Eric “Jake” Lindstrom Chief CRNA and Manager
WVU Medicine: J.W. Ruby Memorial Hospital, Morgantown WV

WVU Medicine


-65 Anesthesia sites
-Jon Michael Moore Trauma Center (Level I)
-WVU Rockefeller Neuroscience Institute
-Heart and Vascular Institute
-WVU Children's Hospital
--Obstetrics
-Vascular
-Neurosurgery
-Orthopedics
-Same Day Surgery
-General Surgery

# Expansion and growth of the Neurosciences at

Erma Byrd Biomedical Research Center


ikm

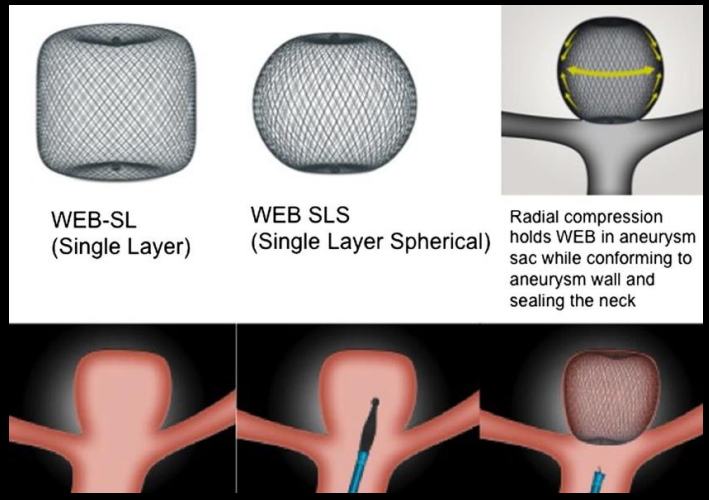
# Stroke Center @ WVUMedicine

## WVU Stroke Center

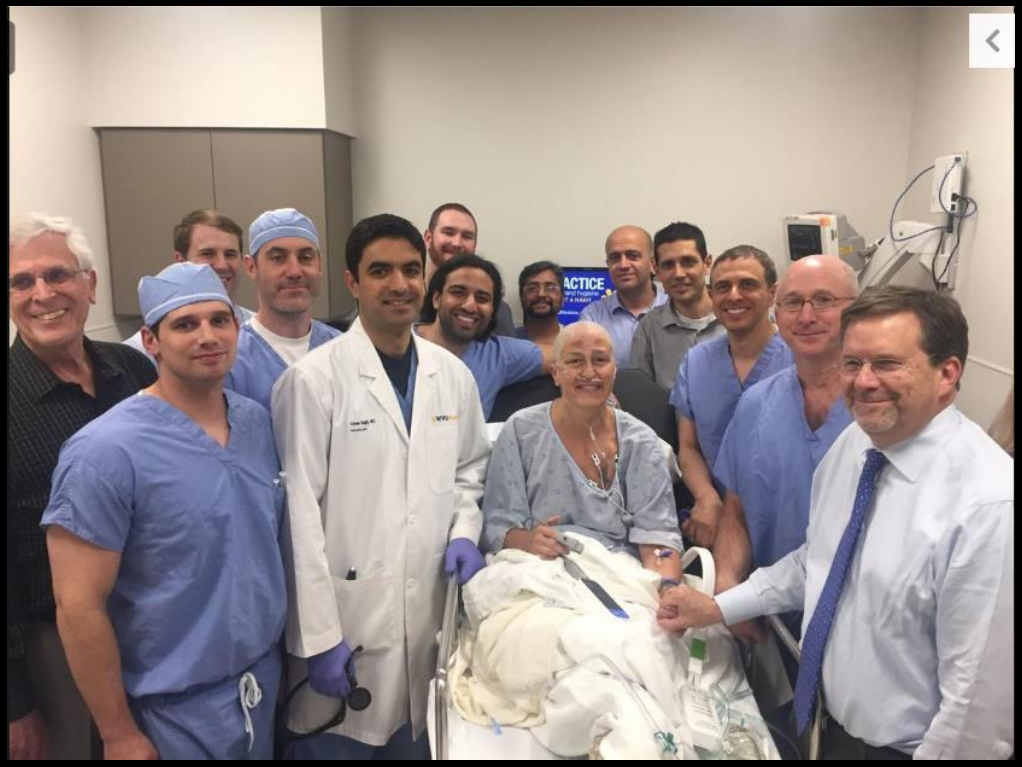
| | |
|---|---|
| Ave. door-to-needle time | 39 min |
| Percentage of Patients under 45min | 77.6% |

## Nationally

| | |
|---|---|
| Ave door to needle time | 52 min |
| Percentage of Patients under 45min | 44.9% |



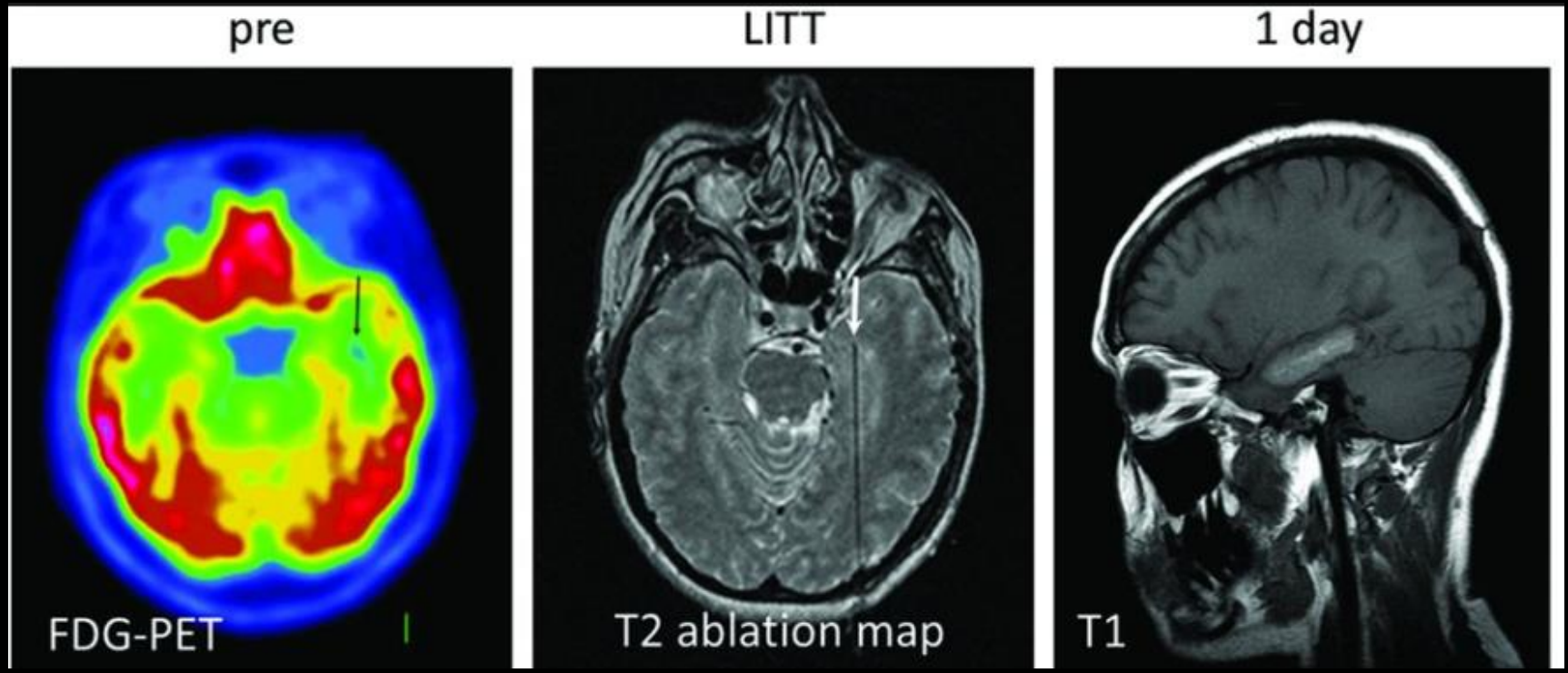
# Innovation



Historic breakthrough: WVU Rockefeller Neuroscience team first to use ultrasound to treat Alzheimer's

# DBS for Opioid Addiction

# Going to forefront: LiTT




MRI Guided Laser Interstitial Thermal Therapy

# Neuroprotection


# Why is this important?

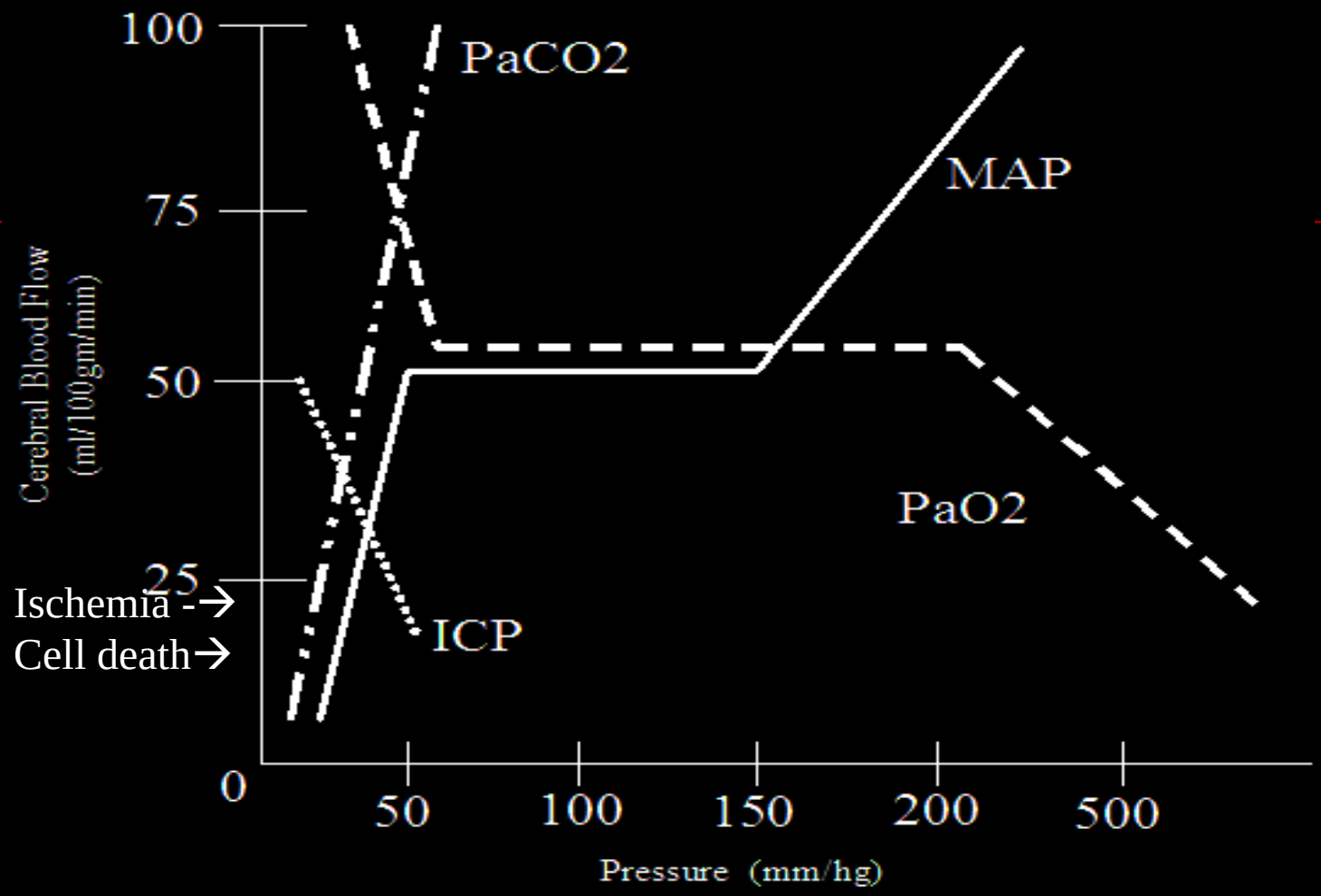
- 30 M Anesthetics
- 46 M elderly persons
  - Expected to be 90M by 2050
- 1 in 7 Children undergo GA prior to the age of 3
- 665K Neurosurgical procedures in US/Can
- TBI occurs every 15min
  - 13% will be fatal or disabling
- 795k people suffer strokes
  - 14% fatality

