

Astrocyte Plasticity Revealed by Adaptations to Severe Proteotoxic Stress

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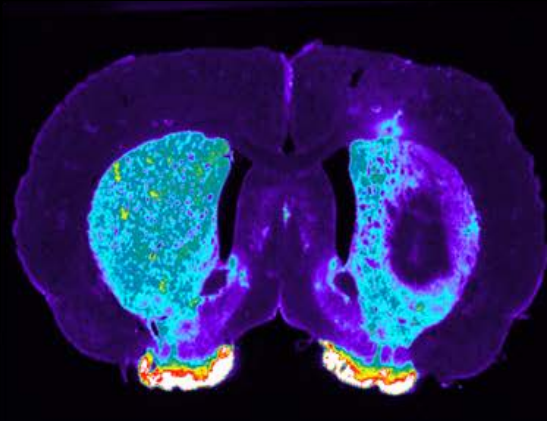
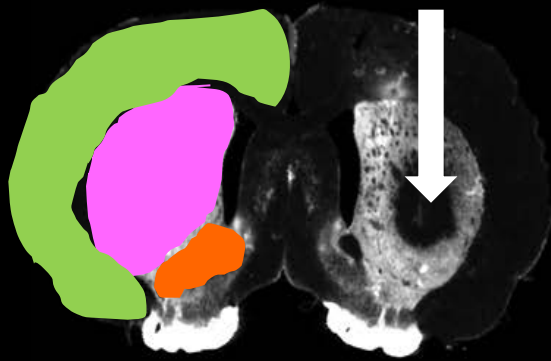
Plasticity

- Short duration stress
- Low dose stress
- Long duration stressors of very low dose

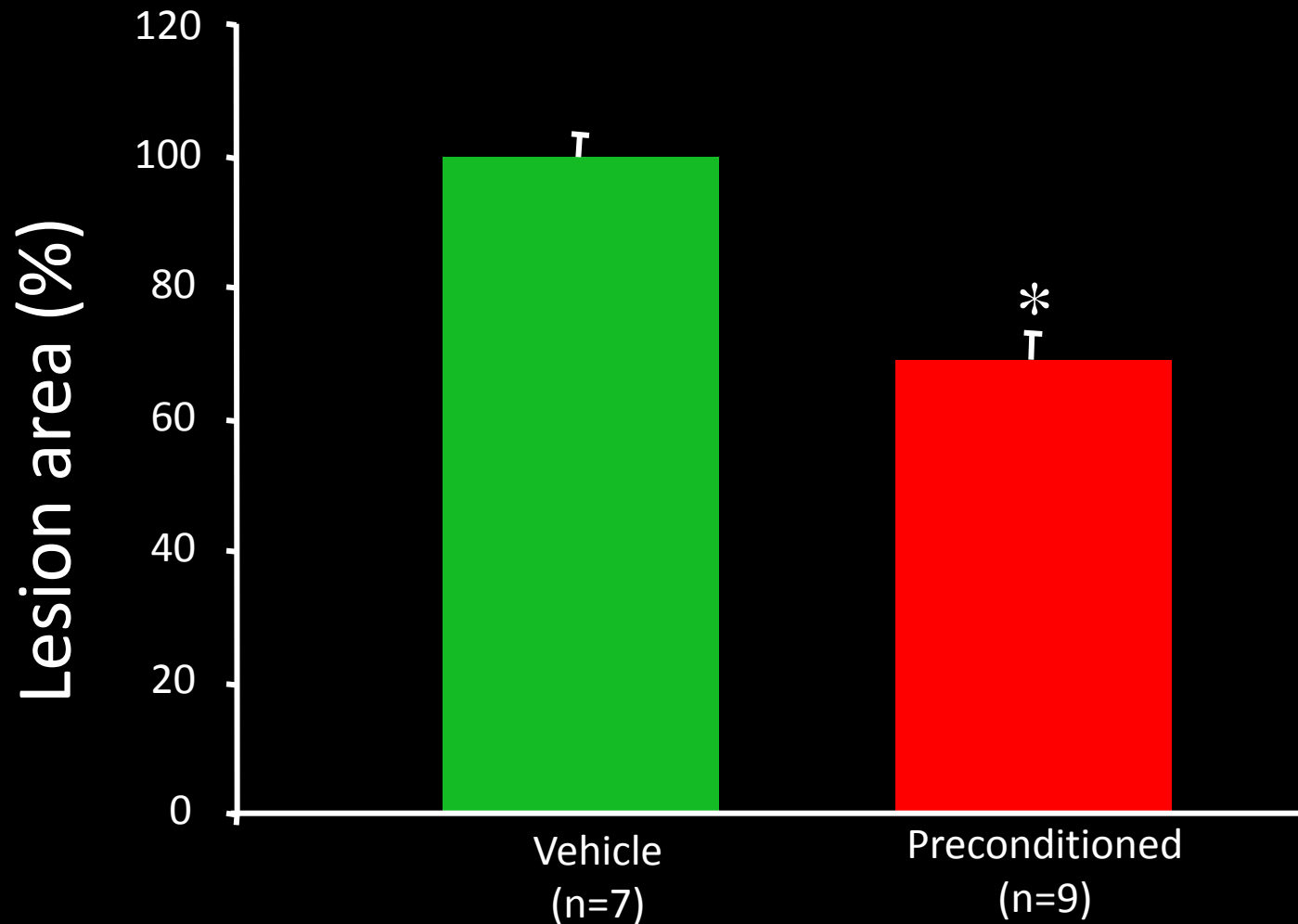
- Quantified by response to a second hit
- Plasticity in neurodegenerative disease models?

