

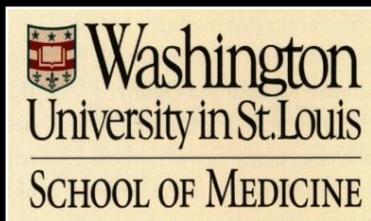
Extending Injury- and Disease-Tolerant Phenotypes by Repetitive Conditioning

Promoting Long-Lasting Protection in the CNS

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Neurosurgery
Ophthalmology & Visual Sciences
Cell Biology & Physiology

Washington University School of Medicine



Contact: gidday@wustl.edu





WHAT DOESN'T KILL YOU

Makes you stronger.

got hypoxia?

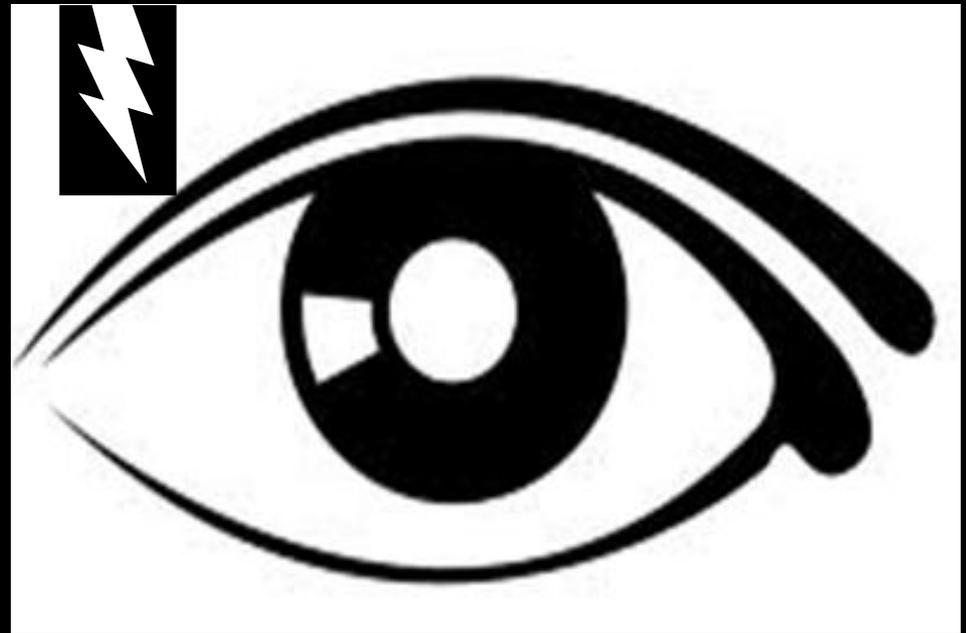
CNS Disease

Acute and Chronic Disease

Stroke

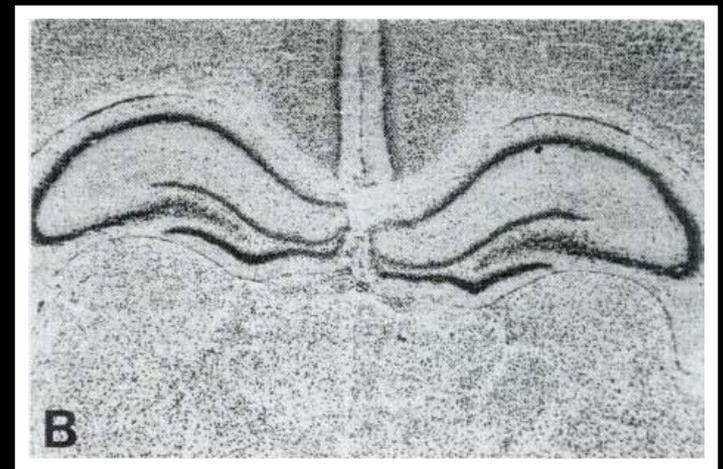
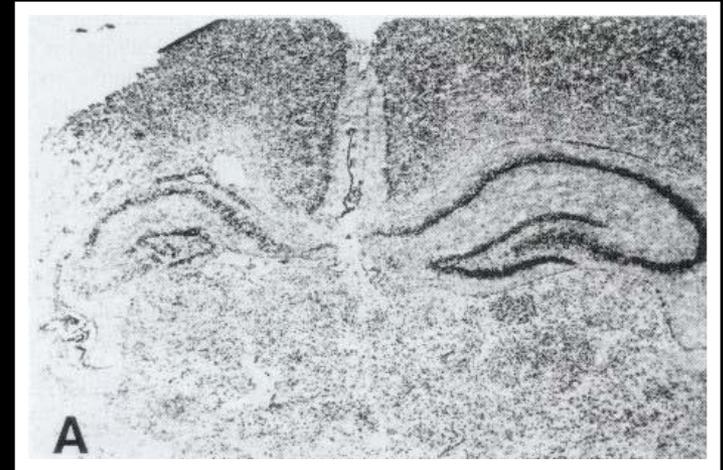
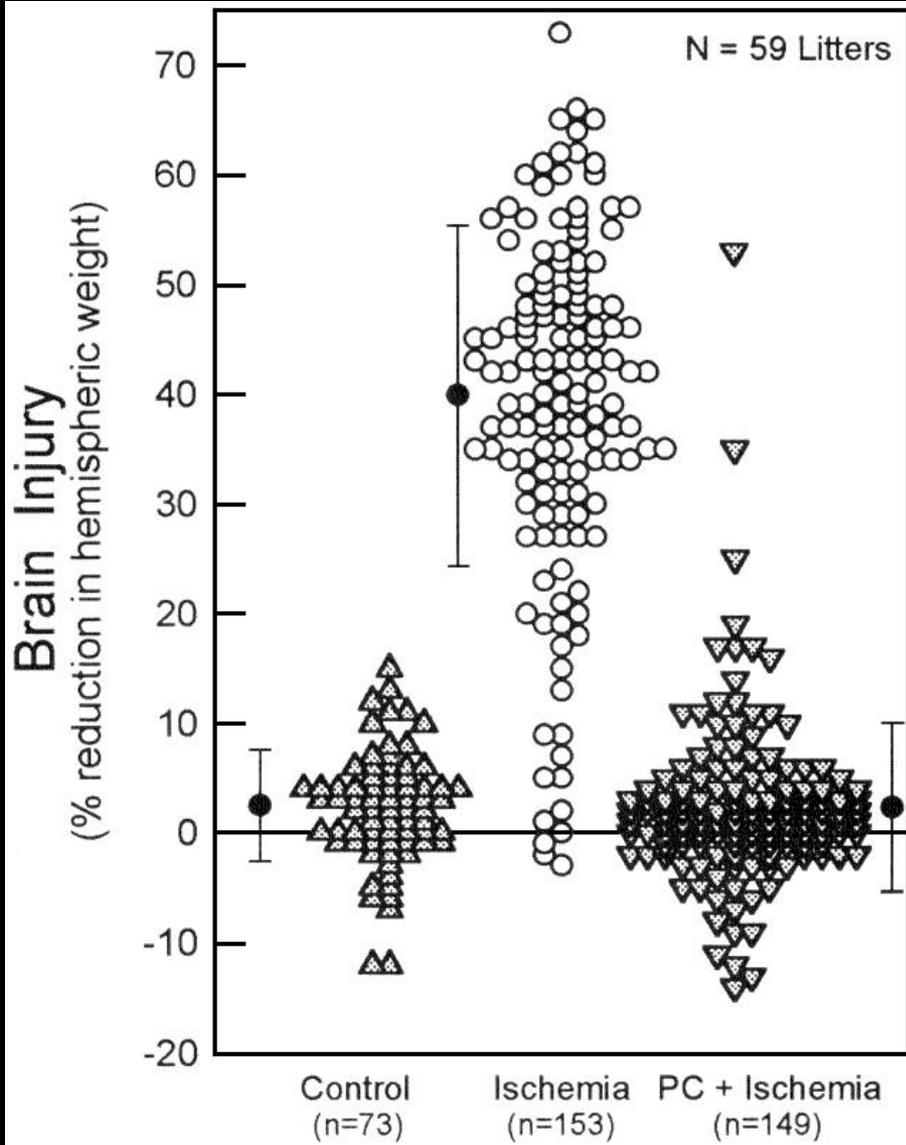


