

Looking for the Silent Fire: Are there signs of Neuroinflammation in Toddlers with ASD and Regression ?

Autism Research Parent Conference
Jan 15th, 2011

Alvin Loh, MD
Developmental Paediatrician, Surrey Place Centre
Assistant Professor, University of Toronto



Living Your Potential - All Your Life!
Enabling Full Participation For People With Developmental Disabilities

STAR – Study of Toddlers with Autism and Regression: Biomarkers of immune activation and oxidative stress

- Could inflammation in the brain be contributing to ASD ?
 - Brain Pathology and fluid (CSF) studies, small sample (Vargas '05)
 - Increase in head circumference in ASD at 6-18 months of life
 - Subtle MRI brain differences: ?atypical cells ? edema (Dager '08)
 - Uncontrolled epilepsy associated with neuroinflammation (Choi '09)
- How can we detect this?
 - Brain imaging?
 - Too mild for MRI, SPECT scans with radioisotopes not ethical
 - EEG? not specific for inflammation
 - CSF? Some enthusiasm but challenging to obtain CSF
 - Is there a correlation between inflammation in blood and CNS
 - Funded: pilot study on biomarkers of immune activation (blood)

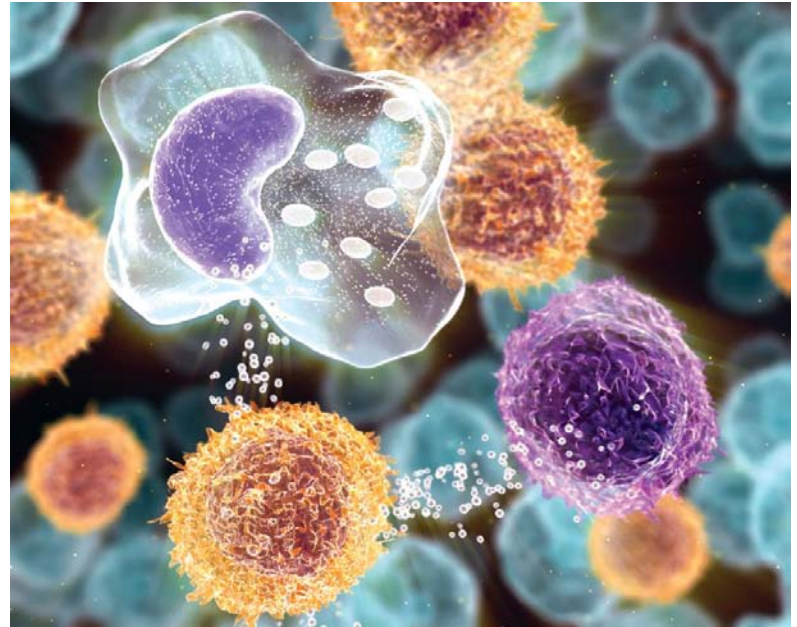


Living Your Potential - All Your Life!

