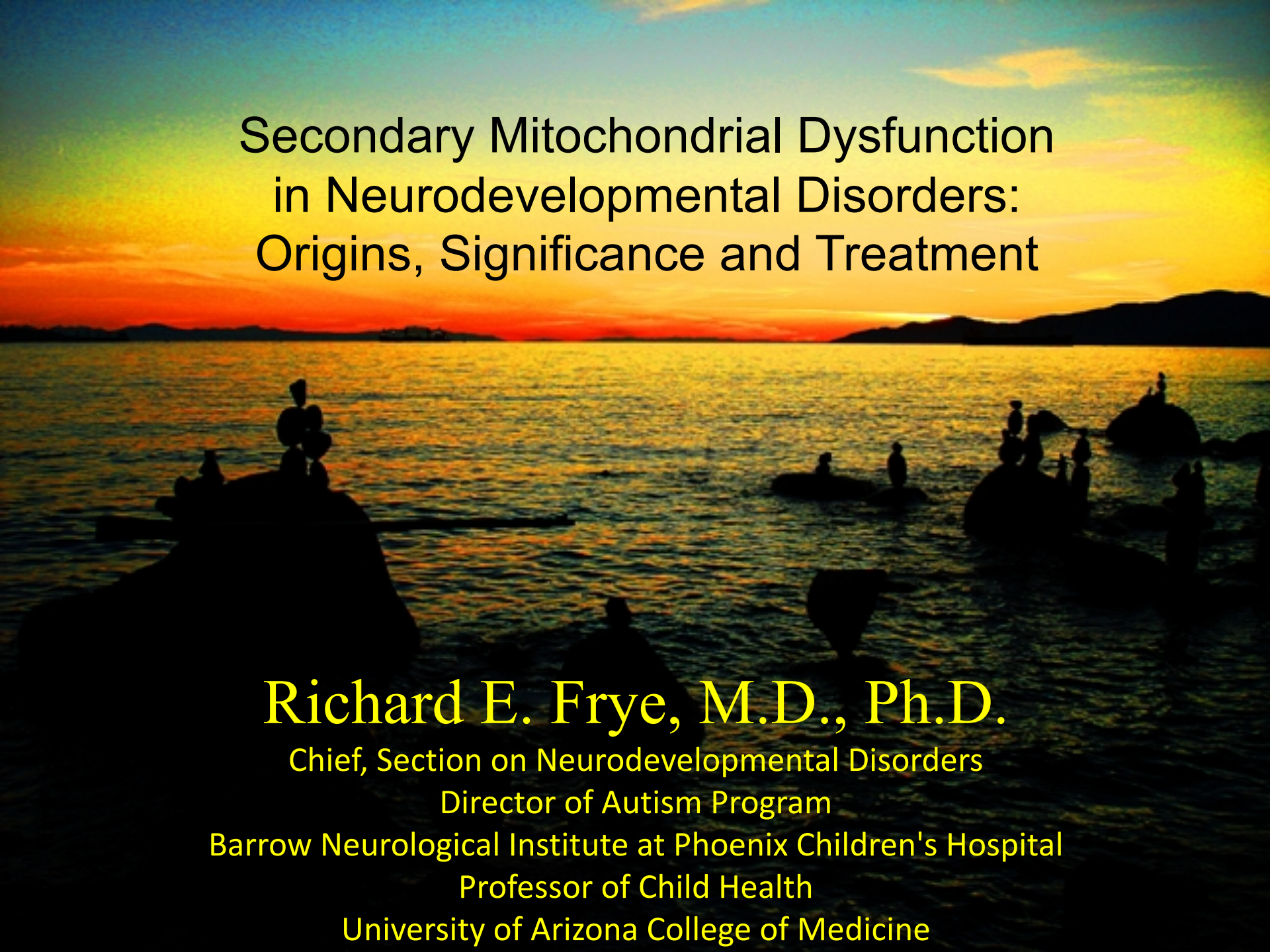


Secondary Mitochondrial Dysfunction in Neurodevelopmental Disorders: Origins, Significance and Treatment

Richard E. Frye, M.D., Ph.D.

Chief, Section on Neurodevelopmental Disorders

Director of Autism Program

Barrow Neurological Institute at Phoenix Children's Hospital

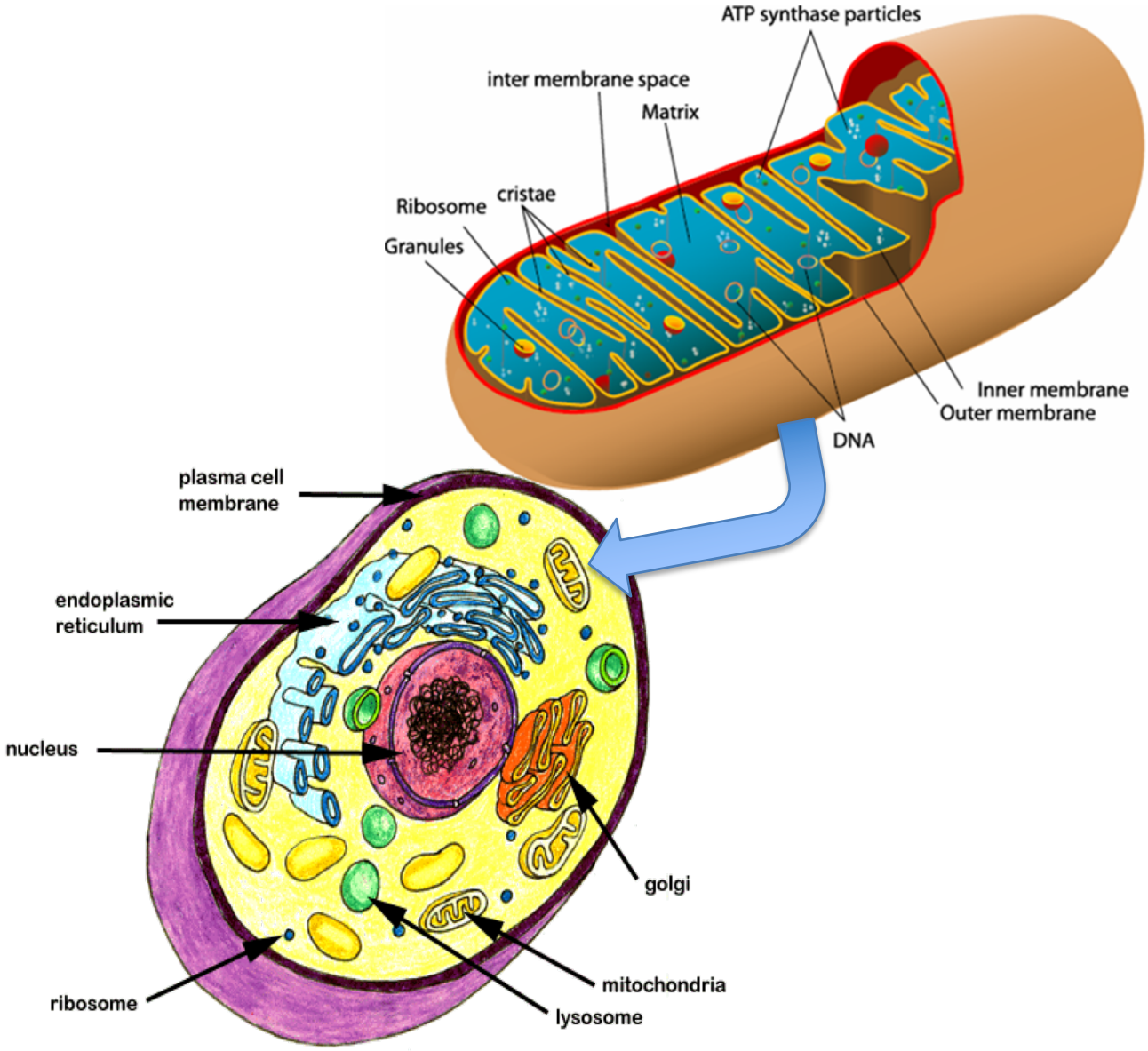
Professor of Child Health

University of Arizona College of Medicine

Disclaimer

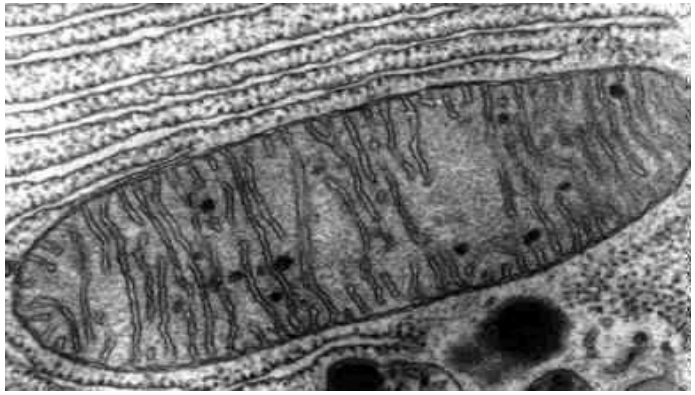
Every attempted has been made to make this presentation as accurate as possible. The information is provided without any expressed or implied warranty. This presentation should not be substituted for medical advice. Treatments in this lecture are considered off-label and are not FDA-approved.

Mitochondrial Dysfunction



Mitochondrial Disease

- Relatively new field
- First diseases described in 1988
  - Wallace, Leber's hereditary optic neuropathy, published in Science
  - Holt, Mitochondrial Myopathy, published in Nature
- Usually defined by extremely clinical symptoms with a progressive course
  - High energy dependent tissues
  - Neurological Disease
  - Gastrointestinal Disease
  - Immune Dysfunction
- Not just powerhouse, involved in
  - programmed (apoptotic) cell death
  - Oxygen Radical Regulation



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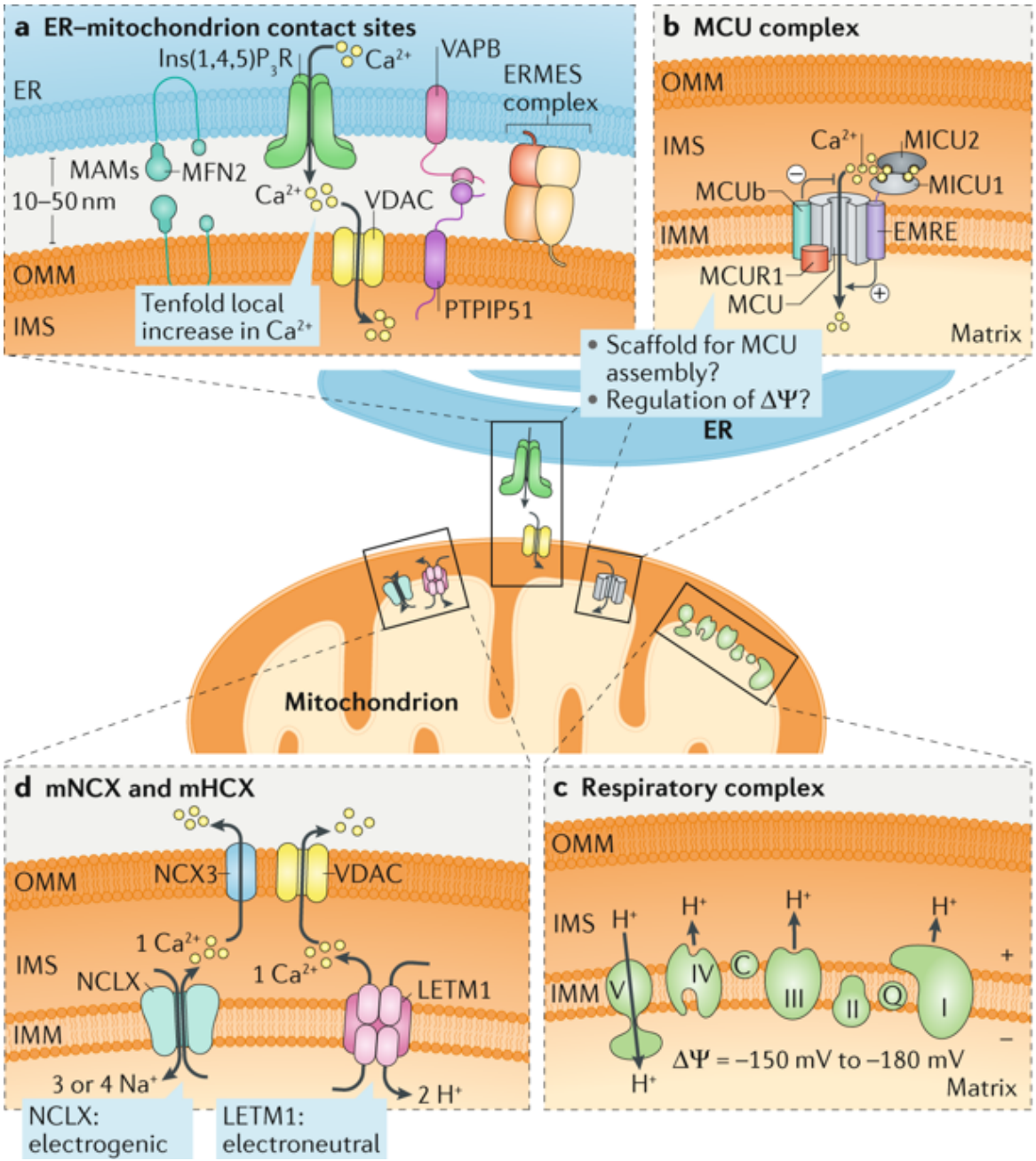
Mitochondrial Dysfunction



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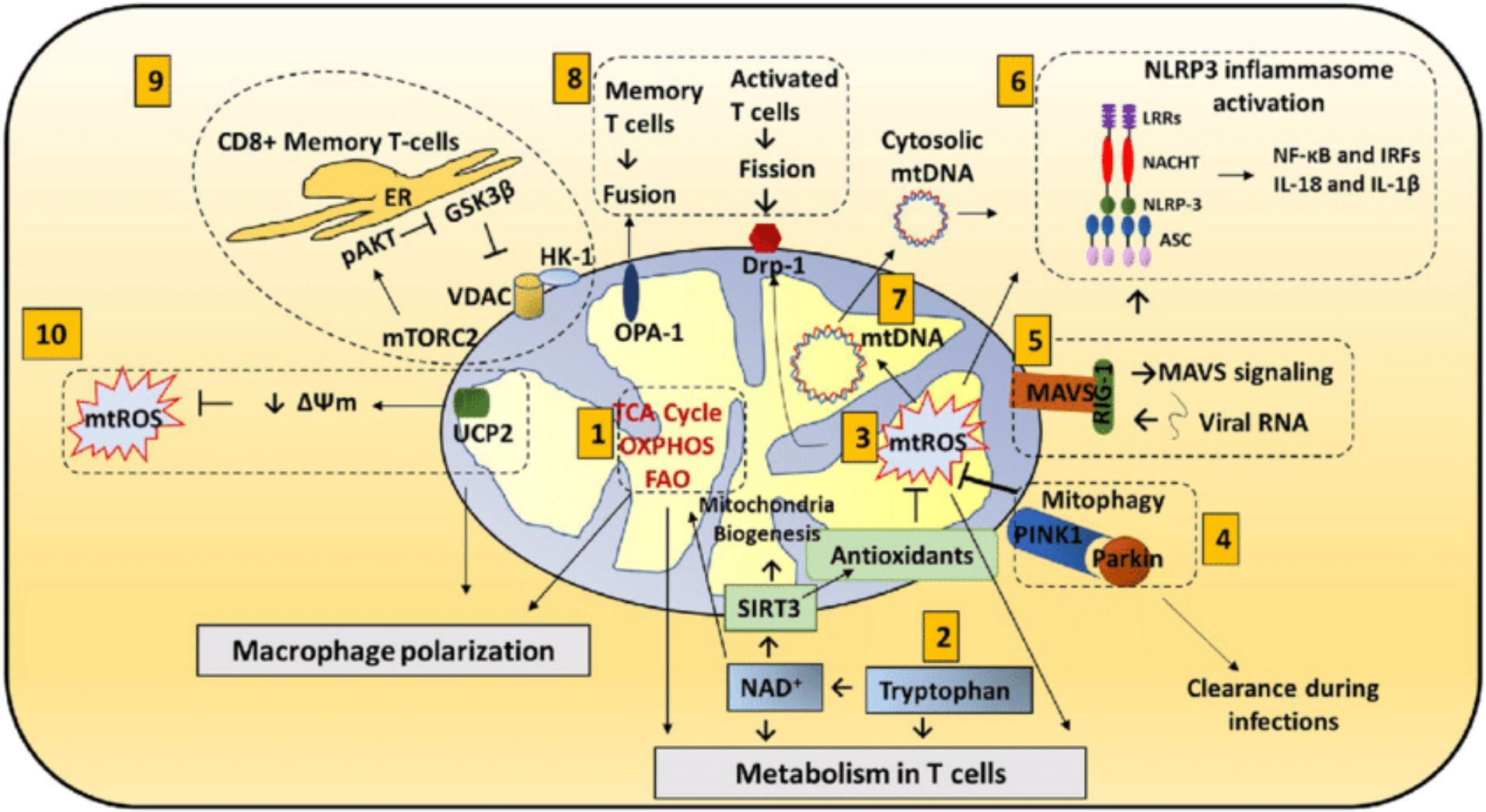
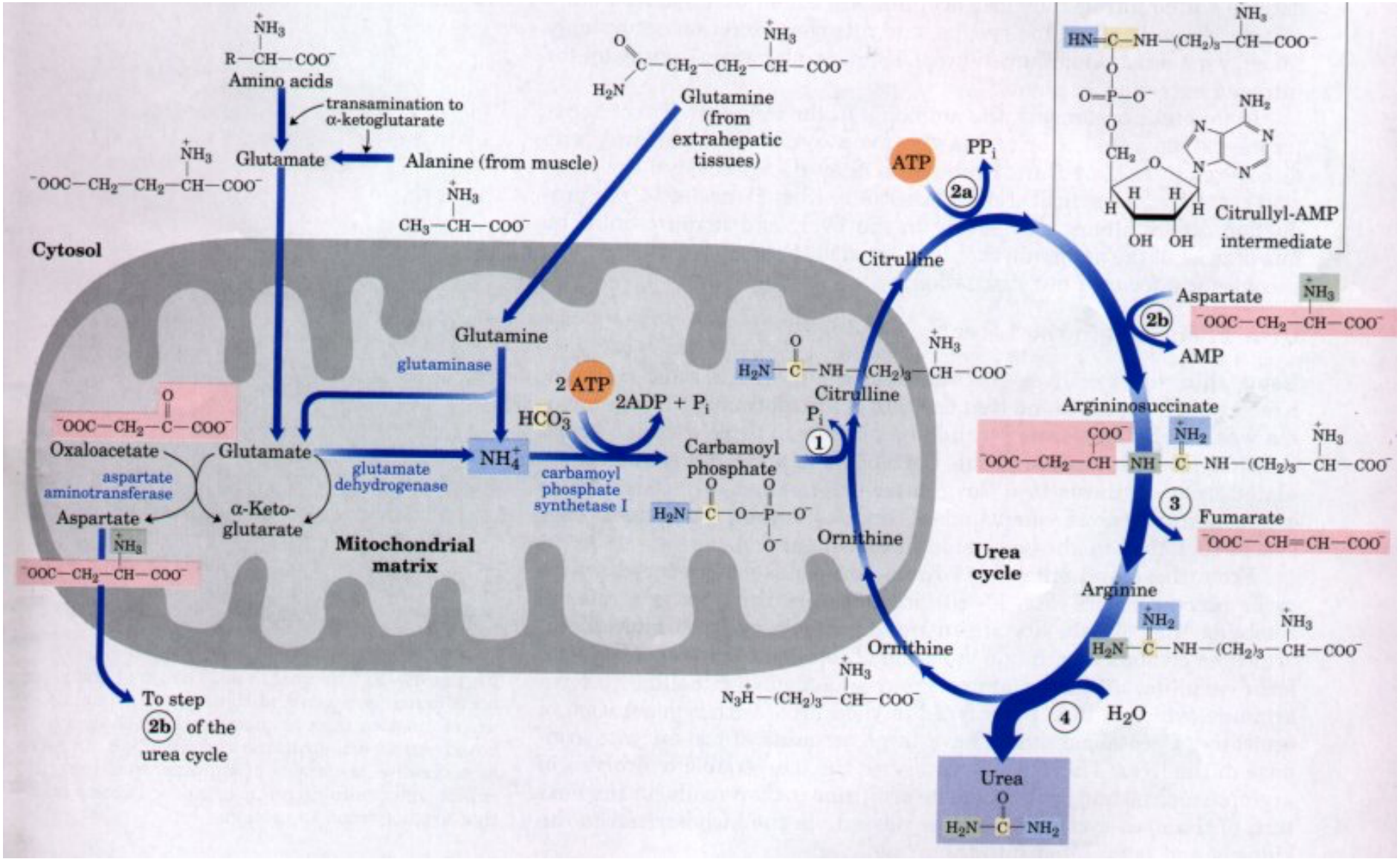
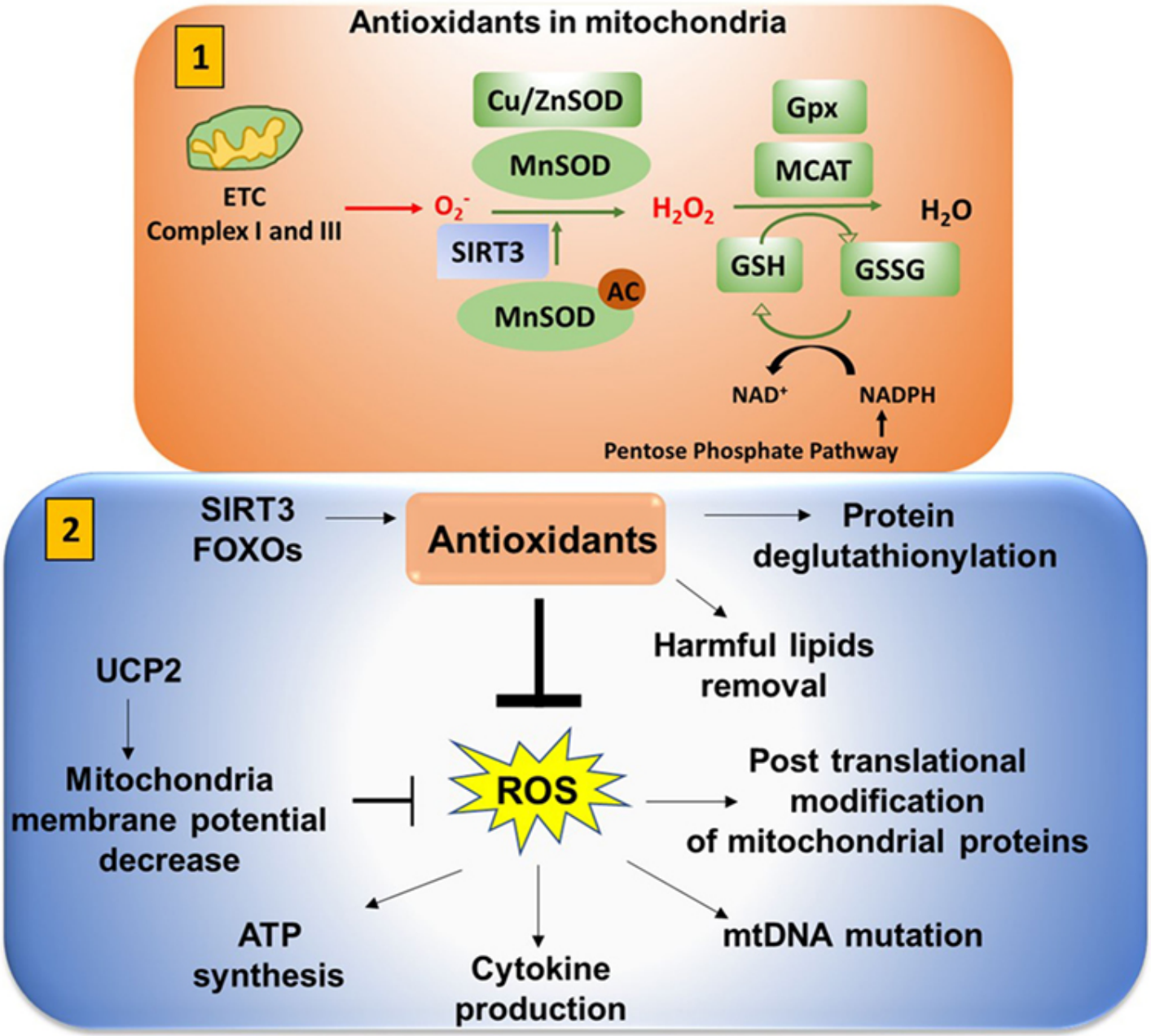
Mitochondrial Dysfunction



Mitochondrial Dysfunction

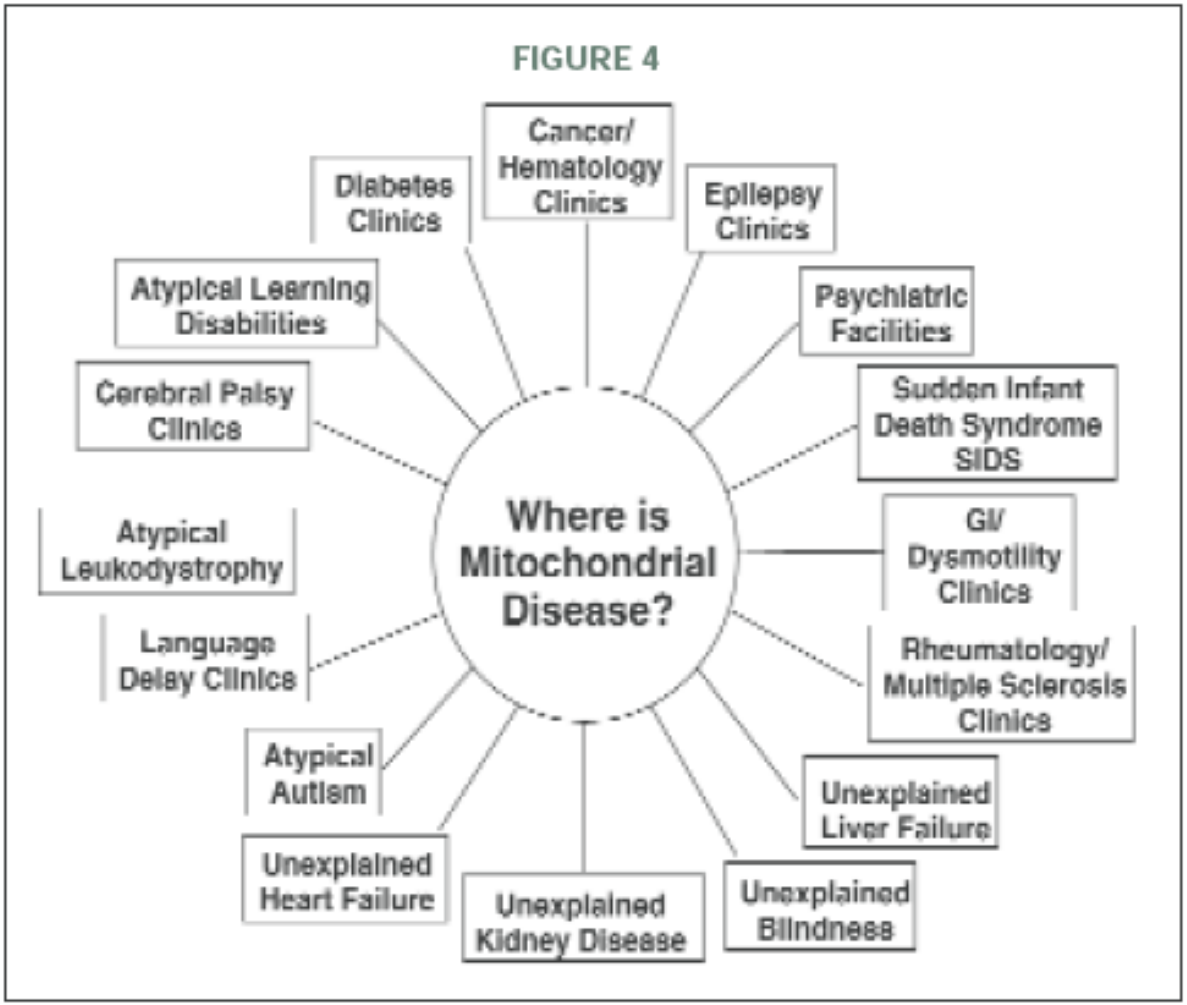


Mitochondrial Dysfunction



Mitochondrial Dysfunction

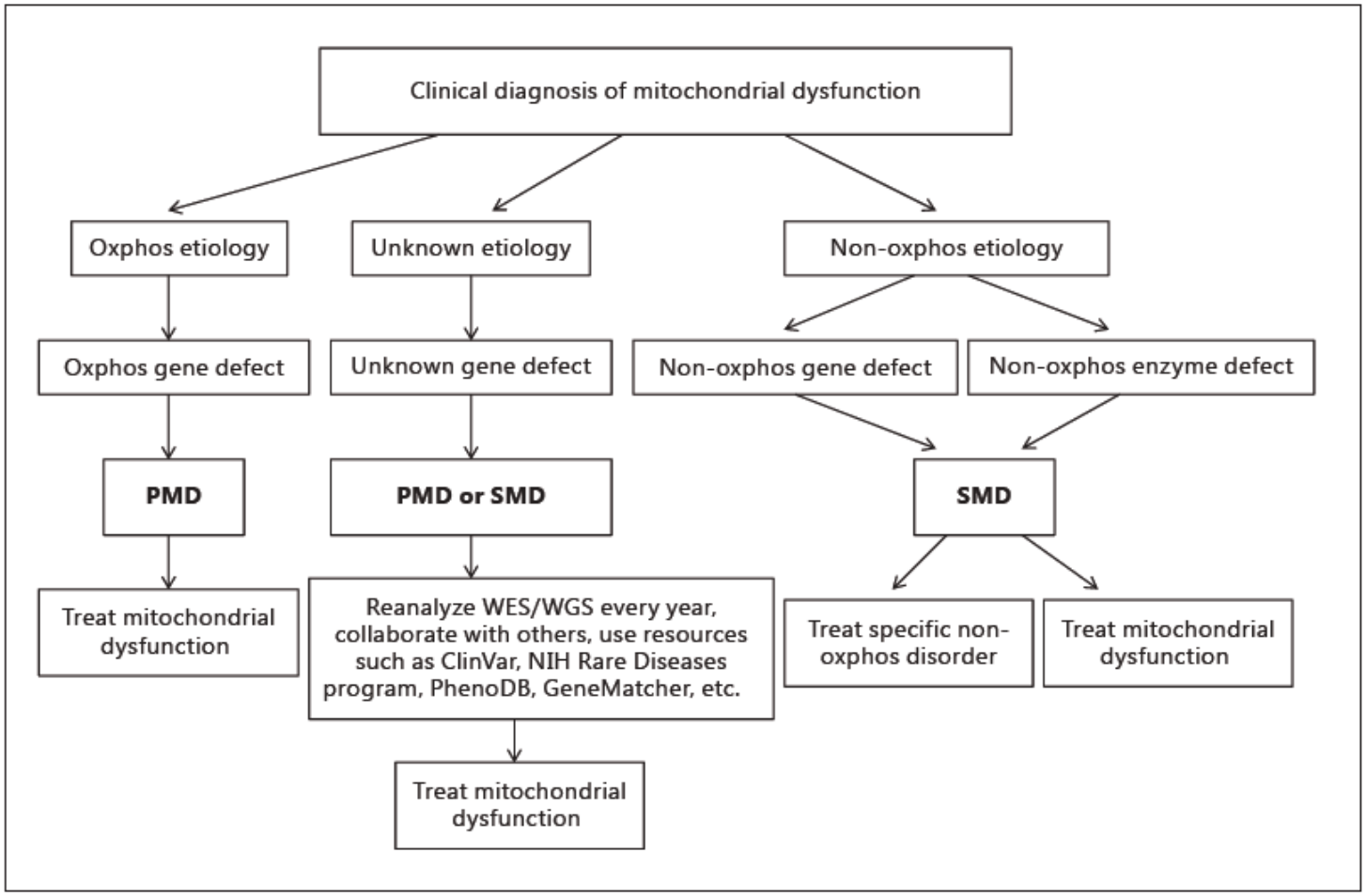
Now believed to that Mitochondrial Dysfunction is Important in Many Diseases



Primary Mitochondrial Disease and Secondary Mitochondrial Dysfunction: Importance of Distinction for Diagnosis and Treatment

Mol Syndromol
DOI: 10.1159/000446586

Dmitriy M. Niyazov[a] Stephan G. Kahler[b] Richard E. Frye[b]