Vehicle pretreatment

Cortex Striatum



6-OHDA toxicity is blunted by preconditioning



* $p \leq 0.05$ vs Vehicle

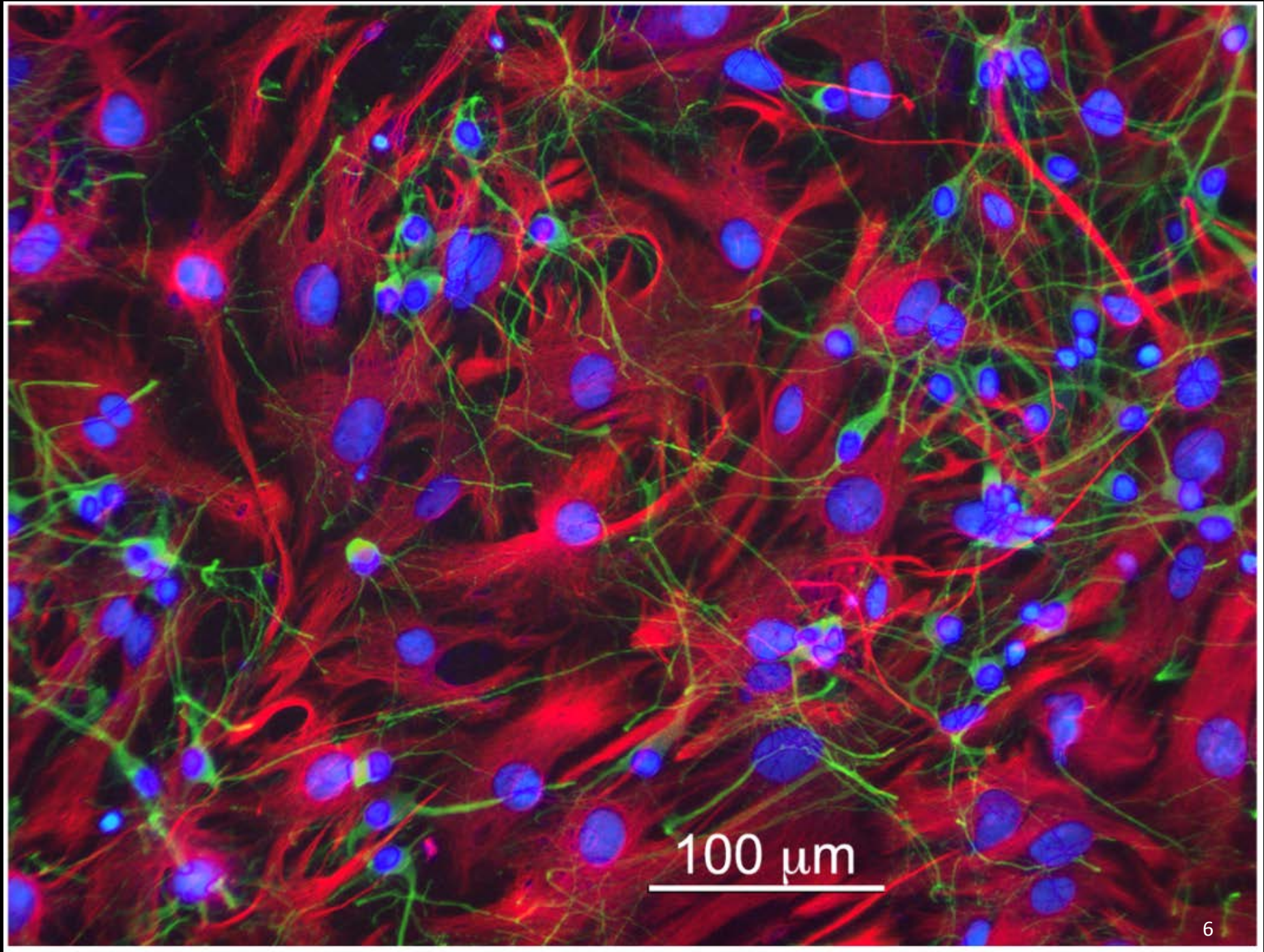
What happens if the stress is severe?

Dual-hit hypotheses

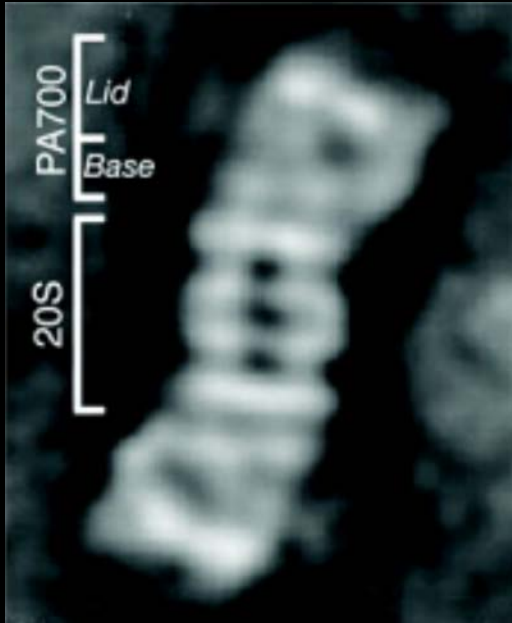
- Severe stress potentiates response to second hit

Alternative dual-hit hypothesis

- Severe stress may leave behind resistant cells
- These survivors may be harder to kill
- A new type of plasticity

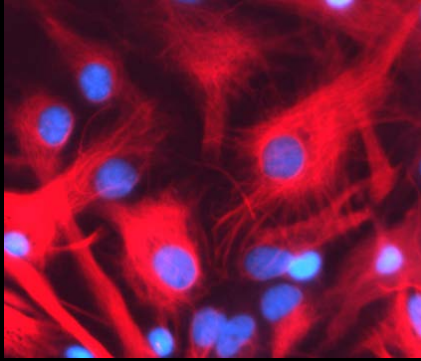


The 26S proteasome



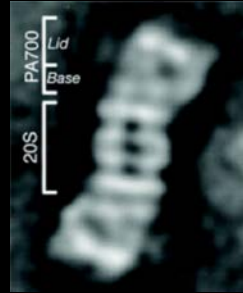
- Proteasome activity is inhibited in PD in nigra
 - Aggregated synuclein clogs proteasome
- Astrocytes contain aggregated synuclein
 - Both glia and neurons undergo protein-misfolding stress in PD

2 Hit Model in Primary Astrocytes



0 h

Plate
Astrocytes



24 h

1st MG132 hit
(pretreatment)



48 h

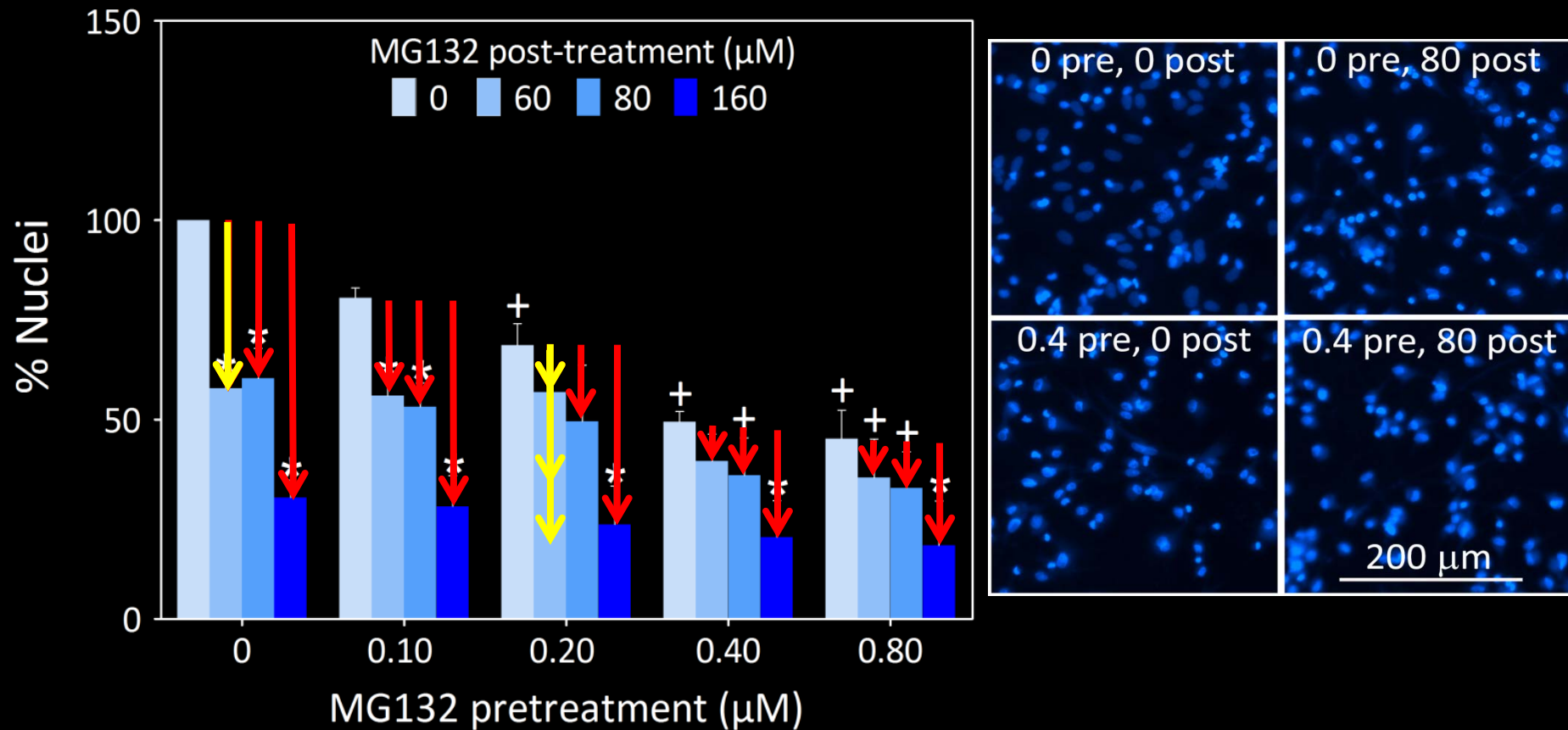
2nd MG132 hit
(post-treatment)



