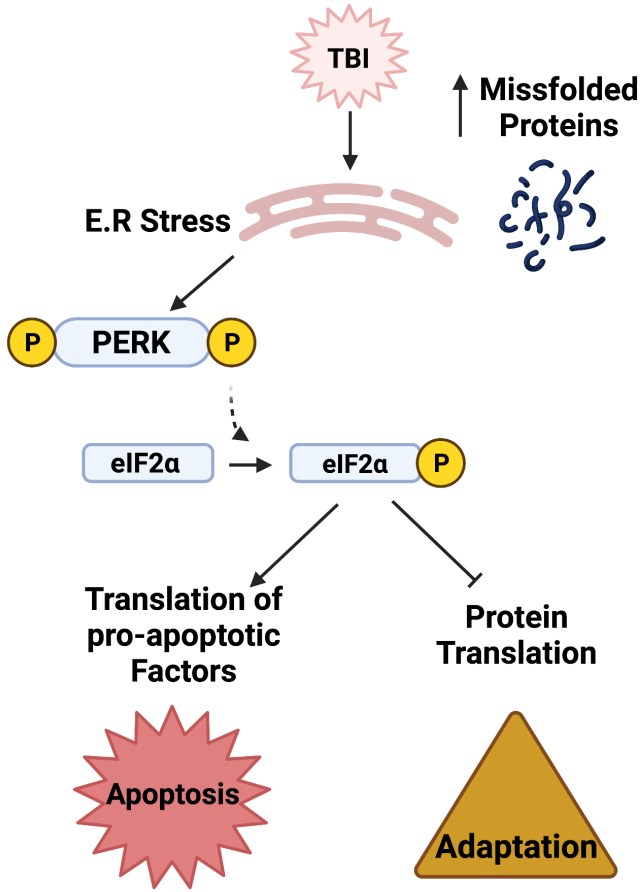
Significance

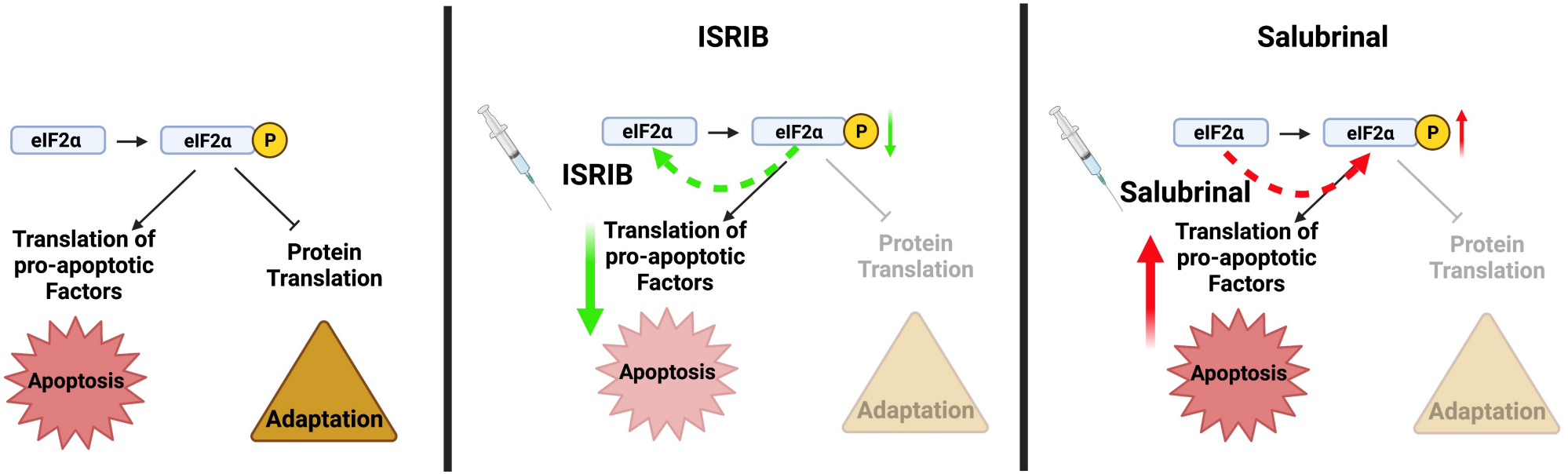
Our lab has shown in previous studies that TBI induced TON leads to Endoplasmic Reticulum (E.R) Stress

- The E.R is the protein manufacturing center of our cells – E.R homeostasis is vital to cellular functioning
- Unbalanced cells will not function appropriately

Currently there are no drug treatments for TBI induced TON

- Unsure of the effects of drug intervention
- Can we find a drug that prevents retinal dysfunction following TBI?

