Mitochondrial Dysfunction in Autism

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Defeat Autism Now! Fall Conference

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Disclosures:

I have received funding for two studies on hyperbaric treatment in children with autism from the International Hyperbarics Association but I have no commercial or financial relationships with chamber manufacturers.

With all treatments and recommendations, please consult with your child's physician before implementation.

The use of every treatment in individuals with autism is "off-label" except for risperidone for the treatment of irritability

Autism: Pathophysiology

- Cerebral hypoperfusion
- Inflammation
  - Cerebral
  - Gastrointestinal
- Dysbiosis
- Mitochondrial dysfunction
- Oxidative stress
- Impaired glutathione production
- Environmental toxicant exposures

Autism: a disorder of brain bioenergetic metabolism?

Autism: a mitochondrial disorder?

J. LOMBARD

Westchester Square Medical Center, 3175 East Tremont Avenue, Bronx, New York, NY 10461, USA

Lombard, **1998** Med Hypotheses 50:497-50

Mitochondrial Disease (MD) and Regression

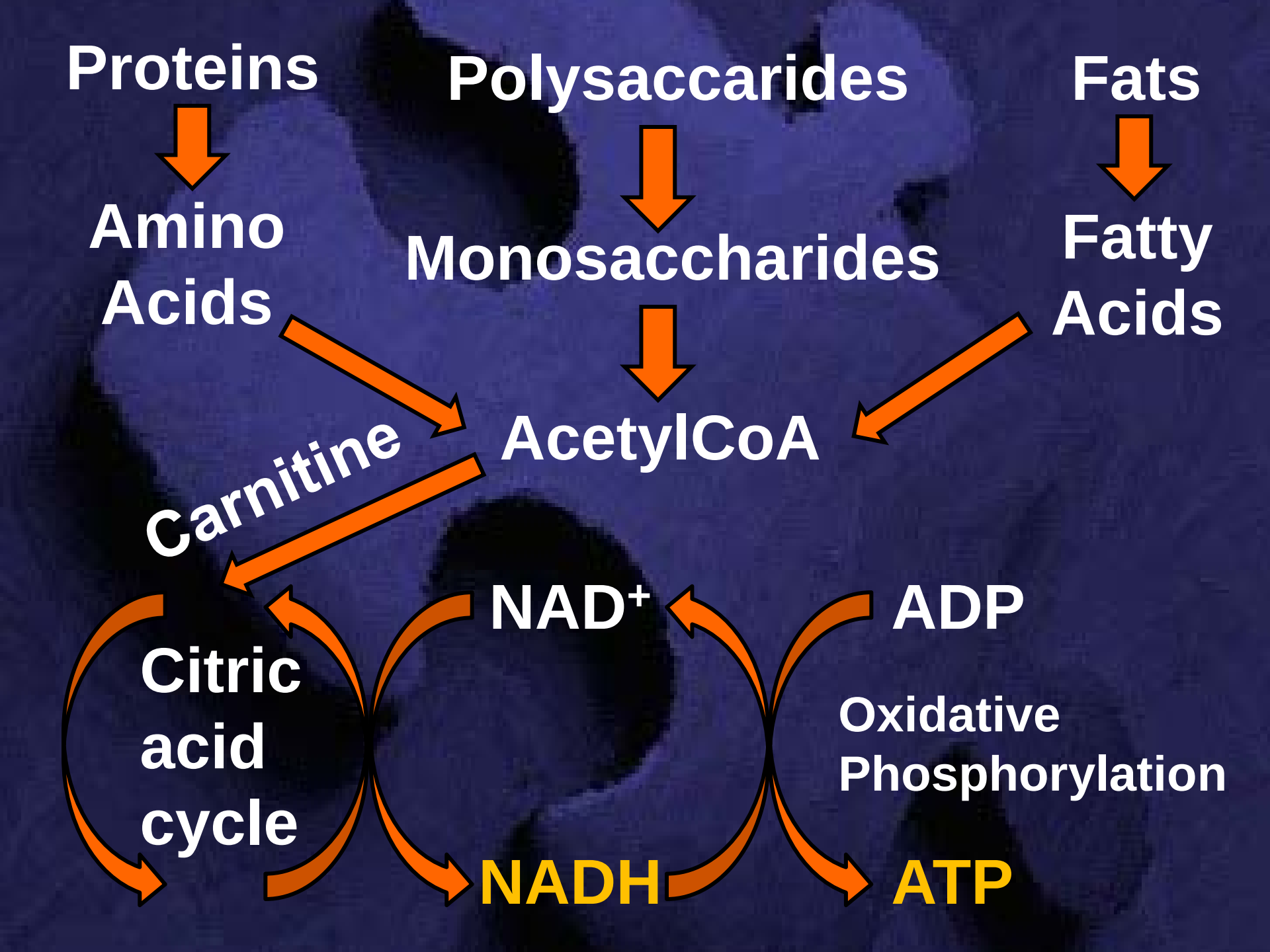
- Illness
- Fever
- Surgery
- Anesthesia
- Fasting
- Dehydration
- High altitude / hypoxia
- Stressors
- Increased oxidative stress

Mitochondria

- ? Descendent of an ancestral purple, non-sulfur, photosynthetic bacteria
- Generate ATP (energy)
- Has its own DNA (genome)
- Contain 5 compartments
- Play a role in programmed cell death
- Involved in porphyrin / heme production
- Mitochondria in the liver are important in ammonia detoxification