72 h

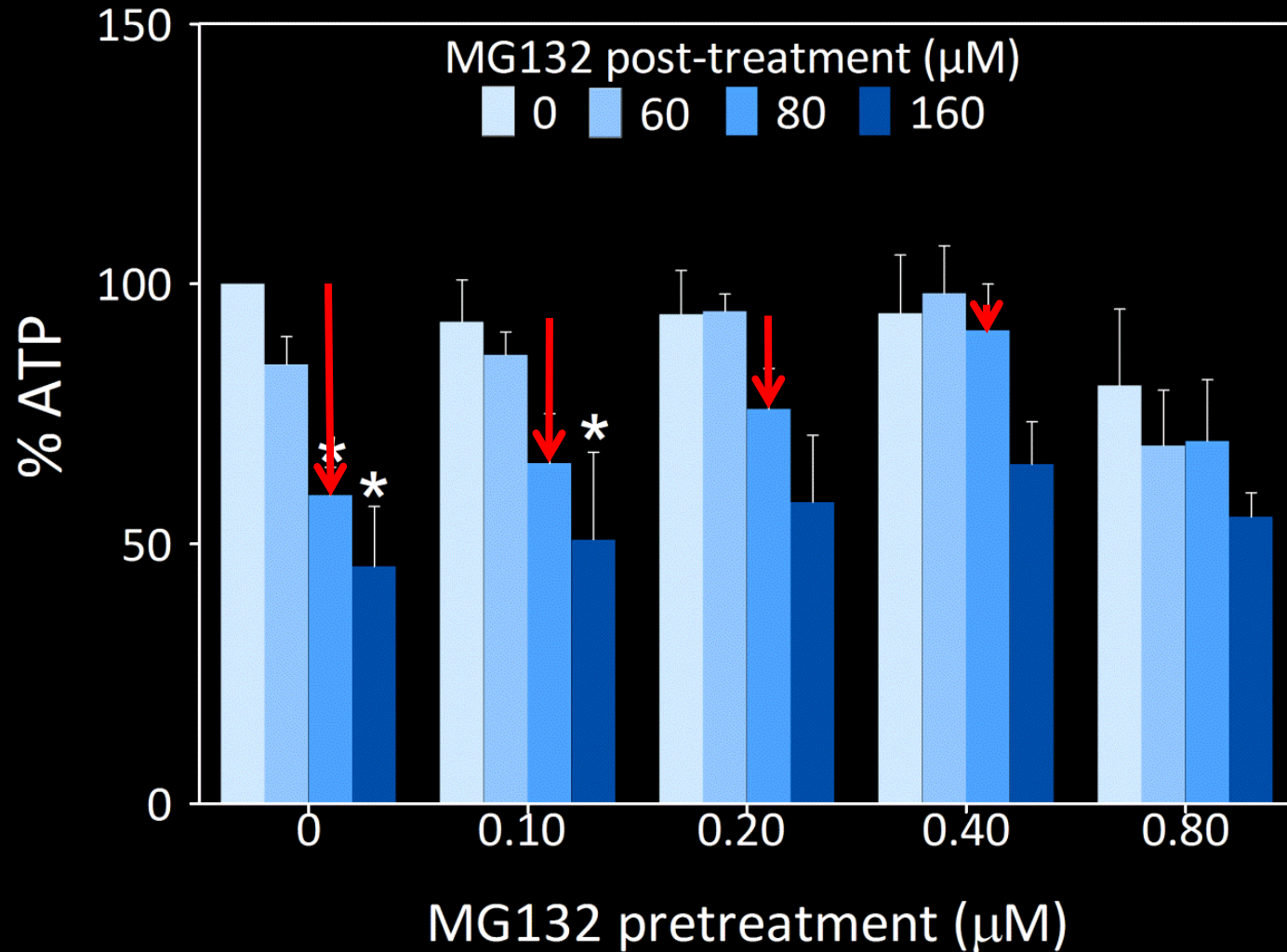
Assay

Severely stressed glia resist 2nd hit



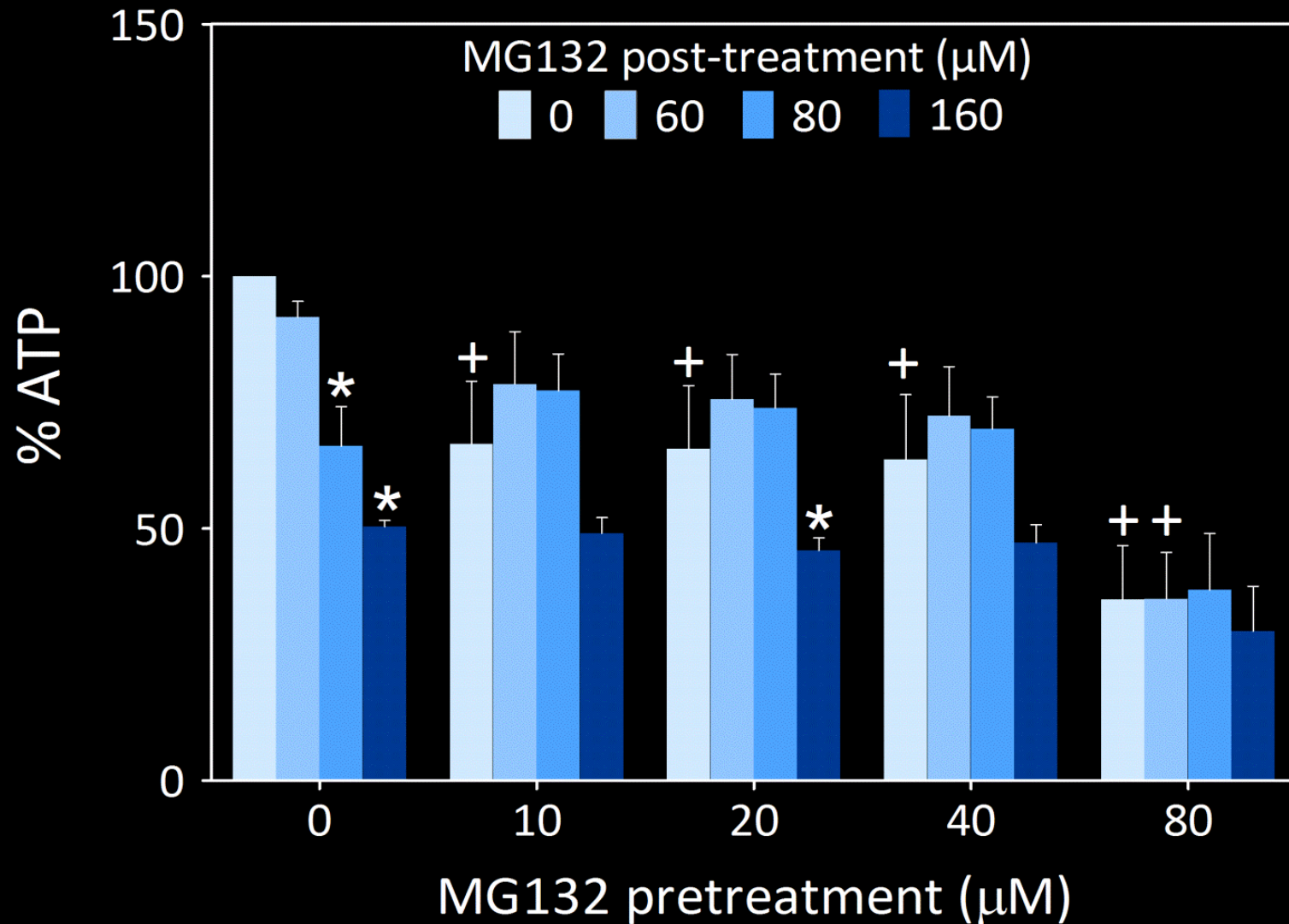
* $p \leq 0.05$ vs 0 μM post-treatment; + $p \leq 0.05$ vs 0 μM pretreatment