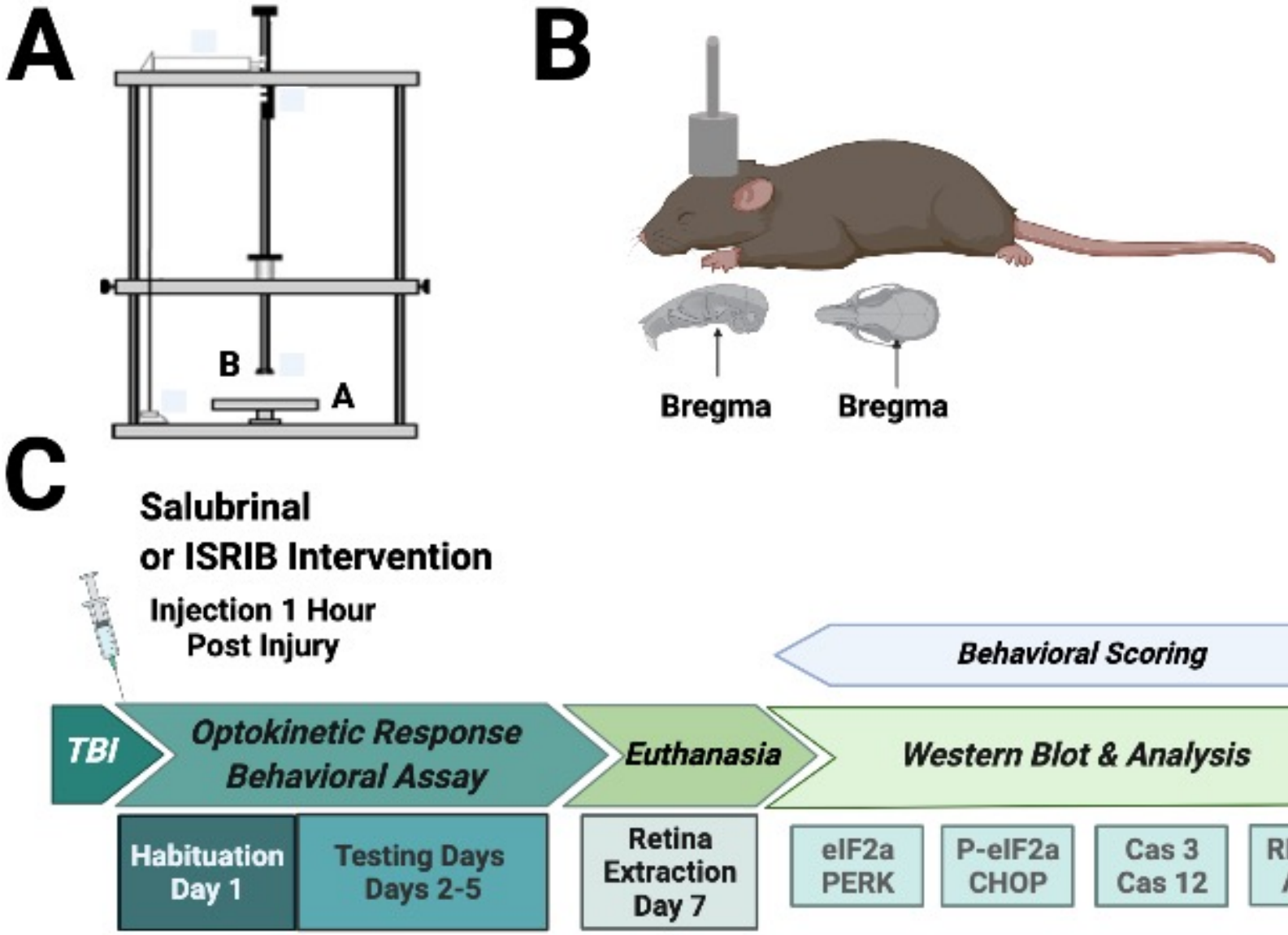

TBI
Missfolded Proteins
E.R Stress
P
PERK
P
eIF2α
eIF2α
P
Translation of pro-apoptotic Factors
Protein Translation
Apoptosis
Adaptation


eIF2α
eIF2α
P
Translation of pro-apoptotic Factors
Protein Translation
Apoptosis
Adaptation
ISRIB
eIF2α
eIF2α
P
ISRIB
Translation of pro-apoptotic Factors
Protein Translation
Apoptosis
Adaptation
Salubrinal
eIF2α
eIF2α
P
Salubrinal
Translation of pro-apoptotic Factors
Protein Translation
Apoptosis
Adaptation

Hypothesis

Manipulation of the PERK pathway via drug intervention of eIF2α phosphorylation and/or dephosphorylation will increase Retinal Ganglion Cell (RGC) survival/functioning and alter ER stress responses.