Enabling Full Participation For People With Developmental Disabilities

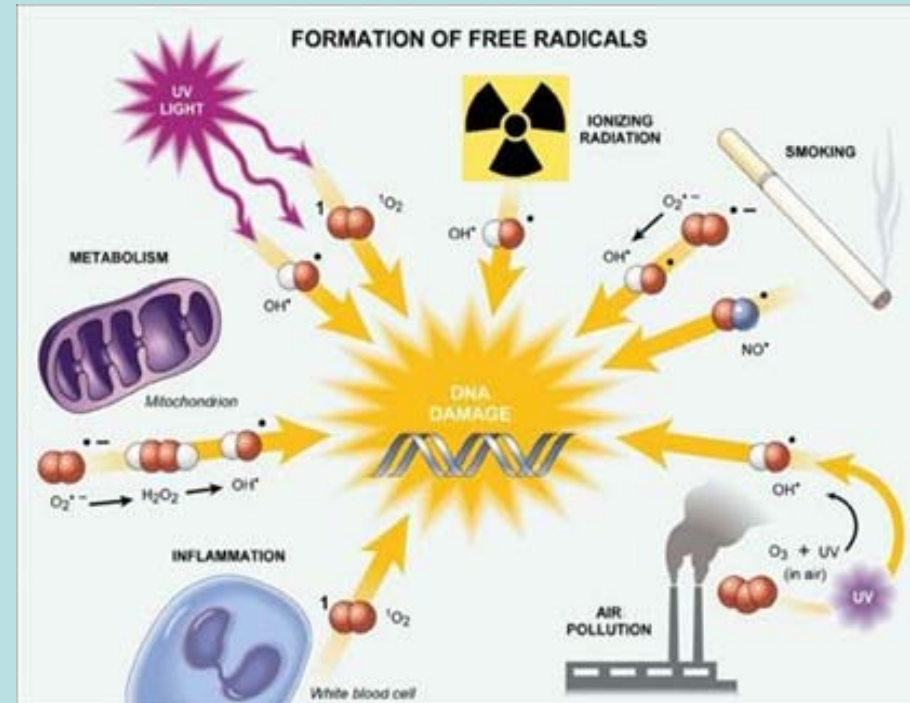
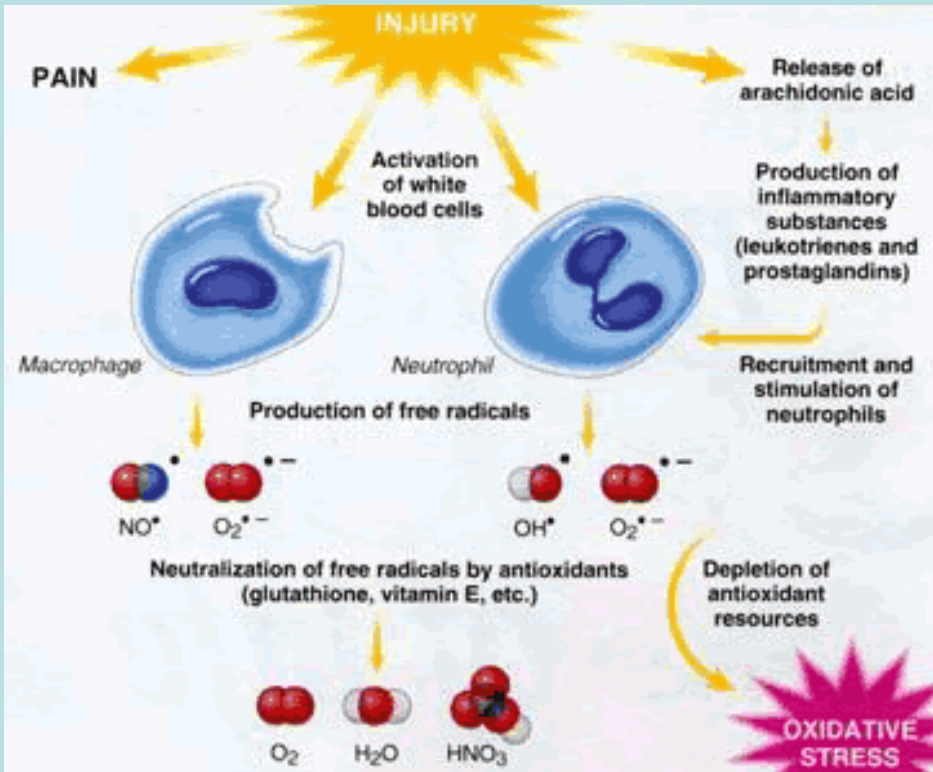
Purpose of STAR protocol

- To compare immune activation and oxidative stress markers in 18-36 month toddlers:
 - autism and regression vs
 - autism and no regression
- 50 cases and 50 controls:
Toronto, Baltimore, Arkansas
- Immune Dysfunction in ASD
 - NIMH: ASD vs Delays, +/- Regression
 - CD 40L, chronic inflammation (Pardo 2009)



