How Off-Target is Your Anesthesia? Effects on the Mitochondria, Autism and Cancer Metastasis

Jason T Maynes, PhD/MD
Director of Research, Anesthesia and Pain Medicine
Program in Molecular Structure and Function
Hospital for Sick Children, SickKids Research Institute
Department of Biochemistry, University of Toronto
Toronto, Canada

Patient Metabolism

Physiology

Pharmacogenetics

You

Physiologic Processes

Watershed Infarction (brain, liver, heart) Reperfusion Injury

Maintenance of Membrane Potential and Integrity, Protein Function and Turnover

Patient Monitoring

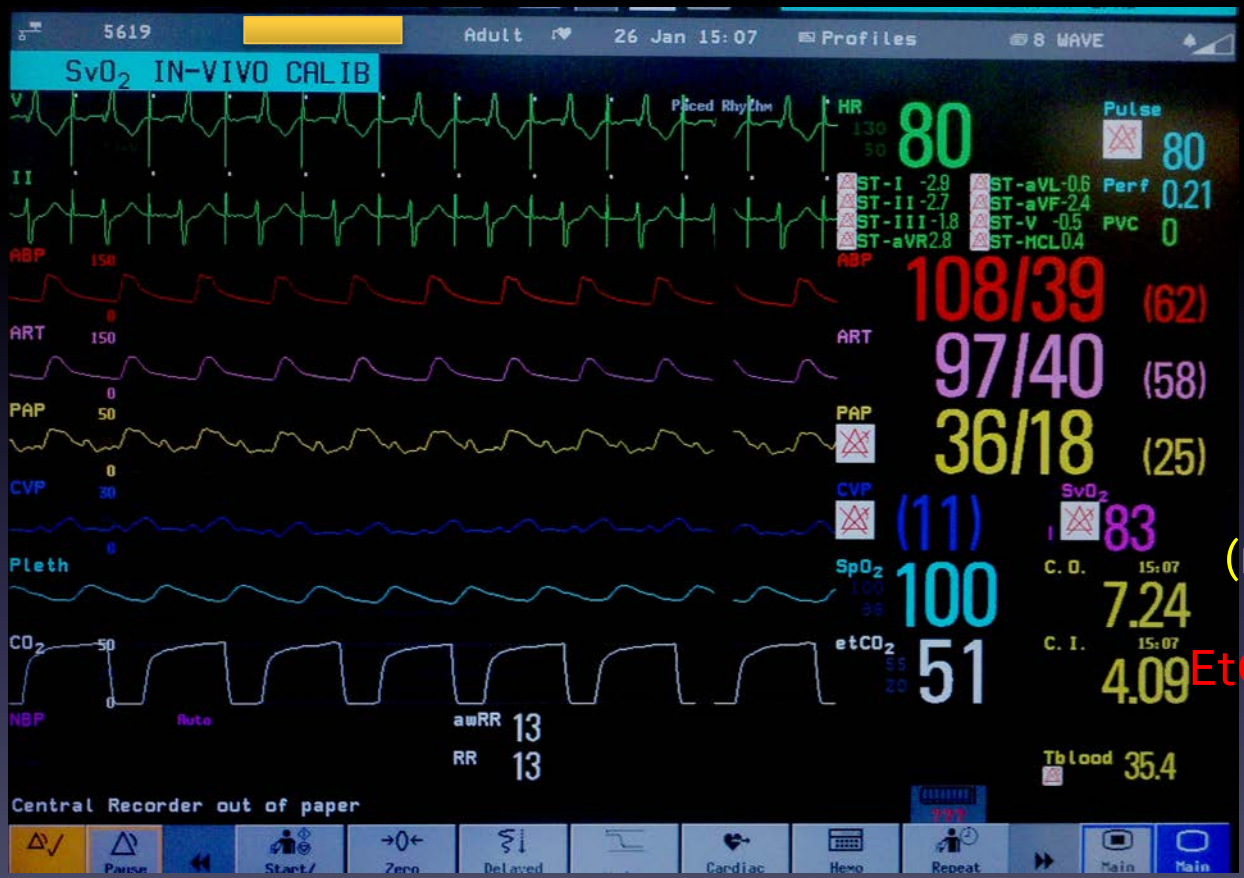
HR (CO)

BP (tissue perfusion)

PAP (oxygenation)

SaO2 (blood oxygenation)

CO/CI (tissue delivery)



EKG (tissue Perfusion)

SvO2 (metabolic use)

EtCO2 (metabolic waste)

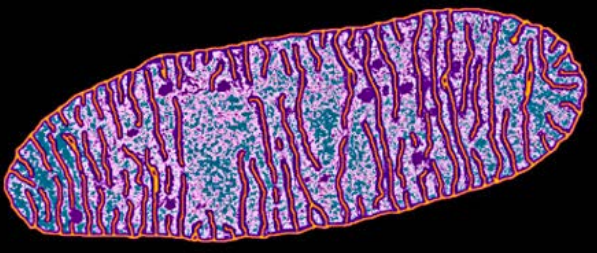
Neuro: BIS/EEG/rSO2(NIRS)

Cardiac: TEE (CO/EF/FS)

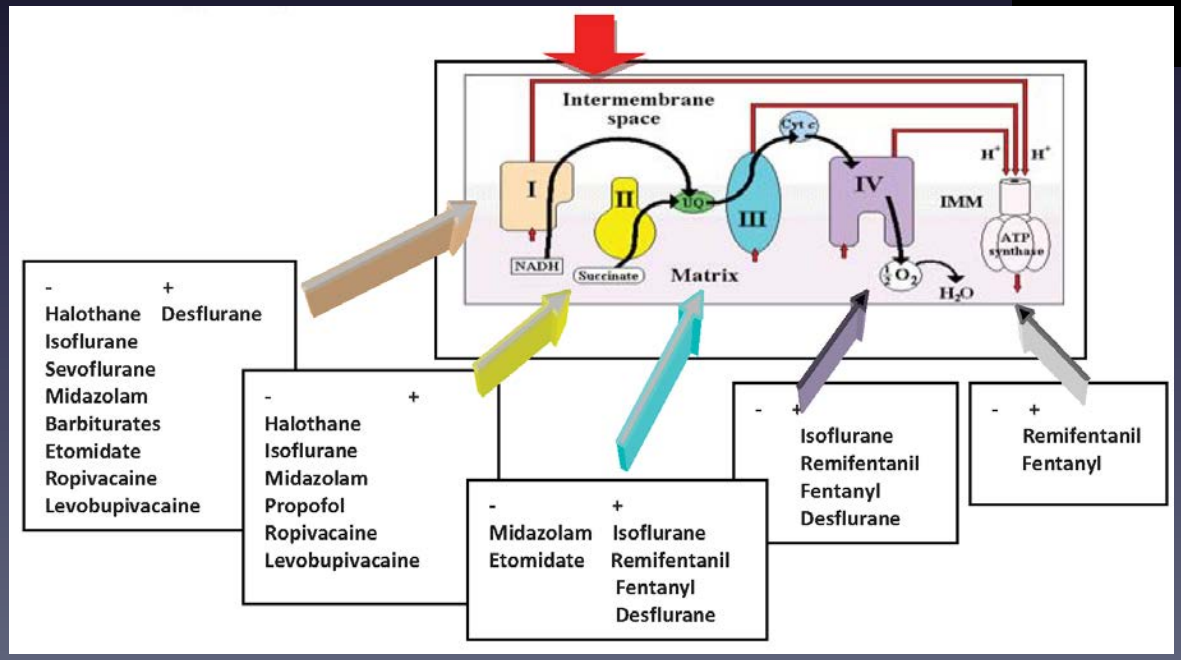
RWMA

Mitochondria as a Mediator of Cellular Physiology

Electron Transport Chain

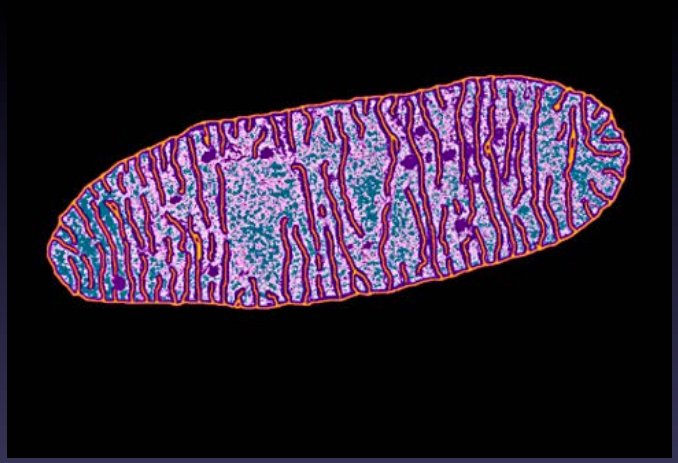


ATP



From La Monaca (2012)