Mitochondrial Dysfunction in Autism

Mitochondrial Dysfunction

Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis

DA Rossignol[1] and RE Frye[2] Mol Psych 2012, 17:290-314

	Studies	Total N	Overall prevalence
General ASD population			
Mitochondrial disease in ASD	3	536	5.0% (3.2%, 6.9%)
Elevated lactate	6	479	31.1% (27.0%, 35.3%)
Elevated pyruvate	2	110	13.6% (7.2%, 20.1%)
Elevated lactate/pyruvate ratio	1	192	27.6% (21.2%, 33.9%)
Elevated alanine	1	36	8.3% (0.0%, 20.1%)
Low total carnitine	1	30	90.0% (81.0%, 99.0%)
Elevated creatine kinase	1	47	46.8% (32.4%, 61.2%)
Elevated ammonia	1	80	35.0% (24.5%, 45.5%)
Elevated AST	1	147	45.6% (37.5%, 53.7%)[a]
Elevated ALT	1	87	7.0% (0.5%, 13.5%)

Discrepancy between prevalence of diagnosed mitochondrial disease and prevalence of biomarkers of mitochondrial disease likely be due to criteria used to define mitochondrial disease

Biomarker	Number of studies	ASD Total N	ASD Mean (95% CI)	Control Total N	Control Mean (95% CI)	F-value	Hedge's g (CI)
Lactate (mM l^{-1})	5	114	1.73 (1.61, 1.88)	114	0.91 (0.87, 0.96)	8.72†	1.42 (0.92, 1.92)†
Pyruvate (nM l^{-1})	1	24	0.12 (0.11, 0.14)	24	0.06 (0.06, 0.06)	20.25†	1.96 (0.85, 3.08)†
Carnitine (mg ml^{-1})	1	30	3.83 (3.44, 4.31)	30	6.40 (6.22, 6.62)	4.61†	2.51 (1.61, 3.42)†
Ubiquinone	1	15	91.4 (81.9, 103.0)	15	144.2 (130.4,161.1)	2.13	1.90 (0.79, 3.01)†

Mitochondrial Dysfunction

Mitochondrial Dysfunction in Autism

Cecilia Giulivi, PhD
Yi-Fan Zhang, BS
Alicja Omanska-Klusek, MS
Catherine Ross-Inta, BS
Sarah Wong, BS
Irva Hertz-Picciotto, PhD
Flora Tassone, PhD
Isaac N. Pessah, PhD

JAMA, December 1, 2010—Vol 304, No. 21 **2389**

- Lymphocytes from 10 children with autism and 10 age and gender matched controls
- 80% demonstrated abnormal function in at least one electron transport chain complex
  - 60% complex I abnormality
  - 40% complex V abnormality
  - 50% multiple complexes
- 20% demonstrated abnormalities in cytB, a mitochondrial DNA gene

Mitochondrial Dysfunction

Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis

DA Rossignol[1] and RE Frye[2] Mol Psych 2012, 17:290-314

ASD children with mitochondrial disease have more medical abnormalities than idiopathic ASD children

Only 23% of ASD children with mitochondrial disease have mitochondrial DNA abnormalities

	ASD/MD		*General ASD*			*General MD*		
	%	N	%	χ^2	P	%	χ^2	P
Male	61	72	81	18.7	<0.0001	58	0.26	0.61
Developmental regression	52	83	25	32.3	<0.0001	60	2.2	0.14
Seizures	41	86	11	79.1	<0.0001	33	2.48	0.11
Hypotonia	62	55	51	2.6	0.10	67	0.62	0.43
Fatigue/lethargy	54	61				19	48.6	<0.0001
Ataxia	58	19				13	34.0	<0.0001
Growth delay	21	73						
Motor delay	51	79	9	170.1	<0.0001			
GI abnormalities	74	35	20	63.8	<0.0001	39	18.0	<0.0001
Cardiomyopathy	24	38				26	0.1	0.79
Myopathy	0	12				11	1.5	0.22
Elevated lactate	78	50	31	51.6	<0.0001	54	12.4	<0.001
Elevated pyruvate	45	22	14	17.6	<0.0001			
Elevated lactate/pyruvate ratio	43	23	28	2.6	0.11			
Abnormal organic acids	36	36						
Elevated creatine kinase	34	29	47	1.96	0.16			
Elevated alanine	32	28						
Abnormal brain imaging	23	69				70	72.6	<0.0001
Normal ETC activity	16	69				3	40.1	<0.0001
Abnormal complex I	53	96				45	2.48	0.12
Abnormal complex II	9	65				8	0.09	0.76
Abnormal complex III	30	96				31	0.04	0.83
Abnormal complex IV	20	97				34	8.47	0.004
Abnormal complex V	23	44				12	5.0	0.03
Multiple complex deficiency	36	59				27	2.43	0.12
Elevated citrate synthase	24	17				44	2.76	0.10
Abnormal light microscopy	18	49				81	126.4	<0.0001
mtDNA abnormality	23	87				16	3.17	0.08

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

	II-1	II-2	I-1	II-3	II-4
I					
II					
Irritable bowel	–	–	+	–	–
Epilepsy	++	–	–	+	+
Learning disability	++	–	–	–	–
Cognitive regression	–	–		+	+++
Leigh syndrome	–	–	–	+++	–
Autism	–	–	–	–	+++
Brain Magnetic Resonance Imaging	Normal	Normal	ND	Abnormal	Normal
Muscle analysis	ND	ND	ND		
Histology				Normal	↑ Lipid
Histochemistry				COX–	Subsarcolemmal+
Biochemistry				↓ CIV & V	↑ CI
G3863A mitochondrial DNA mutation					
PCR analysis in blood	+	+	+	+	+
Percent in blood	ND	ND	28%	82%	60%
Percent in muscle	ND	ND	ND	86%	61%

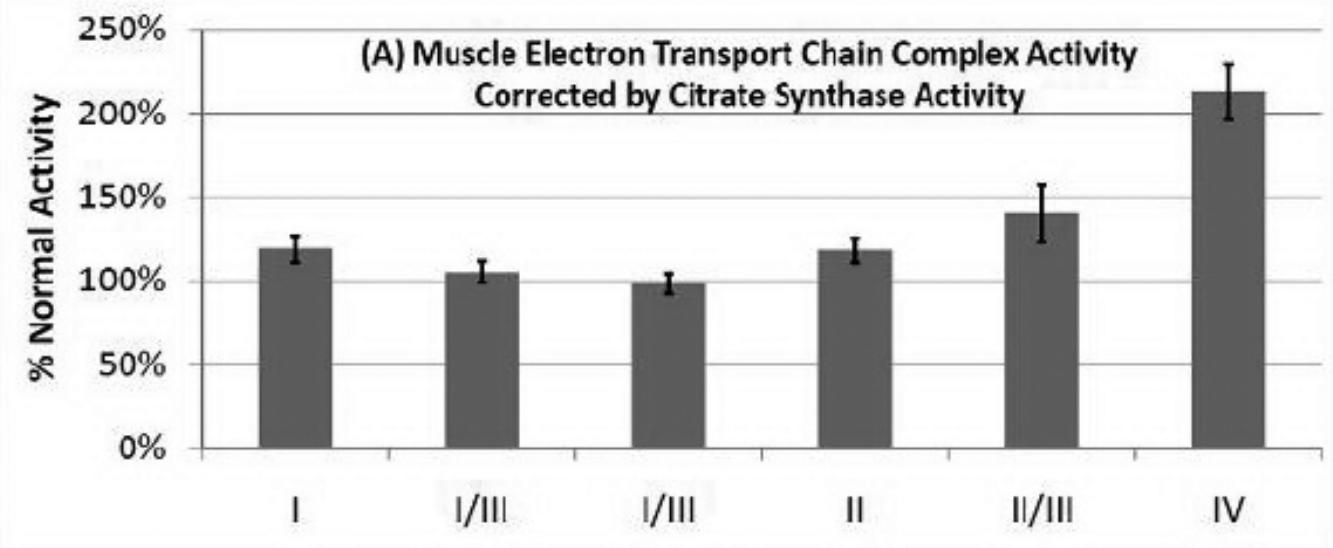
– = absent; + = mild; ++ = moderate; +++ = severe; ND = not determined; ↑ = increased, ↓ = decreased; C = citrate synthase corrected respiratory chain complex activity; COX– = absence of cytochrome *c* oxidase staining; PCR = polymerase chain reaction.

(*J Child Neurol* 2000;15:357–361).

Autistic disorder with complex IV overactivity: A new mitochondrial syndrome

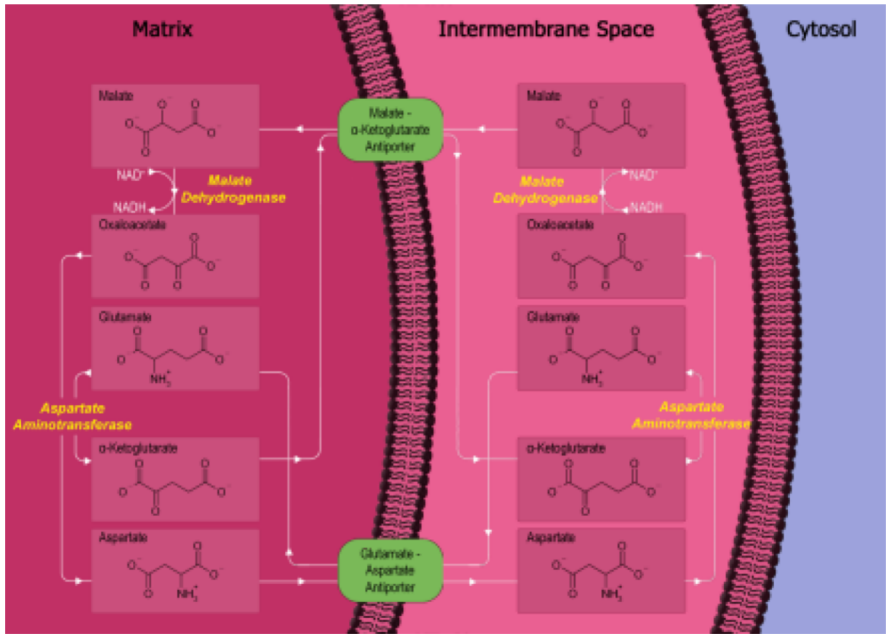
Journal of Pediatric Neurology 9 (2011) 427–434

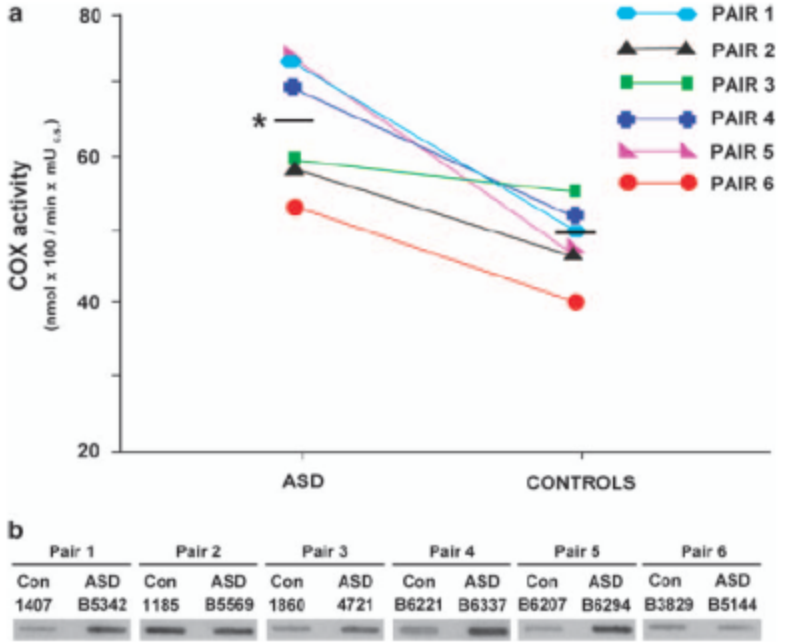
Richard E. Frye[a,*] and Robert K. Naviaux[b]



Mitochondrial Dysfunction

Altered calcium homeostasis in autism-spectrum disorders: evidence from biochemical and genetic studies of the mitochondrial aspartate/glutamate carrier AGC1



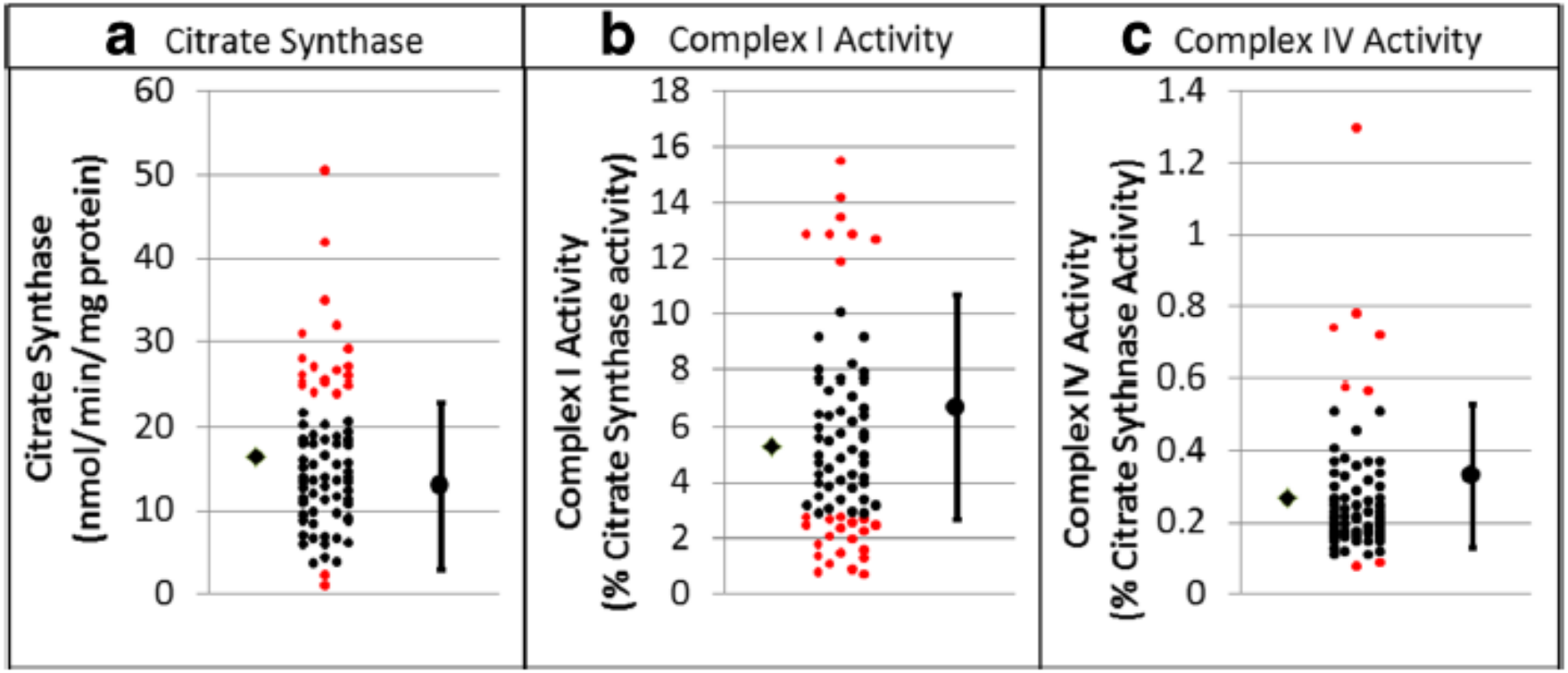


Mitochondrial Dysfunction

Bioenergetic variation is related to autism symptomatology

Leanna Delhey[1,2] · Ekim Nur Kilinc[1,2] · Li Yin[3] · John Slattery[1,2] · Marie Tippett[1,2] · Rebecca Wynne[1,2] · Shannon Rose[1,2] · Stephen Kahler[1,2] · Shirish Damle[4] · Agustin Legido[4] · Michael J. Goldenthal[4] · Richard E. Frye[1,2]

Metab Brain Dis
DOI 10.1007/s11011-017-0087-0



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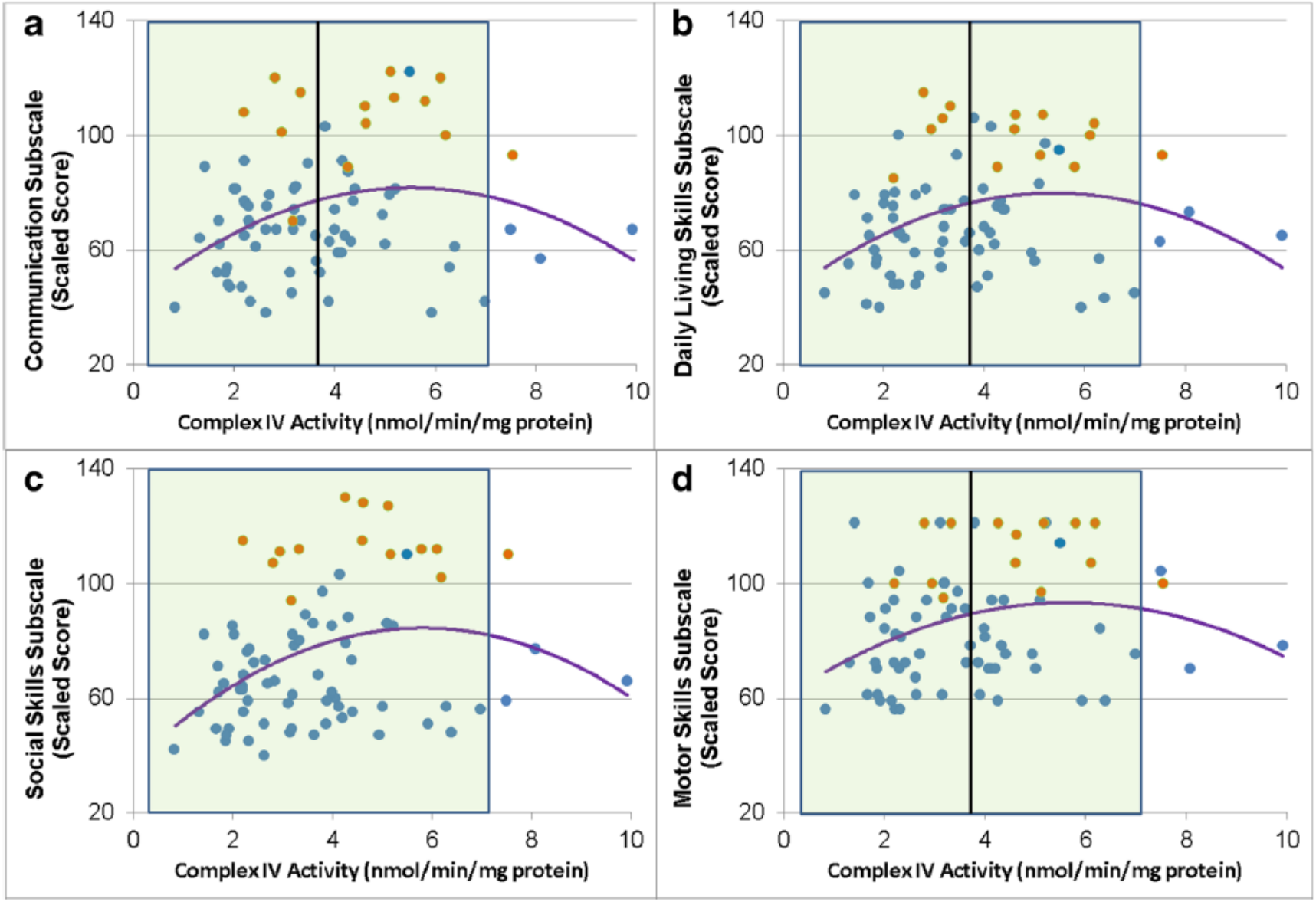
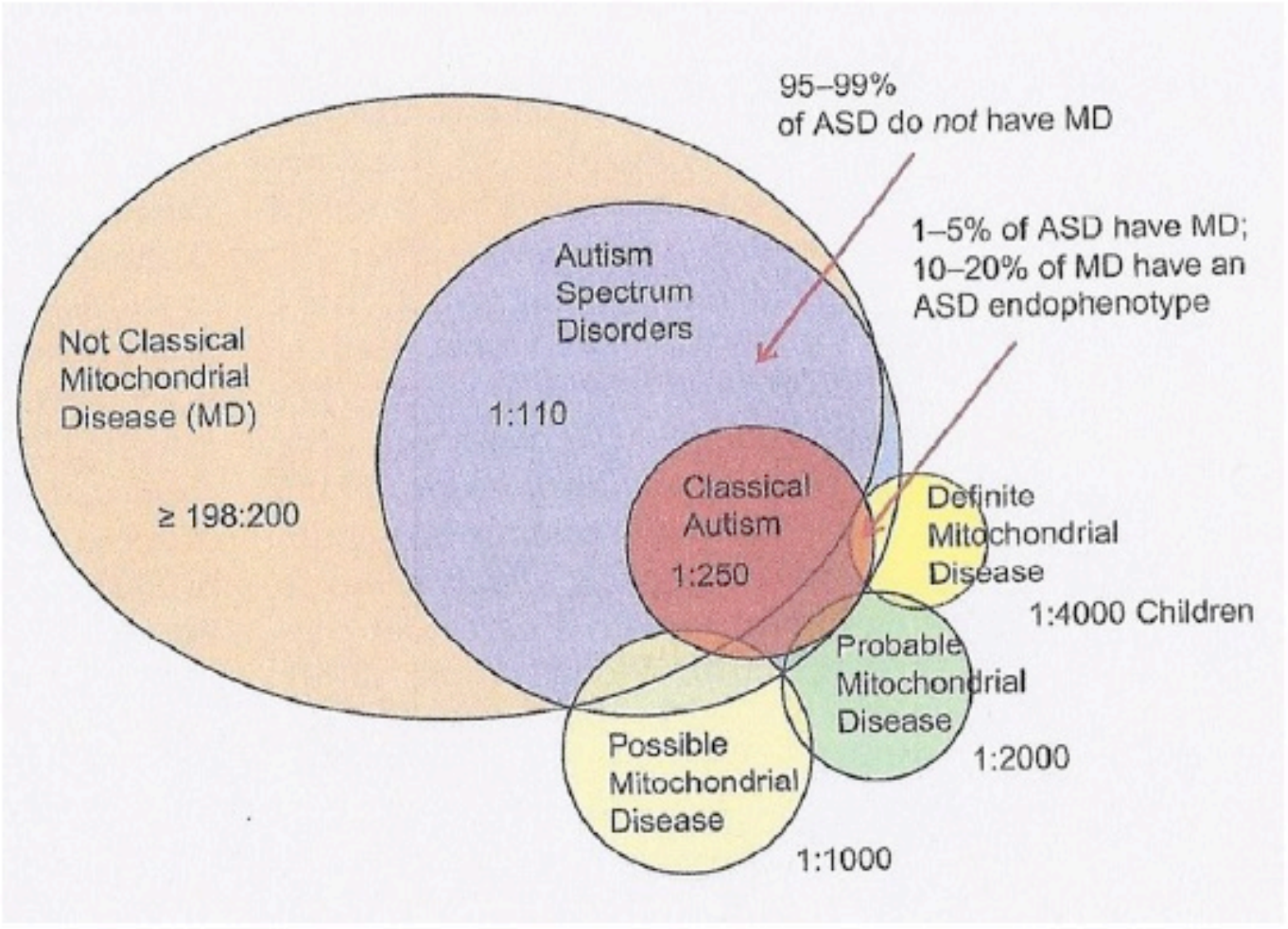
Mitochondrial Dysfunction



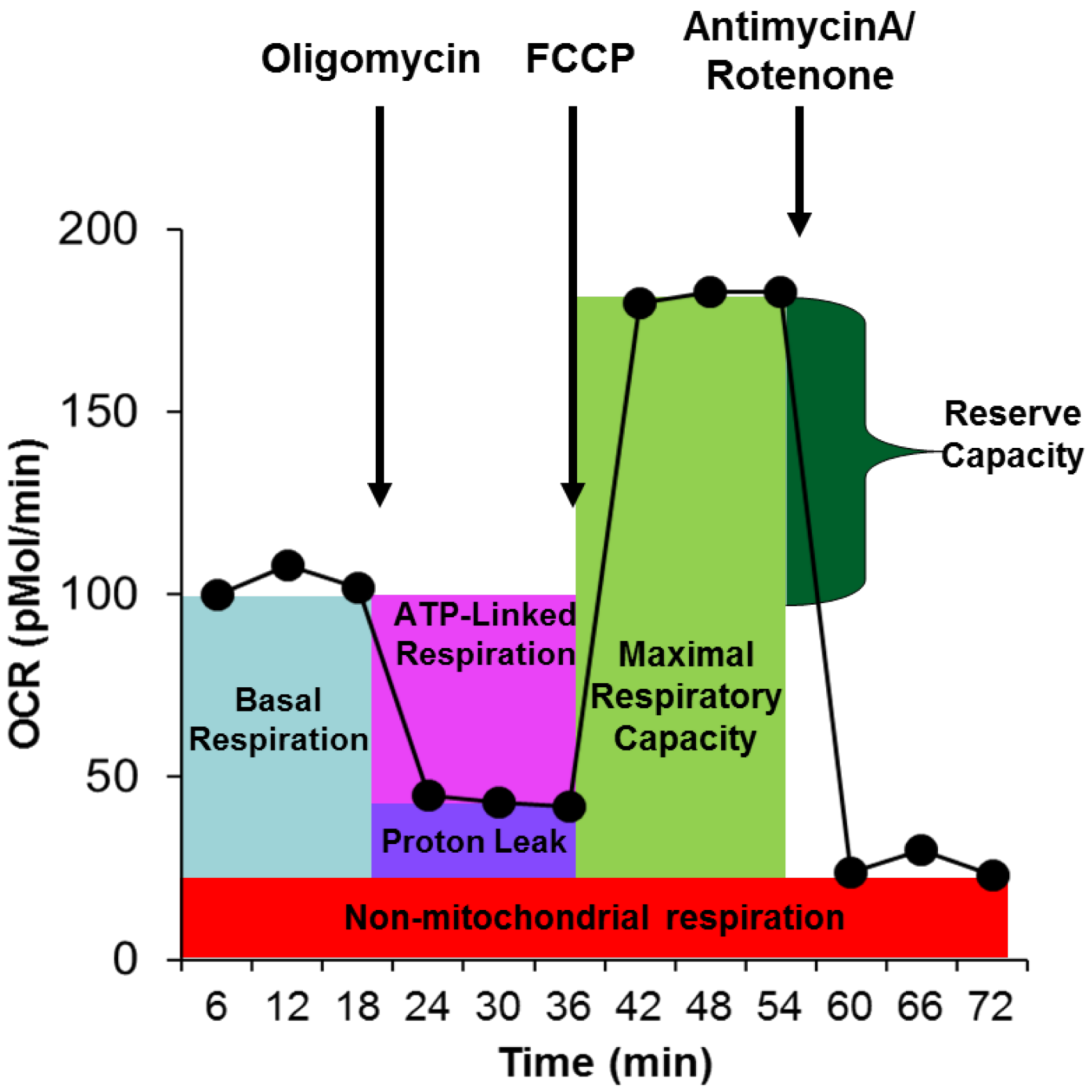
Mitochondrial Dysfunction



Seahorse Bioscience Extracellular Flux Analyzer

- Poly D lysine coated plates
- 110k cells/well
- Plated 1hr prior to assay
- Seahorse DMEM
  - 11mM glucose
  - 2mM glutamax
  - 1mM pyruvate
- DMNQ added directly to cells in plate
- Each plate with an AD/ Control LCL pair

Mitochondrial Dysfunction



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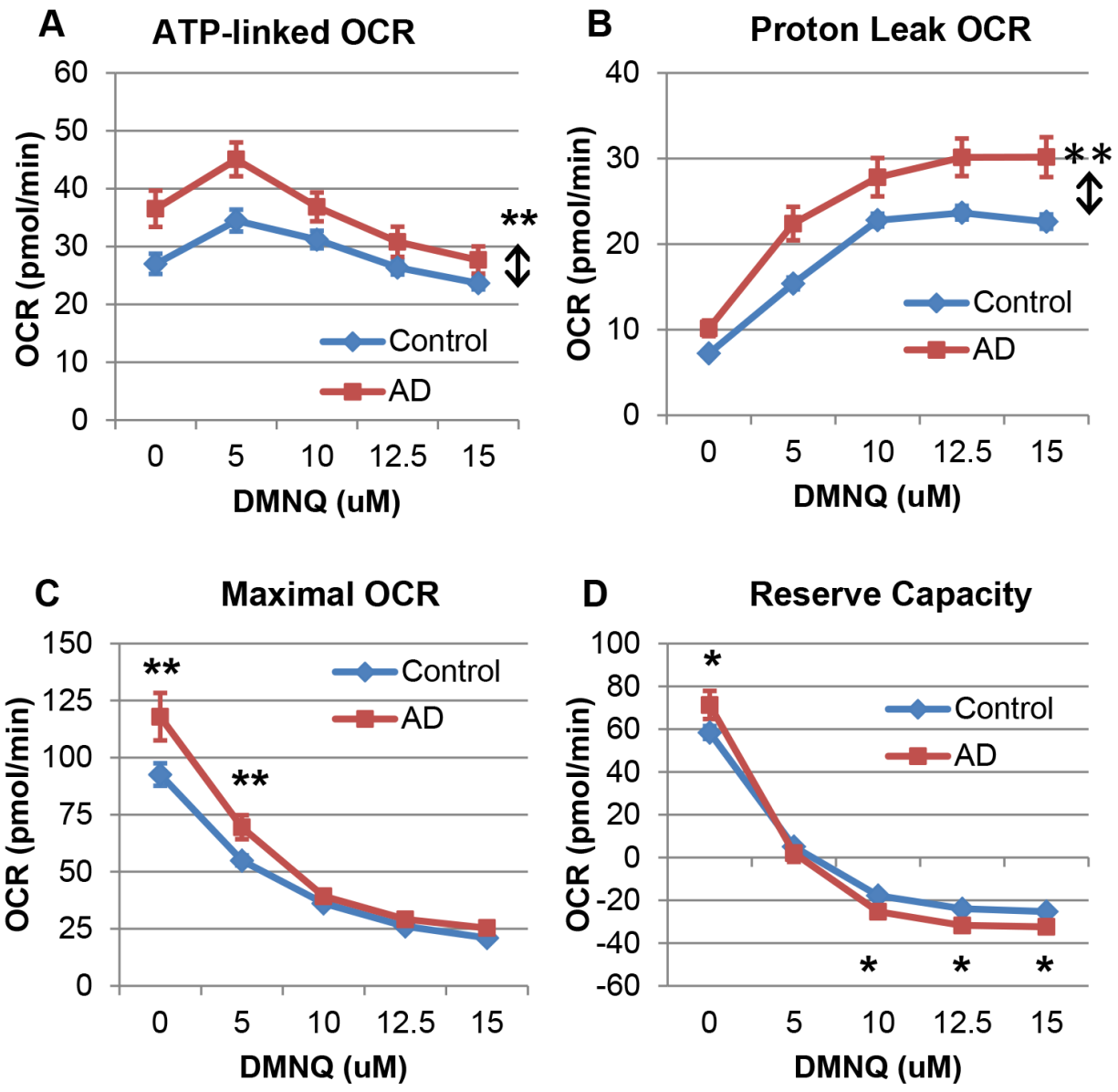
Mitochondrial Dysfunction



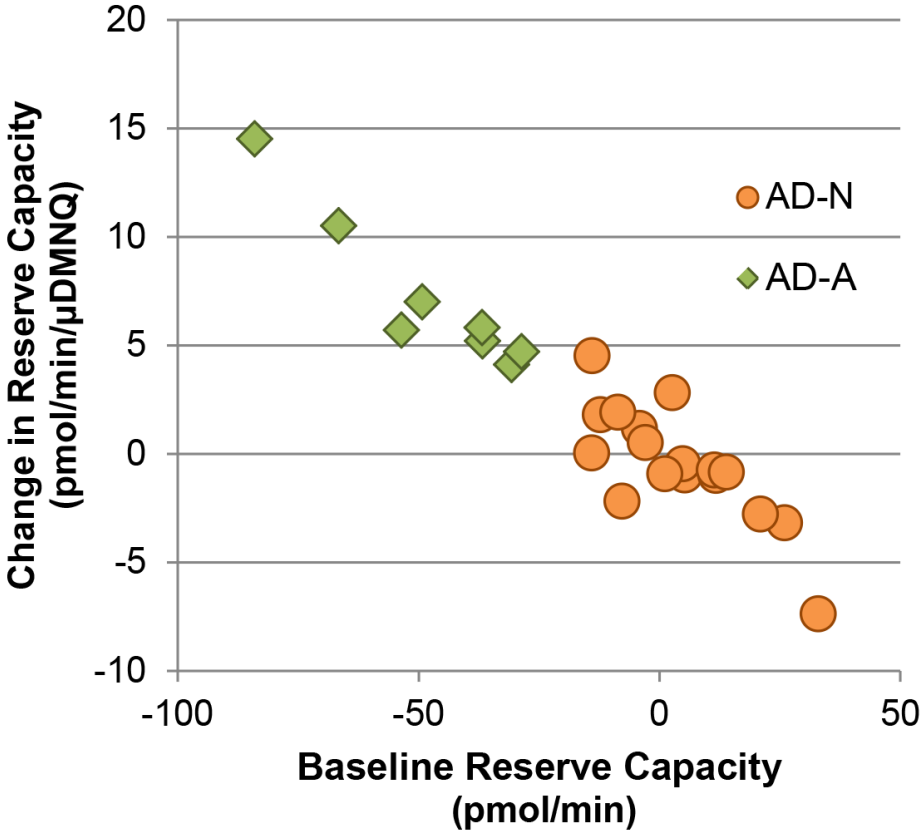
Mitochondrial Dysfunction

OPEN ACCESS Freely available online
PLOS ONE

Oxidative Stress Induces Mitochondrial Dysfunction in a Subset of Autism Lymphoblastoid Cell Lines in a Well-Matched Case Control Cohort

Shannon Rose, Richard E. Frye*, John Slattery, Rebecca Wynne, Marie Tippett, Oleksandra Pavliv, Stepan Melnyk, S. Jill James

Department of Pediatrics, Arkansas Children's Hospital Research Institute, Little Rock, Arkansas, United States of America



Cluster analysis reveals 2 significantly different subgroups.