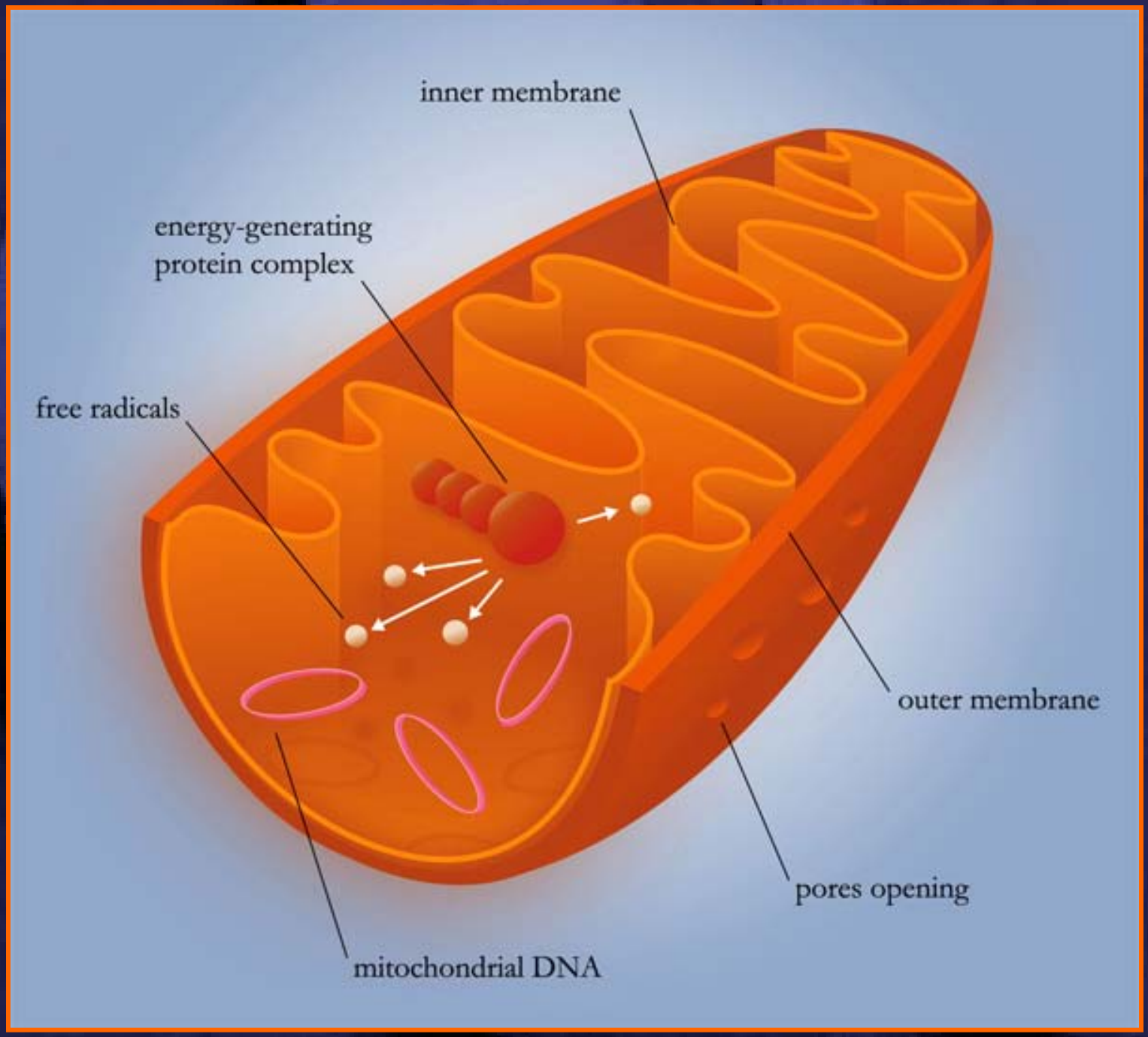
Mitochondria

- ATP production in the mitochondria through the electron transport chain (ETC) from aerobic metabolism creates about 13-fold more ATP from glucose than produced from anaerobic metabolism
- An electrochemical and pH gradient is produced across the inner membrane
- Mitochondria are primary source of ROS by electron leak from the electron transport chain; 1-2% of oxygen normally produces free radicals


Proteins
Polysaccarides
Fats
Amino Acids
Monosaccharides
Fatty Acids
Carnitine
AcetylCoA
NAD+
ADP
Citric acid cycle
Oxidative Phosphorylation
NADH
ATP

Mitochondria

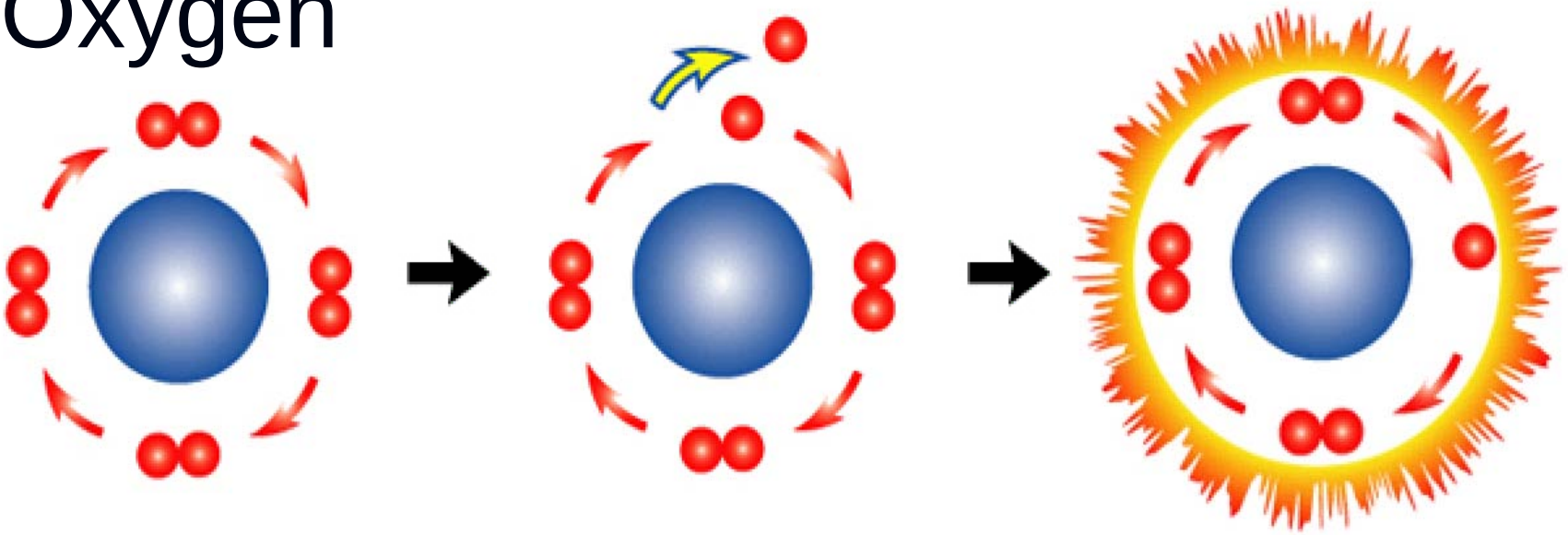
- Increasing inspired PO_2 increases ROS generation
- Major protector against oxidative stress and mtDNA damage in mitochondria is glutathione (GSH)
- Mitochondria cannot produce GSH, but it is made in the cytoplasm
- Accumulation of mtDNA mutations thought to be involved in aging


inner membrane
energy-generating
protein complex
free radicals
outer membrane
pores opening
mitochondrial DNA