**Retinal Ischemia
and
Glaucoma**



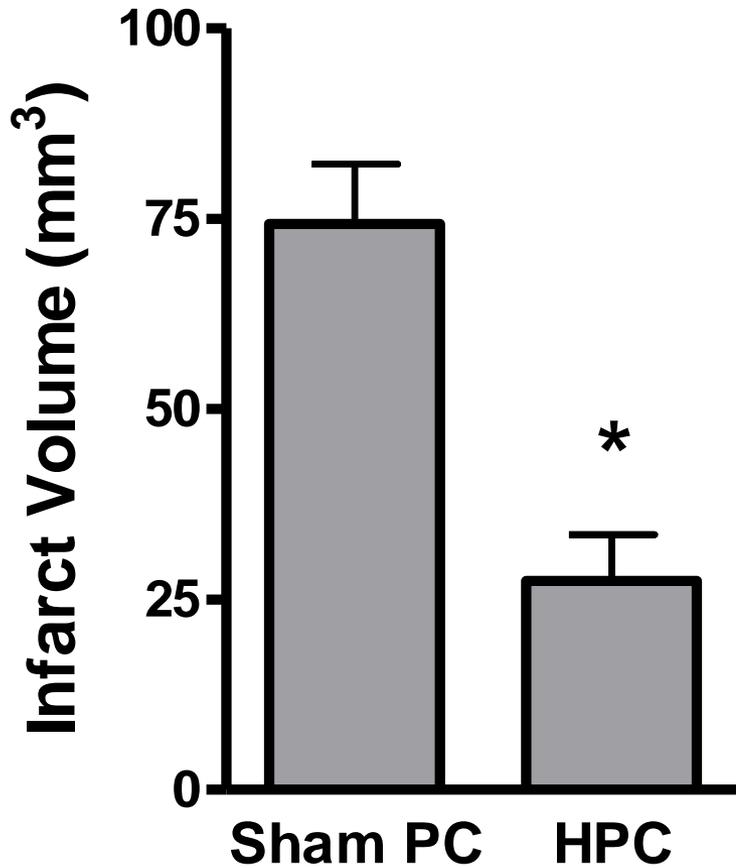
Hypoxic Preconditioning

newborn rat stroke

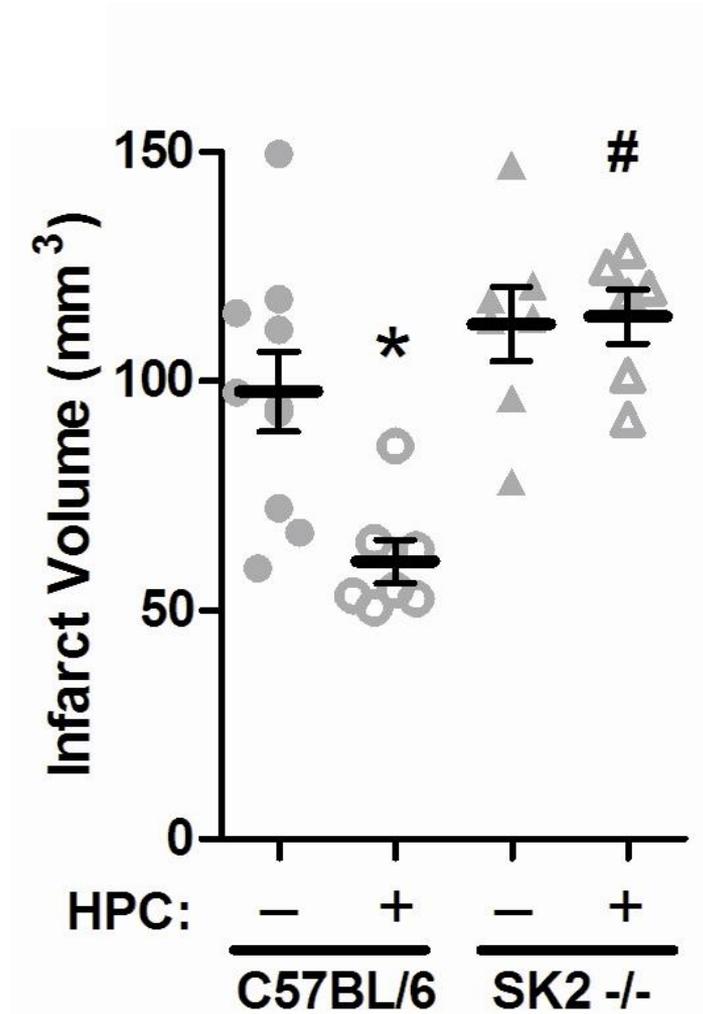


Hypoxic preconditioning

Adult mouse stroke



Miller et al., *NeuroReport*, 2000



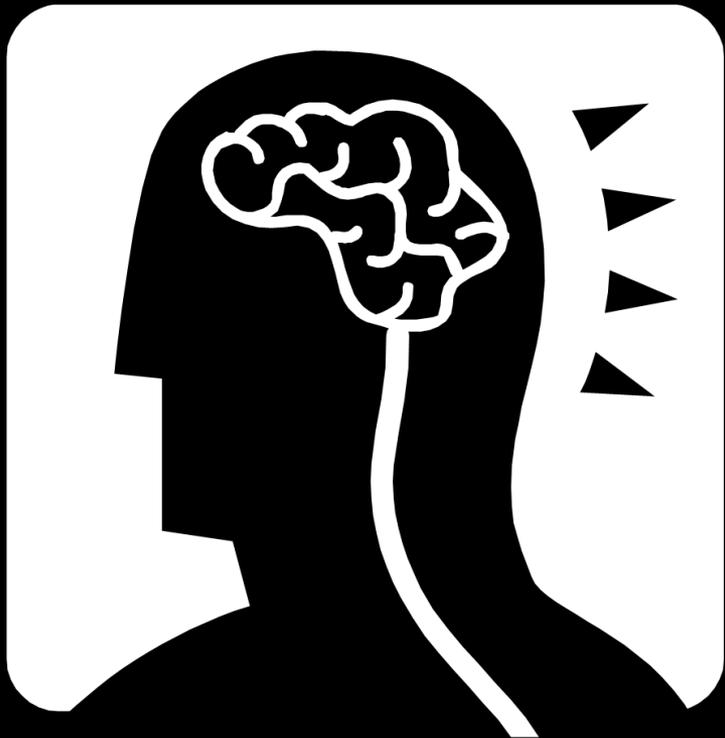
Wacker et al., *JCBFM*, 2012

CNS Disease

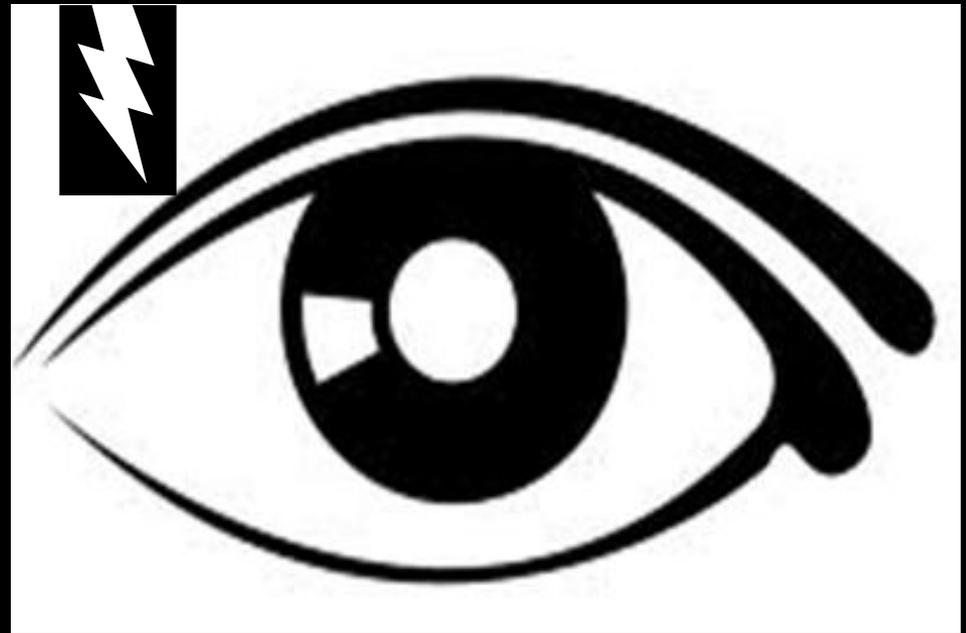
Acute and Chronic Disease

Retinal Ischemia

Stroke

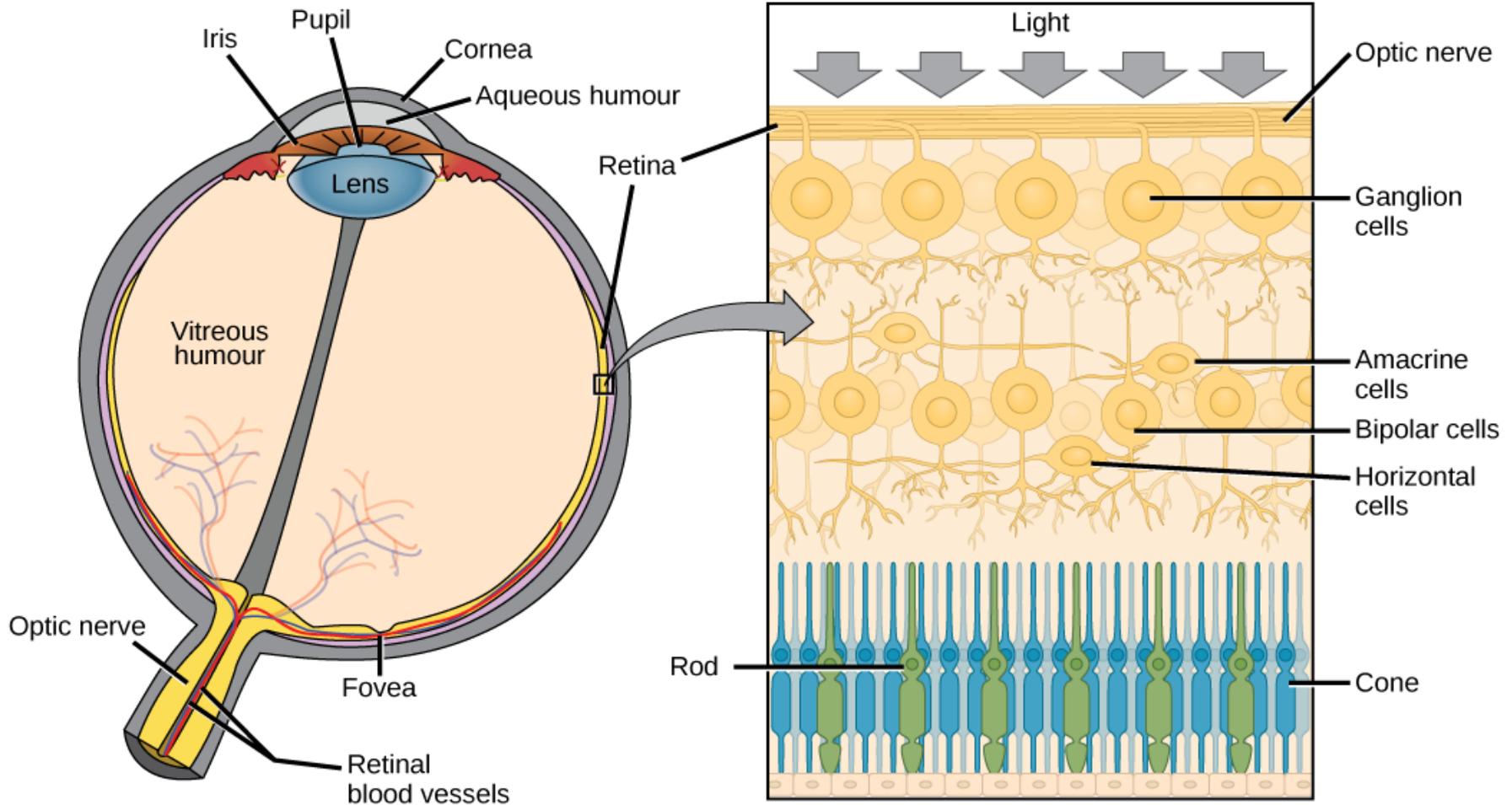


Glaucoma



The Mammalian Retina

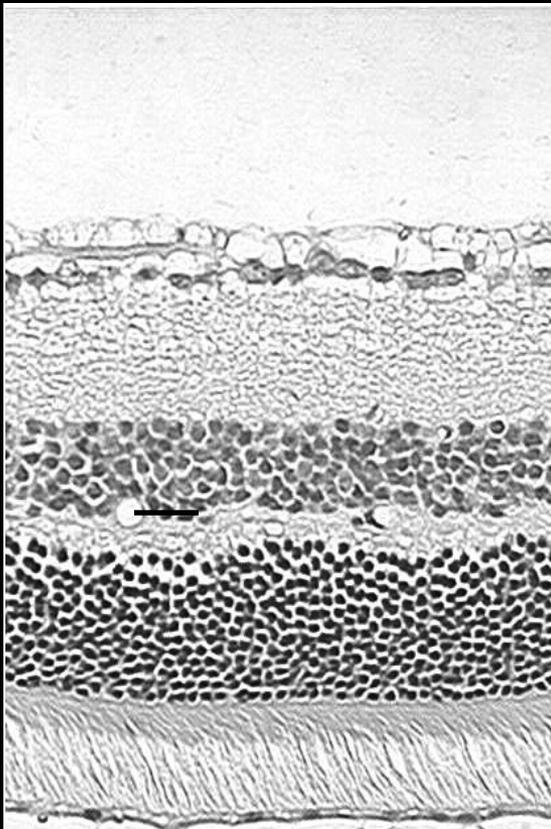
anatomy refresher



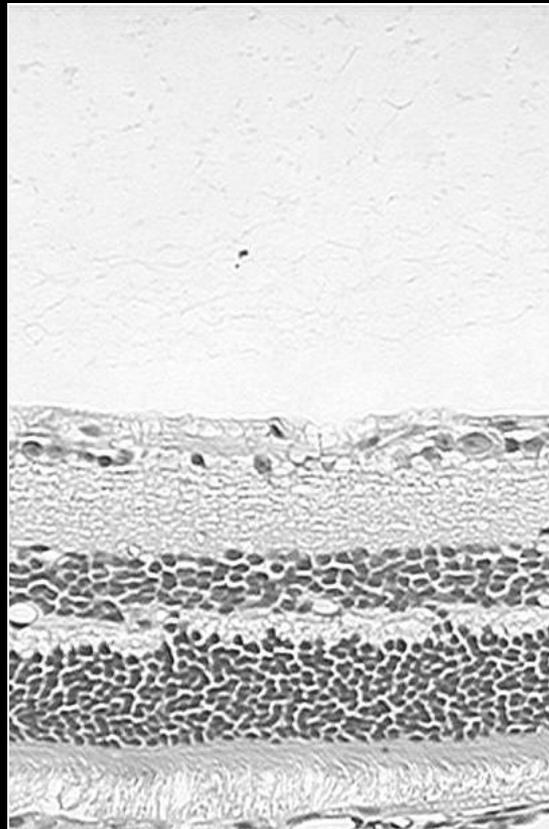
Histology

Hypoxic Preconditioning-Induced Protection

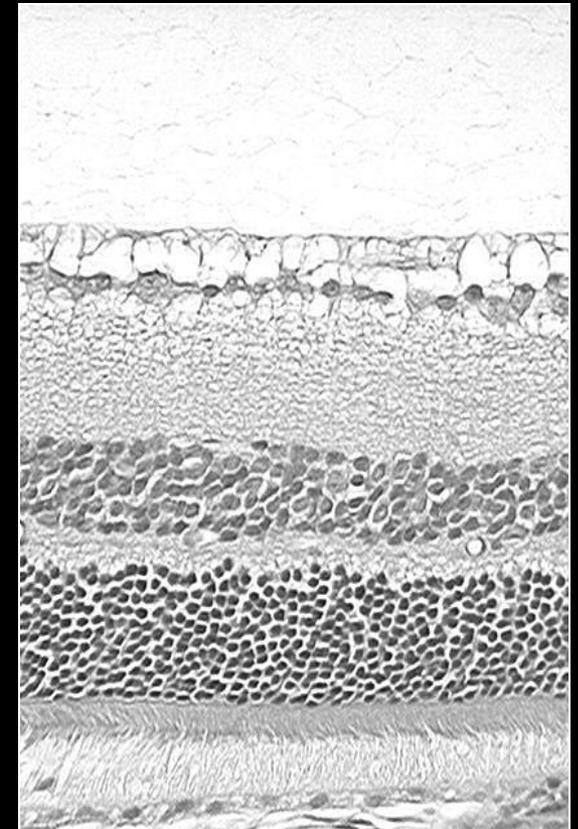
Control



Ischemia

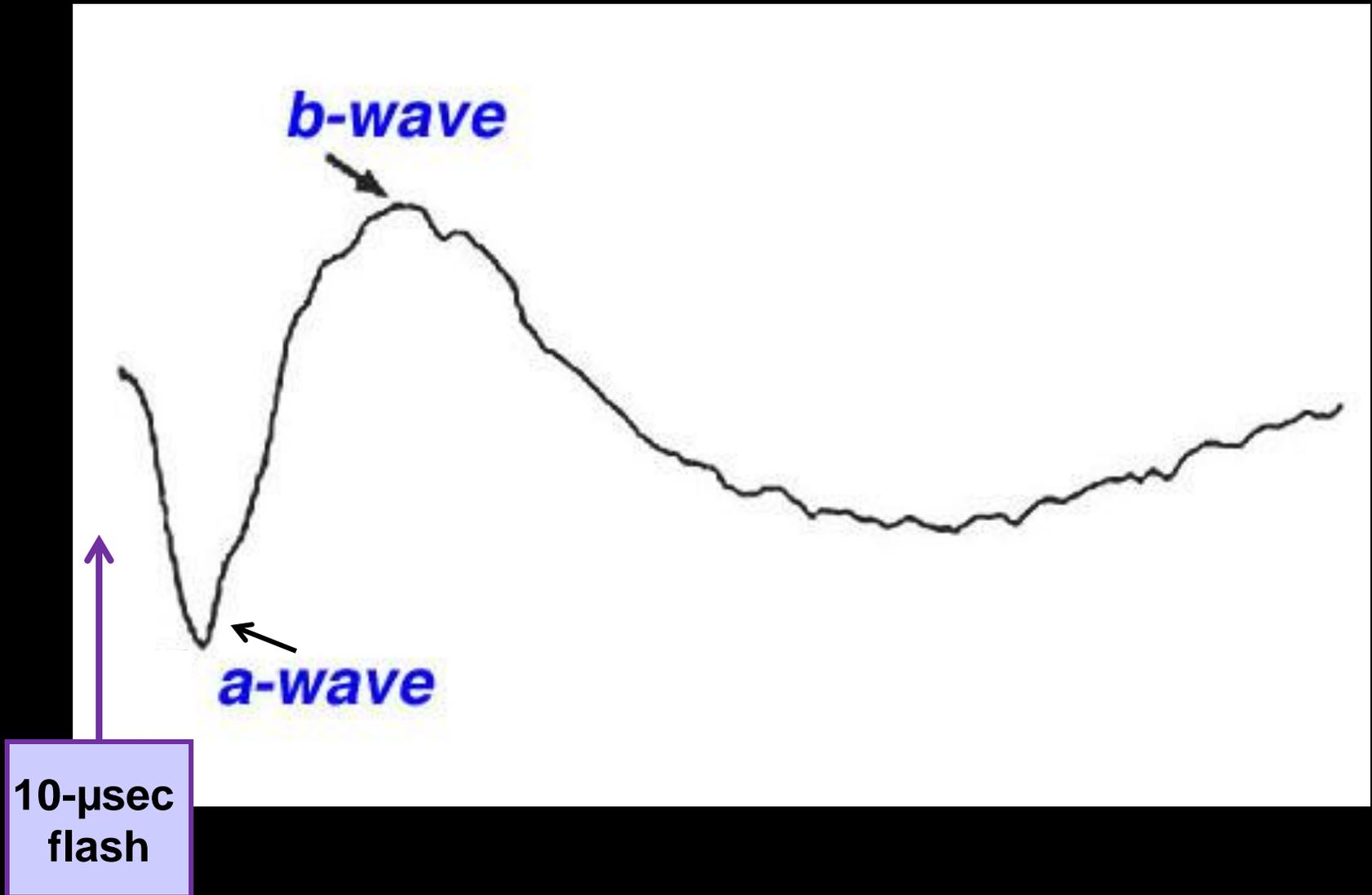


**Hypoxic
Preconditioning
+ Ischemia**



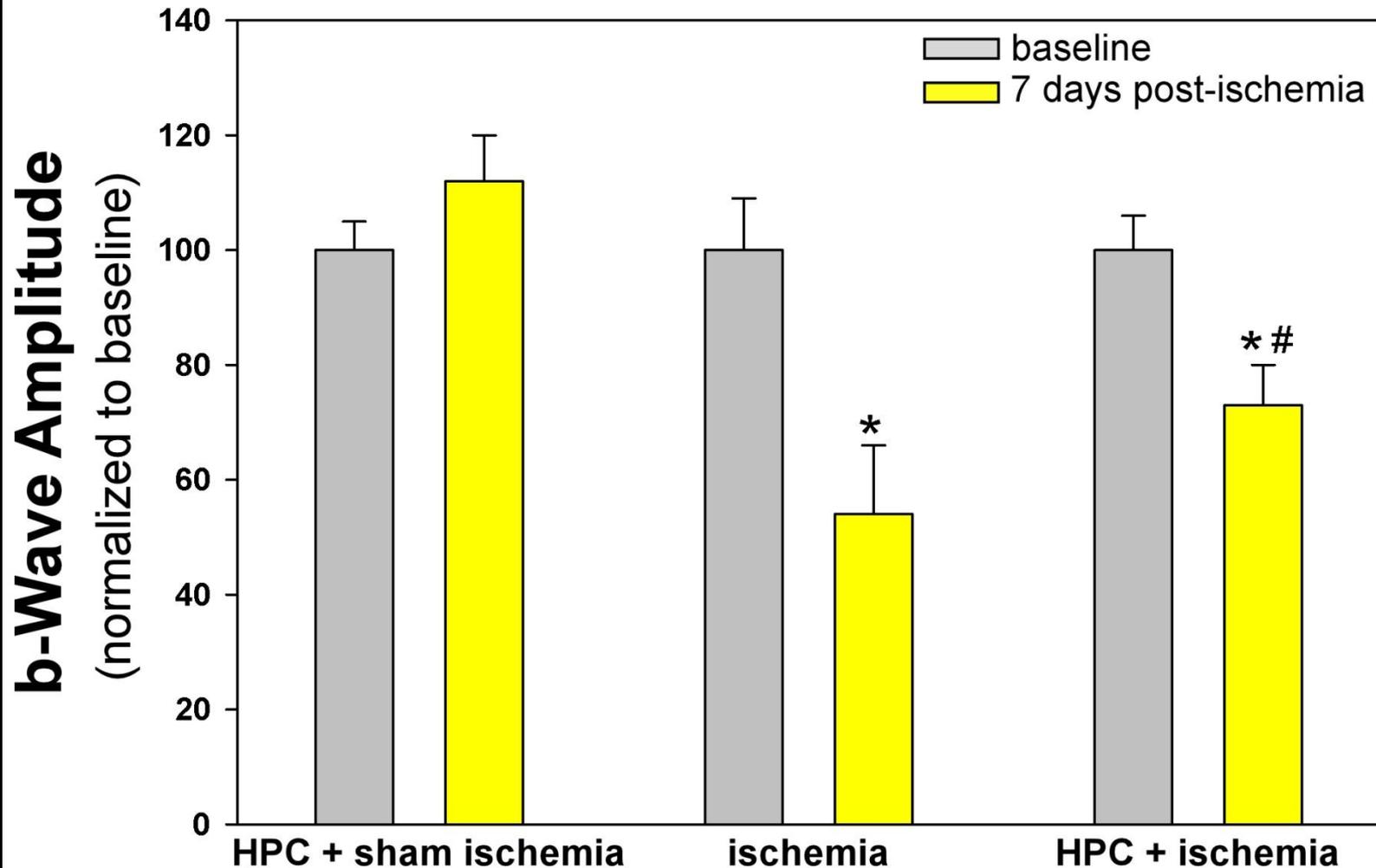
Flash Electroretinogram

Quantifying the Retinal Response to Light



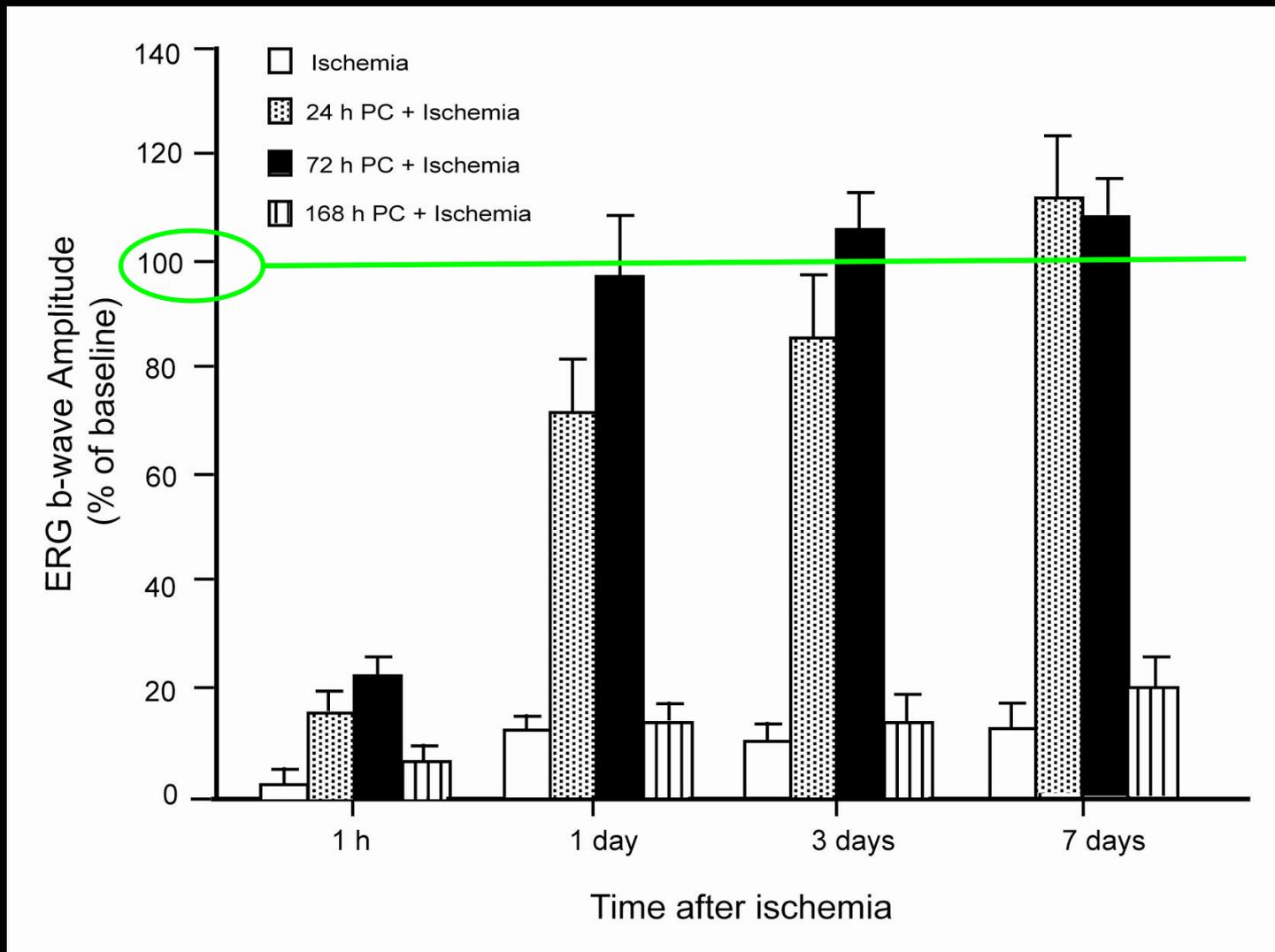
Hypoxic Preconditioning

functional protection against retinal ischemia



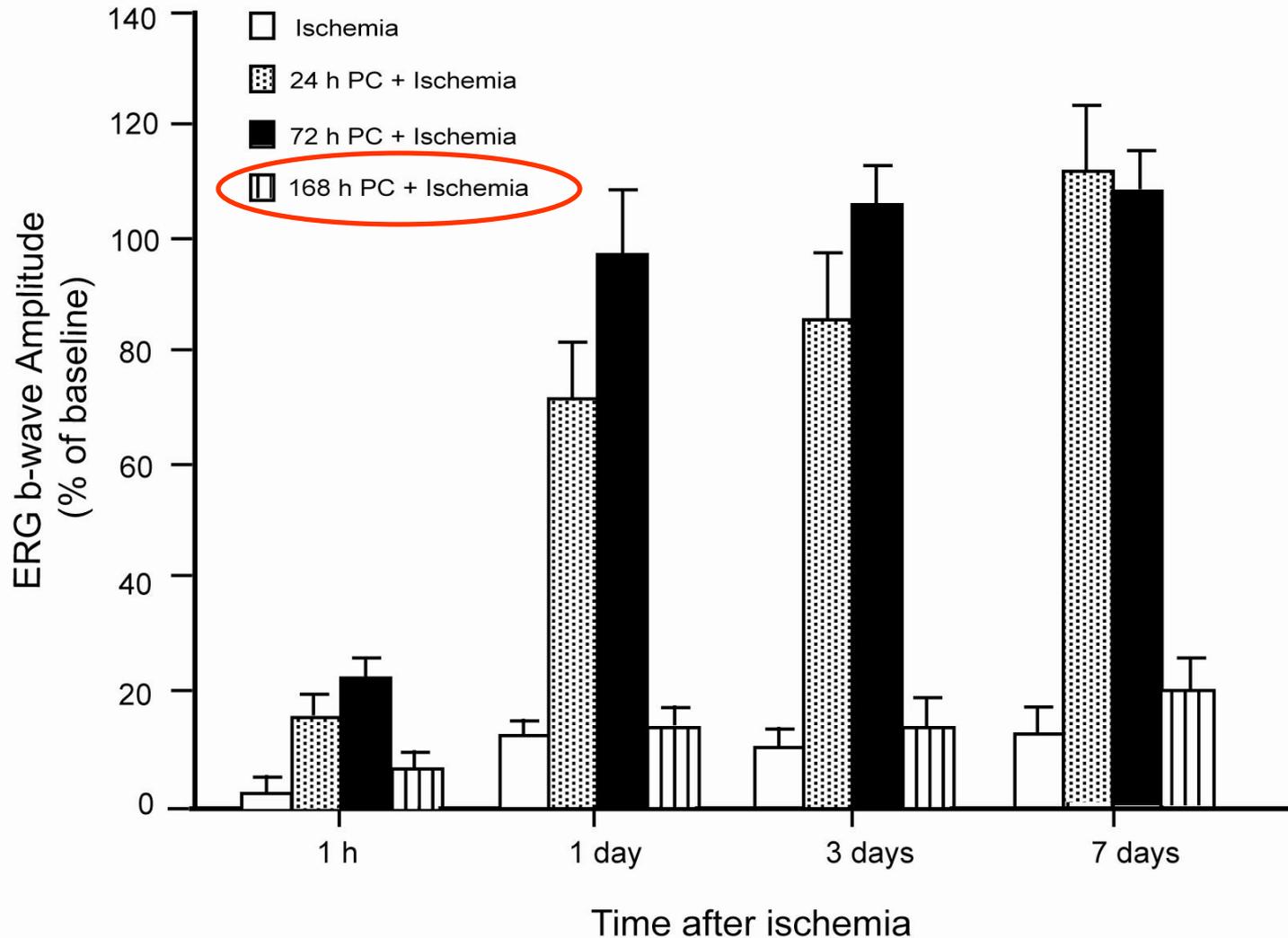
Ischemic Preconditioning

Protection Against Retinal Ischemic Injury

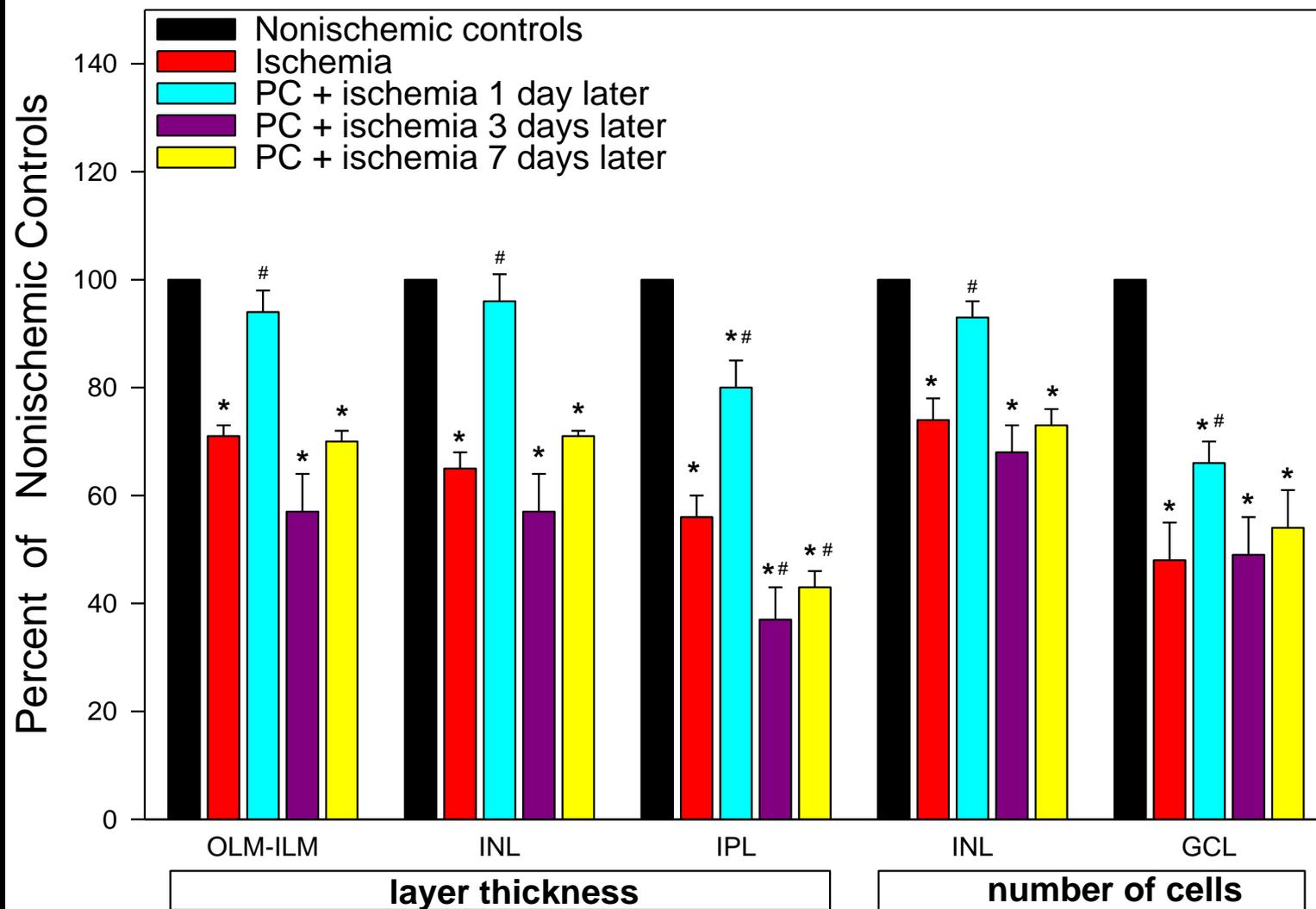




Transient Protection – Rat Retina

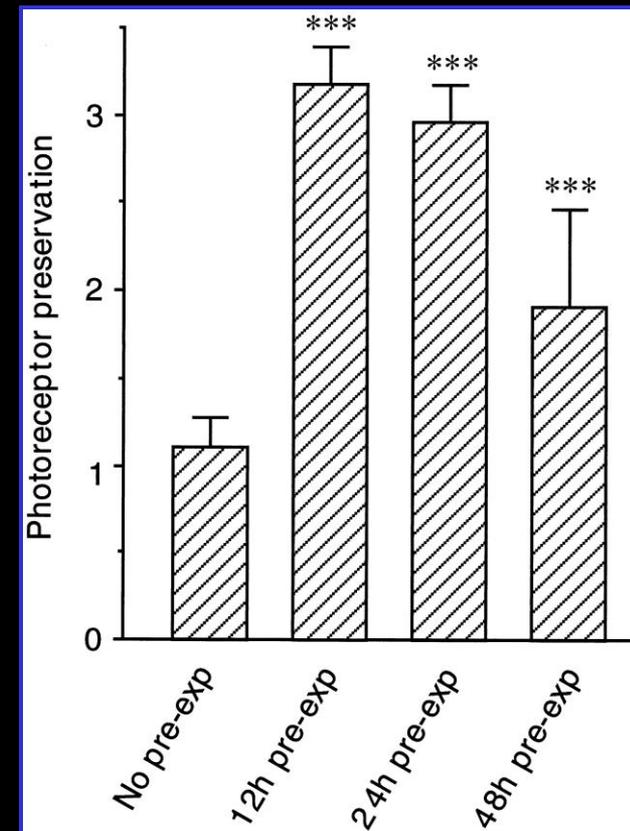
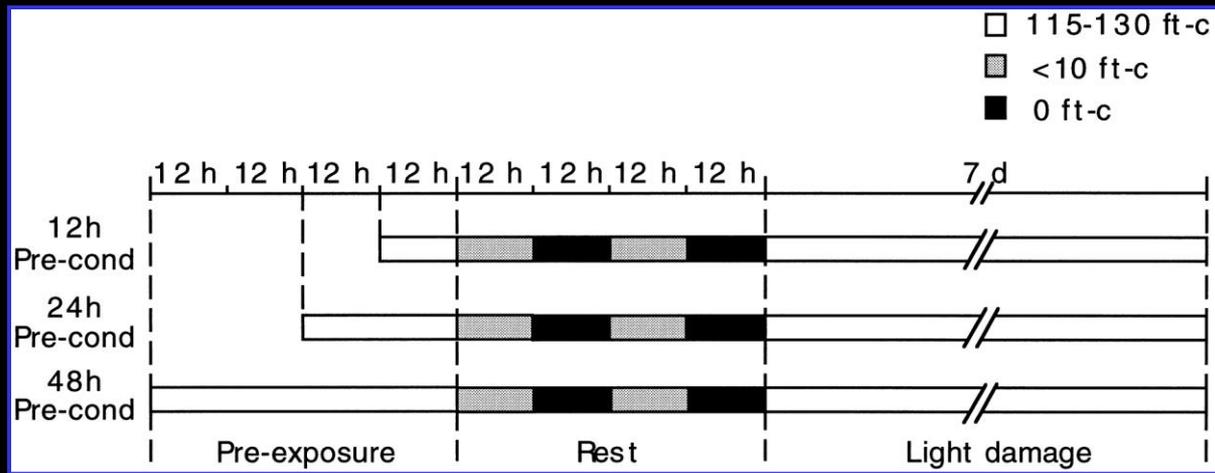


