

PHYSIOLOGY OF CEREBRAL RESUSCITATION

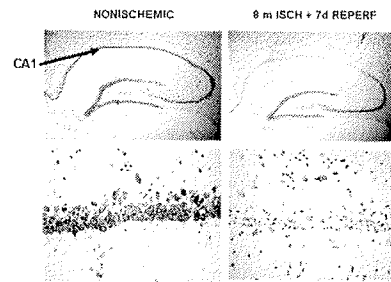
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The Obligatory Disclosure Slide

- Nothing to declare.

Our Problem: Brain Ischemia Sux

- After > 5 min transient global brain ischemia, selectively vulnerable neurons go on to die.
- Unfortunately, these happen to be the neurons you think and remember with.

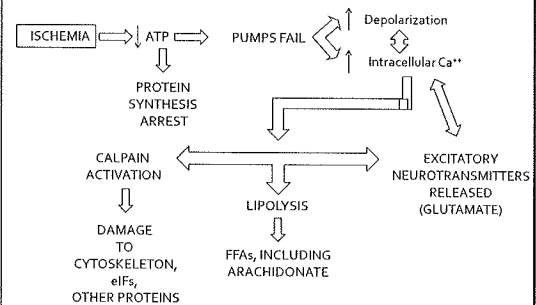


How Does This Happen?

- Ischemia cocks the hammer.
- Reperfusion pulls the trigger.



Bad Things Happen in Ischemia

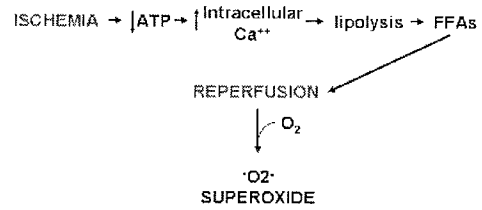


Worse Things Happen During Reperfusion

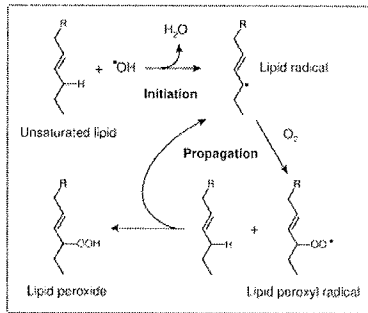
- The Four Horsemen of the Brainocalypse:
 - Free Radical Damage
 - Inhibition of Protein Synthesis
 - Calpain-Mediated Proteolysis
 - Apoptosis



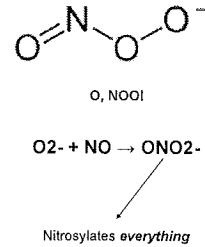
Totally Rad



Free Radicals: The Horror Continues



Free Rads: Son of Superoxide



A Free Radical Bestiary

•O ₂ ⁻ , superoxide anion	From mitochondria. Not very reactive, but initiates chain rxns
H ₂ O ₂ , hydrogen peroxide	From dismutation of •O ₂ ⁻ . Can diffuse across membranes. Bastard.
•OH, hydroxyl radical	Mean SOB. Like Cheney will attack almost anything.
ROOH, organic hydroperoxide	Zombie molecules.
RO•, alkoxy and ROO•, peroxy radicals	More zombie molecules. Lipid forms are particularly ghoulish.
OONO•, peroxyxynitrite	Evil. Just evil.

Calpain...



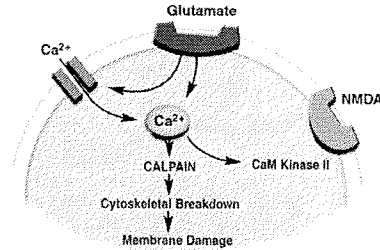
...and his trusty blade, *Fubaring*, sword of mayhem.

Who is this Calpain Dude?

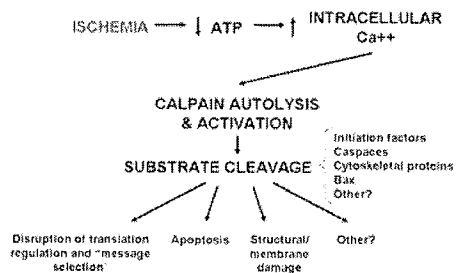
- Usually a nice guy.
- Neutral cysteine proteases
- Two flavors:
 - Calpain I (μ -calpain): neurons
 - Calpain II (m-calpain): glia
- Cytoskeletal remodeling
- Synaptic plasticity
- Neurite outgrowth
- Activated by calcium flux



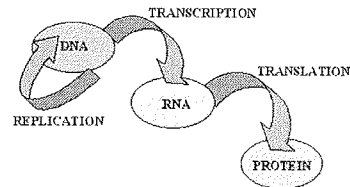
How Calpain Gets His Freak On



Calpain's Crazy Killing Carnival



Let's Review, Shall We?