Oxidative Stress

Free Radical

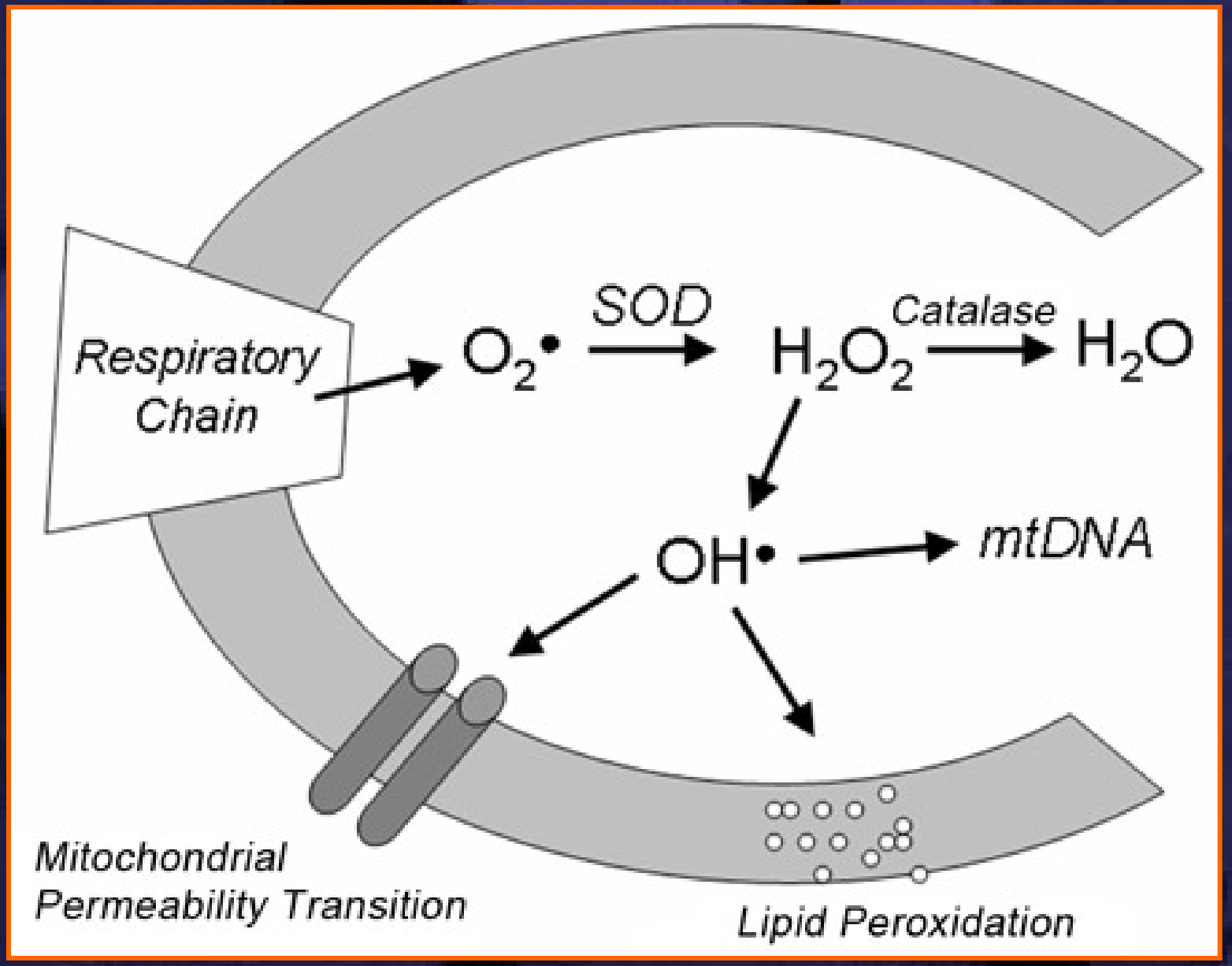
Oxygen

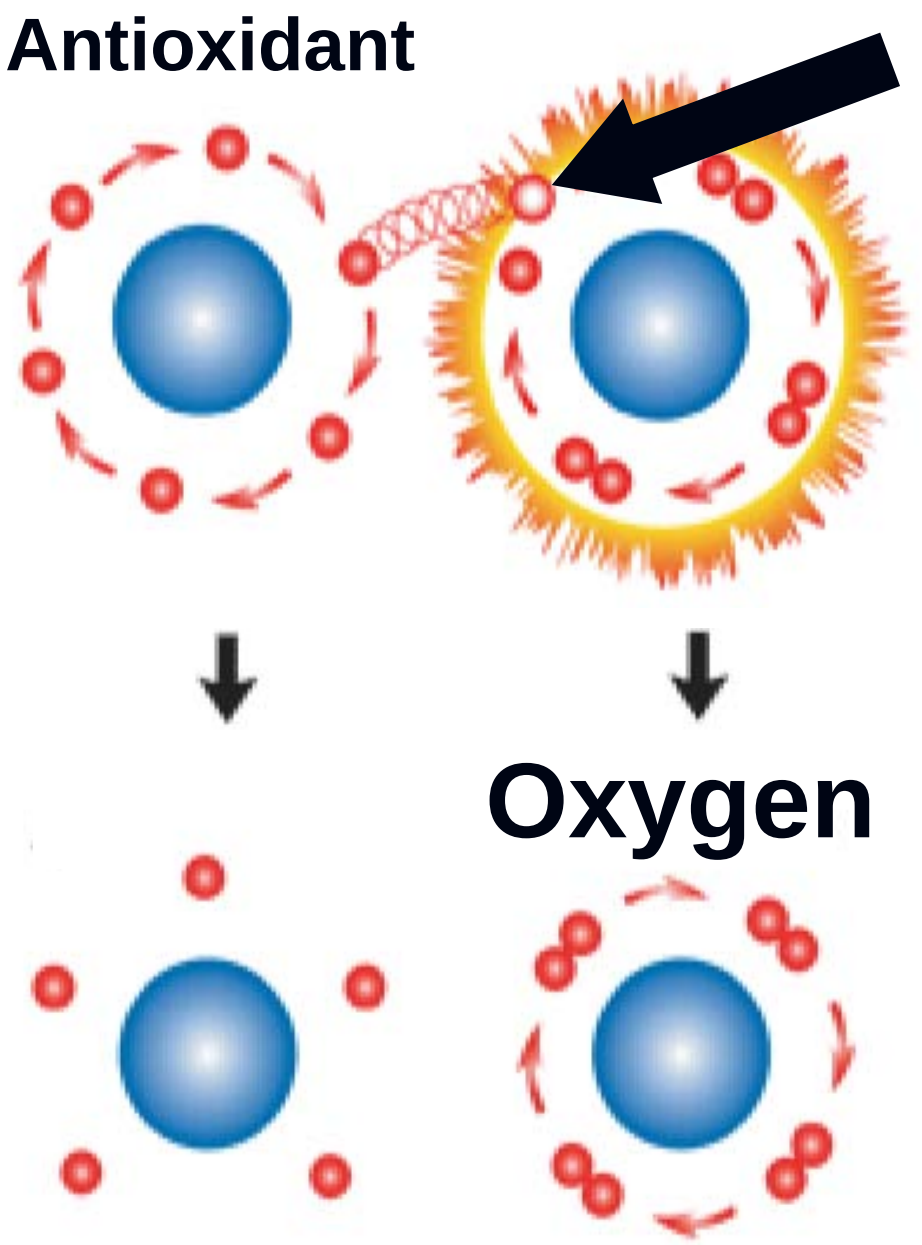


8 electrons

1 electron ejected

7 electrons


Respiratory Chain
$O_2^{\bullet}$
SOD
H_2O_2
Catalase
H_2O
$OH^{\bullet}$
mtDNA
Mitochondrial Permeability Transition
Lipid Peroxidation


Antioxidant
Oxygen
8 electrons

Proc. Natl. Acad. Sci. USA
Vol. 88, pp. 1913–1917, March 1991
Biochemistry

Glutathione deficiency leads to mitochondrial damage in brain

(buthionine sulfoximine/glutathione ester/turnover/hydrogen peroxide/animal model)

AJEY JAIN*, JOHANNES MÅRTENSSON†, EINAR STOLE†, PETER A. M. AULD*, AND ALTON MEISTER†

Departments of *Pediatrics and †Biochemistry, Cornell University Medical College, 1300 York Avenue, New York, NY 10021

Contributed by Alton Meister, December 5, 1990

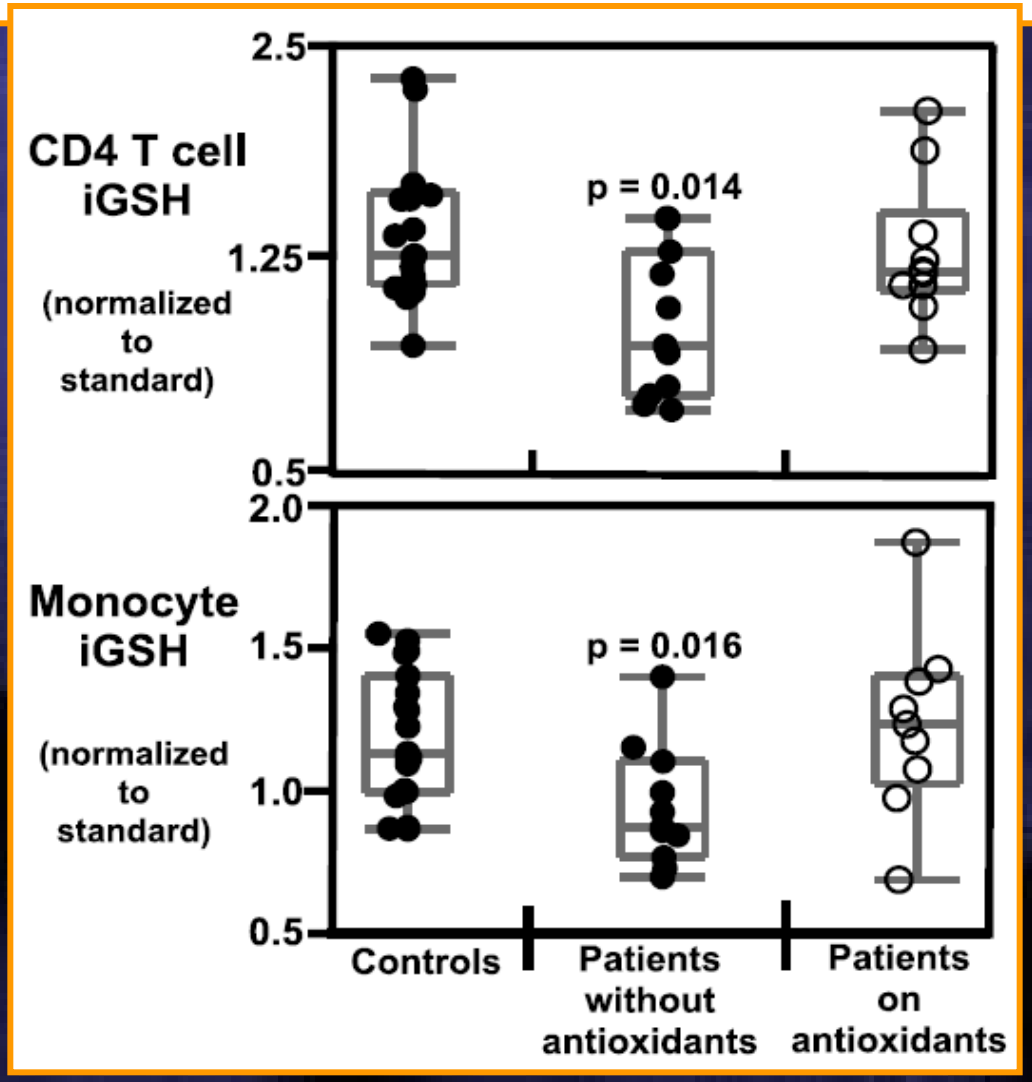
Jain et al., 1990 Proc Natl Acad Sci USA 88:1913-17