# Plan of Attack

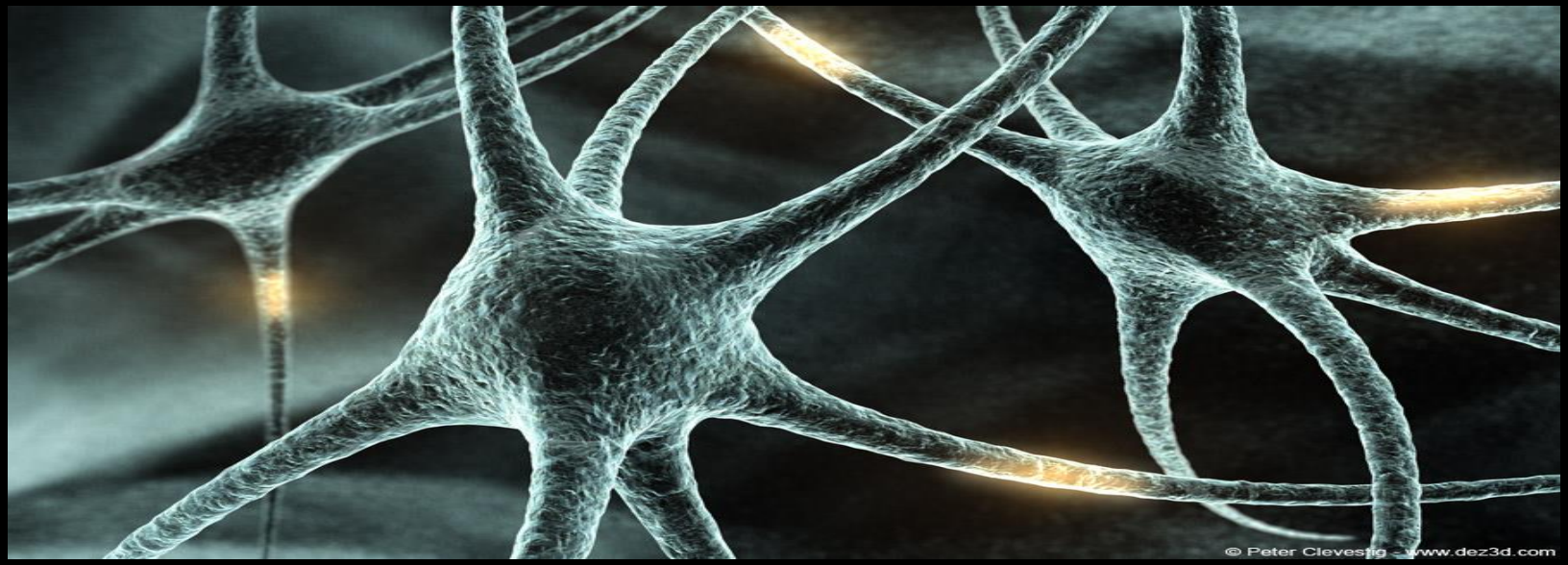
- Review of the brain's ability to protect itself
- **Mechanisms of cerebral ischemia**
- Commonly practiced methods of neuroprotection
- What else do we need to worry about?
- What is the Future?

# Autoregulation of the Brain

- It's Intelligent
  - Wide range pressure
  - $pO_2$
  - $pCO_2$



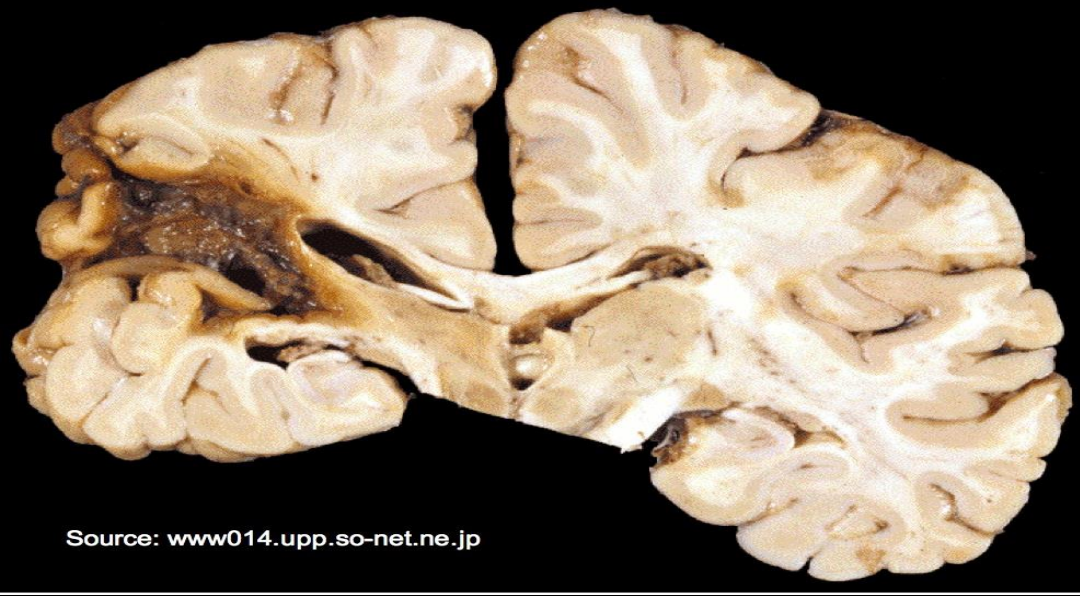

Autoregulation: Cerebral Blood Flow Response




# Cerebral Ischemia

# Pathophysiology of Metabolic Brain Injury

## "**Supply** and Demand"



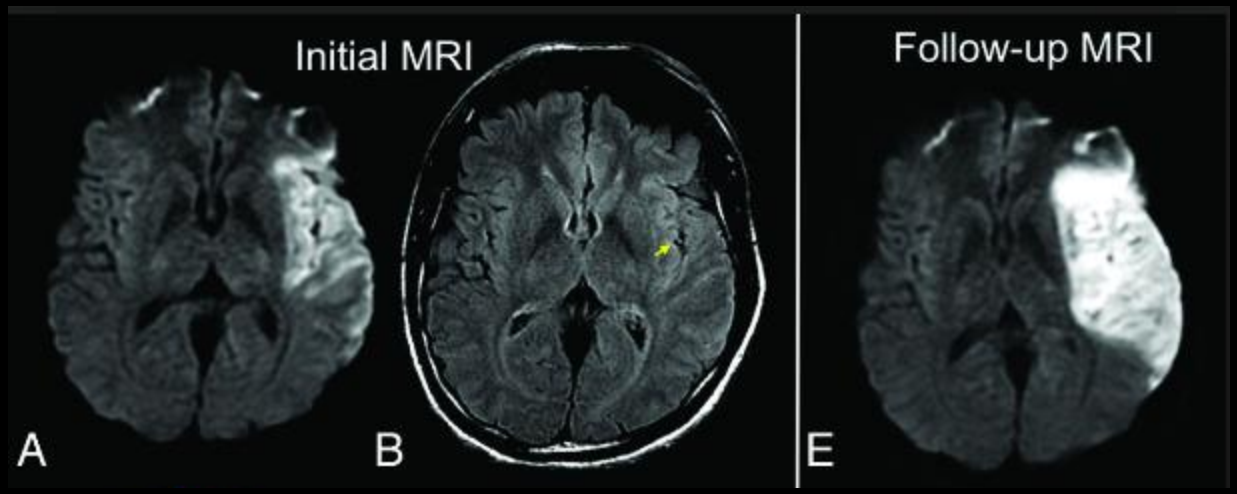

- Ischemia, Reperfusion Injury, Hypermetabolic States…

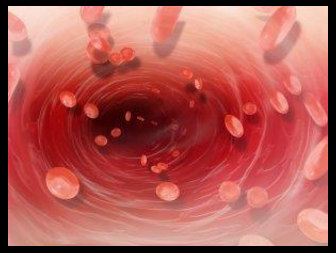
# "Supply and Demand"

- Global Ischemia
  - Cardiac Arrest –
    - 15-20s- Ischemia Cascade
  - Anaerobic Metabolism
    - Lactic Acidosis
  - Depletion of Glucose –
    - 4-7 min

# "Supply and Demand"

- Focal Ischemia
- Its about your neighbors…..





