"How Microbes Can Change Your Mind- Microbial Metabolites in Neurodevelopmental Disorders"

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Why the increase?
Why is this happening?

Anxiety,Depression,Obesity, Eating Disorders,OCD, Alzheimer,Autism

Nature of Things “Autism Enigma” (CBC)

Faculty Disclosure

Commercial Interest	Nature of Relevant Financial Relationship (Include all those that apply)	
	What was received	**For what role**
• None	• N/A	N/A

Presentation Learning Objectives

After participating in this presentation, learners should be better able to:

- To examine evidence for possible dietary, gastrointestinal, metabolic and infective links to autism spectrum disorders (ASD)
- To examine, from a biological perspective that the microbiome, may have evolved to modulate host metabolism and behavior to ensure their survival and spread.
- To explore the possibility that alteration of the enteric microbiome via the Western diet and antibiotics select for ASD associated enteric bacteria (Clostridia, Desulfovibrio), whose metabolic short chain fatty acid fermentation products (i.e. propionic acid) may be environmental triggers of (ASD) in a subset of patients

Presentation Learning Objectives (cont.)

After participating in this presentation, learners should be better able to:

- Through the use of a novel animal model and clinical studies show that enteric short chain fatty acids can induce many behavioral and brain changes, including reversible hyperactive, perseverative, antisocial behavior, seizure and movement disorder, and brain neuroinflammatory, mitochondrial, lipid/acylcarnitine and epigenetic changes consistent with ASDs
- To consider possible heritable and iatrogenic risk factors (maternal/infant long term antibiotics, C-section, hospitalization, colitis, Westernized diet) leading to early alteration in the host microbiome and resultant impairment of carnitine/mitochondrial function being central to ASD pathogenesis and ASD like behaviors in related neurodevelopmental conditions

Presentation Clinical Actions

After participating in this presentation, clinicians should be better able to:

- Potential long term benefits of normal birth practices (vaginal birth, breast feeding) and reduction of inappropriate use of antibiotics when medically appropriate
- Potential physiological mechanisms where diet, gastrointestinal dysfunction, opportunistic infections and metabolic augmentors (i.e. omega 3s, carnitine) may play a role in brain development and behavior
- Cautious optimism regarding ongoing research where preservation or manipulation of the host microbiome may play a role in brain health and disease

Enlarged Brain Size
Increased Neuronal Density
Altered Cell Migration
Seizure Disorder

Systemic Changes
Immune System
Gastrointestinal System
Metabolic Disorder
Detoxification Systems
(glutathione)

Hormonal
Sex Hormones
Oxytocin
Vasopressin

Genetic Factors
Neurotransmitter
Growth Factors
Cell-cell Interaction
Sex Linked (Fragile X)
Metabolism (carnitine synthesis)

White Matter Disorder
Glial/microglial Changes
Neuroinflammation
(Impaired Neurodevelopment and
Cortico-cortical processing)

Environment
Metals
Hydrocarbons
Infectious
Drug (valproate)
Diet- Wheat
Casein Allergy
Carbohydrate?

Genetics is why you look like your father…

And if you don't why you should!

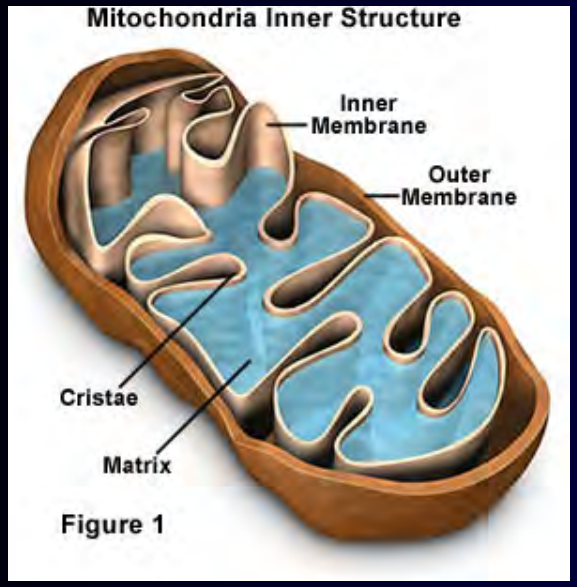
Identical twins often disparate for autism/ severity
Many environmental/infectious factors mimic/impact on Genetic transmissibility
(i.e. Tuberculosis, twins with same/different placenta)
Genetic sensitivity to infection (similar pattern in ASDs!)

Neurodevelopment- “Lets Build a Brain”

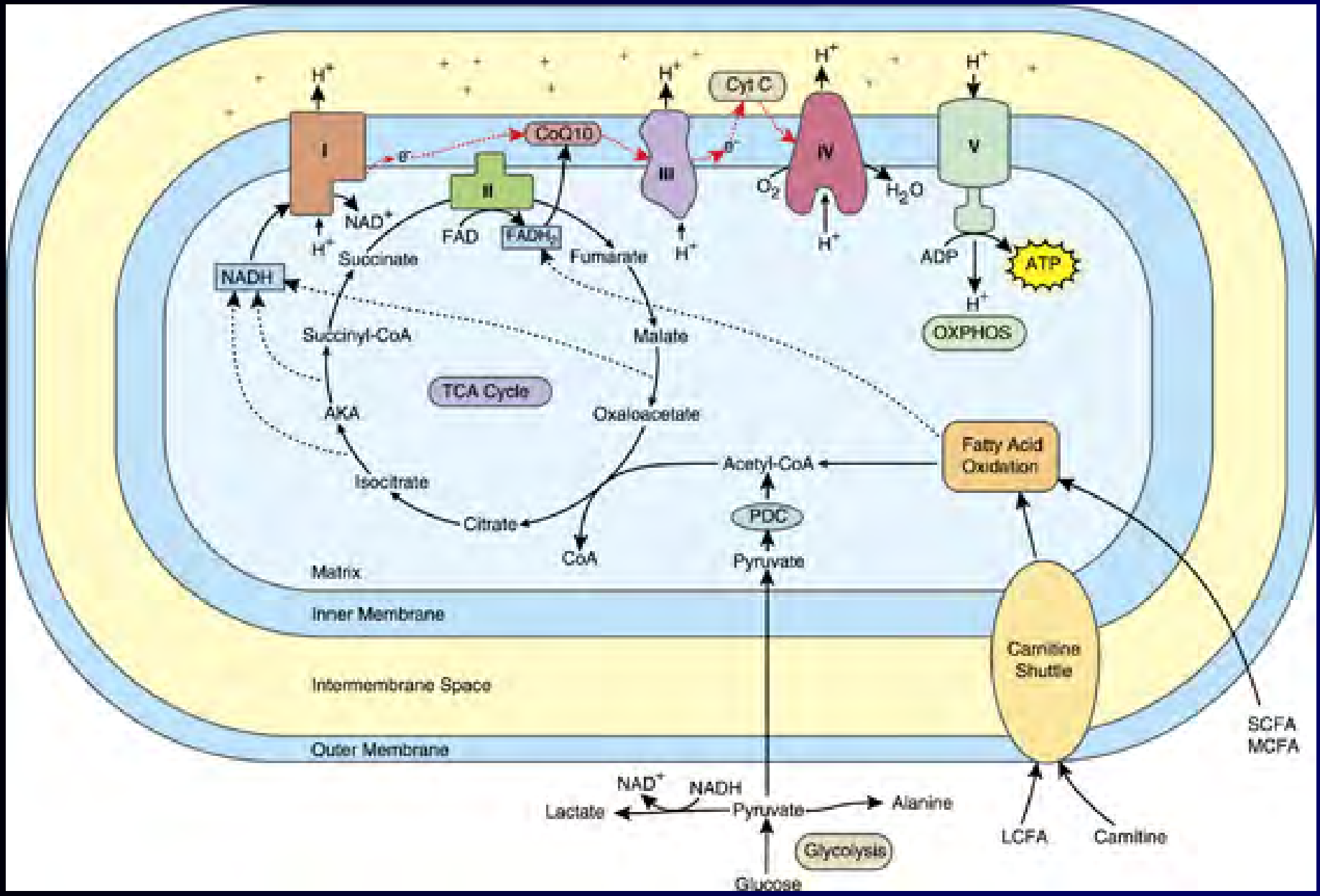
- Complex development
  timing important
- Many neurons die

Genetic (instruction)- Cell Adhesion
Environment
Insults:
Infection (virus)/inflammatory (IL-6)
toxins (alcohol)/metals/drugs(valproate)
Oxidative stress-Redox change- cell fate
(germ cell-fetus-neonate)
Cell to Cell Communication is
Important in the organization of the
developing nervous system
(programmed cell death and ordered cell migration)
Reelin, neurexins , gap junctions, see later……..
environmental factors may alter neurodevelopment

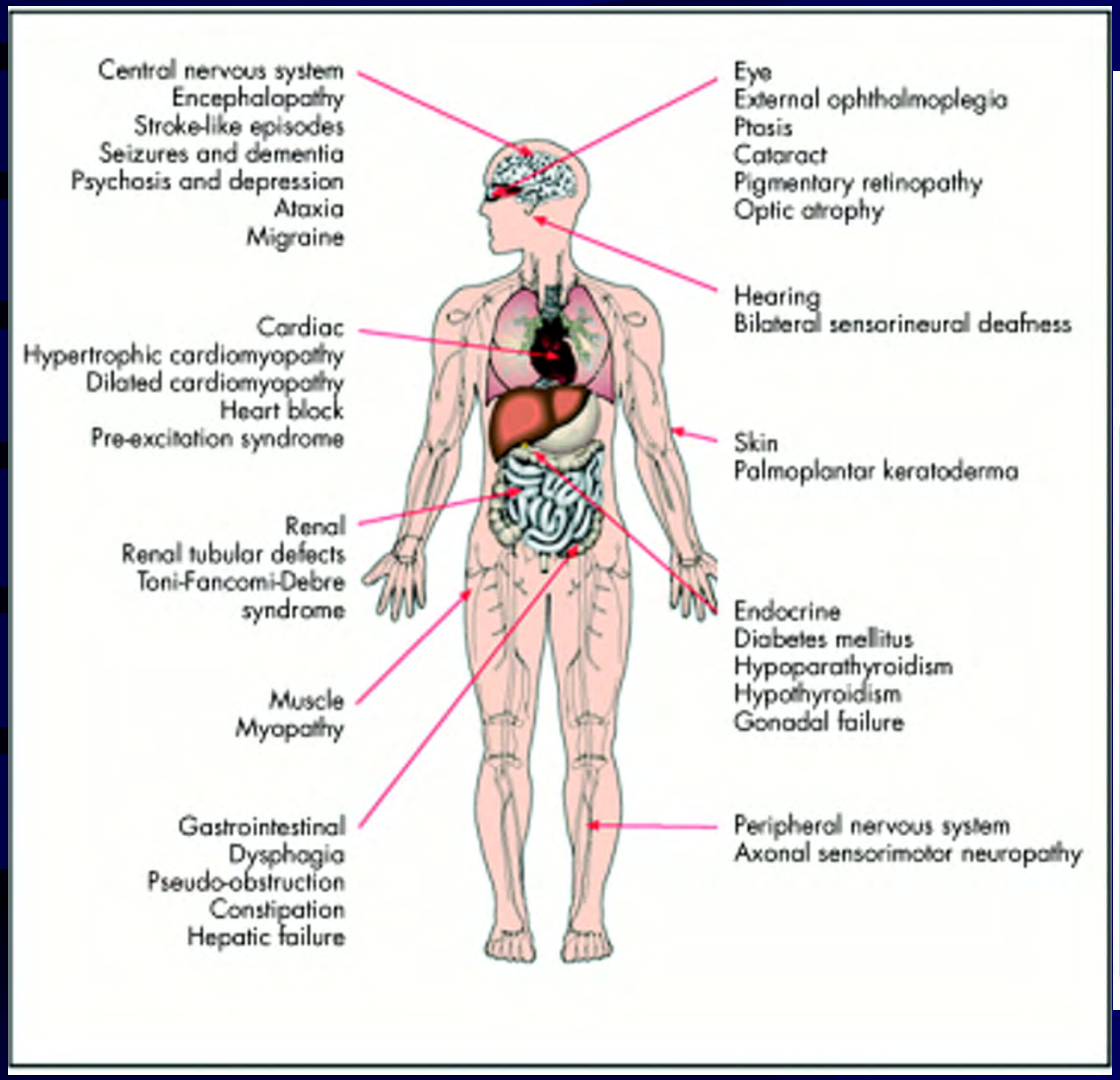
Autism- A Disorder of Energy Utilization and Toxin Elimination

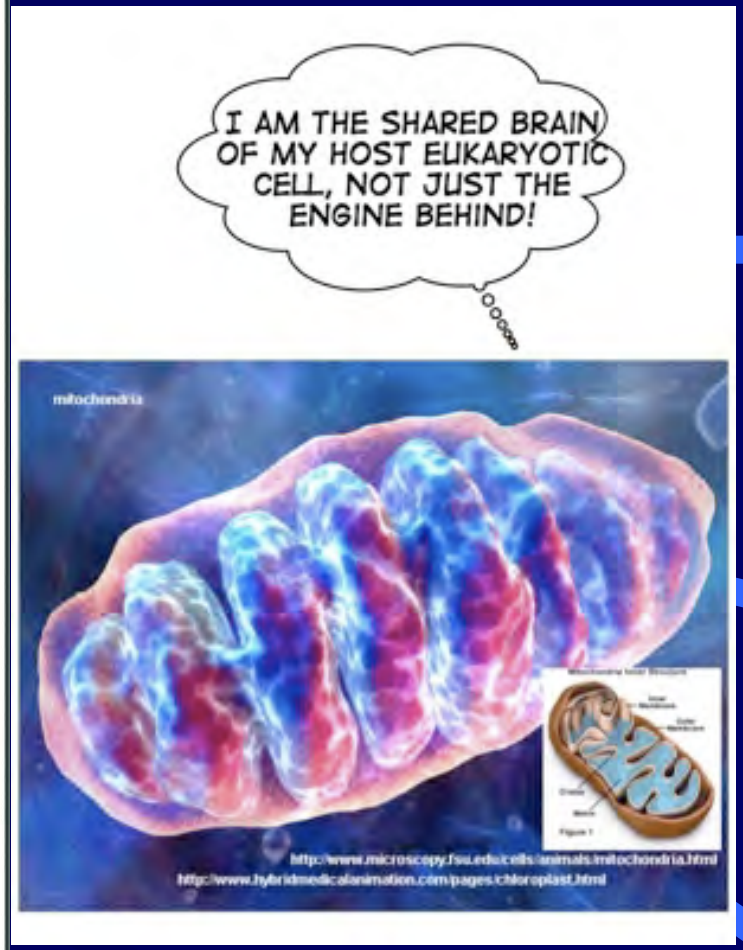


Oxidative Stress (Chauhan, James):
Inflammation, impaired metabolism
Process similar to memory!!!
Antioxidants- glutathione, NAC
Facilitators of mitochondrial function- carnitine, methylation-Methyl B12 (accessibility to CNS?)
A mitochondrial disorder?- Frye
(Mitochondrial DNA mutations- risk)



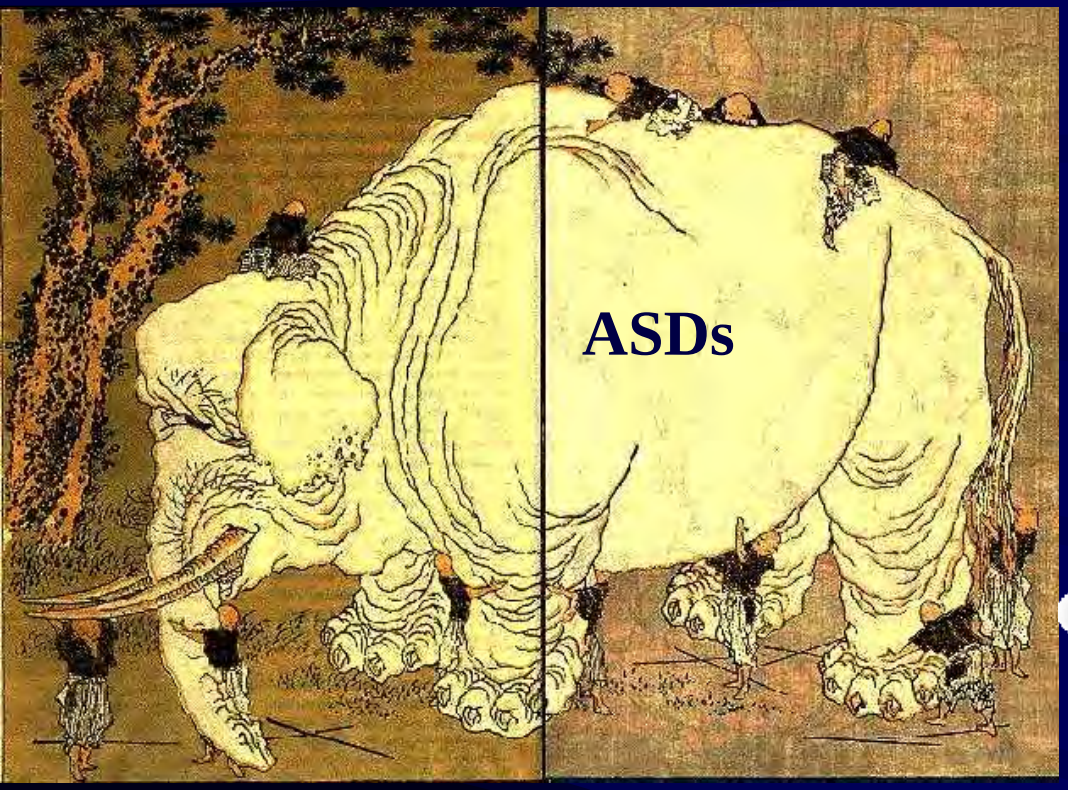
Mitochondrial dysfunction in ASD: Rossignol and Frye 2011

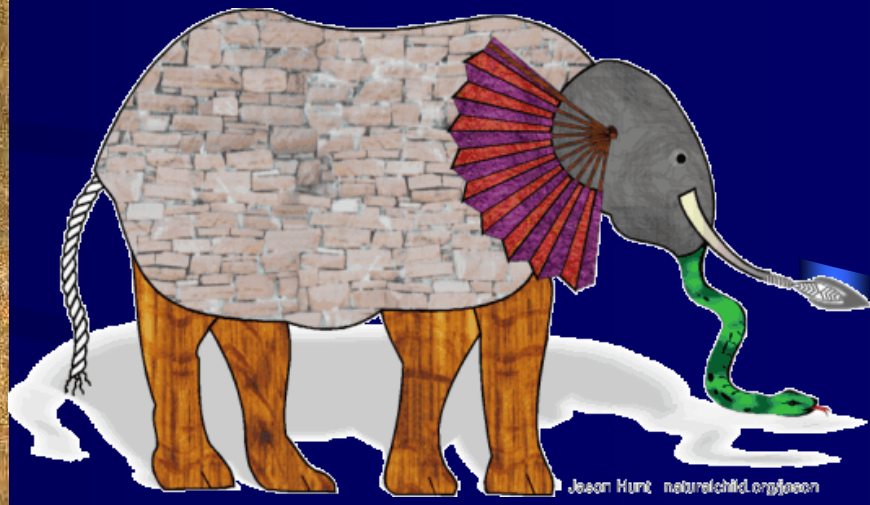




Mitochondrial disease /dysfunction (Frye)
Heterogeneous tissues affected/families/ complex inheritance
Inherited/Acquired mutations/Environmental Worsening

Autism- The Blind Men and the Elephant





Some common underlying cause involving behaviour, brain changes, GI/dietary symptoms, immunology, genetics, oxidative stress, mitochondrial disorder, environment, increase?????