Oxidative stress in ASD

- Glutathione (antioxidant) is decreased in ASD (James 2006)
- Oxygen reacts in our body leading to “oxidants”
- Potentially damaging “free radicals” are made and mopped up
- “an increase in production of oxygen molecules that can damage cells and impair their function” Jill James



Responding Quickly When Regression Occurs

- Make MDs and early childhood centres aware
- Screen with Regression questionnaire – parts of Toddler ADI-R
- Assessment with ASD testing (ADOS), and Developmental testing (Mullen), and Clinical History
- Clinical Tests (metabolic disorders, inflammatory markers)
- EEG and MRI if indicated
- Research Testing (immune overactivation, oxidative stress)
- Research Co-ordinator at SPC – Melanie Fenwick, x 2527
- Subspecialists: E. Anagnostou, W. Logan & B. Banwell (Neurology); S. Benseler (rheumatology); A. Schulze & A. Feigenbaum (Metabolics); J. Brian
- Collaborators: J. James, A. Zimmerman, C. Pardo



Living Your Potential - All Your Life!

Enabling Full Participation For People With Developmental Disabilities

Outcomes from this Pilot Study

- Compare levels of immune overactivation (increased cytokines), and oxidative stress, and also relationship of both in ASD (regression vs non regression)
- Future studies more specific to brain: CSF, Imaging
- Abnormalities in CSF could prompt a trial of therapy (? Antioxidants, ?immune modulation)



Living Your Potential - All Your Life!

Enabling Full Participation For People With Developmental Disabilities

Creatine Deficiency Syndromes in ASD

- Potentially Treatable metabolic cause of
 - Delays
 - Poor speech
 - ASD mannerisms
 - Seizures (in some cases)
- 1-2 % prevalence in populations with DD
- ? similar prevalence in ASD