Mini review

Oxidative stress: Role of mitochondria and protection by glutathione

Fernandez-Checa et al., 1998 BioFactors 8:7-11

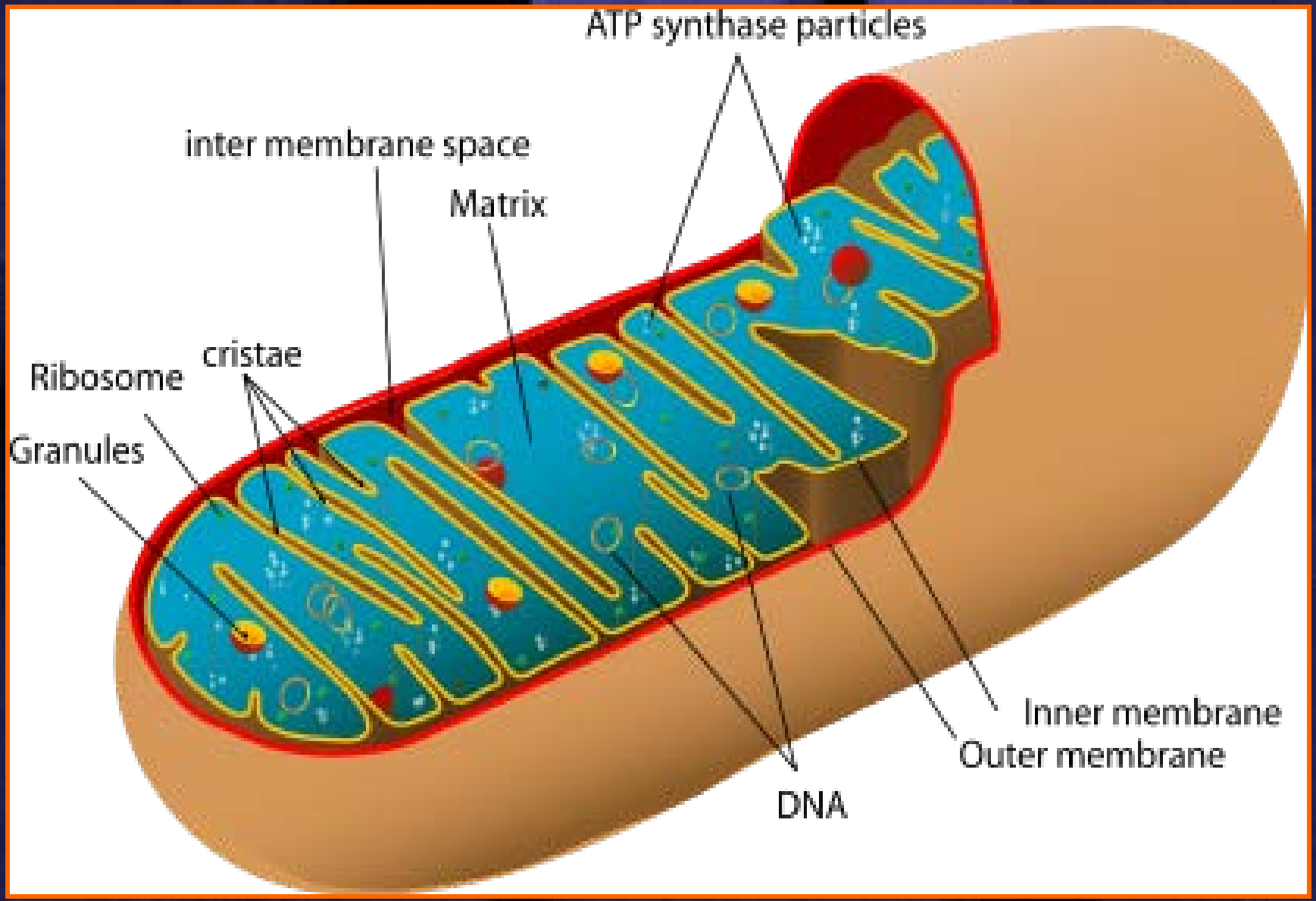
Inherited disorders affecting mitochondrial function are associated with glutathione deficiency and hypocitrullinemia



Atkuri et al., 2009 Proc Natl Acad Sci USA, in press

Mitochondria: 5 Compartments

- Outer membrane
- Intermembrane space
- Inner membrane
- Cristae: invaginations of inner membrane
- Matrix