Severe stress reduces ATP loss in glia



* $p \leq 0.05$ vs 0 μM post-treatment

Very severe stress blocks ATP loss in glia

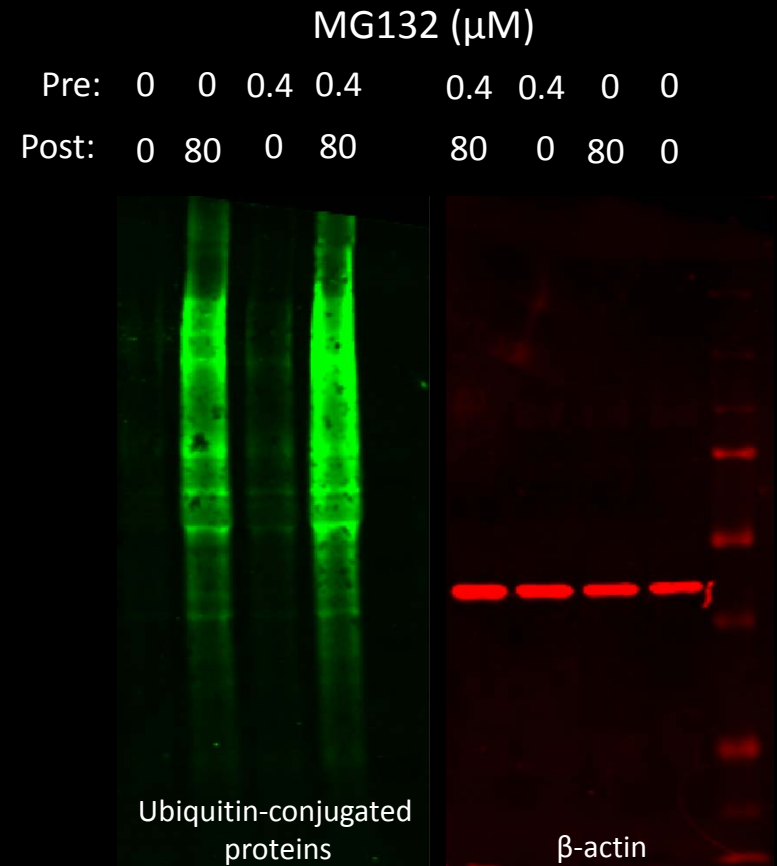
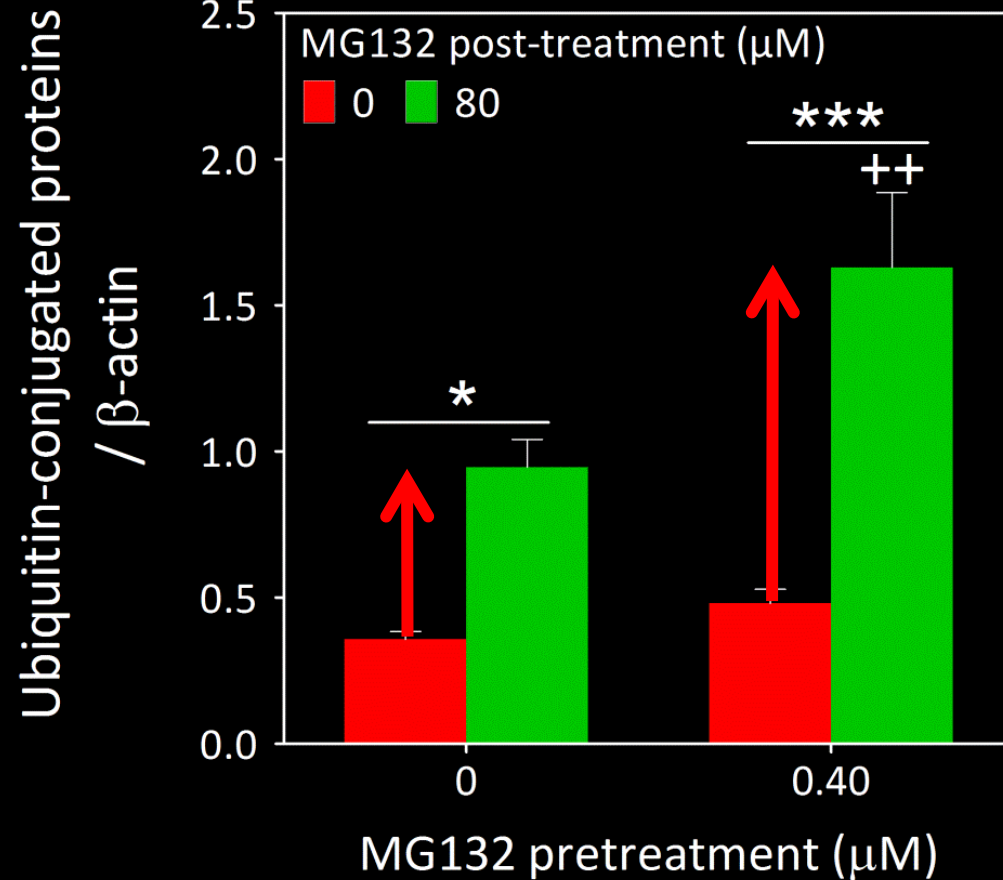