Multidisciplinary International Collaboration- Open Sharing

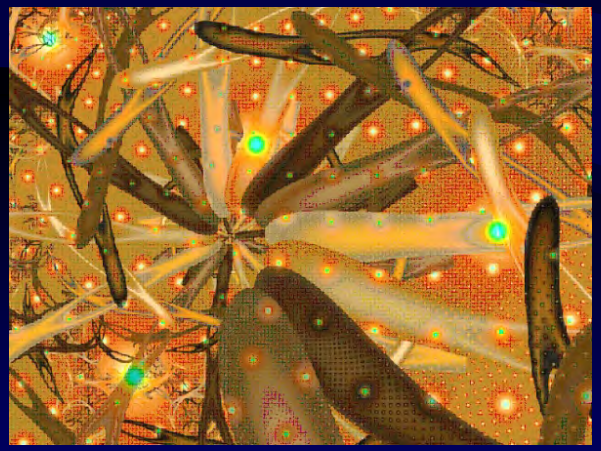
Examining Animal Behaviour to Study Autism

Decreased/altered socialization
fixation on objects
sensitivity to sensory input
repetitive behaviour/ seizure/dystonia
Aggression , variable course
other factors normal/ improved?

Animal autism models
Pre/post natal factors

Examine brain
Development
Electrical Activity
Neuropathology
Gut, Immune
Metabolic markers
for subtle
abnormalities

“GRAIFs” Gut Related Autism Inducing Factors



Microbiome NIH (10x host cells, 100x genes!)

Bacterial metabolites- symbiosis/dysbiosis

Opportunistic Infections- key risk factor
i.e clostridia, yeast (chronic antibiotics)

Cell wall- LPS, beta glucan- innate immunity

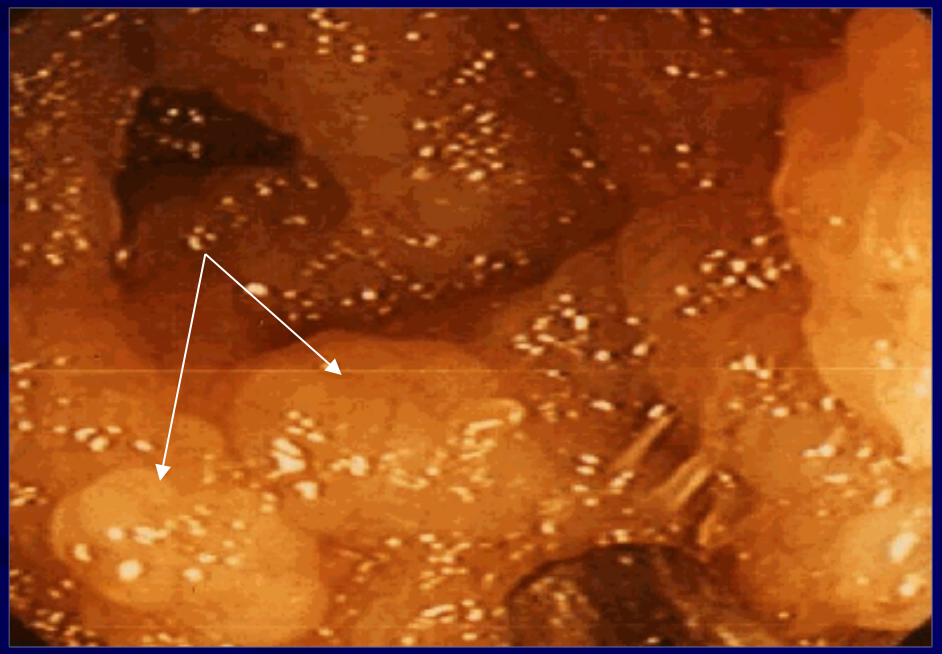
Fermentation products of dietary carbohydrate
- Short chain fatty acids*

Barriers, variable metabolism

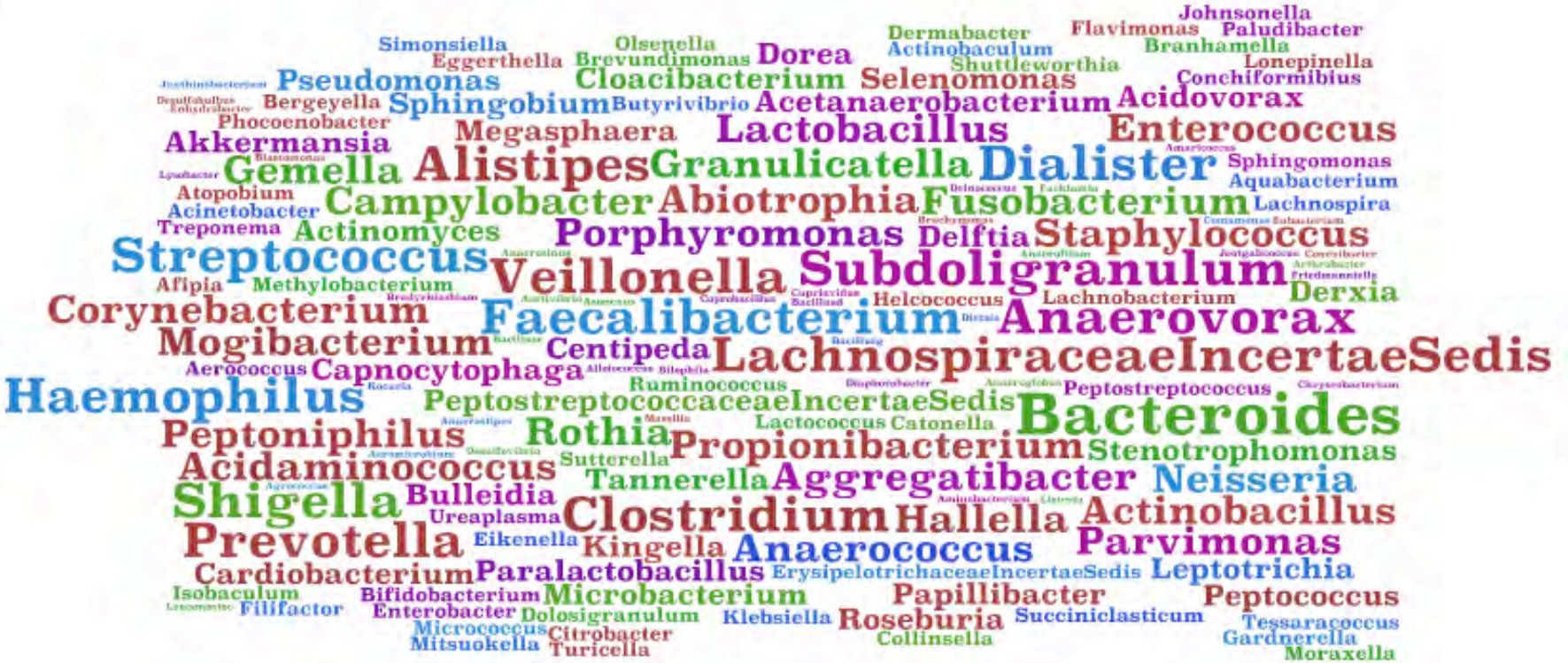
Acquired/genetic (met receptor tyrosine kinase)

Dose, Location & Timing of exposure

Digestive system issues in autism – initially poorly studied But renewed interest/technology (Horvath, Williams, Fasano, Frye ..et MacFabe, 2015 rev)



Intestinal pathology on a subset of autistic patients
Associated with regressive onset and GI symptoms
Impaired carbohydrate digestion, inflammation
unique bacteria- carbohydrate craving
Co morbidity? Consequence? Cause?



The Human Microbiome

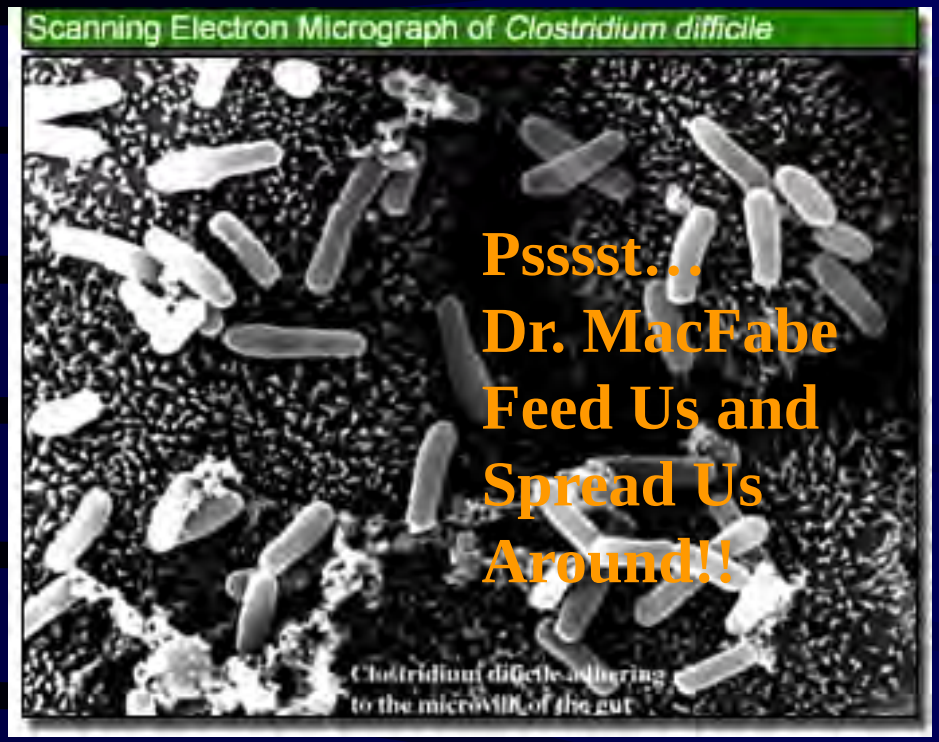
Gut Microbiome- Complex Ecosystem- Alteration with Antibiotics

Obstetrical/Neonatal Microflorae

C section/ Prophylaxis of B Haem Strep
Hospitalization,Antibiotic resistance
Early antibiotic exposure for infection

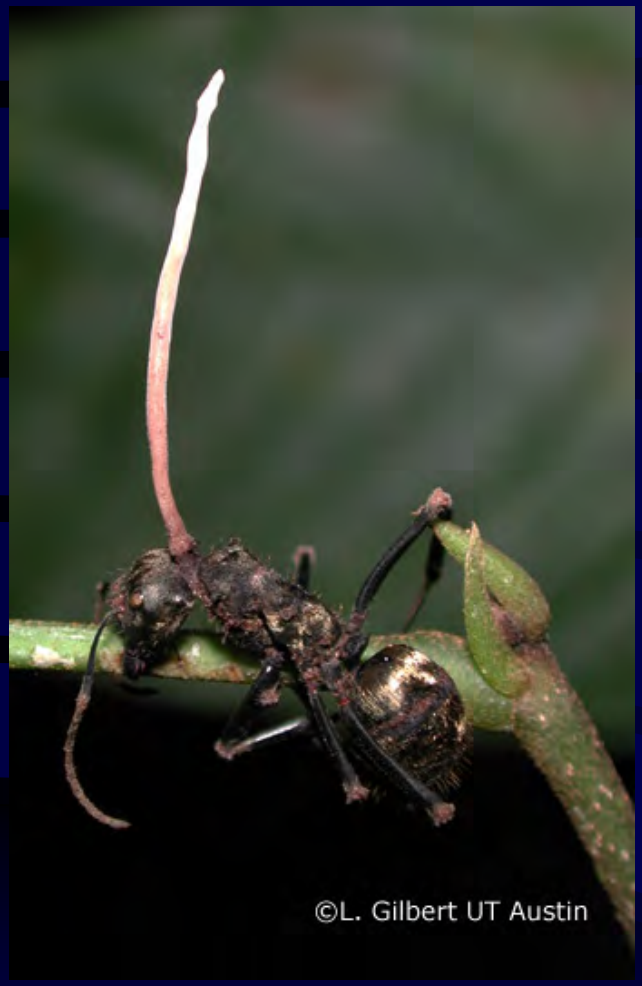
Early alteration of microbiome- risk factor for ASD

Can Enteric Bacteria Affect Brain Development/Behaviour?

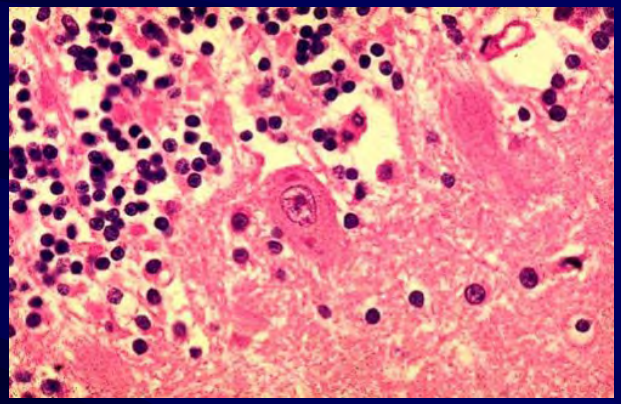


Clinical- Food Craving/Symptom Worsening/ GI symptoms
Gut changes (gluten/casein) poorly studied (antigenic mimicry)
Early gut colonizers- alteration with antibiotics (increased incidence)
Unique bacterial species (clostridials, desulfovibrio, bacteriodetes)
“Leaky” or malabsorbtive digestive tract (impairment of barriers)
Production of bacterial metabolites (fuel for brain)
Effect on Brain development, physiology, behaviour, immune function

Pathogen “Control” of Host Nervous System for Propagation

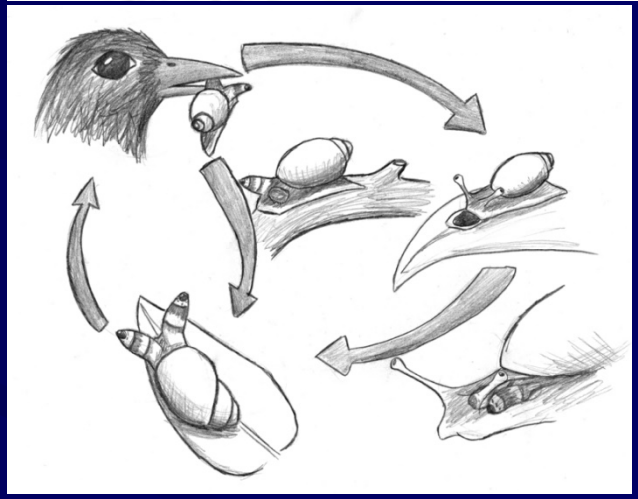


Cordyceps Fungus
Climbing (insects)



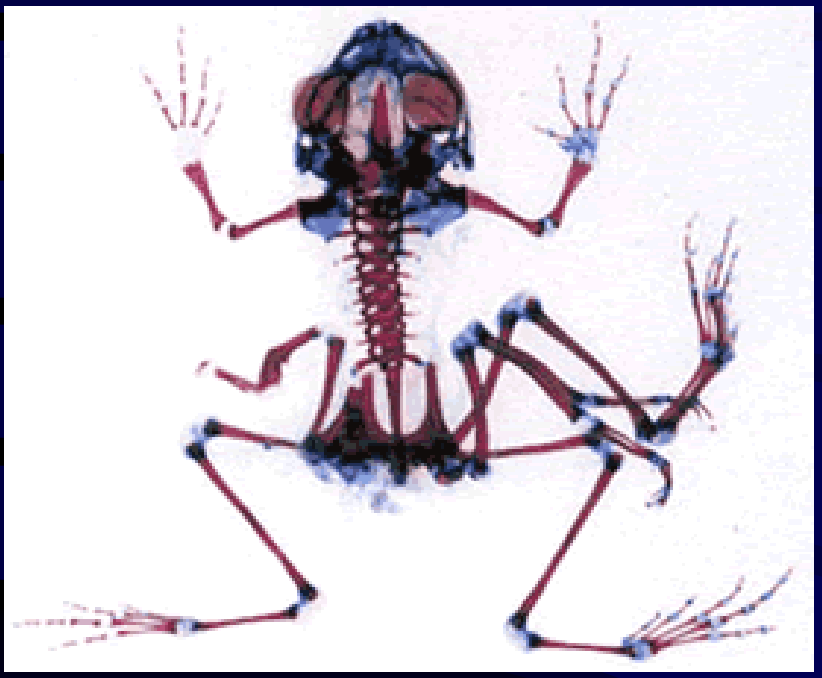
Rabies
biting (mammals)

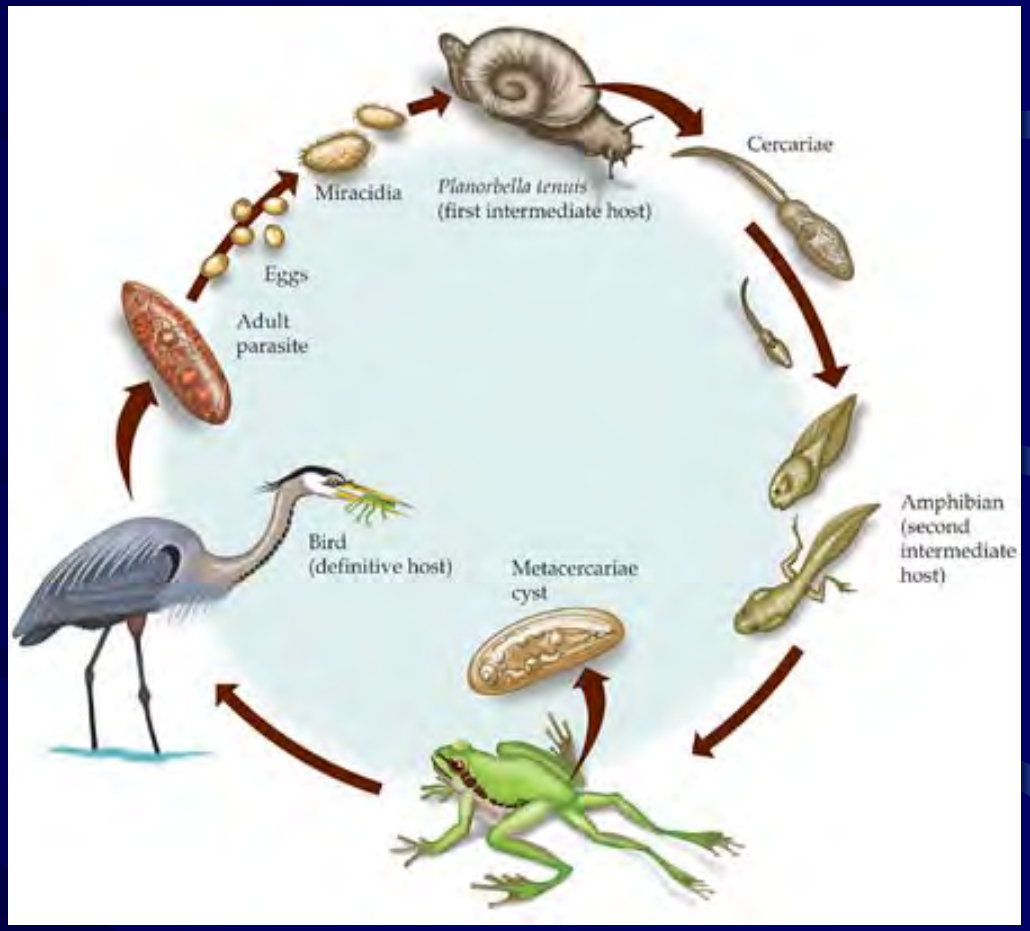
Leucochloridium paradoxum- parasitic flatworm of snails, birds



Parasite passed in feces of bird- eaten by snail
Pulsating eyestocks (mimic caterpillar), attraction to light, eye eaten by bird, but snail has increased longevity!