Mitochondria as a Mediator of Cellular Physiology



Cellular Stress Response:

- Autophagy/mitophagy
- Apoptosis
- Necroptosis
- Mitochondrial dynamics (fusion/fission)
- ER interactions (Ca++, MAM, UPR)

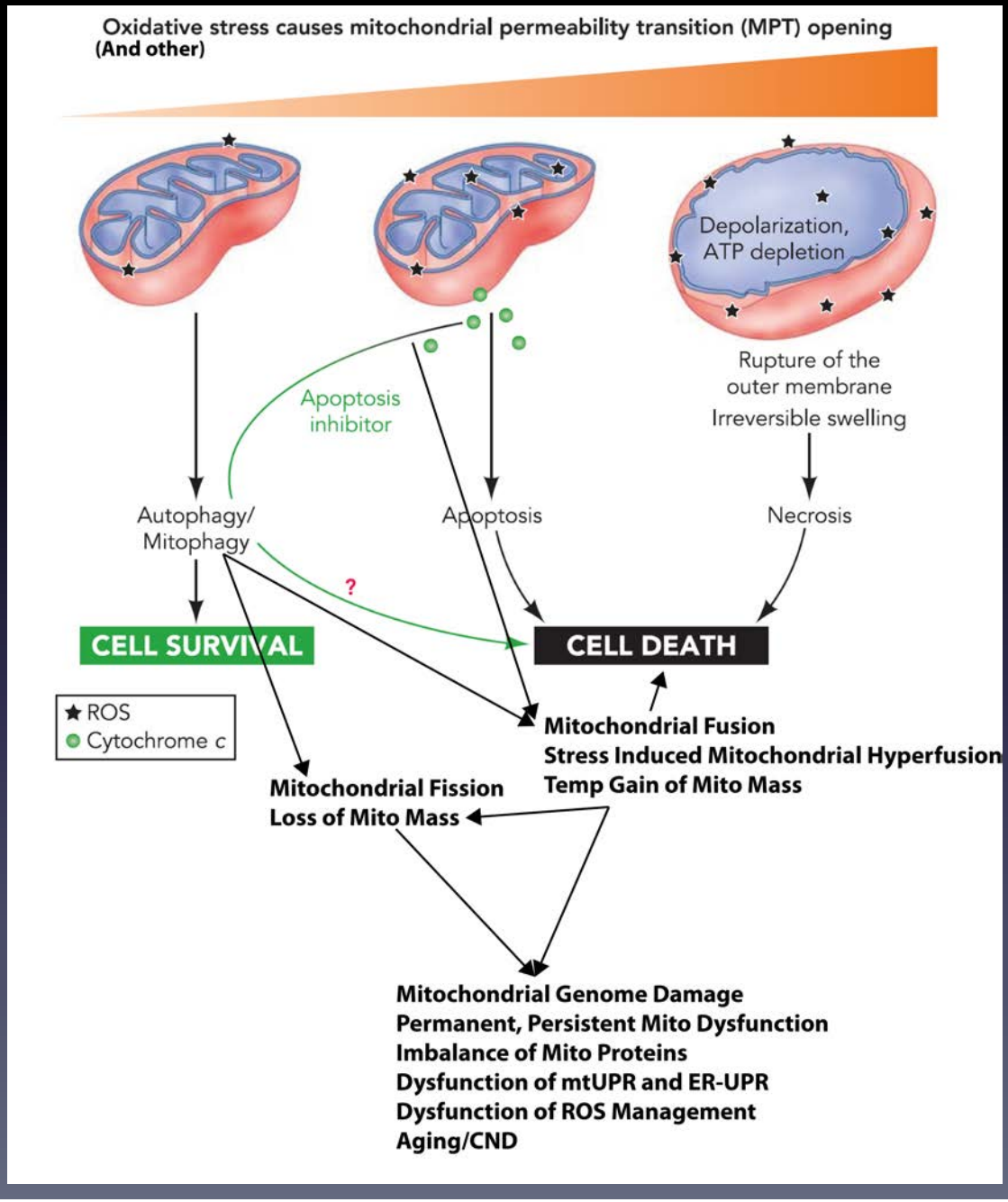
Aging/chronic neurodegenerative disease:

- Alteration of metabolic pathways (non-ETC)
- mtDNA damage/depletion
- Mitochondrial dynamics (fusion/fission)
- Mitochondrial mobility (neuronal function)

ROS as a signaling Mechanism

- Non-pathologic
- Alters nuclear transcription (i.e. TGFb)

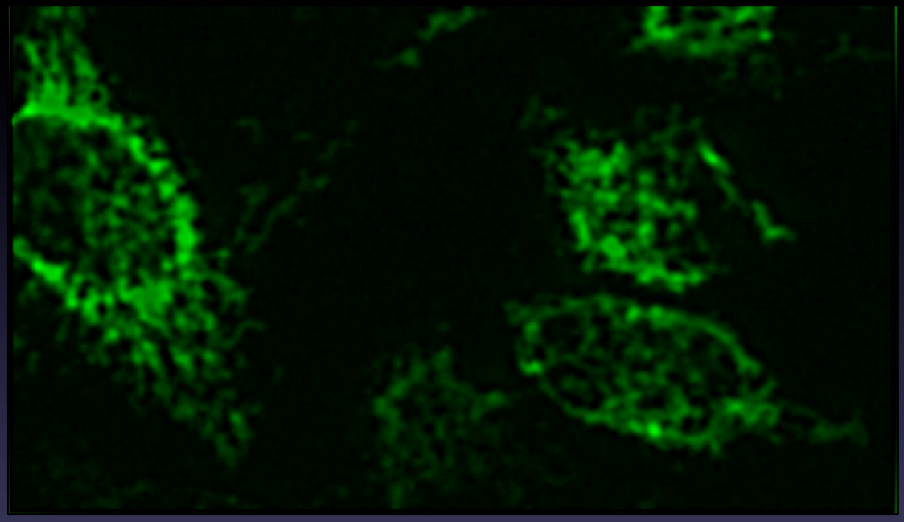
Mitochondrial Stress Responses



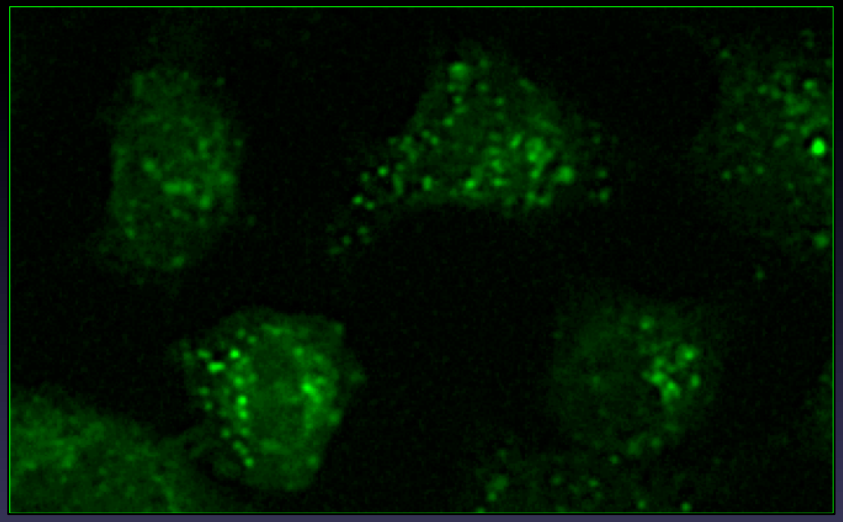
Anesthesia and Mitochondrial Function

- Wound healing
- Infection/Immunity/Inflammation/SIRS/Sepsis
- Post-op cardiac function/recovery
- Short- and Long-term pain, pain modulation pathways
- Long-term patient recovery/tissue repair
- Neurocognition