* $p \leq 0.05$ vs 0 μM post-treatment; + $p \leq 0.05$ vs 0 μM pretreatment

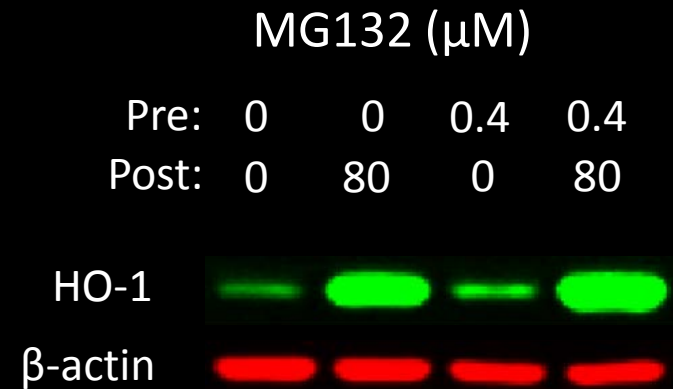
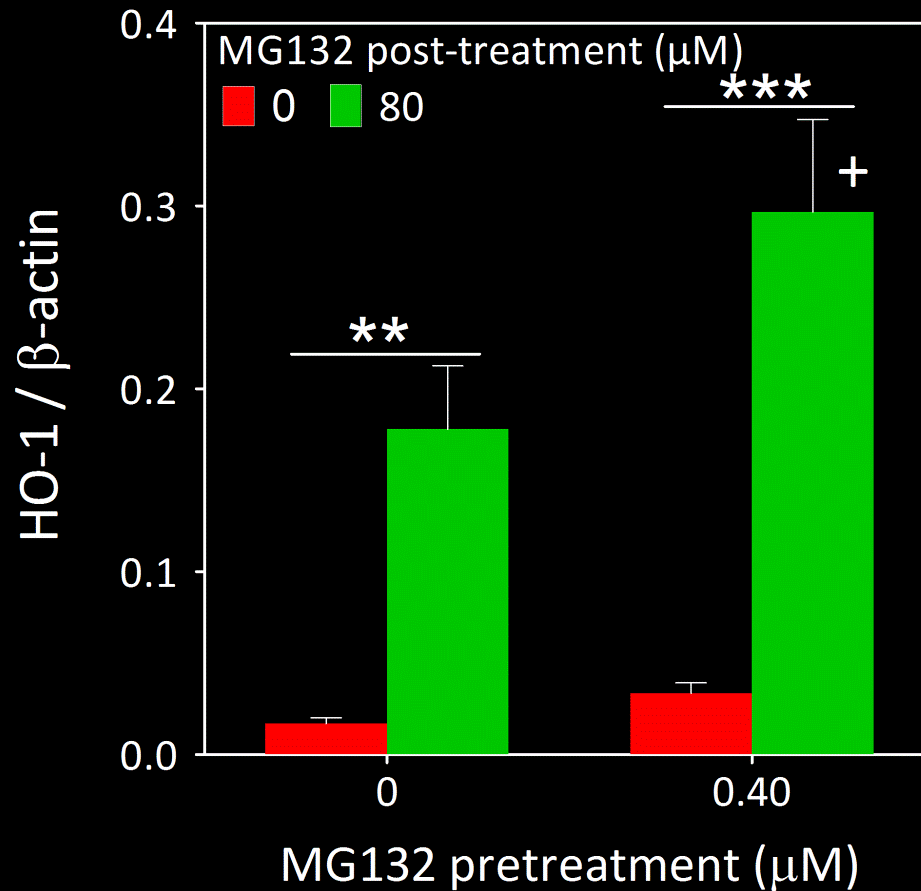
Alternative Interpretations

- Remaining cells are simply refractory to MG132
 - Would not respond to 2nd hit either
- Cells are still responsive to 2nd hit, but do not die
 - 1st hit elicits adaptations (supported by ATP data)

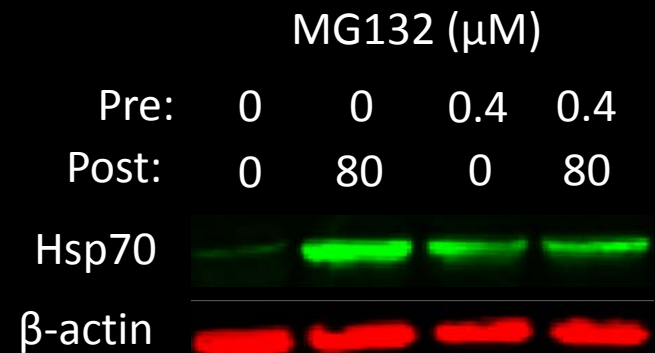
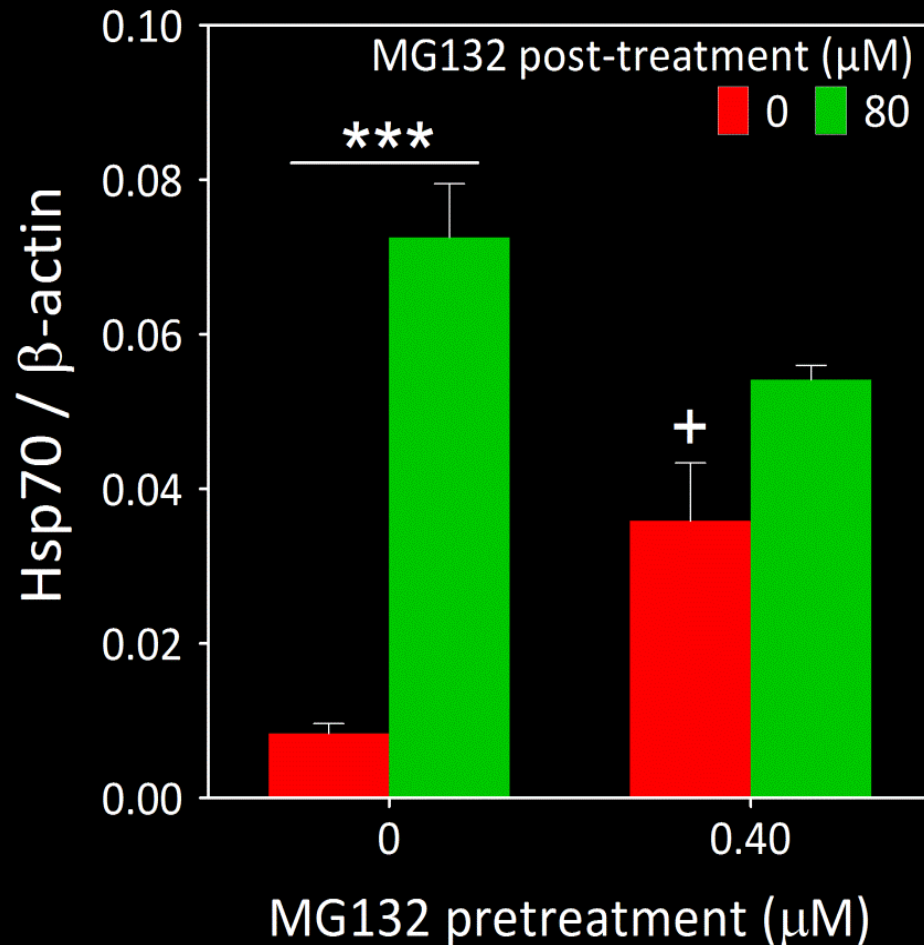
2nd hit still has an impact on stressed cells