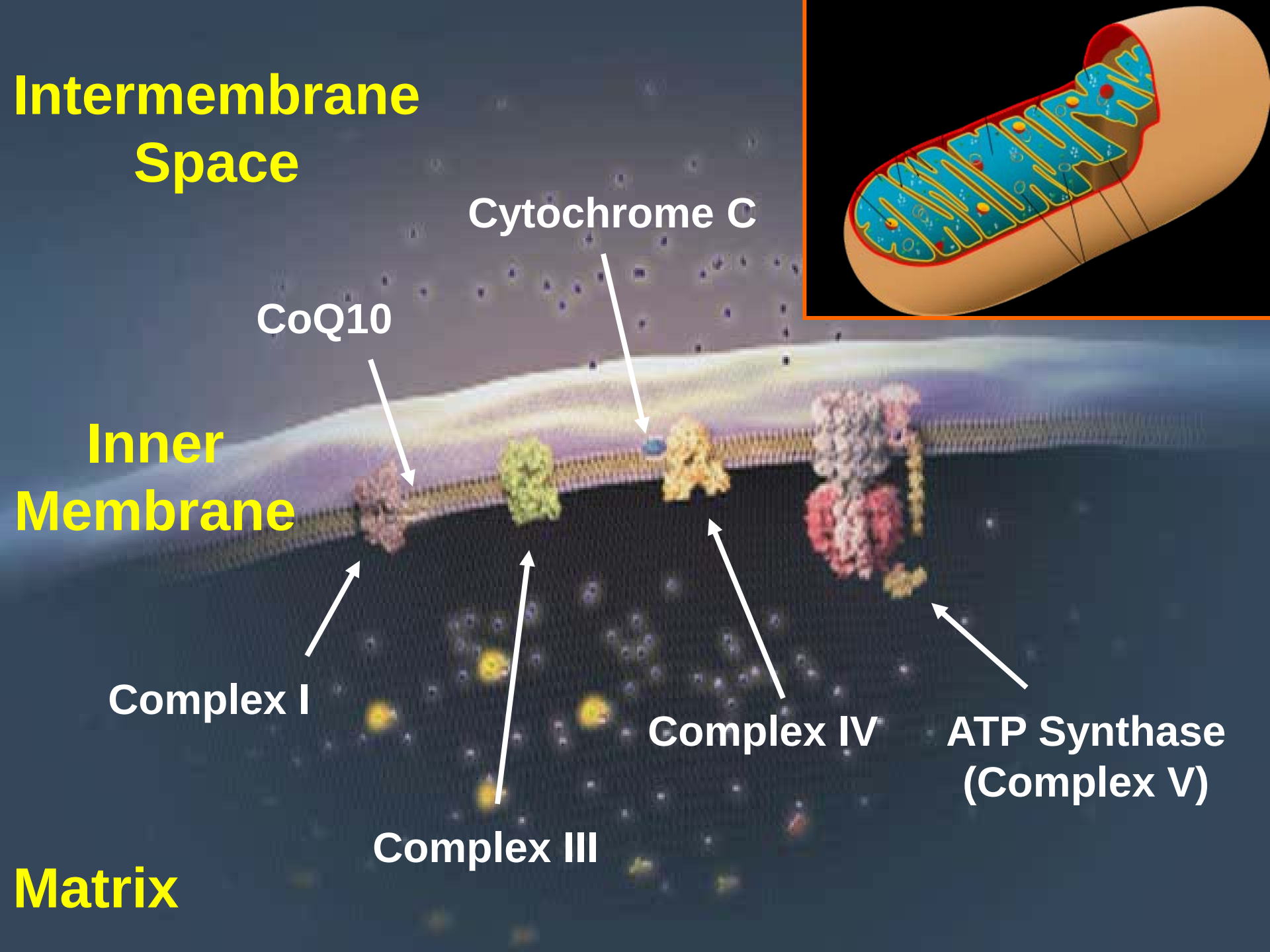

ATP synthase particles
inter membrane space
Matrix
Ribosome
cristae
Granules
Inner membrane
Outer membrane
DNA

Electron Transport Chain (ETC)

- **Five complexes, located in inner mitochondrial membrane**
- **Mitochondrial oxidative phosphorylation occurs here; 2 main functions:**
  - **Generates ATP from electrons (from food) through ATP synthase (complex V)**
  - **Generates heat**
- **Electrons that leak out of the ETC produce free radicals: reactive oxygen species (ROS)**

ETC

- If the ETC is damaged or inhibited, then ROS production may be increased
- ETC can be blocked or impaired ("leaky") and this increases ROS
  - Genetic defects in nDNA and mtDNA
  - Toxins (e.g., cyanide)
  - Medications


Intermembrane Space
Cytochrome C
CoQ10
Inner Membrane
Complex I
Complex III
Complex IV
ATP Synthase (Complex V)
Matrix

Mitochondrial Disease (MD)

- Primary **mitochondrial disease** typically refers to genetic defects leading to mitochondria dysfunction (MtD)
- Secondary mitochondrial disease (**dysfunction**) refers to **impaired functioning** of mitochondria
- Organs with highest aerobic demand are most affected (**CNS**, heart, and skeletal muscle), but any organ can be affected including **GI and endocrine**

MD

- Can present at any age
- Consider family history
- No reliable biomarkers exists
- Under-diagnosed
- Think of MD when 3 or more organ systems are involved without a unifying diagnosis
- Consider specialist referral

MtD and synaptic function

- Synaptic neurotransmitter release decreased by 50% when mitochondrial dysfunction exists
- Neurons firing at high rates affected the most: GABAergic interneurons
- Decreases in GABA release can contribute to seizures and regression

Primary MD

- Genetic defects associated with MD: can be in mitochondrial DNA (mtDNA) or nuclear DNA (nDNA)
- mtDNA mutations estimated at 1 per 5,000; recent study of 3,168 neonatal cord blood samples: 1 in 200 [Elliott, 2008]
- mtDNA haplotype associated with longevity
- Over 150 mtDNA point mutations and 100 mtDNA deletions have been identified

Dual genome: MD

- nDNA encodes for ~850 genes involved in forming structural subunits of mitochondria
- Most common cause of MD is genetic defects in nDNA (often autosomal recessive): classical Mendelian inheritance, accounts for 75-90% of primary MD [Haas, 2008]
- With increasing age, genetic basis for MD is often mtDNA: maternal inheritance

Primary MD in ASD

- Inverted duplicated 15q11-q13 [Filipek, 2003]
- Rare familial associated with SIDS
- SLC22A5: encodes for sodium-dependent carnitine co-transporter OCTN2, causes carnitine deficiency
- A3243G: MELAS [Pons, 2004; Serajee, 2006]
- Defects in L-type calcium channel
- mtDNA G8363A mutation [Graf, 2000]

Secondary MD

- Medications: valproic acid (depletes carnitine), salicylates, antiretroviral HIV meds
- Estrogen increases mitochondrial efficiency [Stirone, 2005]
- Decreased metabolic reserve
  - Oxidative stress
  - Lowered glutathione
- Hypoxia

Secondary MD: Toxins

- Heavy metals (mercury, lead, arsenic, cadmium, aluminum)
- Pesticides
- Diesel exhaust
- Propionic acid from clostridia

- Toxins leading to secondary MD rarely (never ?) discussed in mito literature.

Symptoms / Signs of MtD

- "Any symptom in any organ at any age" [Munnich, 1996]
- Developmental delay
- Hypotonia (low muscle tone)
- Constipation / GI dysmotility
- Slow cognitive processing speed
- Fatigue [Weissman, 2008]
- Seizures
- Oxidative stress

Labs: MtD (blood)

- Basic chemistry (CO_2, anion gap)
- Liver enzymes (AST, ALT)
- **Ammonia**
- Creatine kinase
- **Lactic acid** and pyruvate
- Plasma amino acids: **alanine** (compared to lysine), glycine, proline, sacrosine, tyrosine
- Fasting plasma acylcarnitine analysis

Labs: MtD (urine)

- Urinary organic acid testing
- TCA cycle intermediates
- Ethylmalonate
- 3-methyl-glutaconate
- 2-ketoglutarate
- Dicarboxylic acids
- Urinary oxidized RNA (8-OG)

Other tests: MtD

MRS

- High lactate peak
- Low *N*-acetyl-L-aspartate (NAA)
- Low choline
- High succinate

Biopsy

- Skin (fibroblast)
- Muscle
- Liver
- Cardiac

Review

Hyperammonemia-induced toxicity for the developing central nervous system

Cagnon and Braissant, 2007 Brain Res Rev 56(1):183-97

- **Depletes brain ATP [Kosenko, 1994]**
- **Toxic to brain cells [Cagnon, 2007]**
- **Potential causes:**
  - **High protein intake**
  - **Dysbiosis (e.g., *Clostridia* species)**
  - **Mitochondrial dysfunction**
- **Treatment**
  - **Alpha-ketoglutarate (AKA) 300 mg bid**
  - **Yucca root: 250-500 mg bid**

Diseases with MtD

- Parkinson's disease
- Alzheimer's disease
- Huntington's disease
- Multiple Sclerosis
- Amyotrophic lateral sclerosis (ALS)
- Friedreich ataxia
- Rett syndrome
- Production of ROS correlates well with disease progression

MITOCHONDRIAL DNA ABNORMALITIES AND AUTISTIC SPECTRUM DISORDERS

ROSER PONS, MD, ANTONI L. ANDREU, MD, NICOLETTA CHECCARELLI, M
KRISTIN ENGELSTAD, BS, CAROLYN M. SUE, MD, DIKOMA SHU
RITA HAGGERTY, PHD, DARRYL C. DE VIVO, MD, AND SALVATOR