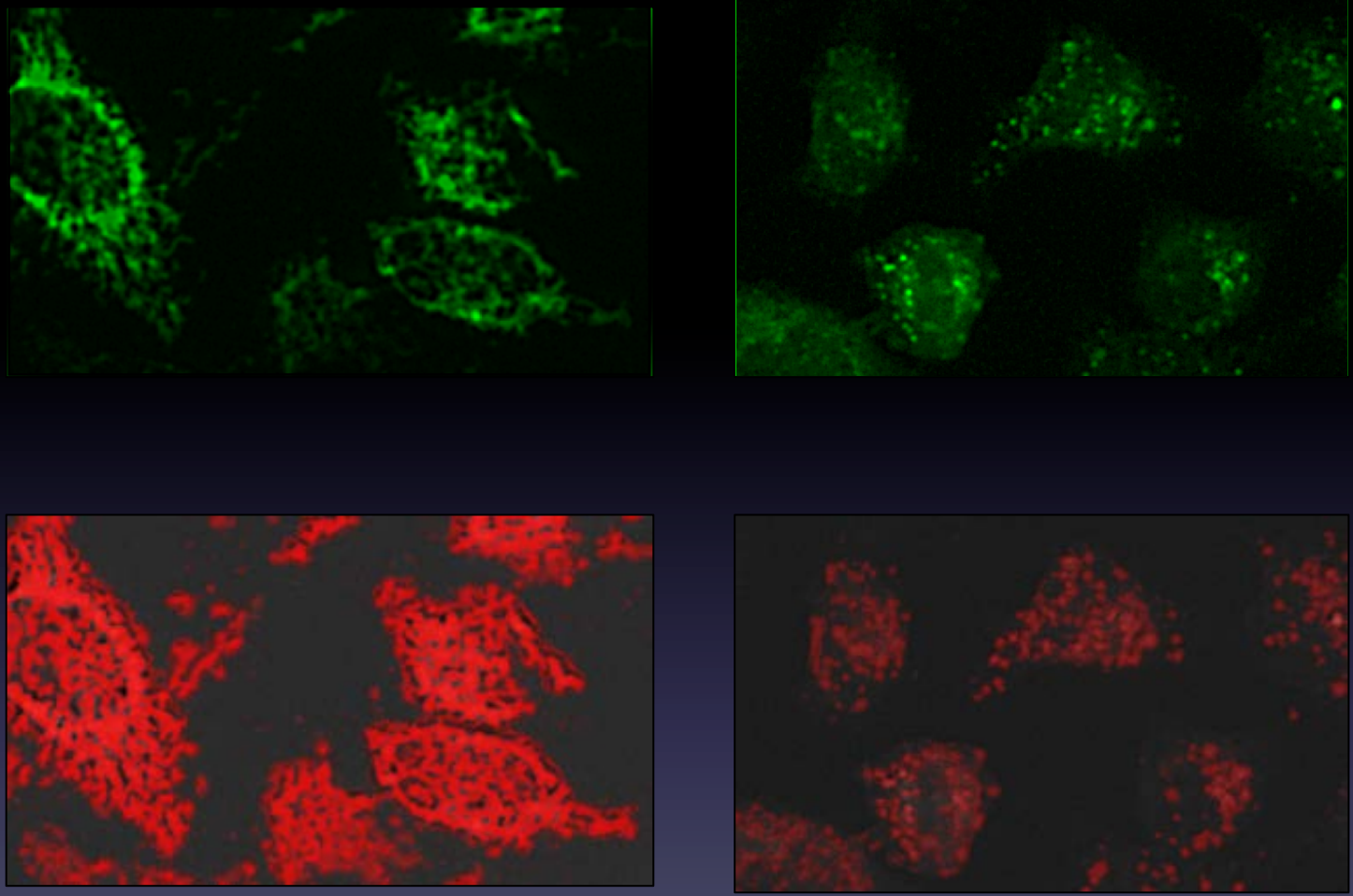
Mitochondrial Morphology

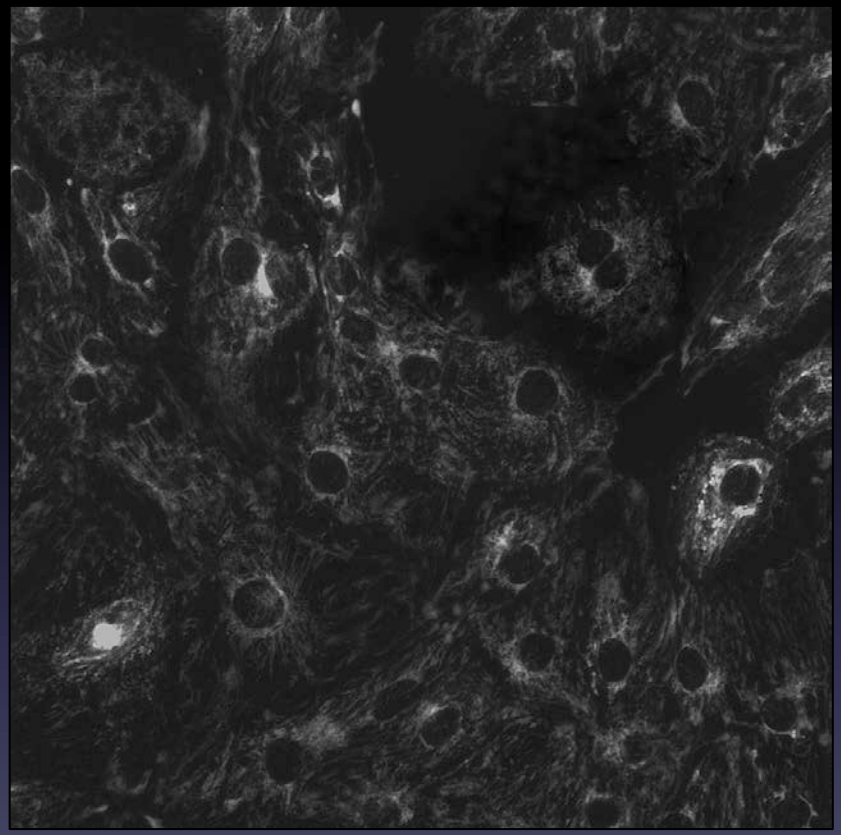


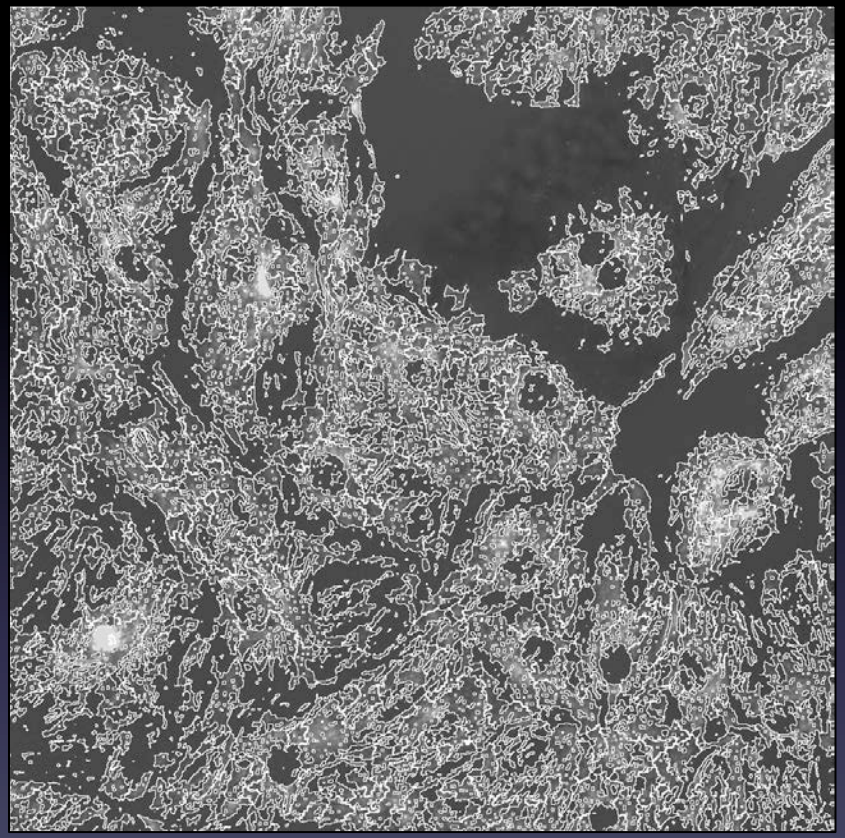
Control



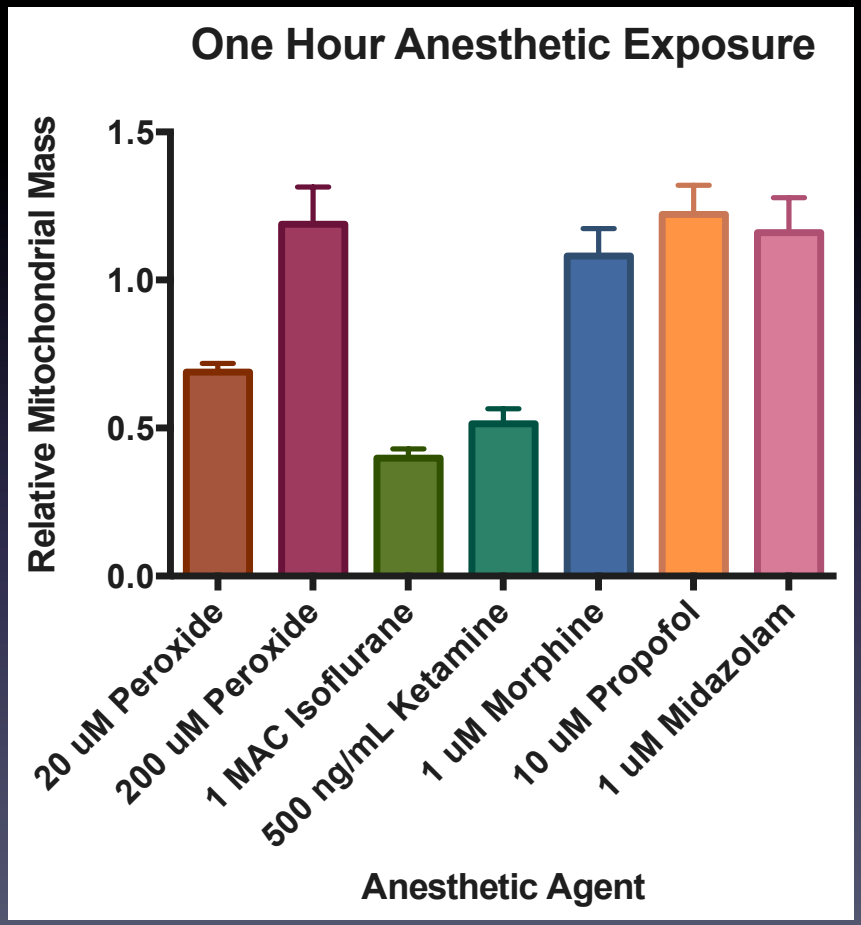
300 uM Isoflurane 4 hour

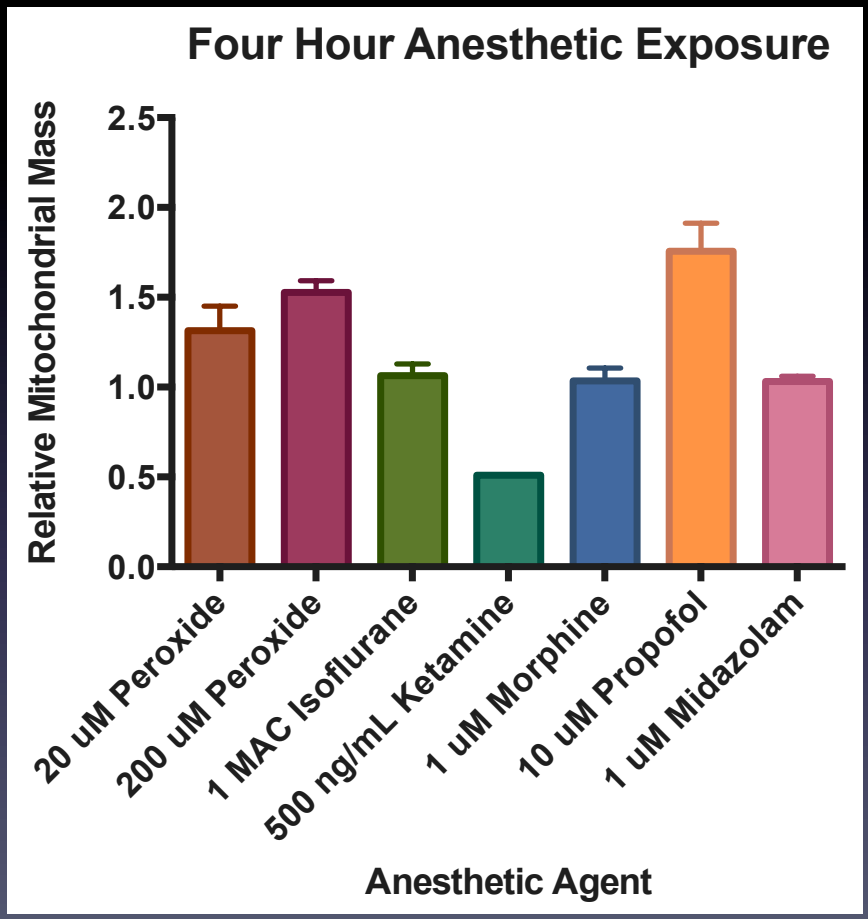