- AD-N (n=17)
- AD-A (n=8)

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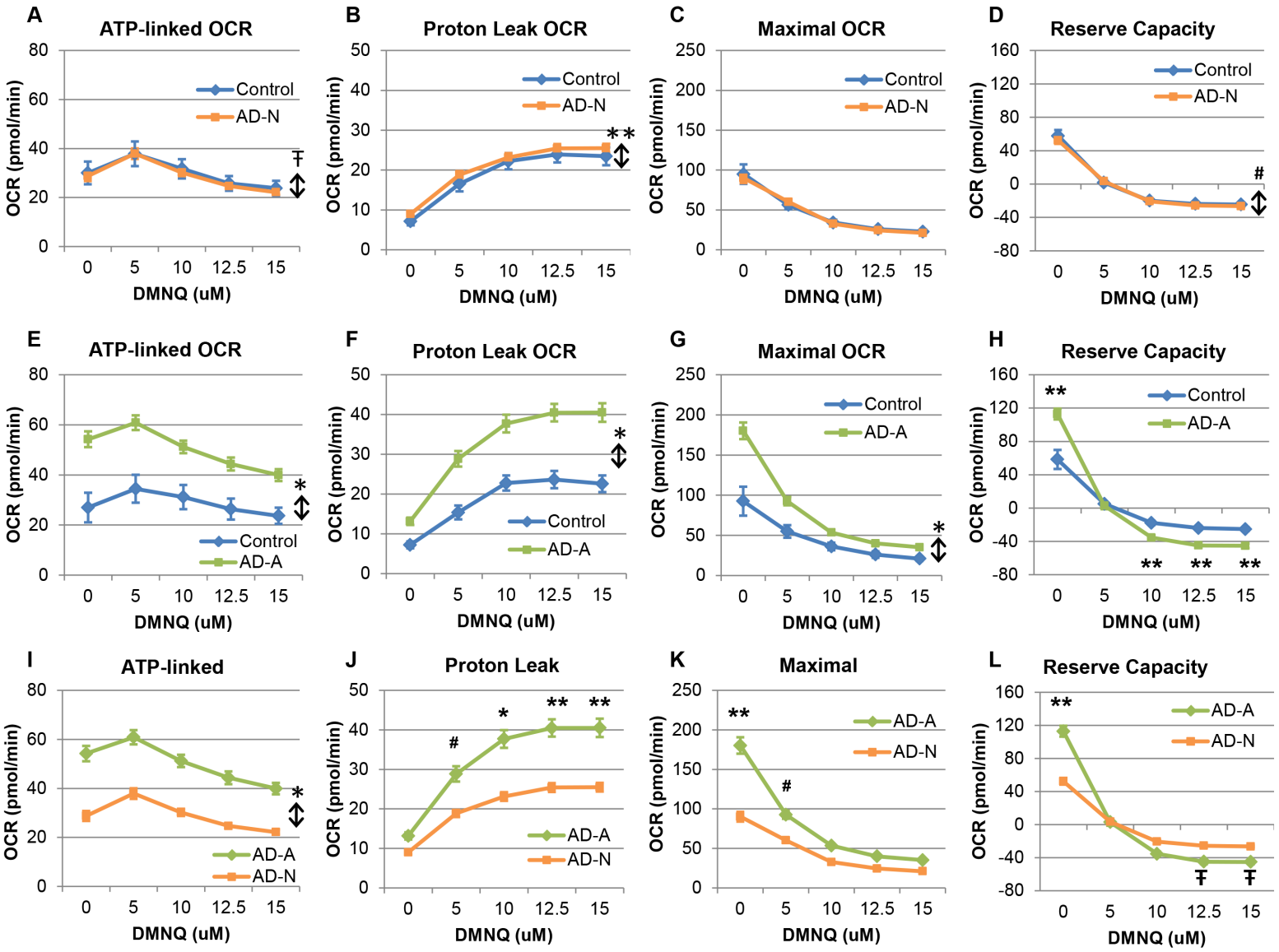
Mitochondrial Dysfunction



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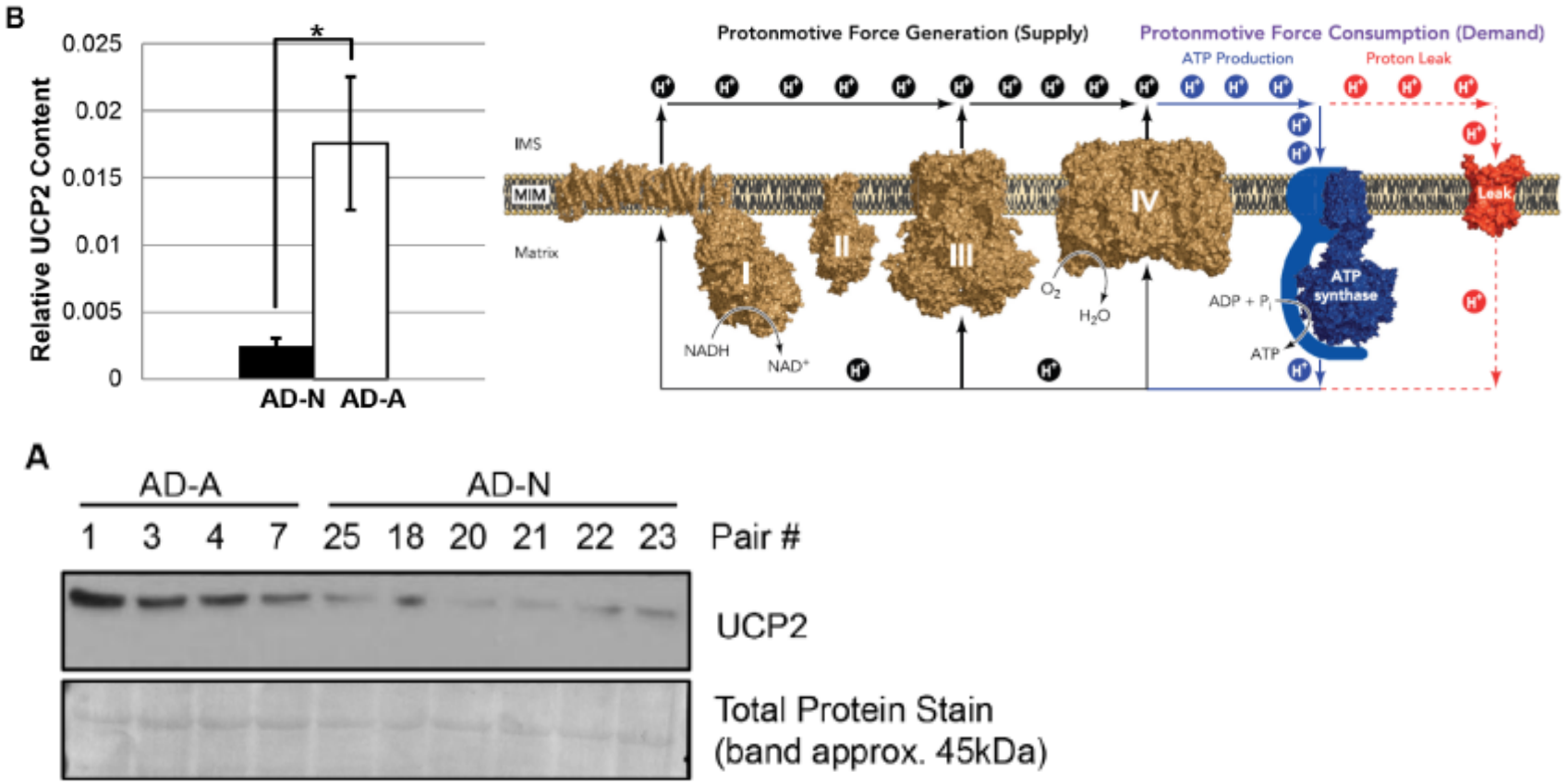
Mitochondrial Dysfunction



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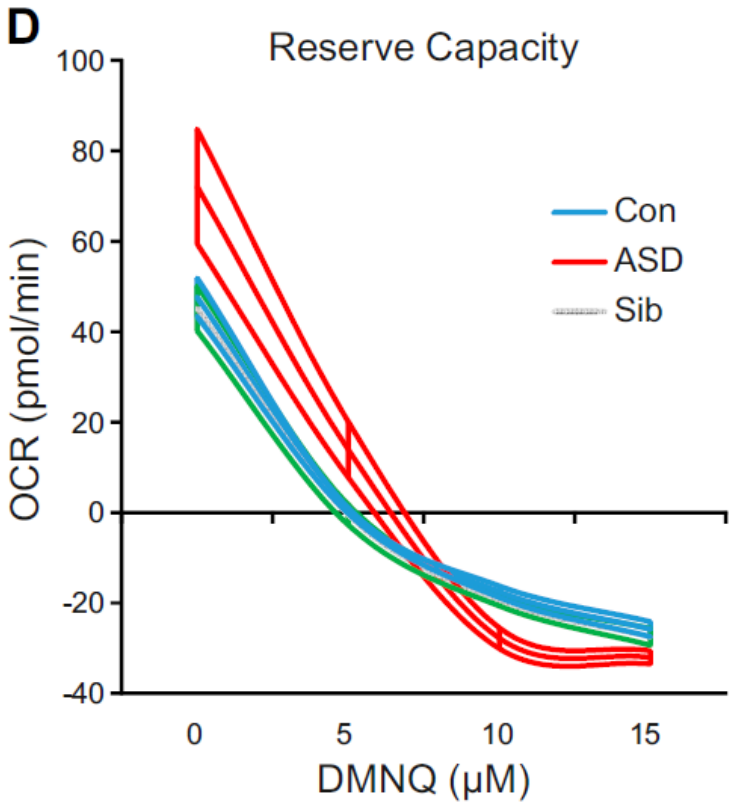
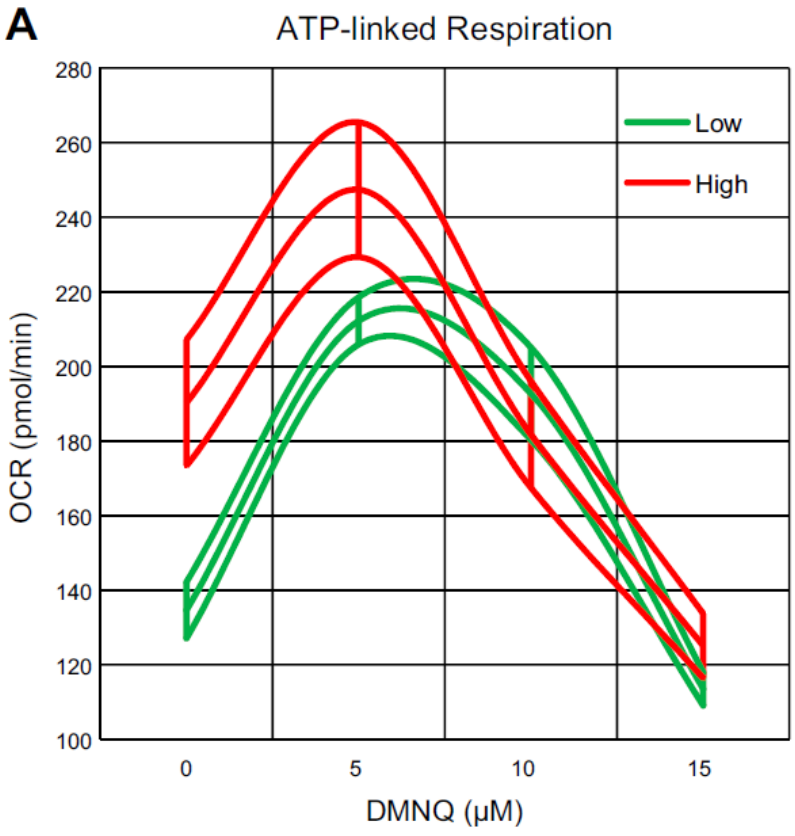
Mitochondrial and redox abnormalities in autism lymphoblastoid cells: a sibling control study

Shannon Rose,*,†,1 Sirish C. Bennuri,*,† Rebecca Wynne,*,† Stepan Melnyk,*,† S. Jill James,*,† and Richard E. Frye*,†





Mitochondrial Dysfunction in Autism

Mechanisms of Molecular Dysregulation

Mitochondrial Dysfunction

Differentiate Typical Development from Autism

Differentiate ASD from Sibling Controls
↓ ↓ miR-320a (PTEN)

Typically Developing Sibling Control

ASD

Differentiate ASD from Both Control Groups
↑ C, ↓S miR-92a (PTEN, CamKinase II)
↓ miR-181a (PTEN, T-Cell Fx)
↓ miR-181b (PTEN, T-Cell Fx)
↑ miR-191 (PTEN, NEURL4)

Differentiate ASD from Unrelated Controls
↑ miR-7a (IL6,IL10)
↓ miR-21 (IL1b,IL10)
↑ miR-26a (IL6,PTEN)
↓ miR-92a (PTEN, CamKinase II)
↑ miR-146b (IL6)

Typically Developing Nonrelated Control

Regulation of Mitochondrial Function

ASD Abnormal Mitochondrial Function

Differentiate Mitochondrial Subgroups
↑↑ miR-30d (CELSR3, SCN2A)
↑↑ miR-181b (PTEN, T-Cell Fx)
↓ miR-874 (MSR3, FMR1, HIF1AN)

ASD Normal Mitochondrial Function

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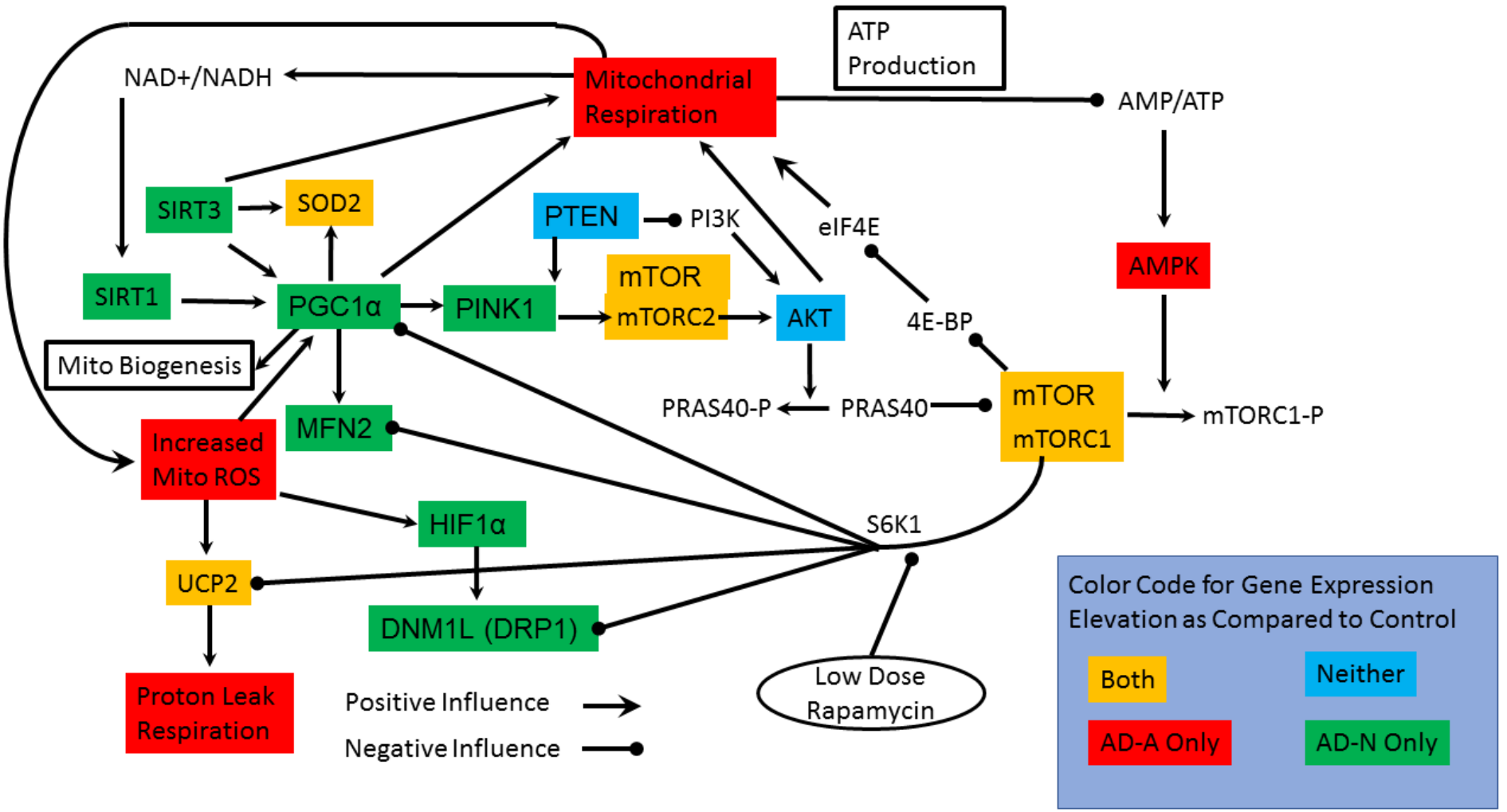
Mitochondrial Dysfunction



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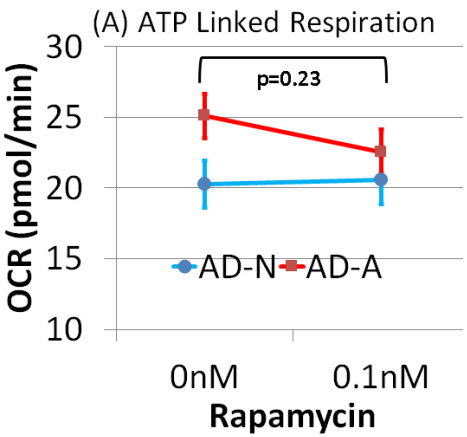
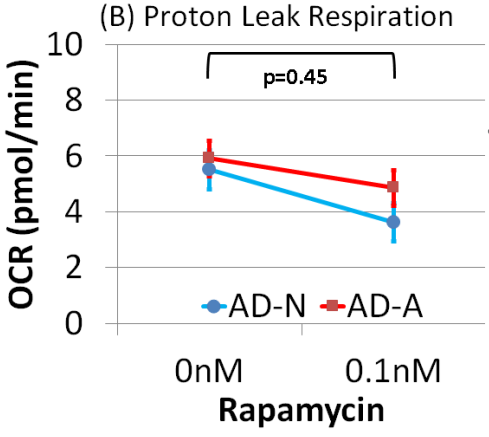
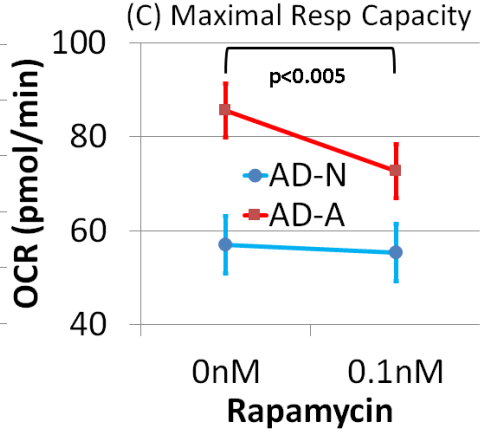
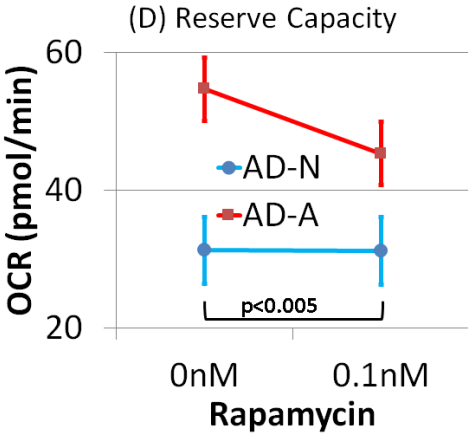
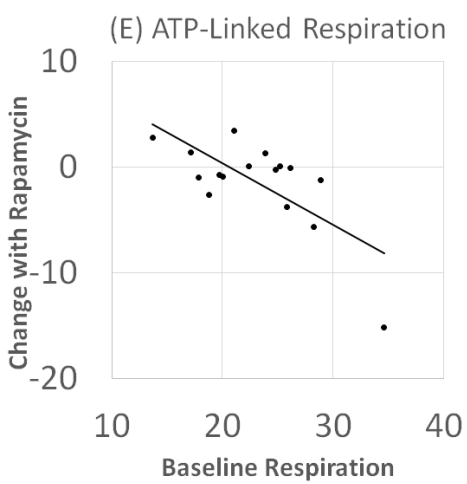
Mitochondrial Dysfunction