Mitochondrial Dysfunction in Autistic Patients with 15q Inverted Duplication

Pauline A. Filipek, MD,[1,2] Jenifer Juranek, PhD,[1] Moyra Smith, MD, PhD,[1,3] Lee Z. Mays, BS,[1,3] Erica R. Ramos, BS,[1,3] Maureen Bocian, MD,[1,3] Diane Masser-Frye, MS,[1,3] Tracy M. Laulhere, MA,[4] Charlotte Modahl, PhD,[1] M. Anne Spence, PhD,[1,3] and J. Jay Gargus, MD, PhD[1,3,5]

Mitochondrial dysfunction in autism spectrum disorders: a population-based study

G Oliveira* MD, Paediatrician, Outpatient Clinic of Autism, Centro de Desenvolvimento da Criança;
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American Journal of Biochemistry and Biotechnology 4 (2): 208-217, 2008
ISSN 1553-3468

Evidence of Mitochondrial Dysfunction in Autism and Implications for Treatment

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International Child Development Resource Center, 3800 W. Eau Gallie Blvd., Suite 105, Melbourne, FL 32934

Abstract: Classical mitochondrial diseases occur in a subset of individuals with autism and are usually caused by genetic anomalies or mitochondrial respiratory pathway deficits. However, in many cases of autism, there is evidence of mitochondrial dysfunction (MtD) without the classic features associated with mitochondrial disease. MtD appears to be more common in autism and presents with less severe signs and symptoms. It is not associated with discernable mitochondrial pathology in muscle biopsy specimens despite objective evidence of lowered mitochondrial functioning. Exposure to environmental toxins is the likely etiology for MtD in autism. This dysfunction then contributes to a number of diagnostic symptoms and comorbidities observed in autism including: cognitive impairment, language deficits, abnormal energy metabolism, chronic gastrointestinal problems, abnormalities in fatty acid oxidation, and increased oxidative stress. MtD and oxidative stress may also explain the high male to female ratio found in autism due to increased male vulnerability to these dysfunctions. Biomarkers for mitochondrial dysfunction have been identified, but seem widely under-utilized despite available therapeutic interventions. Nutritional supplementation to decrease oxidative stress along with factors to improve reduced glutathione, as well as hyperbaric oxygen therapy (HBOT) represent supported and rationale approaches. The underlying pathophysiology and autistic symptoms of affected individuals would be expected to either improve or cease worsening once effective treatment for MtD is implemented.

Rossignol and Bradstreet, 2008 Am J Biochem Biotech 4(2):208-17

Nuclear and Mitochondrial Genome Defects in Autisms

We will review information on alterations of structure of mitochondrial DNA and abnormal mitochondrial function in autism and indications that interactions of the nuclear and mitochondrial genomes may play a role in autism pathogenesis. We include data on two sets of monozygotic twins. Collectively these data provide additional evidence of nuclear and mitochondrial genome imbalance in autism and evidence of specific candidate genes in autism.

Smith et al., 2009 Ann NY Acad Sci 1151:102-32

Autism Associated With the Mitochondrial DNA G8363A Transfer RNA^{Lys} Mutation

We report a family with a heterogeneous group of neurologic disorders associated with the mitochondrial DNA G8363A transfer ribonucleic acid (RNA)Lys mutation. The phenotype of one child in the family was consistent with autism. During his second year of life, he lost previously acquired language skills and developed marked hyperactivity with toe-walking, abnormal reciprocal social interaction, stereotyped mannerisms, restricted interests, self-injurious behavior, and seizures.

Graf et al., 2000 J Child Neurol 15(6):357-61

Developmental Regression and Mitochondrial Dysfunction in a Child With Autism

Jon S. Poling, Richard E. Frye, John Shoffner and Andrew W. Zimmerman

J Child Neurol 2006; 21; 170
DOI: 10.1177/08830738060210021401

A 19-month-old girl was born after a normal full-term pregnancy. Her development was progressing well, with normal receptive and expressive language and use of prelinguistic gestures. Imaginary play and social reciprocity were typical for age. She used at least 20 words and could point to five body parts on command. Within 48 hours after immunizations to diphtheria, tetanus, and pertussis; *Haemophilus influenzae B;* measles, mumps, and rubella; polio; and varicella (Varivax), the patient developed a fever to 38.9 C, inconsolable crying, irritability, and lethargy and refused to walk. Four days later, the patient was waking up multiple times in the night, and could no longer normally climb stairs. Instead, she crawled up and down the stairs.

Poling et al., 2006 J Child Neurol 21:170-2

A Preliminary ^{31}P MRS Study of Autism: Evidence for Undersynthesis and Increased Degradation of Brain Membranes

The autistic group had decreased levels of phosphocreatine and esterified ends (alpha ATP + alpha ADP + dinucleotides + diphosphosugars) compared to the controls. This pilot study provides tentative evidence of alterations in brain energy and phospholipid metabolism in autism that correlate with the neuropsychologic and language deficits.

Minshew et al., **1993** Biol Psychiatry 33:762-73

EVIDENCE OF ALTERED ENERGY METABOLISM IN AUTISTIC CHILDREN

DIANE C. CHUGANI[1,2], BHAVANI S. SUNDRAM[4], MICHAEL BEHEN[3], MEI-LI LEE[1], and GREGORY J. MOORE[4,2]

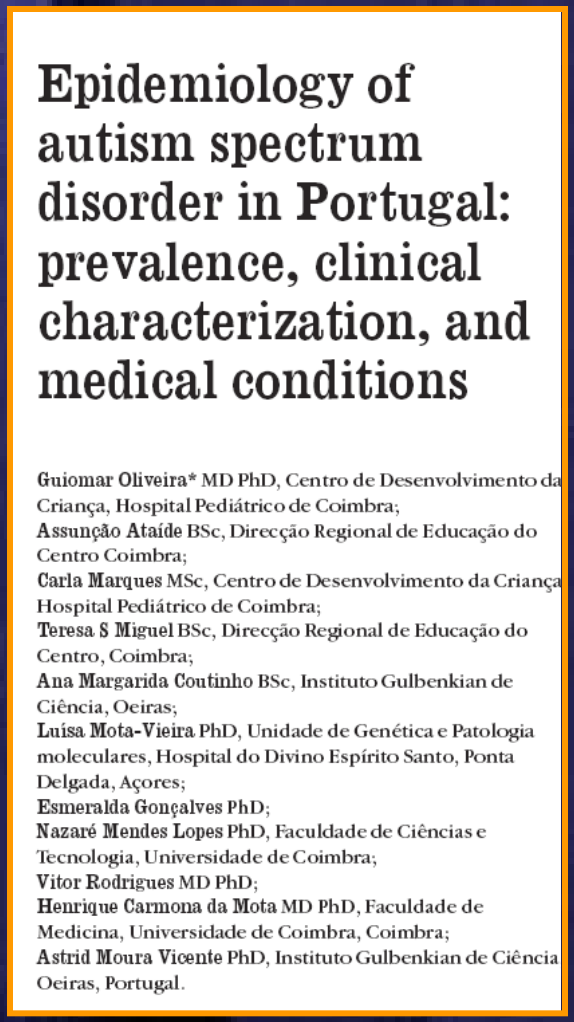
Departments of Pediatrics,[1] Radiology,[2] Psychology[3] and Psychiatry[4]
Wayne State University School of Medicine
Children's Hospital of Michigan
Detroit, MI

Preliminary results show lower levels of NAA cerebellum in autistic children (p = 0.043). Lactate was detected in the frontal lobe in one autistic boy, but was not detected any of the other autistic subjects or siblings. Plasma lactate levels were higher in the 15 autistic children compared to 15 children with epilepsy (p = 0.0003).