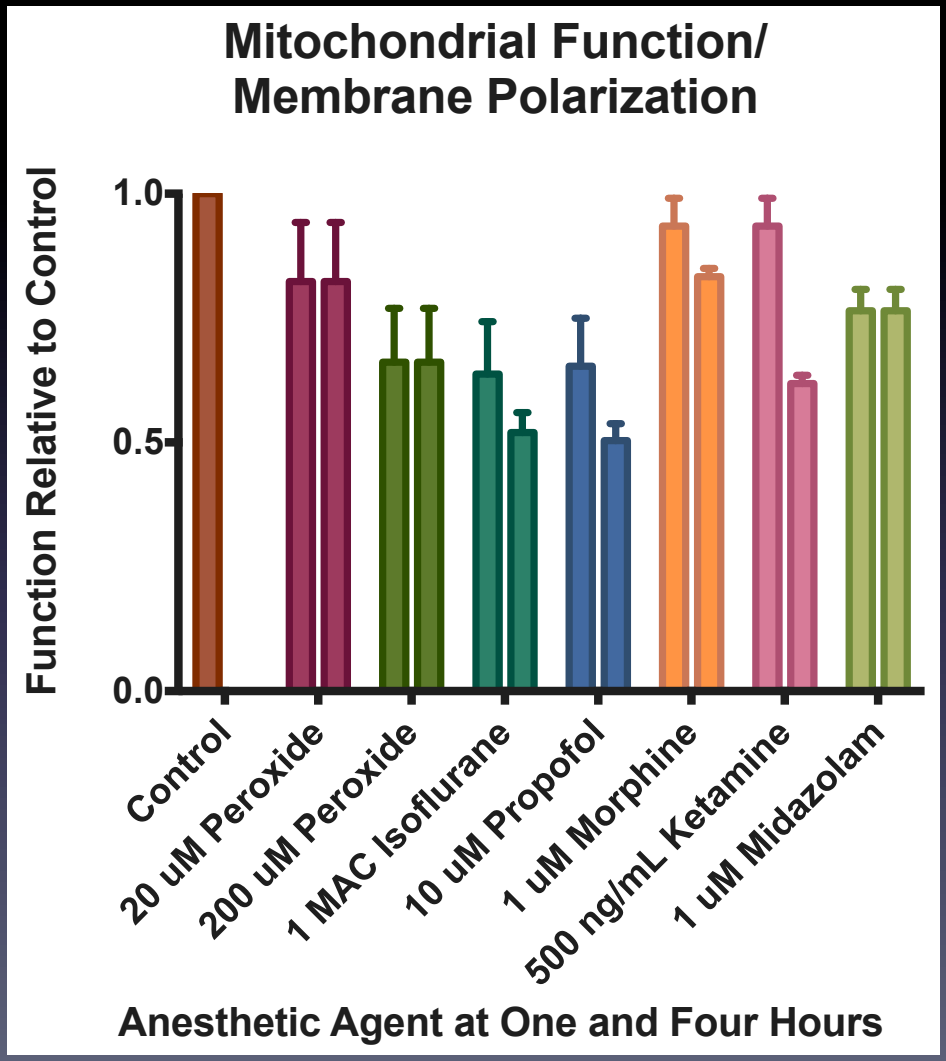


Changes in Mitochondrial Mass

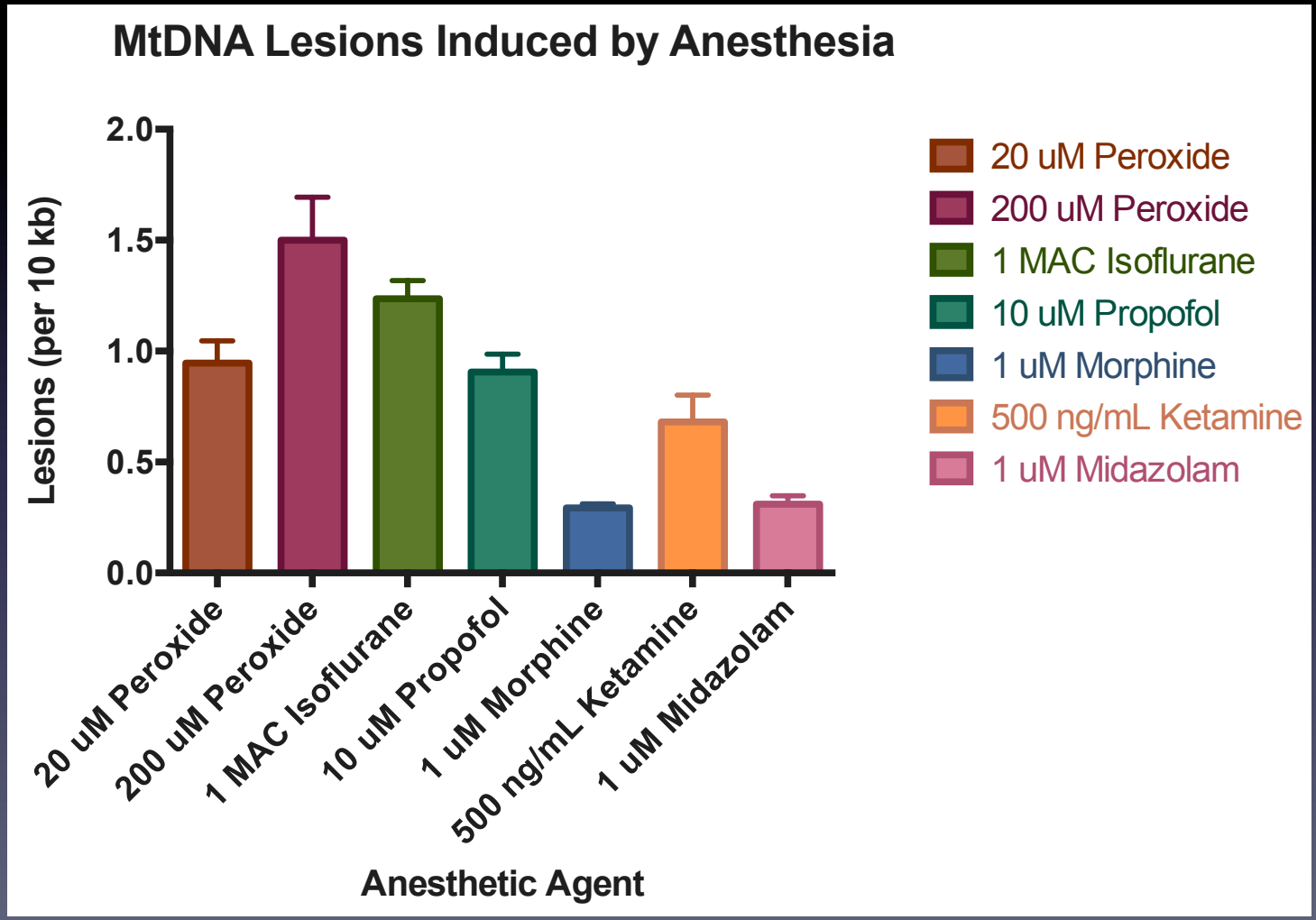




Mitochondrial Function (Polarization) Alterations Observed at One and Four Exposures of Anesthetic Agents

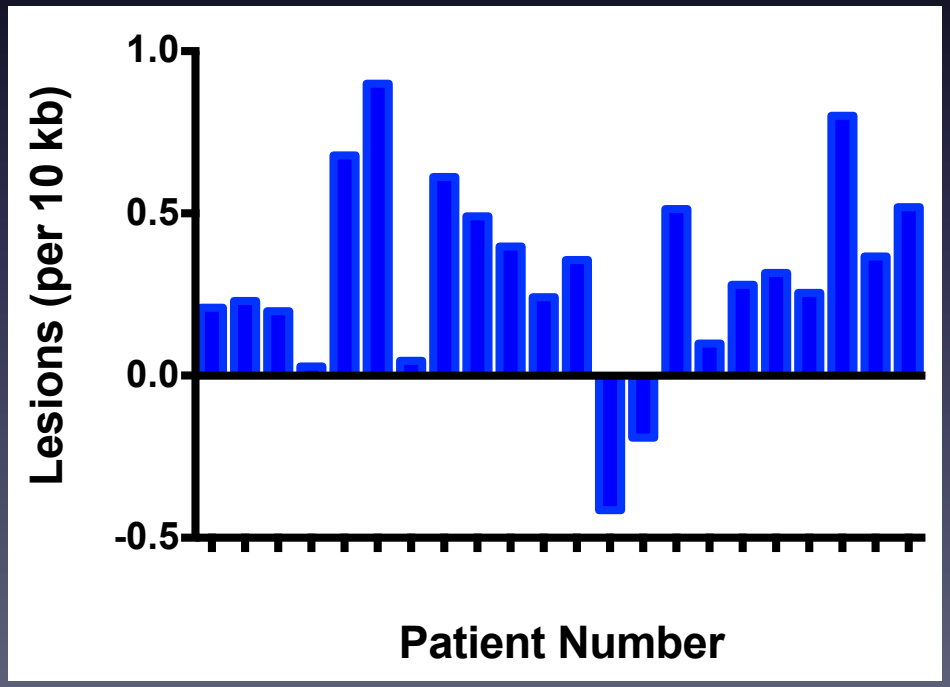