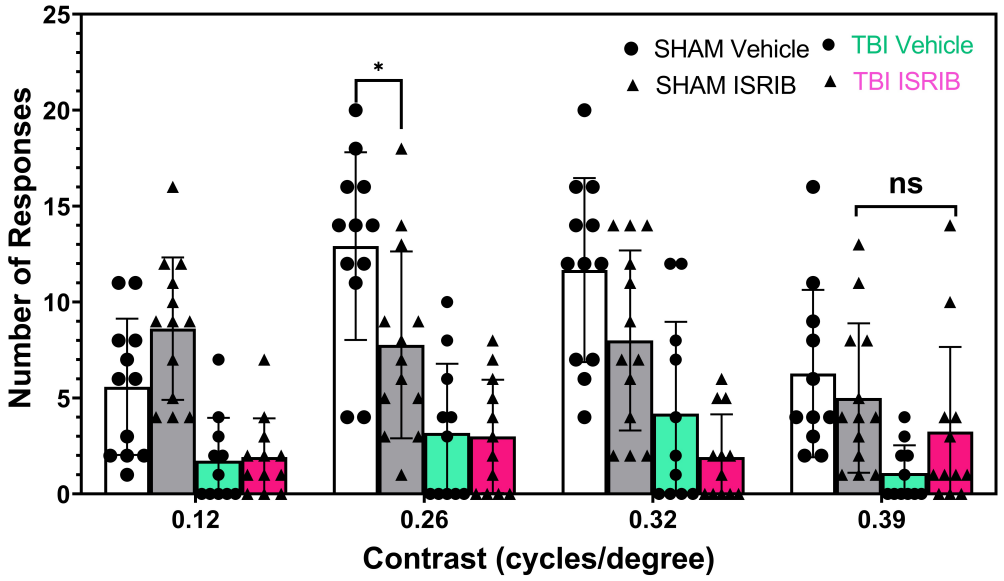
The Process


A
B
A
B
Bregma
Bregma
C
Salubrinal
or ISRIB Intervention
Injection 1 Hour
Post Injury
Behavioral Scoring
TBI
Optokinetic Response
Behavioral Assay
Euthanasia
Western Blot & Analysis
Habituation
Day 1
Testing Days
Days 2-5
Retina
Extraction
Day 7
eIF2a
PERK
P-eIF2a
CHOP
Cas 3
Cas 12
RBPMS
ATF4

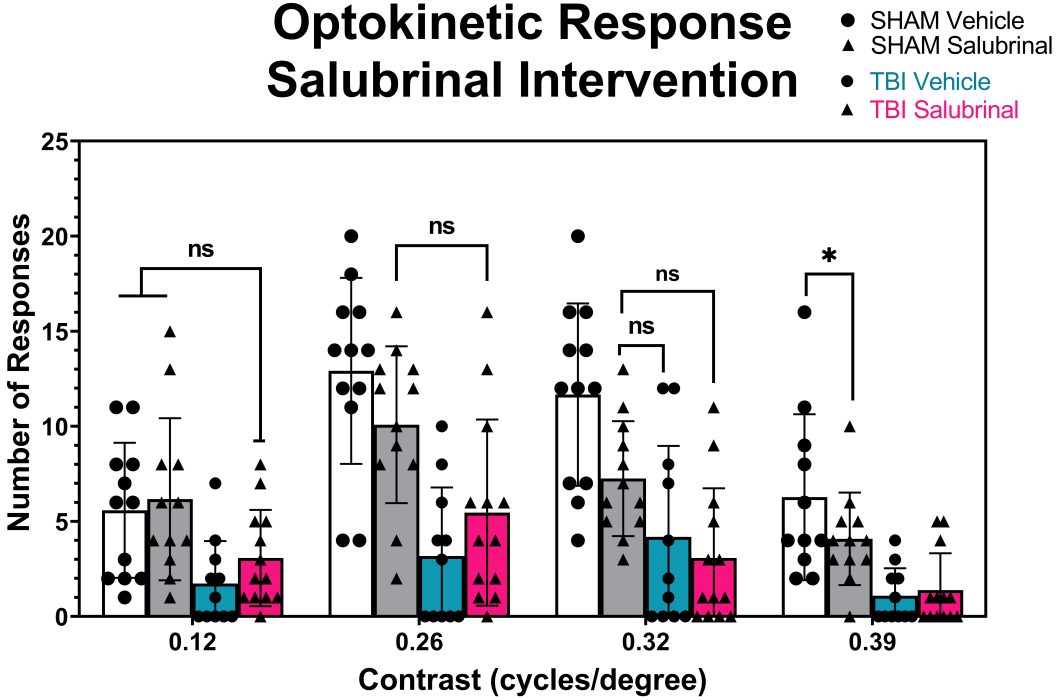
What Happened?