Chugani et al., 1999 Prog Neuropsychopharmacol Biol Psychiatry 23(4):635-41

MtD: autism

- 343,718 children screened for ASD prevalence in Portugal
- 120 children with ASD identified
- 18 children had previously identified medical condition, no blood drawn
- Out of remaining 102, blood drawn for **lactic acid** in 69
- Lactic acid high in 14 (**20.3%**)
- Out of these 14, 11 received deltoid muscle biopsies
- 5/11 were +, had **mitochondrial disease** (5/69 = **7.2%** of the children with ASD)



Epidemiology of autism spectrum disorder in Portugal: prevalence, clinical characterization, and medical conditions

Guiomar Oliveira* MD PhD, Centro de Desenvolvimento da Criança, Hospital Pediátrico de Coimbra;
Assunção Ataíde BSc, Direcção Regional de Educação do Centro Coimbra;
Carla Marques MSc, Centro de Desenvolvimento da Criança Hospital Pediátrico de Coimbra;
Teresa S Miguel BSc, Direcção Regional de Educação do Centro, Coimbra;
Ana Margarida Coutinho BSc, Instituto Gulbenkian de Ciência, Oeiras;
Luísa Mota-Vieira PhD, Unidade de Genética e Patologia moleculares, Hospital do Divino Espírito Santo, Ponta Delgada, Açores;
Esmeralda Gonçalves PhD;
Nazaré Mendes Lopes PhD, Faculdade de Ciências e Tecnologia, Universidade de Coimbra;
Vitor Rodrigues MD PhD;
Henrique Carmona da Mota MD PhD, Faculdade de Medicina, Universidade de Coimbra, Coimbra;
Astrid Moura Vicente PhD, Instituto Gulbenkian de Ciência Oeiras, Portugal.

Oliveira et al., 2007 Dev Med Child Neuro 49:726-33

J Autism Dev Disord
DOI 10.1007/s10803-006-0138-6

BRIEF COMMUNICATION

Brief Report: High Frequency of Biochemical Markers for Mitochondrial Dysfunction in Autism: No Association with the Mitochondrial Aspartate/Glutamate Carrier *SLC25A12* Gene

Catarina Correia · Ana M. Coutinho · Luísa Diogo · Manuela Grazina · Carla Marques · Teresa Miguel · Assunção Ataíde · Joana Almeida · Luís Borges · Catarina Oliveira · Guiomar Oliveira · Astrid M. Vicente

36/210 (17.2%) had elevated lactic acid levels
Out of these 36, 20 were assessed for MD, and 7/20 (35%) had MD (7/36 = 19.4%)

Correia et al., 2006 J Autism Dev Disord 36(8):1137-40

Polyunsaturated Fatty Acids, Carnitine and Lactate as Biological Markers of Brain Energy in Autistic Children

- 30 children with autism, 30 TD
- Autism group had lower carnitine and higher lactate (both $p<0.05$)
- 77% had high lactate
- Children with severe autism (on CARS) had lower carnitine and higher lactate compared to less severe (both $p<0.05$)
- Negative correlation between carnitine and lactate

Mostafa et al., 2005 Int J Ch Neuropsychiatry 2(2):179-88

Mitochondrial Disease in Autism Spectrum Disorder Patients: A Cohort Analysis

- 25 children with initial ASD, later MD
- 64% developmental delay, 76% fatigue, 84% with GI problems (reflux, constipation)
- 32%: more than 5 std dev later in walking
- Lactate high in 76%, alanine in 36%, AST or ALT in 52%
- 40% with unusual regression: repeated regressions, loss of gross motor function, or regression after age 3
- Complex I deficiency in 64%, Complex III in 20%, 2 with rare mtDNA mutations

Weissman et al., 2008 PLoS ONE 3(11):e3815

Mitochondrial Dysfunction in Patients With Hypotonia, Epilepsy, Autism, and Developmental Delay: HEADD Syndrome

- 12 children with autism and hypotonia, seizures, and developmental delay
- Other disorders ruled out.
- Measured mtDNA, ETC, mito structure
  - 5 children with mtDNA deletions
  - 7/8 children with Complex I, III, IV, or V def.
  - 3 out of 4 mito ultrastructural abnormalities

Filiano et al., 2002 J Child Neurol 17(6):435-9

ATPase: involved in cellular potential
Converts ATP to ADP

Groups	*HMG CoA reductase (ratio of HMG CoA/ mevalonate)*	*Digoxin (ng/dl)*	*Dolichol (μg/dl)*	*Ubiqui-none (μg/dl)*	*Na^+-K^+ ATPase (μg/p_i/mg protein)*	*Magnesium (mg/dl)*
1. Control	1.15 ± 0.12	12.80 ± 1.09	39.1 ± 2.36	144.2 ± 8.65	5.04 ± 0.221	2.40 ± 0.24
2. Autism	0.510 ± 0.06**	30.90 ± 1.41**	120.9 ± 9.65**	91.40 ± 5.92**	1.51 ± 0.142**	1.04 ± 0.12**

**p less than .01.

Kurup and Kurup, 2003 Intern J Neuroscience 113:1537-59

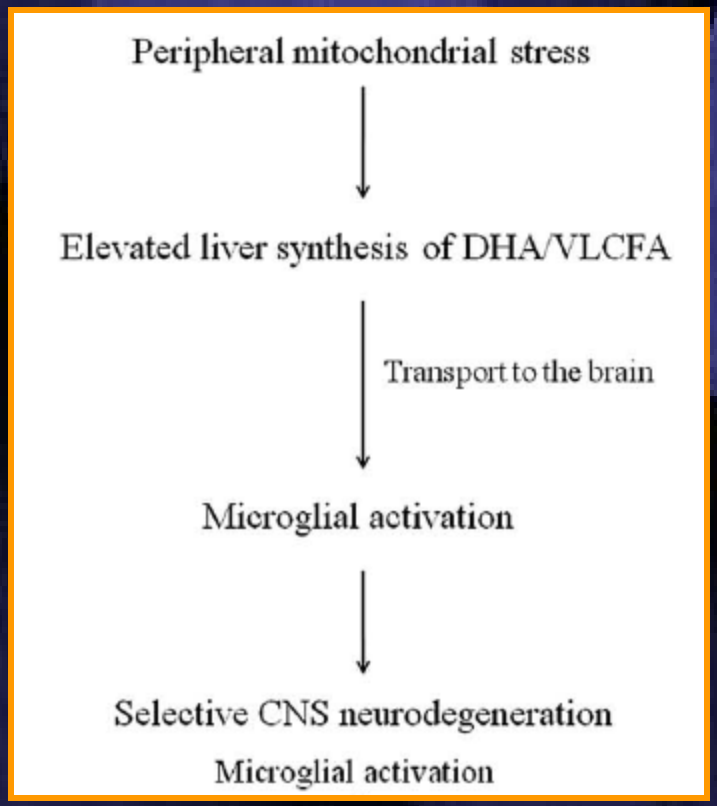
Cellular and mitochondrial glutathione redox imbalance in lymphoblastoid cells derived from children with autism