# Reperfusion Injury

- This is when much of the damage is done
- Cellular Sludging
- Release of Metabolic Waste
- Vasospasm
- Microembolic
- Triggers the Ischemic Cascade

# On the Flip SIDE

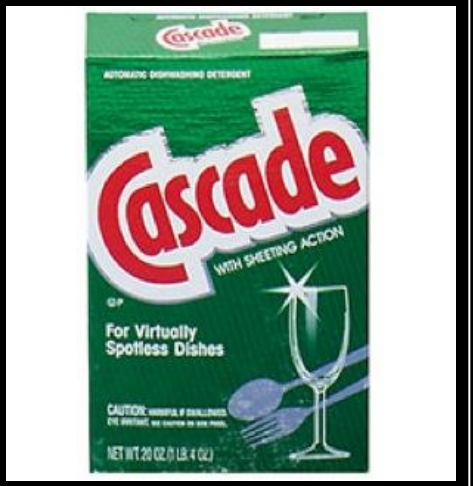
- SUPPLY and **DEMAND**
  - Epilepsy
    - Hypermetabolic state
    - Status Epilepticus >40-60min
    - Necrosis within 2-6 hrs = small treatment window
    - Triggers the Ischemia Cascade

# What is this “Ischemic Cascade?”

WARNING- the next slides will be busy

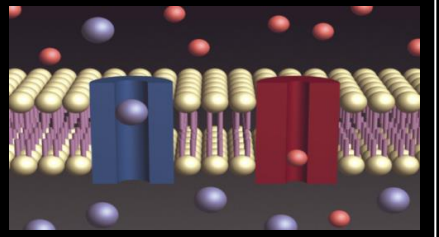
# Ischemia Cascade

- Destruction of Cell Membrane
- Destruction of Mitochondria Membrane
- DNA defragmentation
- Cerebral Edema
- Release of Neurotoxins
- Apoptosis
- Release of Inflammatory Mediators
- Production of Excessive Free Radicals
- Production of Nitric Oxide

# Ischemia Cascade: Cell Membrane

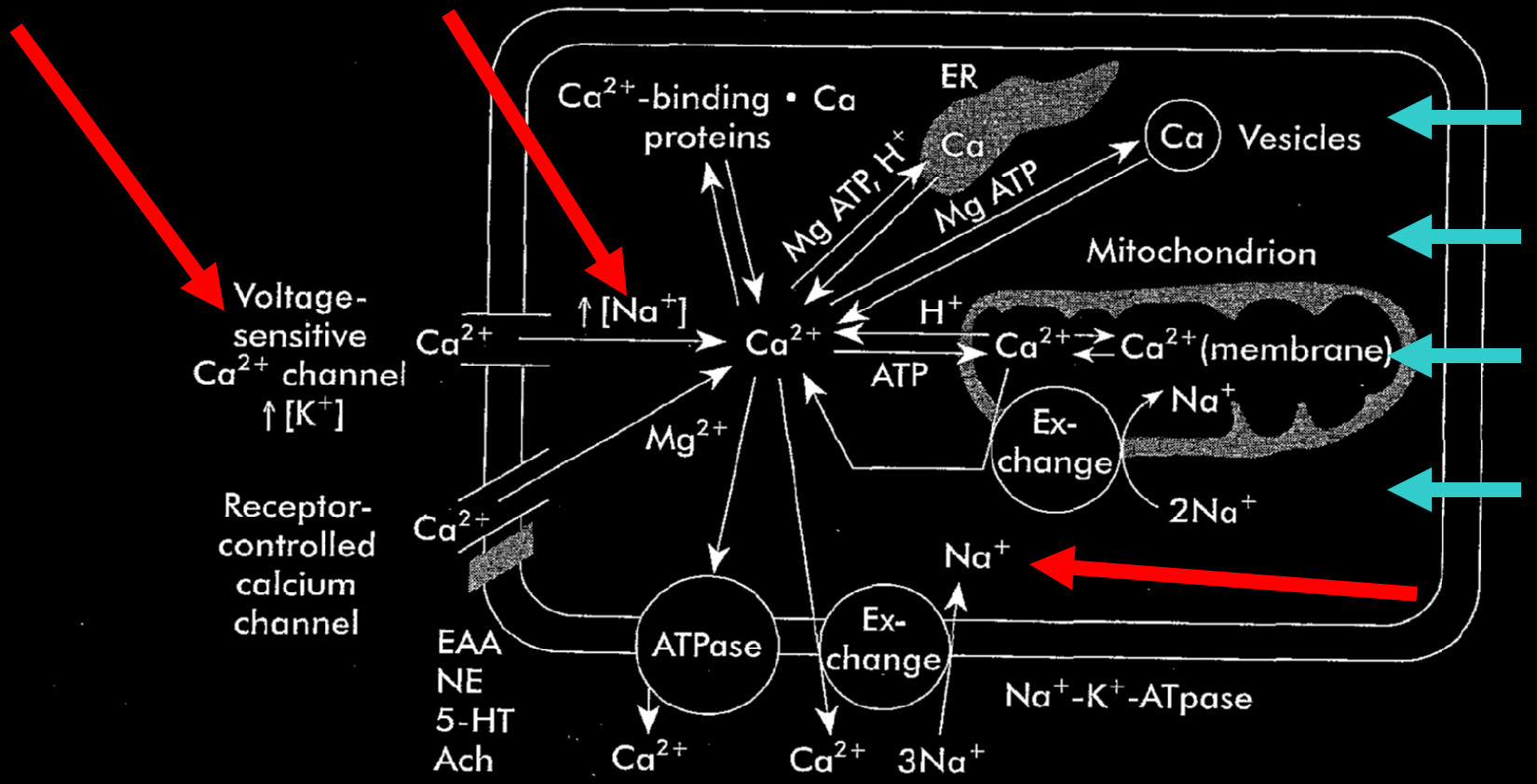
- Decreased ATP, Glucose, Phosphocreatine leads to Membrane depolarization
  - without total repolarization
- Depol leads to Ca++, Na+, Cl-, H20 influx and Efflux of K+
- Efflux of K+ opens more Voltage dependant Ca++ channels
- MASSIVE Influx of CA++



# Ischemia Cascade – Ca++

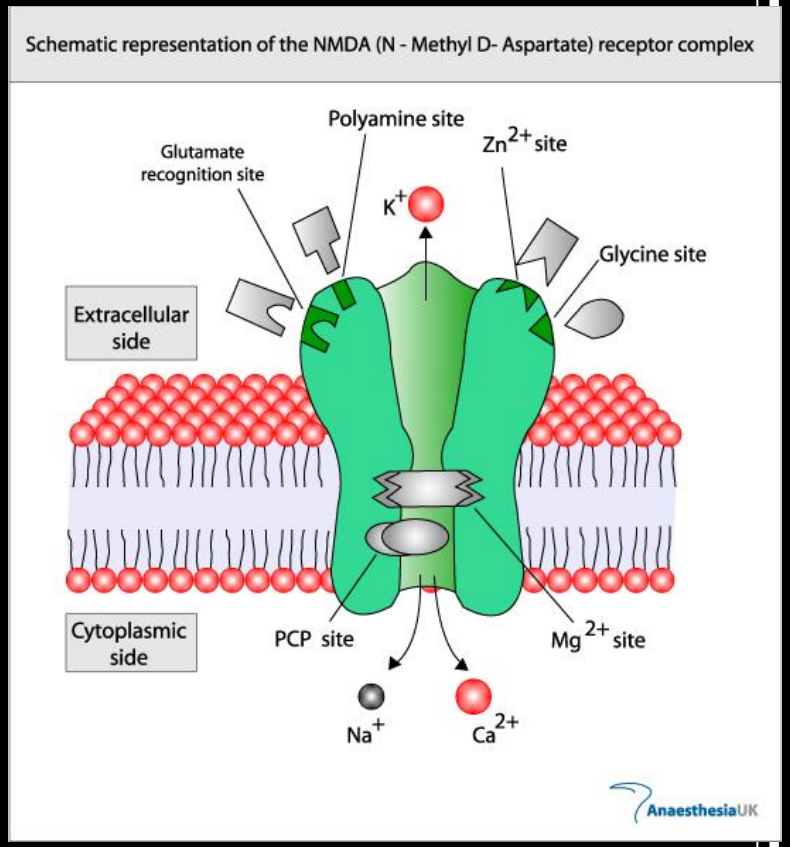
- Calcium Influx causes massive disarray!
  - Lipolytic and proteolytic reactions destroy CM
  - Activation of phospholipids in CM and Mitochondria releases Fatty Acids
  - Fatty Acids act as “Detergents” – Unstable CM
  - Primary FFA is Arachidonic Acid – Prostaglandins and Leukotrienes
  - Stimulates Caspase 3,6,7 leading to Apoptosis

# Ischemia Cascade –Ion transfer



# Ischemia Cascade: NMDA/GABA

- Glutamate released by the Ca++ influx
- Neurotoxic levels
- Influx of Ca++, Na+, Cl-, K+ transfer
- Where Na+ goes, H2O goes….