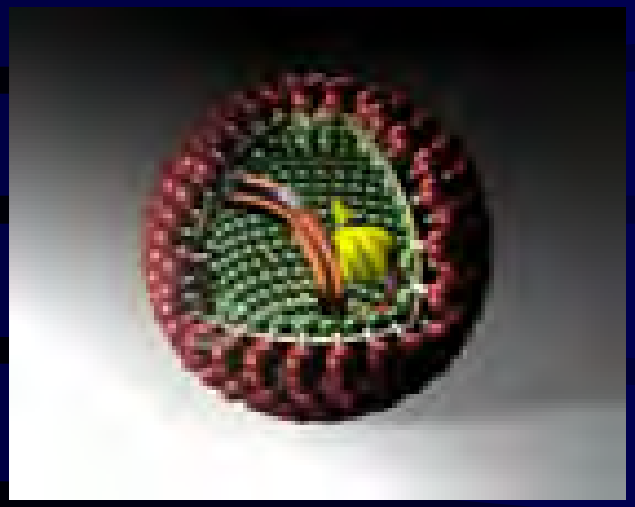
trematode *Ribeiroia ondatrae*

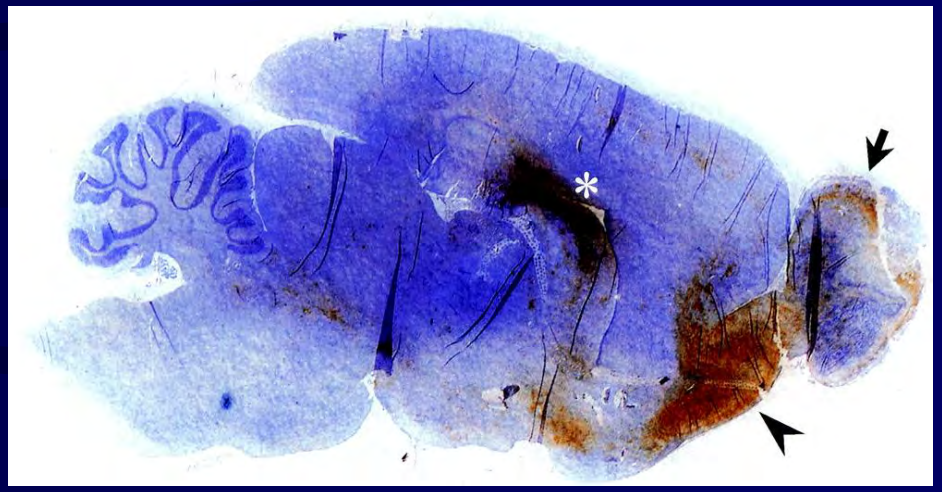




Parasite infects predatory birds, eggs eaten by snails, then infects tadpoles, increased limb development of frog, easier To be eaten by bird etc.!

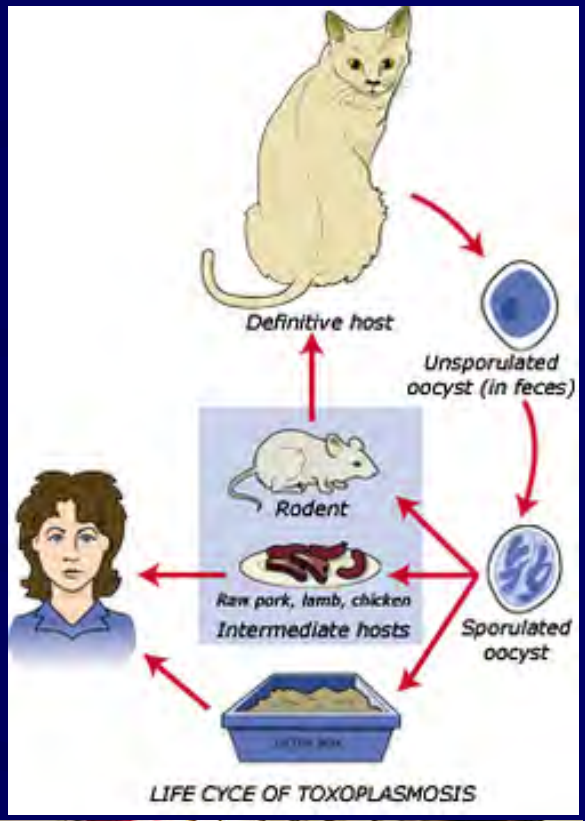
Borna Disease





Brain specific
Mammals, birds
Nasal transmission
Movement disorder
Oral movements
“food in mouth”
Human infection?
(mood disorder
Schizophrenia)

Toxoplasma Gondii

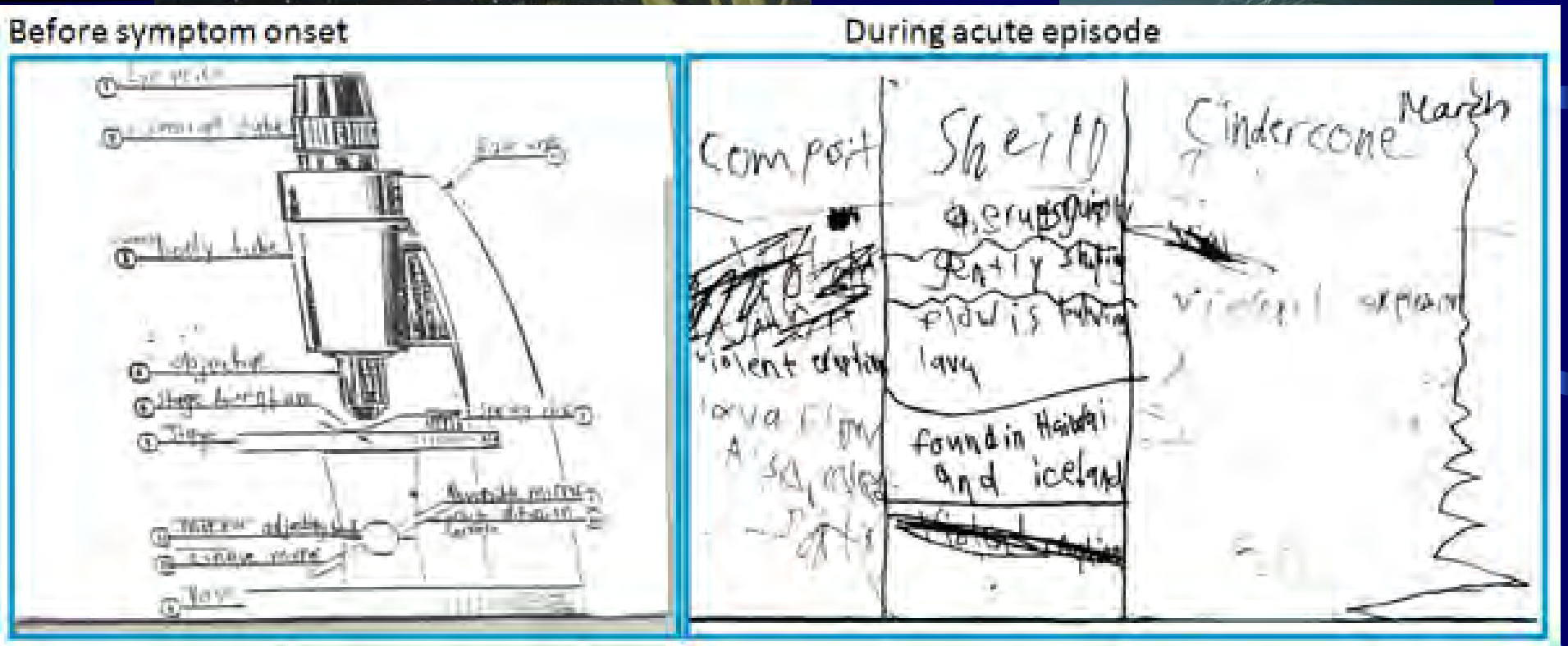


Cat reservoir (gut, stool)

Infected rodent, less “fear” of feline predator, increased dopamine

Link to human depression, risky behaviour, schizophrenia

Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infection (PANDAS)- (Swedo)



Associated with Group A Beta Strep infections”
Clingy- OCD/Tick symptoms, relapsing remitting
Licking, clingy,Autoantibody to basal ganglia
Similar behaviour in family (sensitive population)

Carbohydrate Craving, Unique Opportunistic Bacteria Diarrhea Licking and Fecal Smearing in Autism

Behaviour facilitates growth and spread of autism implicated gut pathogens (clostridials)?

Pathogen affecting host behaviour

Photo- M. Herbert

Autism in Somali Diaspora in North America

3% of general population, 35% of autism in some regions
All conceived in Receiving Country- NOT Somalia
Large exposure to antibiotic/++ gastrointestinal infections

<u>Norwegian cohort/MAL-ED Study (Gates Foundation) –Lange et al.</u>

Effect of early medical intervention by Western medicine in 3rd world

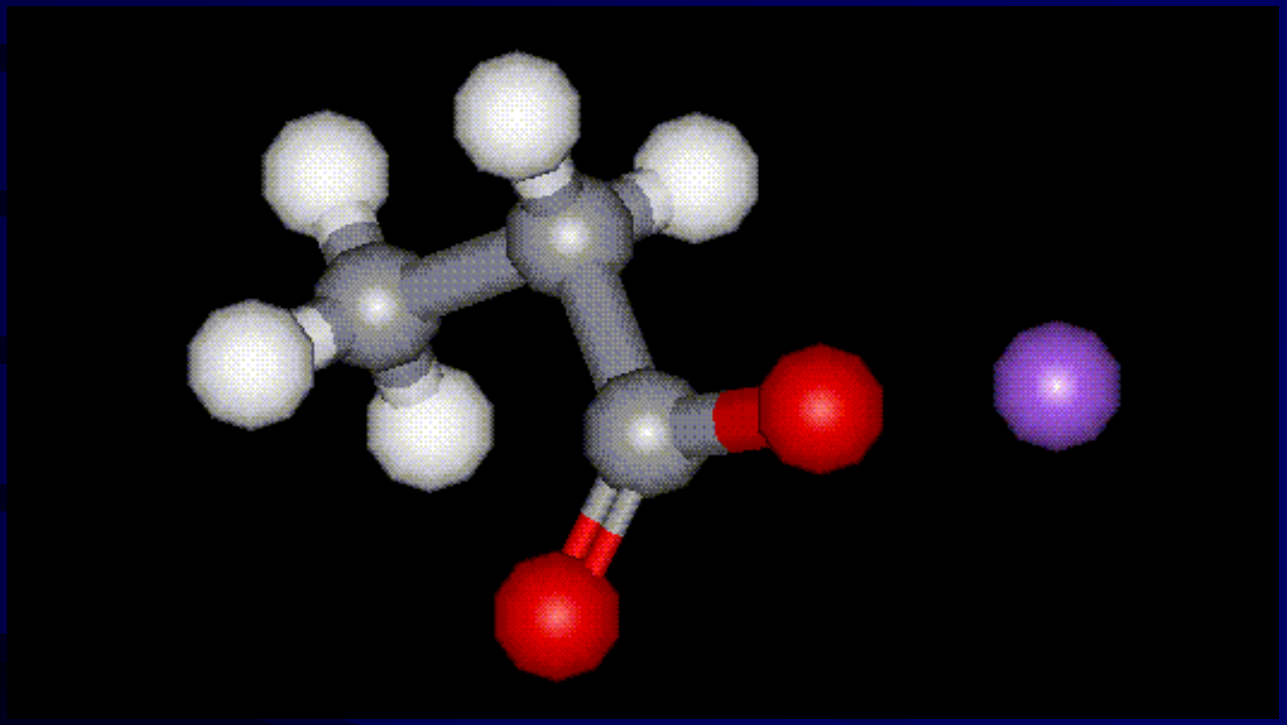
Bangladesh, Brazil, India, Nepal, Pakistan, Peru, S. Africa, Tanzania

Nutrition, antibiotic exposure -impaired immunity, vaccine efficacy

Neurodevelopmental disorders

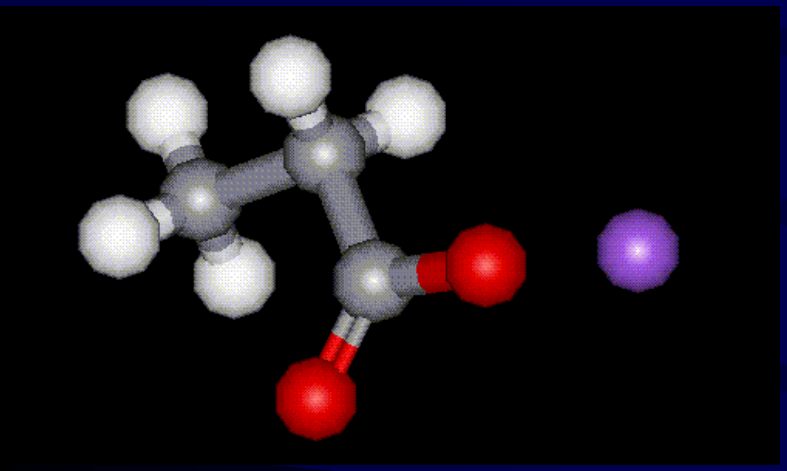
Altered development of infant microbiome

Gut Microbial Metabolites- Short Chain Fatty Acids
Propionic Acid- Neuroactive Properties



Weak organic acid: lipid/water soluble- “small” molecule
Uptake passive active (monocarboxylate transporters) ketones
Specific G protein coupled receptors (brain, gut, immune, fat)
Intracellular concentration (intracellular acidification)
Unique CNS/GI immunological properties

Short Chain Fatty Acids – Propionic Acid (PPA)



Propionic Acid/Propionate:
Byproduct of bacterial metabolism
Clostridium, propionibacteria (gut/acne)
Desulfovibrio, Bacteriodes (Finegold)
(butyrate, acetate)- short chain fatty acids
Increased in ASD stool, wheat substrate
Common preservative of wheat and dairy products, weight loss agent
Increased by ethanol, B12/biotin deficiency carnitine deficiency, aspartame

Variable metabolism of propionate in population – Multiple mechanisms and multiple clinical presentation (organic acidemias) shares similarities with autism- underreported???