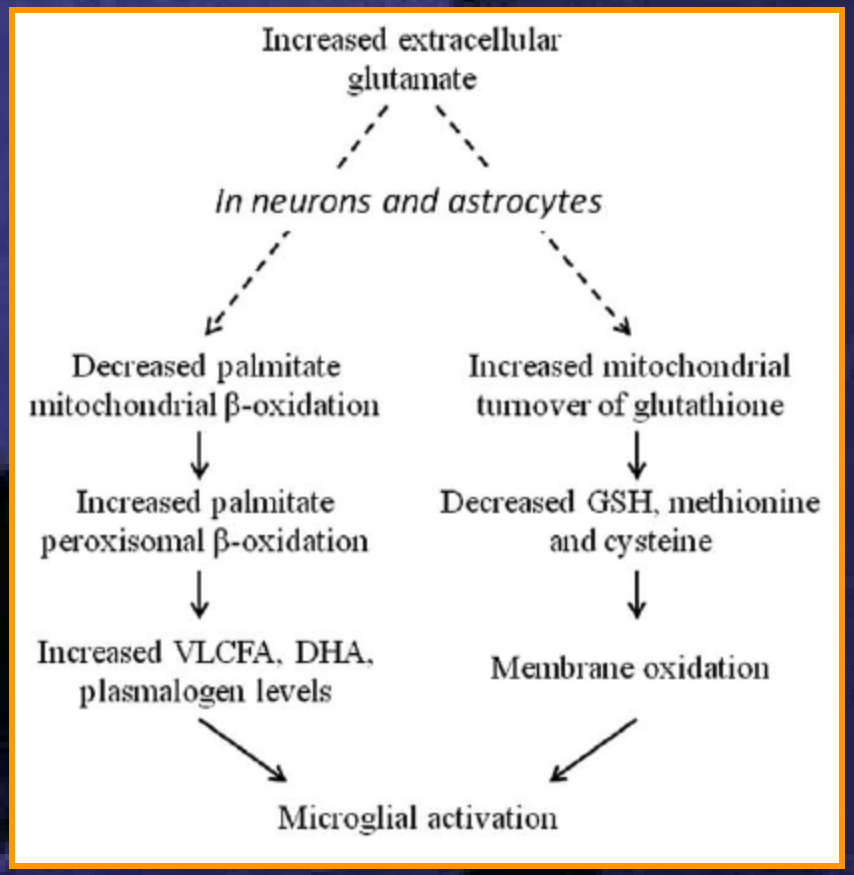
The results indicated that the GSH/GSSG redox ratio was decreased and percentage oxidized glutathione increased in both cytosol and mitochondria in the autism LCLs. Acute exposure to physiological levels of nitric oxide decreased mitochondrial membrane potential to a greater extent in the autism LCLs. These results suggest that the autism LCLs exhibit a reduced glutathione reserve capacity in both cytosol and mitochondria that may compromise antioxidant defense and detoxification capacity under prooxidant conditions.

James et al., 2009 FASEB J, in press

Novel plasma phospholipid biomarkers of autism: Mitochondrial dysfunction as a putative causative mechanism

Élodie Pastural [a], Shawn Ritchie [a], Yingshen Lu [a], Wei Jin [a], Amir Kavianpour [a], Khine Khine Su-Myat [a], Doug Heath [a], Paul L. Wood [a], Maura Fisk [b], Dayan B. Goodenowe [a,*]





Pastural et al., 2009 Prostaglandins Leukot Essent Fatty Acids, in press

Chances of Mito Dysfunction in ASD?

- Epidemiological studies: 4-7% mito disease, 20% mito dysfunction
- If low GSH is a marker of MtD, then may be as high as 70%
- If you suspect mito dysfunction, and especially if lactic acid is elevated, 45-65% chance of mitochondrial defect upon muscle biopsy

Treatments: MtD

- CoEnzyme Q10: 5-10 mg/kg/day
- Idebenone: 45-360 mg/day
- Acetyl-L-Carnitine: 50-100 mg/kg/day
- L-Carnitine (Carnitor)
- Thiamine (B1): 15 mg/kg/day
- Pyridoxine (B6): 5-15 mg/kg/day
- Riboflavin (B2): 15 mg/kg/day
- Pantothenic acid (B5): 15 mg/kg/day
- Vitamin E: 15 IU/kg/day

Treatments: MtD

- Vitamin C: 25 mg/kg/day
- Alpha-lipoic acid: 15 mg/kg/day
- Vitamin K3: 5-80 mg/day
- Folate: 1-10 mg/day
- Creatine monohydrate: 5-10 g/day
- B12, selenium, succinate, Ginkgo biloba
- D-ribose: 0.5-1 gram bid
- Antioxidants
- Chelation / HBOT

Carnitine

- Co-factor that helps transport long chain fatty acids into mitochondria for beta-oxidation
- Antioxidant that neutralizes free radicals, including those produced by ETC
- Supplementation in high doses can lead to GI side effects

Relative Carnitine Deficiency in Autism

Pauline A. Filipek,[1,2] Jenifer Juranek,[1] Minh T. Nguyen,[1] Christa Cummings,[1] and J. Jay Gargus[1,3,4]

Values of free and total carnitine ($p < 0.001$), and pyruvate ($p = 0.006$) were significantly reduced while ammonia and alanine levels were considerably elevated ($p < 0.001$) in our autistic subjects. The relative carnitine deficiency in these patients, accompanied by slight elevations in lactate and significant elevations in alanine and ammonia levels, is suggestive of mild mitochondrial dysfunction. It is hypothesized that a mitochondrial defect may be the origin of the carnitine deficiency in these autistic children.

Filipek et al., 2004 J Autism Dev Disord 34(6):615-23

Medium-term open label trial of L-carnitine in Rett syndrome

Carolyn J. Ellaway[a,b], Jennifer Peat[c], Katrina Williams[b,c], Helen Leonard[d], John Christodoulou[a,b,*]

Compared with the Rett syndrome controls, treatment with L-carnitine led to significant improvements in sleep efficiency (P=0.027), especially in the subjects with a baseline sleep efficiency less than 90%, energy level (P<0.005) and communication skills (P=0.004). In addition, before and after comparisons of the treatment group showed improvements in expressive speech (P=0.011).

Ellaway et al., 2001 Brain and Develop 23:S85-89

Prostaglandins, Leukotrienes and Essential Fatty Acids (2002) 67(1), 33–38

doi:10.1054/yplef.378, available online at http://www.idealibrary.com on IDEAL®

Efficacy of carnitine in the treatment of children with attention-deficit hyperactivity disorder

Randomized, double-blind, placebo-controlled double-crossover trial. In 13/24 boys receiving carnitine, home behavior improved as assessed with the CBCL total score (P<0.02). In 13/24 boys, school behavior improved as assessed with the Conners teacher-rating score (P<0.05). Treatment with carnitine significantly decreased the attention problems and aggressive behavior in boys with ADHD.

Van Oudhesden et al., 2002 Prostaglandins Leukot Essent Fatty Acids 67(1):33-8

Mitochondrial biogenesis

- When energy needs of a cell are high, mitochondria divide
- Increased ROS triggers mtDNA proliferation; nDNA can also trigger increased mitochondrial division
- If mitochondrion cannot maintain ATP production, then undergoes apoptosis
- Cells normally remove old mitochondria (autophagy) and synthesize new mitochondria (biogenesis)

Neuroscience 137 (2006) 493–504

OXYGEN-INDUCED MITOCHONDRIAL BIOGENESIS IN THE RAT HIPPOCAMPUS

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1972; Balentine, 1982). The mechanisms of Cl
icity, although not fully understood, involve the
of reactive oxygen and nitrogen species (ROS
that disrupt the brain's oxidant/antioxidant bala
chenko et al., 2002). This imbalance promotes
ecule oxidation, including lipids, enzymes, and
ids, which in theory produces the neurocher
ations and manifestations of toxicity (Jamies
Fridovich, 1998).

days. The finding that O_2 activates regional mitochondrial DNA transcription, replication, and mitochondrial biogenesis in the hippocampus may have important implications for maintaining neuronal viability after brain injury. © 2005 IBRO.

Gutsaeva et al., 2006 Neuroscience 137:493-504

Oxygen treatment restores energy status following experimental neonatal hypoxia-ischemia

Hyperbaric oxygen and normobaric oxygen both attenuated brain injury, restored the levels of adenosine triphosphate and phosphocreatine, decreased the levels of the glycolytic intermediates, and increased the utilization of energy. These results suggest that oxygen treatment during the initial period of recovery from a hypoxia-ischemic insult is able to attenuate energy deficits in the brain, which ultimately leads to a reduction in brain injury.

Calvert and Zhang 2007 Pediatr Cri Care Med 8(2):165-73

Mito Websites

- www.mitosoc.org: diagnosis
- www.mitomap.org: mtDNA mutations
- www.umdf.org: United Mitochondrial Disease Foundation
- www.cdc.gov/ncbddd/autism/mitochondrial.htm