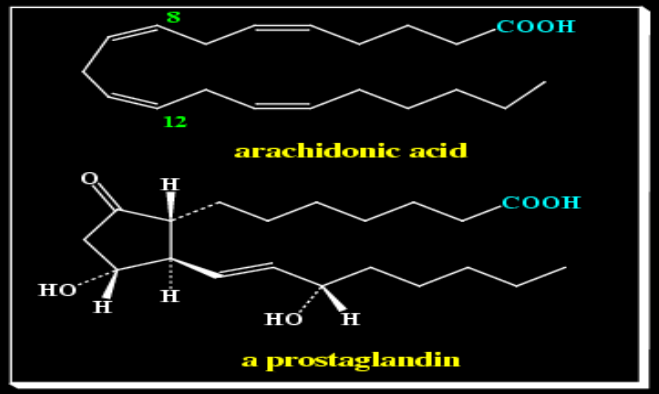


# Ischemia Cascade: Prostaglandins

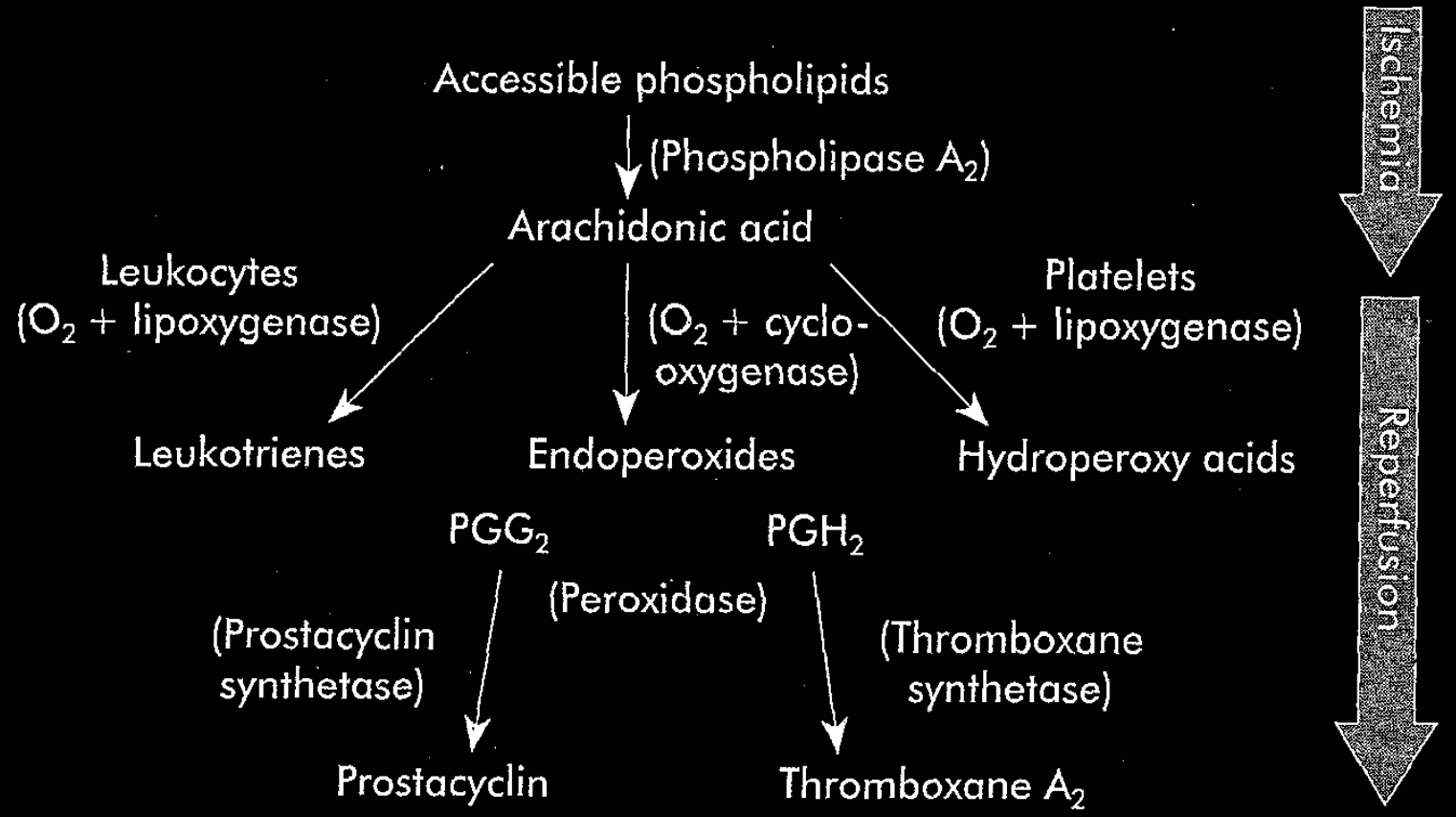
- Phospholipids converted to Free Fatty Acids- (Arachidonic Acid)
- Aerobic- converted to ATP via oxidation to acetyl-coA
- Anaerobic- Increased concentration of FFA's
- Efflux of K+ and Ca++ from mitochondria
- Bigger issue at Reperfusion

# Ischemia Cascade: Prostaglandins

- Increased Vasoconstriction
- Increased Leukotriene production
- Increased Platelet aggregation
- Also leads to Increased Hydroperoxy and peroxy production
  - Free Radicals



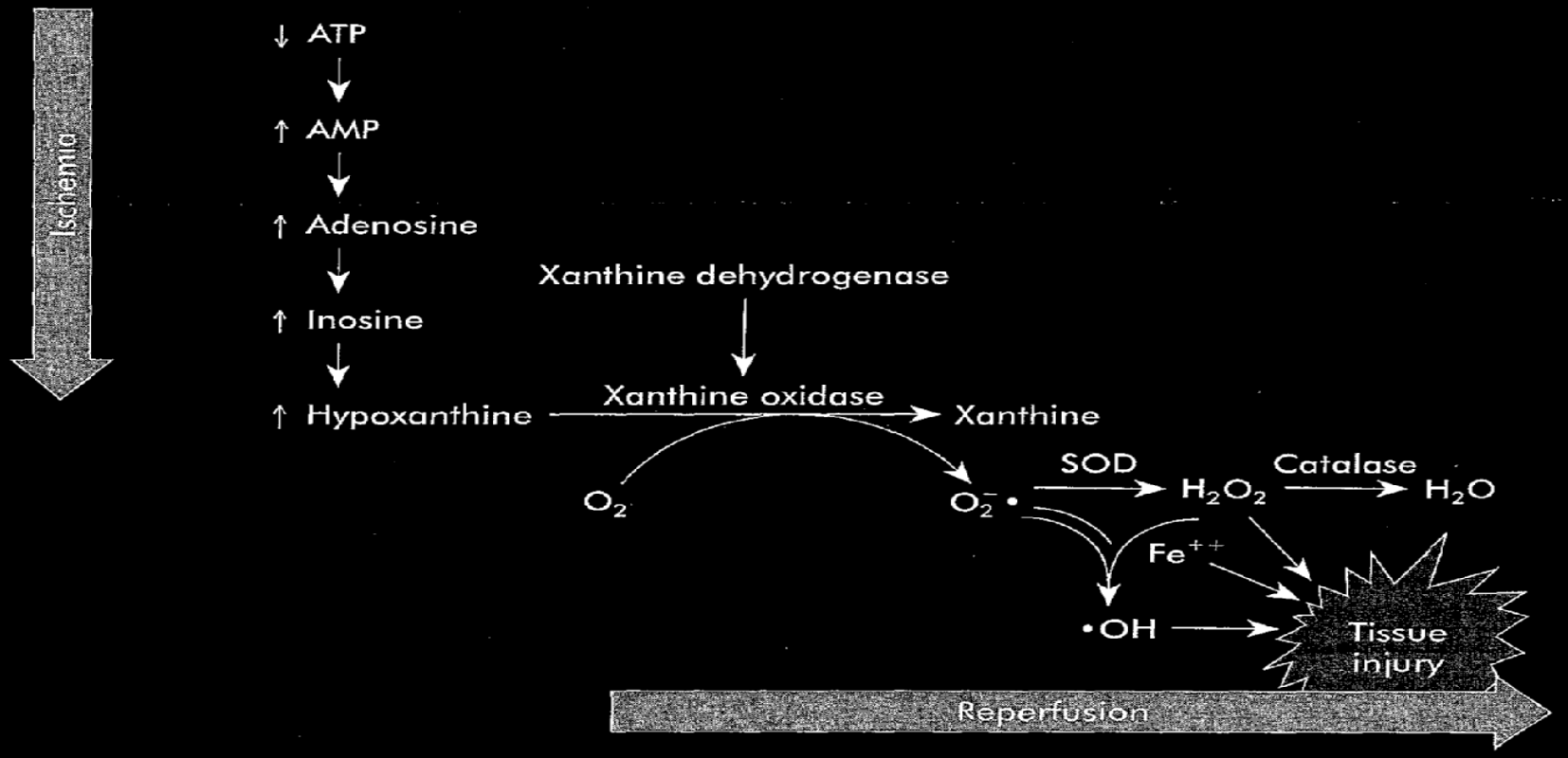
# Reperfusion Injury: Prostaglandins

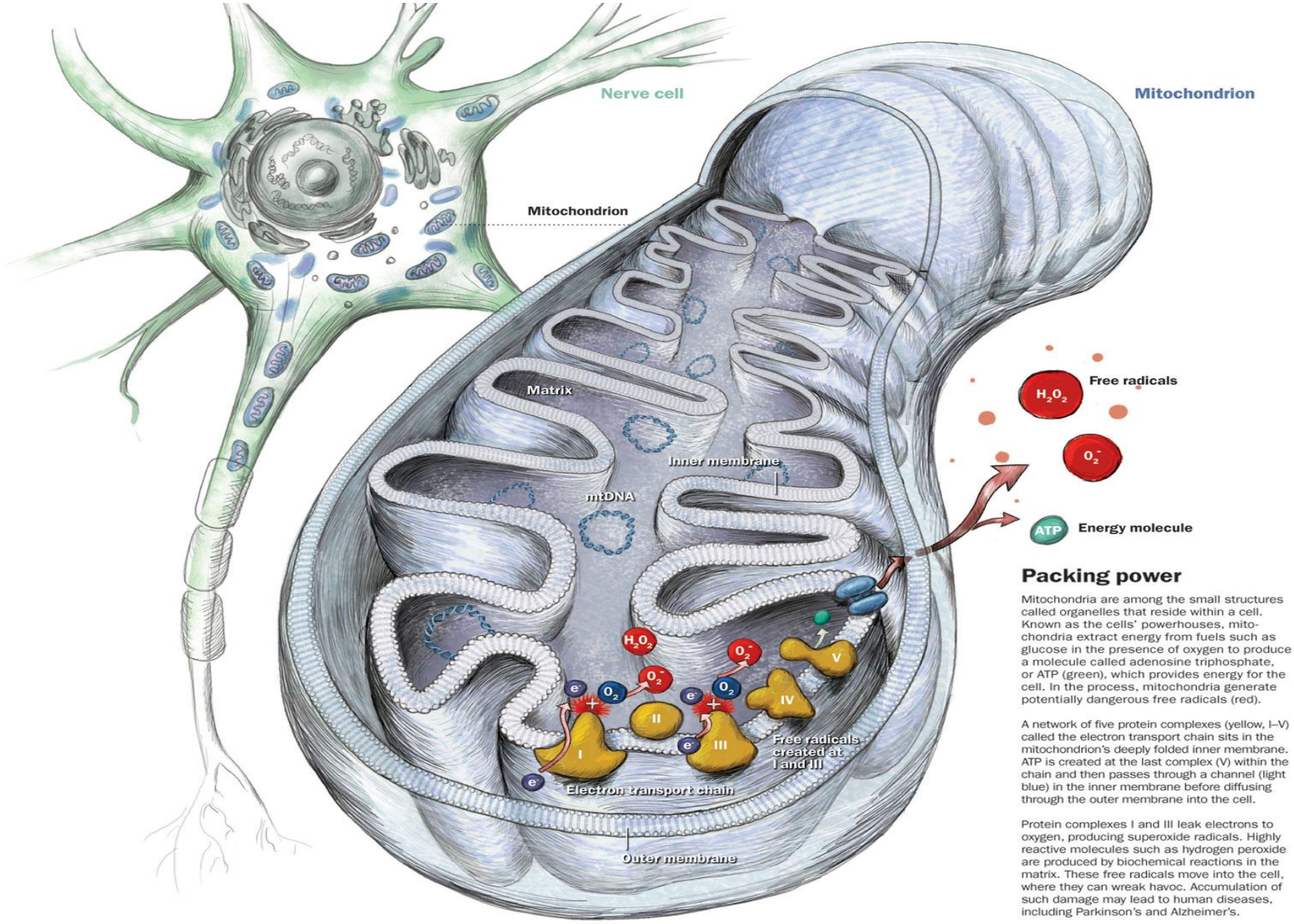


# Ischemia Cascade: Free Radicals

- Unpaired Electron = reactive and unstable
- Hydrogen Peroxide H202-, Superoxide 02-
- Common in Mitochondria as byproduct of ETS
- Destruction of Mitochondrial Membrane
- Pathway: conversion of Adenosine to Xanthine and eventually to O2-