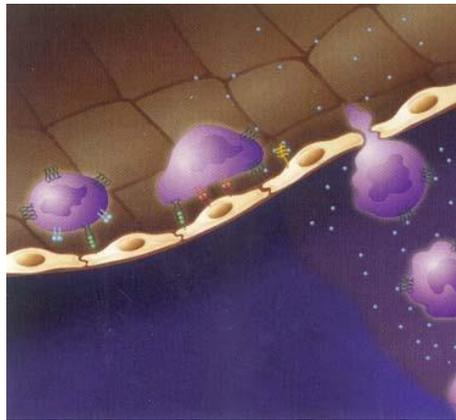
Transient Protection – Mouse Retina



Retinal Phototoxicity Tolerance

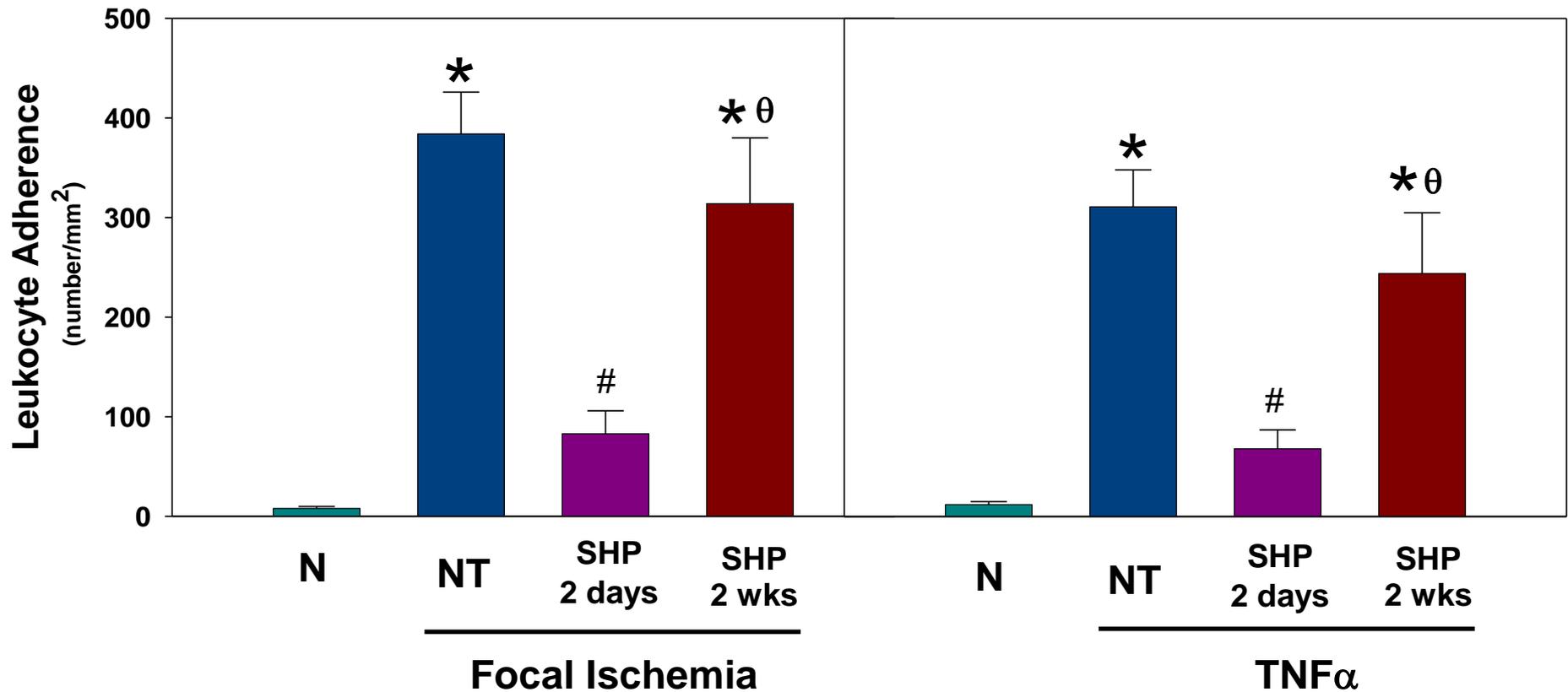
transient protection





Hypoxic preconditioning in adult transient focal stroke

*Reductions in leukocyte-endothelial
adherence and infiltration*



Home Sweet Home...?



www.Go2Altitude.com

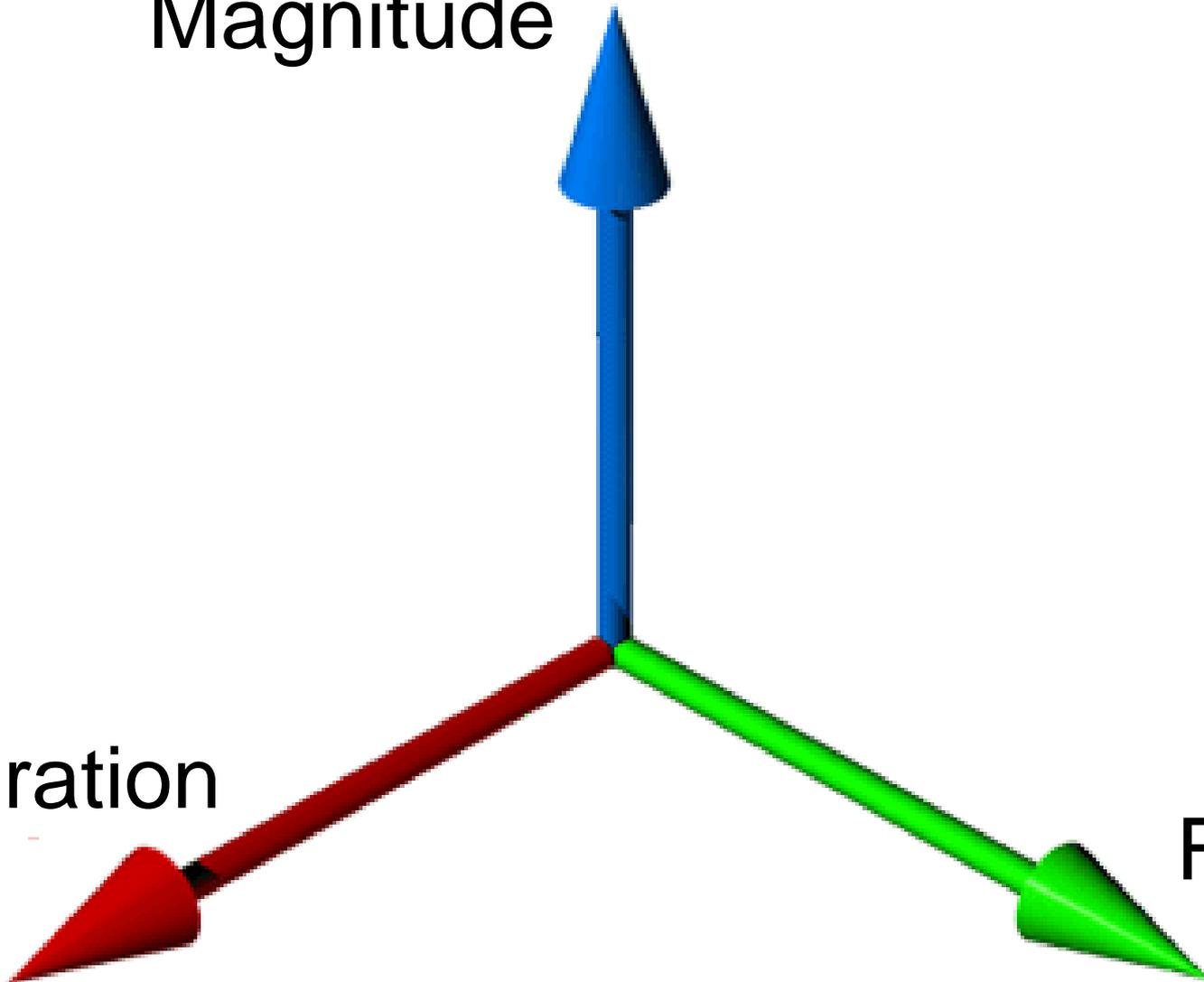


Magnitude

Duration

Frequency

*



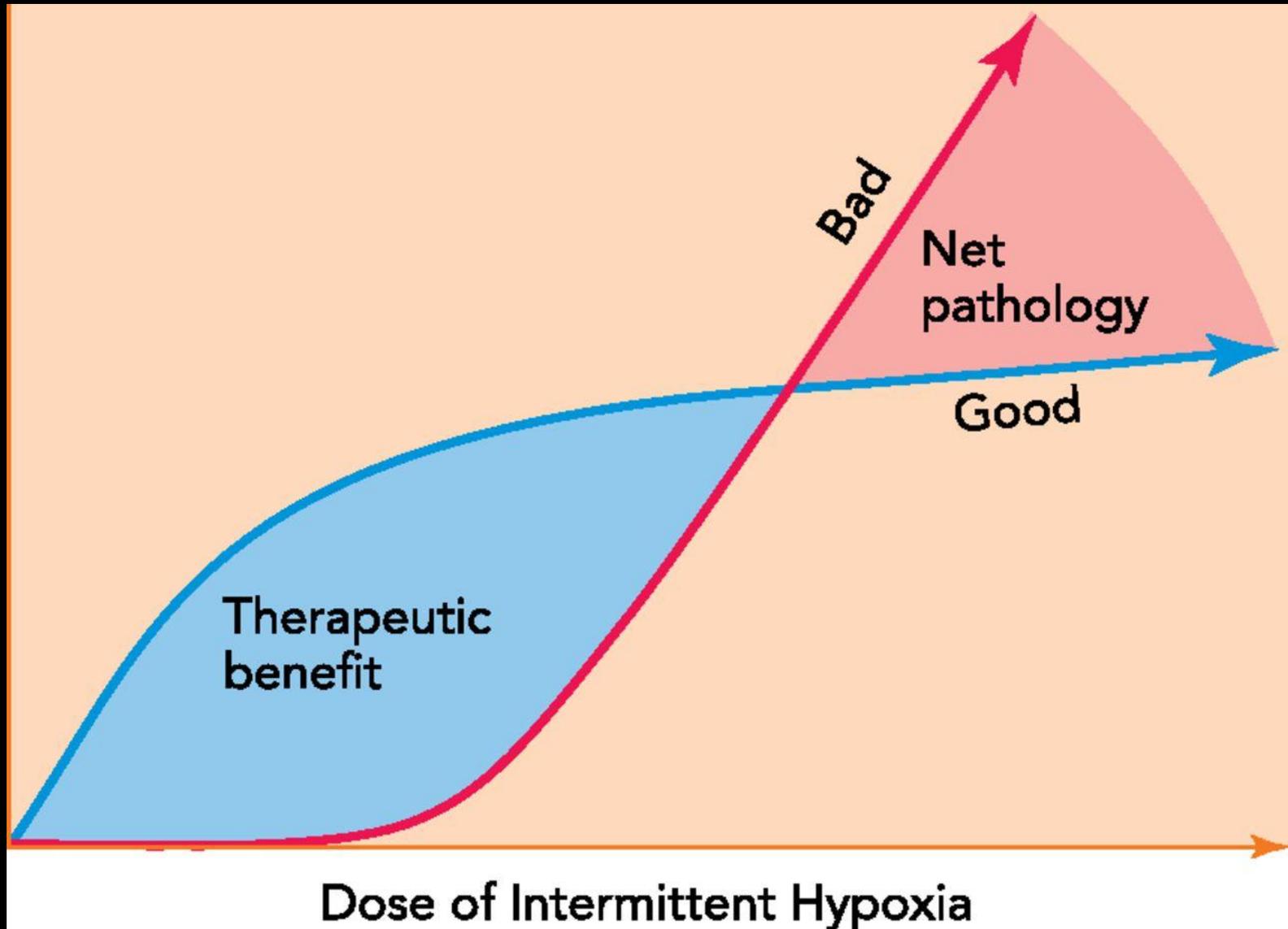
Intermittent Hypoxia

***In vivo* preclinical studies**

- Promotes hippocampal neurogenesis (Zhu et al., *J Neurosci* 2010)
- Enhances proliferation of neuroprogenitor cells (Zhu et al., *Brain Res* 2005)
- Upregulates egr-1 and other survival-promoting transcription factors (Rybnikova et al., *Behav Brain Res* 2005)
- Protects against iron-, MPTP-, and kainic acid-induced neuronal injury (Lin et al., *Exp Neurol* 2002)
- Prevents mitochondrial DNA deletion and inhibits opening of MPTPs in heart (Zhu et al., *J Mol Cell Cardiol* 2006)
- Prolongs survival in a leukemic mouse model via tumor arrest and differentiation induction (Liu et al., *Blood* 2010)

Intermittent Hypoxia

dose titration critical

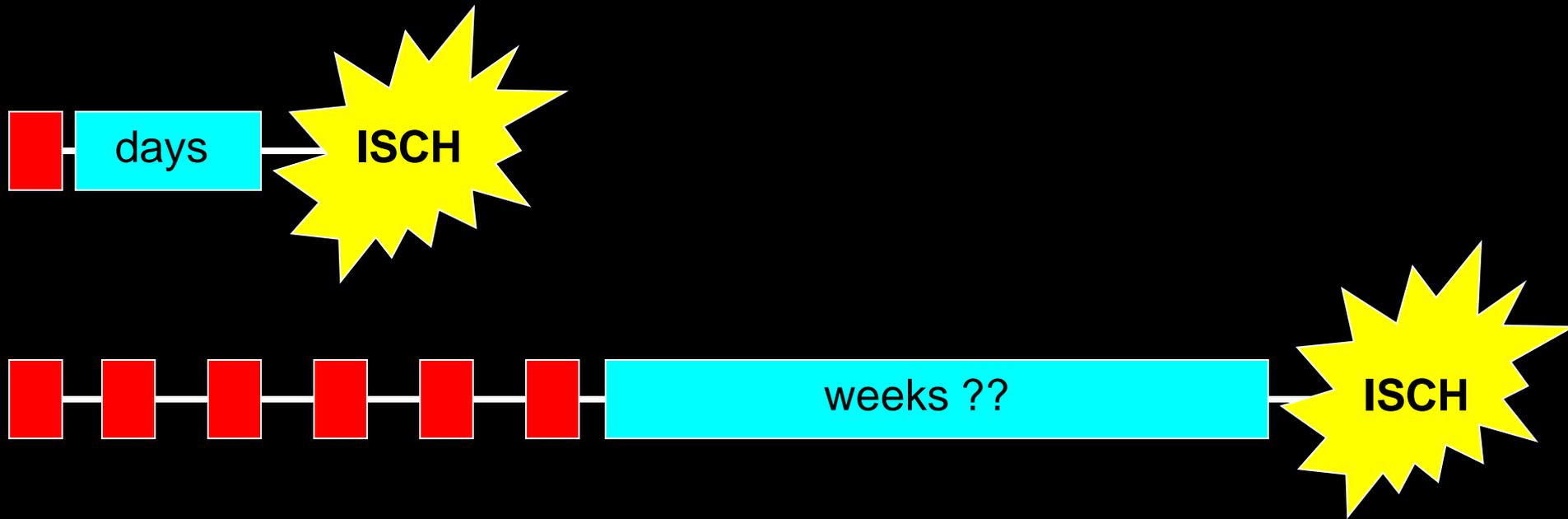


Epaulette shark
Hemiscyllium ocellatum



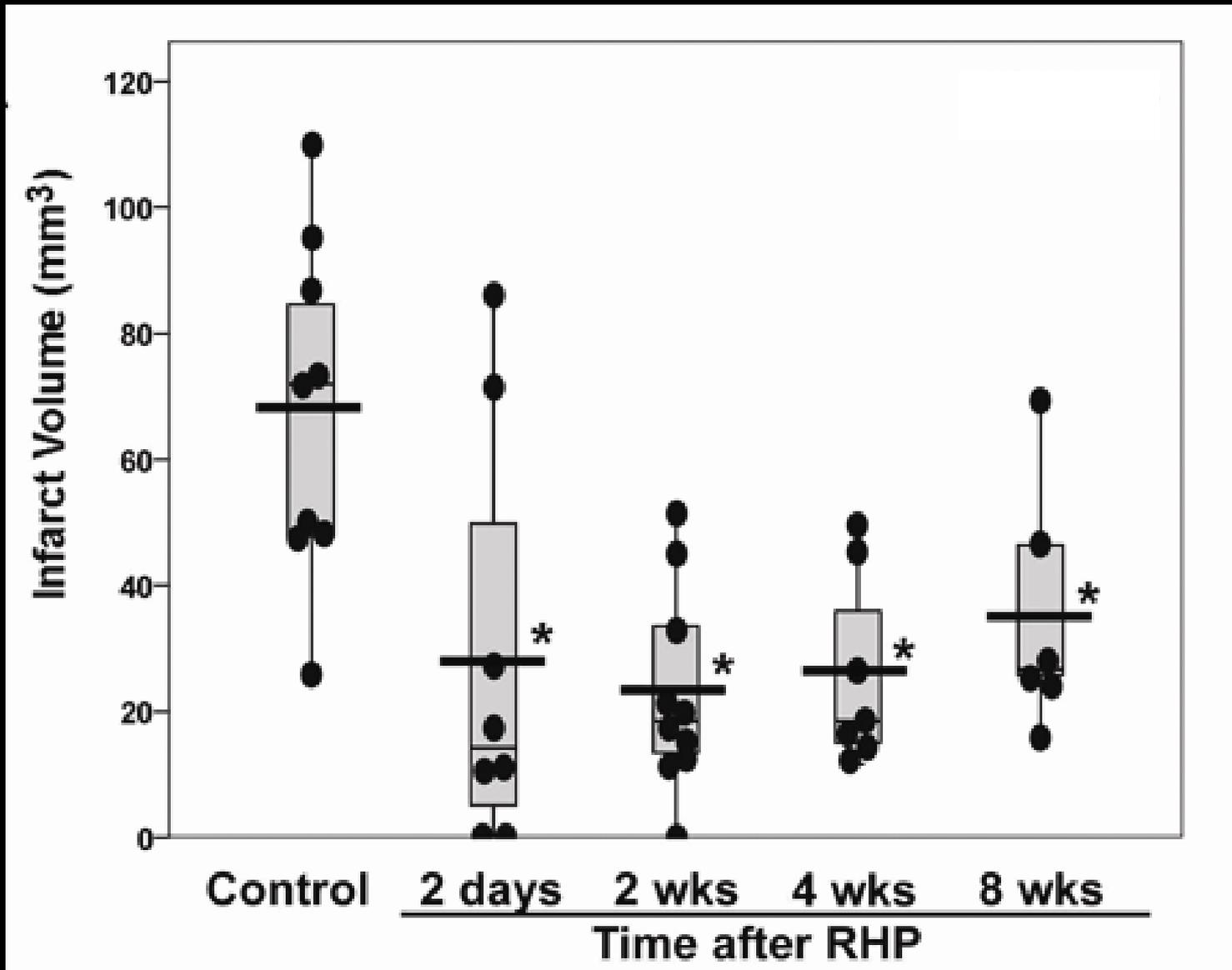
Repetitive Hypoxic Preconditioning “RHP”

Experimental Design



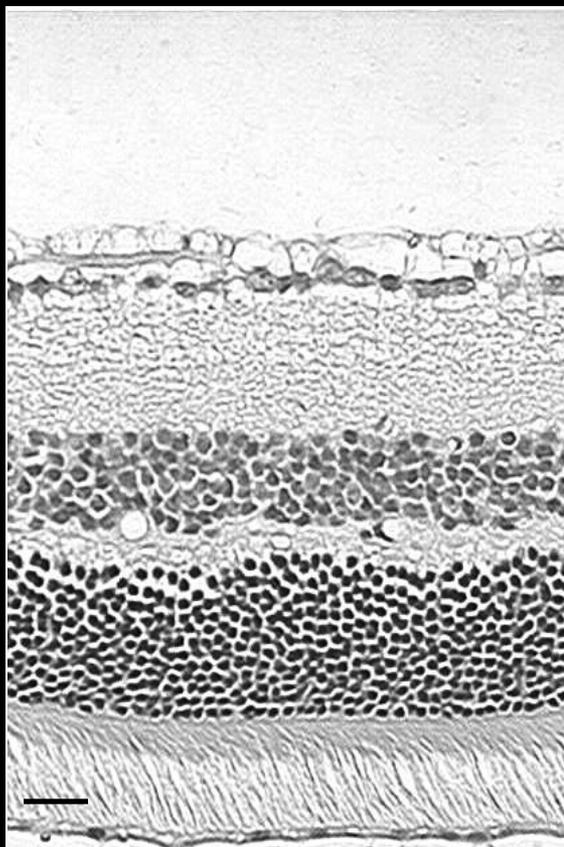
RHP = Systemic hypoxia (11% oxygen, 6 treatments over 2 wks)

“Long-Term Tolerance” Against Stroke

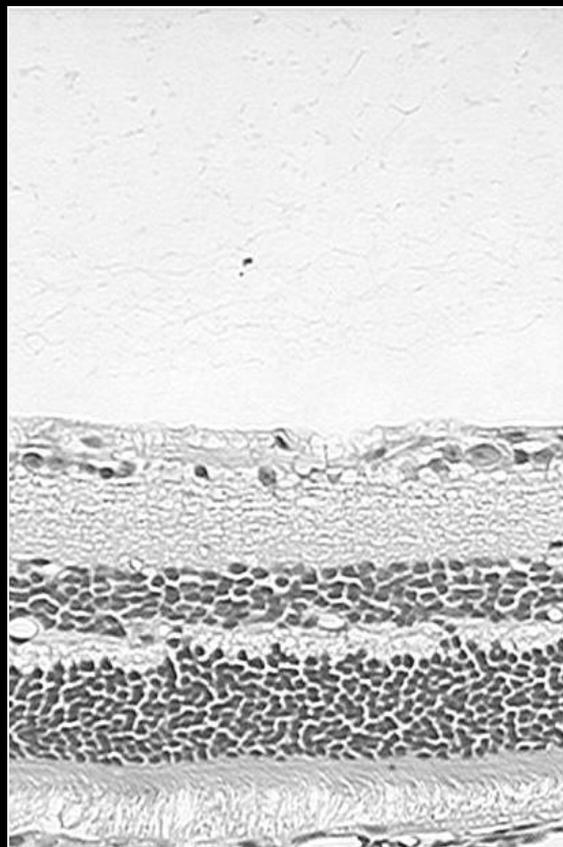


“Long-Term Tolerance” Against Retinal Ischemia

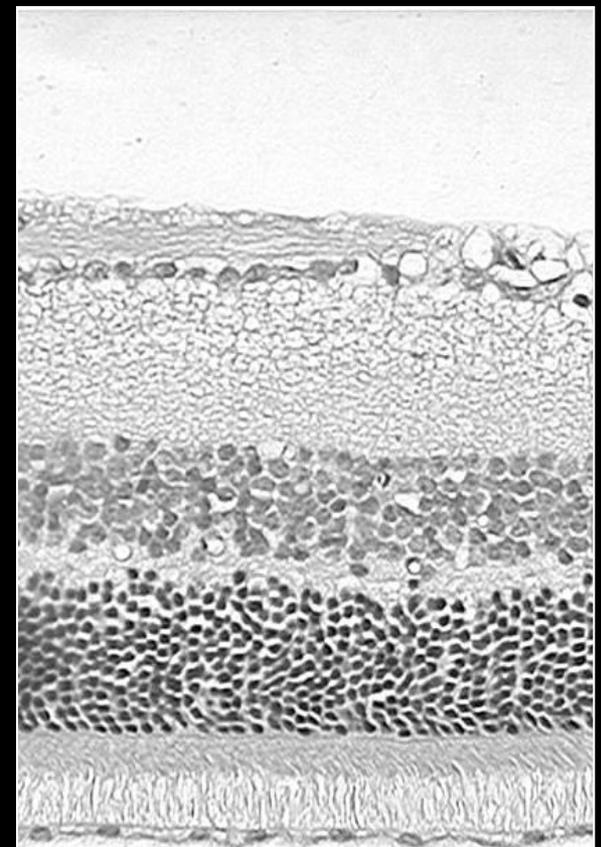
Control



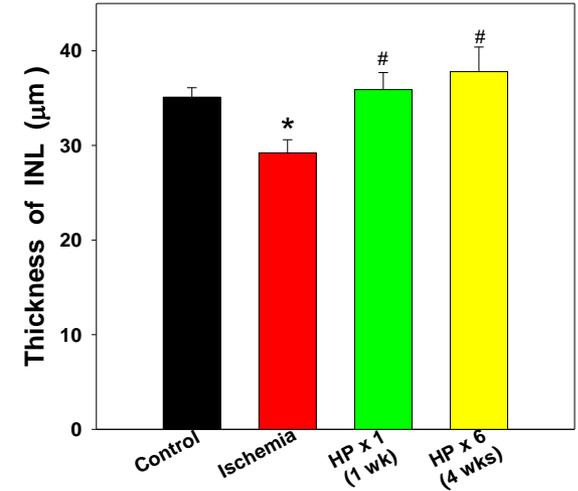
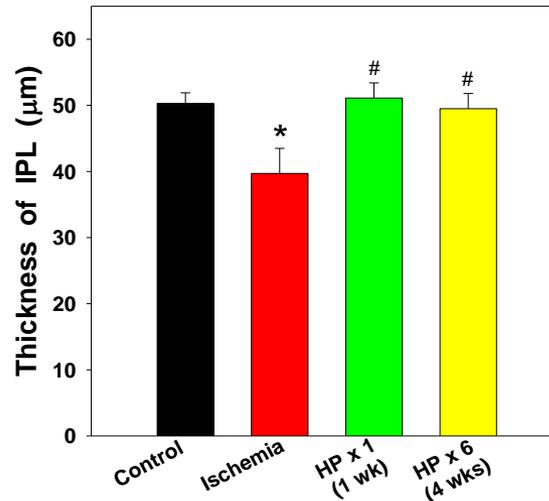
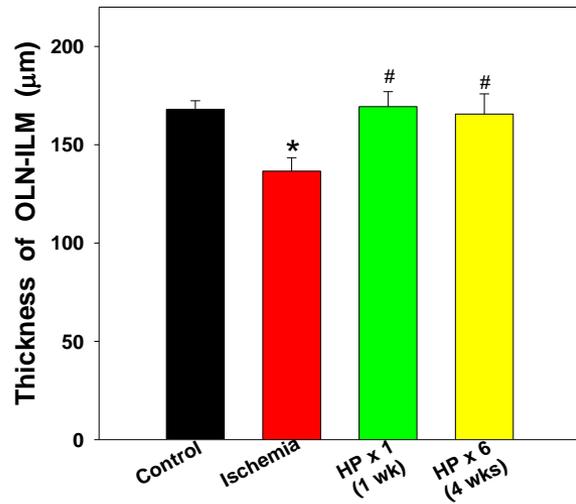
Ischemia