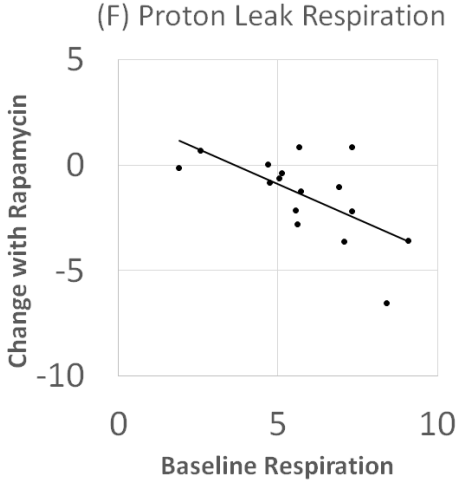


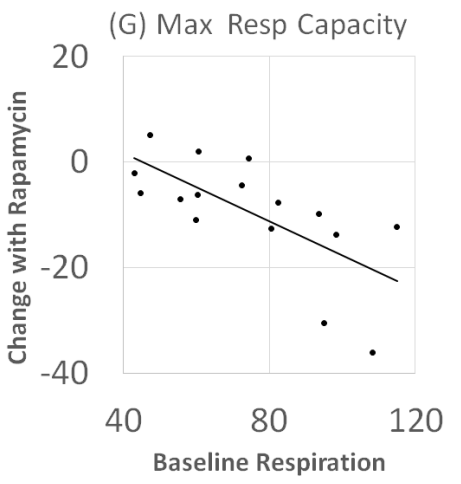


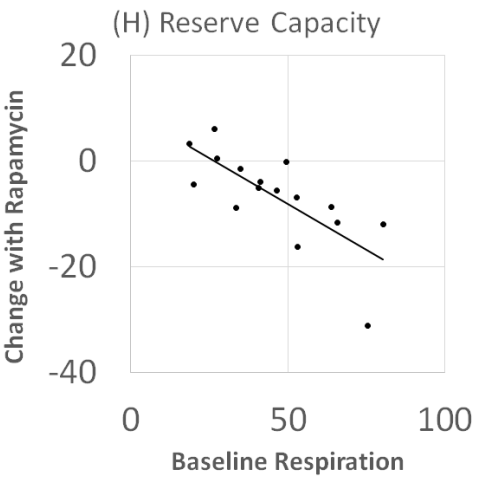








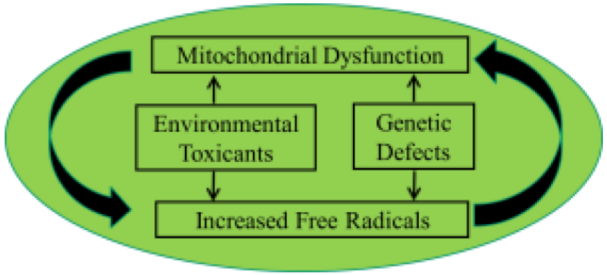


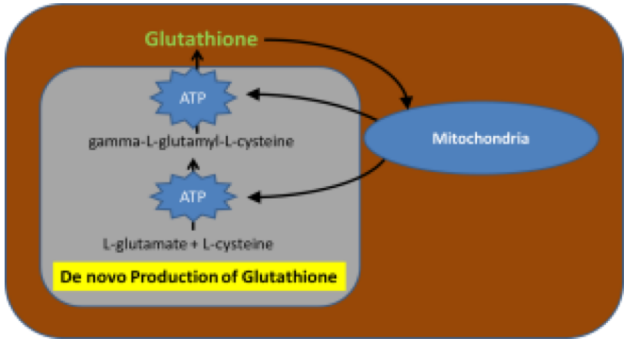


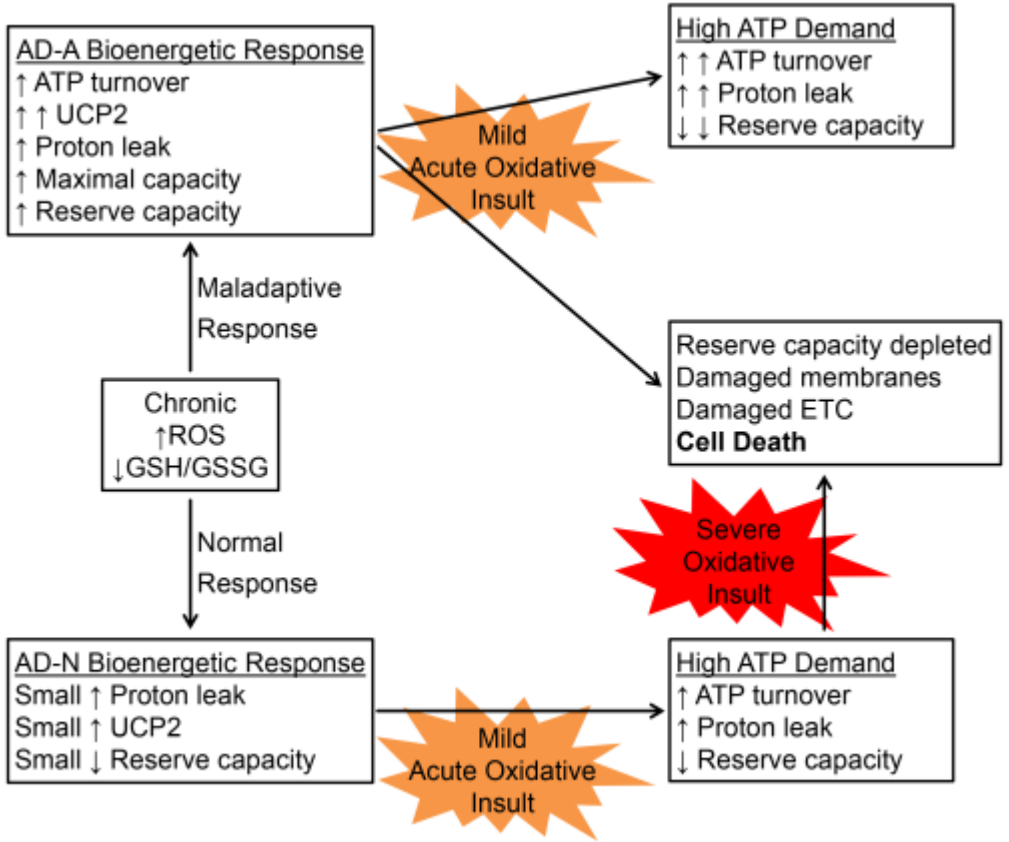
Mitochondrial Dysfunction in Autism

Effects of the Environment

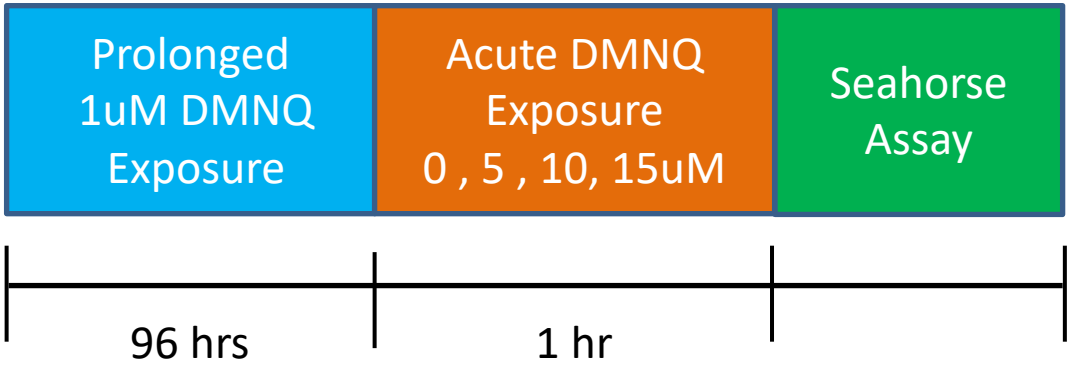
Mitochondrial Dysfunction in Autism

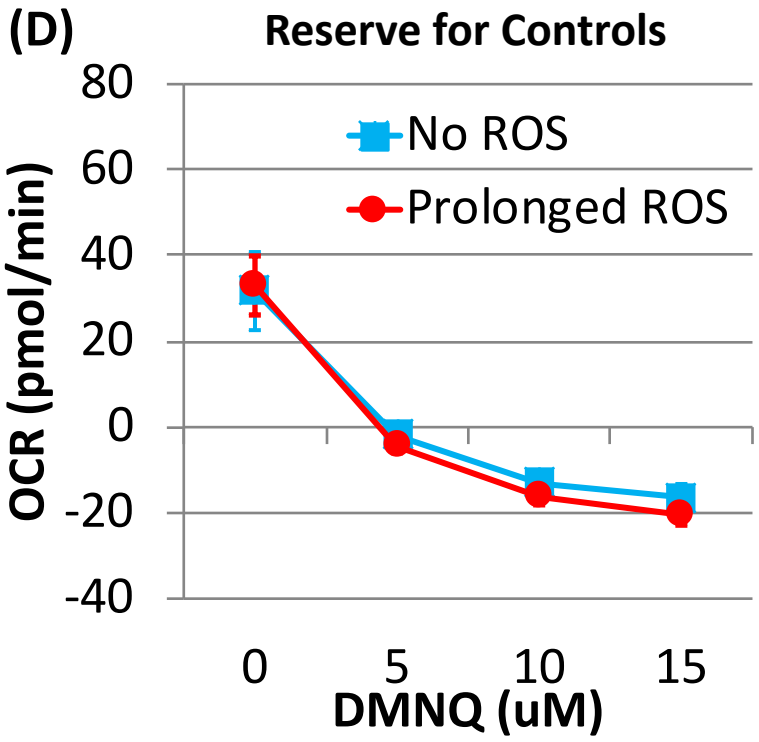


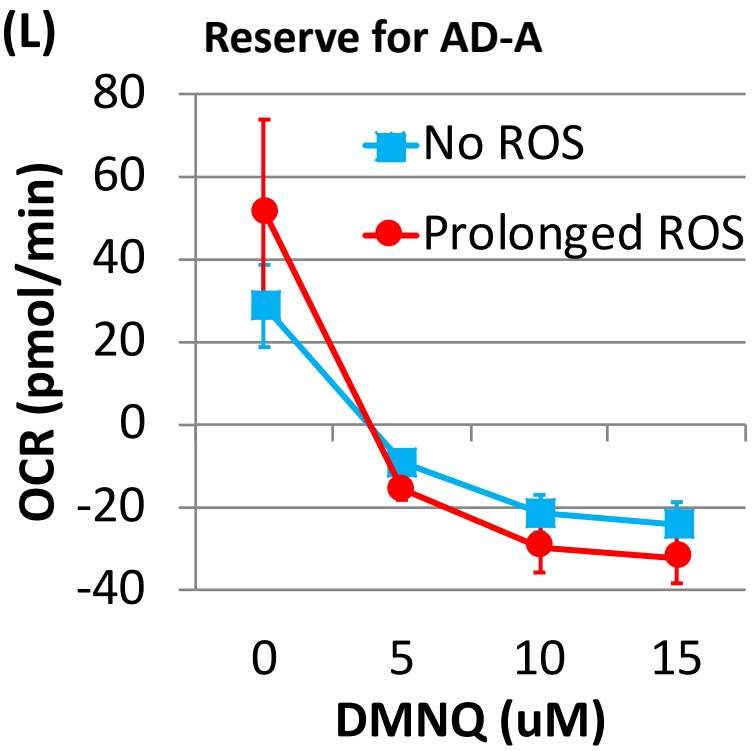




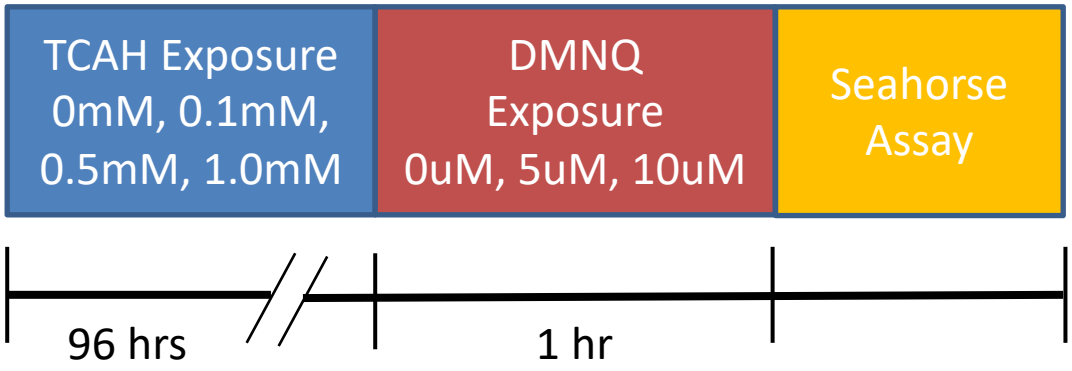
Mitochondrial Dysfunction in Autism

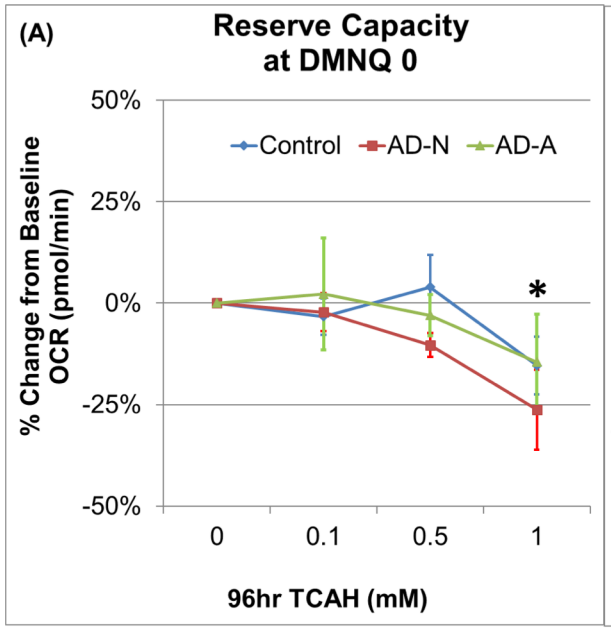


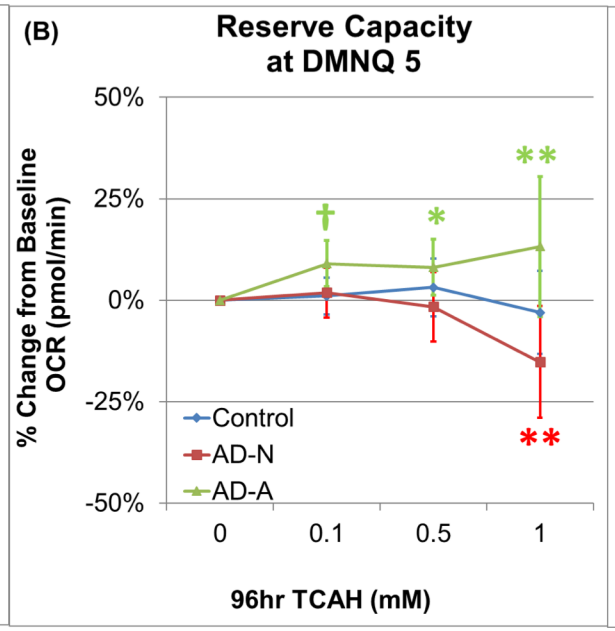


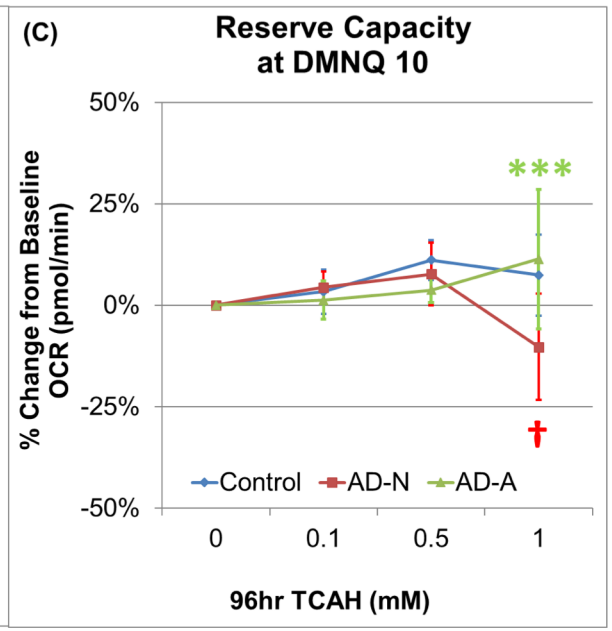


Mitochondrial Dysfunction in Autism



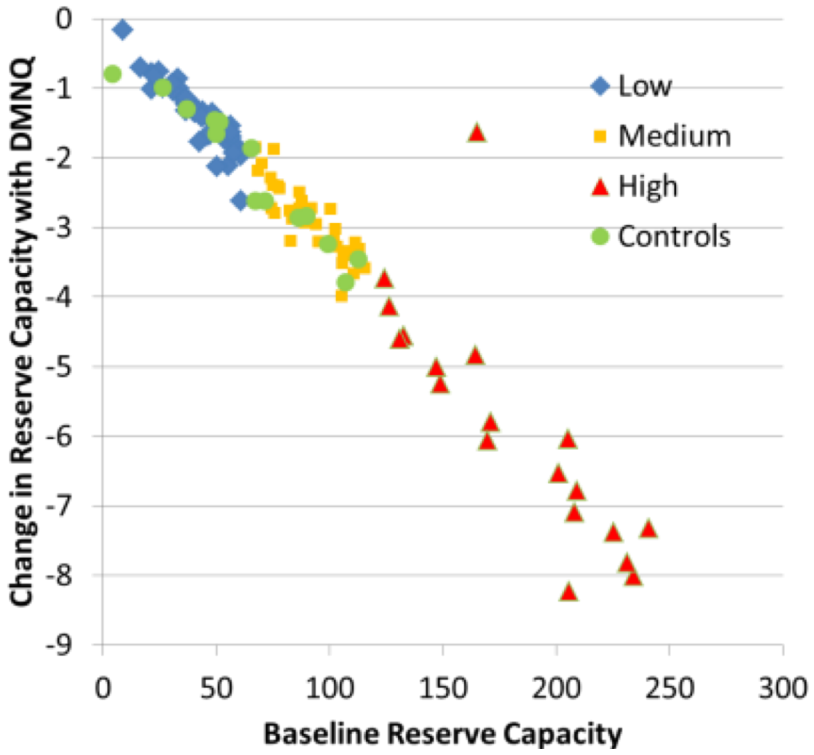




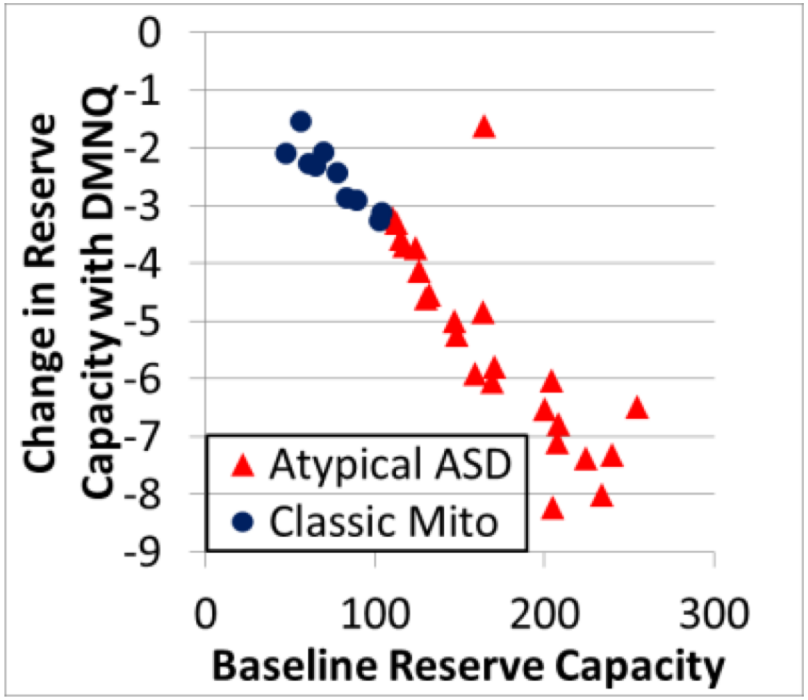


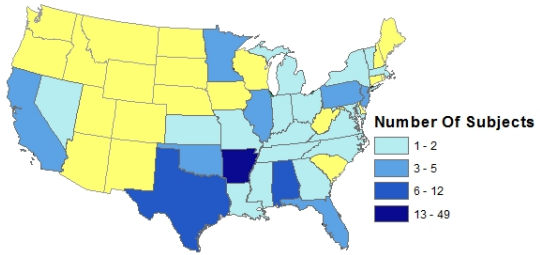
Mitochondrial Dysfunction

25% of Children with Autism also show abnormal Reserve Capacity



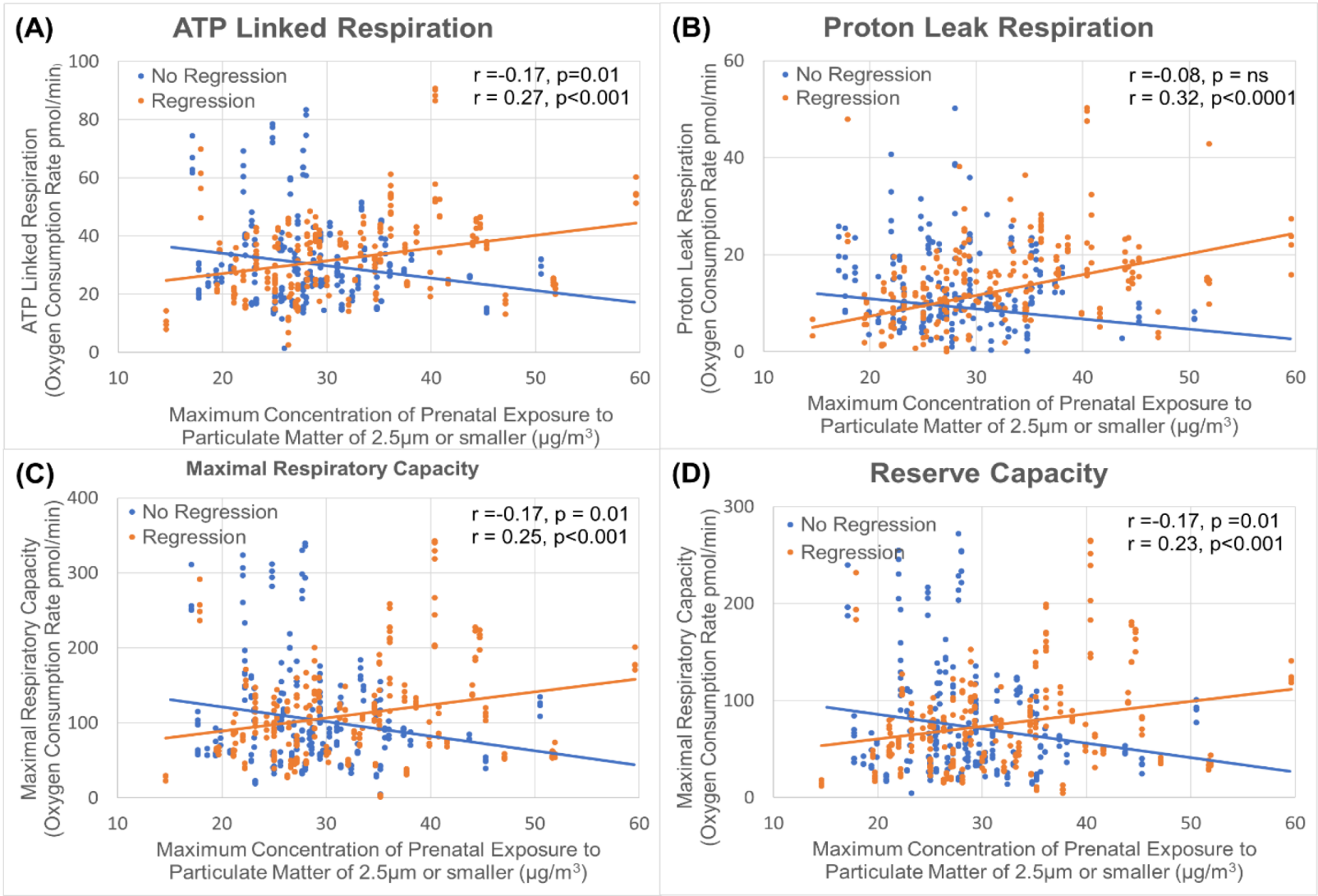
This pattern of abnormal Reserve Capacity is distinct from children with classic mitochondrial disease





Mitochondrial Dysfunction

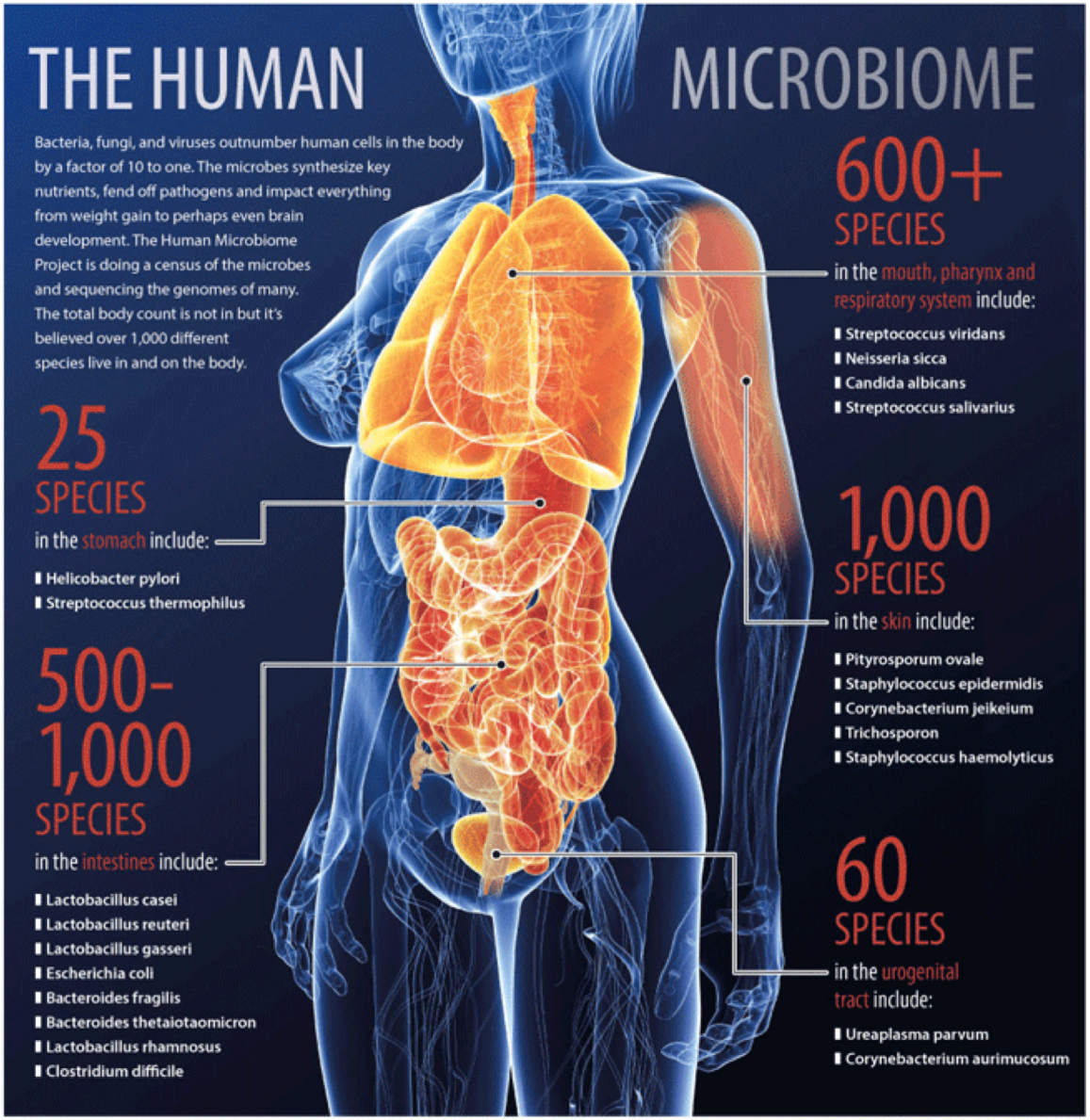
Changes in Mitochondrial Function in Childhood is Associated with Exposure to Air Pollution (PM2.5) during Gestation



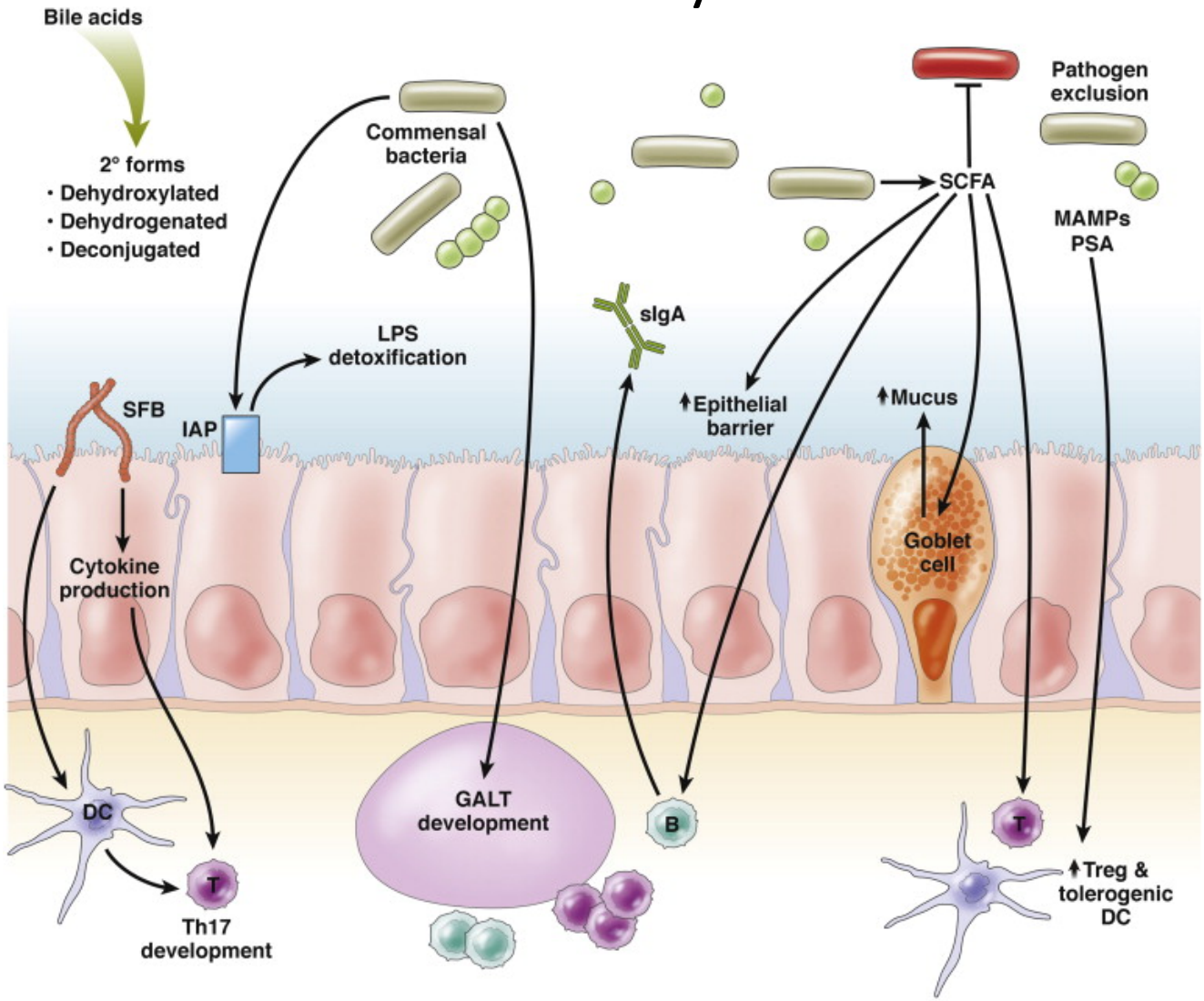
Mitochondrial Dysfunction in Autism

Effects of the Gut Microbiome

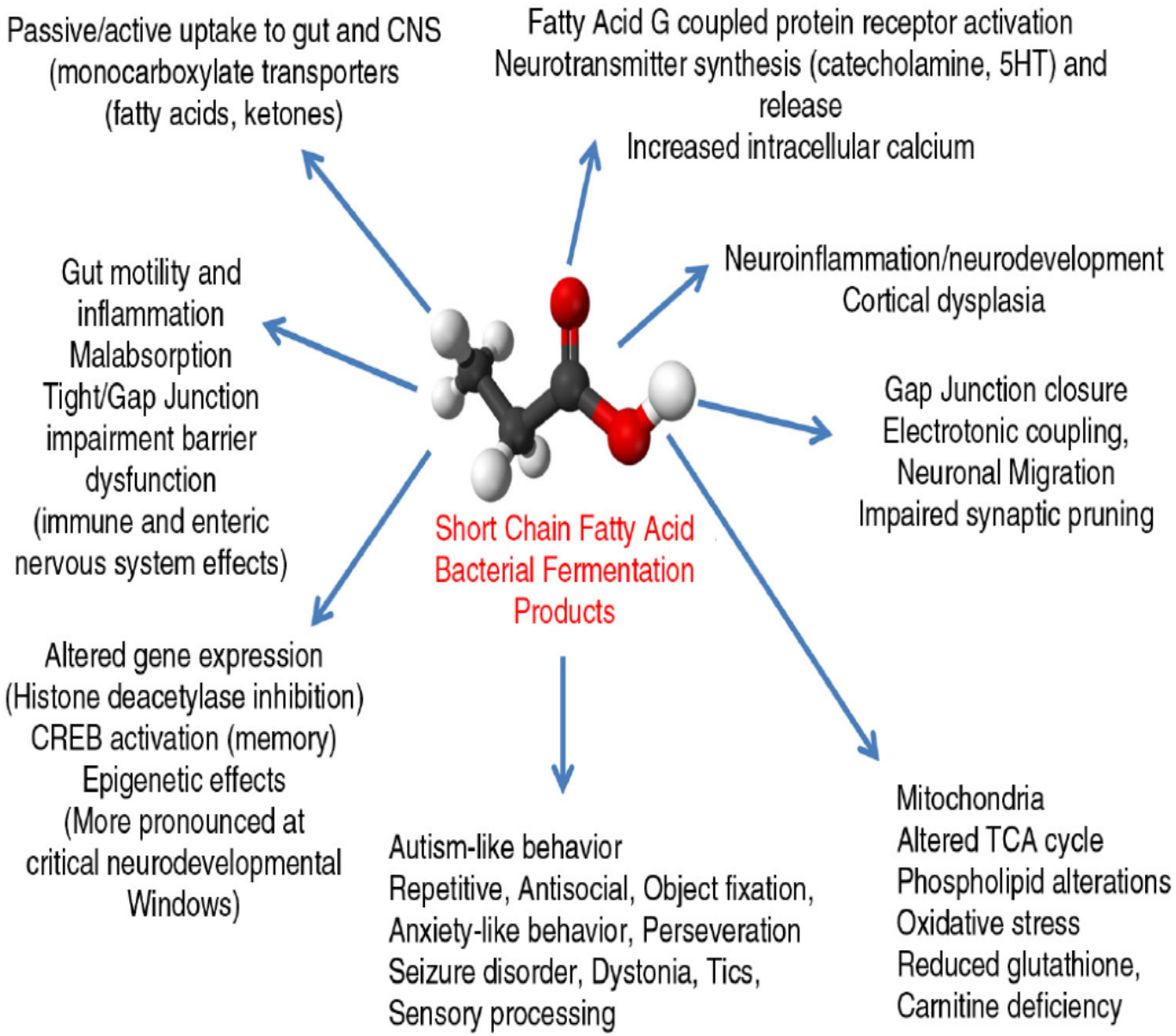
Mitochondrial Dysfunction



The microbiota influences physiology by Short chain fatty acids



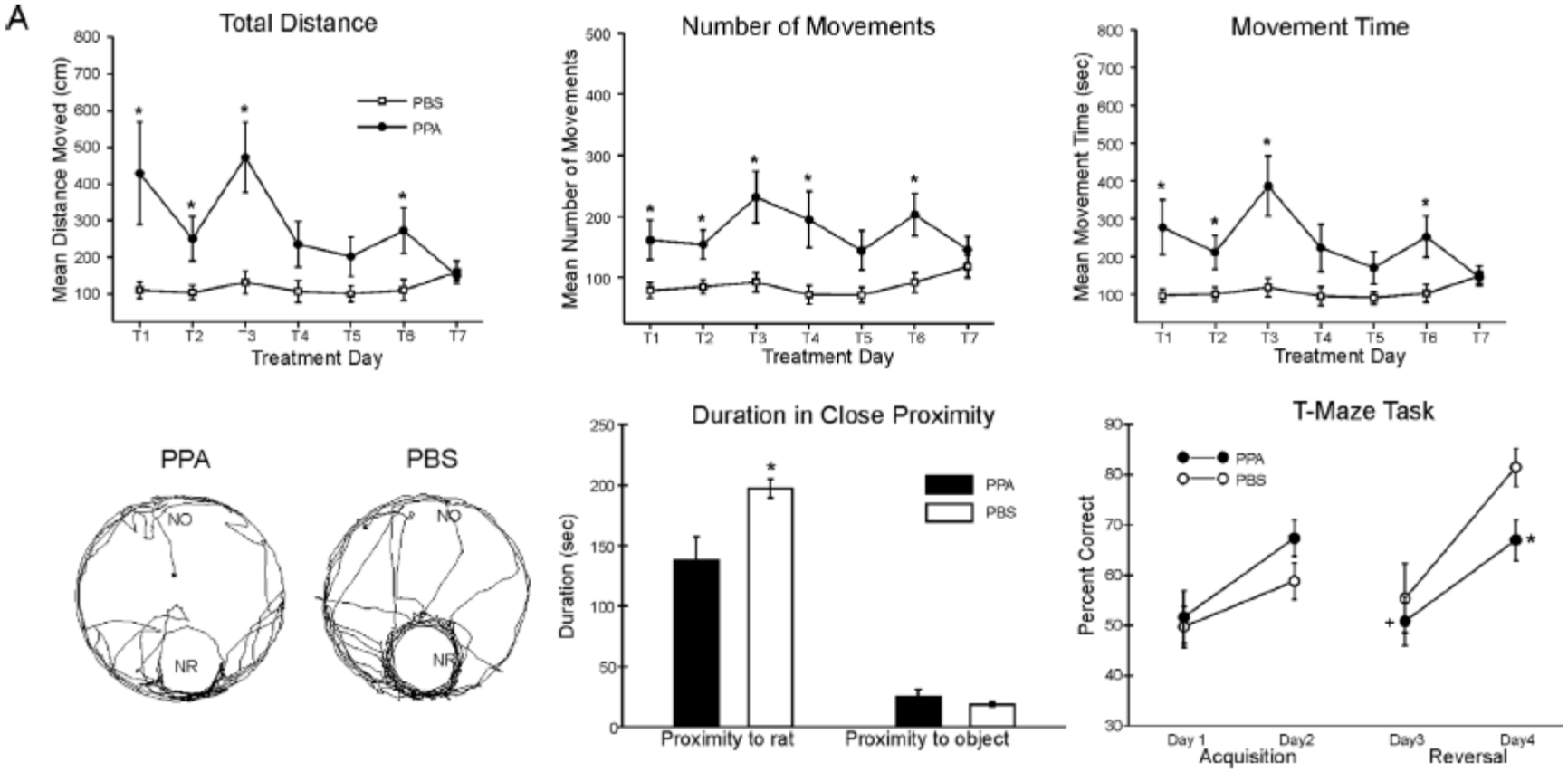
Mitochondrial Dysfunction



Mitochondrial Dysfunction

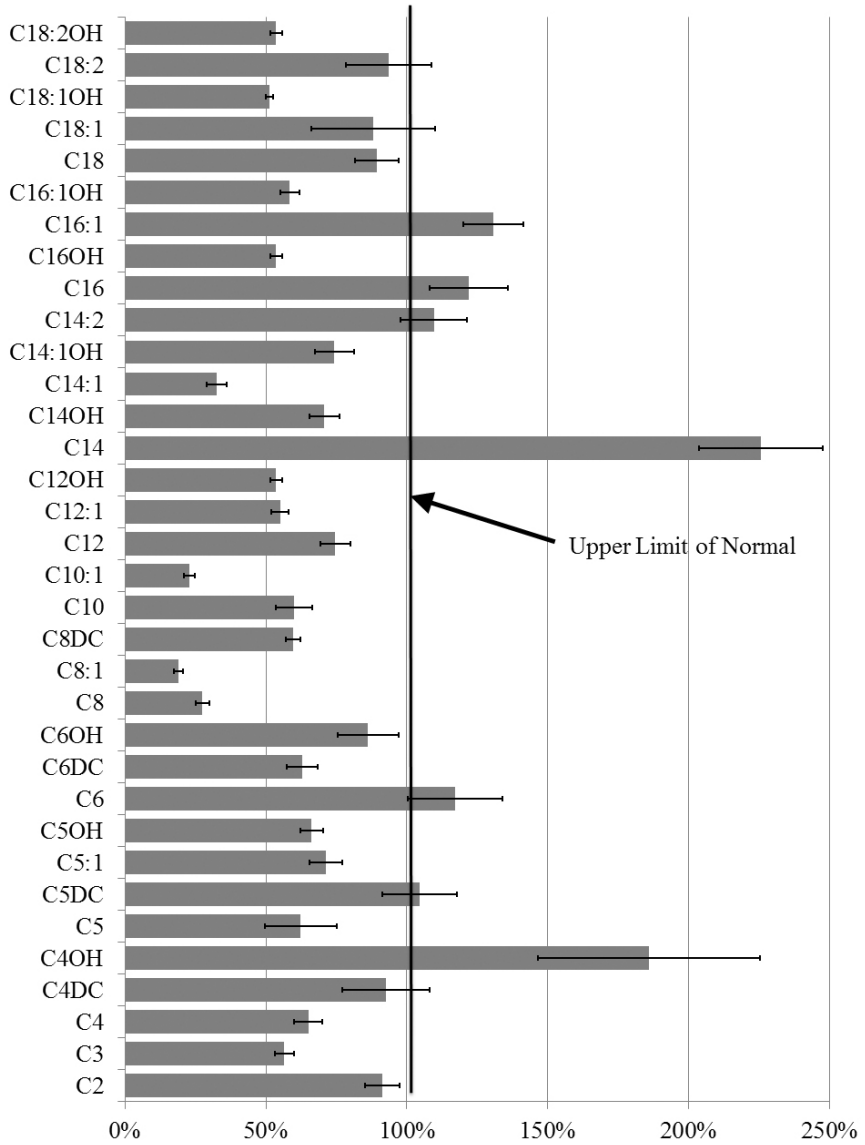
Short-chain fatty acid fermentation products of the gut microbiome: implications in autism spectrum disorders

Derrick F. MacFabe, MD*

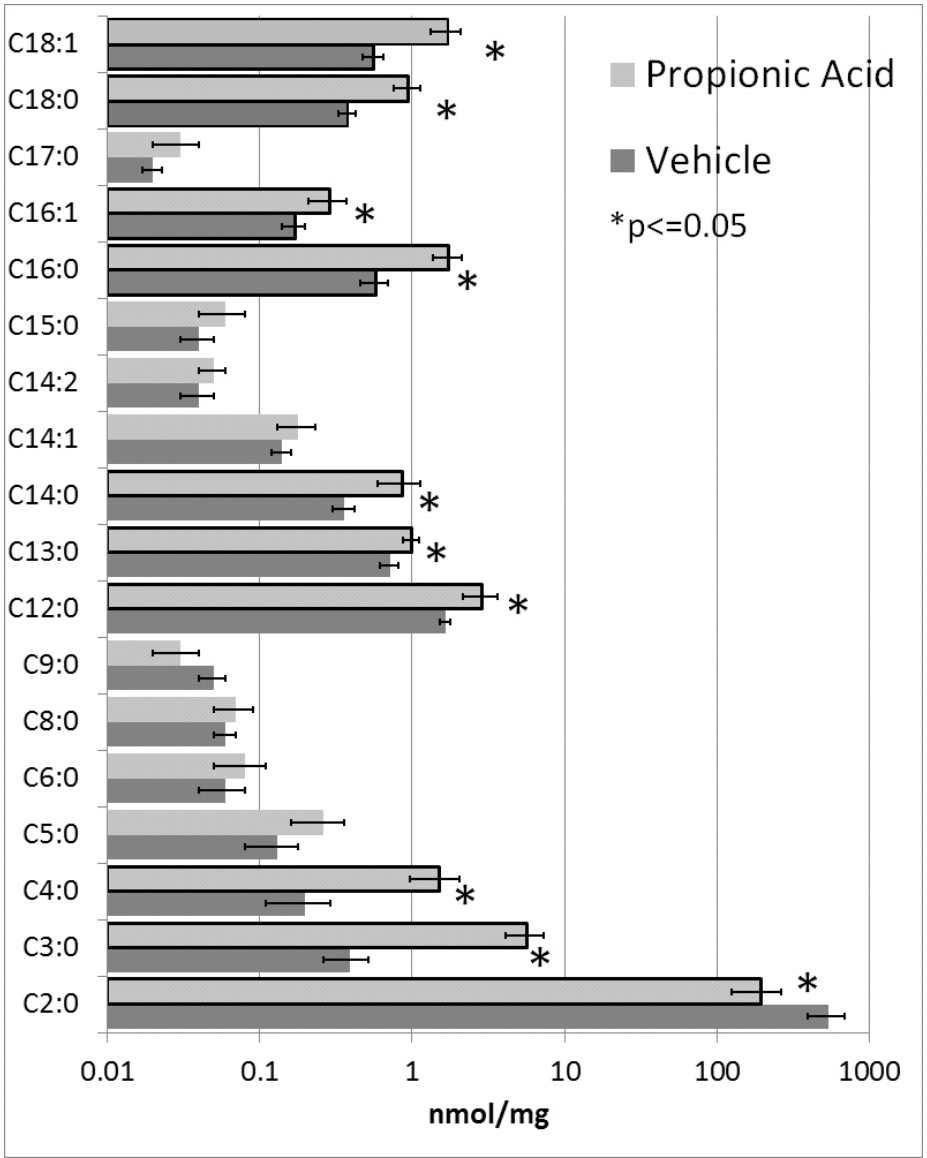


Mitochondrial Dysfunction

Autistic Children



Rodents



Mitochondrial Dysfunction

Citation: Transl Psychiatry (2013) 3, e220; doi:10.1038/tp.2012.143
© 2013 Macmillan Publishers Limited All rights reserved 2158-3188/13
www.nature.com/tp

Unique acyl-carnitine profiles are potential biomarkers for acquired mitochondrial disease in autism spectrum disorder

RE Frye[1], S Melnyk[1] and DF MacFabe[2]

- 213 ASD patients screened with acyl-carnitine biomarkers
- 74 (35%) with >=3 fasting acyl-carnitine elevations
- Acyl-carnitine abnormalities were confirmed in 48%
- Corrected prevalence of 17% of ASD children screened.