Role of diet, gut bacteria/barriers and “sickness” in propionate levels (other short chain fatty acids and metabolites)

Rodent Model of Autism- Behavioural and Brain Effects of Propionic Acid Administration

MacFabe et al, *Behavioural Brain Research* 2007),

and MacFabe *Microbial Ecology in Health and Disease 2012/13/15* for Reviews

Autism Model –Propionic Acid (PPA)- behaviour/EEG

PBS

- Dose approx. that in propionic acidemia (now down to 1/20th)
-Pulse injected into cerebral ventricles
-NB buffered to pH 7.5
- Reversible repetitive behaviour
-Fixation on objects
-Seizure +/behaviour cortex
-Subcortical spiking

Propionate Autism Model

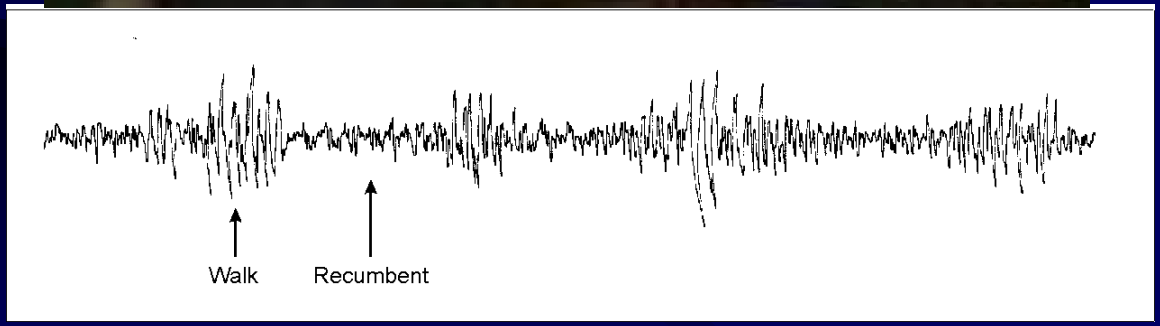
Effect immediate, transient (45min) but some permanent

Enteric short chain fatty acids (gut bacterial metabolite- PPA ,butyrate) induce reversible repetitive, antisocial behaviour, perseveration, object fixation, tics, seizure- Reversible
Early exposure (pre or post natal)- major developmental effects

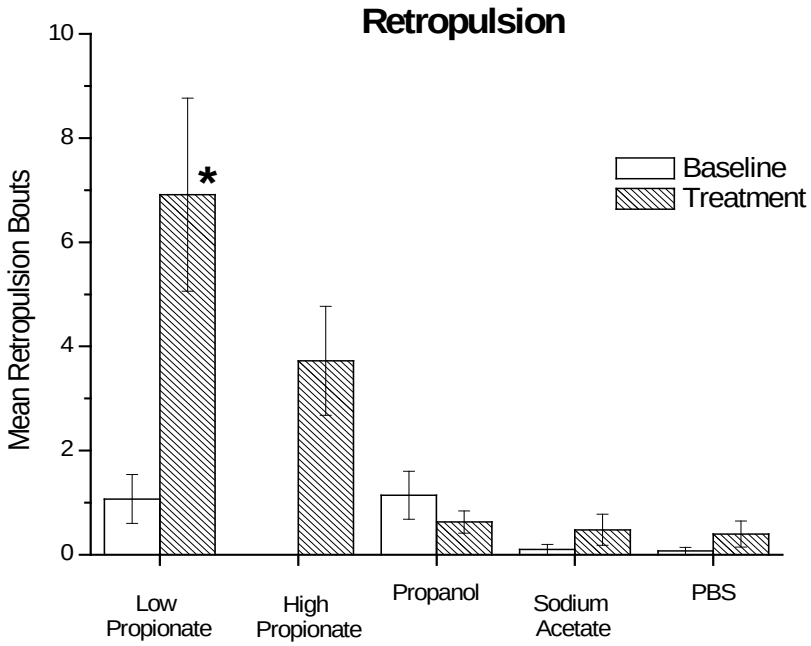
Control

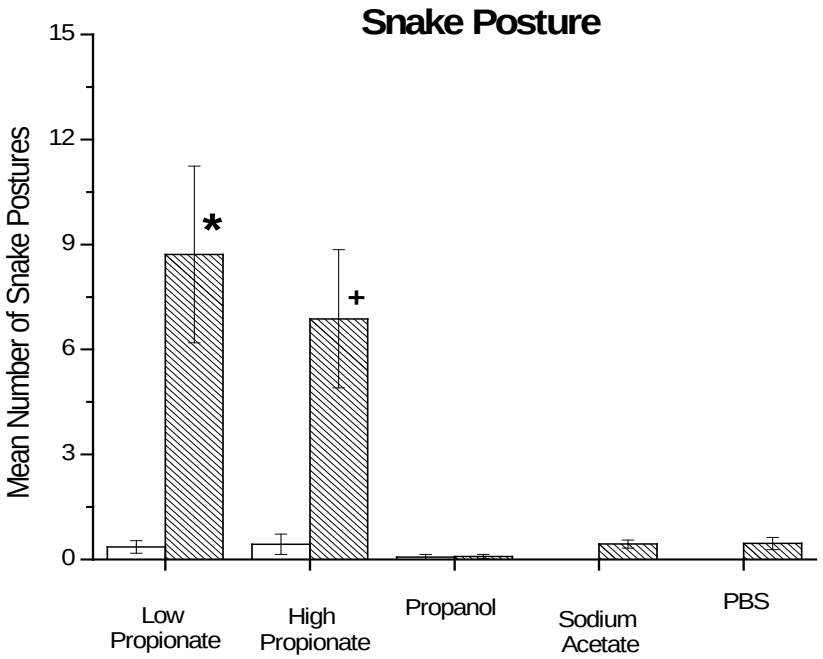
gut bacterial metabolite
(propionic acid- PPA)

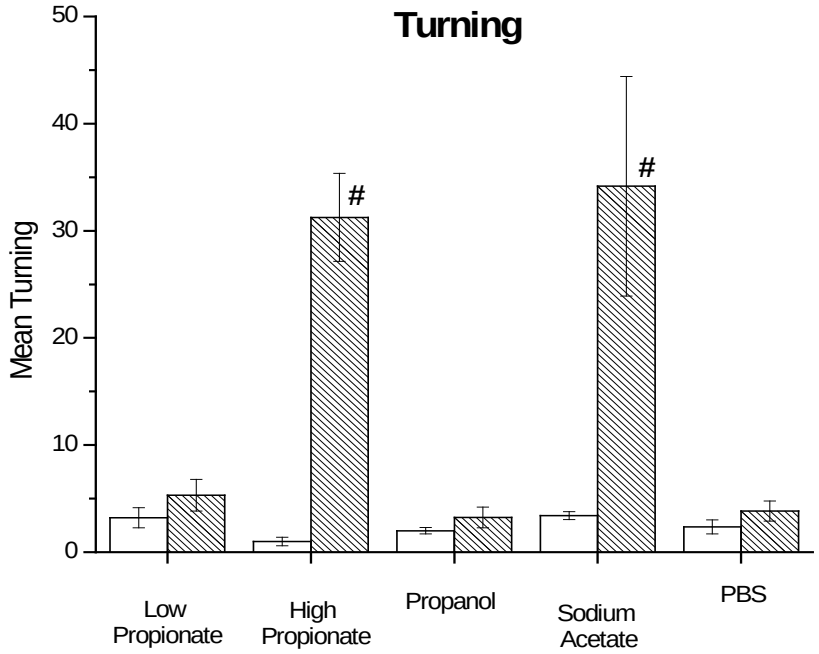
Intraventricular PPA- “ritual”



Hippocampal EEG- Repetitive motor loop
Normal EEG







Legend

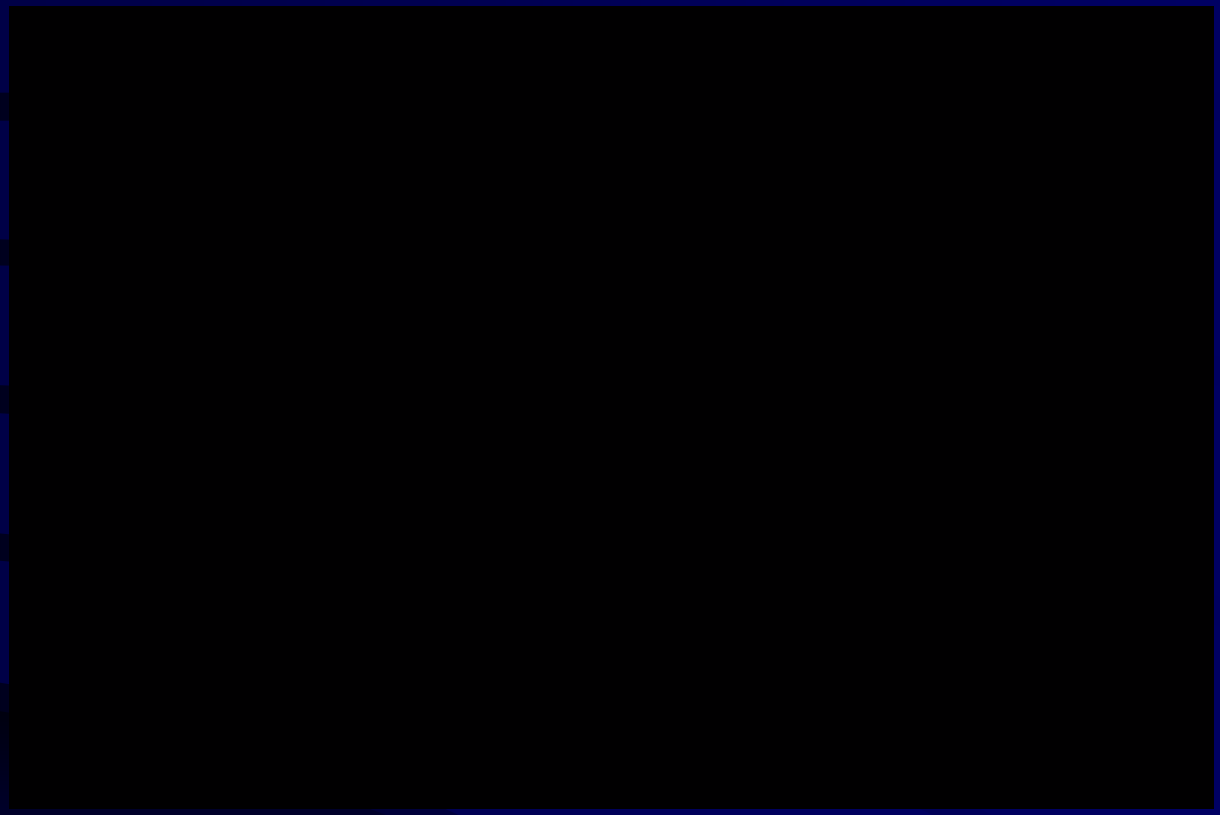
* = Significantly different from all control groups.

= Significantly different from low PA, propanol, PBS.

+ = Significantly different from propanol and PBS

Propionic acid causes movement disorder with caudate spiking

Social Behaviour (Ignoring/Mean Distance Apart) (Shultz *et al*. Neuropharmacology, 2008)



vehicle PPA

Effect apparent after one dose, reversible post metabolism

Reduced play behaviour (Ethovision)

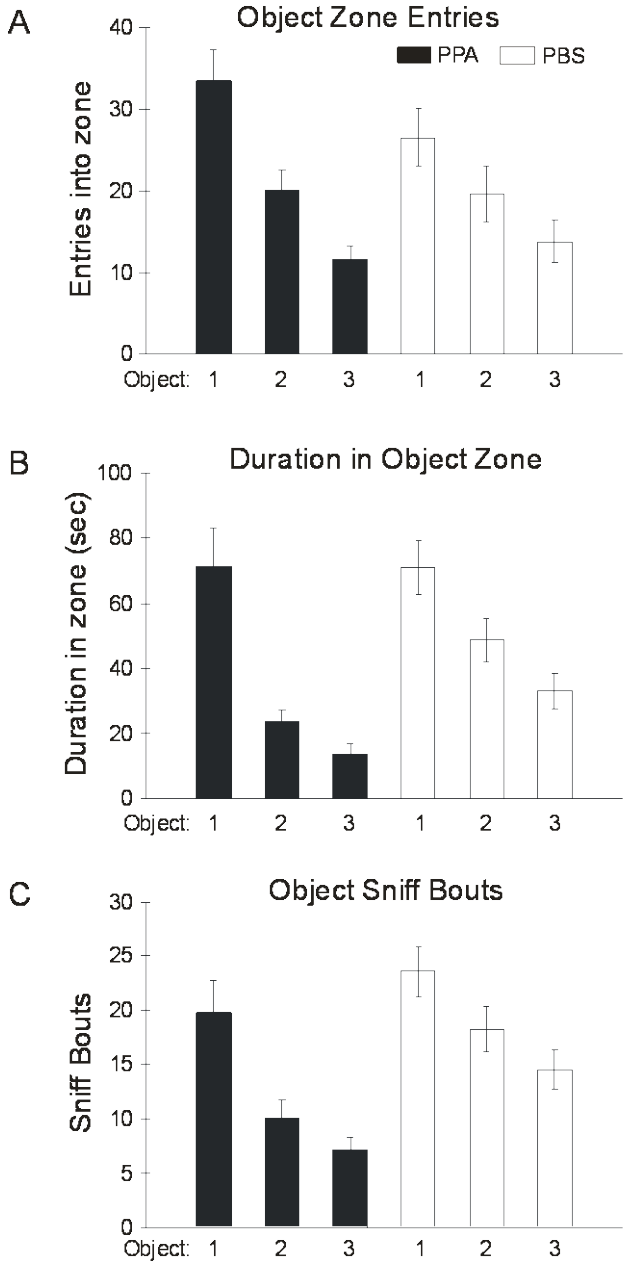
Social “Ignoring” of Normal Rat

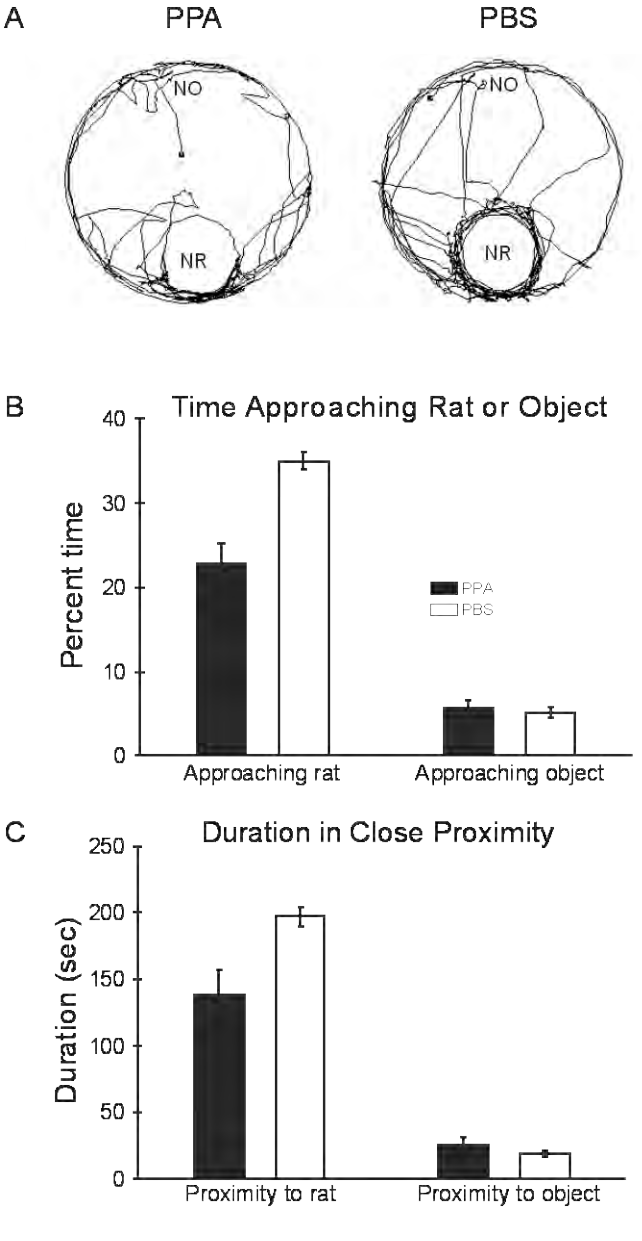
PBS

PPA

MacFabe et al; Behavioural Brain Research (2010)

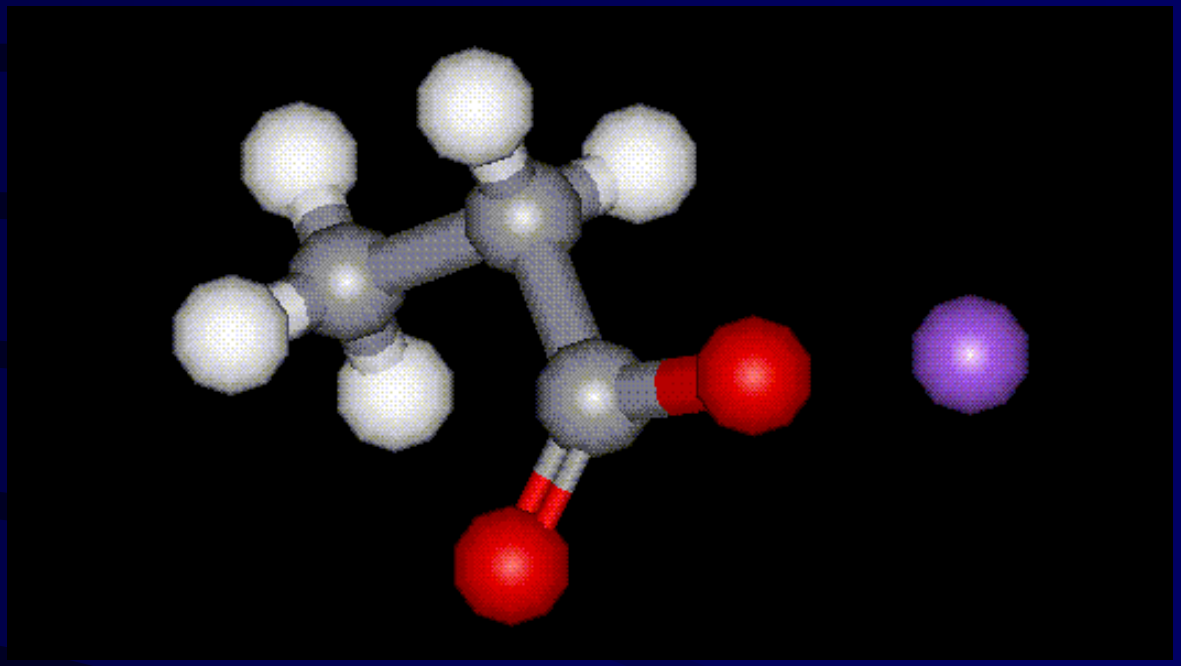
PPA Rats Prefer “Favourite Objects” to other Rodents (MacFabe et al, 2010 BBR)





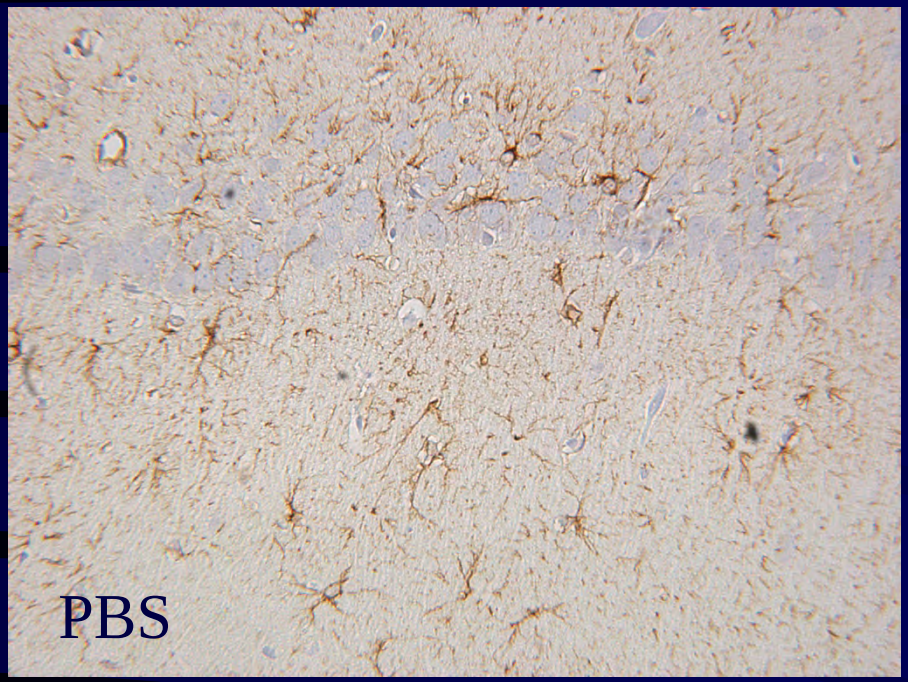
Long term effects- Ethovision- stereotypies/ object fixation