RHP
+ Ischemia
(4 wks after RHP)

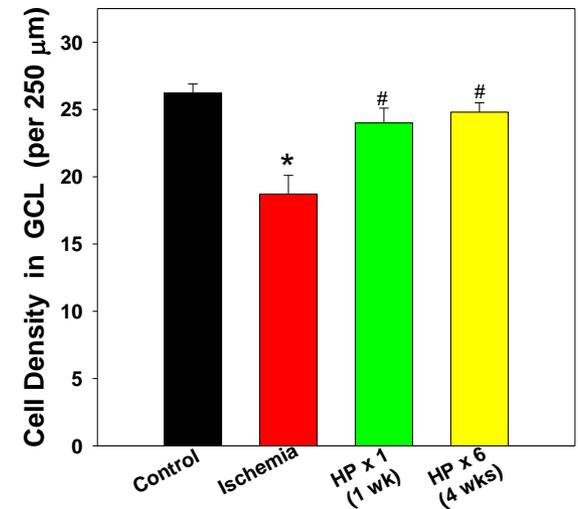
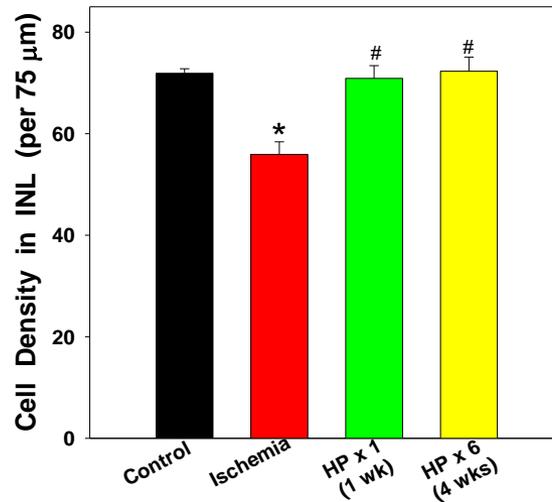


Prolonged Retinal Ischemic Tolerance Following Repetitive Hypoxic Preconditioning (RHP)

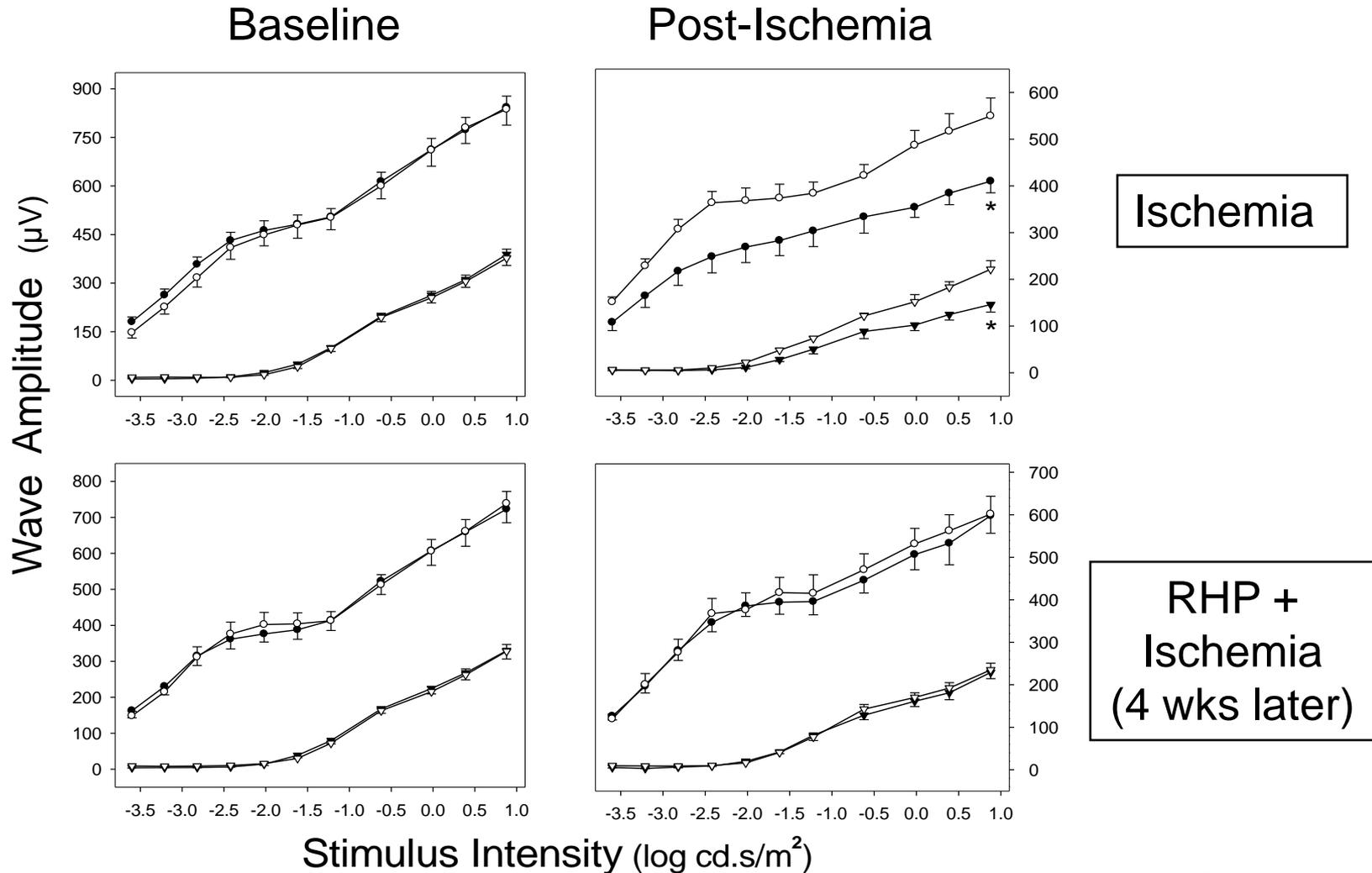


 Single Hypoxic Preconditioning (HP x 1)

 Repetitive Hypoxic Preconditioning over 2 wks (HP x 6)

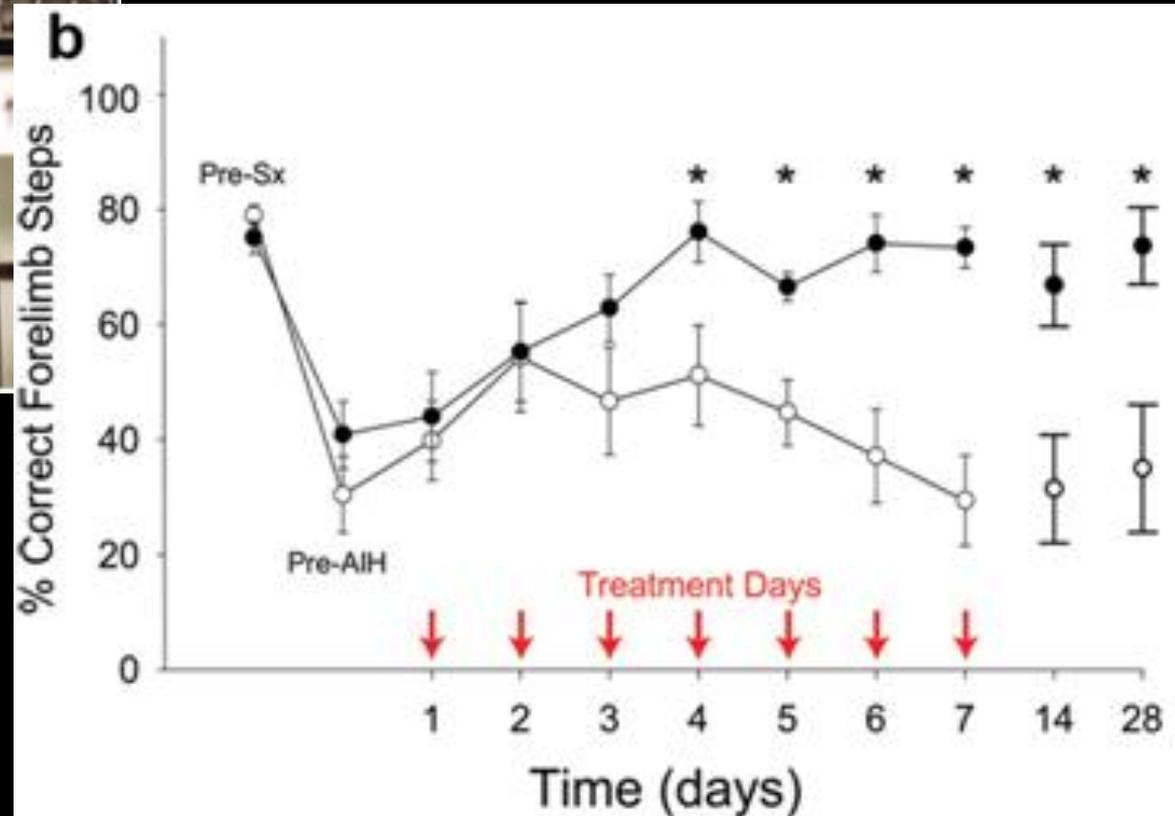


Prolonged Retinal Ischemic Tolerance Following Repetitive Hypoxic Preconditioning (RHP)



Intermittent Hypoxia for SCI

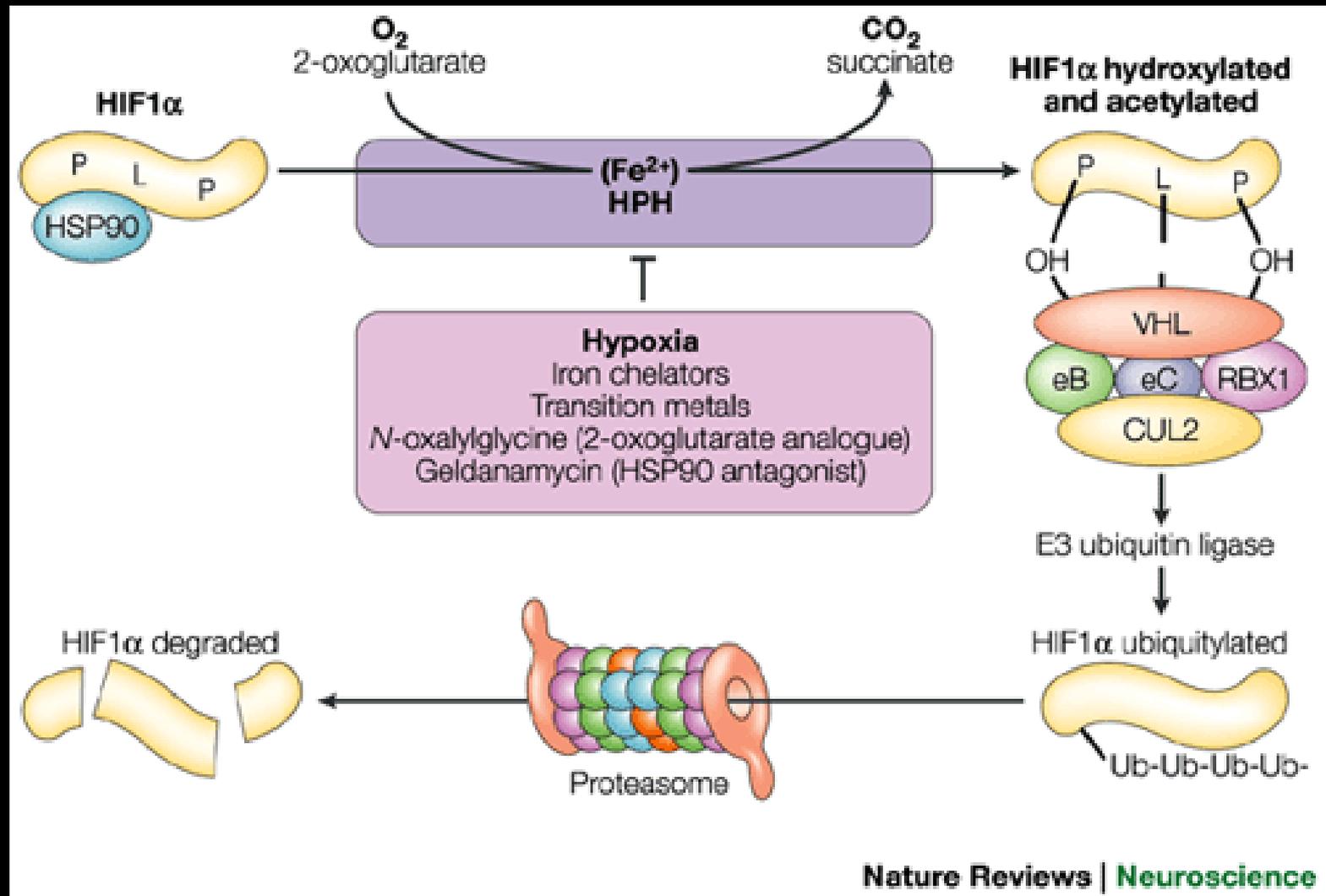
sustained functional protection



Mechanisms?



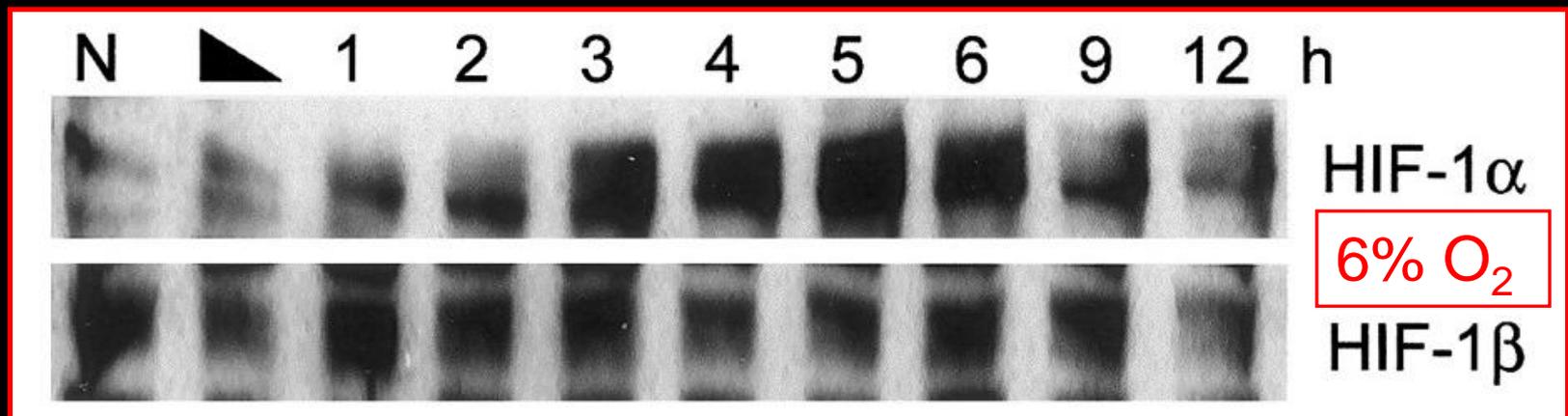
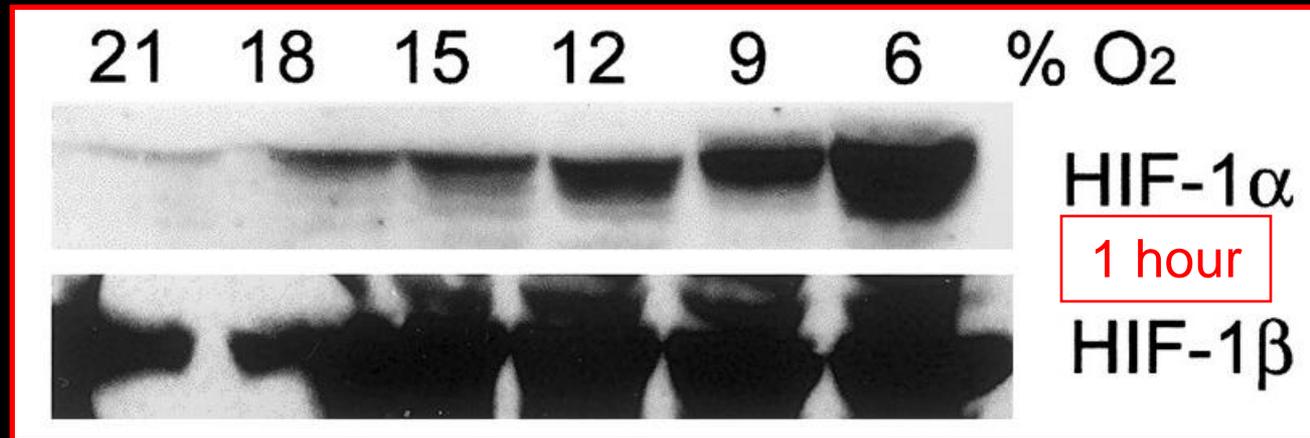
Hypoxia-Inducible Factor-1 α (HIF-1 α) and the Prolyl Hydroxylases



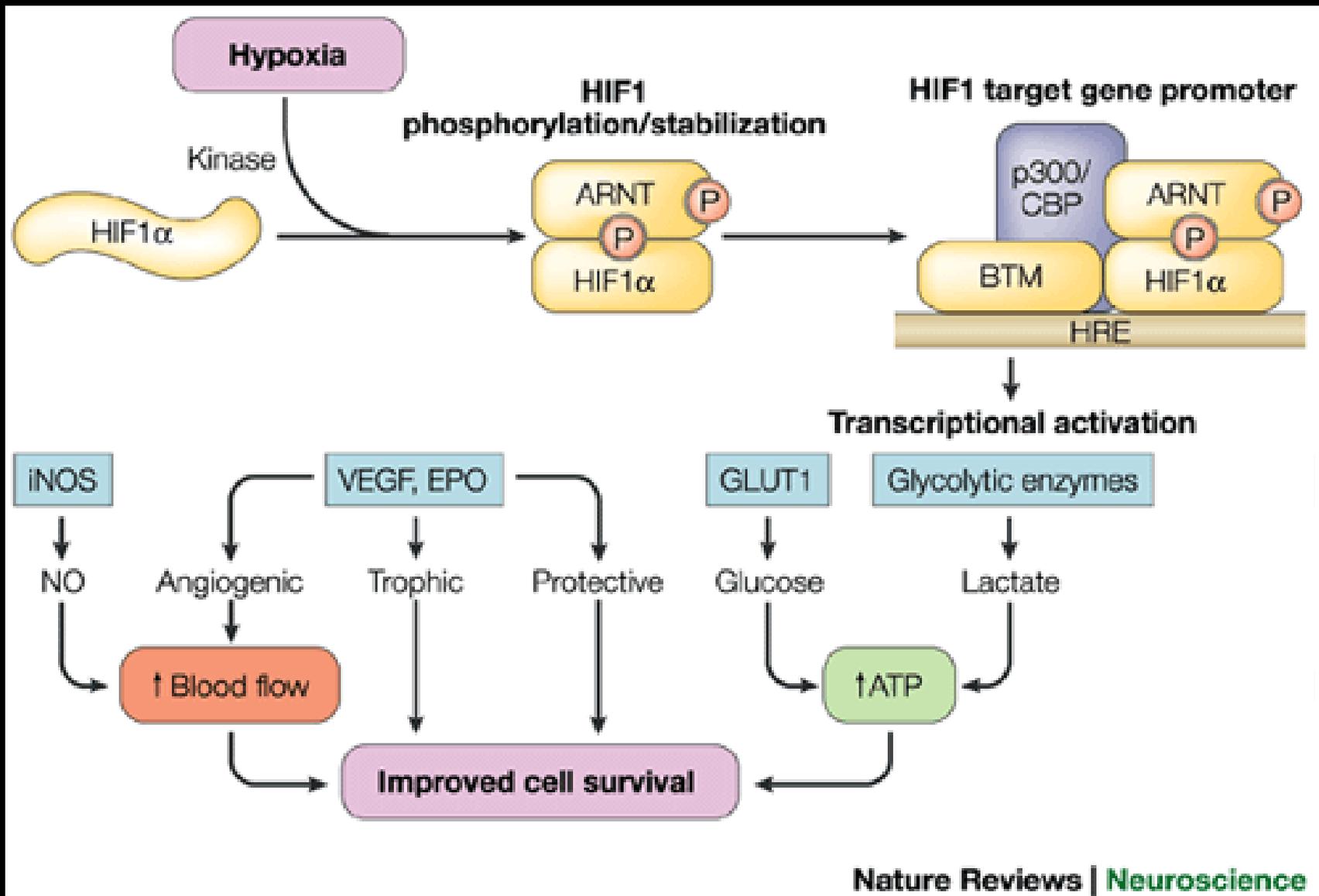
Nature Reviews | Neuroscience

Hypoxia-Induced HIF-1 α Protein Expression

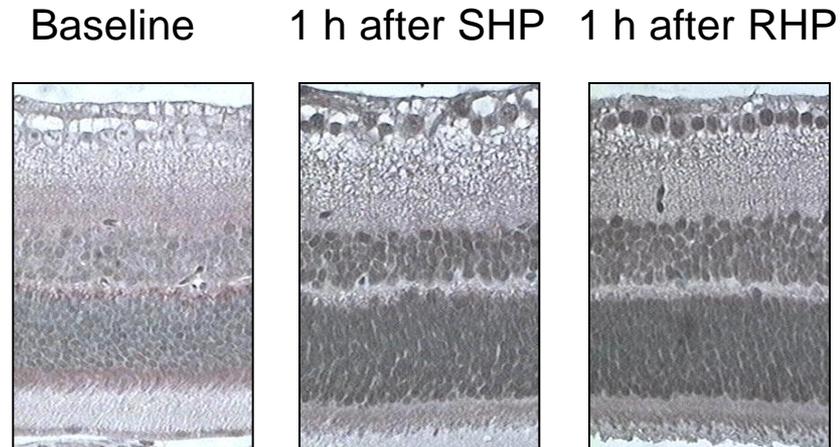
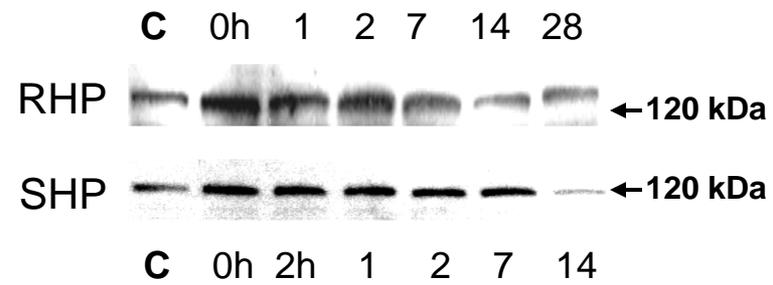
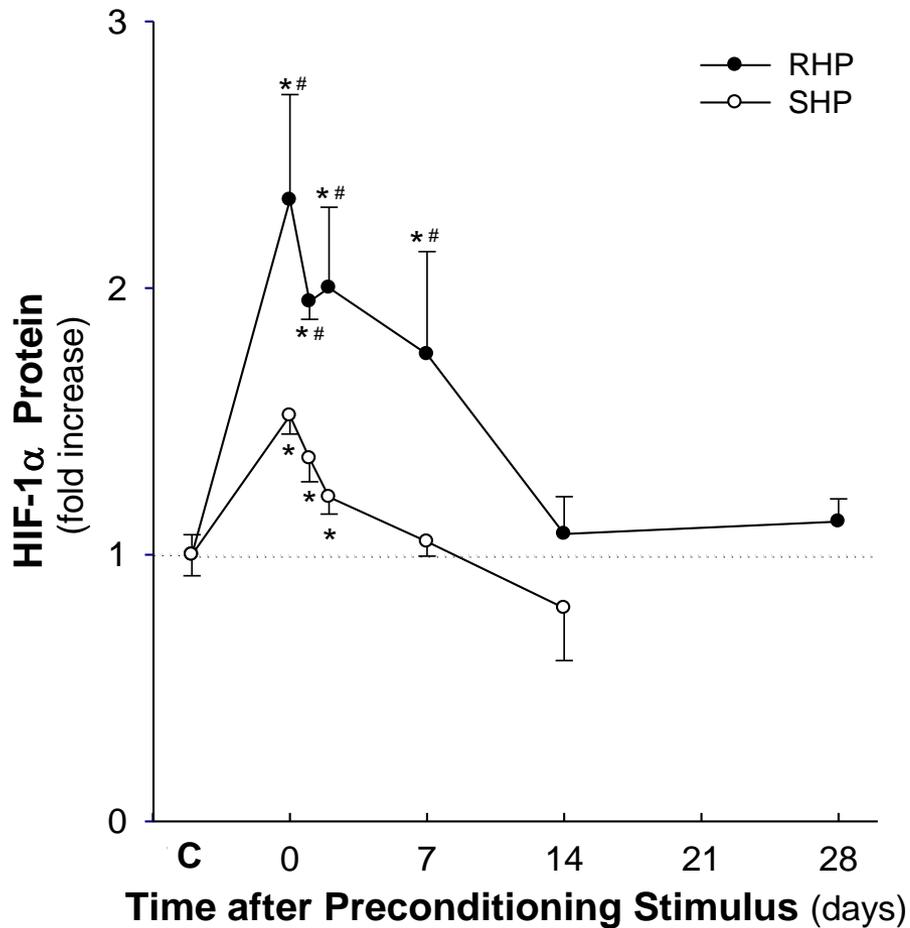
Severity- and duration-dependent regulation