MtDNA Lesions Induced by Anesthetic Agents



Measurements in Patients Receiving Ketamine

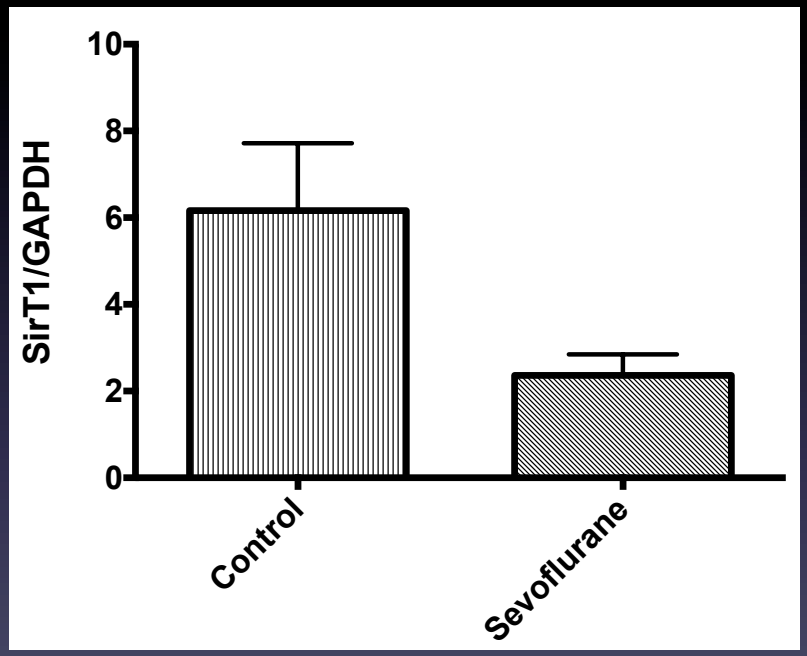
- 39 patients recruited
- 24% reduction in mitochondrial mass (p = 0.004)
- 16% increase in mitochondrial function
- 5% increase in mean polarization