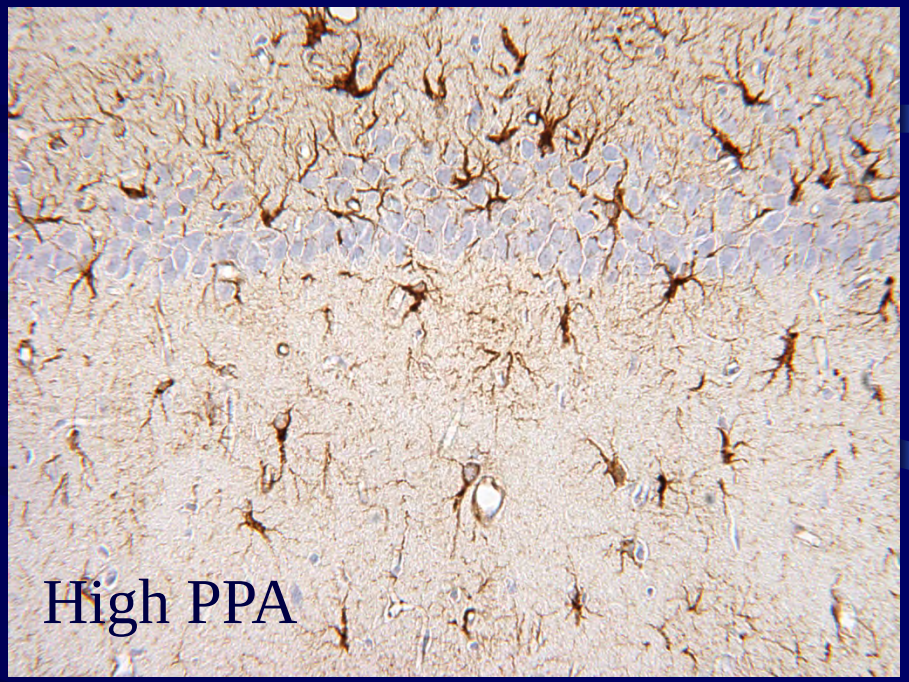
Neuropathology of PPA in Rodent Model:



Similarities to metabolic/autism spectrum disorders
Innate neuroinflammation, oxidative stress, BBB
Altered lipid metabolism/ mitochondrial function
Altered gene expression (epigenetics)
Reversibility?

Hippocampal formation: GFAP (neuroplastic marker)reactive astogliosis

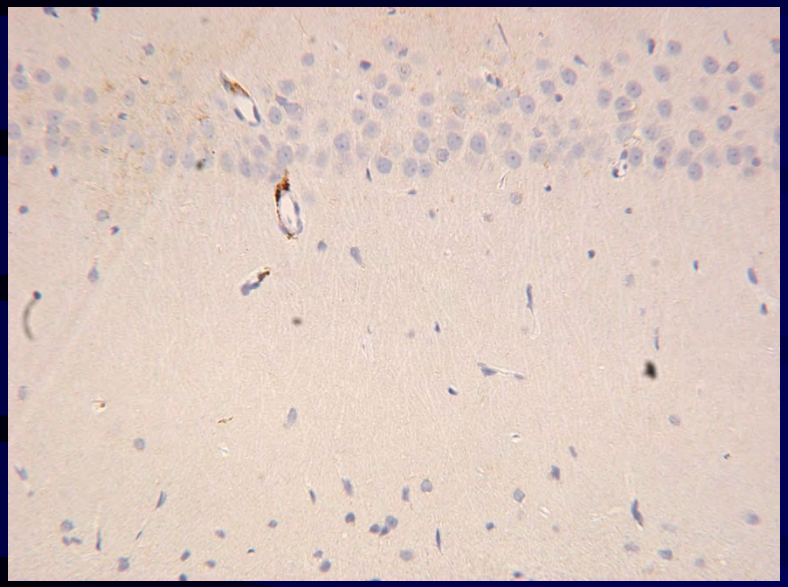




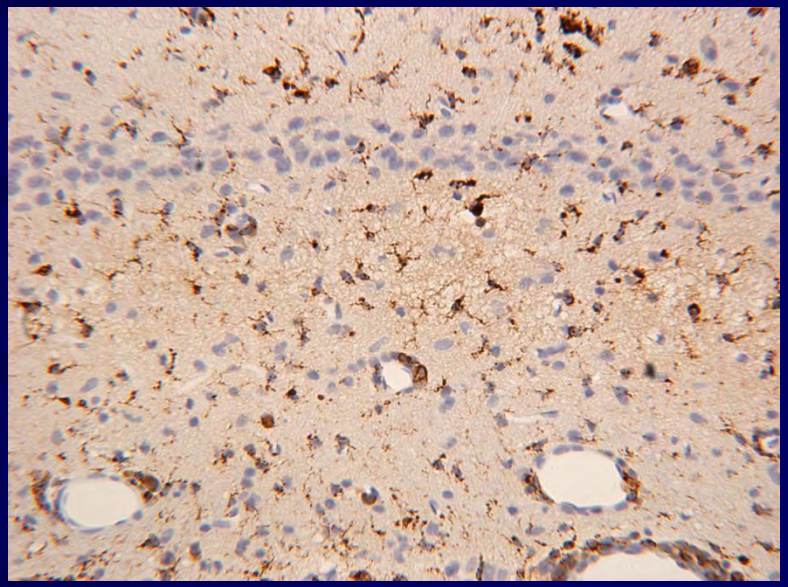
microinjections of propionate - very brief exposure
Astrogliosis - prominent, hippocampus,
cingulum, white matter
Neuroinflammation (TNF alpha)
Toxic or compensatory (neuroplastic response)

Results – CD68 Microglia – 14 day

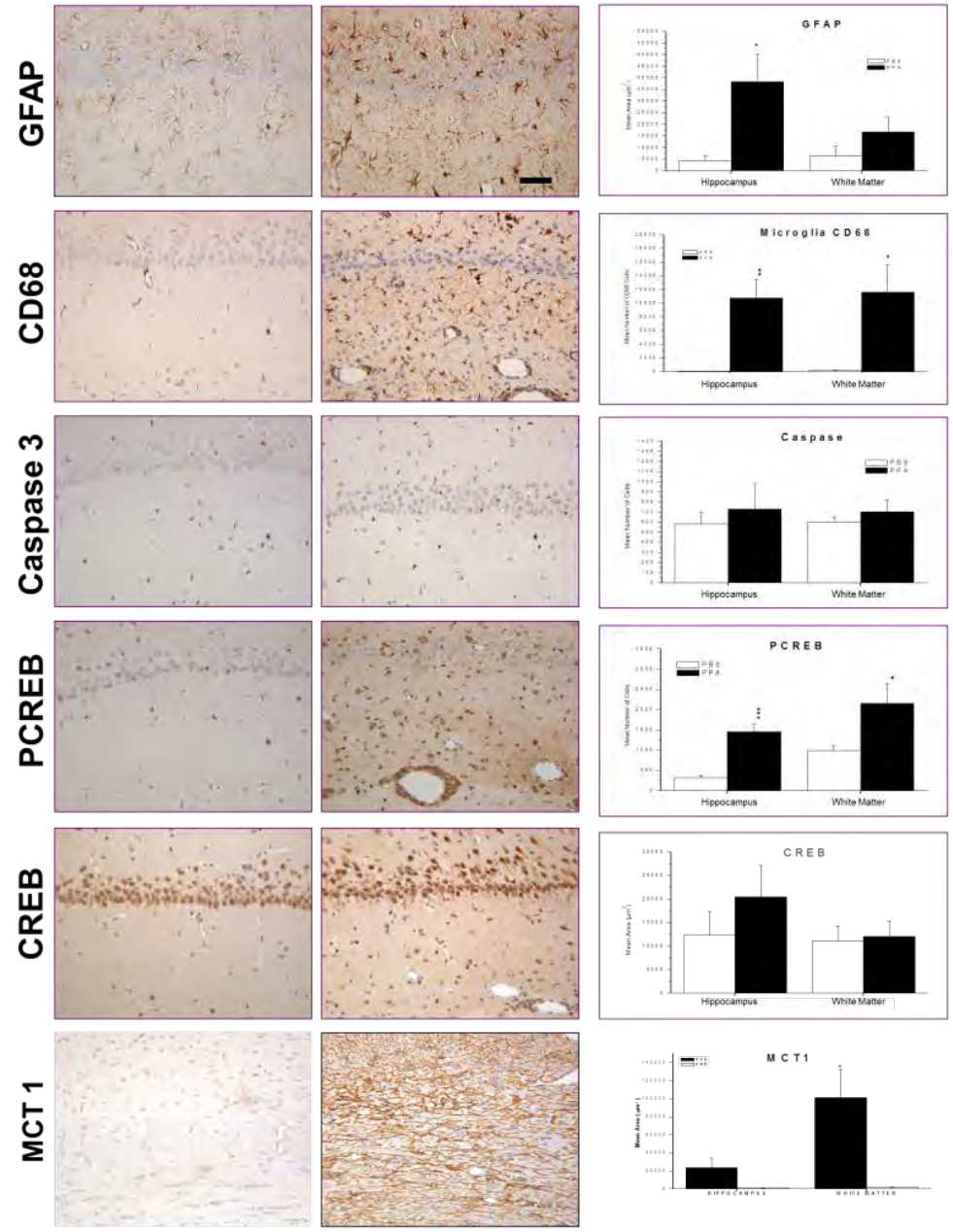
Control (PBS)



PPA



PPA increases activated microglia (neuroinflammation)
Nitric oxide, cytokines, fatty acid receptors on microglia
Endovascular involvement (microcirculation/ BBB)
(c/f human autism!)



Neuropathology of dorsal hippocampus (CA2) and external capsule of adult rats with ICV infusions of PPA or SAL. PPA induced significant astrogliosis (anti-GFAP), microglial activation (anti-CD68), without apoptotic neuronal cell loss (cleaved caspase 3) in rat hippocampus. Nuclear translocation of anti-CREB and an increase of anti phosphoCREB immunoreactivity is observed in neural, glial, and endovascular epithelium by PPA treatment. PPA increases Monocarboxylate Transporter 1 immunoreactivity, primarily in white matter external capsule. Black bars indicate PPA treated animals; white bars indicate PBS (vehicle) treated animals.

Central PPA Infusions: Immunohistochemistry

Innate Neuroinflammation (astrocytes, microglia)
No apoptosis
Activation of CREB (memory)
increased Monocarboxylate Transporters (PPA/Ketones)
(consistent with ASD)

(MacFabe 07/11/13)

Anti Nitrotyrosine Immunoreactivity- oxidative stress

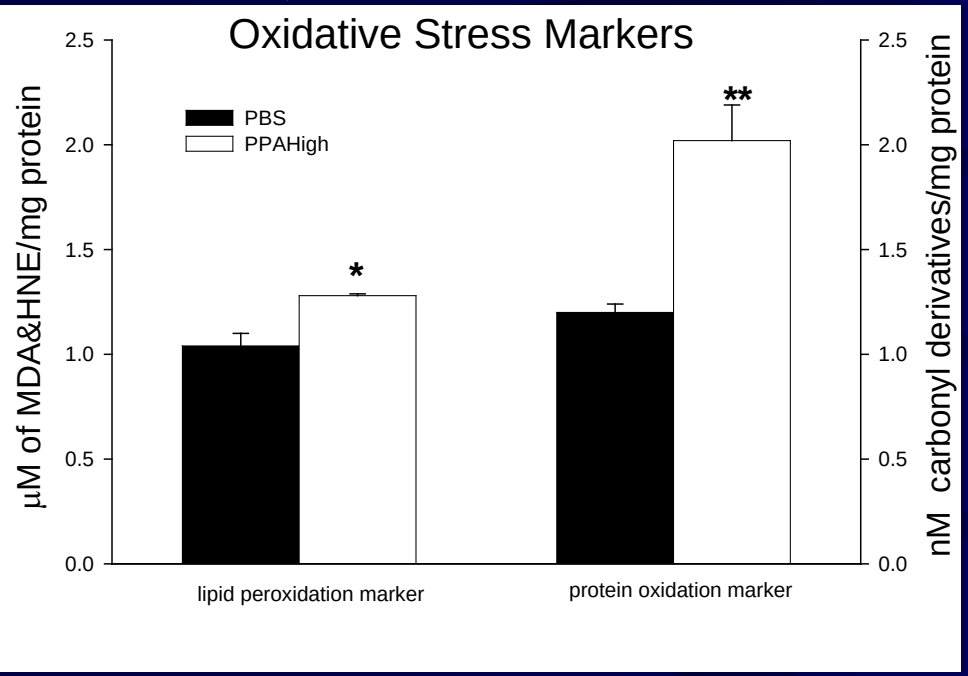
PBS Vehicle

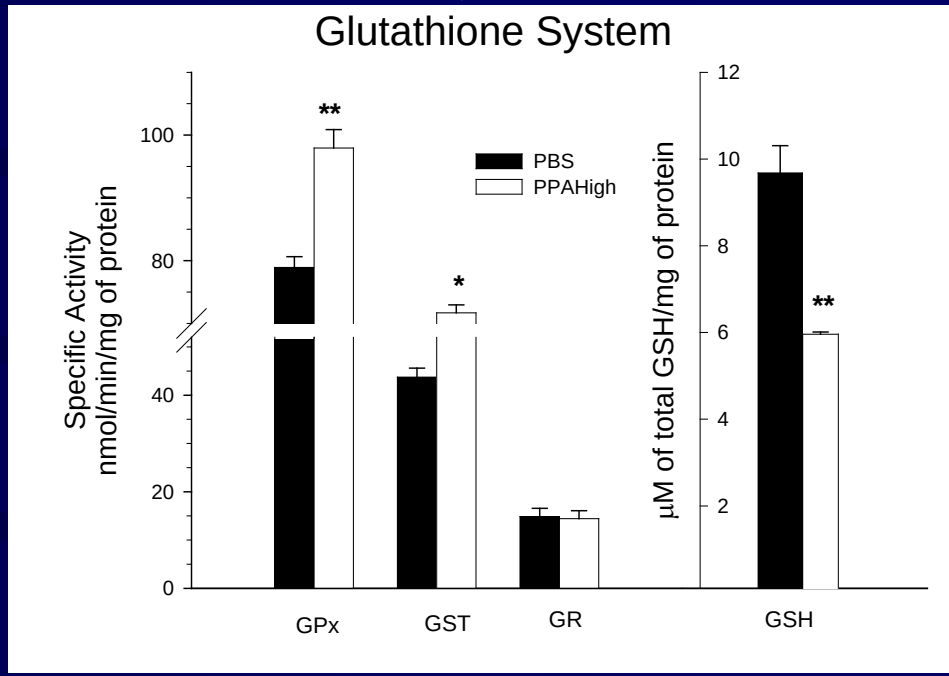
High Dose PPA

PPA causes increase anti Nitro-tyrosine immunoreactivity in hippocampal formation
increases “oxidative stress”

Increased Oxidative Stress in PPA Autism Model

(MacFabe *et al* Am.J. Biochem.Biotech.2008)





PPA increases oxidative stress markers and impairs Glutathione metabolism (sequestration?)

-brain “sensitive” to broad spectrum of environmental agents (ie metals, xenobiotics, Tylenol!!)

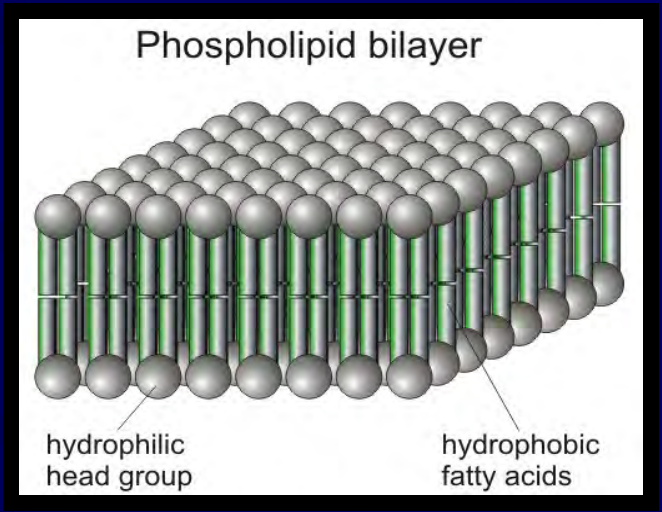
-similarity to evidence of metabolic dysfunction in ASD patients

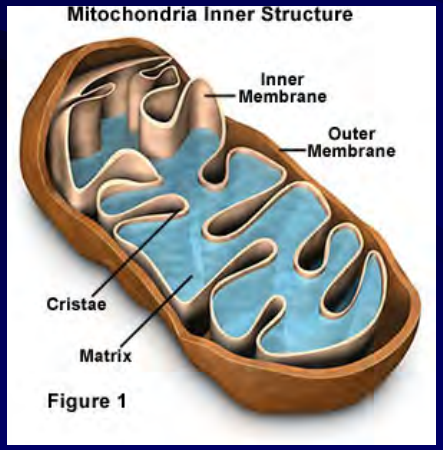
-broad effects- metabolic encephalopathy

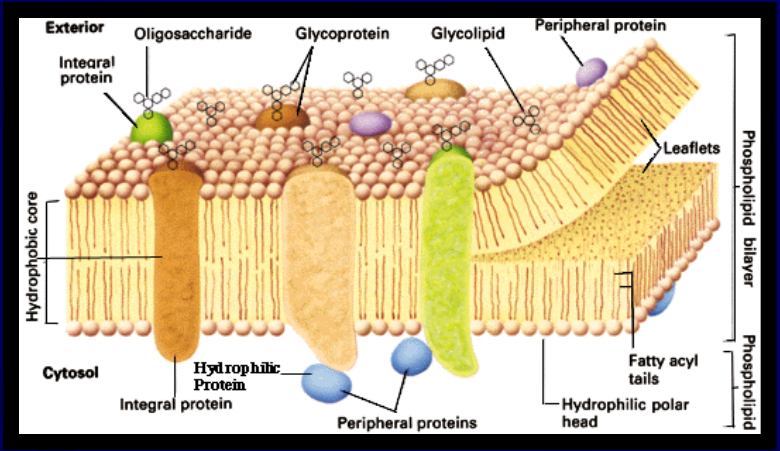
Functions of Fatty Acids

- **Main functions:**
  - Energy storage
  - Structural components of cell membranes, membrane fluidity
  - Act as signal molecules in many metabolic processes
  - Abnormal fatty acid composition in Autism (lower omega 3/6 ratio)
  - Relative carnitine deficiency
  - Mitochondrial disorder?
  - (acquired?)