# Reperfusion Injury: Free Radicals





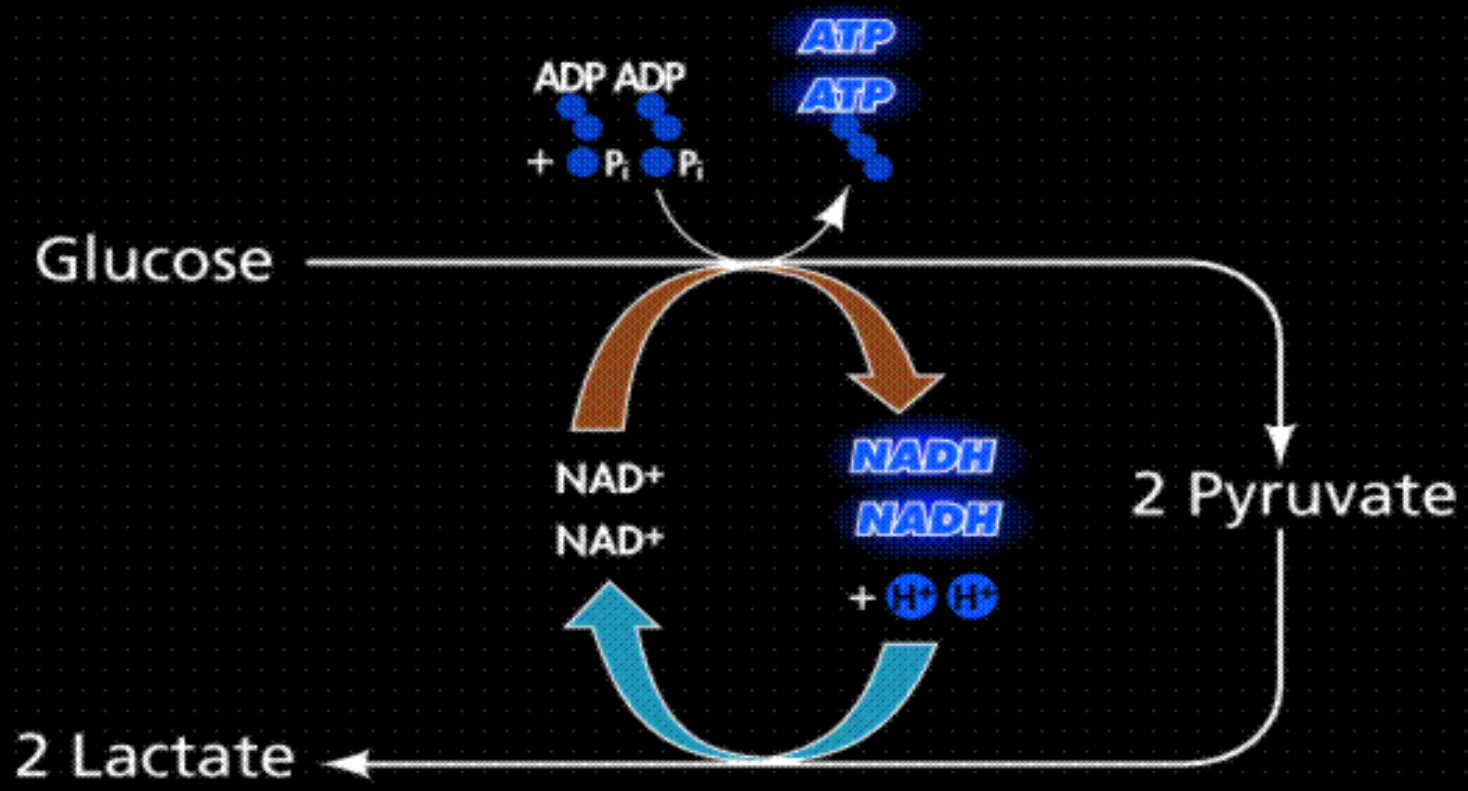

## Packing power

Mitochondria are among the small structures called organelles that reside within a cell. Known as the cells' powerhouses, mitochondria extract energy from fuels such as glucose in the presence of oxygen to produce a molecule called adenosine triphosphate, or ATP (green), which provides energy for the cell. In the process, mitochondria generate potentially dangerous free radicals (red).

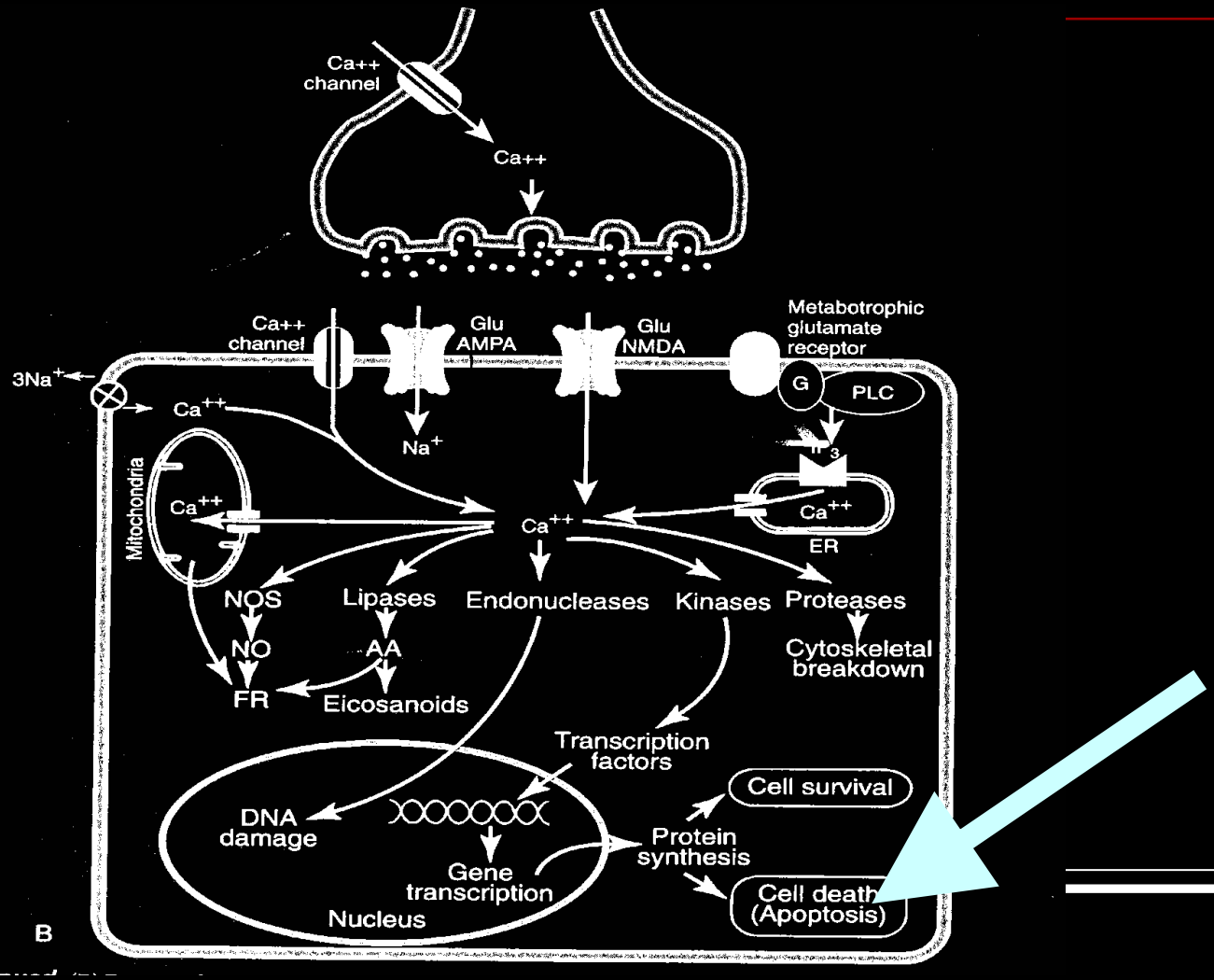
A network of five protein complexes (yellow, I–V) called the electron transport chain sits in the mitochondrion's deeply folded inner membrane. ATP is created at the last complex (V) within the chain and then passes through a channel (light blue) in the inner membrane before diffusing through the outer membrane into the cell.

Protein complexes I and III leak electrons to oxygen, producing superoxide radicals. Highly reactive molecules such as hydrogen peroxide are produced by biochemical reactions in the matrix. These free radicals move into the cell, where they can wreak havoc. Accumulation of such damage may lead to human diseases, including Parkinson's and Alzheimer's.

# Ischemia Cascade:  Glucose



# Ischemia Cascade: Summary



KEEP
CALM
AND
USE
protection

# Do Anesthetic Agents Protect the Brain?

- Supply and Demand….RIGHT?
- In Vivo vs In Vitro
- Rat model vs human or higher order?
- What is preconditioning?

# Inhalational Agents

- All Agents increase ICP
- >.6 MAC = dec CVR and Inc CBF
- Autoregulation is impaired
- Decrease in CMR by 40-50%
  - In Vitro vs In Vivo

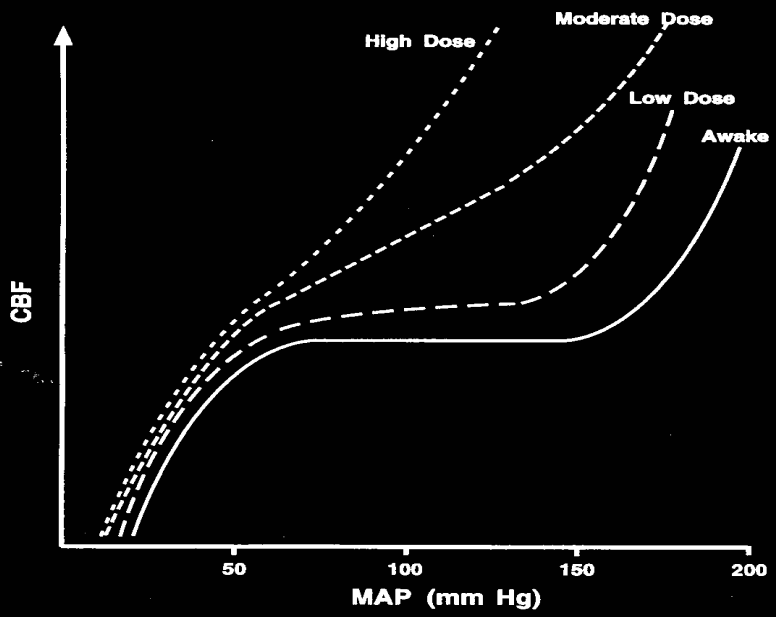
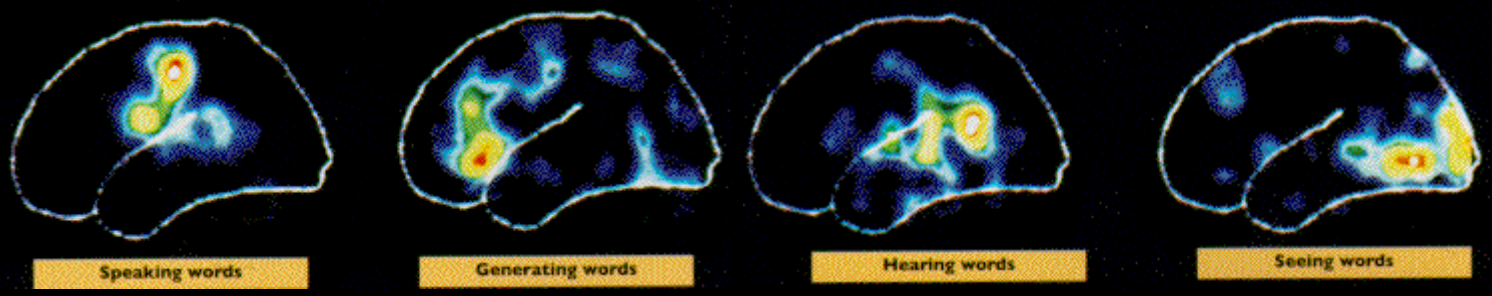



***Figure 19–5.*** Schematic representation of the effect of increasing concentrations of a typical volatile anesthetic agent on cerebral blood flow (CBF) autoregulation. Both the upper and lower thresholds are shifted to the left. MAP, mean arterial pressure.