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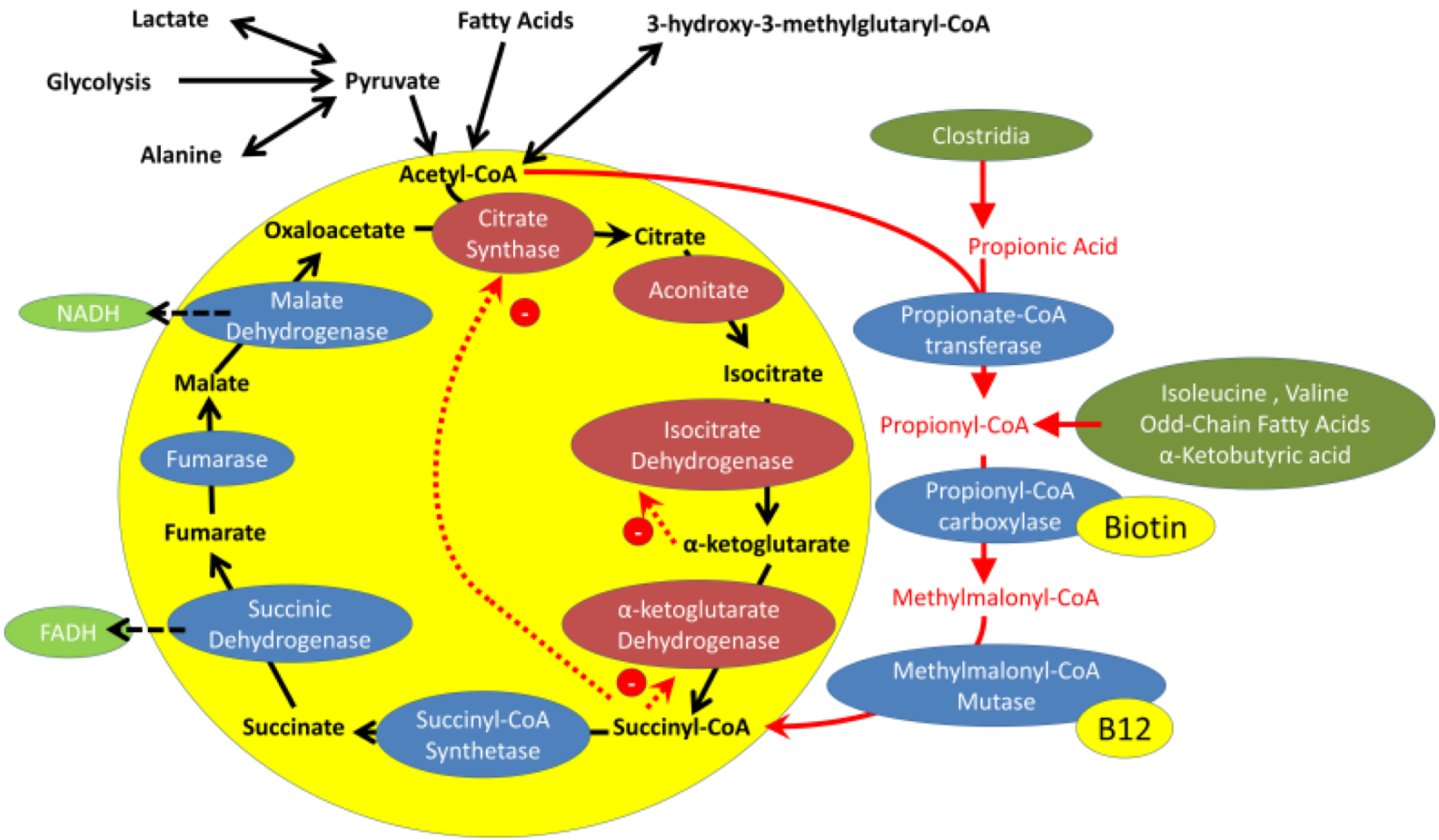
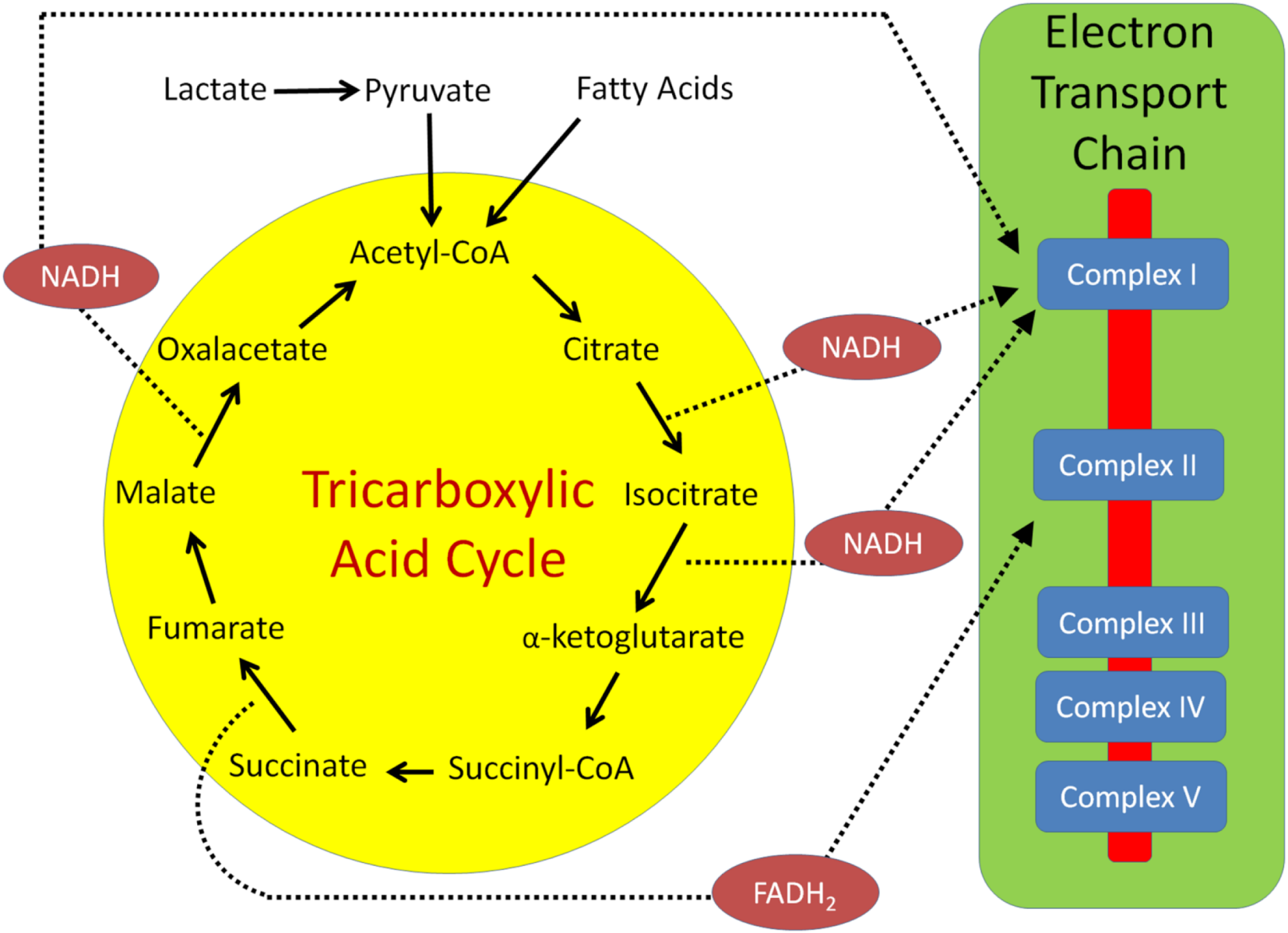
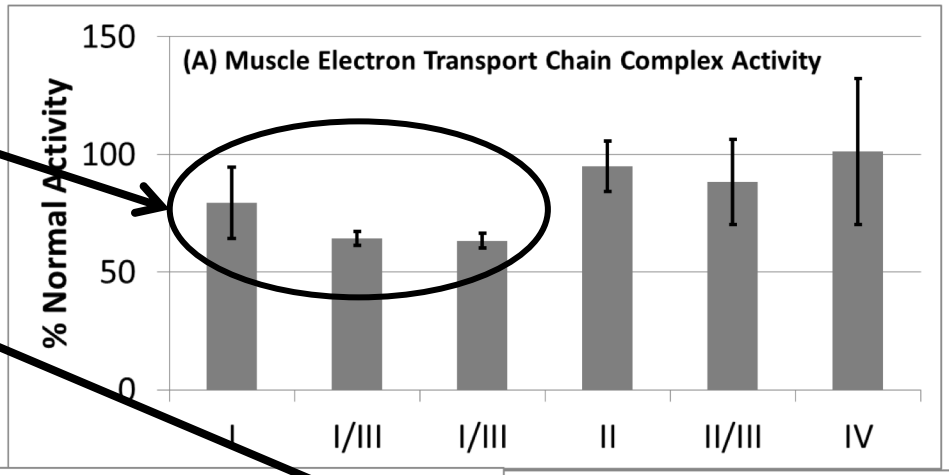


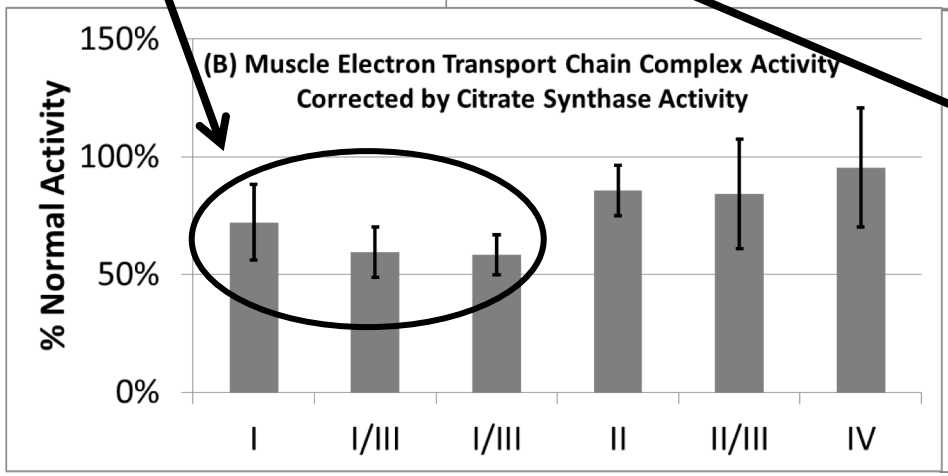
Mitochondrial Dysfunction

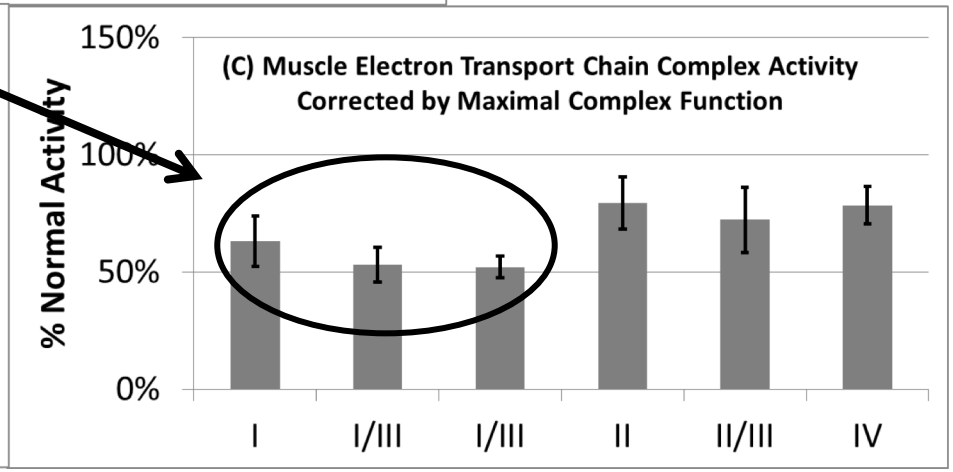


Mitochondrial Dysfunction

Decreased Complex I Activity







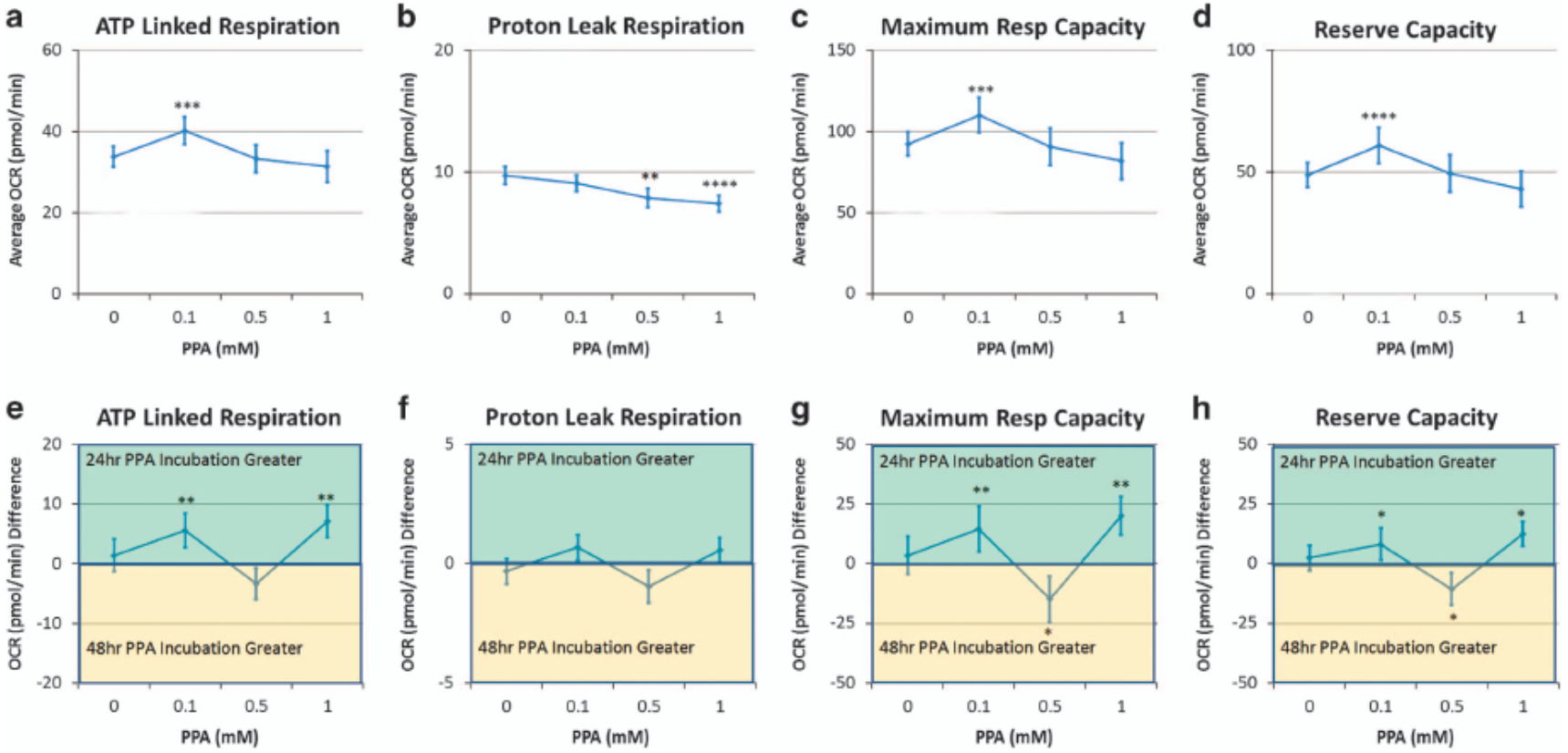
Mitochondrial Dysfunction

Citation: Transl Psychiatry (2016) 6, e927; doi:10.1038/tp.2016.189

ORIGINAL ARTICLE

Modulation of mitochondrial function by the microbiome metabolite propionic acid in autism and control cell lines

RE Frye[1,2], S Rose[1,2], J Chacko[1], R Wynne[1,2], SC Bennuri[1,2], JC Slattery[1,2], M Tippett[1,2], L Delhey[1,2], S Melnyk[1,2], SG Kahler[1,2] and DF MacFabe[3]



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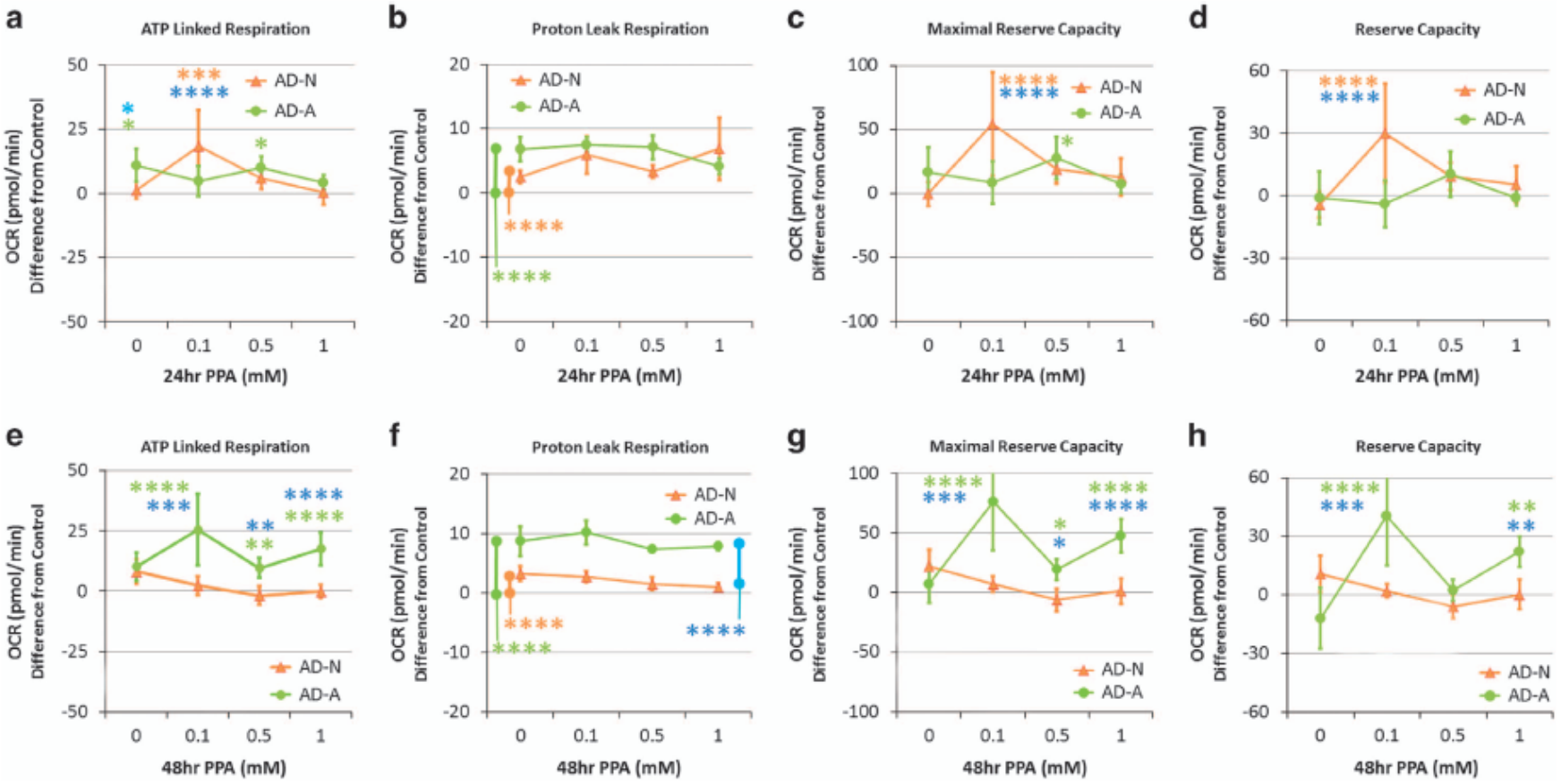

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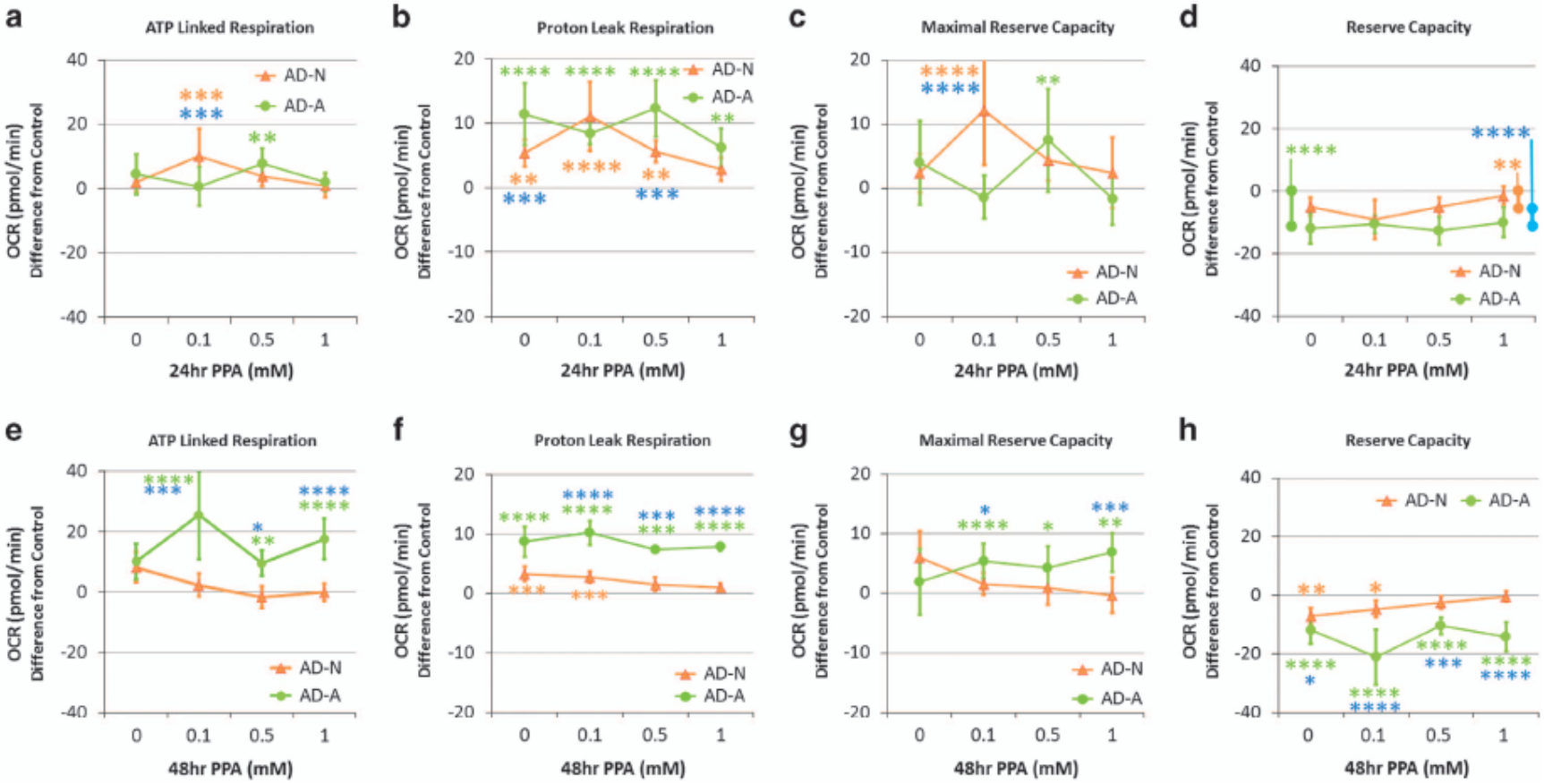


Rose *et al. Translational Psychiatry* (2018)8:42
DOI 10.1038/s41398-017-0089-z

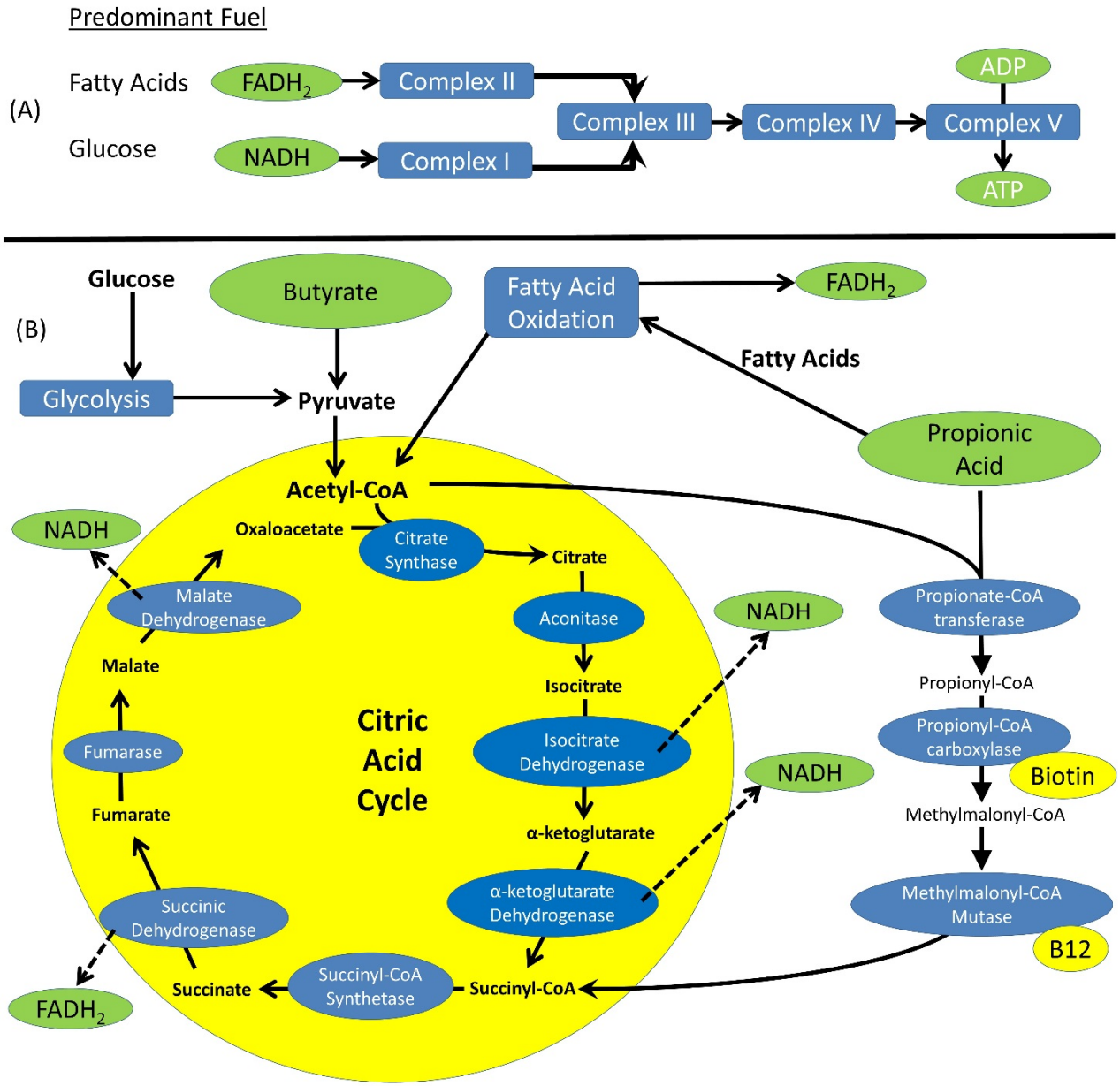
Translational Psychiatry

ARTICLE Open Access

Butyrate enhances mitochondrial function during oxidative stress in cell lines from boys with autism

Shannon Rose[1], Sirish C. Bennuri[1], Jakeira E. Davis[1], Rebecca Wynne[1], John C. Slattery[1], Marie Tippett[1], Leanna Delhey[1], Stephan Melnyk[1], Stephen G. Kahler[1], Derrick F. MacFabe[2] and Richard E. Frye[1,3]

Mitochondrial Dysfunction



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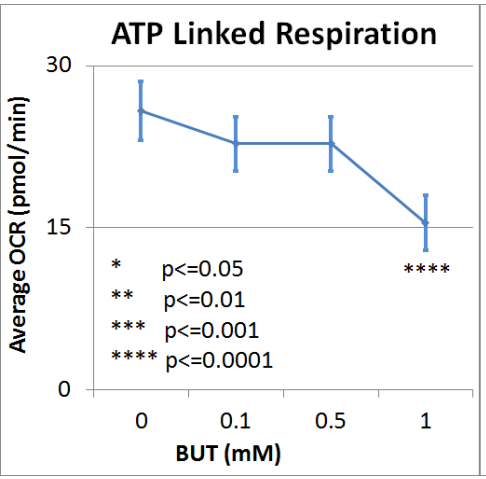