2nd hit still has an impact on stressed cells

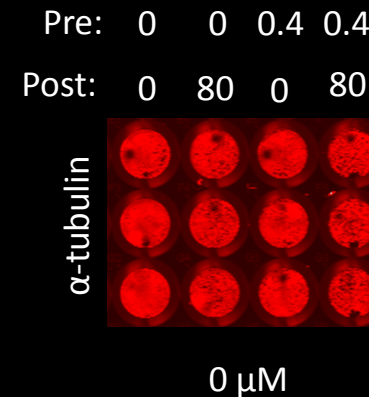
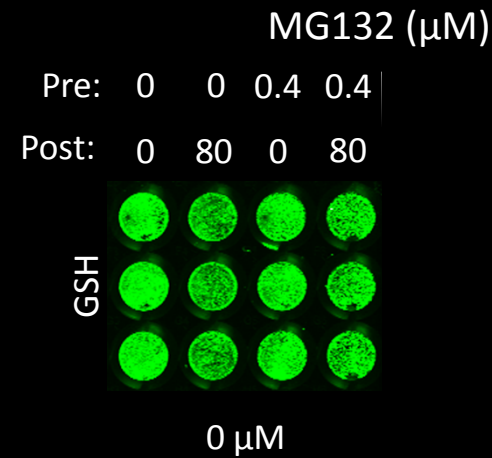
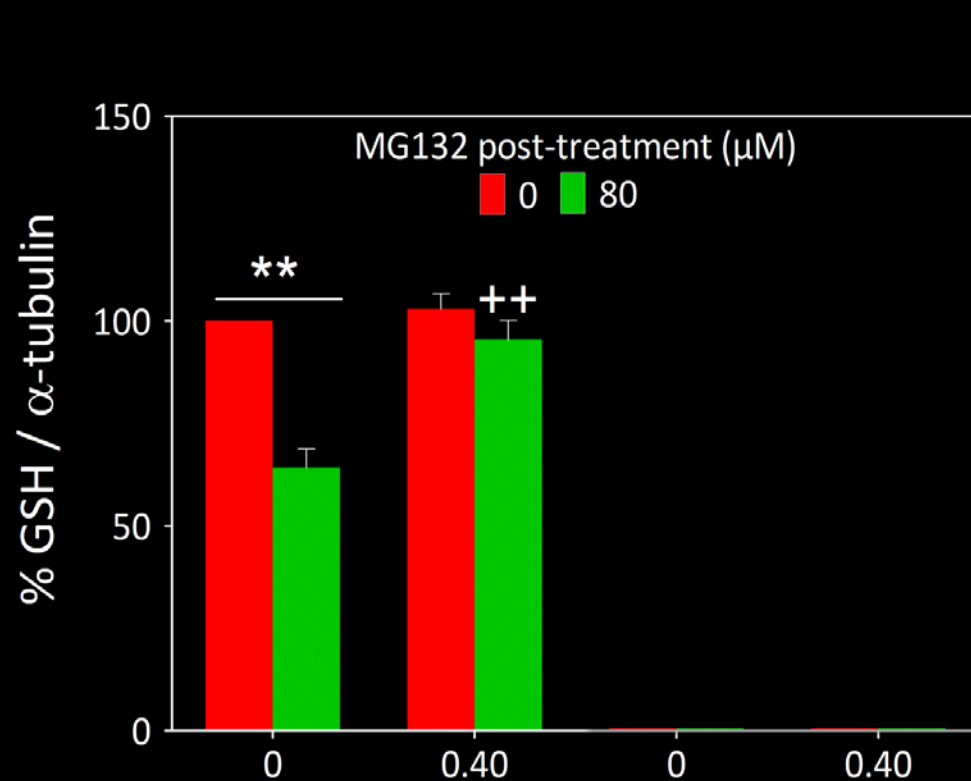