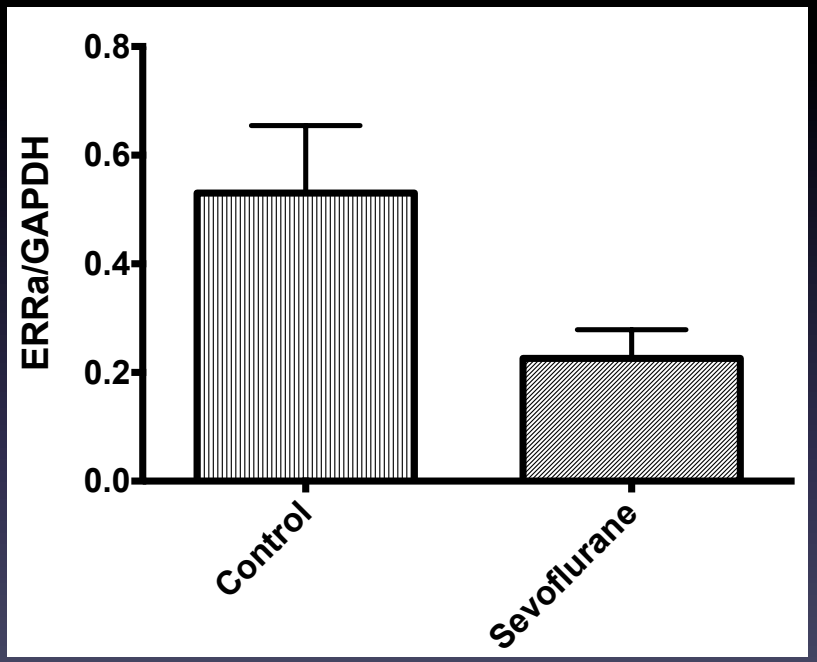


Anesthesia Neurotoxicity Model

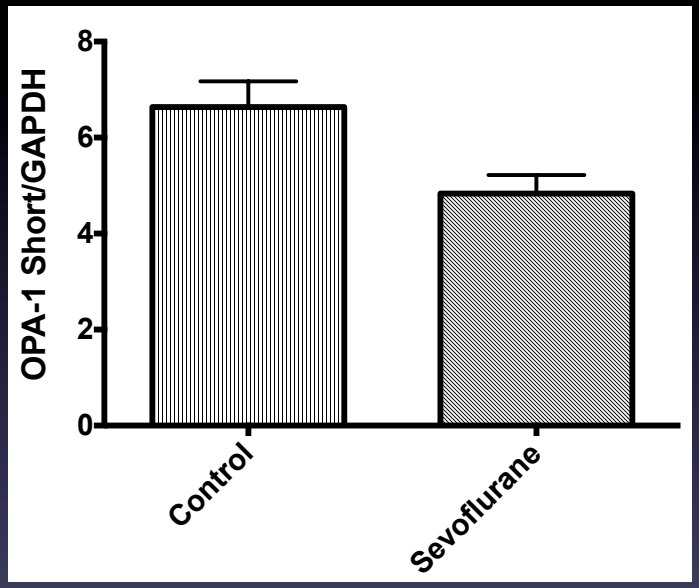
- Stratmann et. al. (2009)
- Rats exposed to sevoflurane at P6, grown to 10 months, undergo cognitive testing
- Six controls, Six sevo exposed

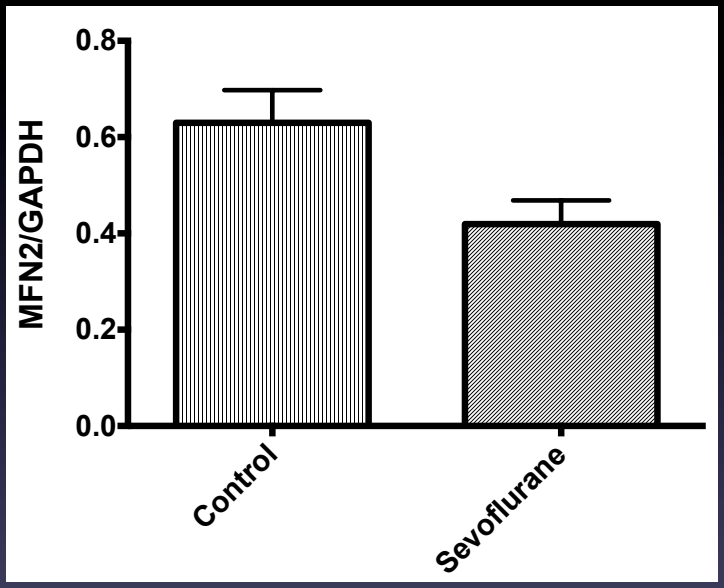
Alternations in Mitochondrial Transcription