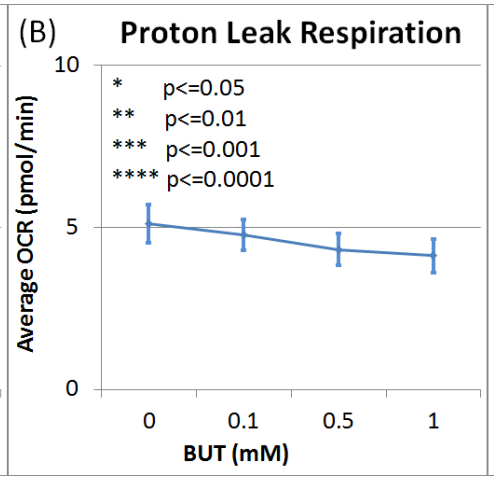

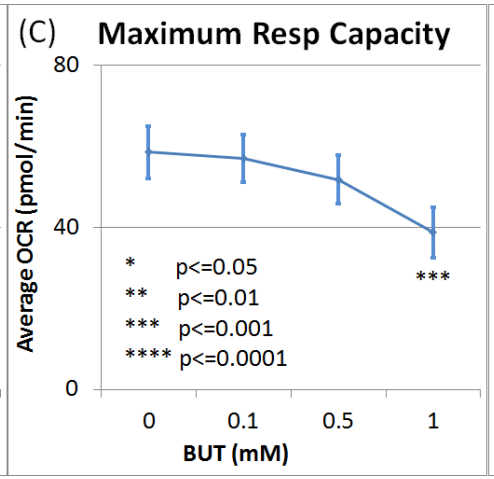

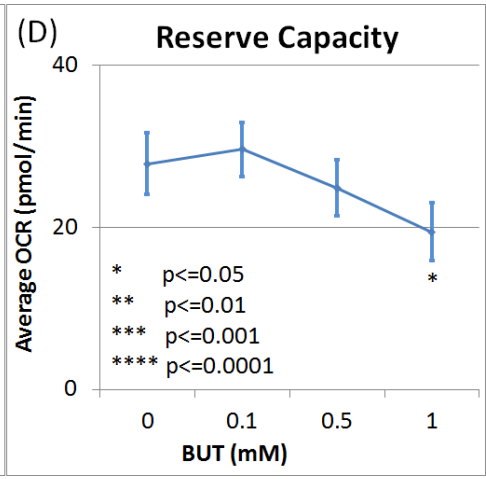

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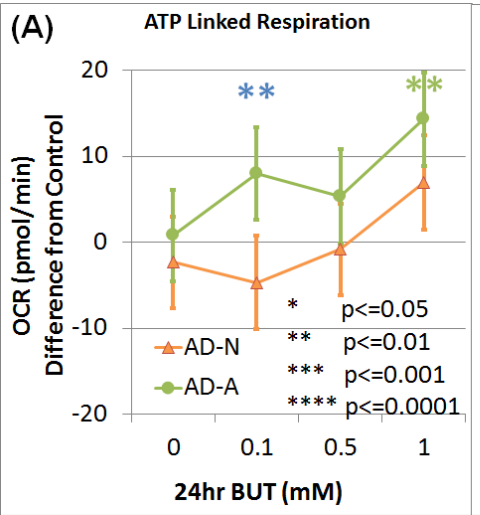

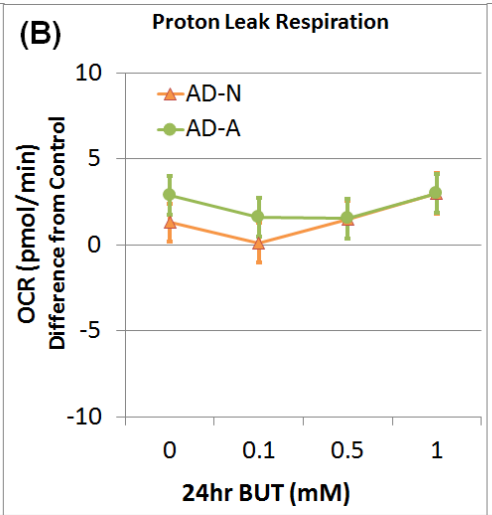

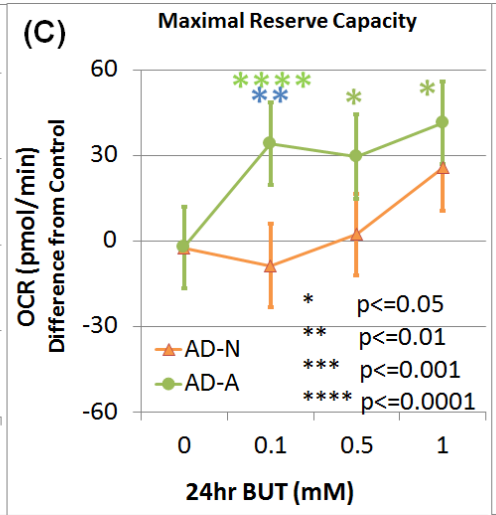

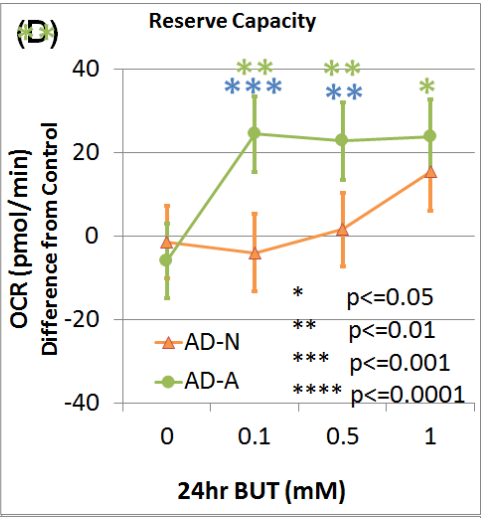

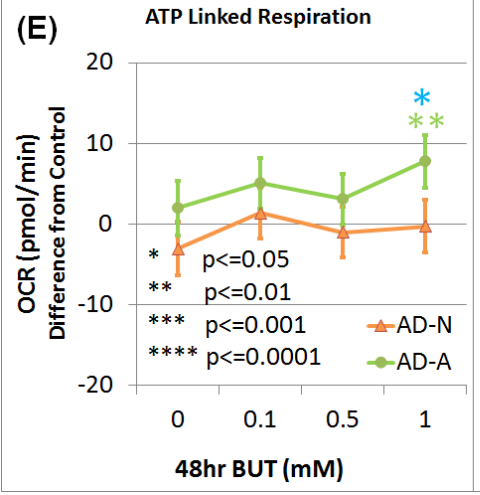

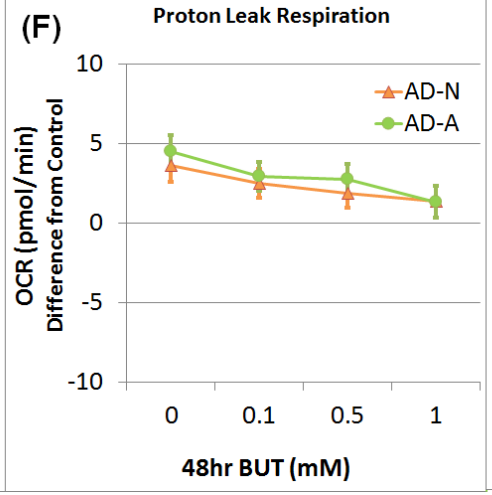

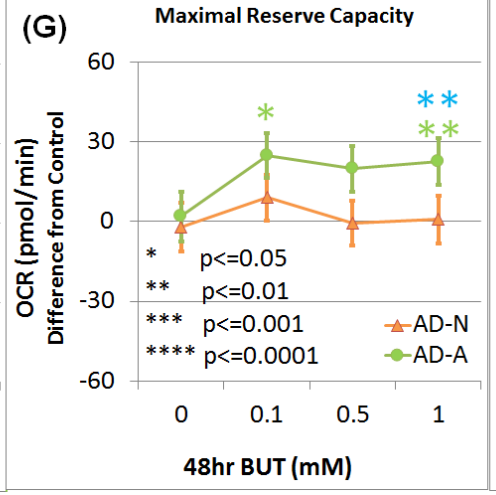

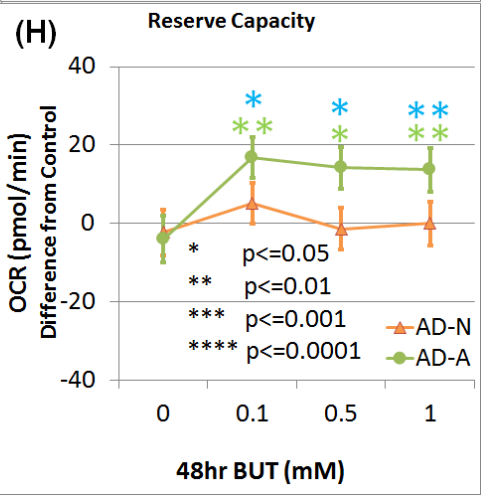

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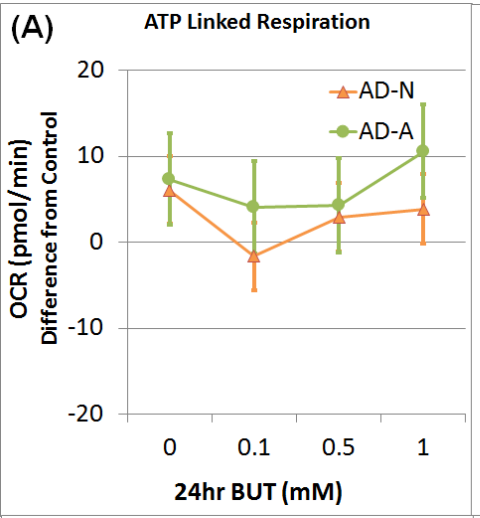

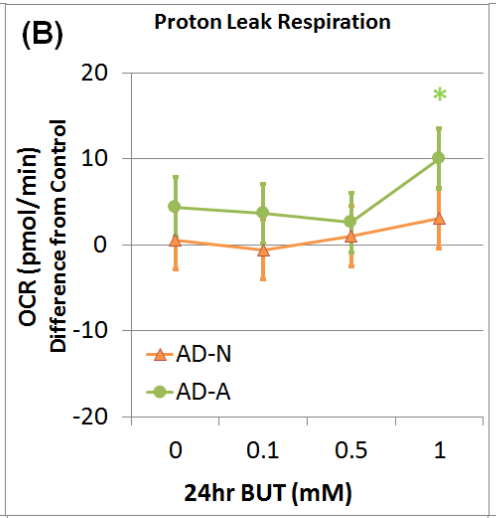

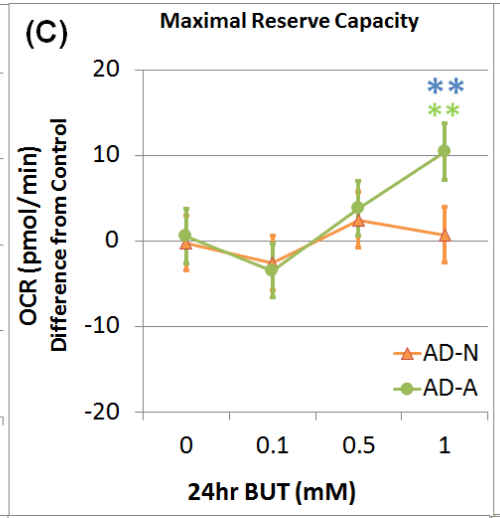

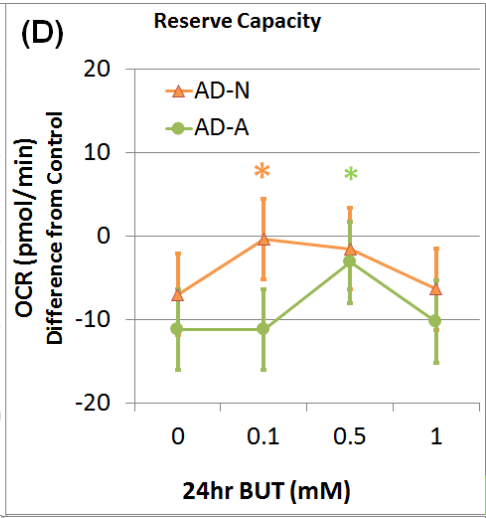

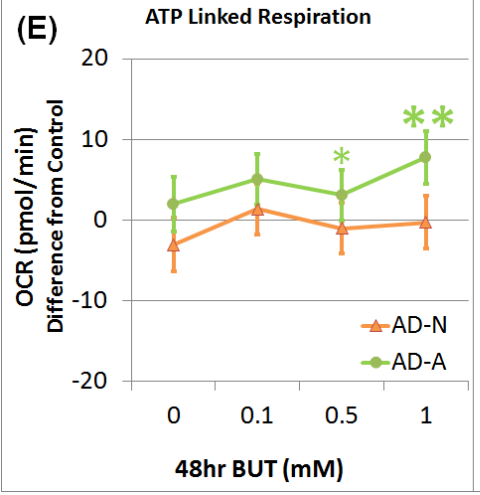

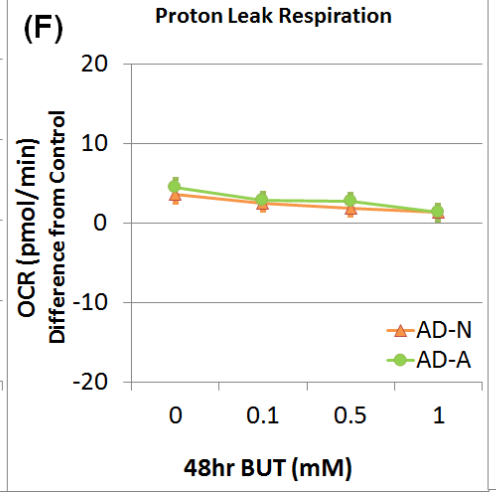

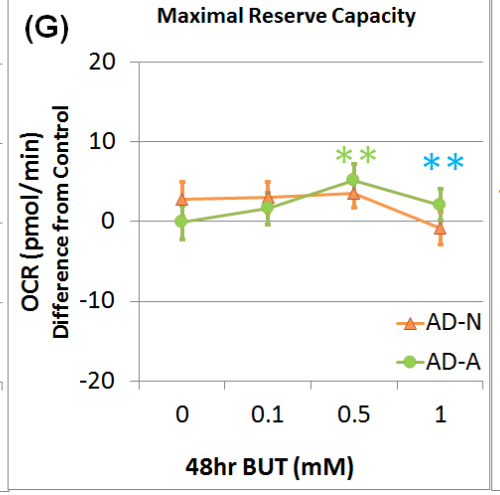

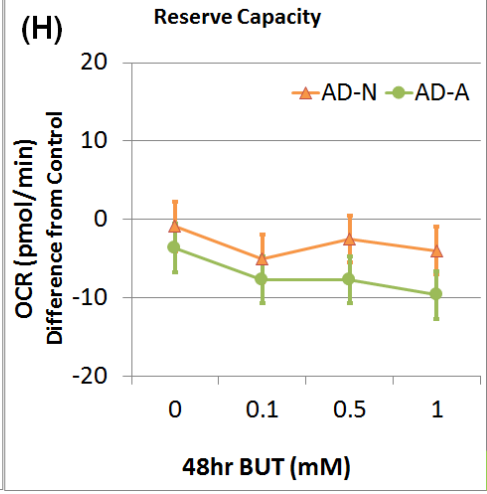

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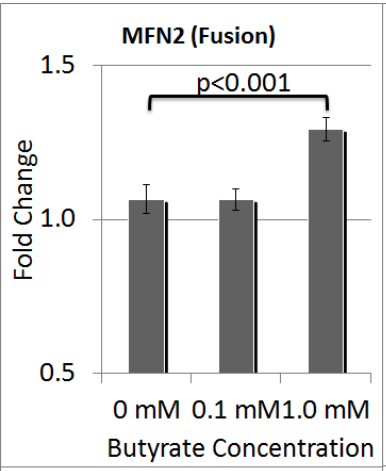

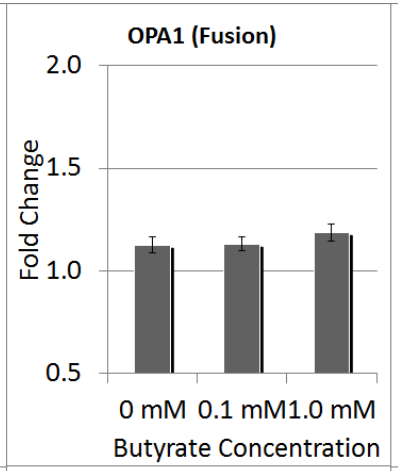

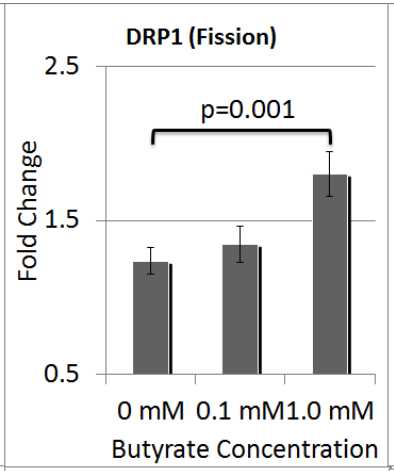

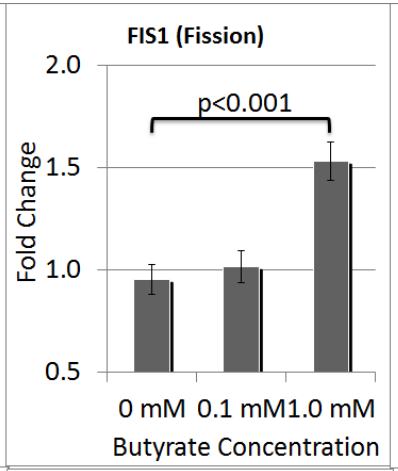

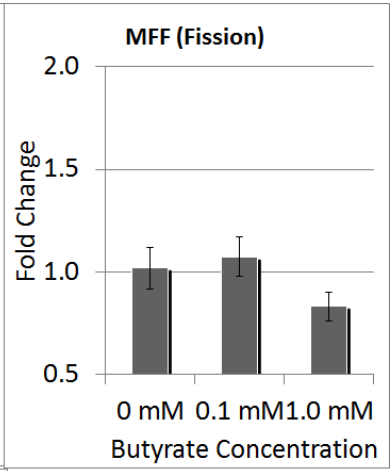

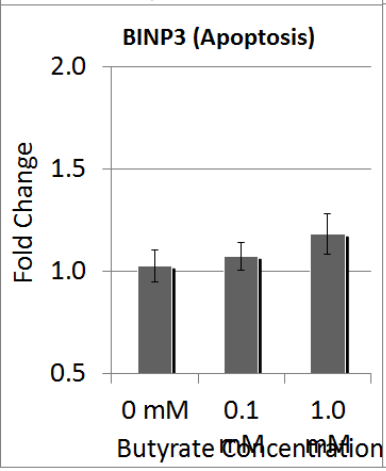

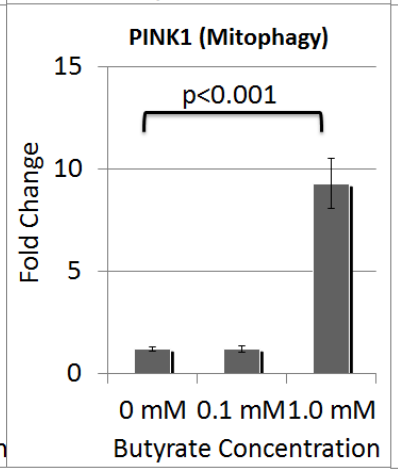

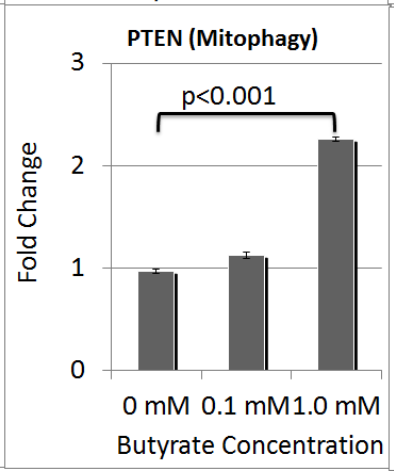

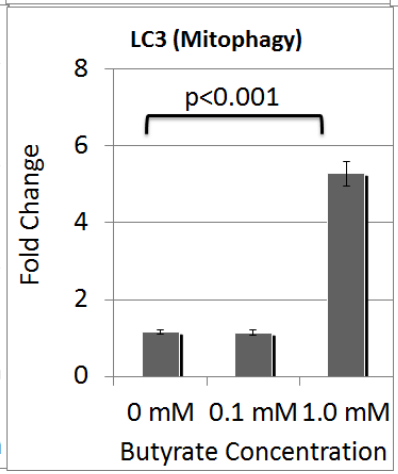

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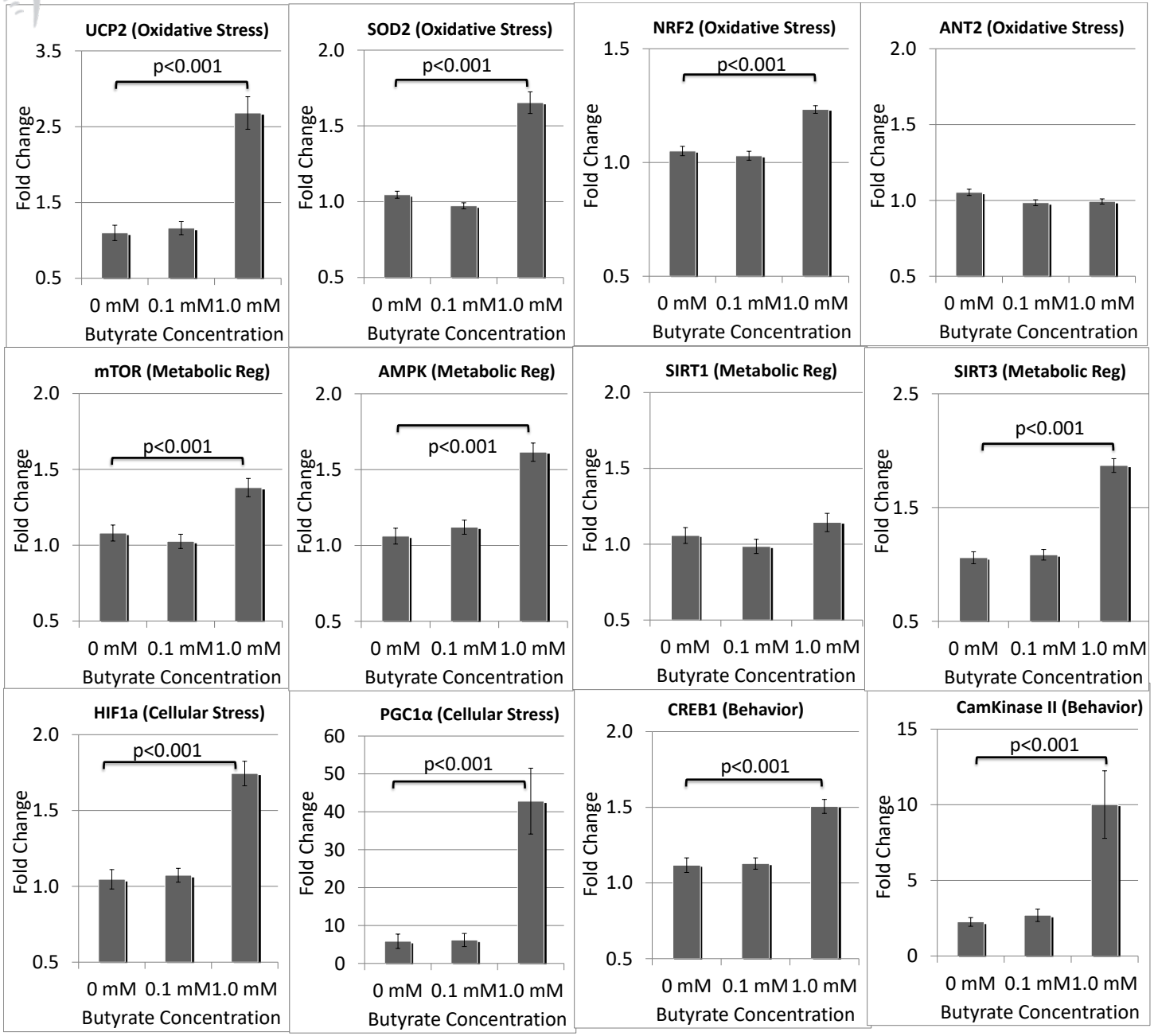
Mitochondrial Dysfunction



PLOS ONE

RESEARCH ARTICLE

Mitochondrial dysfunction in the gastrointestinal mucosa of children with autism: A blinded case-control study

Shannon Rose[1], Sirish C. Bennuri[1], Katherine F. Murray[2], Timothy Buie[3], Harland Winter[2], Richard Eugene Frye[1]*

1 Autism Research Program, Arkansas Children's Research Institute, Little Rock, Arkansas, United States of America, **2** Department of Pediatric Gastroenterology and Nutrition, MassGeneral Hospital for Children, Boston, Massachusetts, United States of America, **3** Department of Gastroenterology, Boston Children's Hospital, Boston, Massachusetts, United States of America

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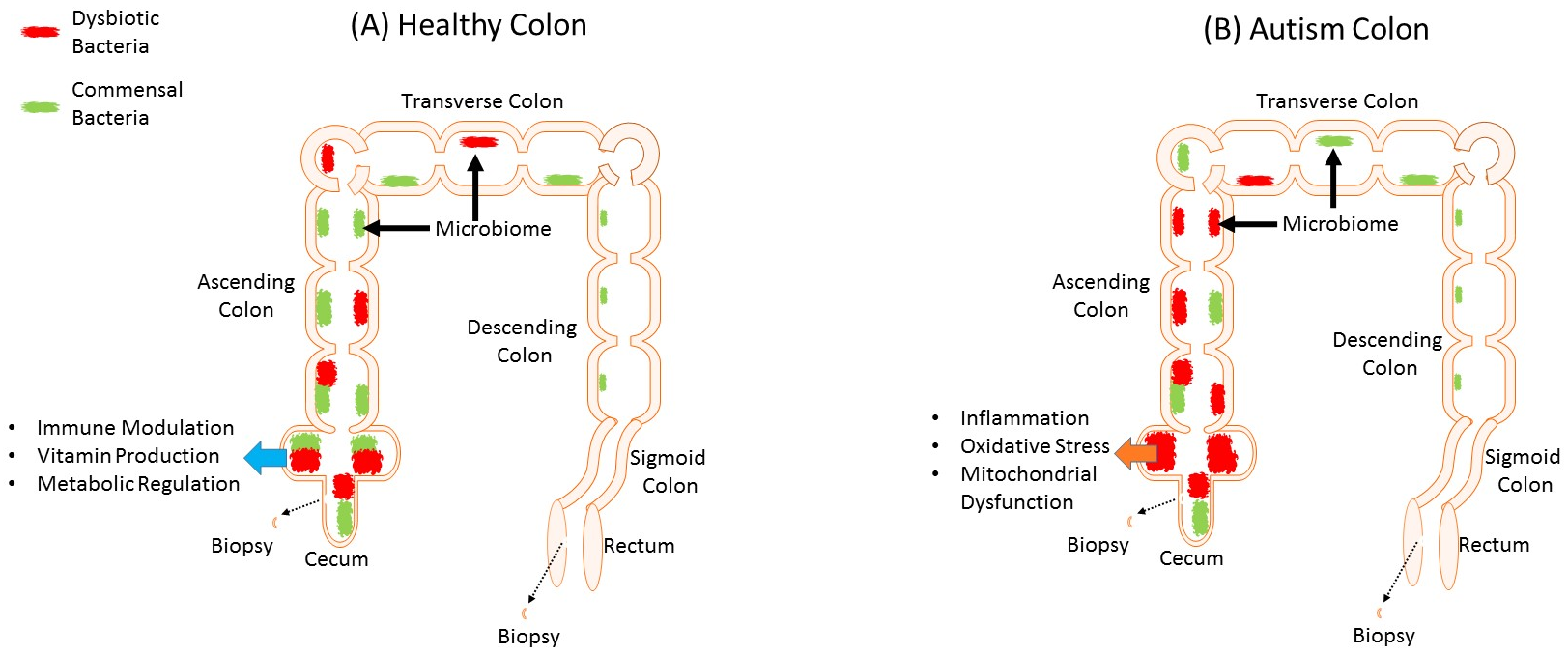
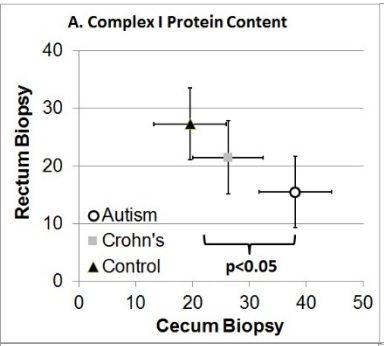
Mitochondrial Dysfunction