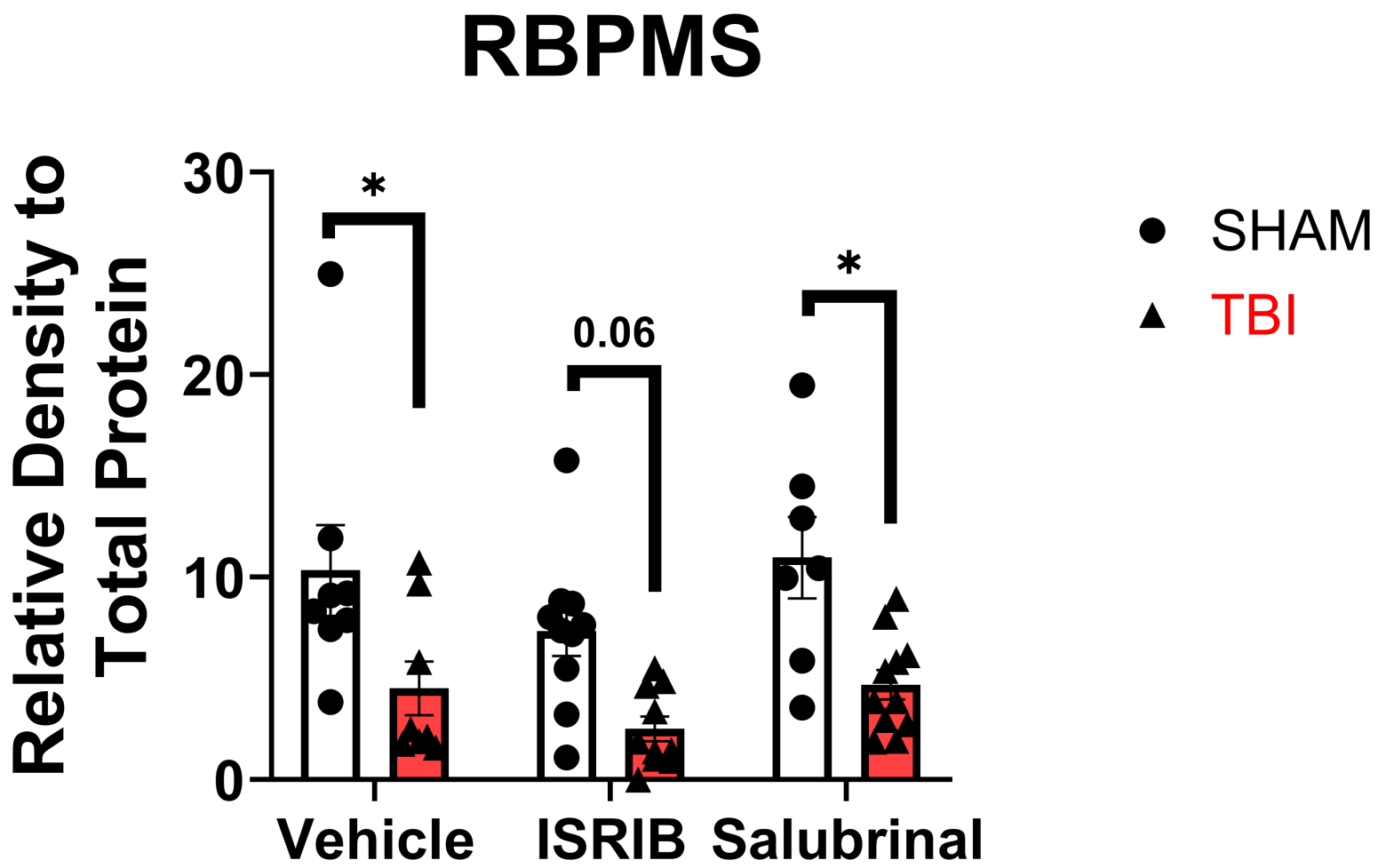
RESULTS

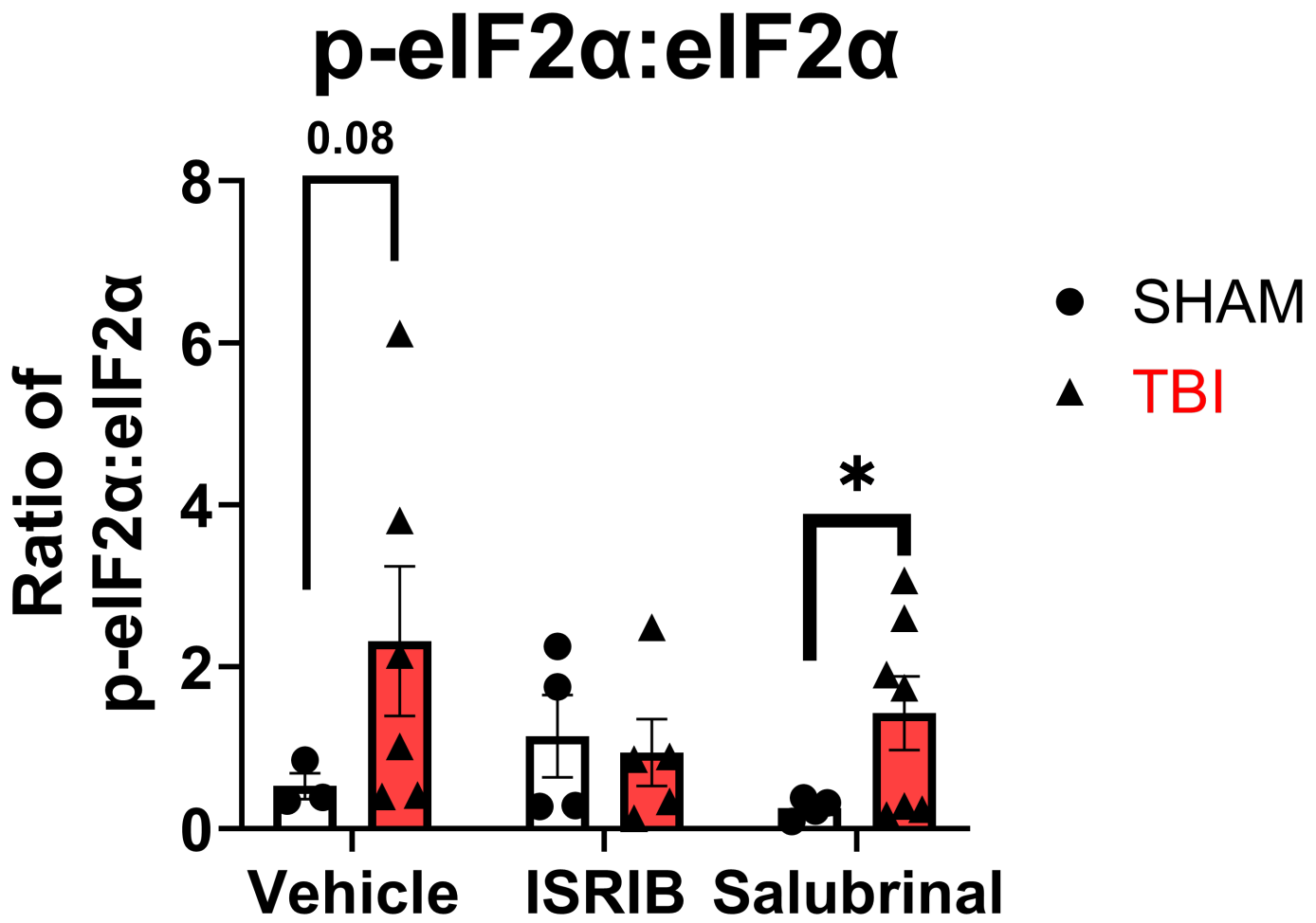
Optokinetic Response
ISRIB Intervention



Optokinetic Response
Salubrinal Intervention




RBPMS
Relative Density to Total Protein
30
20
10
0
*
0.06
*
Vehicle
ISRIB
Salubrinal
SHAM
TBI


p-eIF2α:eIF2α
0.08
*
Ratio of p-eIF2α:eIF2α
8
6
4
2
0
Vehicle
ISRIB
Salubrinal
SHAM
TBI

What's next?

Further studies need to be completed in order to fully understand the effects of each therapeutic within the context of TBI

The dose response needs to be examined and retested

Further analysis of cellular death markers as well as other markers of varying E.R stress pathways outside of PERK need to be examined

While neither drug showed significant improvement in saving retinal cells, they should be examined further

Acknowledgements

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