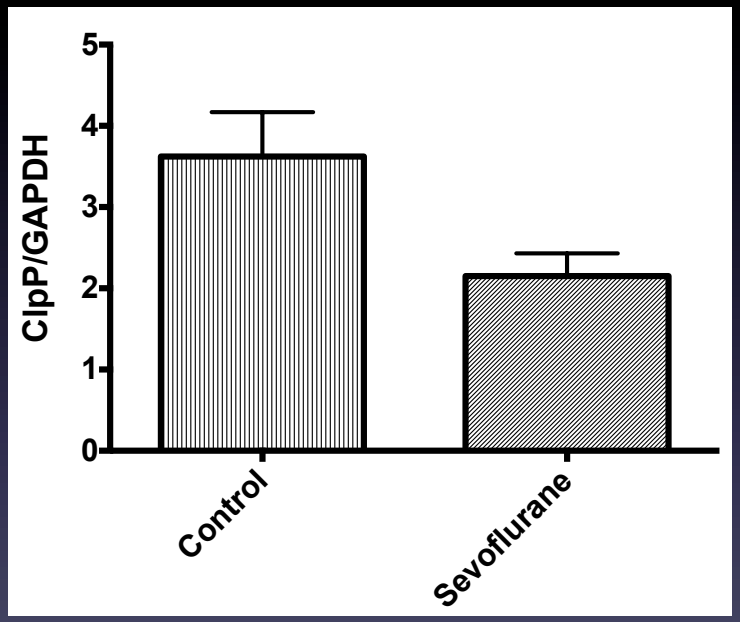


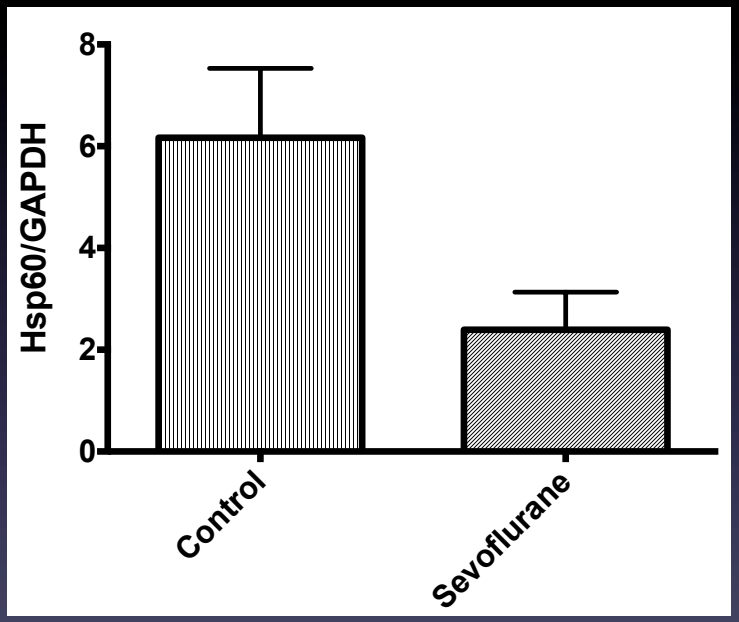
Mitochondrial Fusion/Quality Control





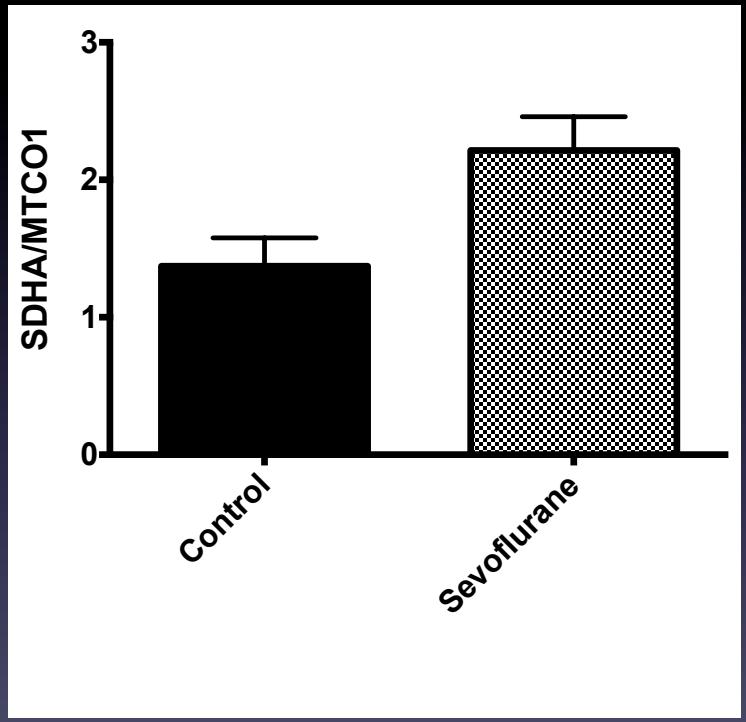
Mitochondrial UPR



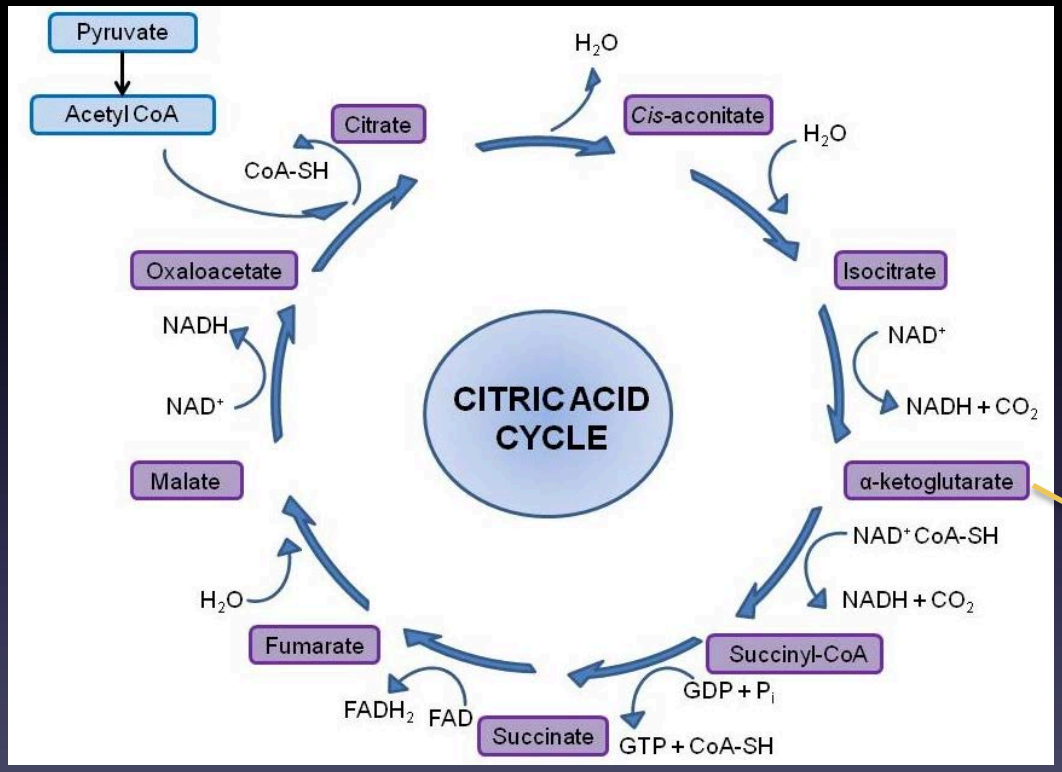


Anesthesia-induced protein misfolding
and effects on the ER-UPR
See presentation by E. Richards