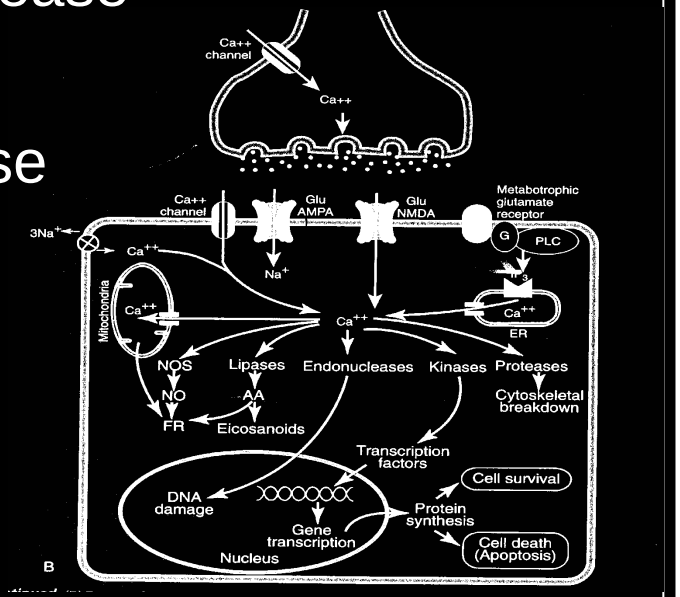
# Cerebral Protection of Inhaled Agents

- Preconditioning effect
  - Isoflurane likely the best
  - Nitrous Oxide = bad
  - May be better for focal vs global ischemia



# Inhaled agents and other potential mechanisms of Cerebral Protection

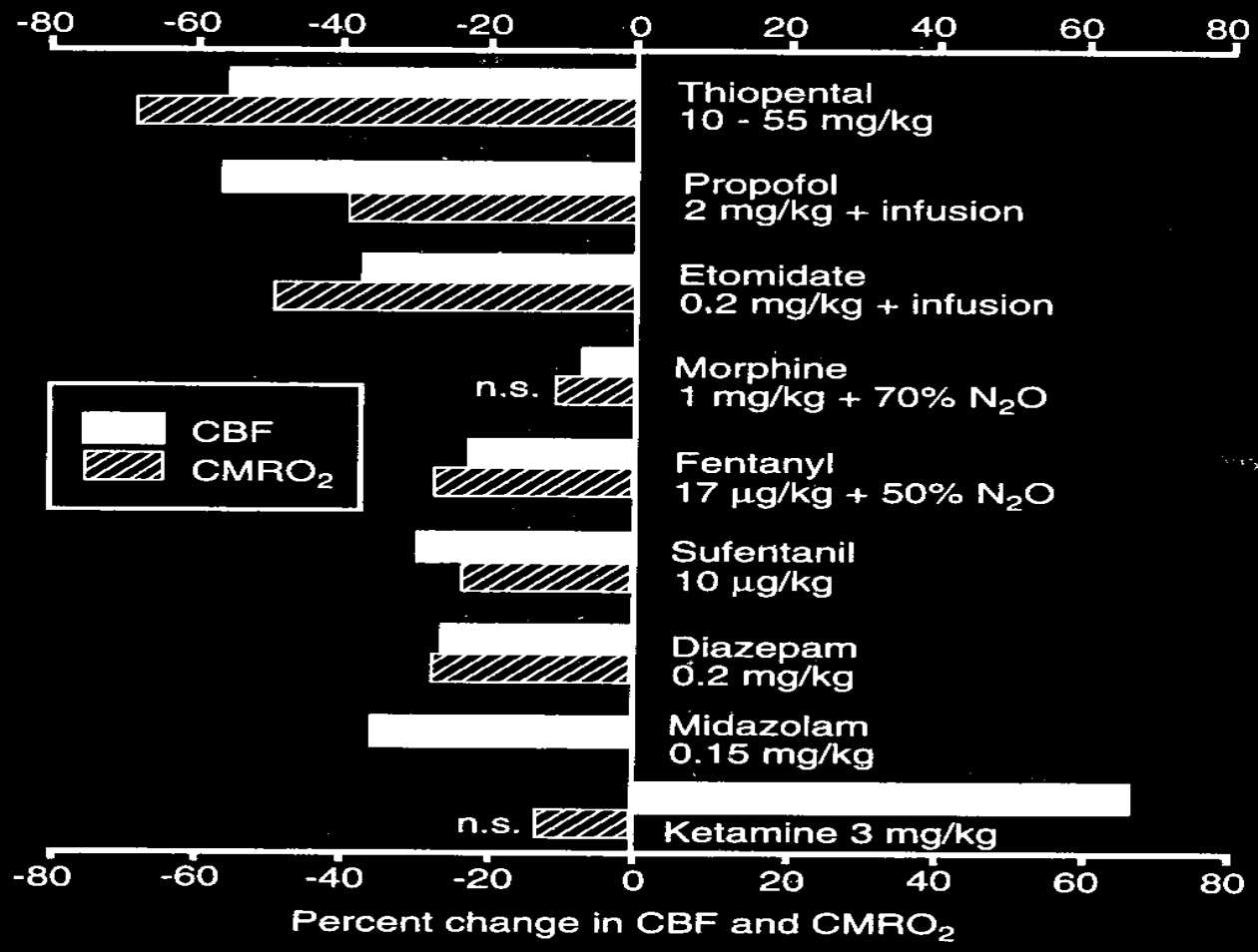
- Inhibition of Glutamate Release
- Reduction of Intracellular Calcium release
- Antiapoptotic Mechanisms
- Suppression of Catecholamine release
- Antioxidant mechanisms



# Intravenous Anesthetics

- Propofol
- Dexmedetomidine
- Ketamine

# Supply and Demand



# Propofol

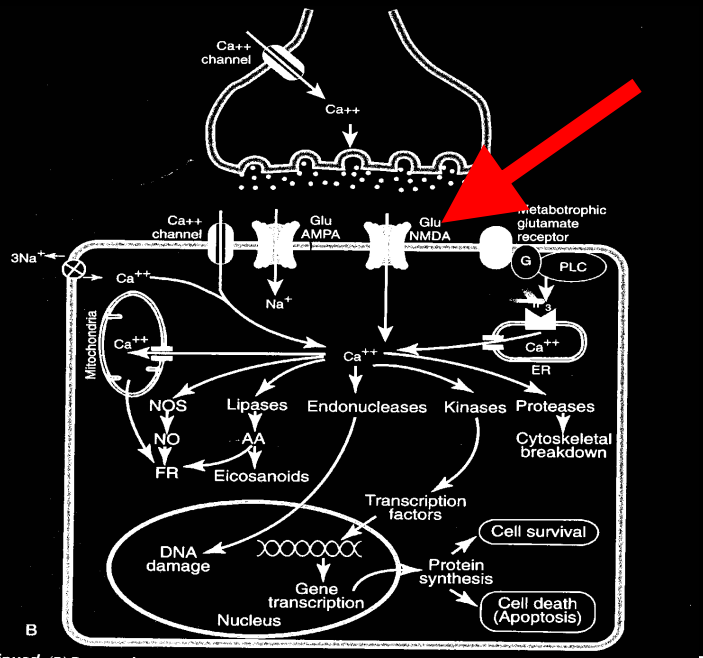
- One of the few that has been proven In VIVO
- Effective in Global and Focal ischemia
- Antioxidant effects
- Glutamate, dopamine release, GABA receptor activation

# Dexmedetomidine

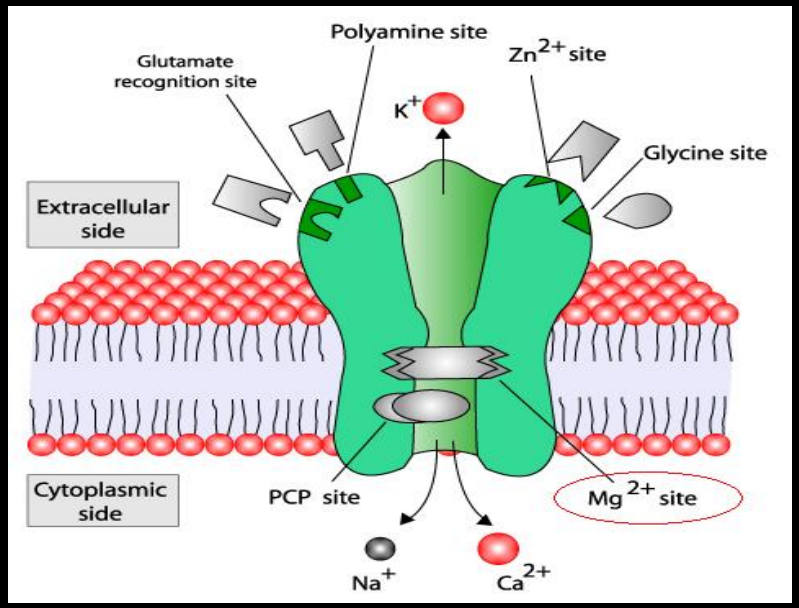
- Effective protection IN VITRO and in Rat models
- Biggest effect comes from pre conditioning
- Catecholamine suppression

# Ketamine

- NMDA Antagonism
- In VITRO…..shows promise
- In VIVO…..no so much
- High doses required
  - S-(+) > Racemic > R-(+)