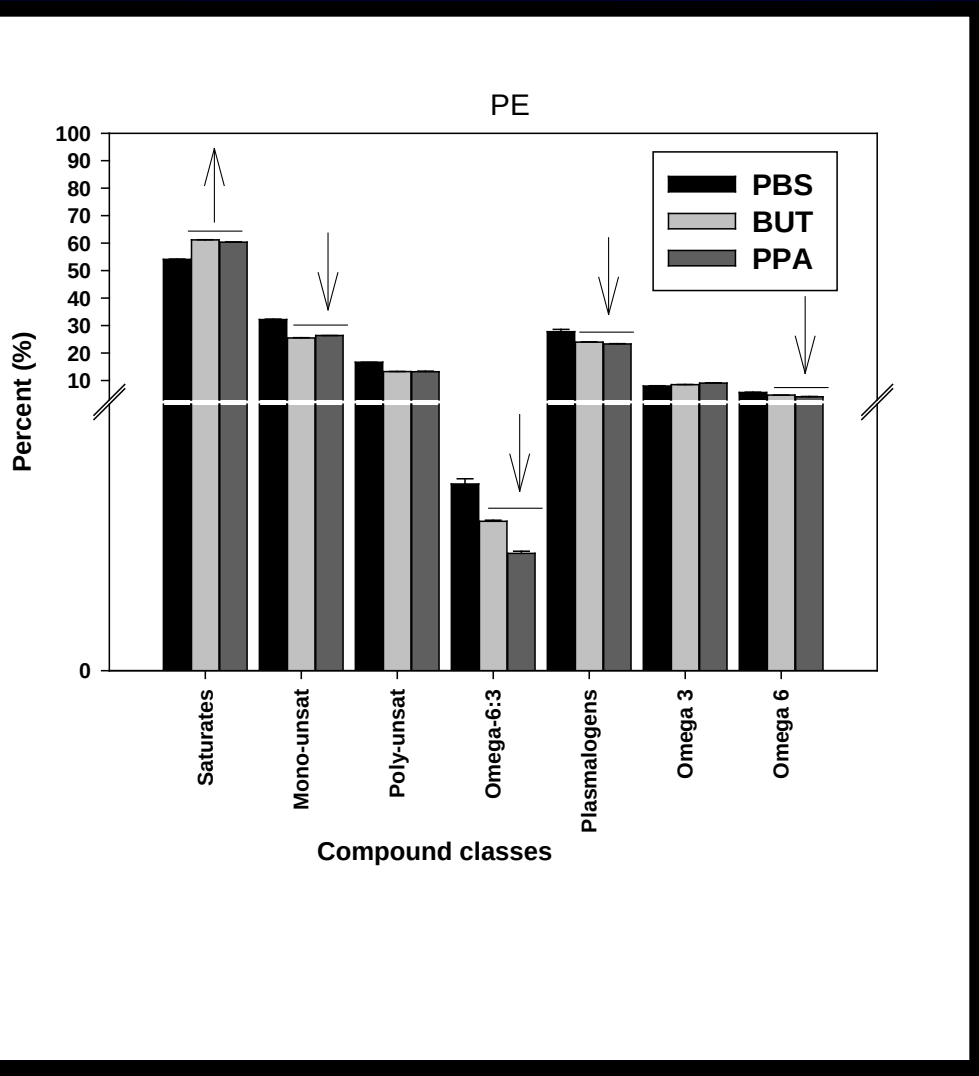
e.g. neuronal cell membrane







Thomas et al, J.Neurochem, 2010

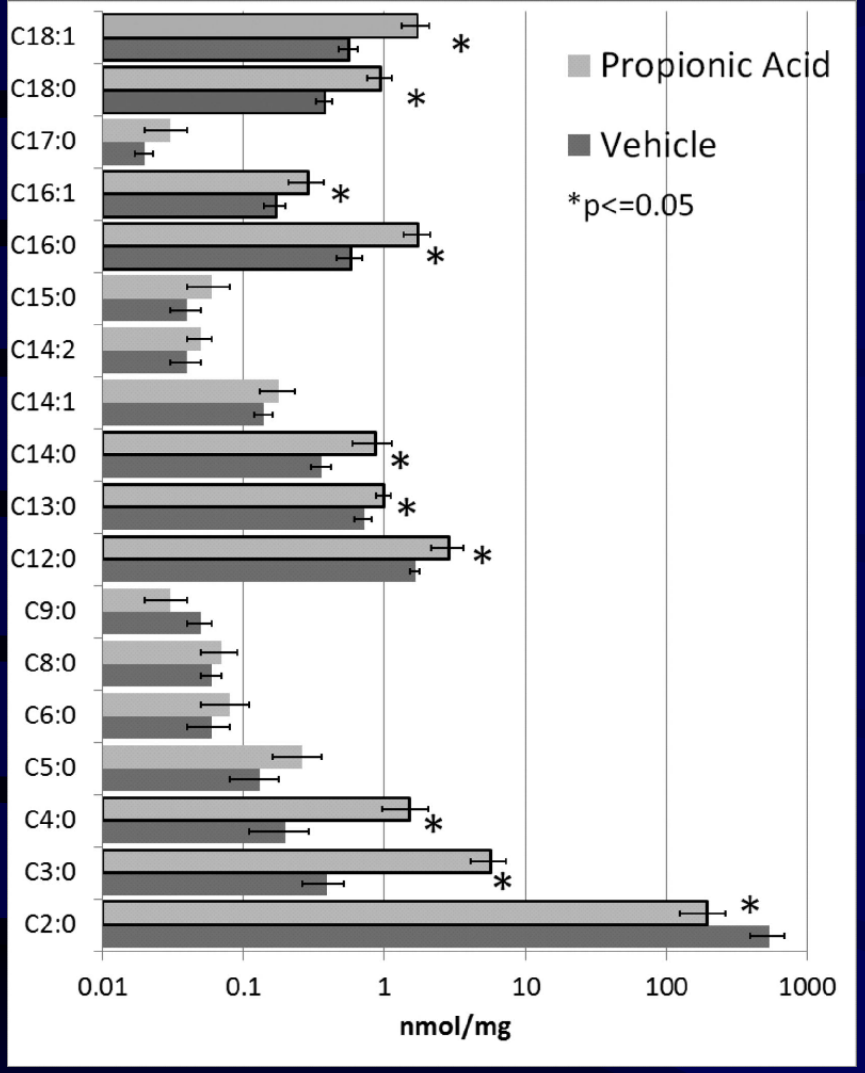


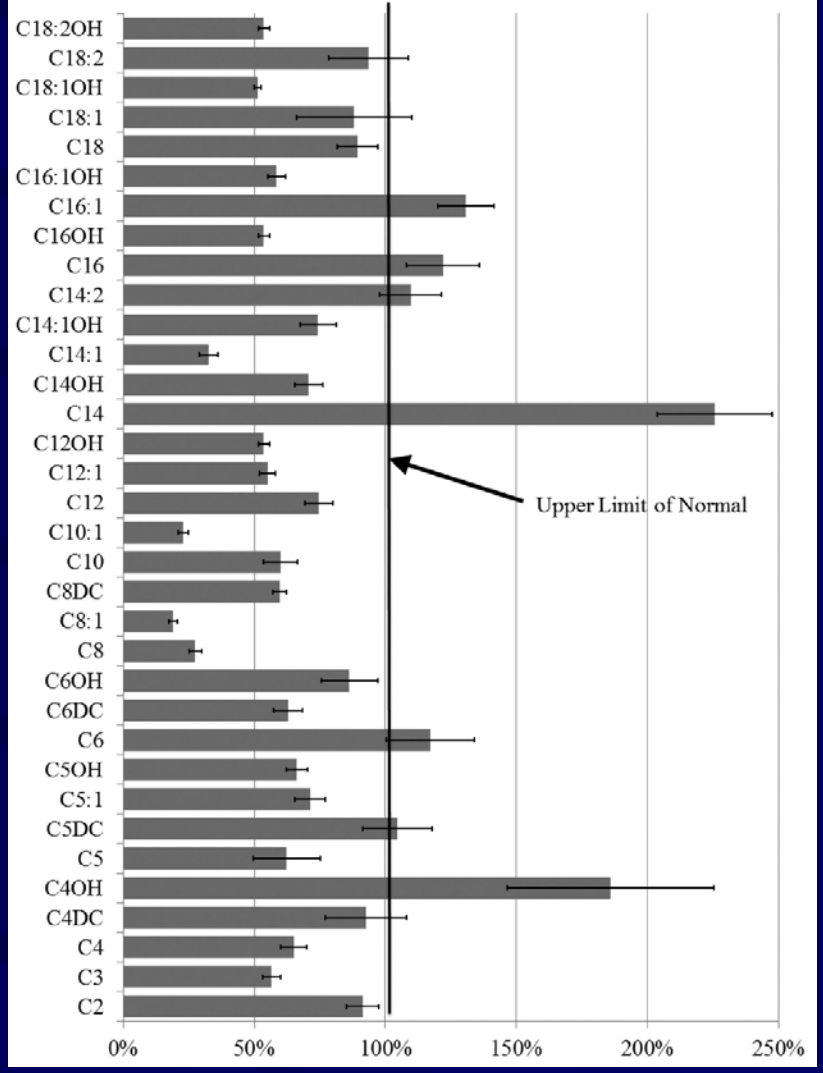
I.E Phosphatidylethanolamine
Increase saturates
Decrease:
monosaturates
omega 6/3
Plasmologens (antioxidant)

Same trend in

Phosphatidylcholine
Phospatidylserine/inositol
Sphingomyelin (White matter)
Cardiolipin (mitochondria)

SCFA alter membrane fluidity, Signallng, Antioxidant, mitochondrial function



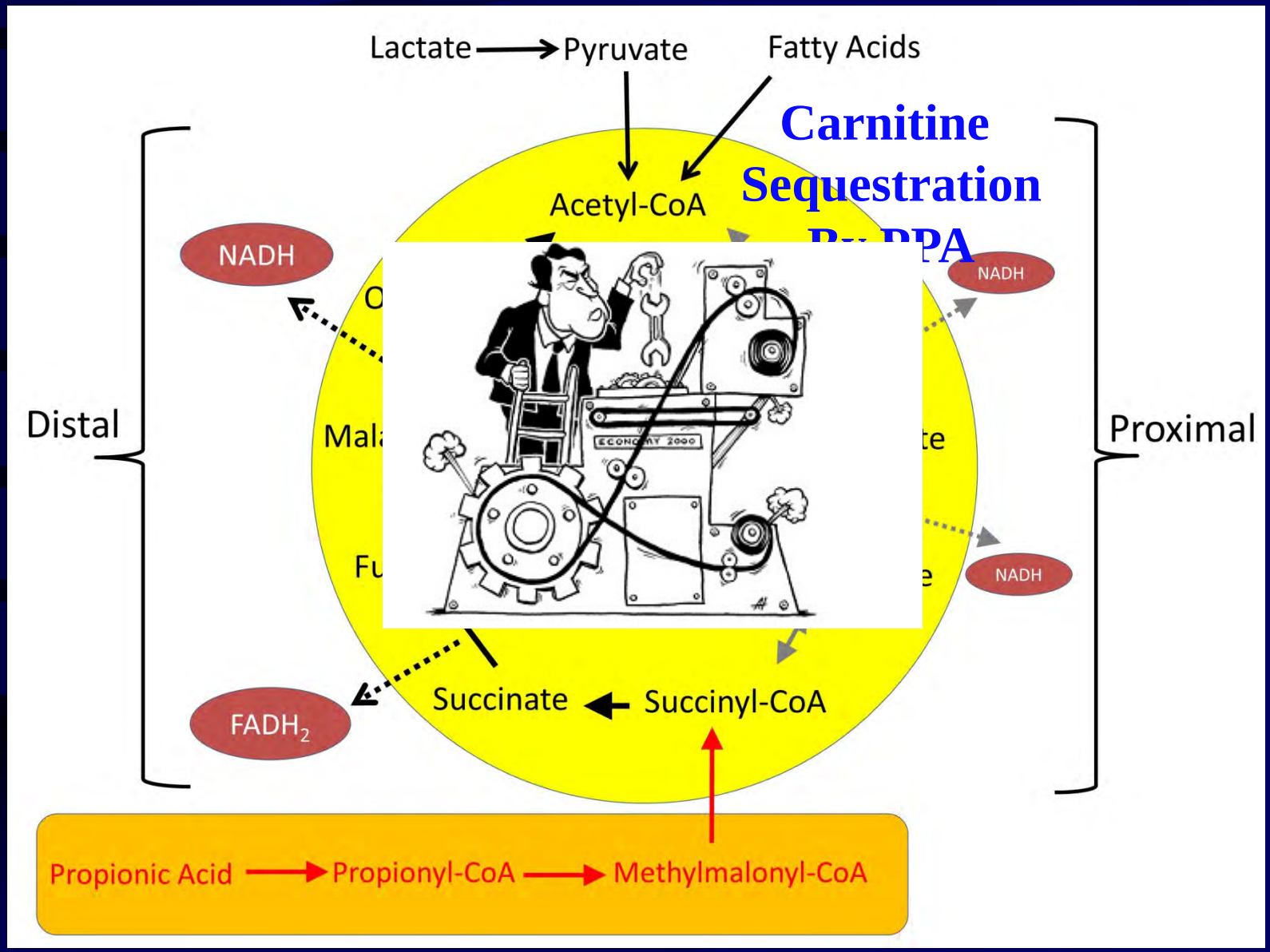


PPA Rodent Model **ASD Patients**

217 patients-17%Similar short and long chain acylcarnitines

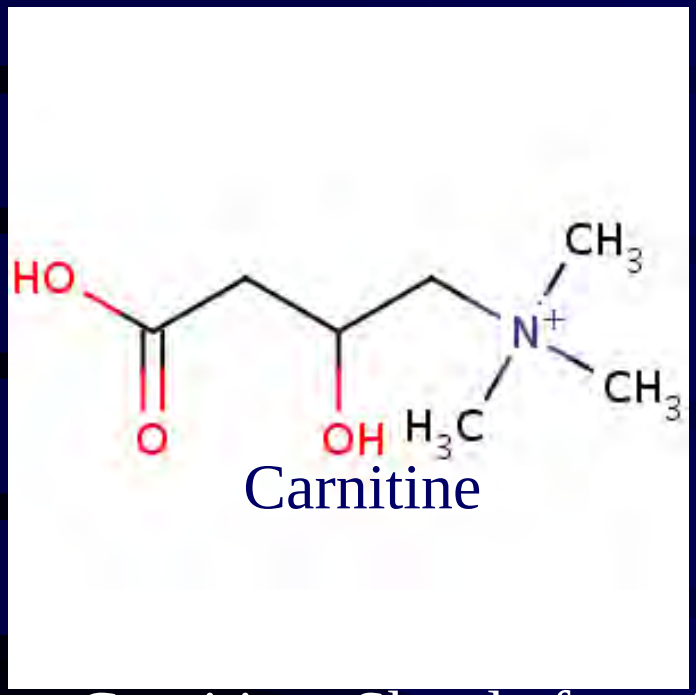
Also decreased glutathione, Redox changes

Frye , Melnyk & MacFabe 2013, Trans. Psych.

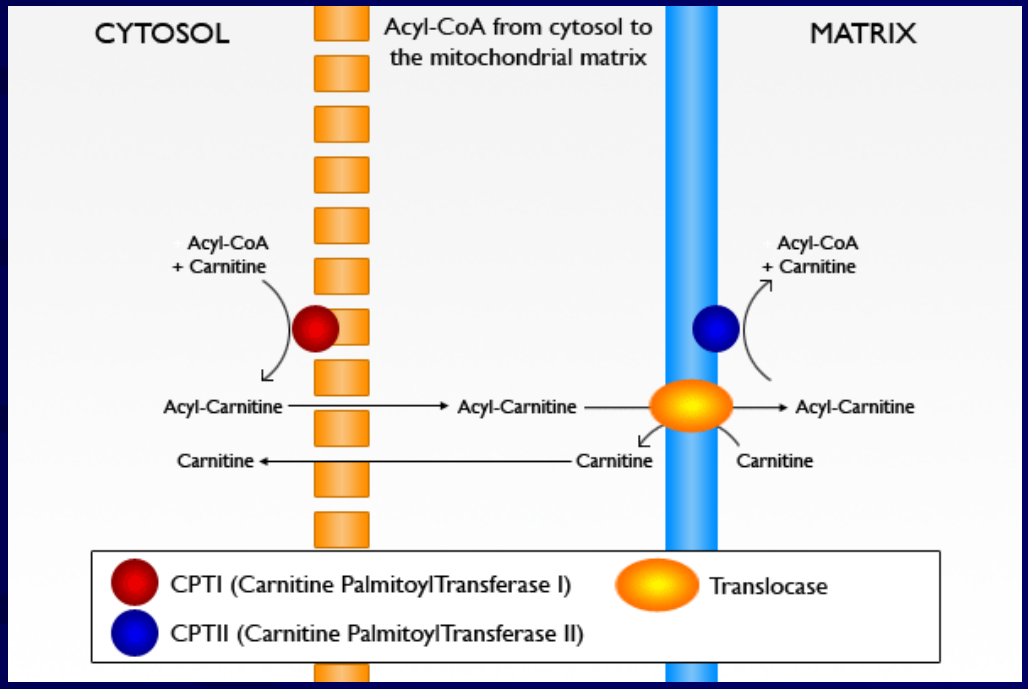


Gut Bacteria Products Impairing Cellular Energy Metabolism (Mitochondria/Fat metabolism) biomarkers/therapeutics (carnitine)

Common Infections, Chronic Antibiotics, Clostridia and Carnitine Collapse Leads to Constipation, Carbohydrate Malabsorbtion, Convulsions and Compulsions!