MitoNuclear Protein Balance



Citric Acid Cycle

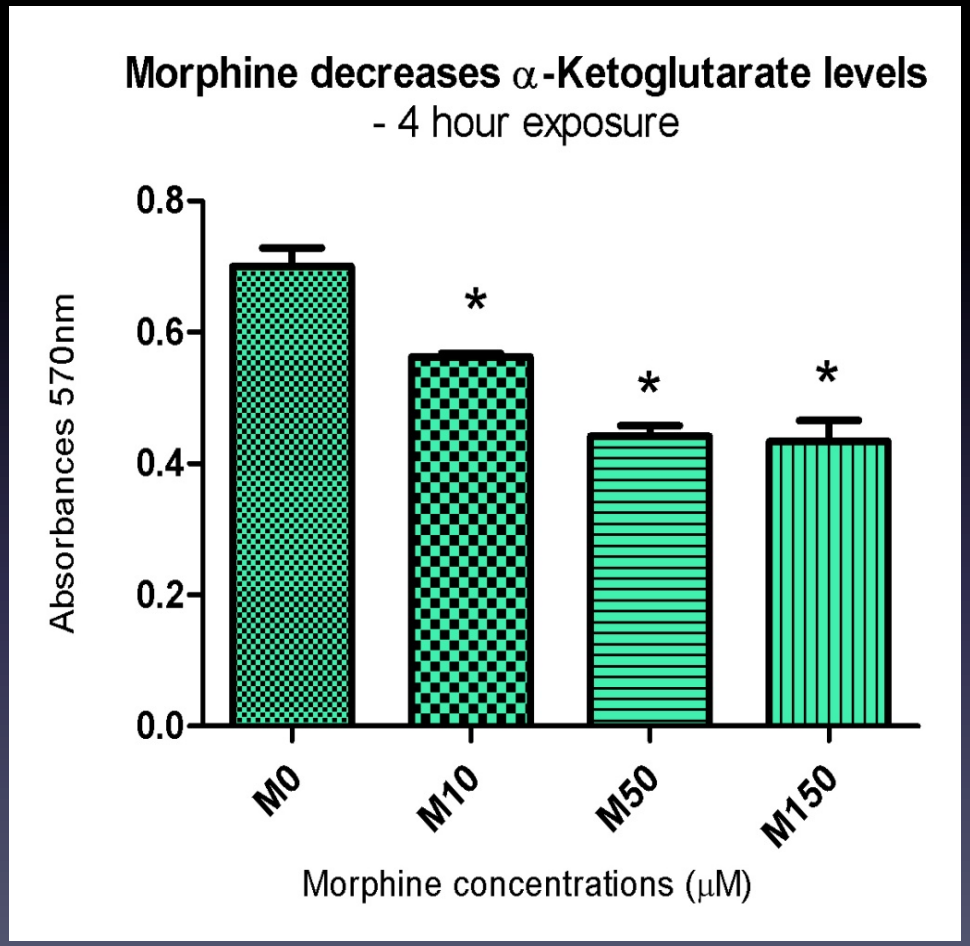


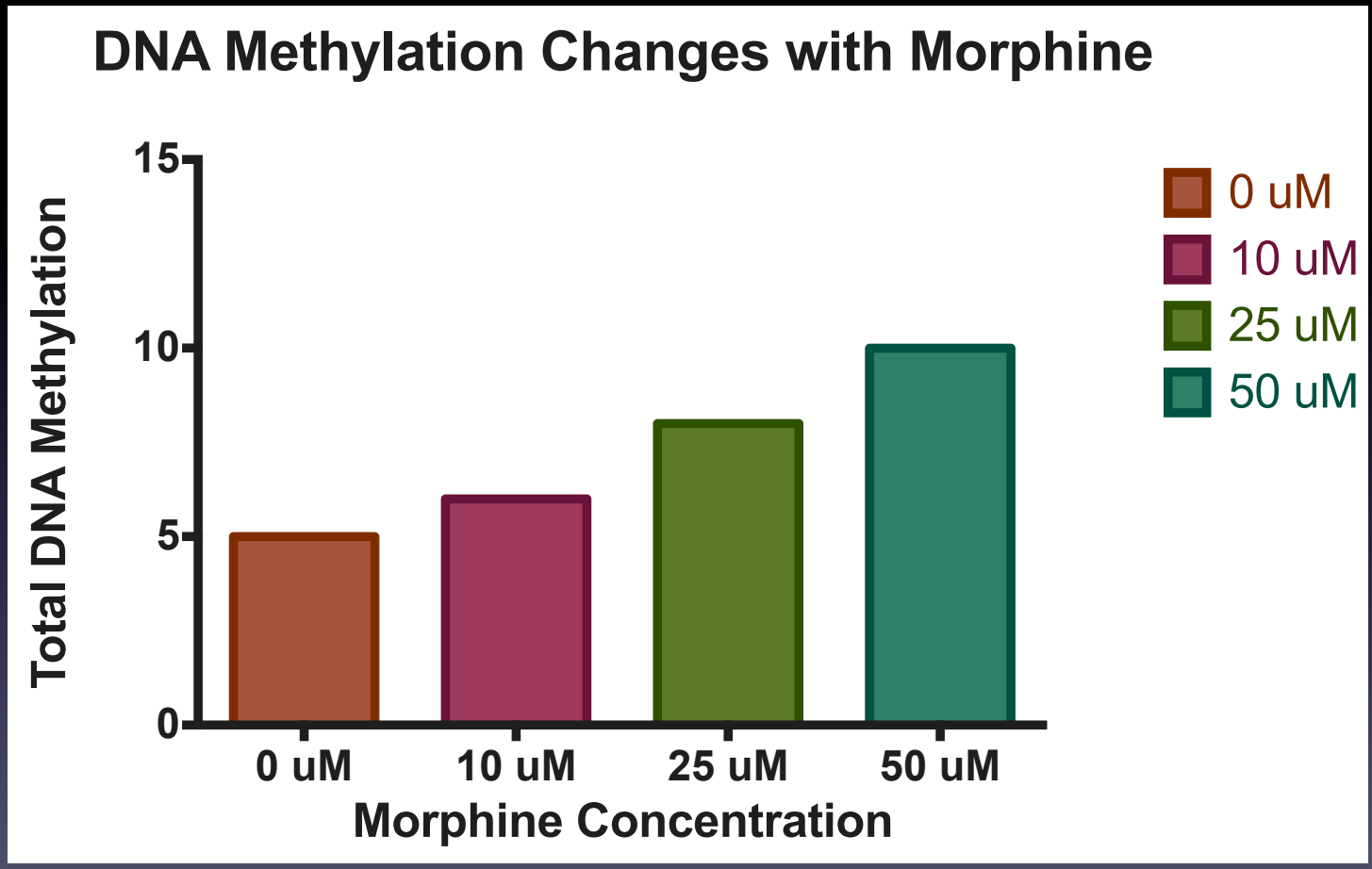
Isocitrate Dehydrogenase

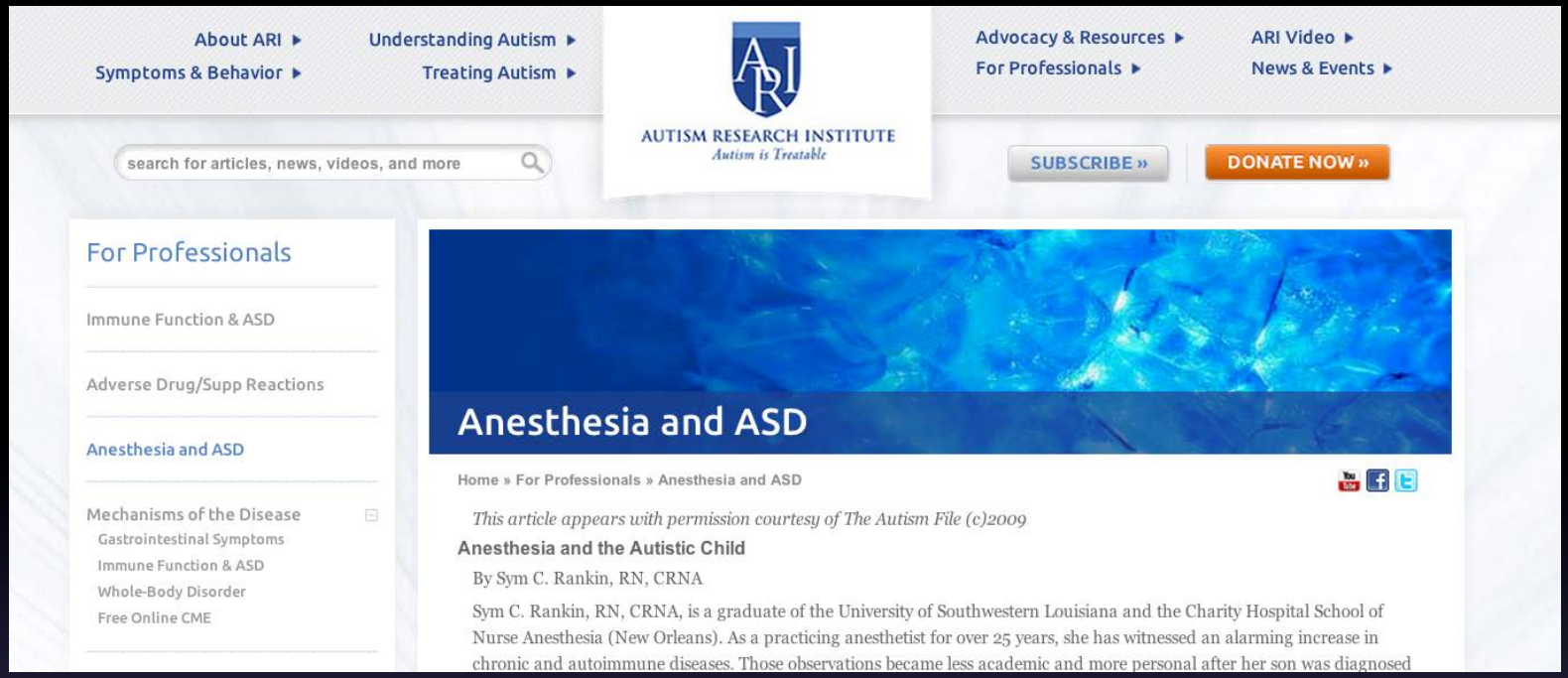
Dioxygenases Jumanji DeMe

DNA Demethylation

Agent	IDH1 (cytoplasmic)	IDH2 (mitochondrial)
Isoflurane	No inhibition	No inhibition
Midazolam	No inhibition	No inhibition
Ketamine	No inhibition	No inhibition
Propofol	No inhibition	No inhibition
Lidocaine	No inhibition	No inhibition
Morphine	Ki = 36.5 uM	No inhibition
Fentanyl	No inhibition	No inhibition
Hydromorphone	No inhibition	No inhibition


Morphine decreases α-Ketoglutarate levels
- 4 hour exposure
Absorbances 570nm
0.8
0.6
0.4
0.2
0.0
*
*
*
M0
M10
M50
M150
Morphine concentrations (μM)


DNA Methylation Changes with Morphine
Total DNA Methylation
15
10
5
0
0 uM
10 uM
25 uM
50 uM
Morphine Concentration
0 uM
10 uM
25 uM
50 uM



Many parents tell me their child was different, or that they regressed, after an anesthetic. To those of us who have taken a hard look at the biochemical problems underlying our children's autistic manifestations, these anecdotal reports should come as no surprise. An anesthetic might represent yet another toxic insult our children experience; we must help anesthesia providers understand the physical and biomedical problems our children have, so that providers might minimize the insults. Not surprisingly, part of the problem is the mindset we see in the mainstream medical community.

Mainstream physicians generally react to the physical problems of ASD children in the way their training taught them. Clinicians prescribe drugs to manage behaviors, without looking at what might be the cause. Because most anesthesia providers are very much part of the mainstream, they see only "autistic" behaviors, and they try to compensate for those behaviors by sedating the child. Such a provider does not understand the metabolic problems underlying those behaviors. So, they will default to protocols that might include drugs that might cause further problems.

http://www.autism.com/

Autism Spectrum Disorder at SickKids:

	2009 (n = 11,321)	2010 (n = 11,455)	2011 (n = 9,131)
Autism	215 (1:53)	263 (1:43)	248 (1:37)
Congenital heart disease	301 (1:38)	233 (1:49)	232 (1:39)
Cerebral palsy	176 (1:64)	137 (1:84)	127 (1:72)
Prematurity	102 (1:111)	120 (1:95)	116 (1:79)
Down syndrome	177 (1:64)	170 (1:68)	115 (1:79)
Asthma	136 (1:83)	86 (1:133)	105 (1:87)
Cystic fibrosis	20 (1:566)	26 (1:441)	30 (1:304)

Autism as a Metabolic Phenotype

- Mitochondrial genes directly < 0.5%
- "Atypical" mitochondrial deficiency ~40% (Oliveira 2005)
- Evidence that the serum level of mito markers correlates to autism clinical severity
- Reduced brain ATP on MRI
- Decrease in protective glutathione/ increase ROS/RNS

Autism and Anesthesia

- Basic:
  - Lymphoblastoid and iPSC-neurons from 50 autistic patients
  - Testing metrics of mitochondrial function, response to anesthetics
- Prospective:
  - Pre-cognitive testing
  - Post-cognitive testing: immediate, 3, 6 months
  - Mitochondrial markers

Conclusions

- Anesthetic Agents cause:
  - Adverse changes in mito morphology and function
  - Induction of mtDNA damage
  - Real-time damage after a single dose in vivo
  - Alterations in cellular energy balance, transcription and stress responses
  - Aging phenotype
- Morphine is an inhibitor of IDH1, affecting DNA methylation, cancer cell growth

Acknowledgements

Hospital For Sick Children:

- Ramesh Vanama
- Grant Stuart
- Vannessa Chin
- Sadiq Shah
- Lawrence Wengle
- Diana Raj
- Matthew Coghlan
- Daniel Stocki
- Michael Tropak
- Yaron Finkelstein

UCSF

- Greg Stratmann

Canadian Anesthesiologists' Society / Société canadienne des anesthésiologistes

University of Toronto

Canada Foundation for Innovation
Fondation canadienne pour l'innovation

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