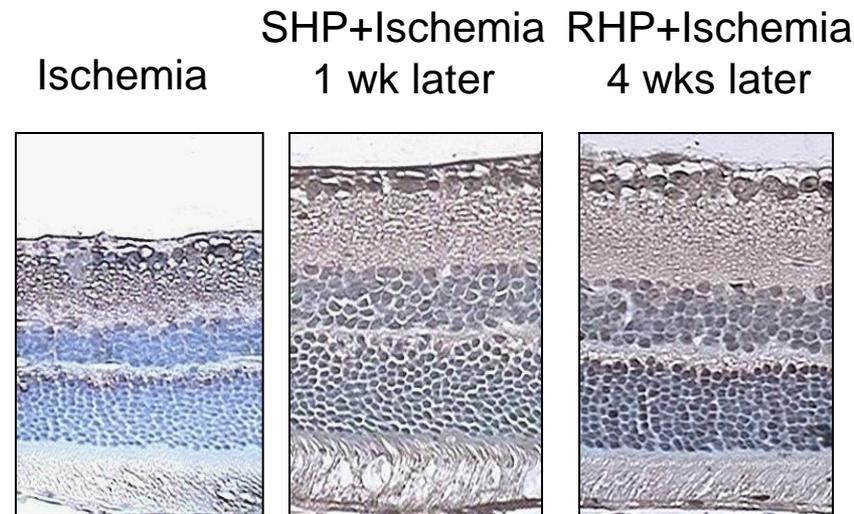
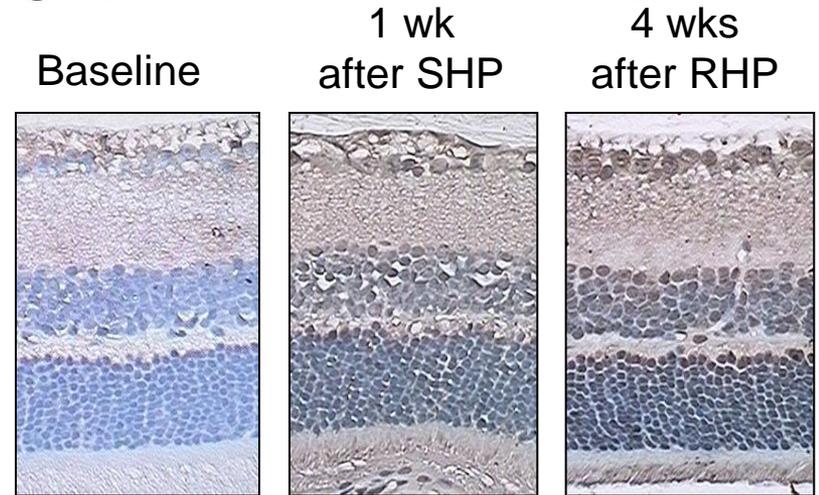
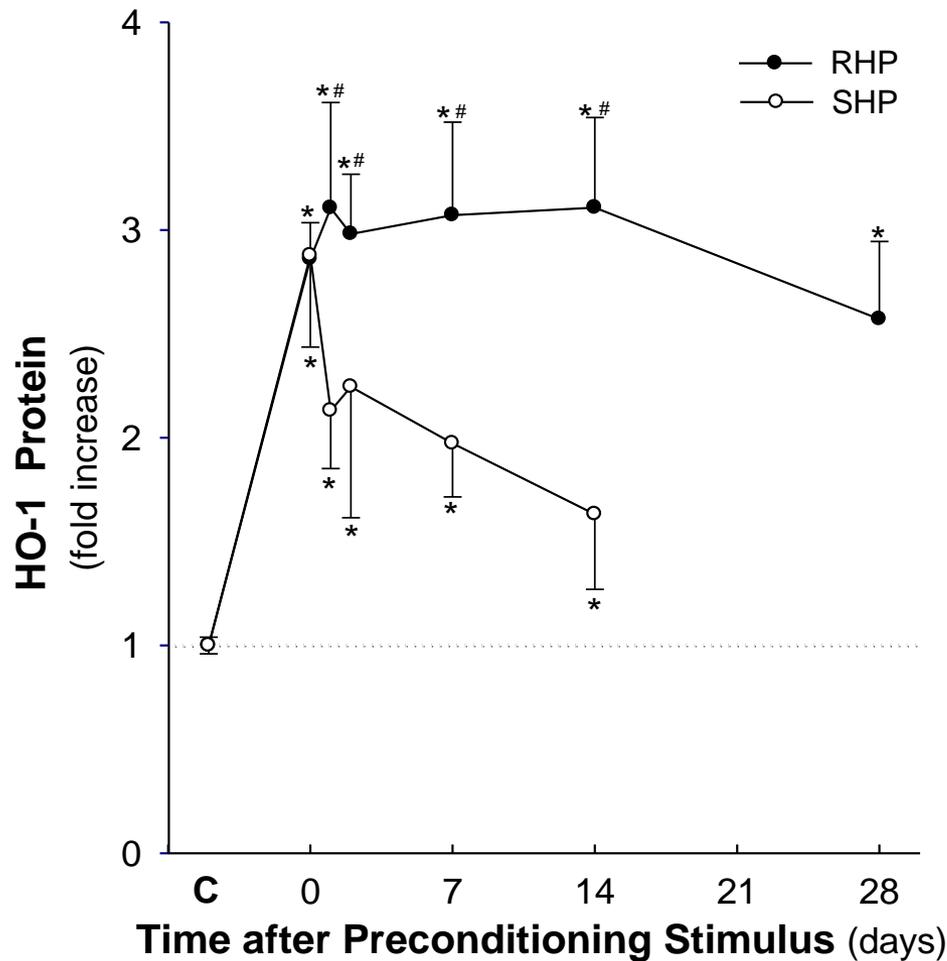
HIF-1 α Drives Many Cell Survival Responses



Retinal HIF-1 α protein expression following hypoxic preconditioning (SHP vs. RHP)

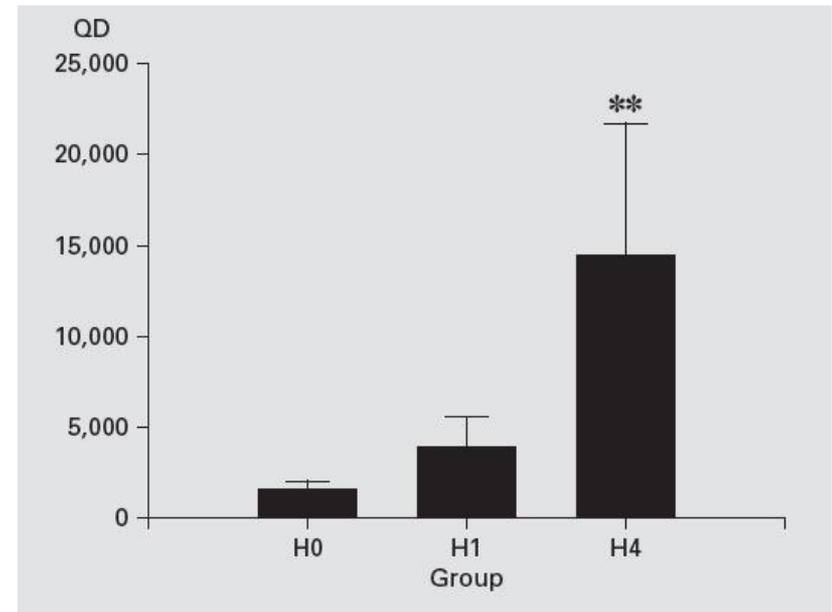
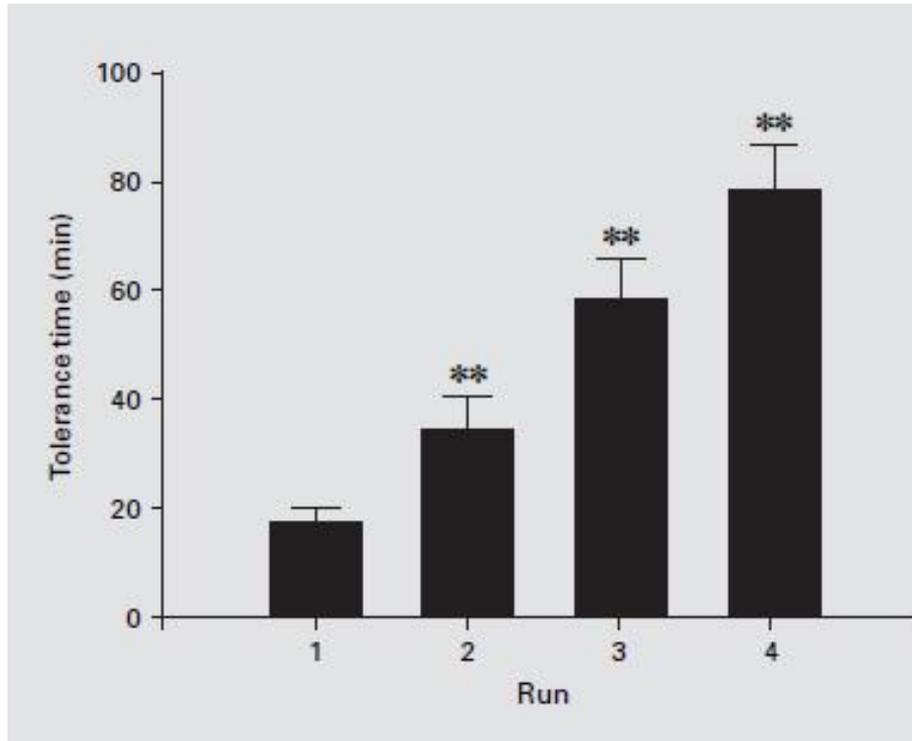


Retinal HO-1 protein expression following hypoxic preconditioning (SHP vs. RHP)



Cerebral HIF-1 dose-response

single or repetitive hypoxia



Daily
Hypoxia...

...for Good
Health

????



Repetitive Pre-Conditioning *for Neurodegenerative Disease ?*



Repetitive Pre- and **Post**-Conditioning *for Neurodegenerative Disease ?*



CNS Disease

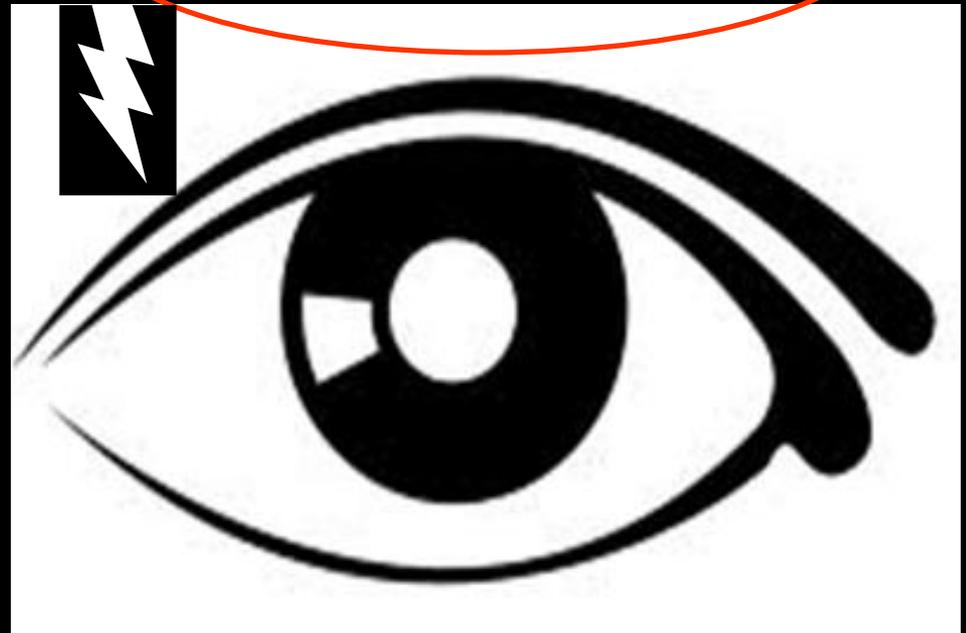
Acute and Chronic Disease

Stroke



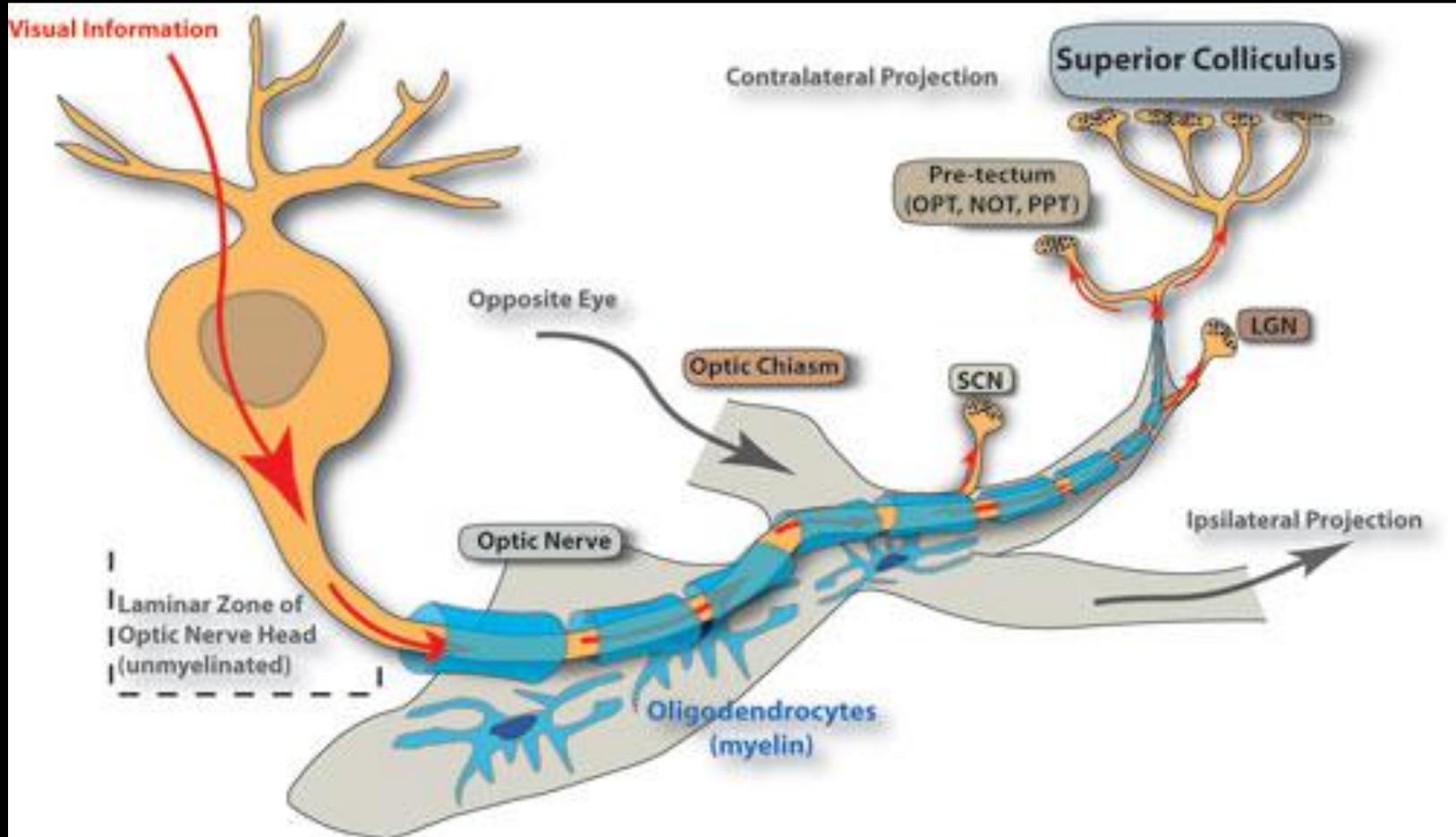
Retinal Ischemia

Glaucoma



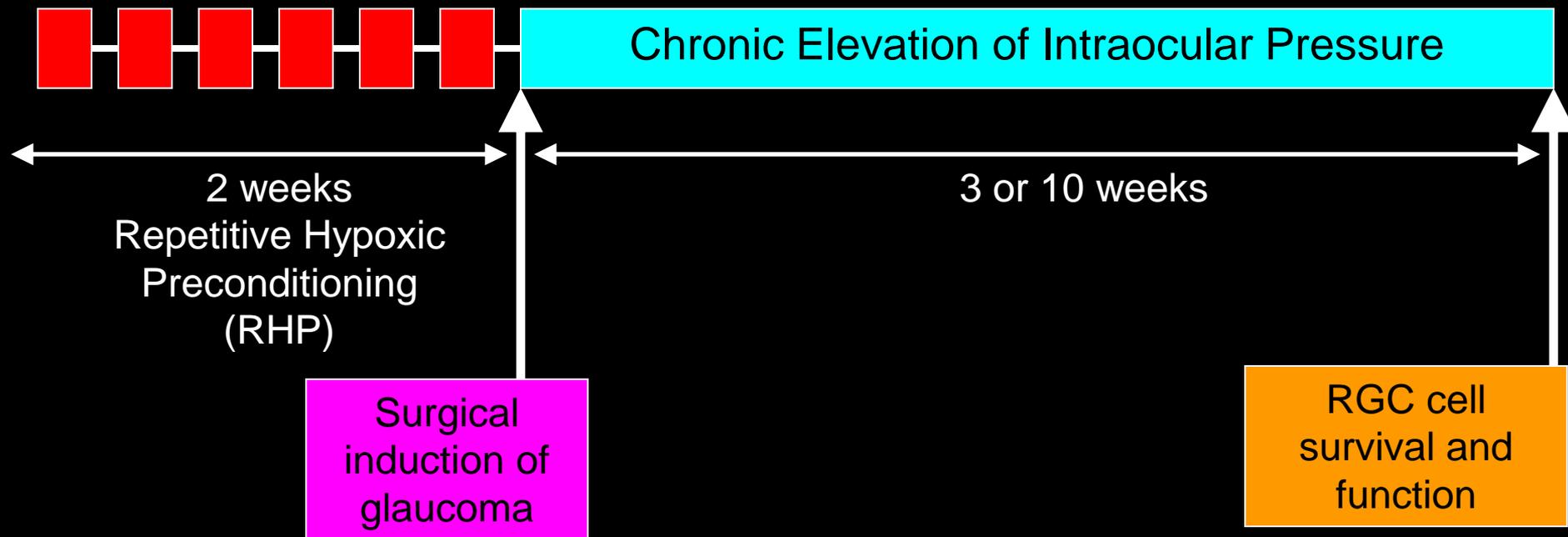
Glaucoma

Progressive retinal ganglion cell (RGC) death



Repetitive Preconditioning for Glaucoma

Experimental Design



 = Hypoxia (11% oxygen for 2 h)

Glaucoma

Retinal ganglion cell injury/protection

Morphology

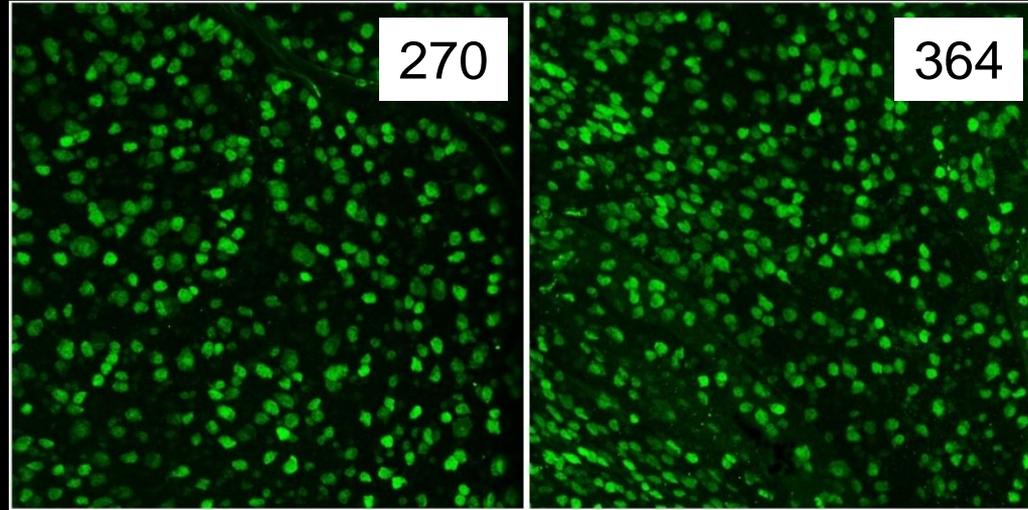
- Cell bodies (in retina)
- Axons (in retina and optic nerve)