# Magnesium




- 4gm over 15min IVB
- 16gm IV Infusion over 24 hours may improve outcomes

Saver et all- FAST-MAG, Int J Stroke 2014 9:215-9

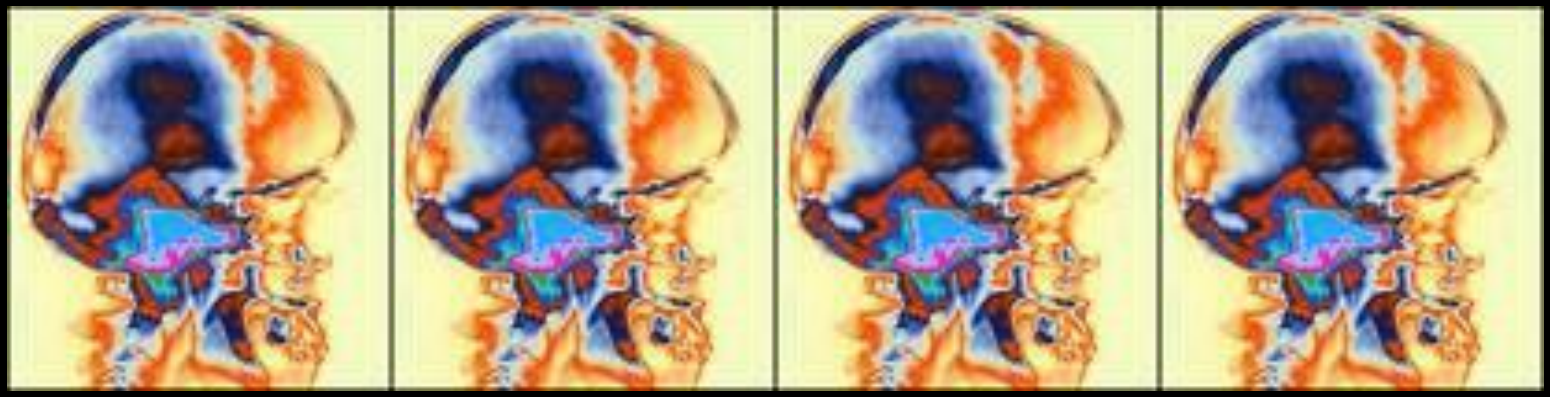
# Hypothermia

# Hypothermia

- Moderate hypothermia:  Core temp of 32-33°C
- The many negative aspects of hypothermia are well known and include:
  - Ventricular arrhythmias
  - Coagulatory disturbances
  - Electrolyte changes like hypokalemia
  - Increased incidence of infections
- Literature goes both ways

# NABIS the National Acute Brain Injury Study

- ’94-’98 RCT with N= 500.  GCS<8,  CBI
- Aborted at N=392
- No improvement in outcomes
- Increased vasopressors, complications, LOS, hypotension and bradycardia



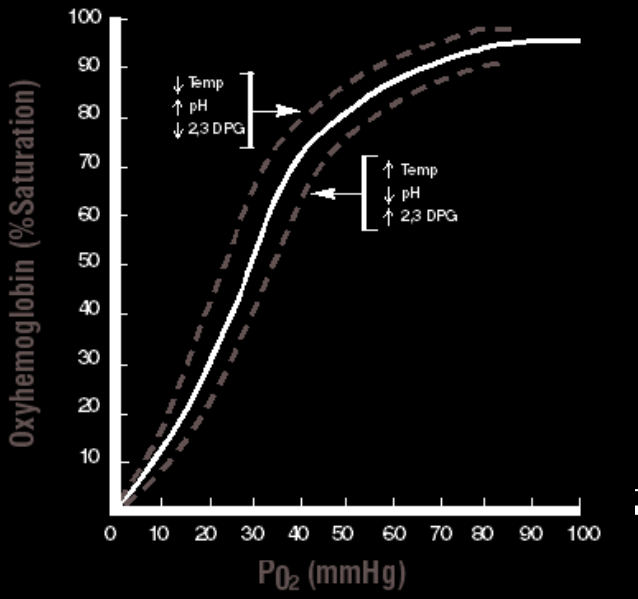
# IHAST

## Intraoperative Hypothermia for Aneurysm Surgery Trial

- ‘00-’03 - Multicenter RCT  N> 1000 SDH - Aneurysm Clipping
- No reduction in mortality
- > incidence of bacteremia

# Hypothermia

- British Journal of Anaesthesia 2002
  - N=30  Severe CBI
  - Brain temp of 35°C is best, below that brain tissue oxygenation may be impaired
  - Why? Left shift of the oxyhemoglobin dissociation curve

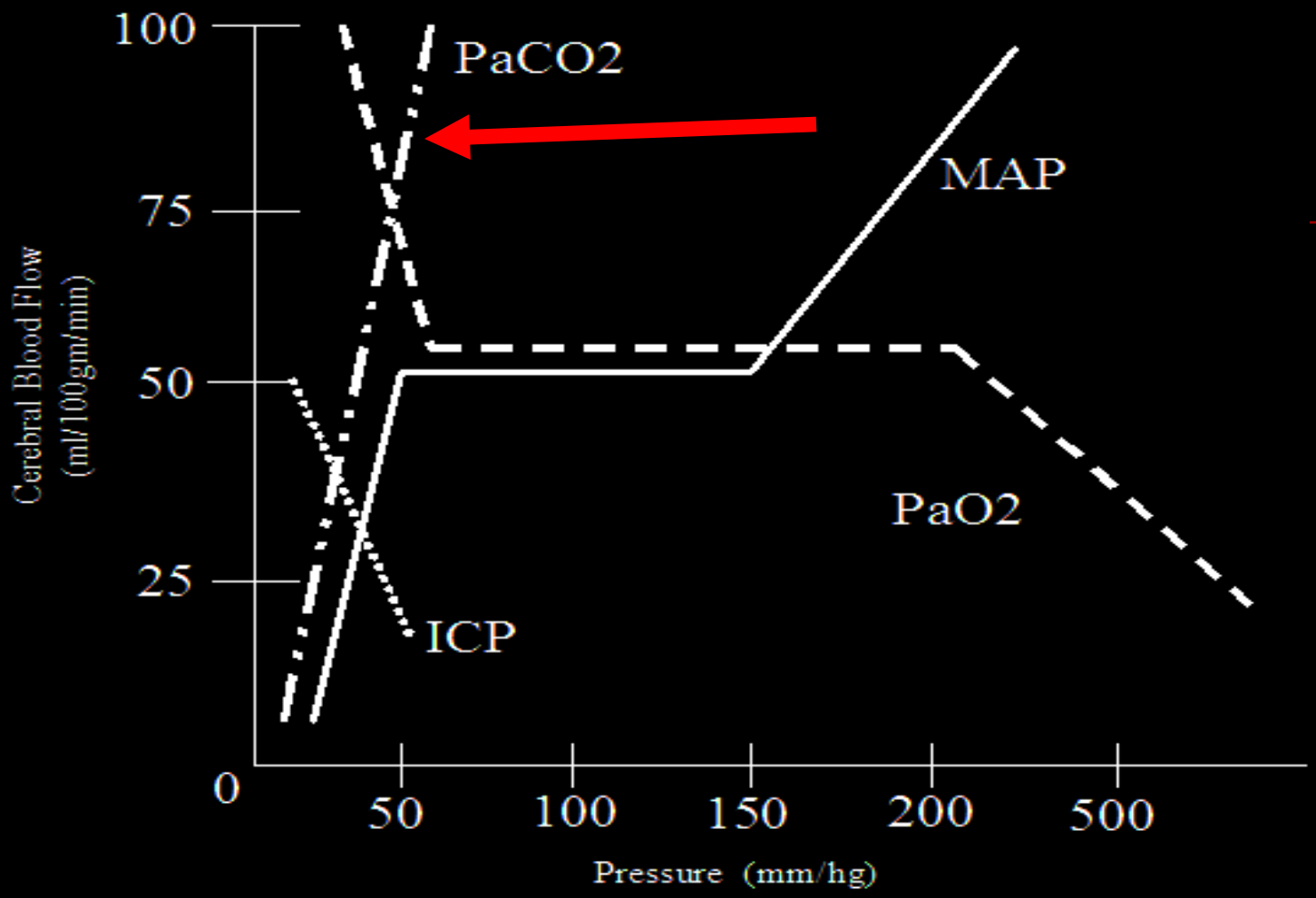


# The Cold Conclusion:

- If you really dive into the literature- this is what you find-
  - Some small RCTs have shown clinical improvement
  - Don’t extend study findings across the spectrum: ischemia protection ≠ trauma protection.

# Other Methods

- Hyperventilation:
  - Hypocapnia is effective for decreasing CBF acutely.
  - Ineffective >6 hour
  - Recommend goal of PaCO2 of 32-35mmHg
    - Lower PaCO2 may lead to ischemia

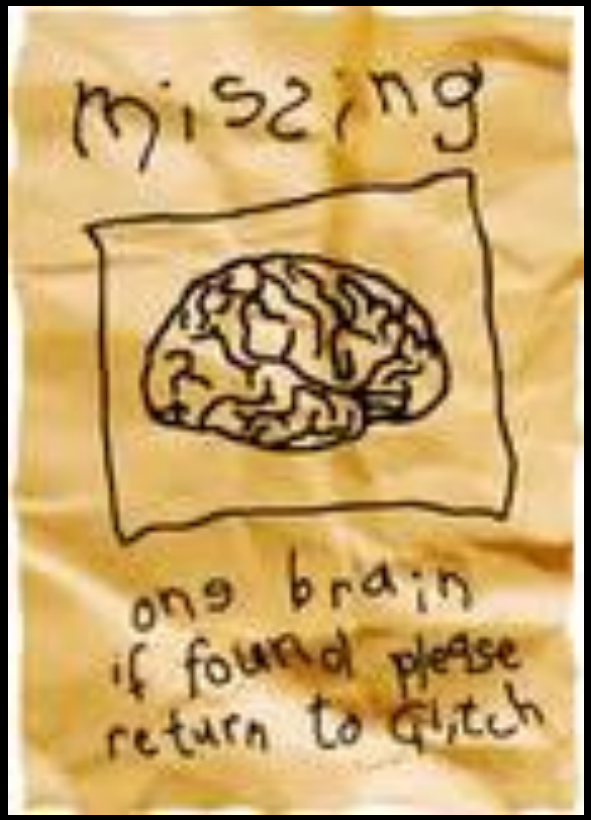



Autoregulation: Cerebral Blood Flow Response

# Other Methods

- Mannitol
  - Osmotic Diuresis decreases cerebral edema
  - Free Radical Scavenger
- Lasix
  - Decreases overall intravascular fluid volume
- Steroids
- Hemodilution
  - Prevent reperfusion ischemia due to sludging of RBCs and Platelets