Impact of 2nd hit on Hsp70 is blunted



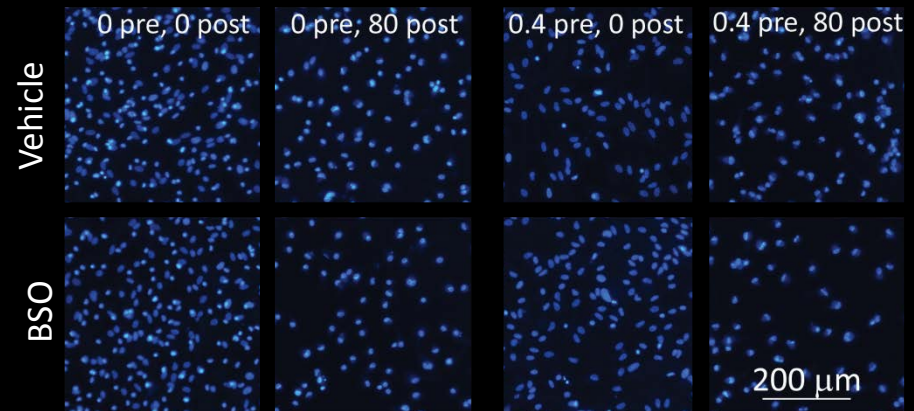
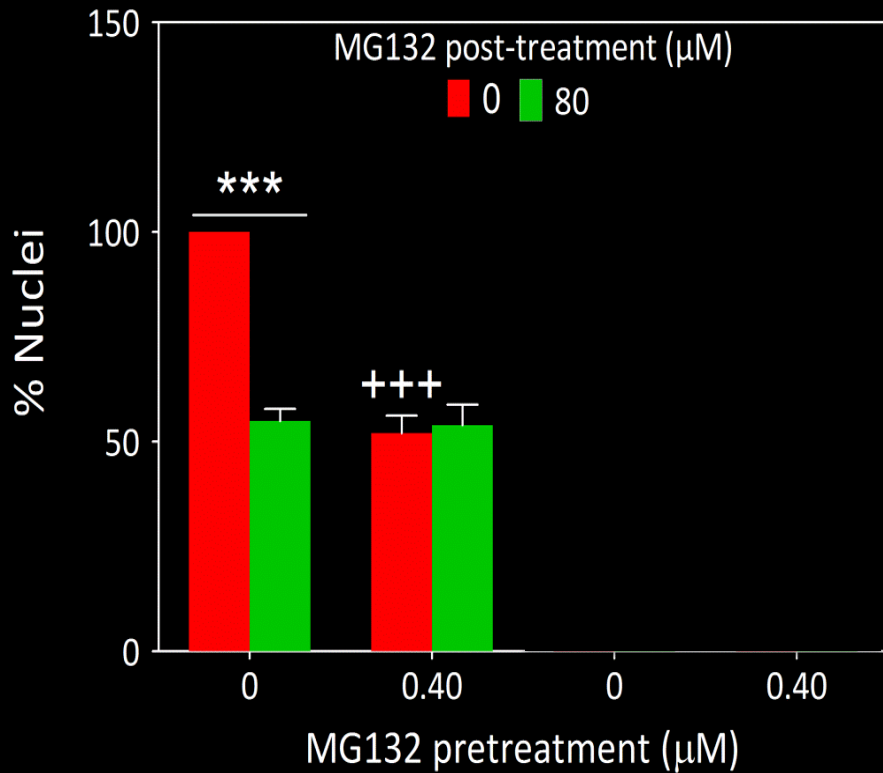
*** $p \leq 0.001$ vs 0 μ M post-treatment; + $p \leq 0.05$ vs 0 μ M pretreatment