RGC Cell Body Survival

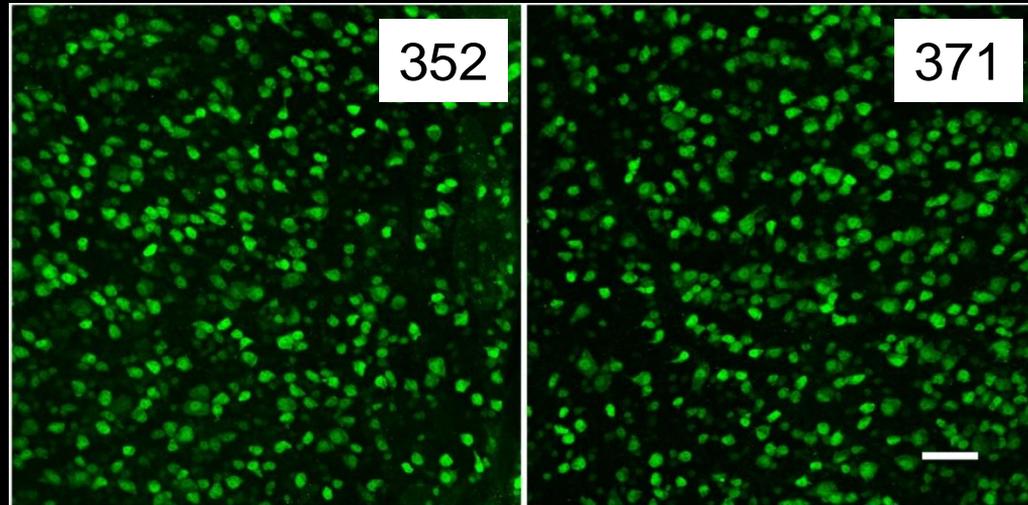
Glaucoma eye

Fellow eye

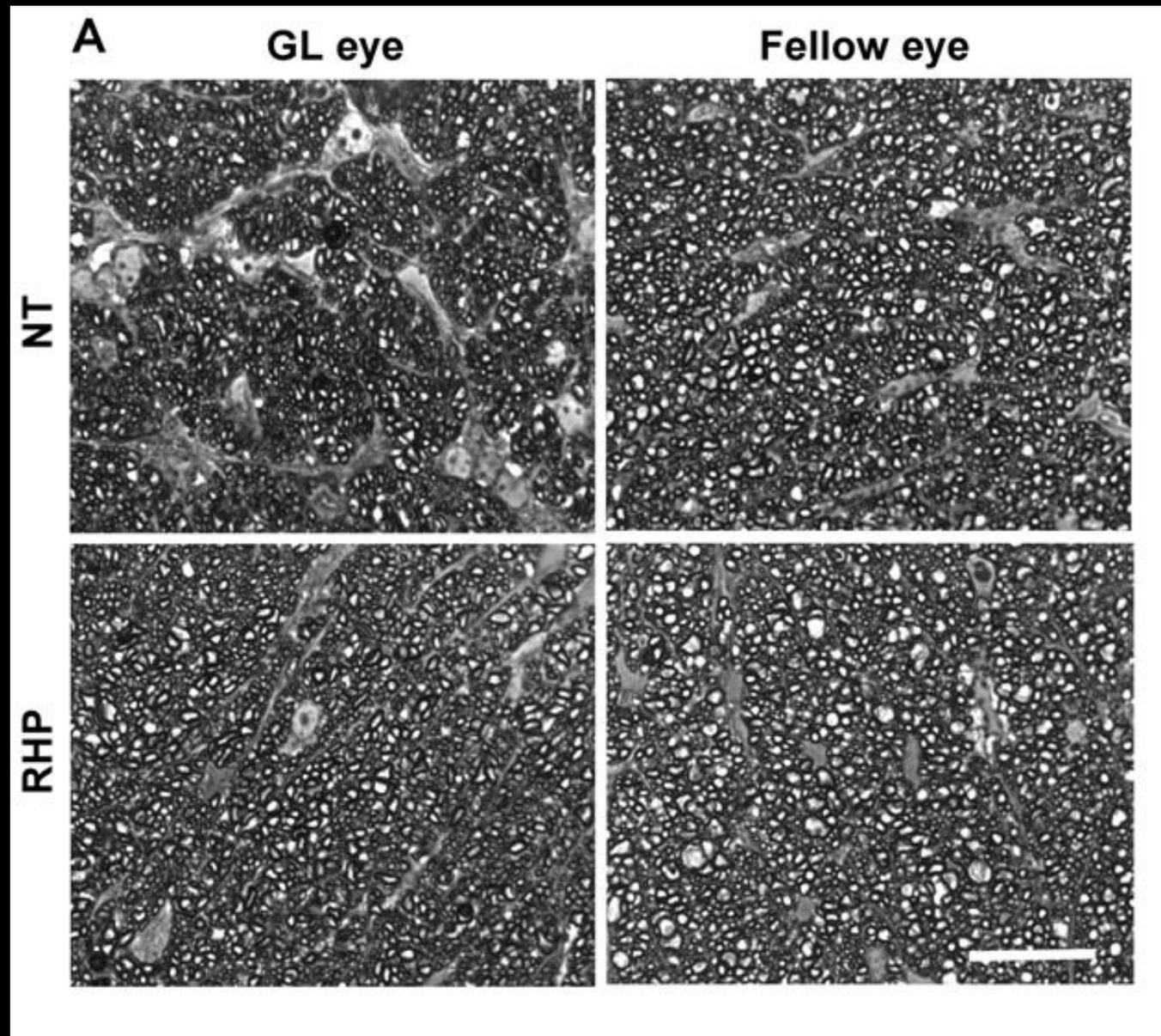
Untreated



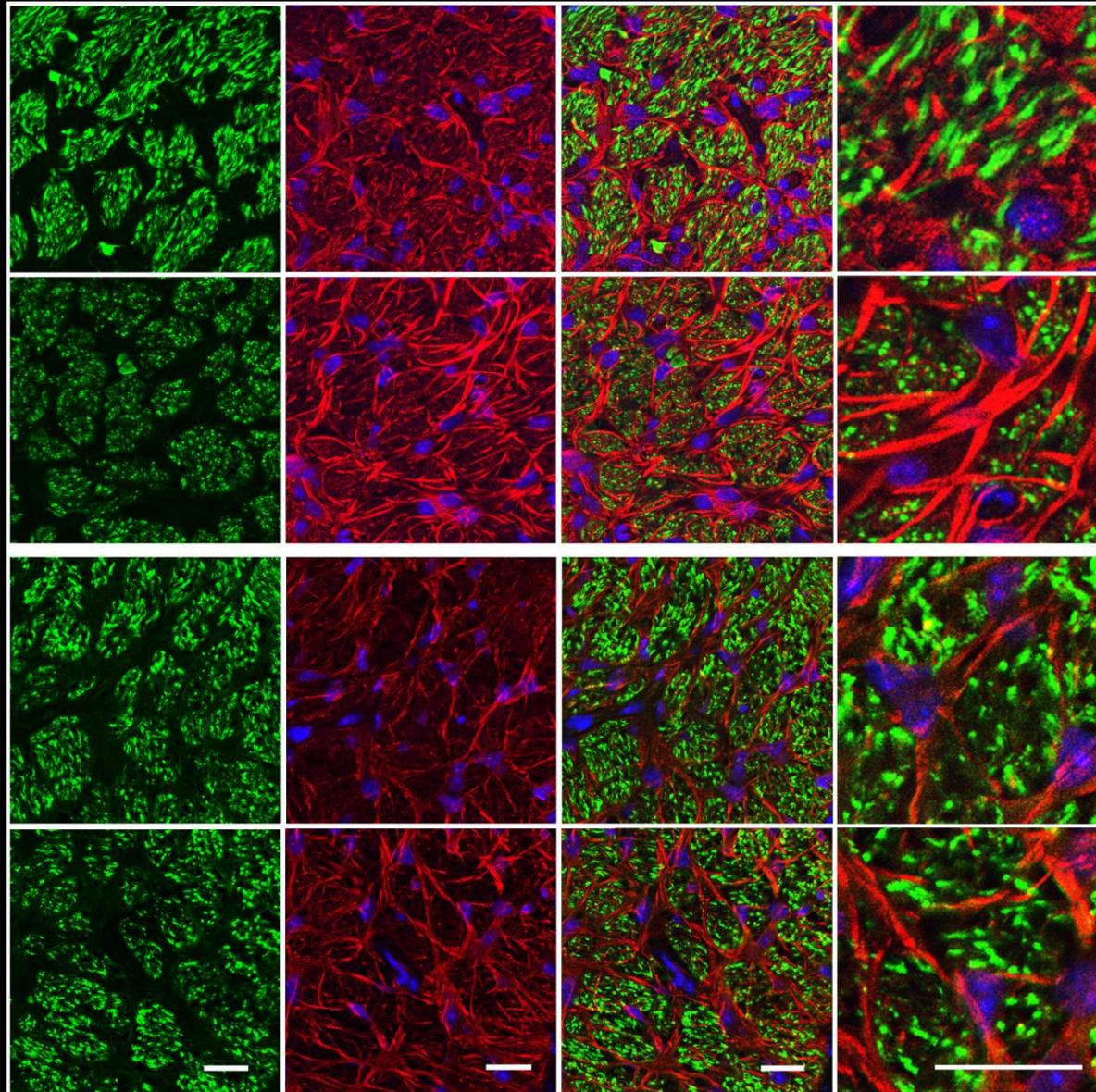
RHP



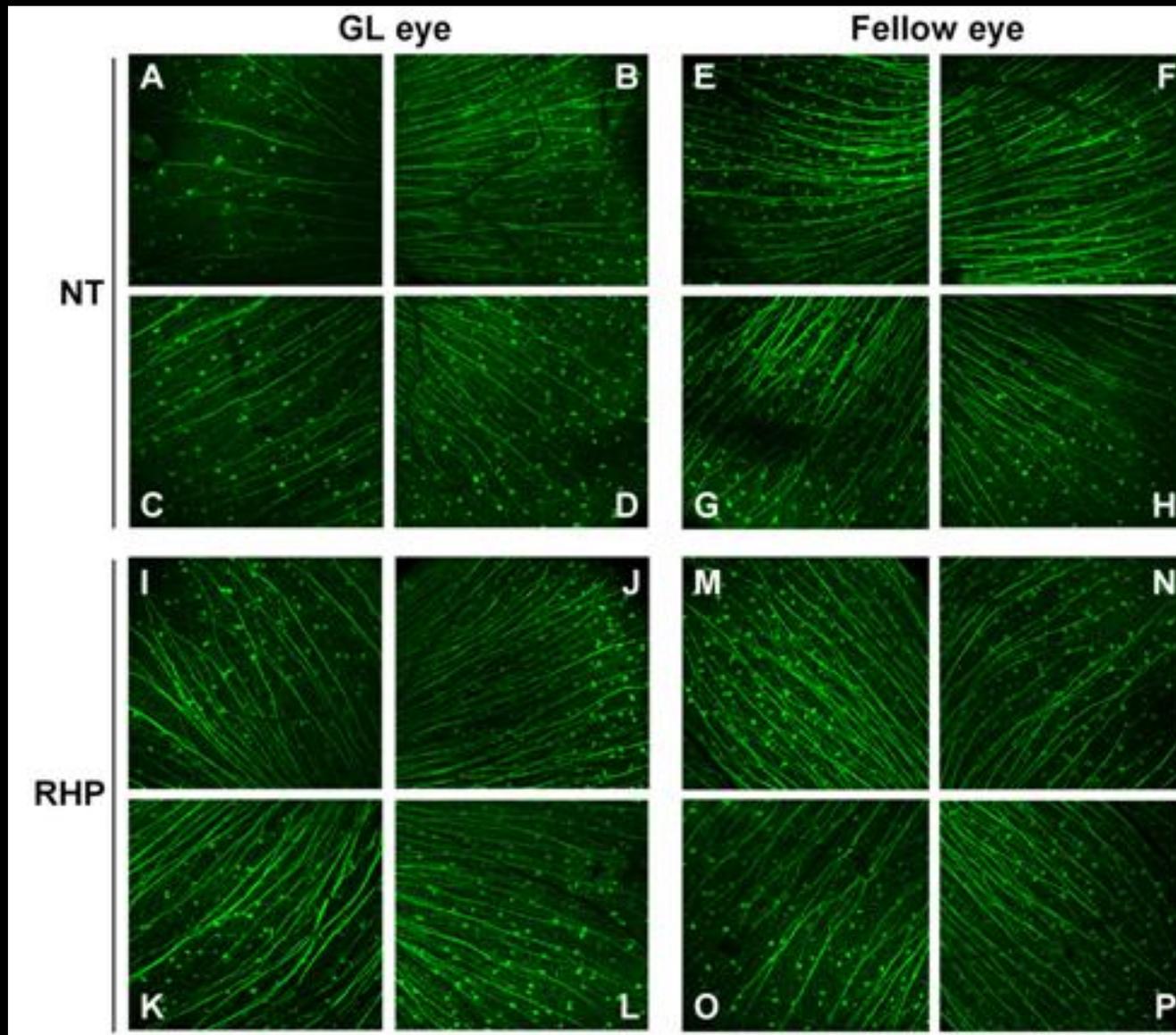
RGC Axon Survival



RGC Axon Survival



RGC Axon Survival



Glaucoma

Retinal ganglion cell injury/protection

Morphology

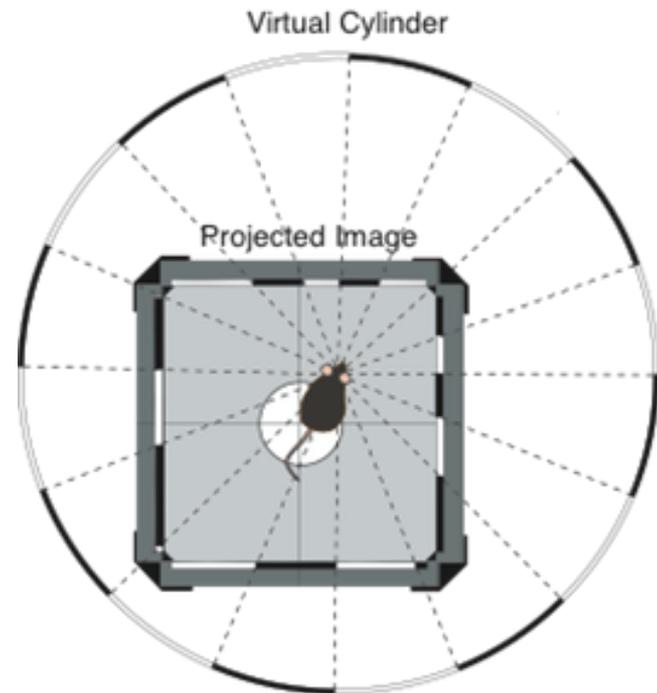
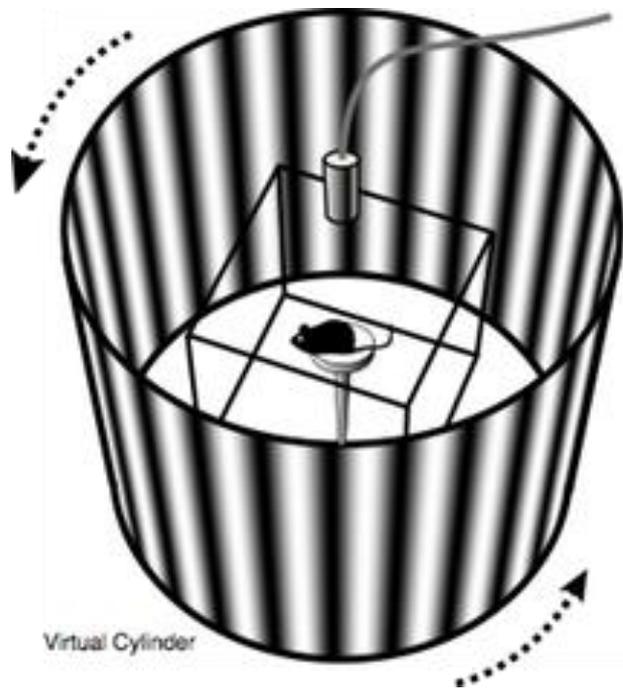
- Cell bodies (in retina)
- Axons (in retina and optic nerve)

Function

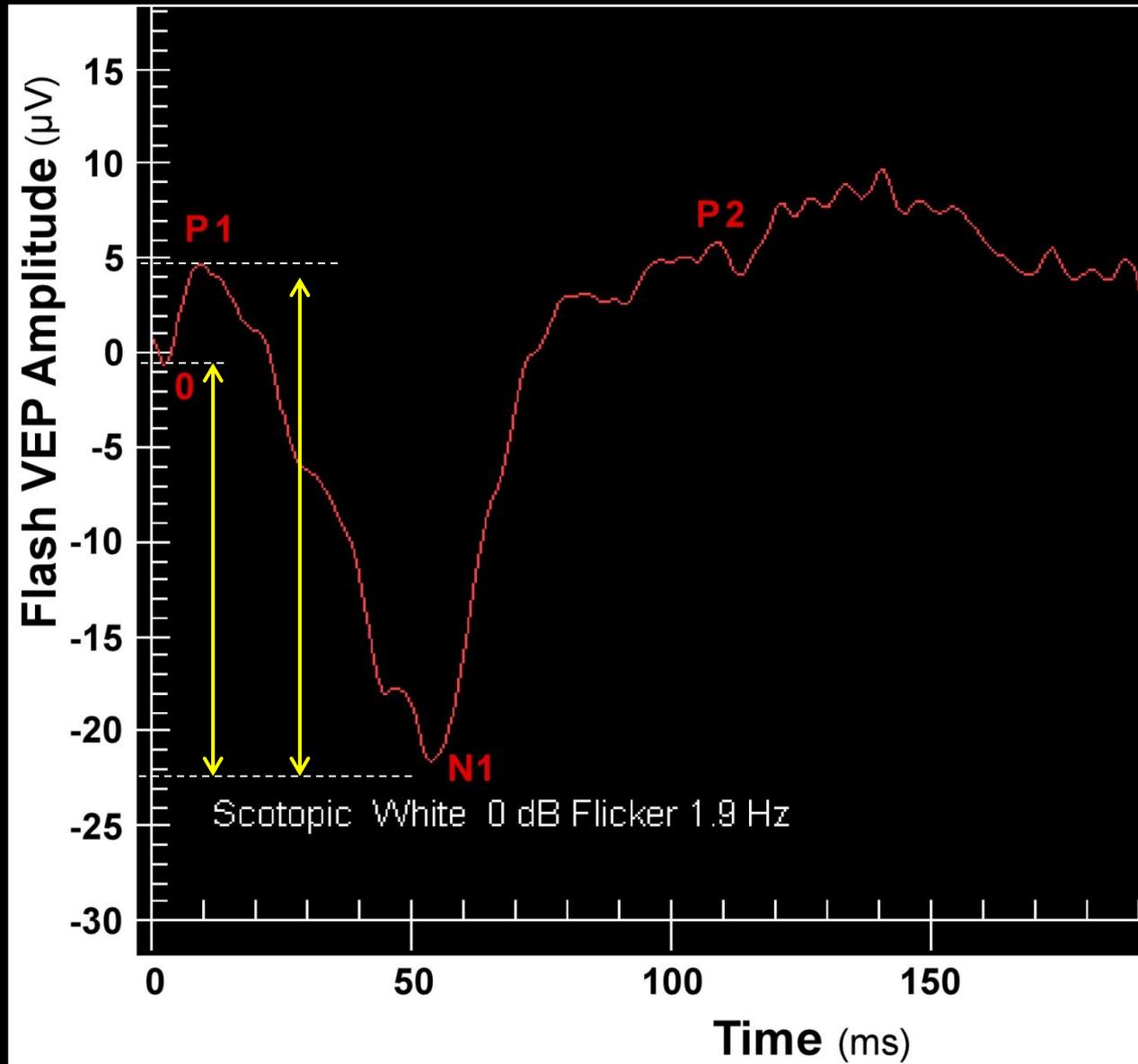
- Visual acuity
- Visual performance
 - visual evoked potentials (VEPs)