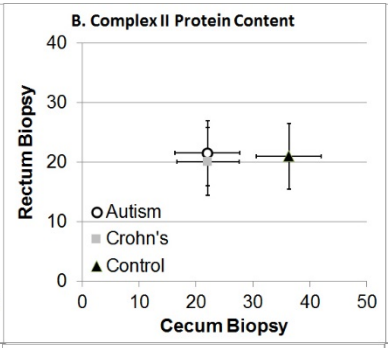


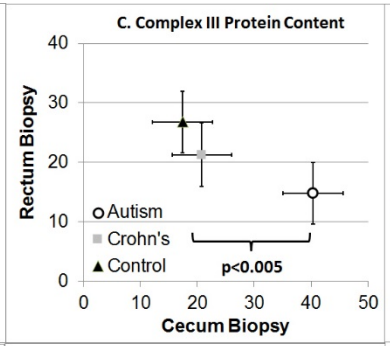
BARROW Neurological Institute

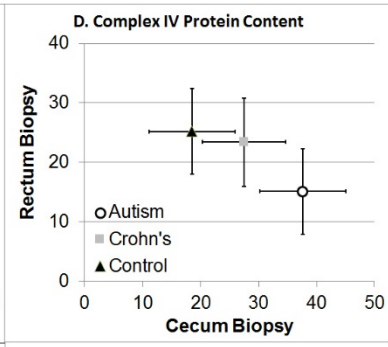
PHOENIX CHILDREN'S Hospital

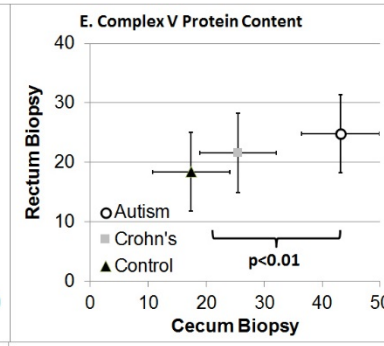
Mitochondrial Dysfunction

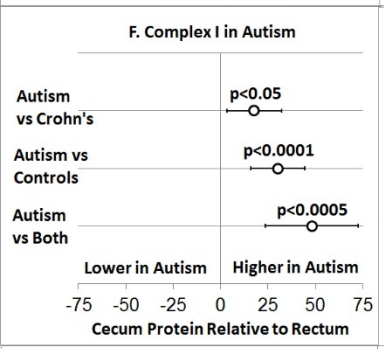


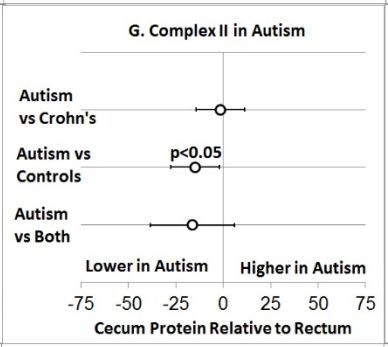


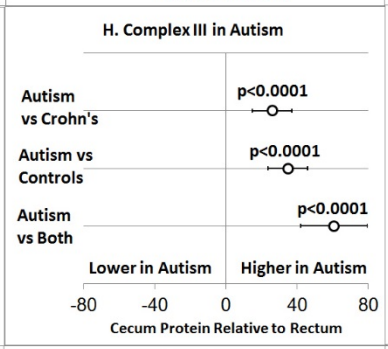


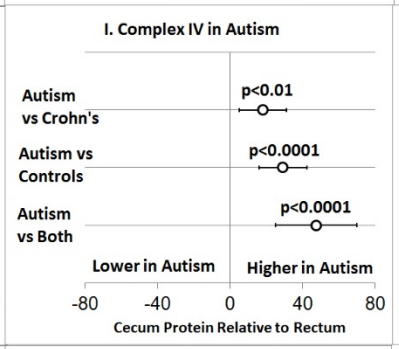


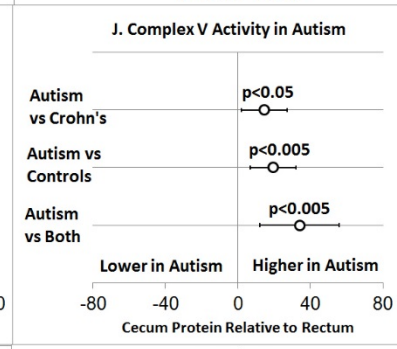


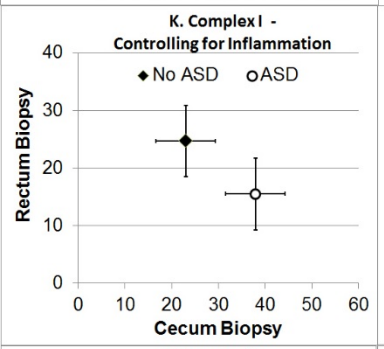


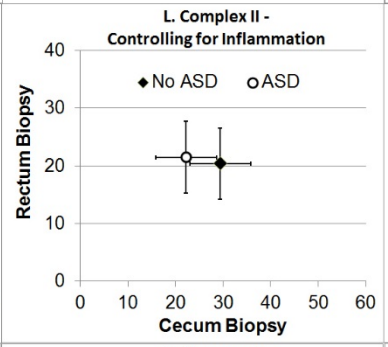


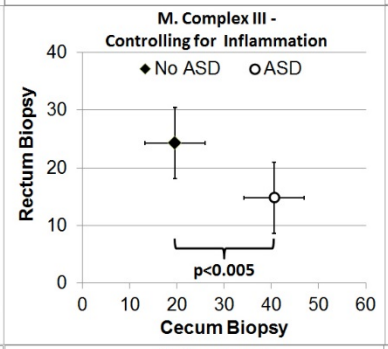


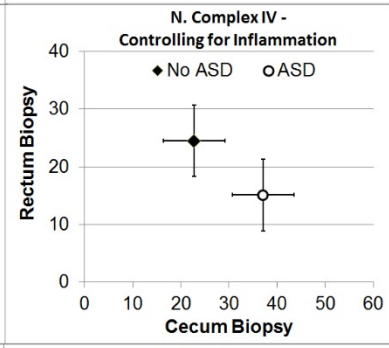


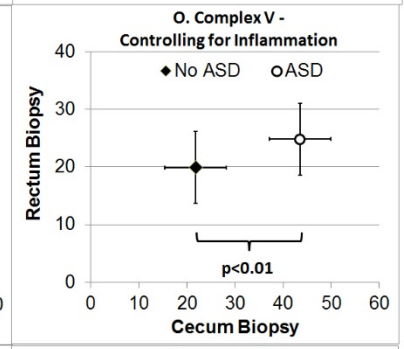


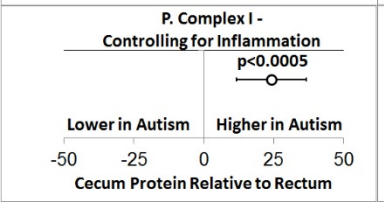


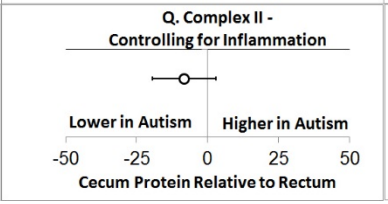


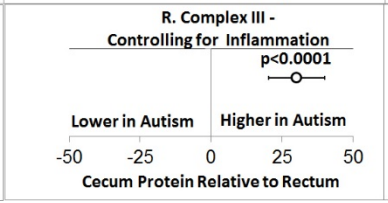


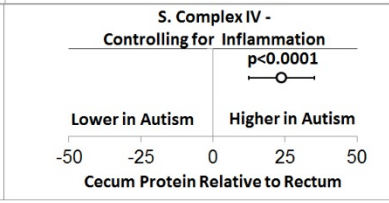


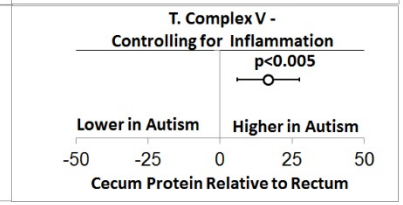




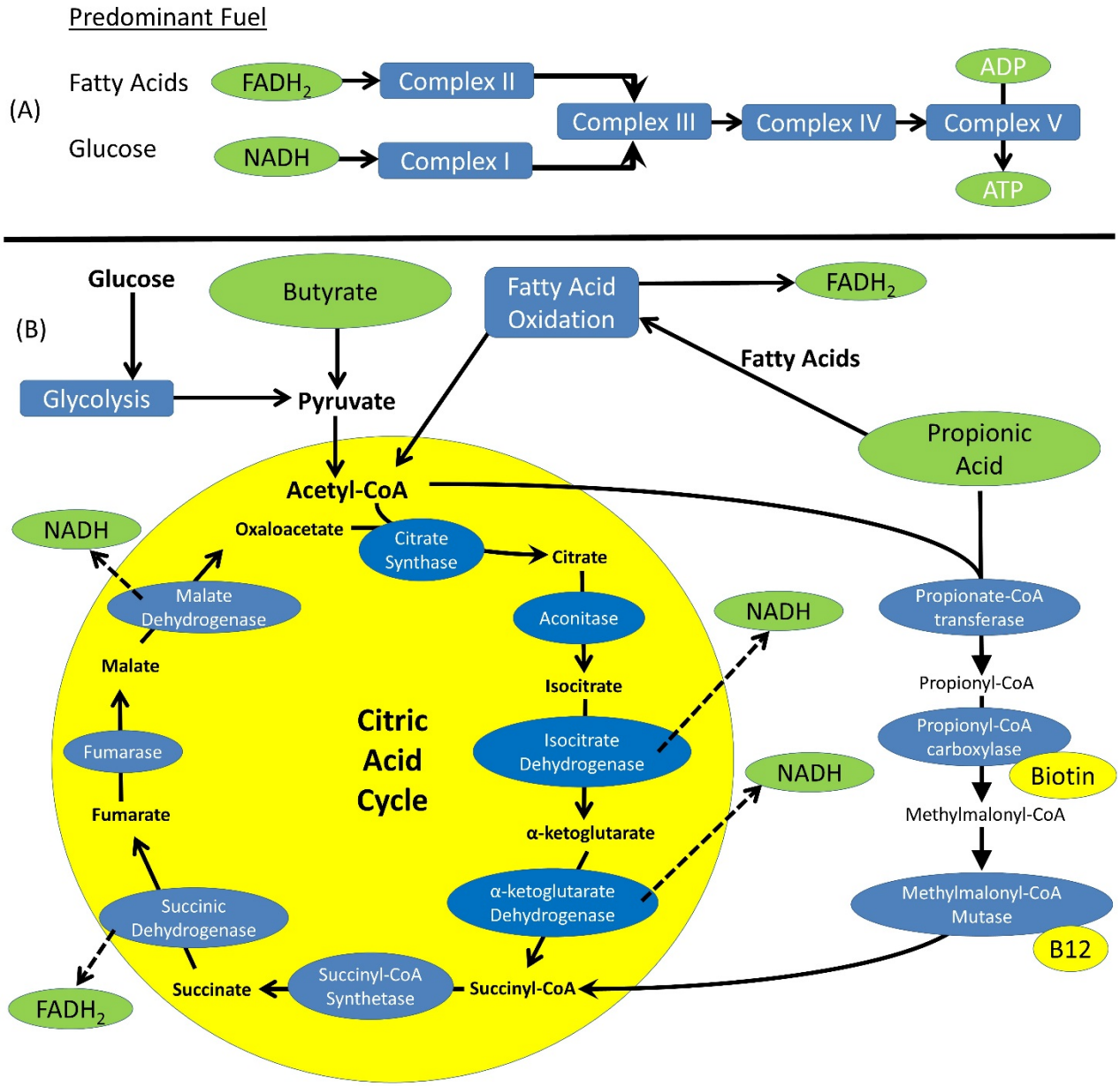




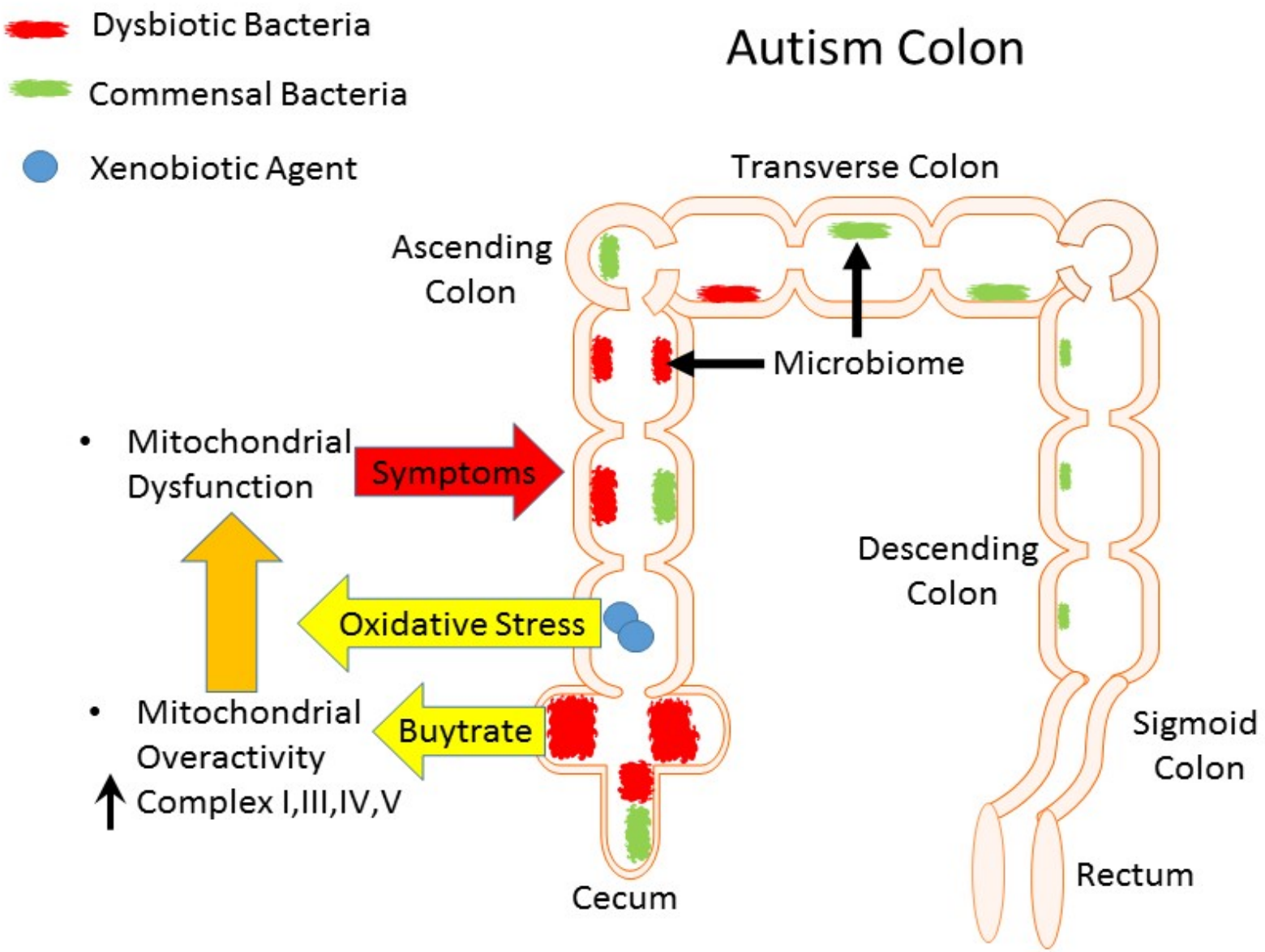




Mitochondrial Dysfunction



Mitochondrial Dysfunction



Examples of Genetic Disorder

Examples of Genetic Disorder

Down Syndrome

Shamim I. Ahmad *Editor*

Neurodegenerative Diseases

OXIDATIVE STRESS AND MITOCHONDRIAL DYSFUNCTION IN DOWN SYNDROME

Giovanni Pagano* and Giuseppe Castello

CROM, Cancer Research Center, Mercogliano, Italy

**Corresponding Author:Giovanni Pagano—Email: gbpagano@tin.it*

Mitochondrial Dysfunction

Table 1. Reported changes in oxidative stress parameters in cells, tissues or body fluids from DS patients

Cells/Tissues/ Body Fluids	Endpoints	References
Foetal Brain	↑ SOD-1; ↔ glutathione peroxidase (GPx); ↑ MDA	5
Brain	↑ reactive carbonyls and carbonyl reductase;	9
Amniotic Fluid	↑↑ Isoprostanes	10
Erythrocytes and Neutrophils	↑ SOD-1 and GPx; ↔ catalase (CAT); ↑↑ ratio SOD-1:(GPx + CAT); ↑ MDA and lipofuscin ↑ SOD-1 and GPx; ↔ CAT; ↑ MDA	12-16
Leukocytes, Whole Blood and Plasma	Age-dependent ↑ 8-hydroxy-2′-deoxyguanosine (8-OHdG); Age-related ↑↓ GSSG:GSH; ↑ Plasma Glx levels in young patients; ↑ Plasma uric acid and ascorbic acid; ↔ Vitamin E	17-18
Plasma	↑ Uric acid and allantoin; ↓ hypoxanthine and xanthine	19
Plasma and Urine	↓ Plasma melatonin and urinary kynurenine; ↑ Urinary kynurenic acid and anthranilic acid	20
Plasma	↑ Citrulline:arginine and neopterin in demented patients; ↑ NO production	21
Serum	↑ Uric acid	22
Urine	↑ 8-OHdG and MDA	23
Urine	↑ Isoprostane 8,12-iso-iPF2alpha-VI	24
Amniotic Fluid (mRNA transcription profile)	Dysregulation of oxidative stress response genes; phospholipids, ion transport molecules, heart, muscle, structural proteins, and DNA damage repair genes	25

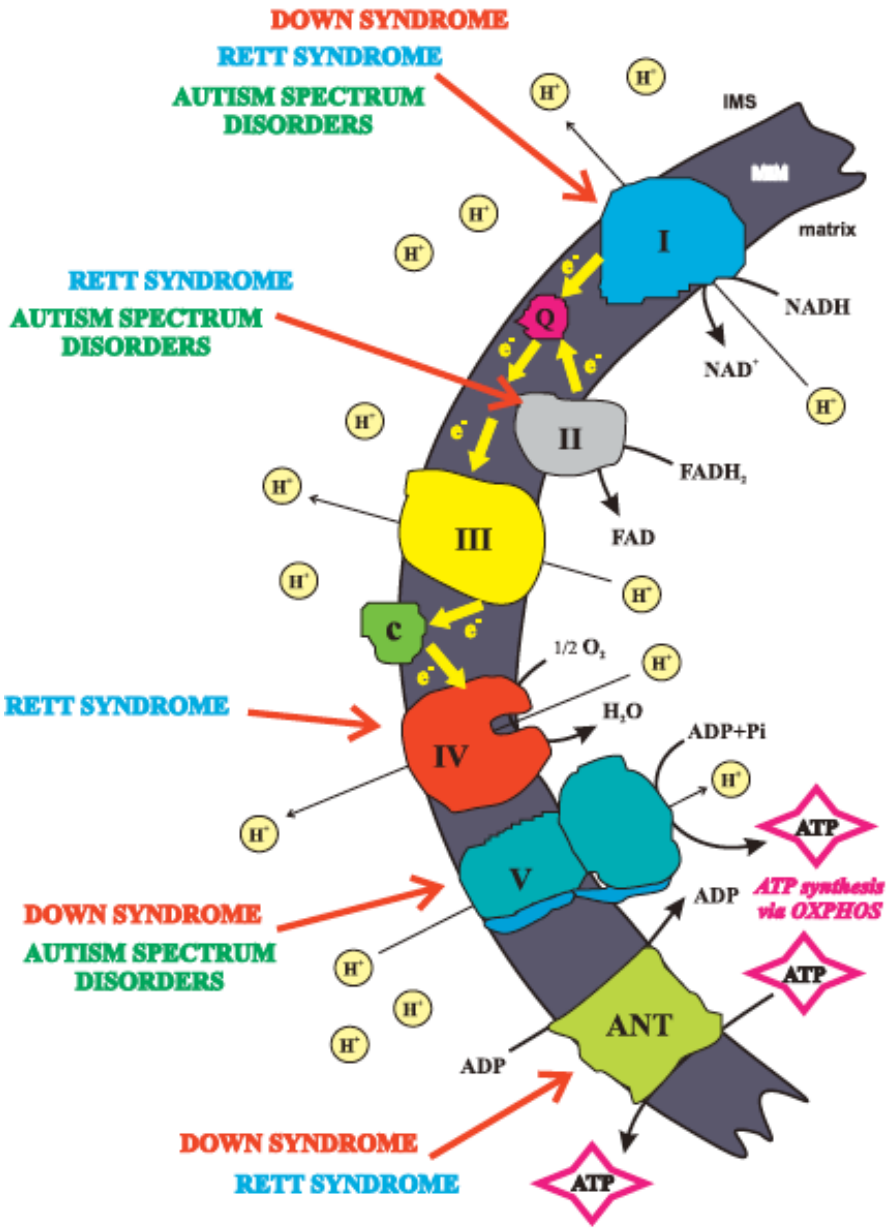
Mitochondrial Dysfunction

Table 2. Main mitochondrial anomalies/dysfunctions reported in cells from DS patients or from trisomy 16 mice

Cells/Organisms	Endpoints	References
Platelets from DS patients	↓ Monoamine oxidase, cytochrome oxidase and isocitrate dehydrogenase	39
Trisomy 16 cerebellar neurons	↑ Levels of microtubules, abnormally shaped mitochondria and dense bundles of abnormal filaments	40
Brain of mouse trisomy 16	↑ $O_2^{-\cdot}$ formation; ↓ respiration with the Complex I substrates malate and glutamate but not with the Complex II substrate succinate; ↓ the 20 kDa subunit of Complex I; ↓ pyruvate dehydrogenase levels	41-43
Astrocyte and neuronal cultures from foetal DS brain	Alterations in the processing of amyloid beta precursor protein (AbetaPP); impaired mitochondrial function in DS astrocytes	44
Fibroblasts from DS patients	Impaired repair of oxidative damage to mtDNA	45
Heart of DS fetuses	Oligonucleotide microarrays: downregulation of genes encoding mitochondrial enzymes and upregulation of genes encoding extracellular matrix proteins	46
PBMC from DS children	↑ Lucigenin-derived chemiluminescence; ↓ $\Delta\Psi(m)$	47

Mitochondrial Dysfunction

D. Valenti et al. / Neuroscience and Biobehavioral Reviews 46 (2014) 202–217



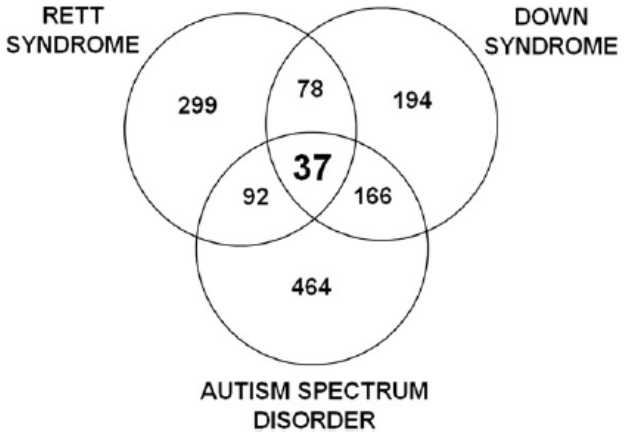
Mitochondrial Dysfunction

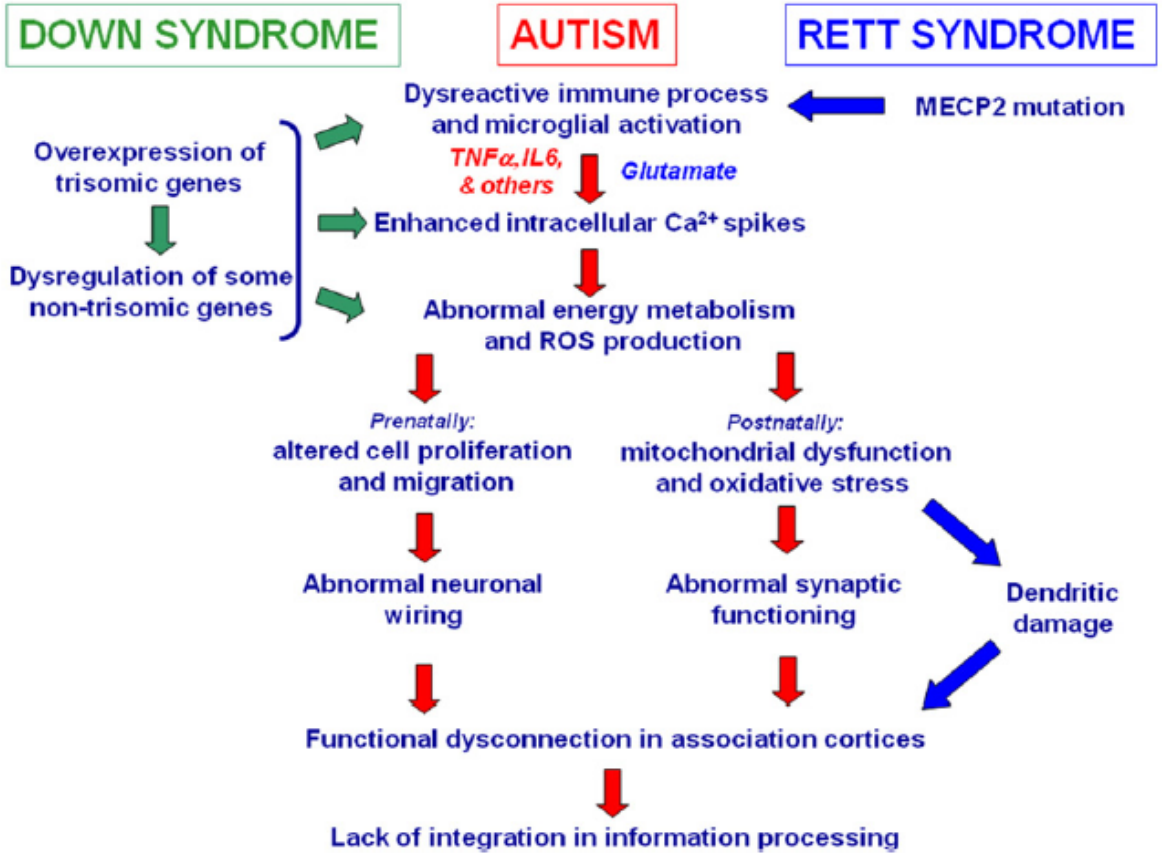
Genome-wide expression studies in Autism spectrum disorder, Rett syndrome, and Down syndrome

Neurobiology of Disease 45 (2012) 57–68

Carla Lintas, Roberto Sacco, Antonio M. Persico *

Laboratory of Molecular Psychiatry and Neurogenetics, University "Campus Bio-Medico", Rome, Italy
Department of Experimental Neurosciences, I.R.C.C.S. "Fondazione Santa Lucia", Rome, Italy





Examples of Genetic Disorder

Phelan-McDermid Syndrome

SCIENTIFIC REPORTS

Mitochondrial Dysfunction may explain symptom variation in Phelan-McDermid Syndrome

Richard E. Frye[1], Devin Cox[2], John Slattery[1], Marie Tippett[1], Stephen Kahler[1], Doreen Granpeesheh[3], Shirish Damle[4], Agustin Legido[4] & Michael J. Goldenthal[4]

Gene	Position	Enzyme Name and Function	Disease Conditions
ACO2	22q13.2	• Mitochondrial aconitase	• infantile cerebellar-retinal degeneration
		• Second enzymes in the tricaboxylic acid cycle	
NDUFA6	22q13.2	• Nicotinamide adenine dinucleotide-ubiquinone oxidoreductase 1 alpha subcomplex 6	
		• Subunits of electron transport chain complex I[5]	
TRMU	22q13.31	• Transfer ribonucleic acid 5-methlaminomethyl-2-thiouridylate methyltransferase	• Aminoglycoside-induced and nonsyndromic deafness[7]
		• Modification of mitochondrial transfer ribonucleic acid[6]	• Acute infantile liver failure[8]
SCO2	22q13.33	• Homolog of S. Cerevisiae	• Fatal infantile cardioencephalomyopathy[9–13]
		• Assembly of electron transport chain complex IV[9]	• Spontaneous abortion[12]
		• Cytochrome c oxidase deficiency[10]	• Autism[14]
TYMP	22q13.33	• Thymidine phosphorylase	• Mitochondrial deoxyribonucleic acid depletion syndrome-1
		• Deoxynucleotide metabolism[15]	• Mitochondrial neurogastrointestinal encephalopathy[10,16]
CPT1B	22q13.33	• Mitochondrial carnitine palmitoyltransferase	• Heterozygous deletions can result in embryonic death or fatality after cold-challenge in mice[18]
		• Transports long-chain fatty acyl-CoA from the cytoplasm into the mitochondrial[17]	

SCIENTIFIC REPORTS

Mitochondrial Dysfunction may explain symptom variation in Phelan-McDermid Syndrome

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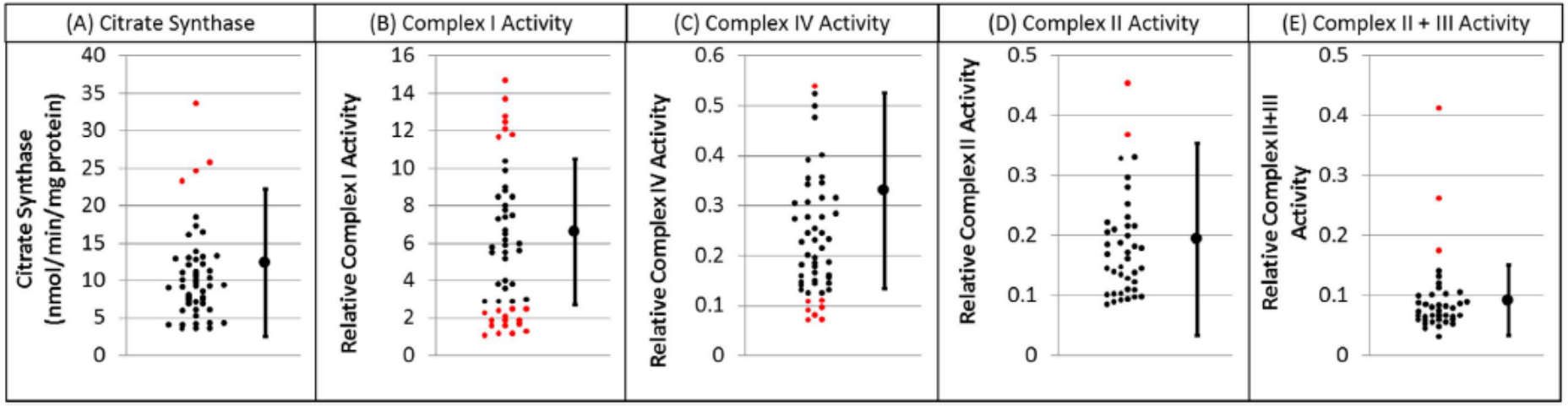

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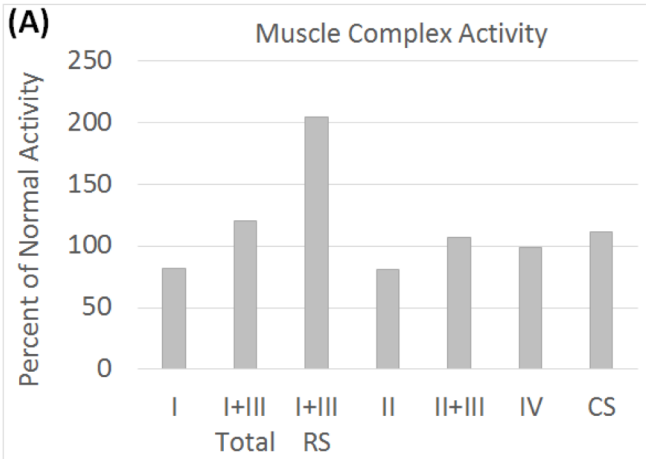
	Complex I Underactivity	Complex I Overactivity
Development		
ASD	44% (4/9)	75% (3/4)
Regression	63% (5/8)	100% (4/4)
Loss of Language	80% (4/5)	75% (3/4)
Loss of Social Skills	40% (2/5)	100% (4/4)
Loss of Gross Motor Skills	60% (3/5)	0% (0/4)
Loss of Fine Motor Skills	80% (4/5)	25% (1/4)
Proximal Trigger	80% (4/5)	0% (0/4)
ASD Regression Typical Age	20% (1/5)	75% (3/4)
Mean (SD) Age at Regression	63 m (29 m)	27 m (16 m)
Multiple Regressions	60% (3/5)	25% (1/4)

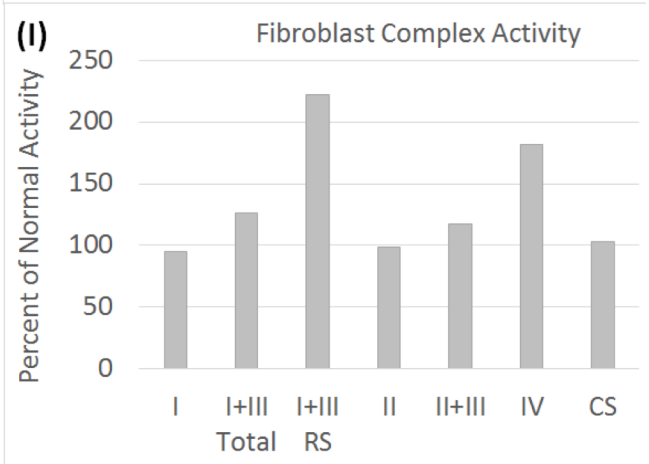
Examples of Genetic Disorder

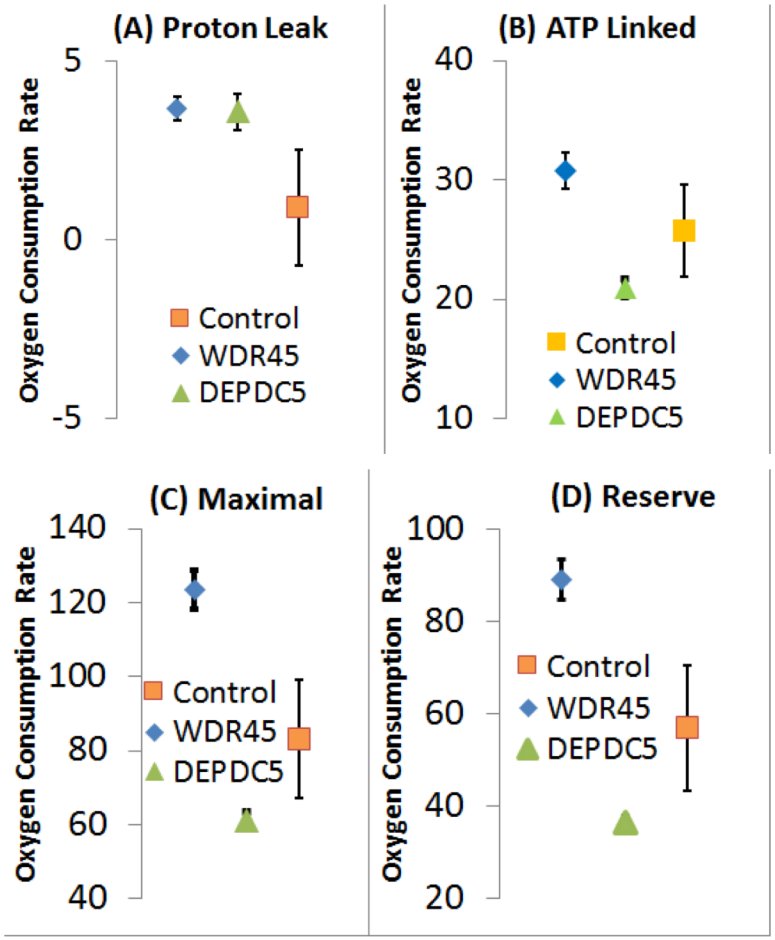
WDR45

Mitochondrial Dysfunction

De novo mutations in the autophagy gene *WDR45* cause static encephalopathy of childhood with neurodegeneration in adulthood







Mitochondrial Dysfunction

Potential Treatments

Mitochondrial Dysfunction in Autism

Table 3. Agents commonly used to treat PMD and SMD

Vitamin	Dose	Adverse effects	Function
Electron transport chain support			
CoQ10 (reduced): ubiquinol	5–30 mg/kg/day, 1–2×/day	appetite loss, nausea, diarrhea at high doses	energy carrier between complex I and III, and complex II and III
CoQ10 (oxidized): ubiquinone	10–30 mg/kg/day, 1–2×/day		
Electron carrier support			
Niacin (B_3)	50–100 mg given daily	flushing reaction	nicotinamide adenine dinucleotide (NAD) precursor
Riboflavin (B_2)	100–400 mg given daily	nausea at high doses	flavin adenine dinucleotide (FAD) precursor
Energy Storage			
Creatine monohydrate	100 mg/kg/day; 1–2×/day	increased urination	high-energy phosphate buffer precursor to phosphocreatine
Fatty acid oxidation support			
L-carnitine or acetyl-L-carnitine	30–120 mg/kg/day, 1–2×/day	stool loose/fishy smell	carrier of long-chain fatty acids
Biotin (B_7)	5–10 mg/day given daily	none	cofactor for carboxylase enzymes
Mitochondrial enzyme cofactors			
Thiamine (B_1)	50–100 mg given daily	none	cofactor for citric acid cycle enzymes
Pantothenic acid (B_5)	5–1,200 mg/day, 1–3×/day	diarrhea at high doses	precursor to coenzyme A
Pyridoxine (B_6)	200 mg given daily	headache, paresthesia, nausea, headache at high doses	cofactor for over 100 enzymes
Biotin (B_7)	as above	none	cofactor for carboxylase enzymes
Alpha-lipoic acid	50–200 mg given daily	headache, paresthesia, rash, muscle cramps	cofactor for citric acid cycle enzymes
Antioxidants			
CoQ10	as above	as above	targets ETC oxidative stress
L-carnitine	as above	as above	scavenger of organic acids
Vitamin E	200–400 IU given daily	bleeding at high doses	protects cell membranes
Vitamin C	100–500 mg given daily	diarrhea at high doses	protects iron and copper
Redox metabolism support			
Methylcobalamin (B_{12})	5–2,000 μg every 1–3 days	hyperactivity, sleep disruption	supports methylation and folate cycles, and glutathione production
Reduced folate (B_9)	folinic acid 400–800 μg/day	none	supports methylation and folate cycles
N-acetyl-L-cysteine (NAC)	10–70 mg/kg/day, 1–3×/day	diarrhea at high doses	precursor to glutathione
Zinc	10–40 mg daily	suppresses iron and copper absorption	supports superoxide dismutase
Central folate support			
Folinic acid/leucovorin calcium (B_9)	0.5–4 mg/kg/day, 1–3×/day	hyperactivity	supports adequate folate levels in the brain

The Effect of Mitochondrial Supplements on Mitochondrial Activity in Children with Autism Spectrum Disorder

Journal of *Clinical Medicine*

Leanna M. Delhey [1,2], Ekim Nur Kilinc [1], Li Yin [3], John C. Slattery [1,2], Marie L. Tippett [1,2], Shannon Rose [1,2], Sirish C. Bennuri [1,2], Stephen G. Kahler [1,2], Shirish Damle [4], Agustin Legido [4], Michael J. Goldenthal [4] and Richard E. Frye [1,2,*]

Table 3. Means (Standard Error) of Normalized Complex I activity on and off supplements by Mitochondrial Disease group. Supplements that are confirmed to be significant in the stepwise regression are bolded and italicized.