Carnitine



Carnitine- Shuttle for mitochondrial fatty acid beta oxidation

Routine pre- peri or post natal infections-

Long term antibiotics (beta lactams)- deplete carnitine transport

“Barren Gut”->Growth of clostridials- increased SCFA production

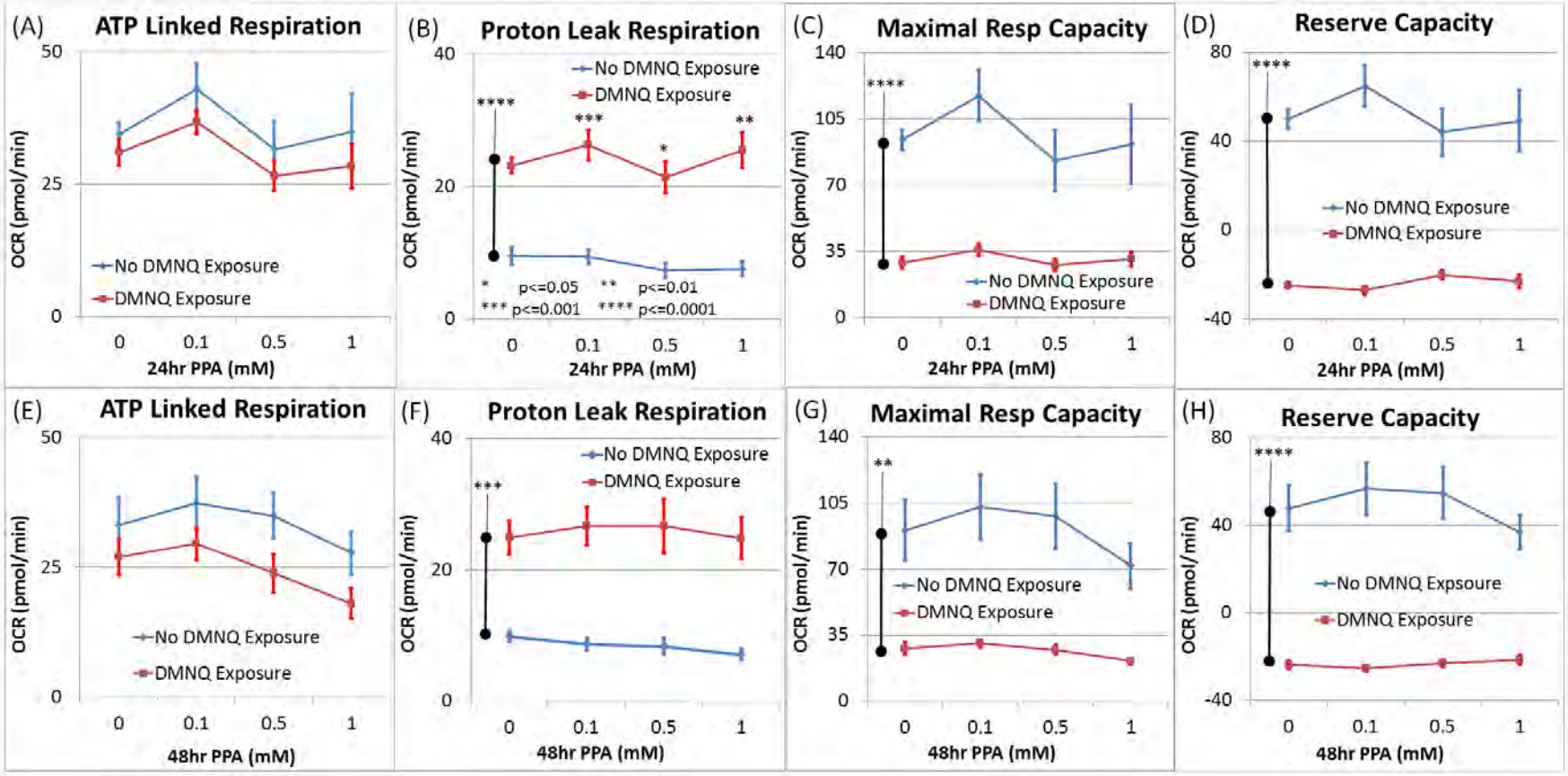
Further sequestration of carnitine

Impaired fatty acid metabolism- mitochondrial encephalopathy

Causes	Consequences of SCFAs
Long term antibiotics for routine infection (maternal /infant)Treatment of maternal β hemolytic strep	Gut dysmotility/inflammation/carbohydrate malabsorbtion/altered gut permeability (tight junction impairment)
Hospitalisation (colonization of nosocomial bacteria) i.e. C-section, neonatal distress	Active uptake of SCFA to CNS (monocarboxylate transporters)
	pH dependent intracellular concentration of SCFA
Prenatal drugs (valproate, ethanol)	Neurotransmitter synthesis and release (catecholamines, enkephalins) CNS/sympathetic nervous system
Opportunistic infection (*Clostridium* spp., *Desulfovibrio* spp.)	Receptor activity (+NMDA, -GABA) SCFA G protein coupled receptors/Ca++ influx
Maternal/Infant gut dysbiosis	Gap junction closure, altered neurodevelopment, neuroinflammation
Organic acidemias (propionic/methylmalonic, biotinidase/ holocarboxylase deficiency)	Impaired mitochondrial function/ increased oxidative stress
(B12/biotin deficiency)	Reduced glutathione/increased sensitivity to xenobiotics (i.e. acetaminophen)
Genetic/acquired impaired carnitine synthesis/ absorption (TMLHE/OCTN$_2$ genes, β- lactam antibiotics)	Decreased carnitine/altered lipid metabolism/ membrane fluidity
Mitochondrial disorder/dysfunction (inherited, acquired)	Altered gene expression (CREB activation, histone deacetylase inhibition)
Colitis (impaired barrier/SCFA metabolism), i.e. celiac disease, Met-receptor tyrosine kinase mutation	Antisocial/perseverative/anxiety-like behavior, seizure/movement disorder, Restrictive food interests/carbohydrate craving
Increased refined carbohydrate consumption – substrate for bacterial fermentation	

Many Roads Lead to Rome!

Recent Data –Just published- Mitochondrial function with PPA

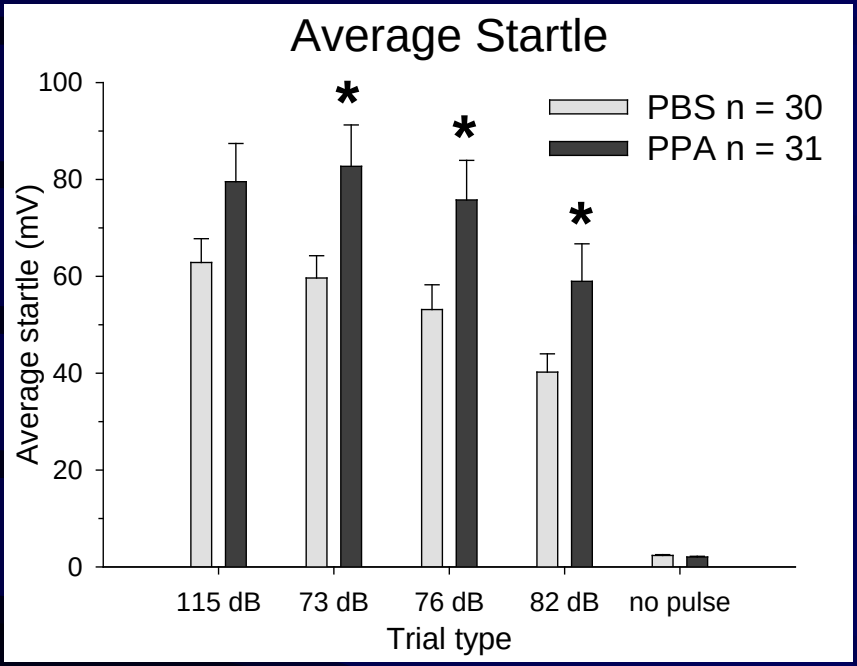


PPA increases mitochondrial function in concentration manner

ASD lymphoblasts have altered PPA metabolism, pretreatment with oxidative stress challenge (DMNQ) reverses this (worse in ASD Cell lines) Frye et al- Translational Psychiatry in press

Critical Developmental Windows:

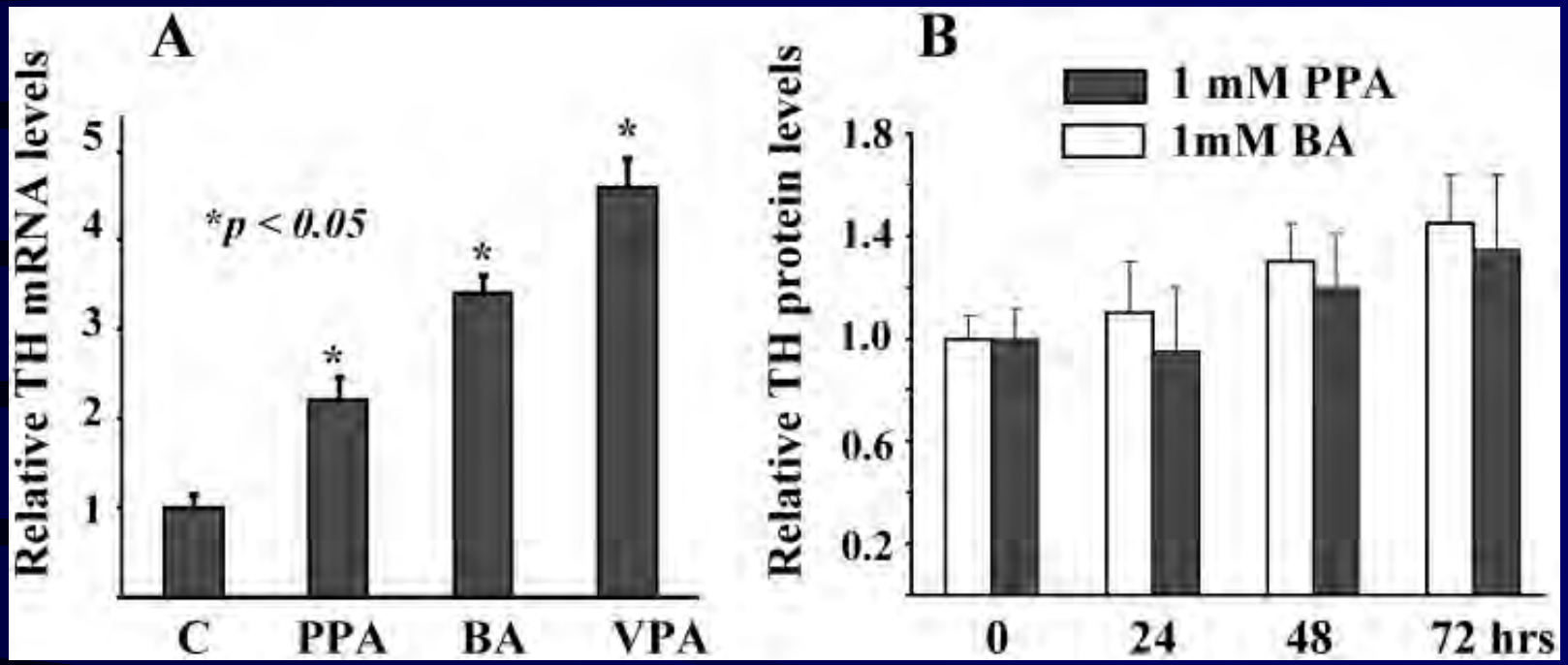
Adolescent Behavioural Changes in Response to Early Exposure to PPA: Locomotor, Social,Sensory,Sex diff.- (Foley et al 2014abc, Ossenkopp etal 2014



During first few days of life, rat pups are injected with sub cut PPA or PBS and Behaviourally tested as adolescents.

The amount that an animal is startled (“jumps”) in response to an acoustic stimulus is measured. PPA animals are more sensitive to stimuli – jump more – than PBS animals.
-Reduced inhibition (i.e GABAergic dysfunction), also hyperactive, social impairment
SENSITIVE TIME WINDOWS

SCFA activate the transcription of TH gene- PC12 Nankova et al ,2014 PLos



PPA , BUT and valproate induce tyrosine hydroxylase RNA-PC12 cells
(valproate modified SCFA- autism risk factor)
Via a CREB dependant mechanism (same in brain homogenate)
Epigenetic control of catecholamine synthesis, neuroligins, FMR
(Neuroplasticity, oxidative stress, mitochondria/lipid metabolism)

Differential expression of autism candidate genes in SCFA rat model

Category/ gene product/	Description	PPA	BA (Fold change)	Ref.
Immune system related genes (cell-cell communication, differentiation, cell cycle regulation, chaperone system)				
GADD45 (growth arrest and D				arbett K. et al., 2008
IFITM3 (interferon induced t				
SPPI (osteopontin precursor)				
MAP2K3 (MAP kinase kinase				
CYR61 (Cysteine rich 61/CC				
HLA-A (human leukocyte ant				orres AR et al., 2006
Innate immune inflammation				
PAF (PCNA associated factor				ellizzi, MJ et al., 2005
IL2RG (interleukin 2 receptor				regg JP et al., 2008
Synaptic cell adhesion molecu				
NLGN3 (neuroligin 3, postsyn				007, Jamain S. et al., 2008
NRXN3 (neurexin N3, presyn				08;Bourgeron T. 2007
Hyperserotonemia (Altered le				
TPH (tryptophan hydroxylase)				008, Wendland JR et al., 2008
GCH1 (GTP cyclohydrolase)				
Mitochondrial disfunction (DN				
PARP9 (ADP-ribose polymera				ruman, II et al., 2000
PARP10				
PARP12				
PARP14				
CASP1 (Caspase 1)				
CASP4 (Caspase 4)				
CASP8 (Caspase 8)				
Neurodevelopmental genes (re				
GABRD (GABA receptor delt				cCauley, JL et al., 2004
GABRG1(GABAreceptor gan				
SLC6A11 (GABA transporter				
ADA (Adenosine deaminase)				ottini, N. et al., 2001
CP (ceruloplasmin)				atemi et al., SH 2005
IL-6*, IL-6R				mith S.E.P. et al.
Oxidative stress: MGST1 (mi				mes SJ et al., 2006
Genes controlling affiliative b				. M. Yrigollen et al., 2008
ATF3 (transcription factor AT				.W. Hu et al., 2006
CD38 (ADP-ribosyl cyclase 1				
F13A1 (Coagulation factor XI				
CR2 (C-C chemokine receptor type 2)		14.9	16.4	
SAMSN1 (SAM domain-containing protein SAMSN-1)		6.8	5.1	
PBEF1(Nicotinamide phosphoribosyltransferase)		2.3	2.3	
HCK (Tyrosine-protein kinase HCK)		8.8	6.6	
LSP1 (Lymphocyte-specific protein 1)		29.5	26.1	

SCFA dependant gene expression:
neurodevelopment,
decreased GABA, Neurexins,
Neuroligins,Reelin
Many GI expressed

Increased Serotonin,
Innate Neuroinflammation,
Oxidative Stress,
Mitochondrial damage!!
Modulates ASD related genes!
(histone deacetylase inhibition)
Activation of Learning Pathways
Epigenetics

Diabetes **Autism**

Type 1

Type II

Can’t metabolize glucose **Can’t metabolize SCFAs?**

Multi- system involvement

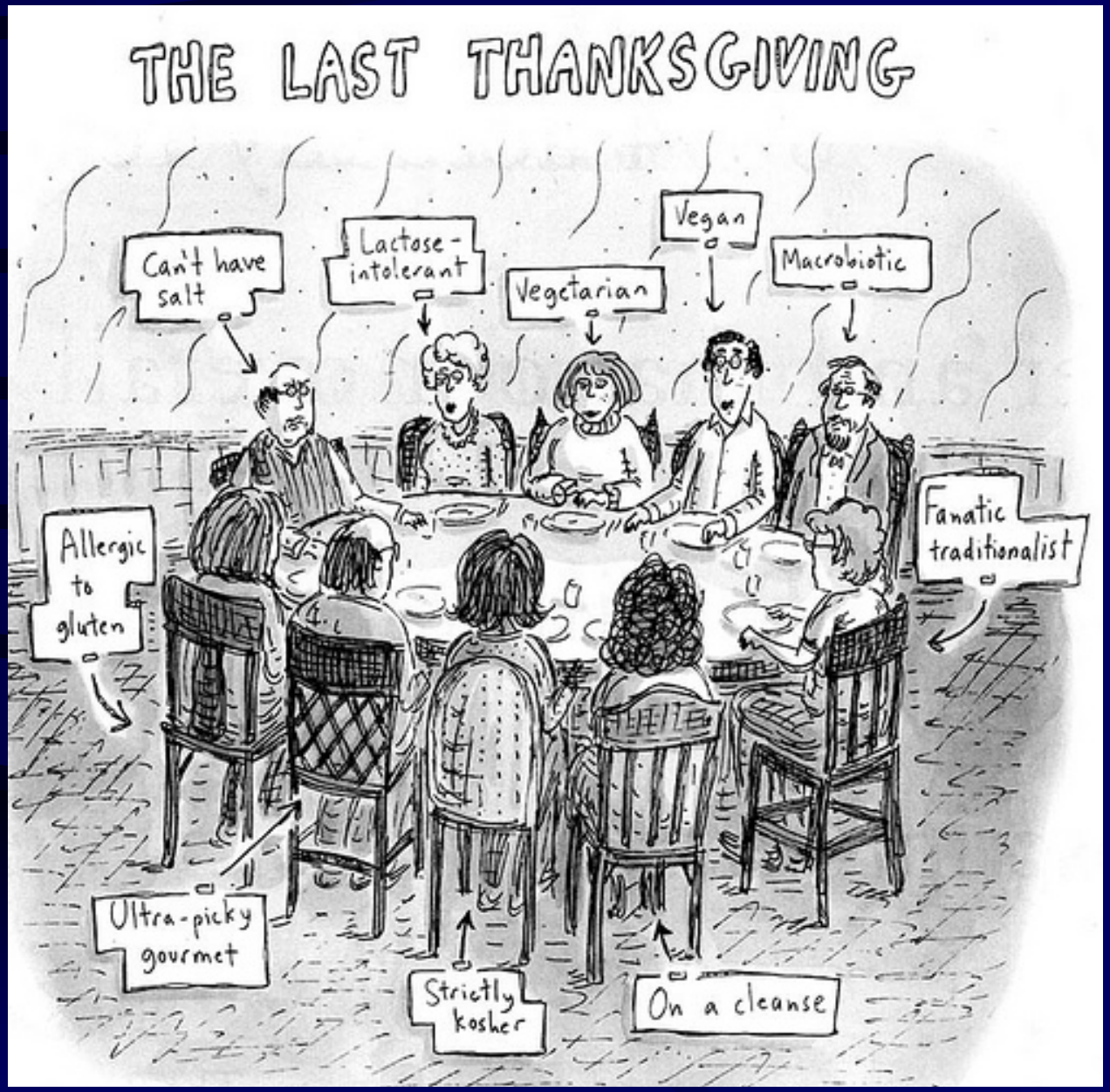
Multiple Causes (Genes/diet/environment)