Visual Acuity

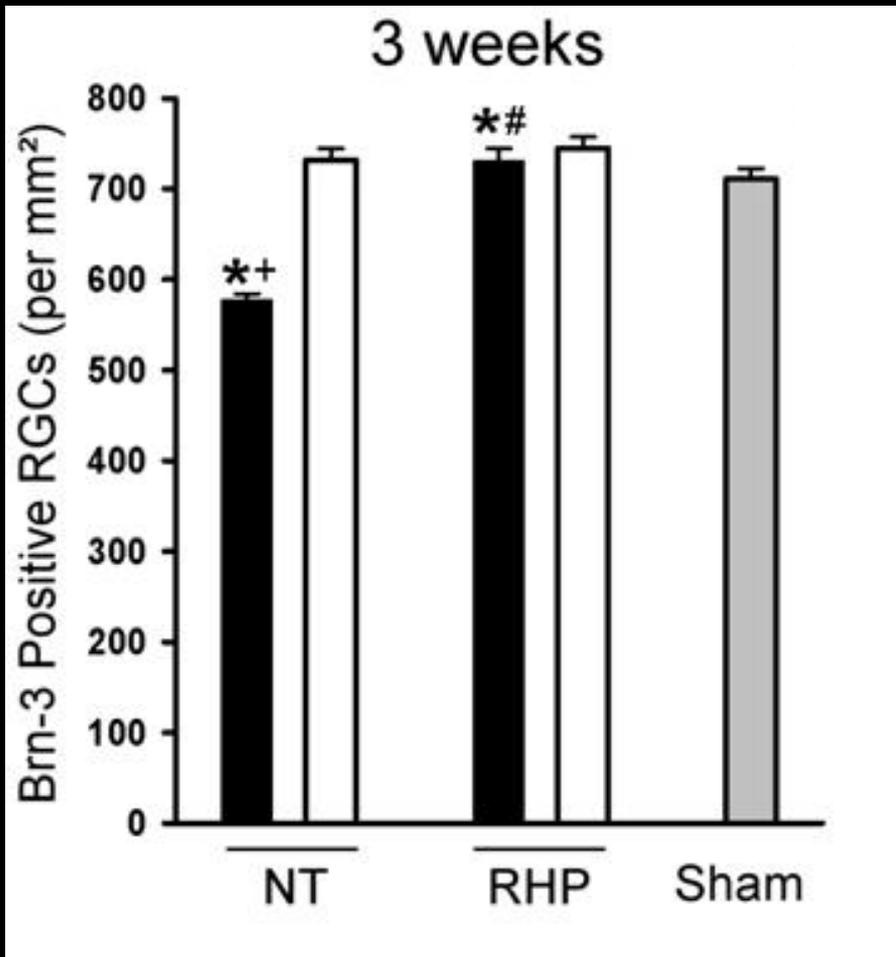
Optokinetic Response



Flash Visual Evoked Potentials



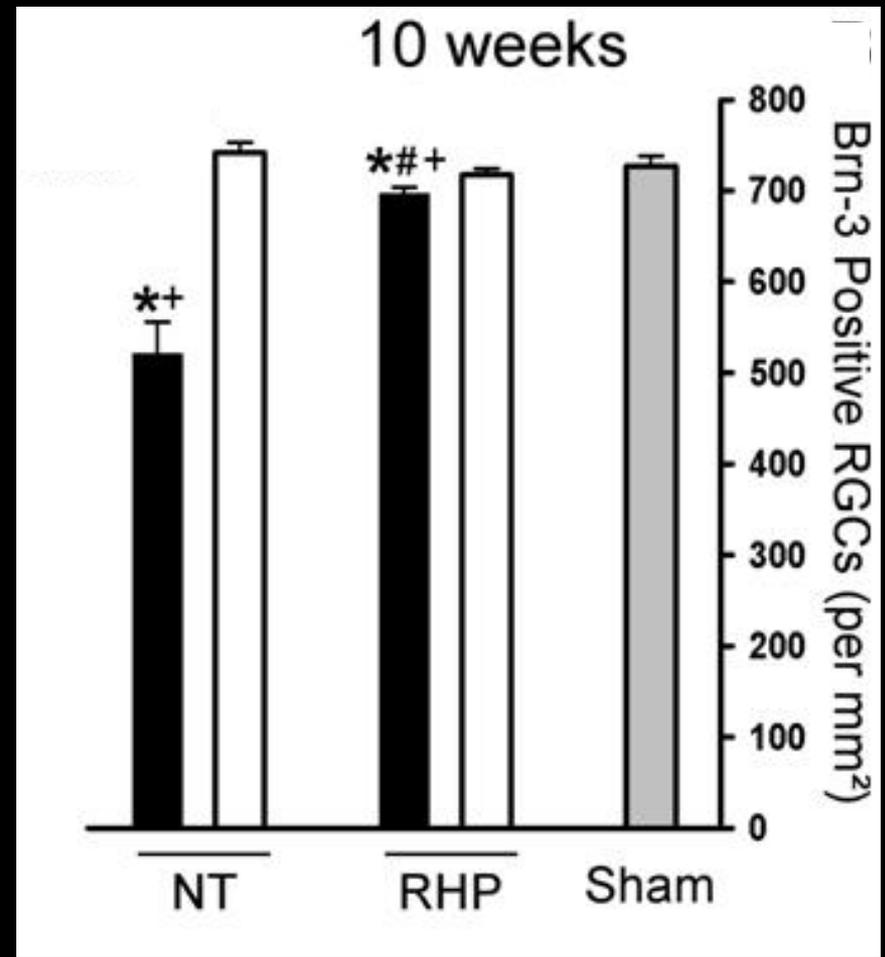
Cell Body Survival



21%
loss

2%
loss

91%
protection

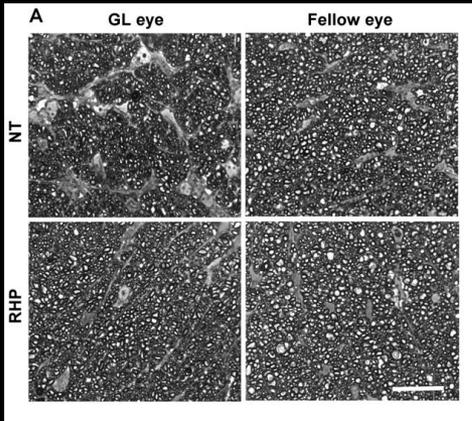


30%
loss

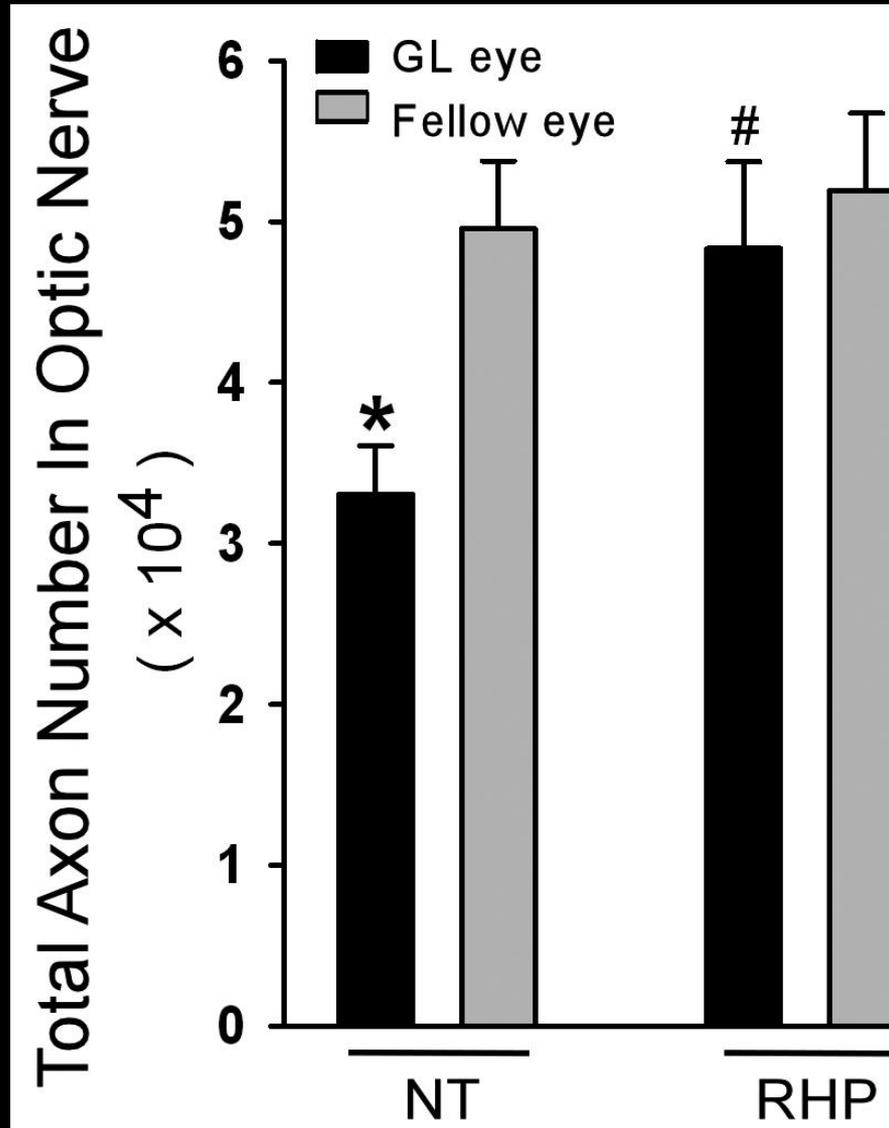
3%
loss

87%
protection

Axon Survival



35%
loss



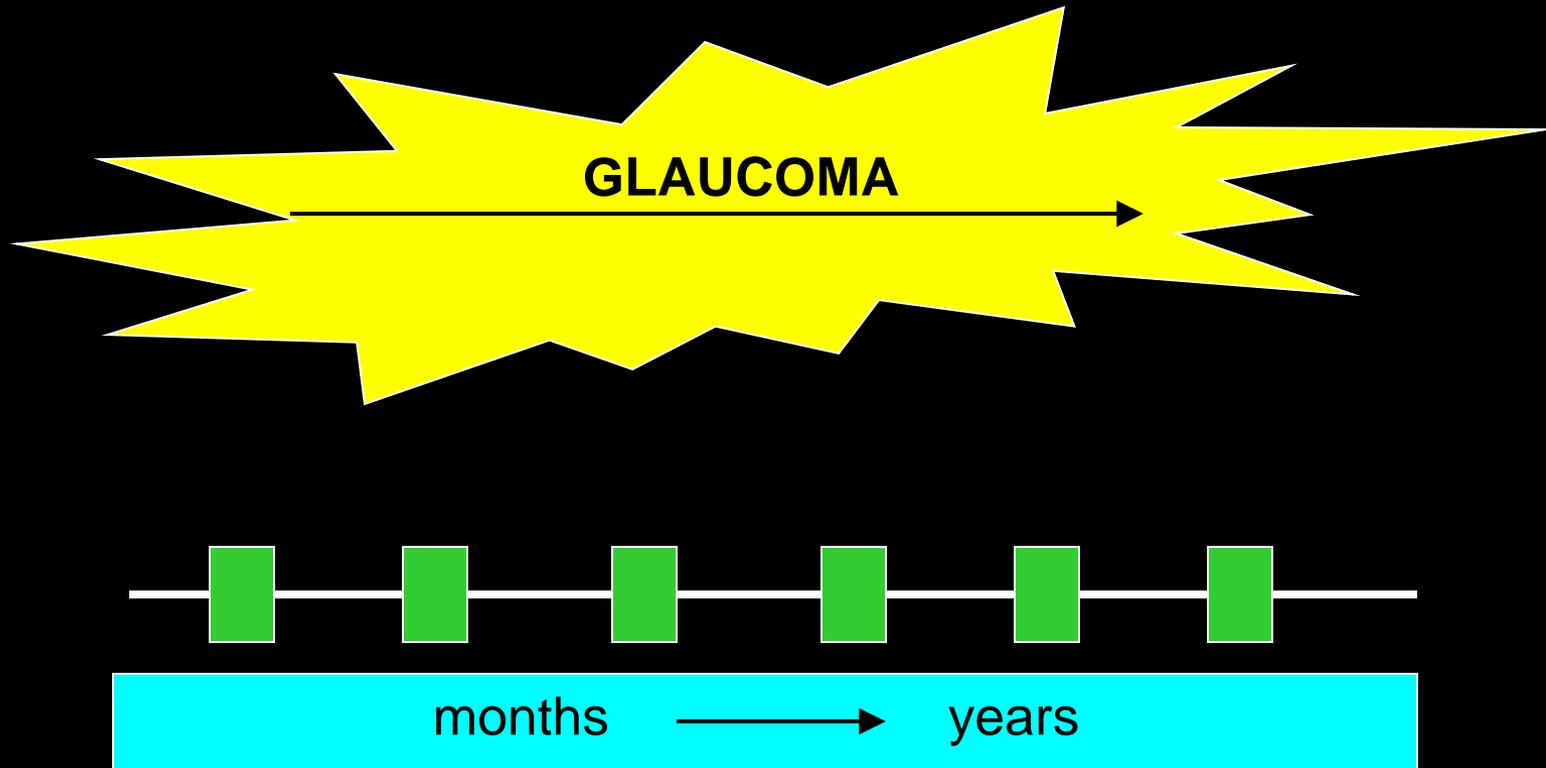
5%
loss

87%
protection

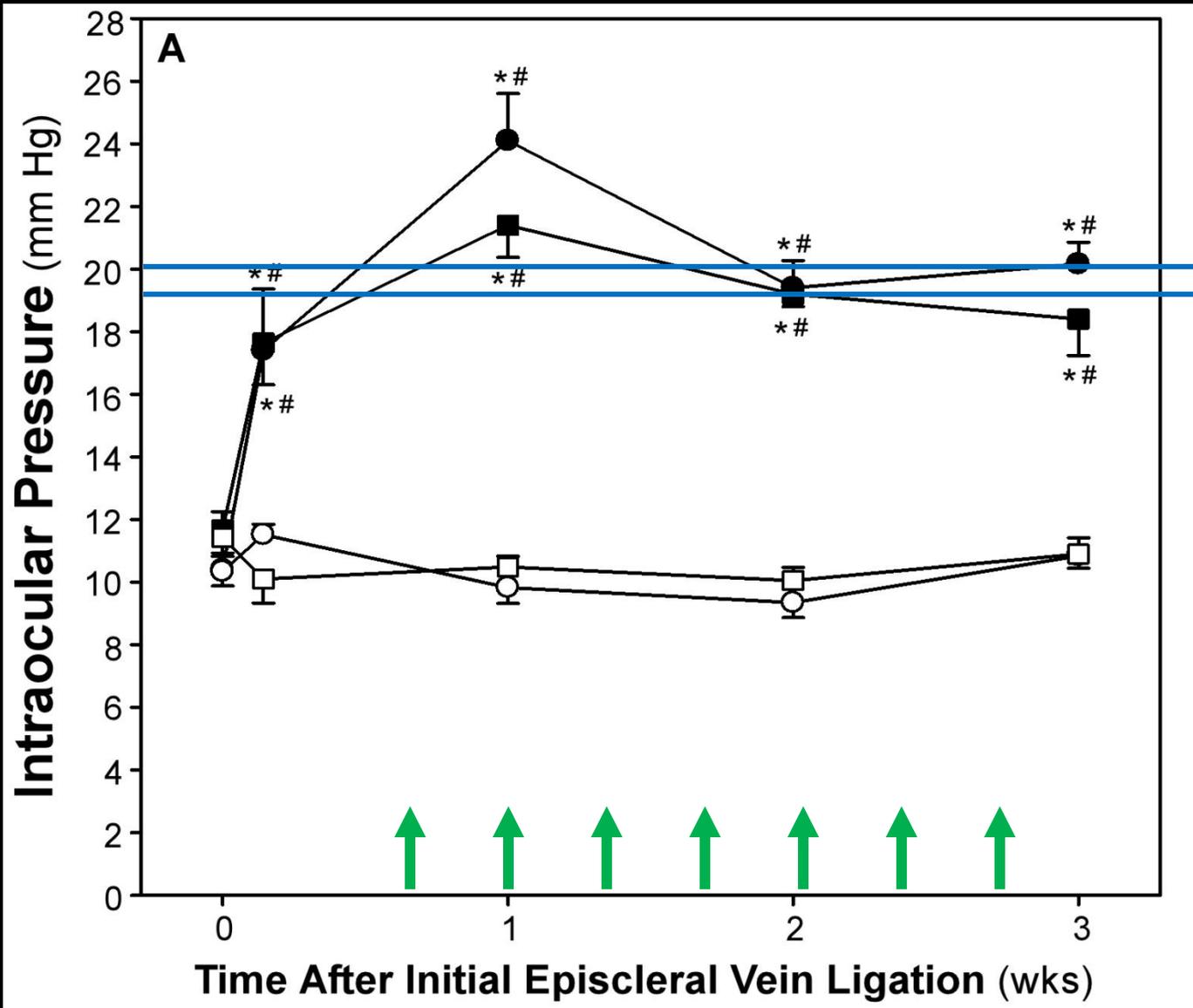
Repetitive Preconditioning



Repetitive **Post**conditioning

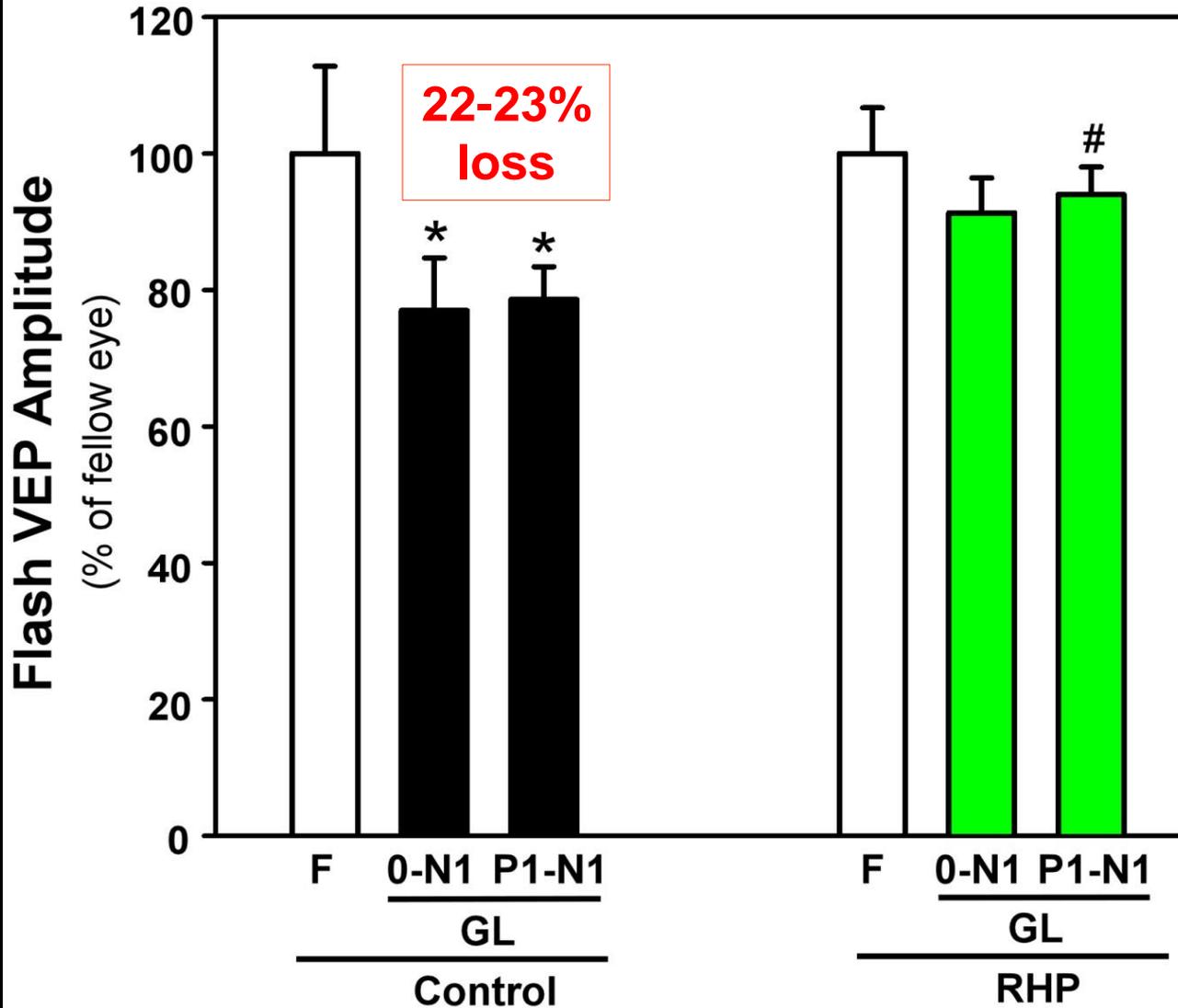


Intraocular Pressure



● Control
 20.4 ± 0.6 mmHg
 19.2 ± 0.6 mmHg
■ RHP

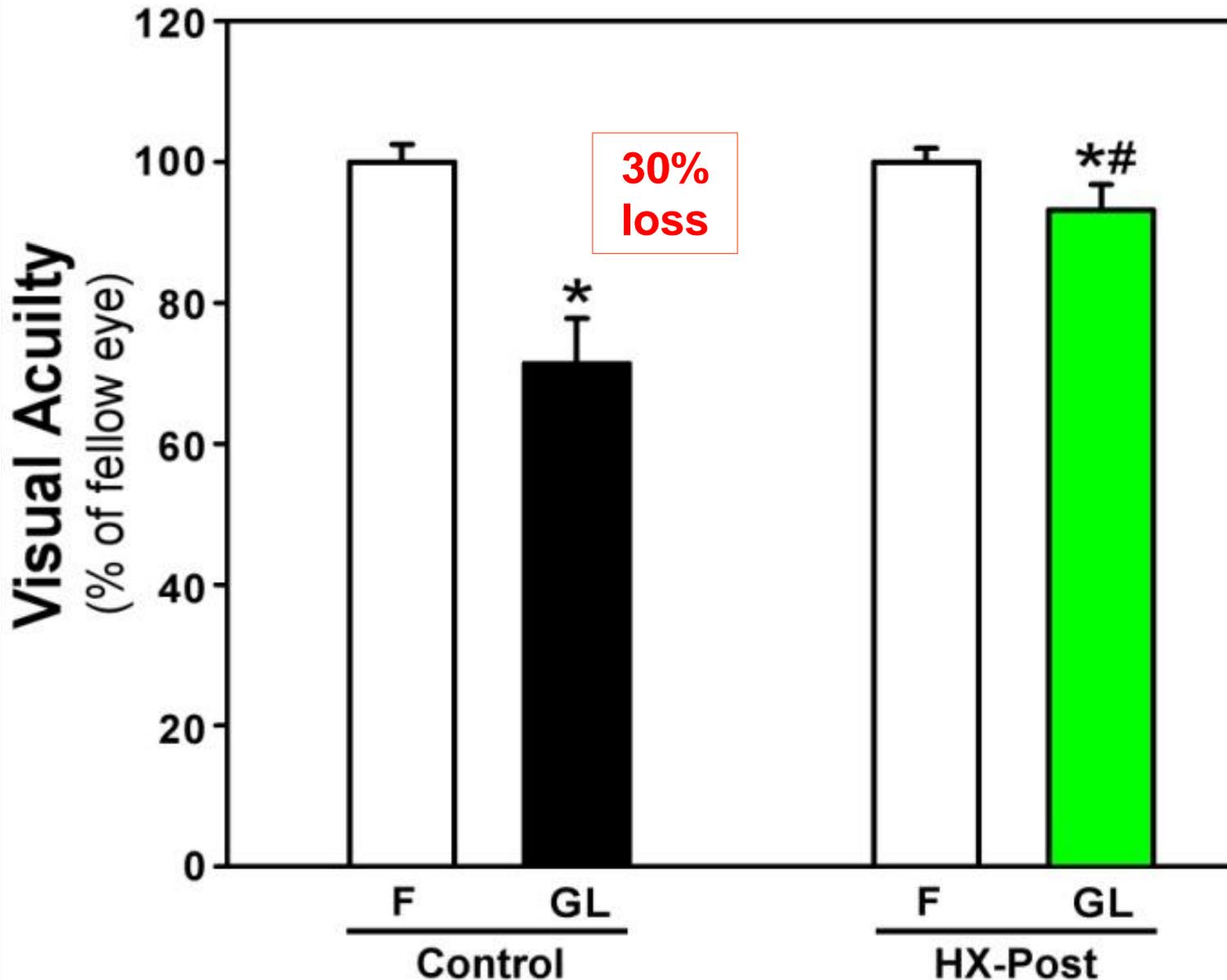
Visual Performance



6-9%
loss

62-73%
protection

Visual Acuity



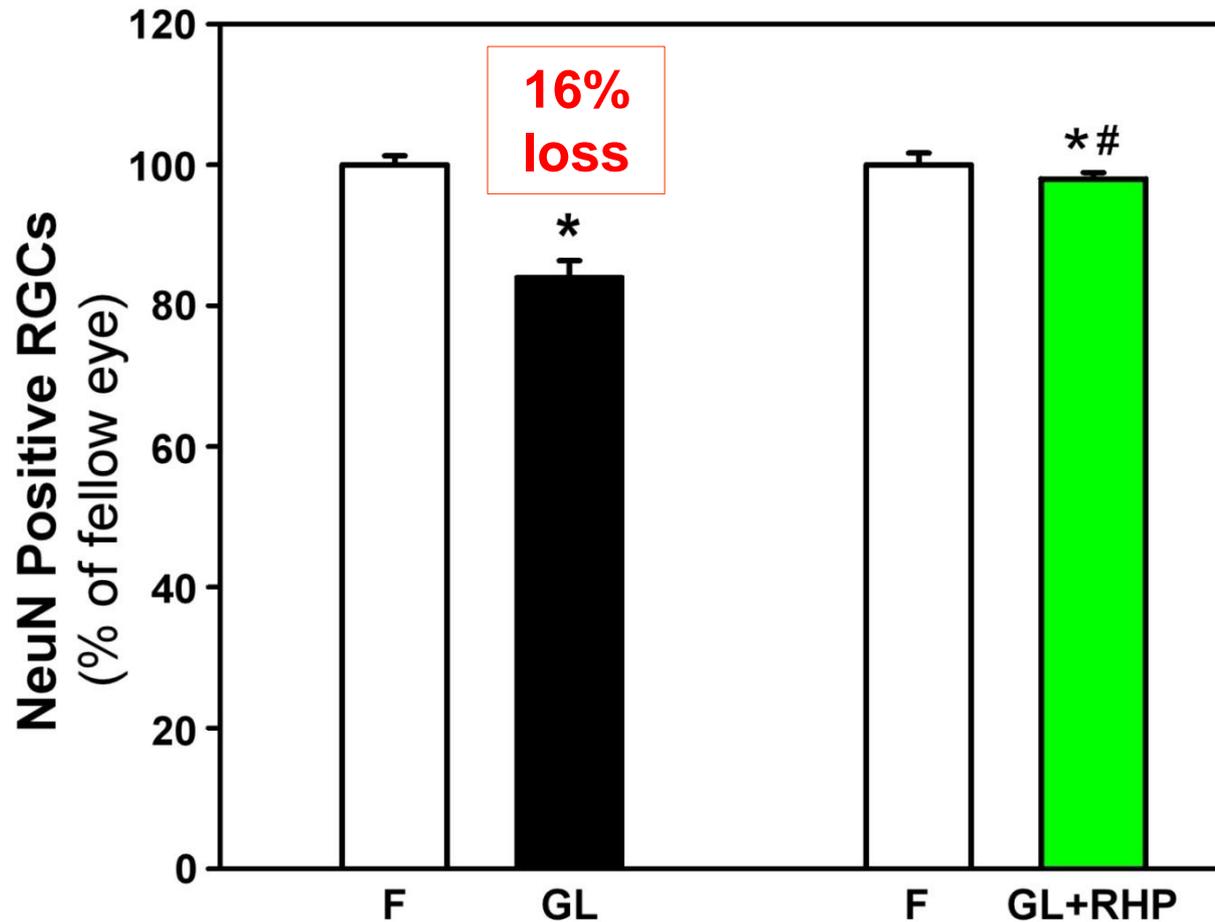
30%
loss

10%
loss

67%
protection

Retinal Ganglion Cells

Cell Body Survival

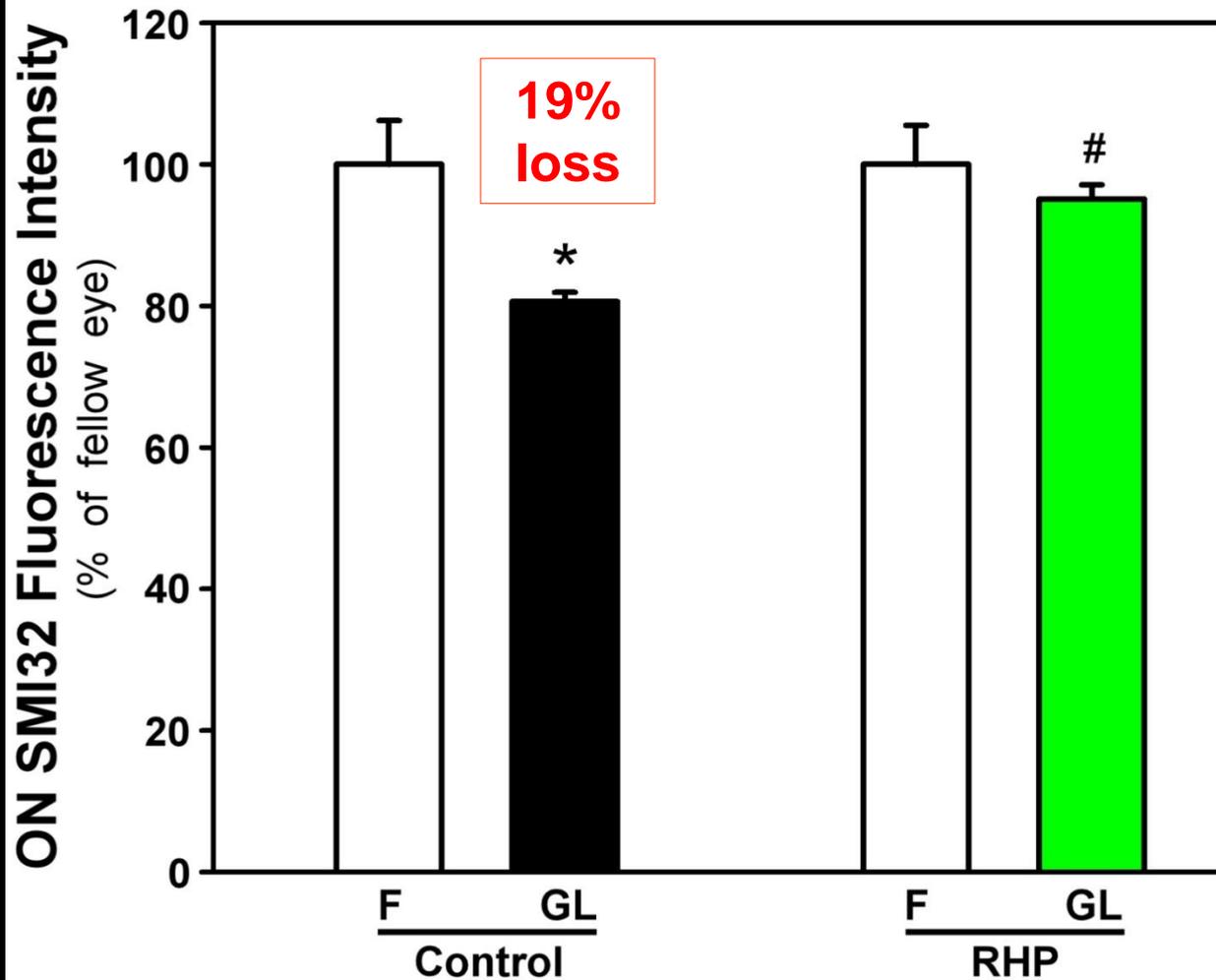


2%
loss

85%
protection

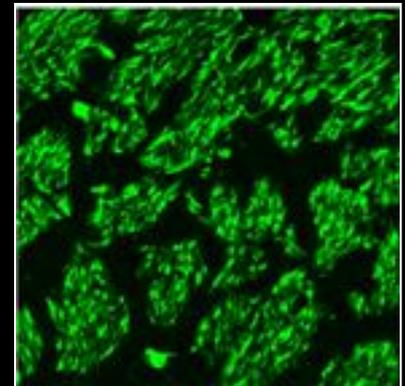
Retinal Ganglion Cells

Axon Survival



5%
loss

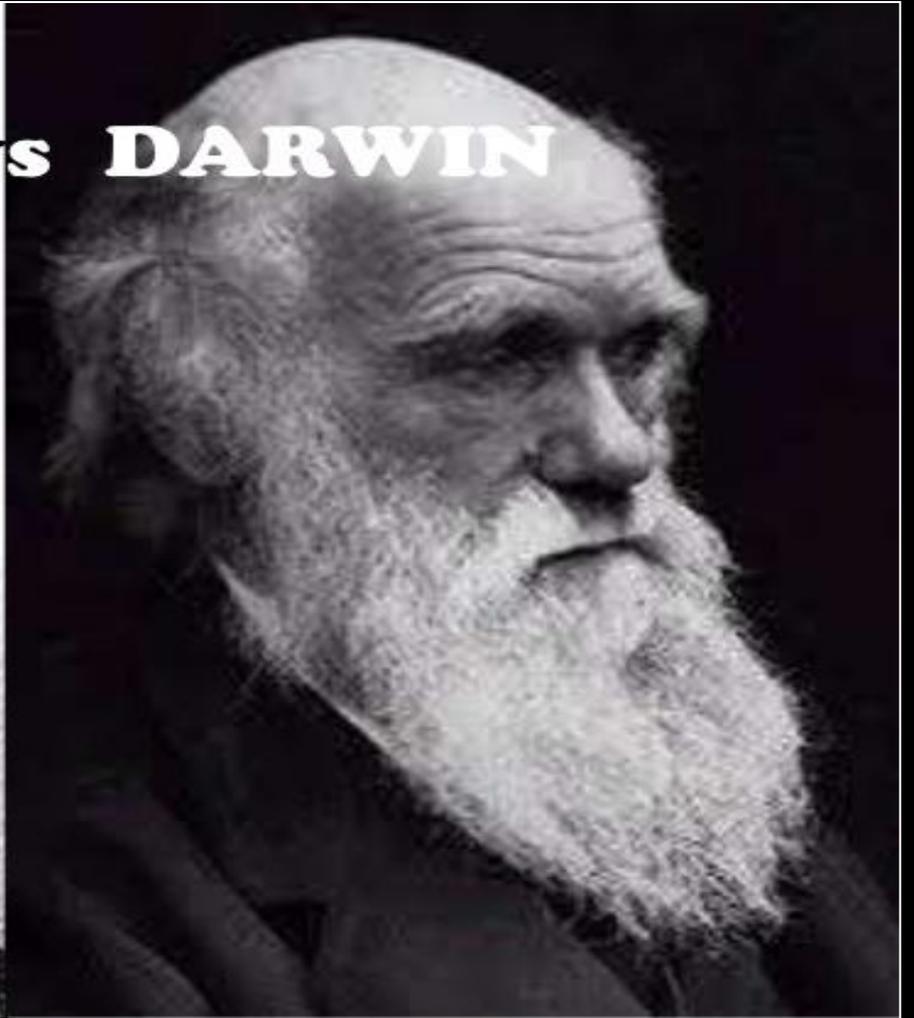
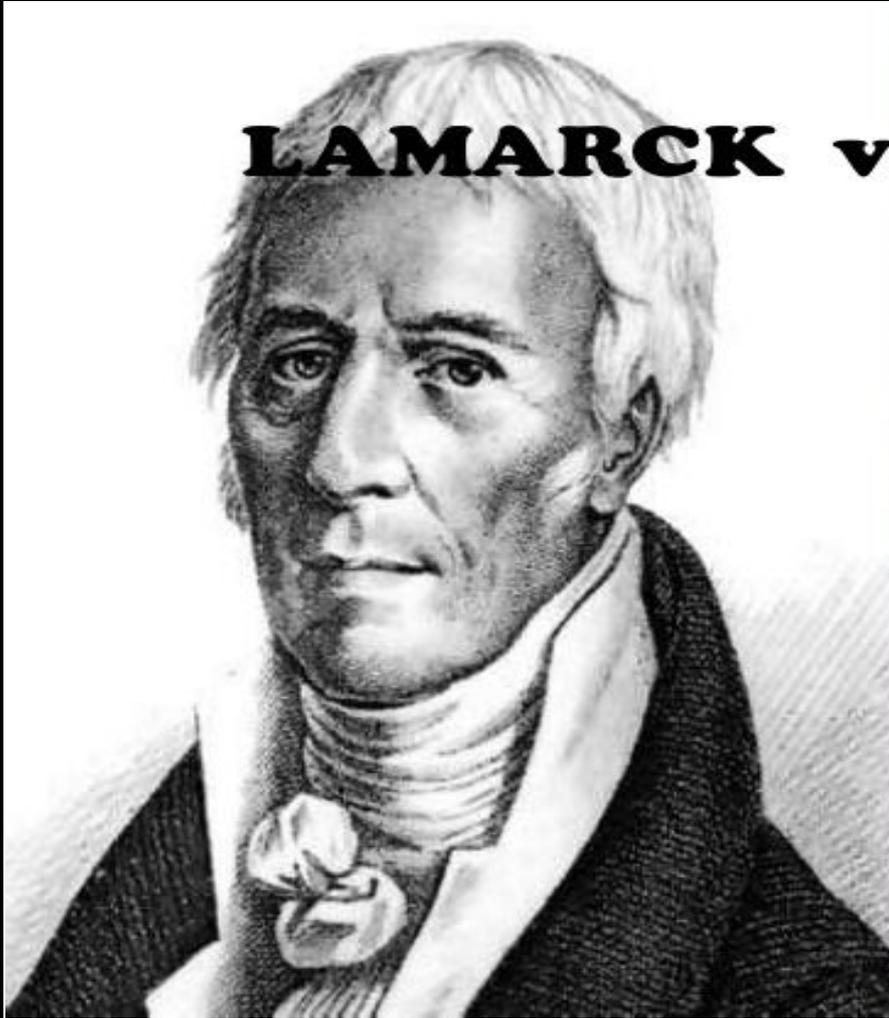
74%
protection





FROM
STRESS TO
SUCCESS

LAMARCK vs DARWIN



Natural Selection vs. Lamarckism