A Target-Rich Environment

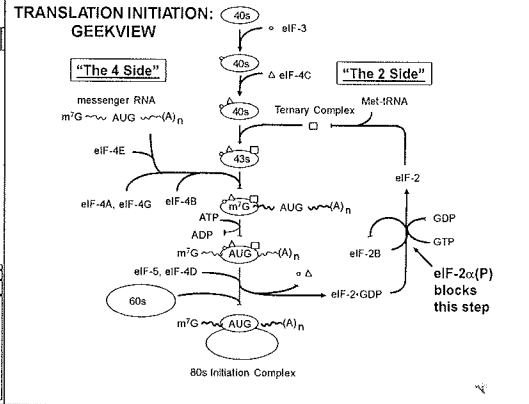
- **All tuckered out.**
 - Not enough ATP during reperfusion
- **DNA badness.**
 - Free Rads or nucleases go all over the place on the DNA.
 - Denaturation or other physical/chemical changes
- **Transcriptional badness.**
 - RNA polymerase is confused, damaged, drunk or dead.
- **mRNA badness.**
 - mRNA can't be processed correctly, or
 - gets damaged, or
 - fails to get out of the nucleus.
- **Translational badness.** Ribosome can't translate the mRNA into protein.

The Long March: Nucleus to Ribosome

- Brain ATP levels return to near-normal levels during early reperfusion (early 80s).
- Brain nuclear and mitochondrial DNA is undamaged during early reperfusion. (Your lab, 1991 and 1992)
- The transcriptional machinery is intact (early 90s).
- mRNA makes it out of the brain intact (Your lab, early 90s).
- "Washed" or purified ribosomes isolated from brains after an ischemic insult could still translate mRNA to protein in an *in vitro* system (Your lab, mid-90s).
- And that's it!

Wait a Minute!

- What about *dirty* ribosomes?
- Experiments demonstrated that inhibition of translation during reperfusion was at the level of translation *initiation*.
- Translation initiation is a complex process, involving the assembly of over 140 proteins, ribonucleotides, and ribonucleoproteins in a *translation initiation complex*.



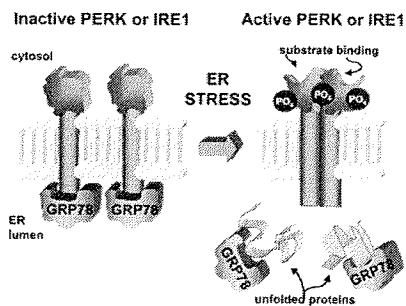
Short answer: eIF2α (P)

- eIF2α gets phosphorylated during early brain reperfusion (DeGracia, 1998)
- eIF2α(P) maps to selectively vulnerable neurons (DeGracia and Sullivan, 1999)
- Dephosphorylation of eIF2α during early reperfusion restores protein synthesis (Sullivan, 1999).

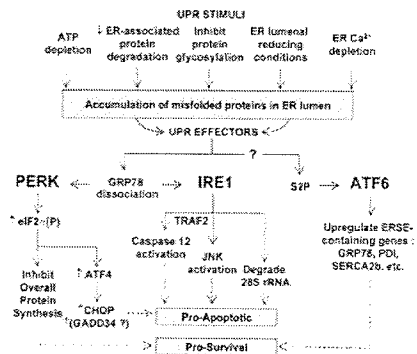
So...who's the kinase?

- The usual suspects:
 - GCN2
 - Nope
 - PRK
 - Nope
 - HRK
 - Nope
 - PERK
 - Bingo

PERKy isn't always cute



More Geek-o-vision



Apoptosis...

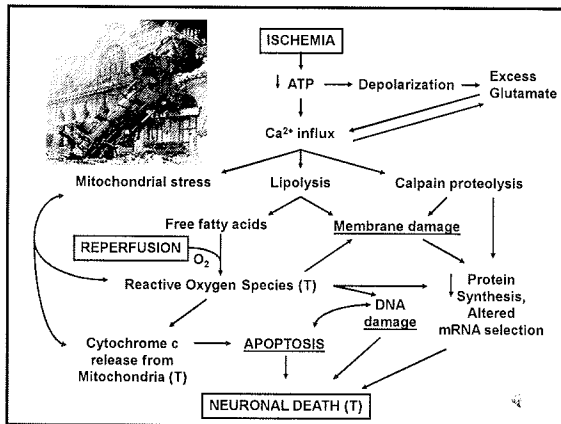


...and his unbalanced suicidal depression.

A Little Cell-Death Humor



Integrating signals hinting at his obsolescence, George undergoes apoptosis.



Several Conclusions Follow

- The earliest events (during ischemia) are probably *not preventable*.
- Even so, treatment must begin *early* to be effective (upon ROSC), to prevent propagation and intercalation of pathologic processes.
- Target Rich Environment.
- Most important:

SINGLE-DRUG THERAPY WILL NEVER WORK