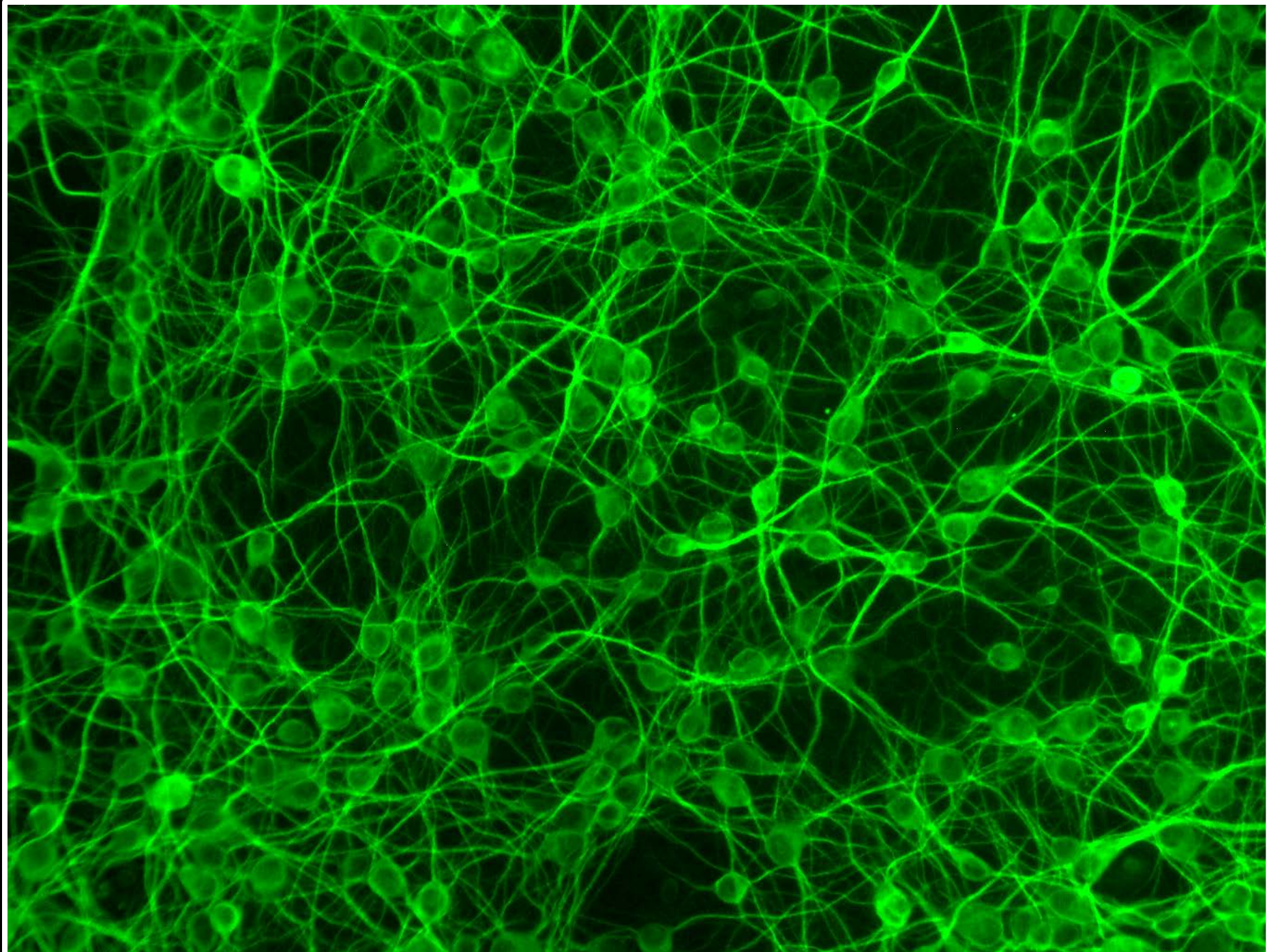
1st hit prevents loss of glutathione



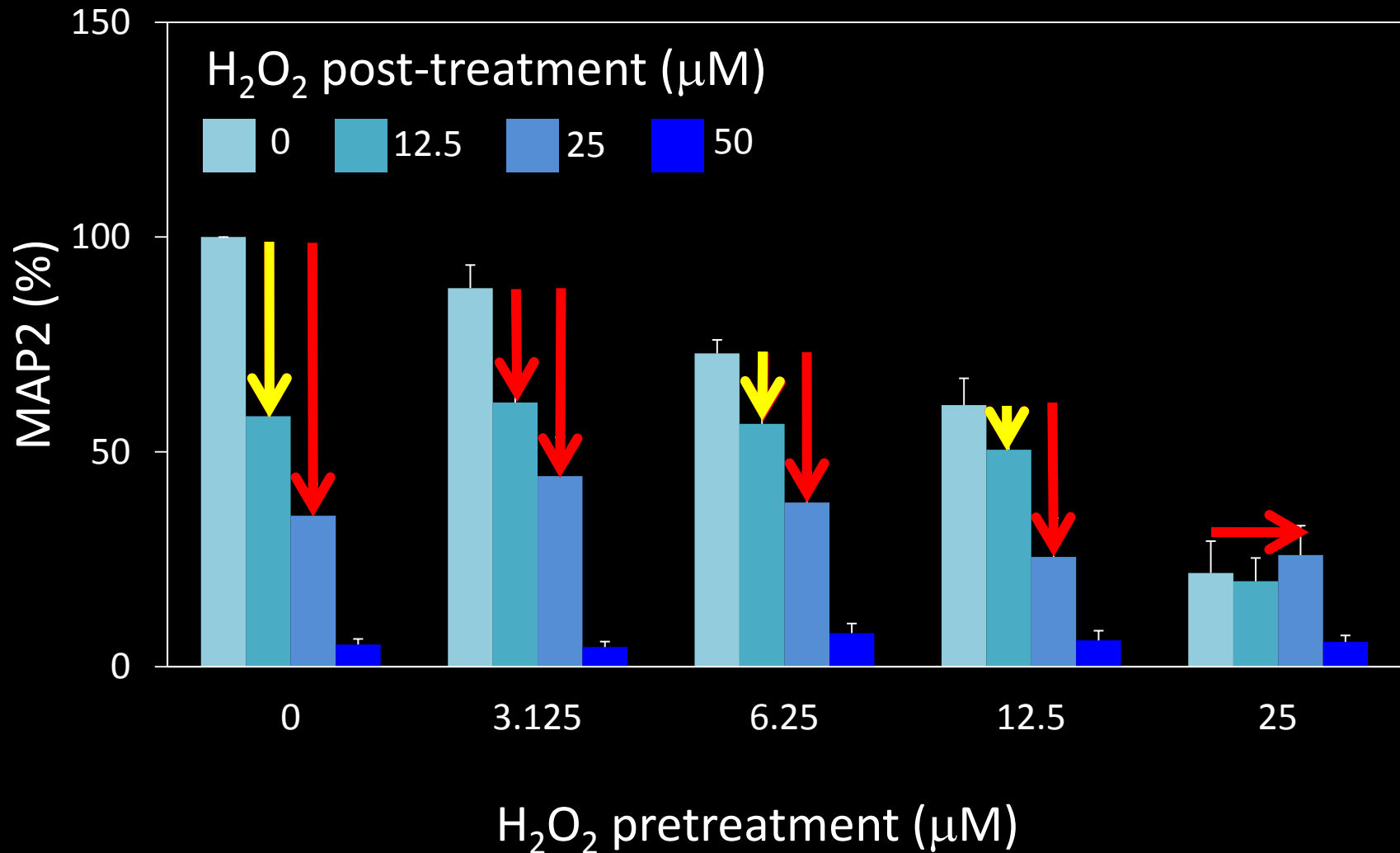
- Does BSO elicit vulnerability to 2nd hit?

Glutathione loss makes stressed cells vulnerable to 2nd hit

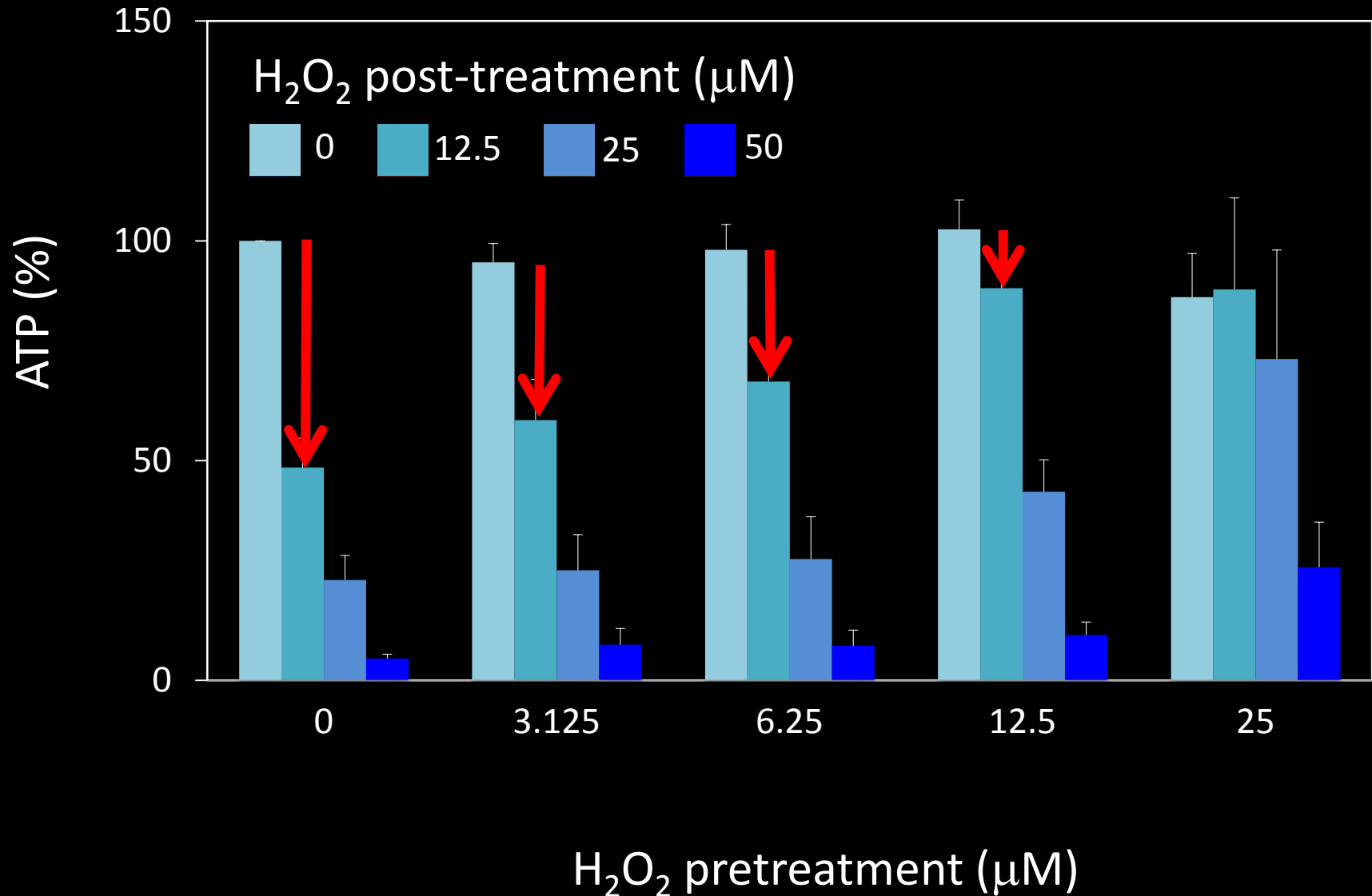




Severely stressed primary neurons resist 2nd hit



Severe stress reduces ATP loss in primary neurons



Astrocytic responses to severe stress

Conclusions

- Astrocytes become progressively harder to kill
- Adaptation is glutathione dependent
- Adaptation may be fueled by a rise in ATP
- Adaptation is not dependent on autophagy

- Can stressed astrocytes retain their neurosupportive roles in disease states?

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