Taller neck



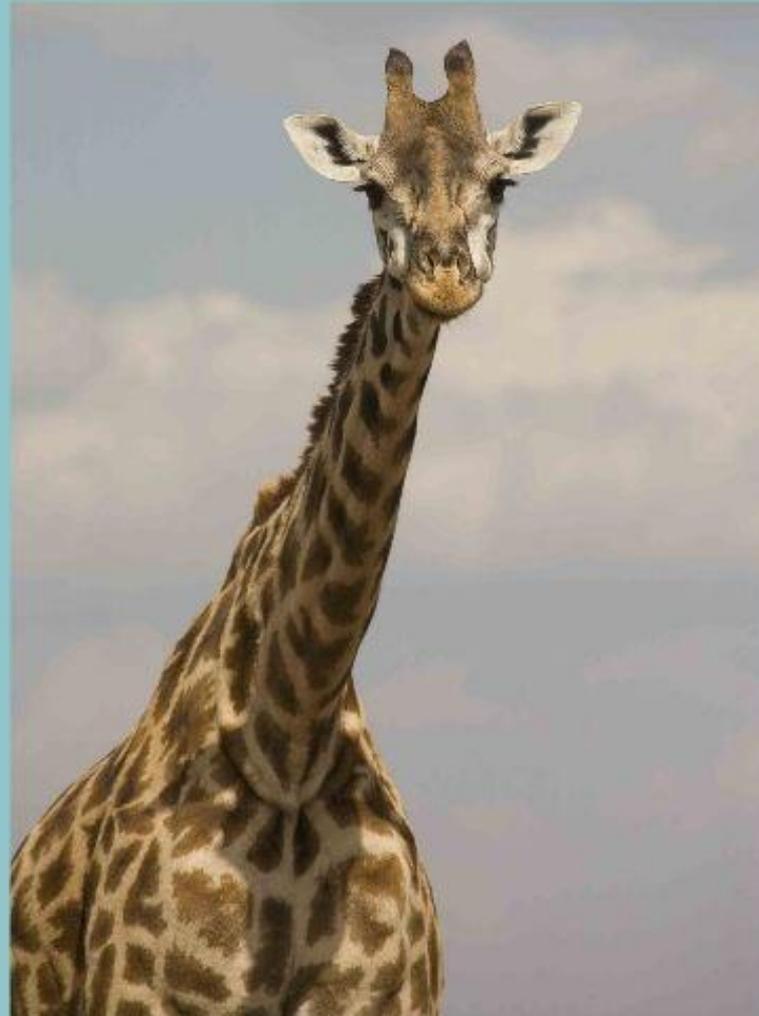
Reaches more food than short neck



Reproduces more than short neck



Long necks more common in population



© gmcfdyen

Cannot reach taller branches

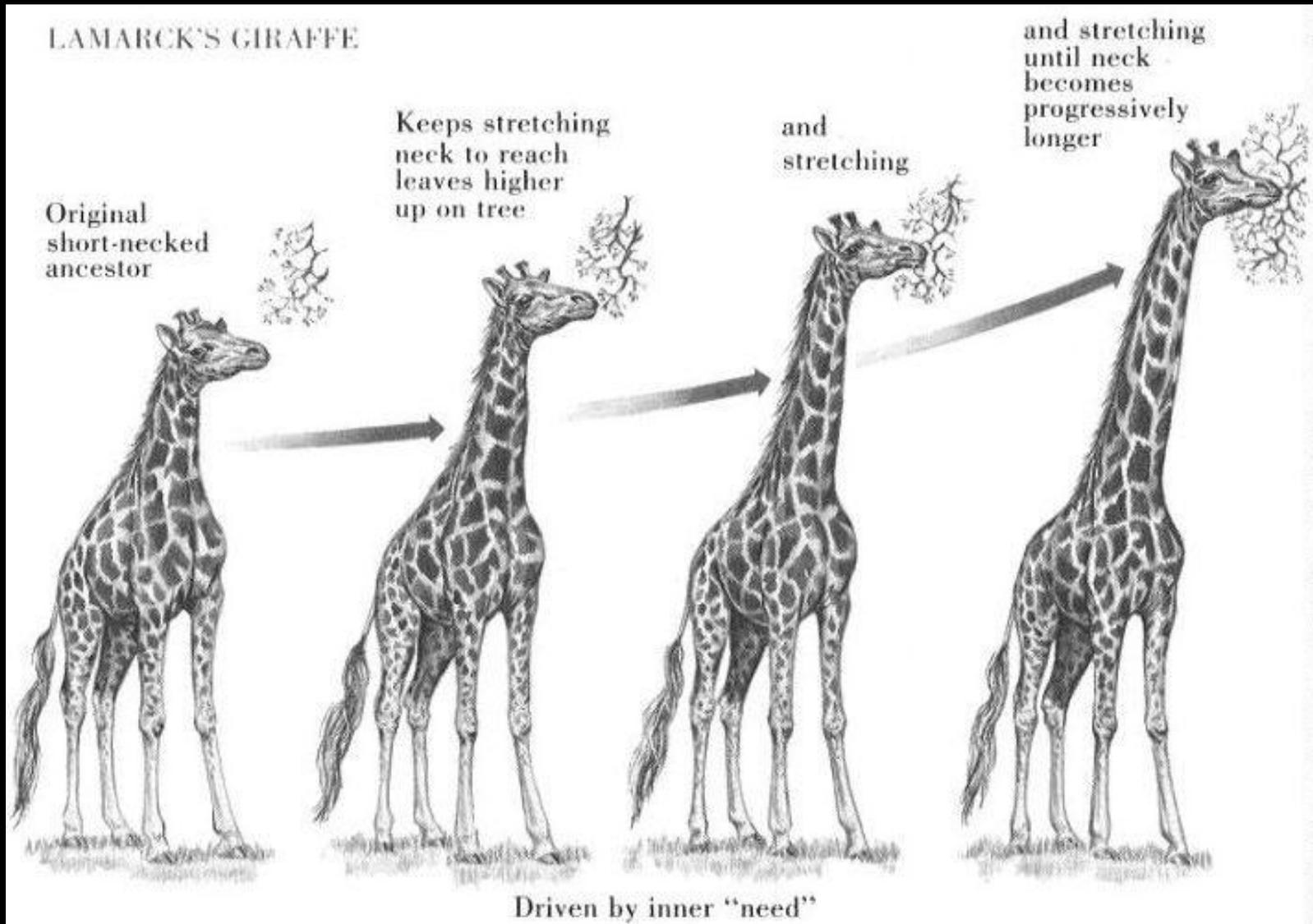


Neck lengthens



Offspring born with longer neck

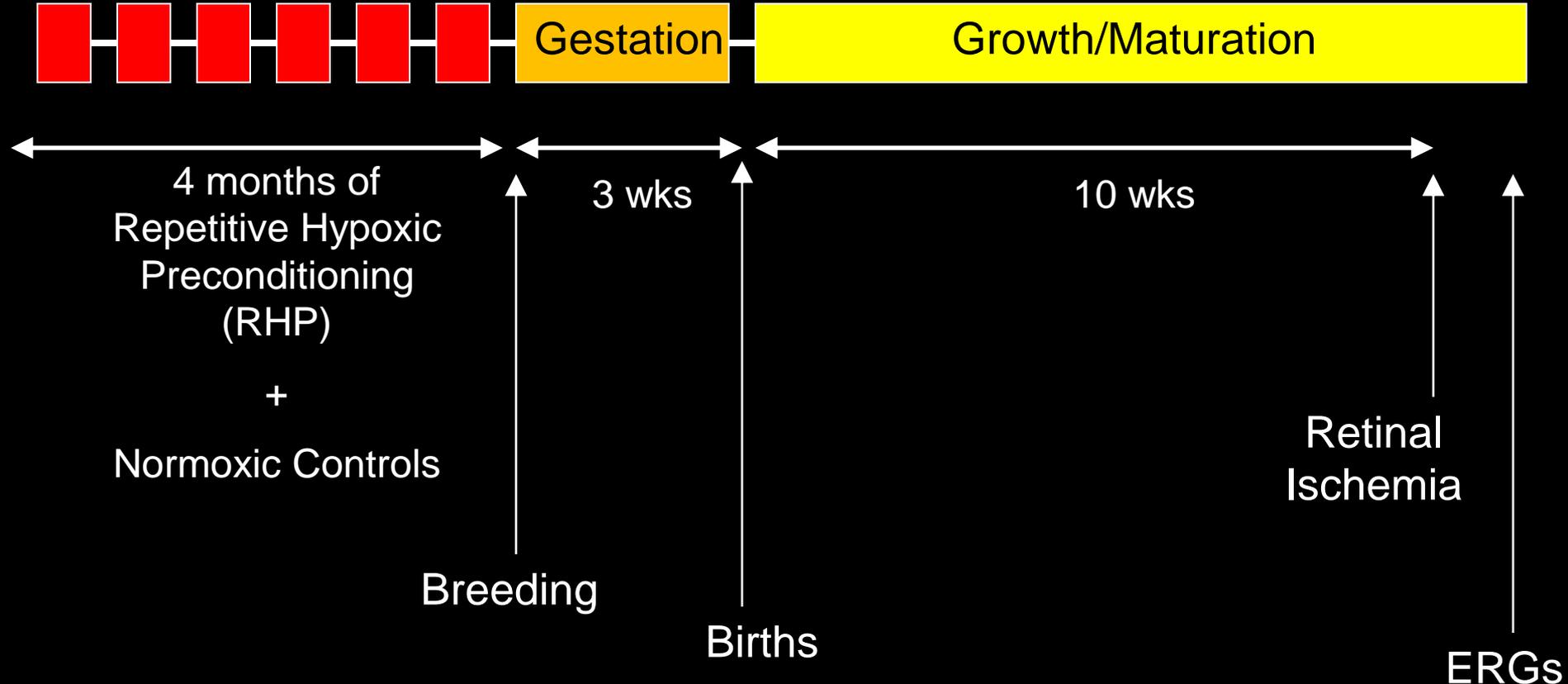
Inheritance of Acquired Characteristics





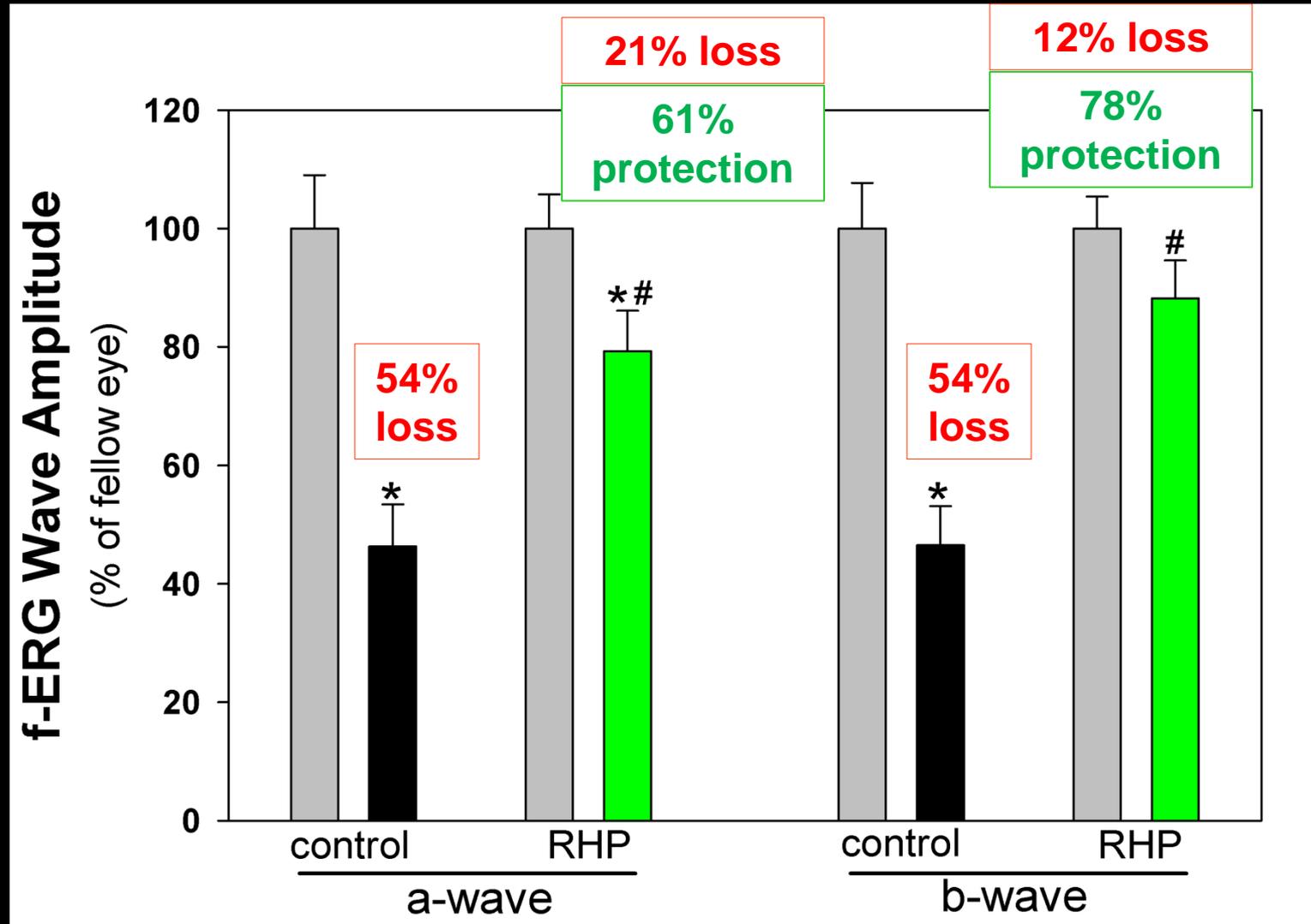
Transgenerational Epigenetics

Experimental Design



Transgenerational Epigenetics

children inherit injury resilience of parents



Joe Klein:
The CIA's
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Yemen: The
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Why the Recession
Hasn't Been Cool
To Teens

TIME

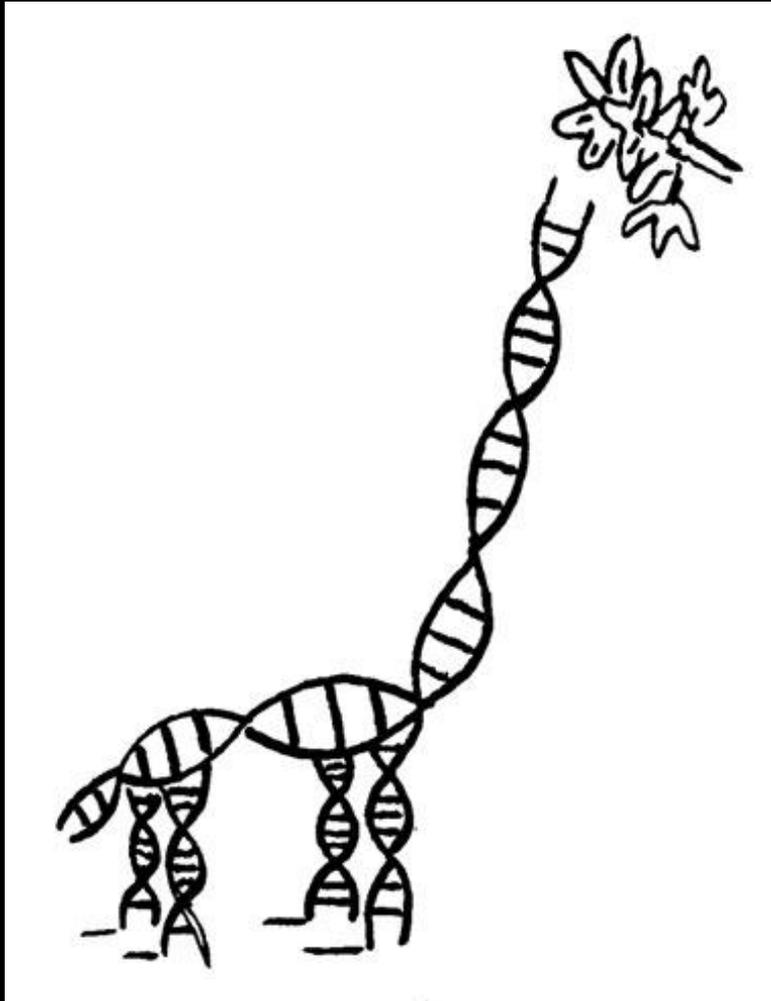
WHY YOUR DNA ISN'T YOUR DESTINY

The new science of epigenetics reveals how the choices you make can change your genes—and those of your kids

BY JOHN CLOUD



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Foundation

BrightFocus (AHAF)

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Research Foundation of
the Illinois-Eastern Iowa
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