# So…….What else is Missing?



# What About Blood Pressure Control?

- Don’t forget: Maintaining an adequate BP is an important aspect of brain protection
- Patient and Surgery Specific
- Stroke outcomes improved
  - SBP >140mmHg and <180mmHg
- The less swings…the better. Tight control

# Cleviprex® (clevidipine butyrate):

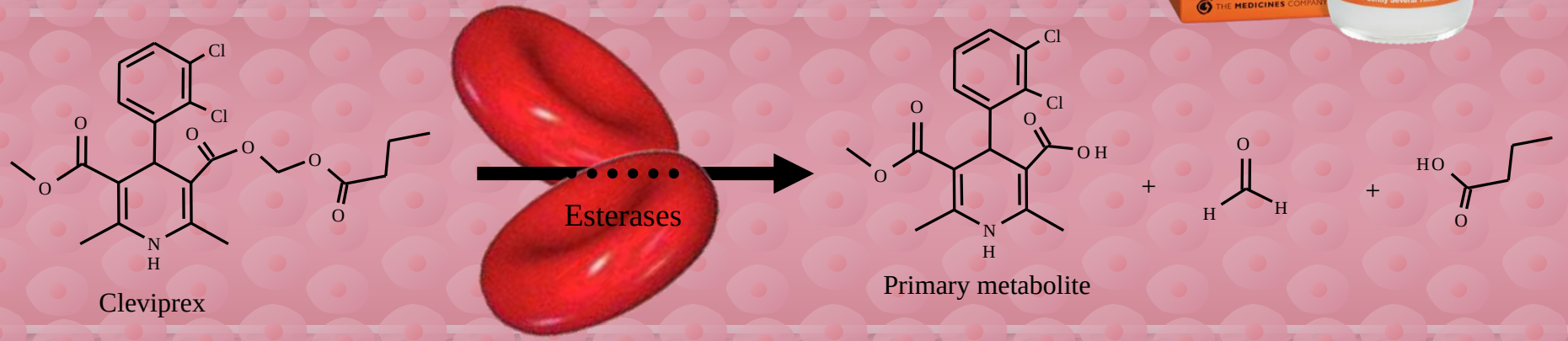




Figure adapted from Ericsson H, et al. *Drug Metab Dispos*. 1999;27:558-564.

Cleviprex Prescribing Information; August 1, 2008.

Please see Important Safety Information and accompanying full Prescribing Information.

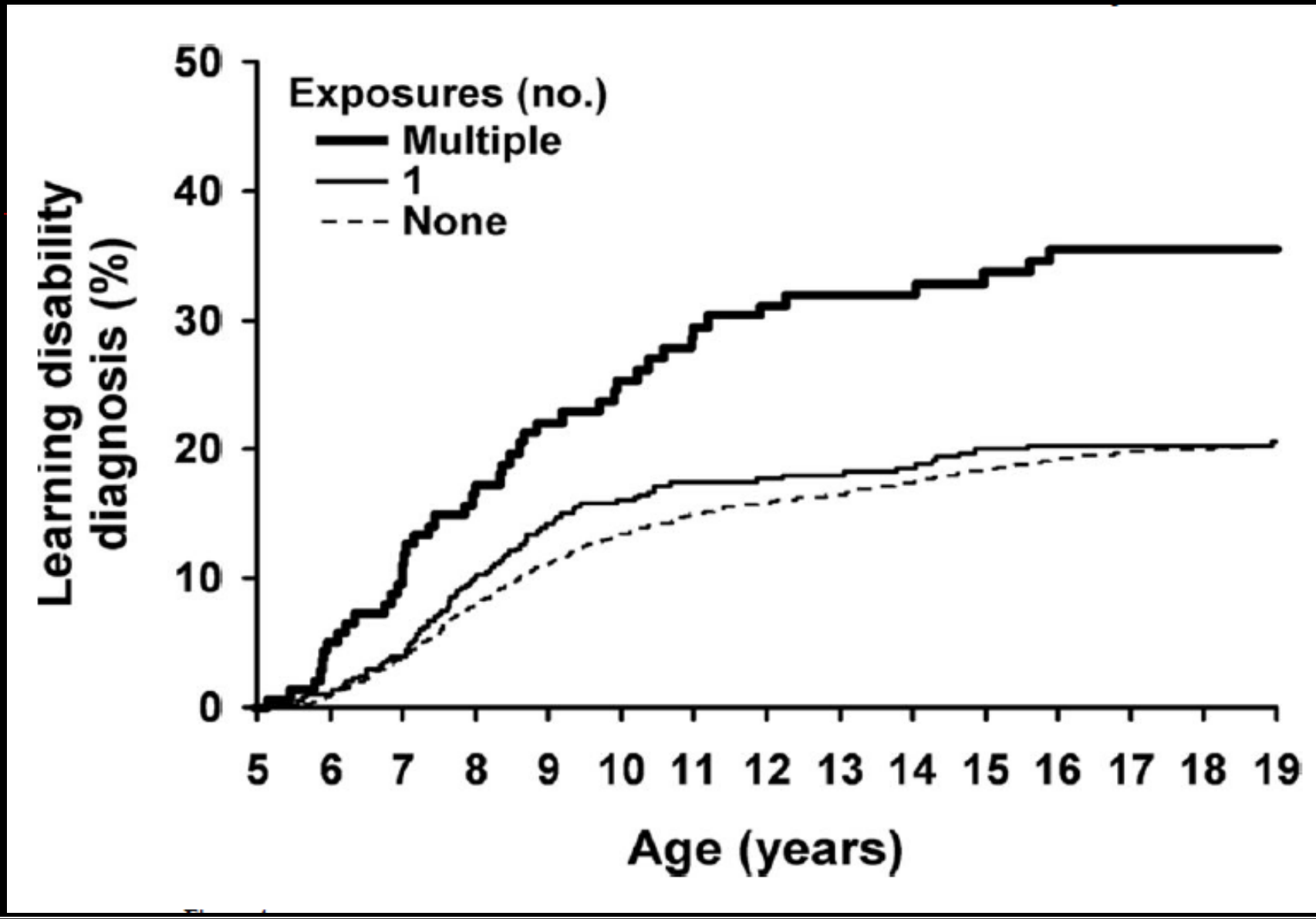
# Let’s get to the scary stuff….

# The Developing Brain and Anesthesia

- GA = “Turn off” the brain or “slow it down”
- Immature brain at birth
  - 335gm
  - 670gm
  - 1000gm
- Synaptogenesis
  - Axonal, dendritic and glial development
- Neurodegenerative effects of anesthesia?

# The VERY SCARY stuff

- Sun et al Anesthesiology 2008
  - Retrospective  N=228,961 (kids with disabilities)
  - “Children who had procedures requiring anesthesia before the age of 3 years required more Medicaid services for learning disabilities than those not having procedures”


Exposures (no.)
Multiple
1
None
Learning disability diagnosis (%)
50
40
30
20
10
0
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
Age (years)

# What does this mean?

- Studies are still premature
- Existing literature cannot account for all intrinsic and extrinsic factors
- Single agents may be better than multiple
- MANY years away from an answer
  - RCTs…….  how do you do it?
- Smarttots.org

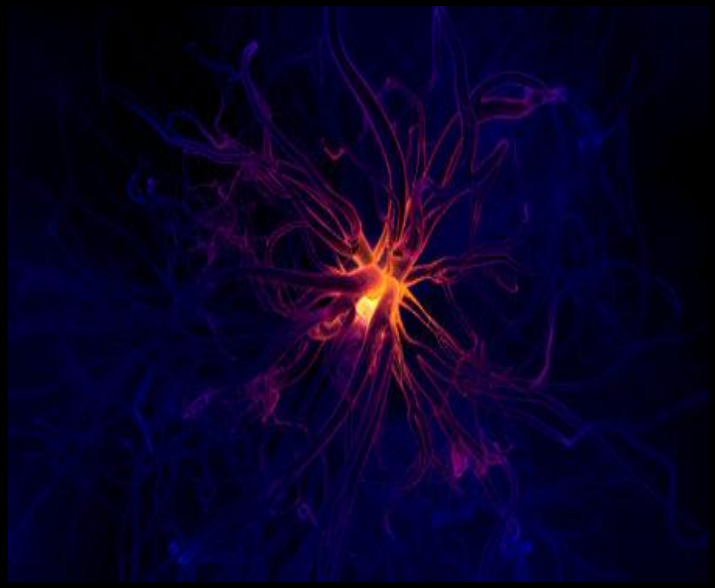
Jevtovic-Todorovic, V, Anesthesiol Clin. 2016 Sept; 34(3): 439-451

# What about the FUTURE?

- Evaluate our research methods
  - Neuroprotective properties of current anesthetics is uncertain
  - Find out where we have gone wrong
- The New goal will be to prevent the progression of ischemia cascade
- What are we going to do about the kids?

# Current Trends in Research

- COX inhibitors
- Growth Factors
- Epoetin
- Cannibinoids
- BDNF
- Define bench to bedside



# Finally, the Conclusion

# What should MY plan of Attack Be?

Diversify your approach:
Brain Protection can be accomplished through many methods, that together may provide a better outcome for your patient.

Understanding the Basics of Metabolic Ischemia and Cerebral Pathophysiology is essential to accomplish your goal

## Potential cerebral protective mechanisms

- Decrease cerebral metabolism
- Increase cerebral blood flow
- Mild hypothermia
- Prevent hyperthermia
- Maintain normoglycemia
- Inhibit release of excitatory neurotransmitters (eg, glutamate, aspartate)
- Enhance release of inhibitory neurotransmitters (eg, GABA)
- Block neuronal calcium influx
- Decrease nitric oxide formation
- Decrease Neuronal free radical formation
- Prevent apoptosis
- Scavenge free radicals
- Prevent $Ca^{++}$ and $Na^{+}$ influx

# ALWAYS USE PROTECTION!!

Inhibit glutmate release
- Inhalational anesthetics
- Adenosine A1 receptor blockers
- $\alpha$2 agonists
- Hypothermia
- Sodium channel inhibitors
- Lamotrigen
- Etomidate

NMDA, AMPA, and kainate receptor blockers
- Barbiturates (mainly AMPA, Kainate)
- ? Inhalational anesthetics
- Hypothermia

Prevent apoptosis
- Isoflurance
- Halothane

Inhibit lipid peroxidation
- Lazariods (21 aminosteroids)
- Hypothermia

Statins
Hypothermia

Noncompetative receptor blockers
- Dizoclipine (MK801)
- Phencyclidine
- Dextromethorphan
- Ketamine
- Magnesium
- Propofol

Block calcium influx
- Propofol
- Ketamine
- Inhalational anesthetics
- Lidocaine

Reduce inflammatory cytokines
- Statins
- Anti-inflammatorv drugs
- Estrogen
- Heparin

Decrease free radicals
- Mannitol

GOT THAT?
Then you shouldn’t get caught with your pants down!!