Present with Metabolic Crisis (i.e infection)

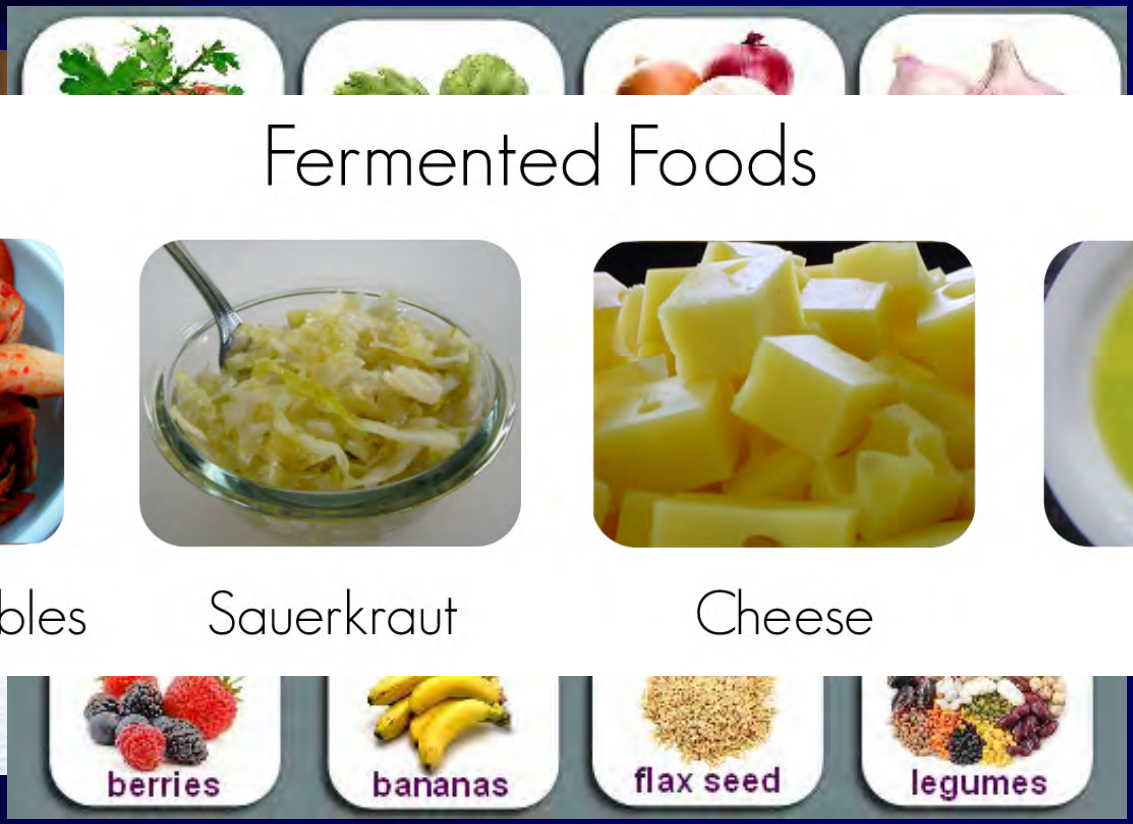
Treatment-Carbohydrate restriction (direct/indirect) GCFD?

Treatment-Insulin/glyburide **Inulins/carnitine/NAC probiotics/microbiome alteration?**

Multi- system approach



Fad Diets vs. Rational Evidence Based Approach to Nutrition



Feed Yer Bugs:

Less refined (hidden) carbohydrates (high fructose corn syrup)

Less white bread, pastas (propionic)- and if so more whole grains

more whole vegetables (inulins, beta glucans) prebiotic (BUT/PPA)

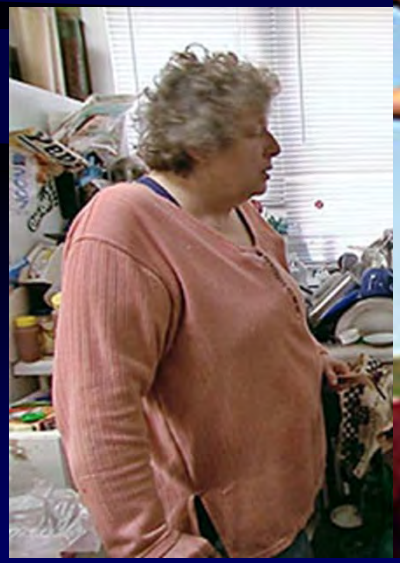
“Bright” foods- antioxidants

Fermented foods (yogurt, kefir, sauerkraut)

Lean meats, fish (omega 3s), eggs

Evolutionary Psychiatry- population vs individual

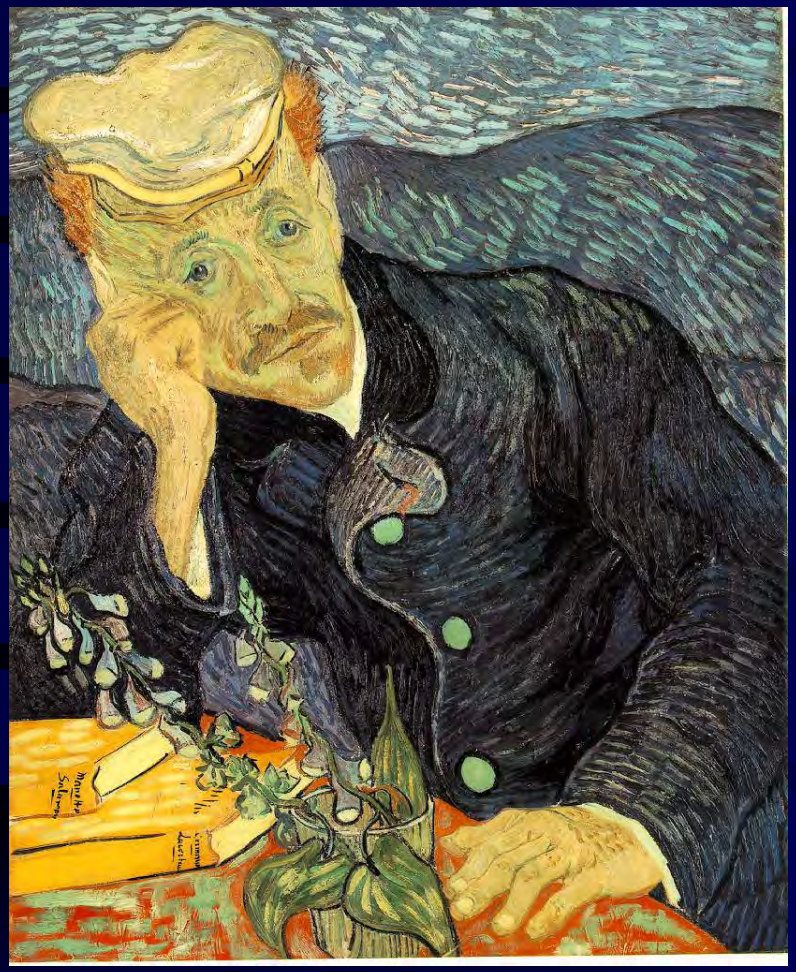
Some direct/ indirect advantage to behavioural trait



Anxiety, Obesity, Eating Disorders,OCD, Nodding Disease, Autism

Microbial message to our “spaceship”
The world is changing- Please listen to us!!!

DEVELOPMENTAL DISORDERS - HOPE FOR THE FUTURE



Meta- genomics, metabolomics, microbiome- longitudinal studies
Pre symptomatic biomarkers – metabolic, immune, microbial
Risk reduction (pre /post natal infection/GI/gyn/obstetrics/nutrition/ID
Therapeutics(metabolic augmentors-carnitine, microbiome reconstitution)

Kilee Patchell-Evans Autism Research Group
Director- Dr. Derrick MacFabe

HUMAN TISSUES/CLINICAL

- **Dr. Mohammad Alanazi** (Chair)
- **Dr. Afaf Al Ansary** Dept. of Biochemistry, King Saud University, Yasmen Al-Jadaani (Jeddah) PPA metabolism, oxidative stress markers in Saudi children
- **Dr. Laila Al-Ayadhi**, Director KSU Autism Research Treatment Centre (EEG, neurometabolic screening)
- **Dr. Richard Frye-Neurology** (Paed Neuro) U.of Arkansas
- **Dr. B. Devryer** (Ob/Gyn) Lawson, UWO
- **Dr. Clive Friedman** (dentistry) UWO
- **Dr. Erica Claud** (Neonatology) U. of Chicago- NEC

Needs to further productivity:

- Development of Twin Saudi/Canadian Center/ PAFC (UBC)
- Infastructure/Personnel: fellowships, studentships

EPIGENETICS

- **Dr. Bistra Nankova**, New York Medical College molecular, gene arrays, tissue culture, PC12
- **Dr. Edmond LaGamma**, New York Medical College Neonatalogist-Infection in Devel. Disabilities
- **Dr. Marco Aztori** (U. Texas) electrophysiology
- **Dr. Rochellys-Diaz-Heijtz** (Karolinska) SCFA CNS develop.
- **Dr. Koen Venema** (University Med Centre,Amsterdam) SCFA in gut

Needs to further productivity:

- Seed funding– molecular biology/lipidscreening/neonatology
- Personnel: Postdoctoral fellowships, studentship

~~Simons Foundation, US Dept of Defense, CIHR~~

METABOLISM

- **Dr. Fred Possmayer (Emeritus)** Biochem, (Ob/Gyn), UWO
- **Dr. Charlies McKenzie**, Biophysics-Lawson, UWO
- **Dr. Jim Staples**, Biology, UWO
- **Dr. B. Devryer** (Ob/Gyn) oxidative stress, mitochondrial function, lipid profiles, cytokines (autism, at risk mothers)

Needs to further productivity:

- Seed funding – interface with U. of Alberta metabolomics
- Personnel: Postdoctoral fellowships, studentship
- Equipment: GC Mass Spec, clinical FA assays

AUTISM RODENT MODEL-NEUROSCIENCE

Kilee Patchell-Evans Autism Research Group, University of Western Ontario

Core Faculty:
Dr. Derrick MacFabe – Director
Dr. Peter Cain (Emeritus)
Dr. Peter Ossenkopp
Dr. Martin Kavaliers

Core Staff:
Lisa Tichenoff
Francis Boon
Roy Taylor

Students:
Kelly Foley
Stacey Holbrook

Main studies conducted pricipally on site in facility:

- Neurobiology of GRAIFS (Gut Related Autism Inducing Factors)
- Behavioural rodent model (hyperactivity, OCD, perseveration, social impairment, anxiety)
- Central/peripheral/diet/colitis
- EEG (cortical, hippocampal, striatal)
- Developmental studies
- Genetic ASD model (i.e. GABARB ko mice- Dr. Tim Delorey)
- Pathology, Immunology, in Situ
- Tissues (brain, liver, gut, blood, placenta, liver, muscle, stool)

Needs to further productivity:

- Personnel: stable salaries, chairs, postdoctoral fellowships, studentships
- Equipment: fluorescent microscope, updated imaging program, startle apparatus, hole poke apparatus, cameras with computer, digitized EEG, tissue culture, western blots
- Facility: administrative offices, wet lab, level 2 infection facility (clostridial infection of rodents/ behavioural facility, additional animal facility (germ free?- Karolinska, U. of Chicago, UBC)

METABOLIC IMAGING

- **Dr. David Shoesmith**-Surface Science Western, UWO
- **Dr. Heng-Yong Nie**, Surface Science Western, UWO
- **Mary Jane Wazack**, Surface Science Western, UWO Tof-SIMS metabolic Brain/tissue imaging
- **Drs. Charlie McKenzie/Tim Scholl** –Lawson Research- fatty acid metabolic imaging

Needs to further productivity:

- Personnel: Postdoctoral fellowships, studentship
- Equipment: cryostat, tissue preparation area
- Imaging time, seed funding
- NSERC funding applied for

MICROBIOLOGY

- **Dr. Emma Allen-Vercoe**, University of Guelph- microbiology (clostridia from ASD patients), metabolic profiling of micriobiome isolates, synthetic stool,
- **Dr. Terry Van Raay**, University of Guelph teratogenicity of clostridial isolates (zebrafish model)
- **Dr. Sydney Finegold**, UCLA infectious disease, bacterial isolates from ASD patients
- **Dr. Gregor Reid**, Jeremy Burton (Lawson- Probiotics)
- **Dr. Ingrid Surono** (Bogor, Indonesia)-probiotics, GI
- **Dr. Lee Yuan Kun** (U. of Singapore)-Asia-microbiome
- **Dr. Tore Midvedt** (Karolinska) microbiome/development

Needs to further productivity:

- Seed funding
- Personnel: Postdoctoral fellowships, studentship

Partnership- Food/Agriculture (Fed, Govt,-Guelph)

POPULATIONS/GENETICS

- **Dr. Suzanne Lewis** (Genetics/Paeds-ASD-CARC)Director PAFC (clinical patient base)
- **Dr. Xudong Liu**, Genetics (Queen's University)
- **Dr. Helen Ouellette-Kuntz**, Epidemiology
- **Dr. Clive Friedman**, Paed. Dentistry (Western)
- **Dr. Garth Smith**, Developmental Paeds.
  - Genetic/environmental interactions, Somali population
  - ASD/ARDC consortium- 8000 subjects

Needs to further productivity:

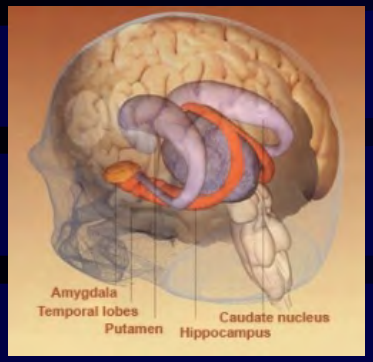
- Seed funding /collabororation with Life Science Inst. UBC)
- Personnel: Postdoctoral fellowships, studentship
- ~~linkages to Beijing Genomics Institute (genetics) and~~ PAFC

EDUCATION/PHILANTHROPY

- **Megan Cameron** - GoodLife Fitness/Special Projects
- **Stephen Chan** - (Dapasoft) and **Niall Wallace** (Infonaut)
  - Surveillance of clostridial infections in obstetrical/paediatric populations- interface with UBC
  - Research/Clinical Education, video conferencing, liason with ministry of Public Health
- **Fatima Kedyie**- Somali expatriates
- **Sergio and Wendy Cocchia**- PAFC

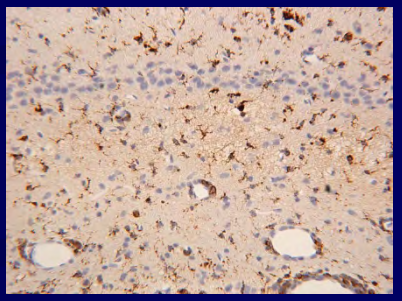
Needs to further productivity:

- Personnel: translation, English/French/Somali/Arabic
- Government awareness/lobbying

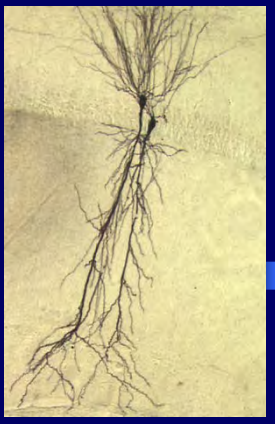


Active uptake to CNS

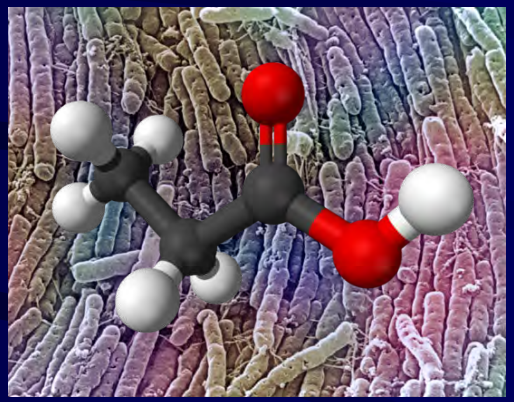
SCFA G protein receptors
Neurotransmitter Synthesis and release
Increased intracellular Calcium



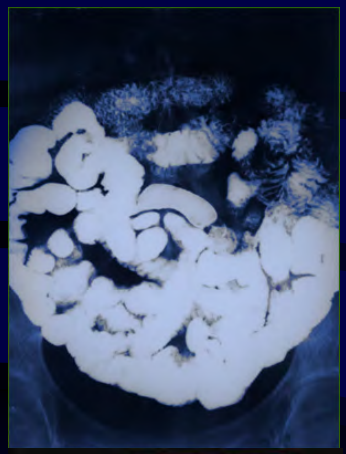
Neuroinflammation/neurodevelopment



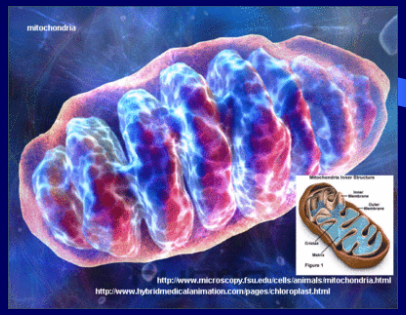
Gap Junction Closure

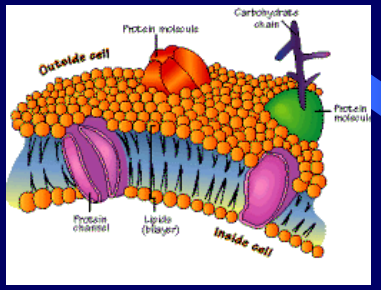


Short Chain Fatty Acid Bacterial
Fermentation Products

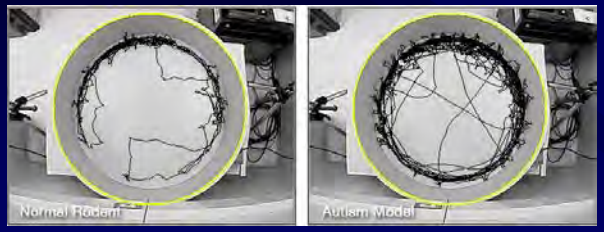


Gut motility and inflammation
Malabsorbtion





Mitochondrial function/oxidative stress
Altered lipid/membrane metabolism



Repetitive/antisocial behaviour/Seizure

Altered Gene Expression