Supplement	No Mitochondrial Disease		Mitochondrial Disease	
	Off Supplement	On Supplement	Off Supplement	On Supplement
Fatty Acids	***0.1 (0.20)***	***1.2 (0.48)***	***−0.3 (0.47)***	***3.1 (0.84)***
Folate	0.2 (0.21)	0.7 (0.5)	***−0.3 (0.49)***	***2.7 (0.79)***

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Table 4. Means (Standard Error) of Normalized Citrate Synthase activity on and off supplements by Mitochondrial Disease group. Supplements that are confirmed to be significant in the stepwise regression are bolded and italicized.

Supplement	No Mitochondrial Disease		Mitochondrial Disease	
	Off Supplement	On Supplement	Off Supplement	On Supplement
Fatty Acids	0.8 (0.17)	1.2 (0.40)	0.3 (0.40)	2.6 (0.70)
Folate	0.9 (0.18)	0.8 (0.40)	0.2 (0.42)	2.4 (0.66)
Antioxidants	0.9 (0.17)	0.8 (0.42)	***0.2 (0.41)***	***2.7 (0.71)***

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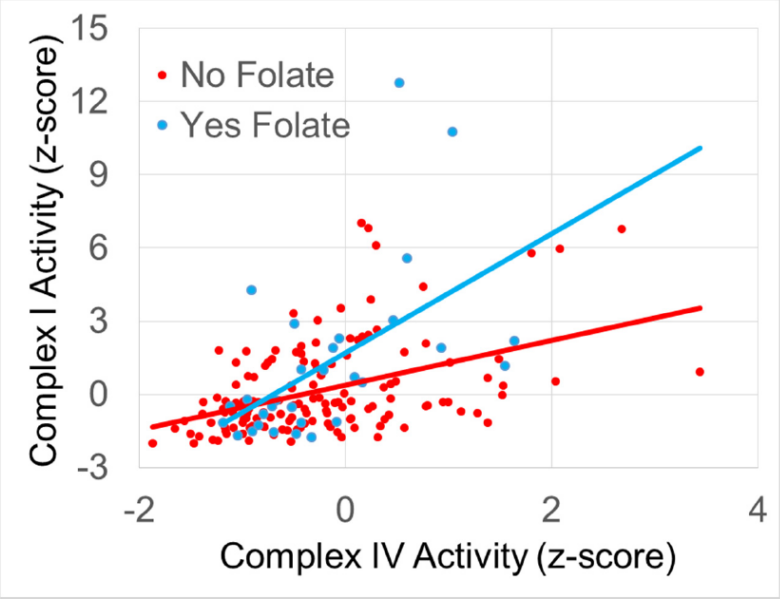

Figure 1. The relationship between Normalized Complex I and IV activity. Folate supplementation is associated with a significantly greater slope in the relationship between complex activities.

The Effect of Mitochondrial Supplements on Mitochondrial Activity in Children with Autism Spectrum Disorder

Journal of *Clinical Medicine*

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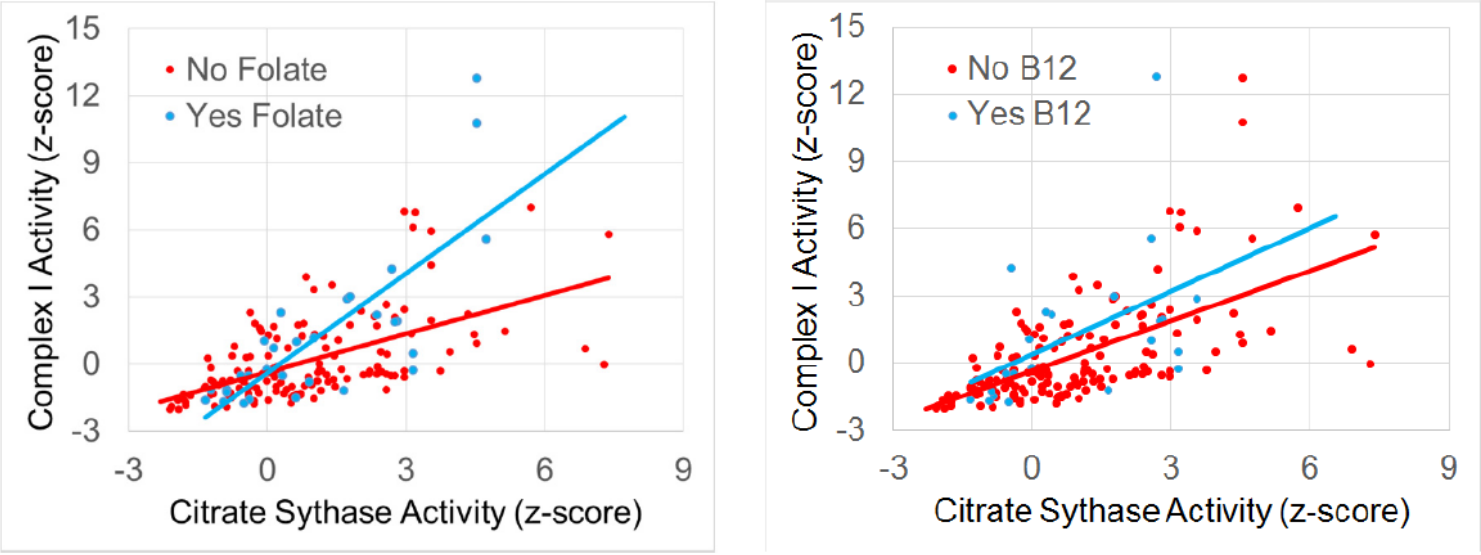

Figure 2. The relationship between normalized Complex I and Citrate Synthase activity. (**a**) Folate and (**b**) B12 supplementation are associated with a significantly greater slope in the relationship between Complex I and Citrate Synthase.

Mitochondrial Dysfunction in Autism

Effect of a Combination of Carnitine, Coenzyme Q10 and Alpha-Lipoic Acid (MitoCocktail) on Mitochondrial Function and Neurobehavioral Performance in Children with Autism Spectrum Disorder

Legido A, Goldenthal MJ, Garvin B, Damle S, Corrigan K, Connell J, Thao D, Valencia I, Melvin J, Khurana D, Grant M, Newschaffer CJ

Objective: To determine if patients with ASD and mt dysfunction would improve clinically and/or biochemically on a combination of carnitine, coenzyme Q10 and alpha-lipoic acid *(MitoCocktail)* in an open-label pilot trial with a baseline-treatment-baseline design.

Results: Mean buccal complex I/IV activity ratio was significantly ($p<0.02$) reduced during *MitoCocktail* treatment compared to baseline. All subjects showed at least one specific sign of metabolic improvement, which waned 3 months post-treatment in 7 of the 11 participants. Of the 11 total or subscale scores considered, all showed change in means from Time 1 to Time 2. Statistically significant changes were observed for the Unusual Behavior subscale from the ASRS ($p<0.006$), the Lethargy subscale from the ABC ($p <0.01$), and the Inappropriate Speech subscale from the ABC ($p<0.02$). From Time 2 to Time 3, scores worsened on each of these three subscales with statistically significant changes on Lethargy ($p<0.01$) and Inappropriate Speech subscales ($p<0.007$).

Adams *et al. BMC Pediatrics* 2011, **11**:111
http://www.biomedcentral.com/1471-2431/11/111

BMC Pediatrics

RESEARCH ARTICLE Open Access

Effect of a vitamin/mineral supplement on children and adults with autism

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BARROW Neurological Institute

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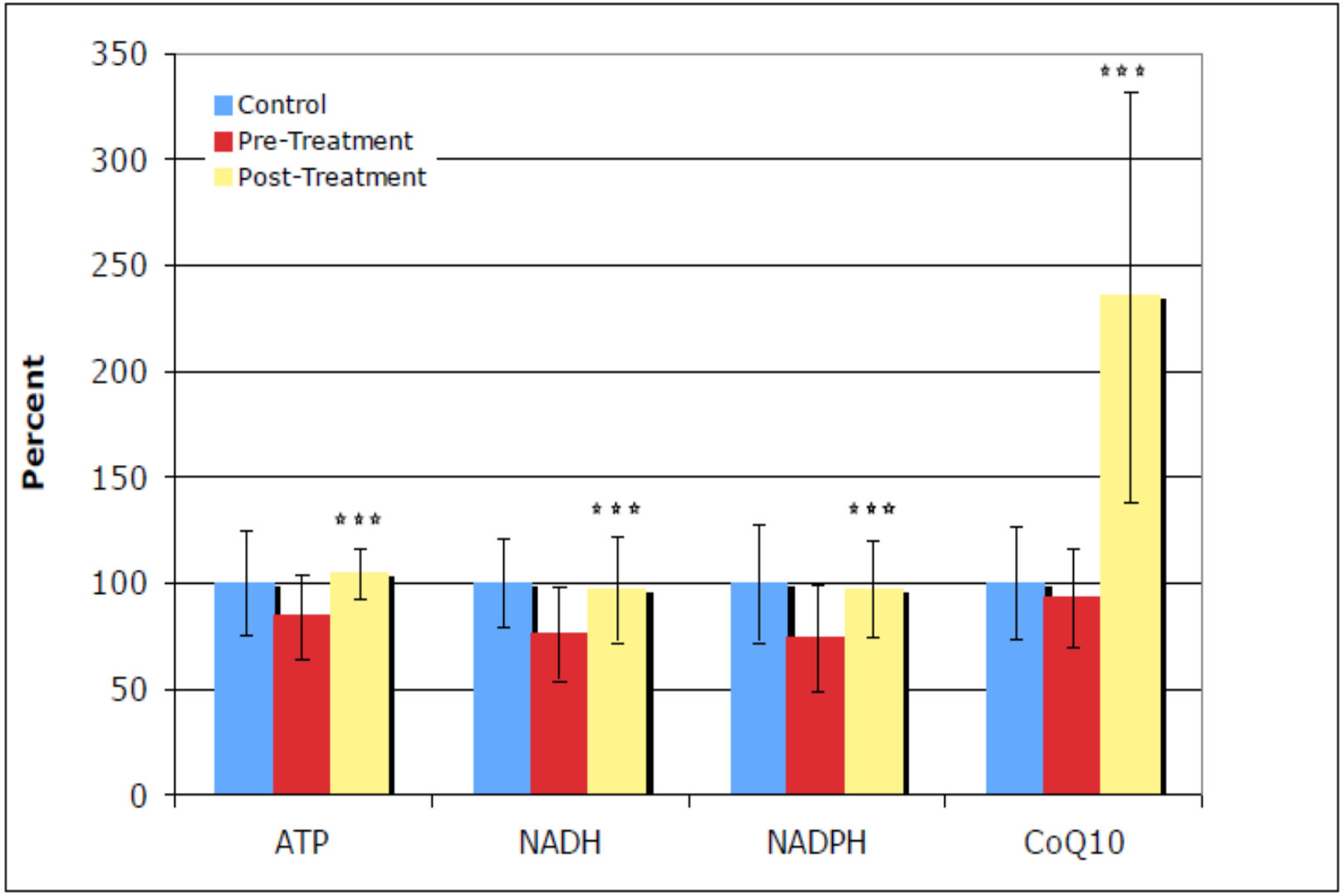
Mitochondrial Dysfunction in Autism



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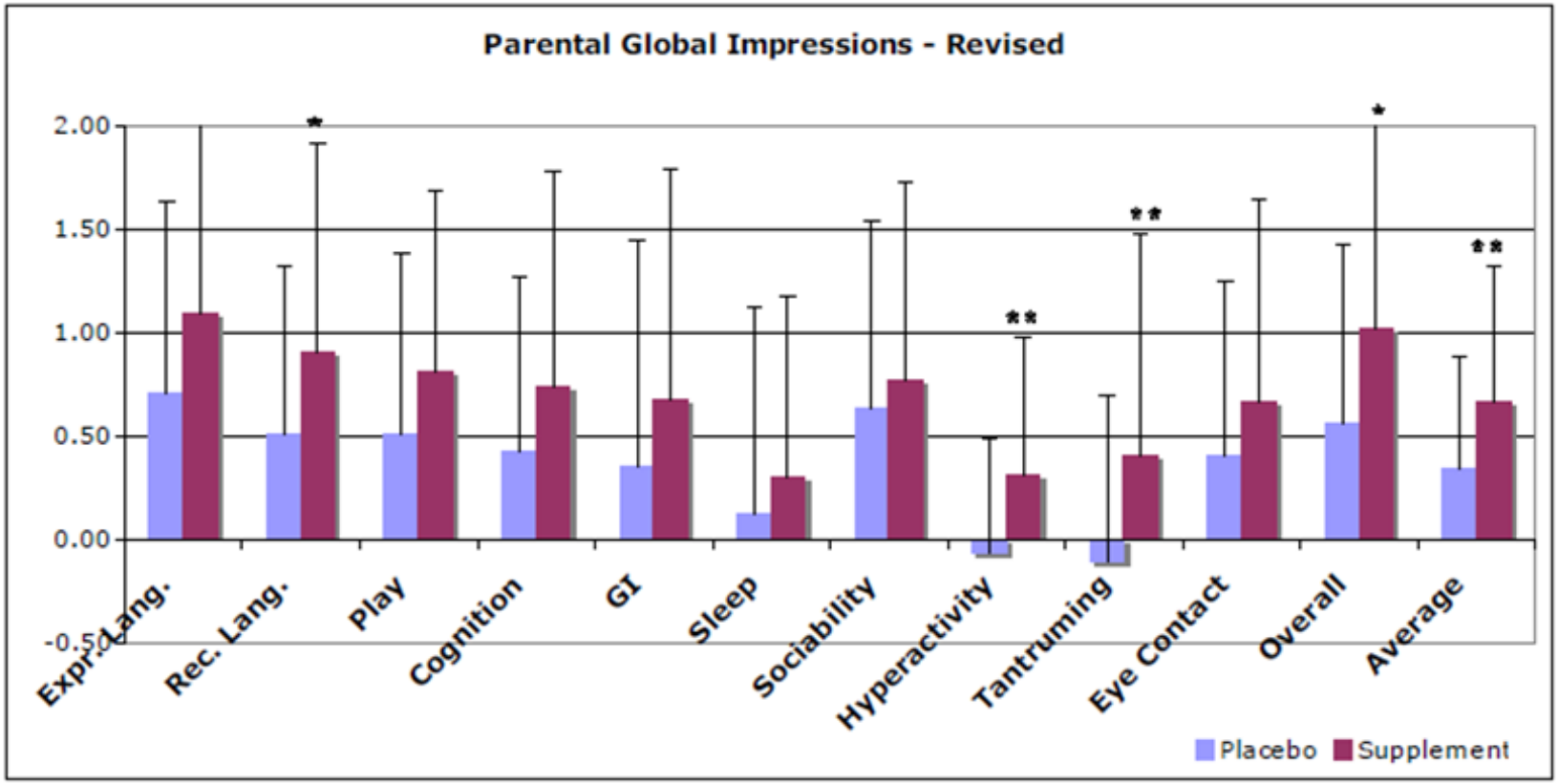
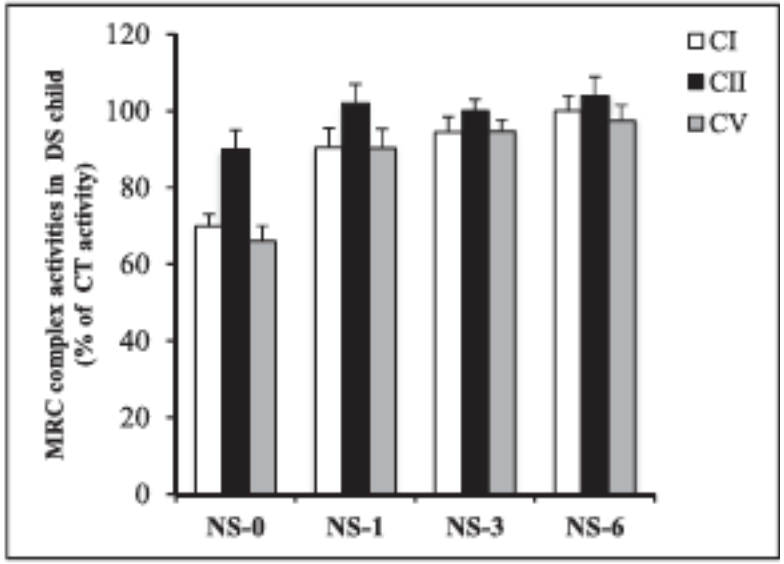


Mitochondrial Dysfunction

Clinical Nutrition 34 (2015) 783–784

Green tea EGCG plus fish oil omega-3 dietary supplements rescue mitochondrial dysfunctions and are safe in a Down's syndrome child



Laboratory analysis				
		EGCG/fish oil diet supplementation		
	Basal	1 month	3 months	6 months
Creatinine (ref 0.6-1.3 mg/dL)	0.69	0.66	0.69	0.65
GOT/AST (ref. 0-35 U/L)	23	27	26	30
GPT/ALT (ref. 0-45 U/L)	21	21	26	35
Total Cholesterol (ref. < 200 mg/dL)	166	162	172	165
HDL Cholesterol (ref. 30-75 mg/dL)	64	65	62	70
LDL Cholesterol (ref. < 150 mg/dL)	87	83	92	79
Triglycerides (ref. 40-160 mg/dL)	74	72	91	80
Folic acid (ref 3-20 ng/mL)	3.01	1.90	18.40*	6.20**
FT3 (eu. 2.75-7.80 nmol/L)	5.36	5.46	6.25	7.90
FT4 (eu. 10.2-22.7 pmol/L)	13.9	14.3	13.8	16.1
TSH (eu. 0.40-4.00 uU/mL)	6.26	6.63	5.82	3.57
Thyroglobulin (ref 0-78 ng/mL)	112.70	44.8	37	57
Ab anti-Thyroglobulin (Neg. < 18.00 UI/mL)	19.00	17.1	9.4	5.9
Ab anti-TPO (Neg. < 28.0 UI/mL)	18.6	25	20.7	16

*supplementation of 1 cp (0.4 mg folic acid)/die
** supplementation of 1 cp (0.4 mg folic acid)/2 die

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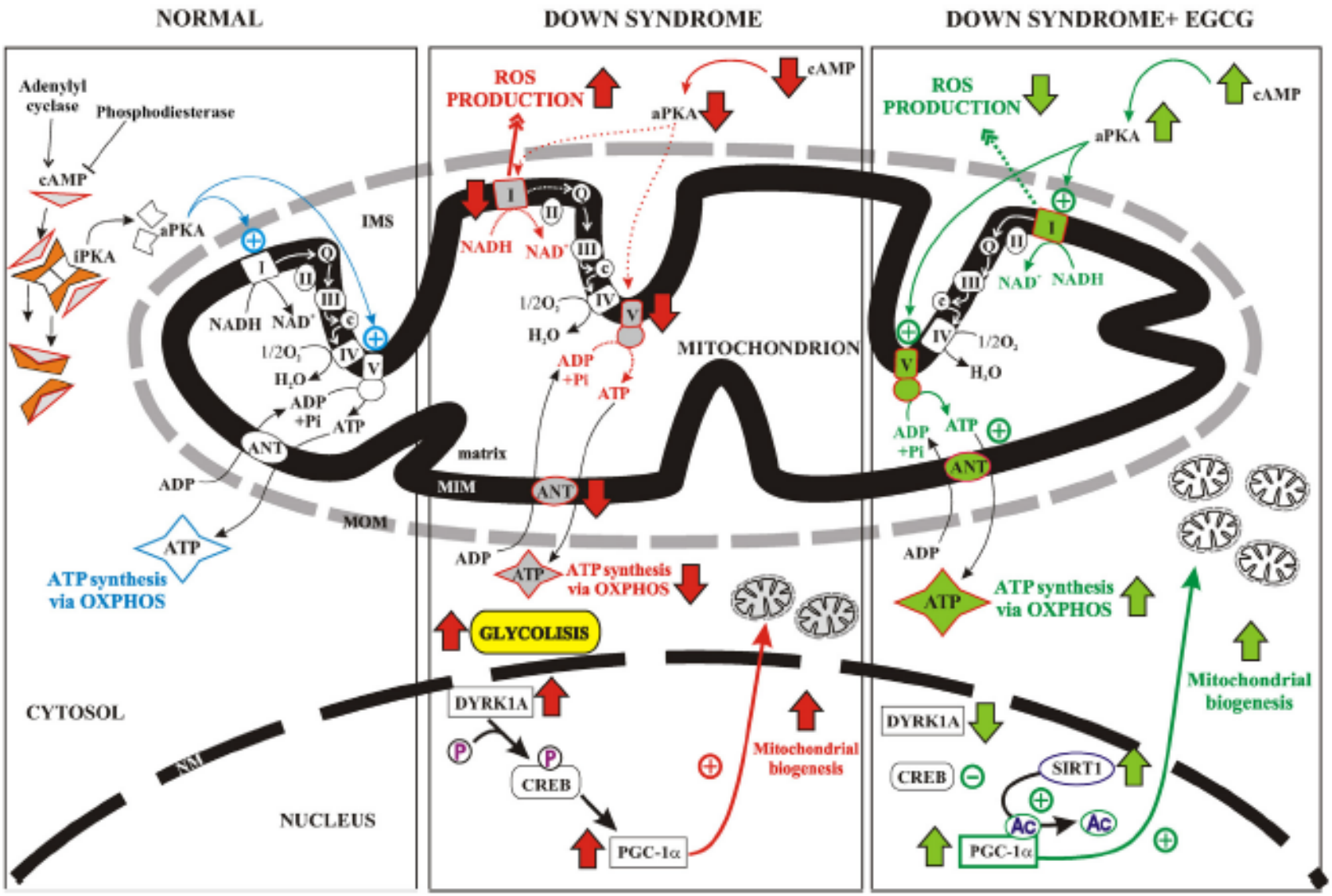
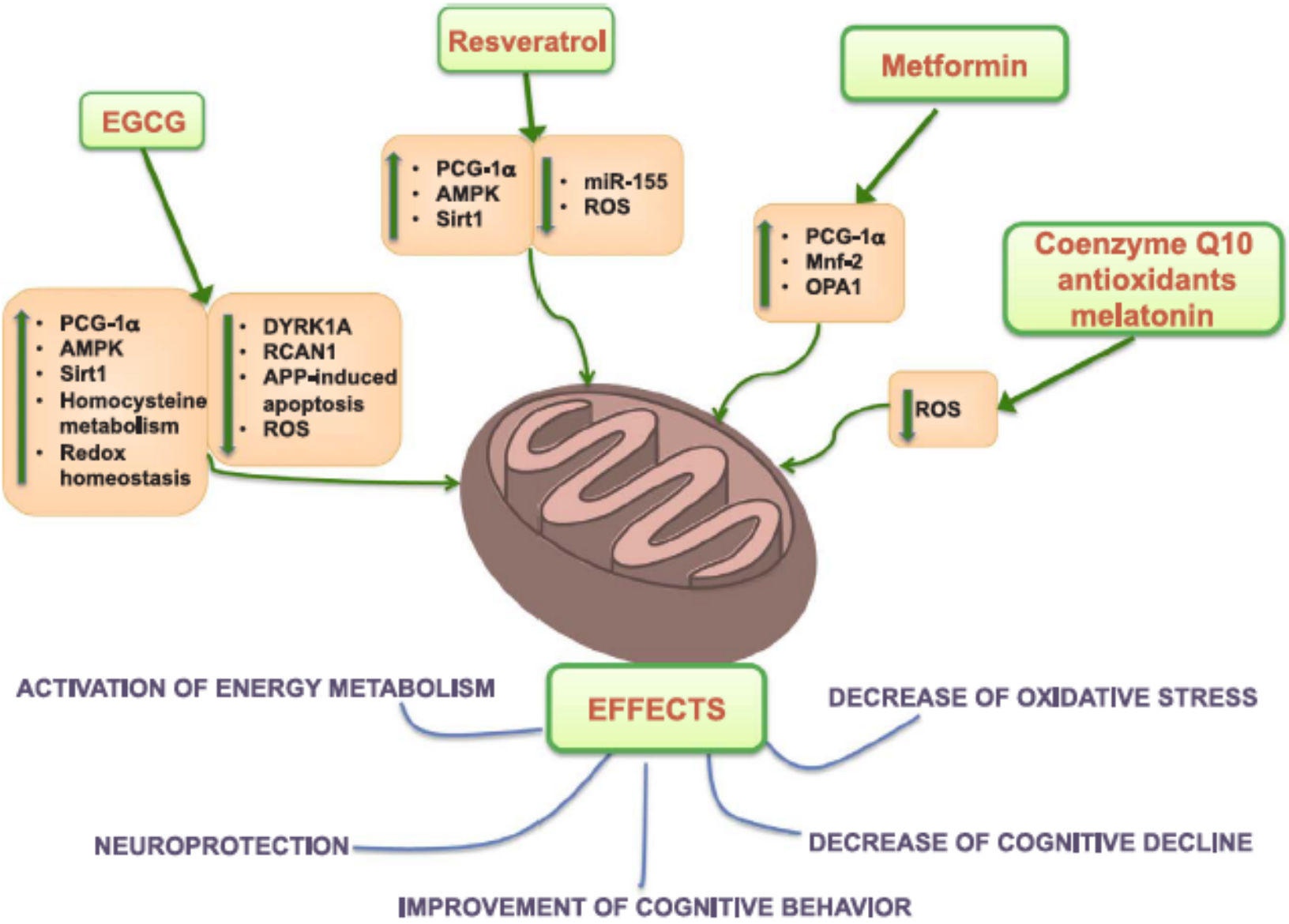
Mitochondrial Dysfunction



Mitochondrial Dysfunction



Mitochondrial Dysfunction in Autism

REVIEW ARTICLE
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Treatments for biomedical abnormalities associated with autism spectrum disorder

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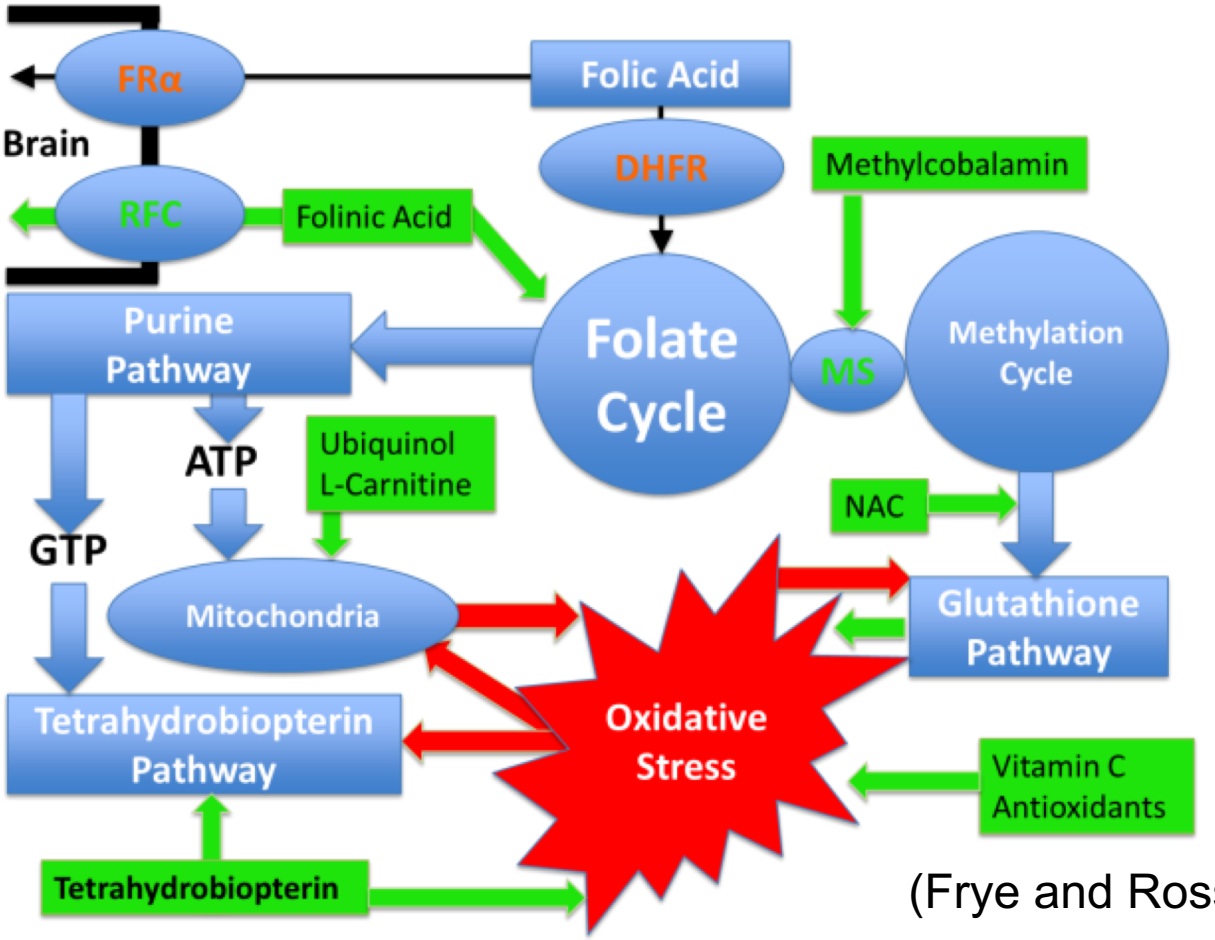

(Frye and Rossignol, 2014)

Identification and Treatment of Pathophysiological Comorbidities of Autism Spectrum Disorder to Achieve Optimal Outcomes

Libertas Academica
FREEDOM TO RESEARCH

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ABSTRACT: Despite the fact that the prevalence of autism spectrum disorder (ASD) continues to rise, no effective medical treatments have become standard of care. In this paper we review some of the pathophysiological abnormalities associated with ASD and their potential associated treatments. Overall, there is evidence for some children with ASD being affected by seizure and epilepsy, neurotransmitter dysfunction, sleep disorders, metabolic abnormalities, including abnormalities in folate, cobalamin, tetrahydrobiopterin, carnitine, redox and mitochondrial metabolism, and immune and gastrointestinal disorders. Although evidence for an association between these pathophysiological abnormalities and ASD exists, the exact relationship to the etiology of ASD and its associated symptoms remains to be further defined in many cases. Despite these limitations, treatments targeting some of these pathophysiological abnormalities have been studied in some cases with high-quality studies, whereas treatments for other pathophysiological abnormalities have not been well studied in many cases. There are some areas of more promising treatments specific for ASD including neurotransmitter abnormalities, particularly imbalances in glutamate and acetylcholine, sleep onset disorder (with behavioral therapy and melatonin), and metabolic abnormalities in folate, cobalamin, tetrahydrobiopterin, carnitine, and redox pathways. There is some evidence for treatments of epilepsy and seizures, mitochondrial and immune disorders, and gastrointestinal abnormalities, particularly imbalances in the enteric microbiome, but further clinical studies are needed in these areas to better define treatments specific to children with ASD. Clearly, there are some promising areas of ASD research that could lead to novel treatments that could become standard of care in the future, but more research is needed to better define subgroups of children with ASD who are affected by specific pathophysiological abnormalities and the optimal treatments for these abnormalities.

KEYWORDS: autism spectrum disorders, carnitine, cobalamin, epilepsy, folate, genetic disorders, mitochondrial dysfunction, review


Questions