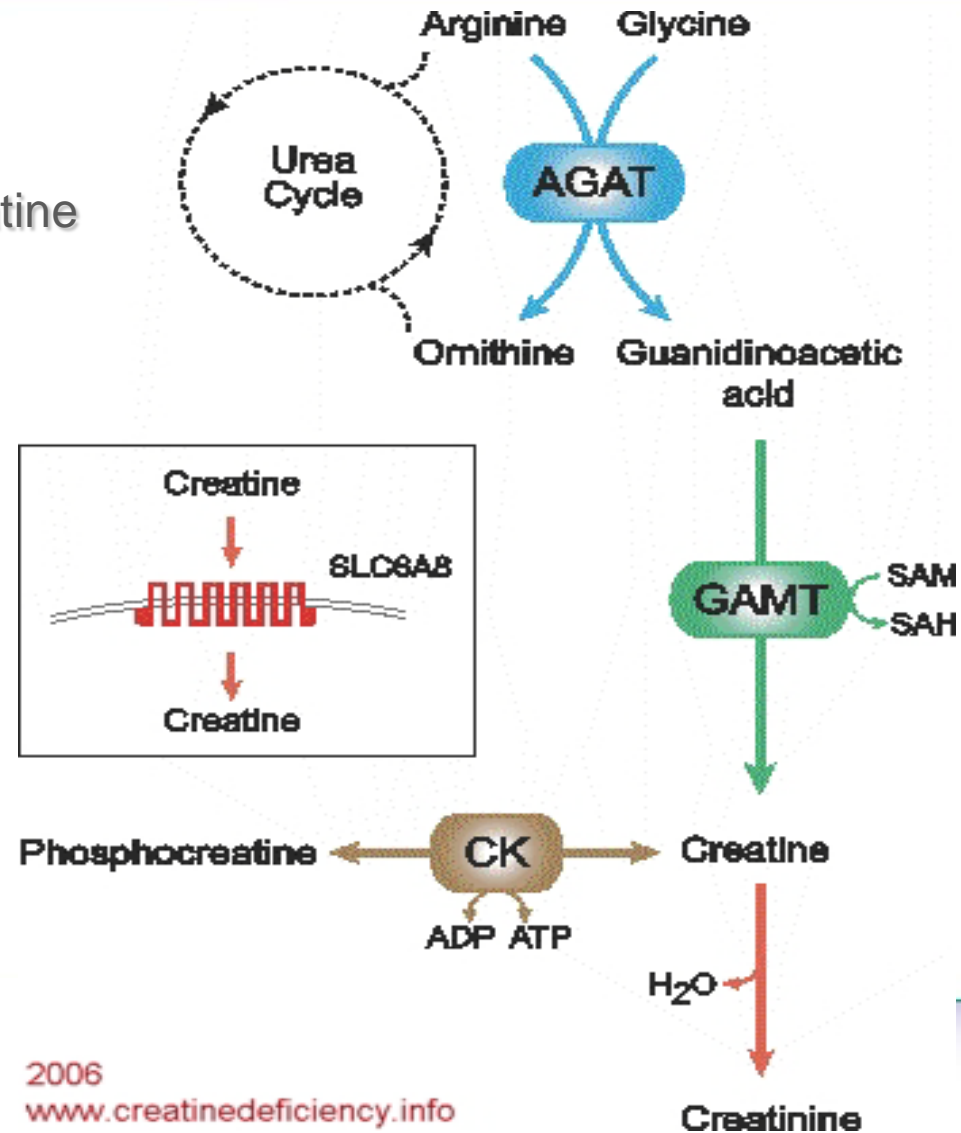


Living Your Potential - All Your Life!

Enabling Full Participation For People With Developmental Disabilities

Creatine Metabolism

- Creatine - energy delivery
 - muscle and brain
 - Actively moved into brain by Creatine Transporter pump
- Brain also makes creatine
- Three disorders in CDS
 - GAMT, guanidinoacetate methyltransferase (1994)
 - AGAT, arginine:glycine amidinotrasferase (2001)
 - CrT1, creatine transporter defect (2001)



	GAMT (severe)	AGAT (mild)	Creatine Transporter Deficiency
Prevalence	< 2.7%	rare	0.3-2.7%
Genetics	AR	AR	X linked
Clinical	Dev Delay Speech Delay Hypotonia, Dyskinesia Refractory seizures Autistic Mannerisms/SIB	Dev Delay Speech Delay (Seizures)	Dev Delay Severe Speech Delay Autistic mannerisms (Mild seizures)
Pathophysiology	High GAA, Low creatine	Low creatine	Low creatine
Treatment	Creatine, restrict arginine	Creatine 400mg/kg/d	Diet
Outcome	Some improvement	Improvement	No clear changes

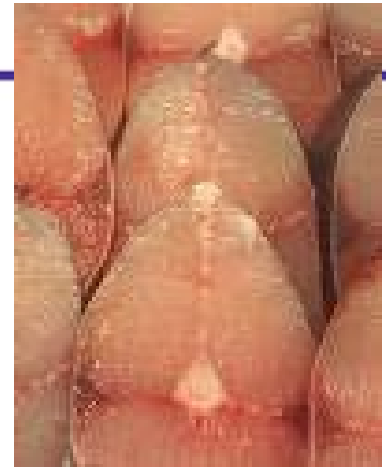


Living Your Potential - All Your Life!

Enabling Full Participation For People With Developmental Disabilities

Testing for Creatine Deficiency

- Clinical Indication in Toronto
Global Delays, Poor Speech
(+/- abnormal movements, seizures)
- Research Indication
 - ASD (supported by ADOS)
- Screening
 - First morning urine, Sick Kids, Dr Andreas Schulze's Lab
 - If abnormal, repeat urine (12-24 hr collection ideal)
- Diagnostic Confirmation
 - Genetic (blood test): GAMT, AGAT, SLC 6A8
 - Brain Scan (MRS) shows Absent Creatine
- **Adults** – Genetic Metabolic Consultation at TGH
 - Dr Hannah Fagfoury taking clinical referrals from your MD



http://www.uhn.ca/Clinics & Services/services/adult_genetics/docs/agp_referral_form.pdf



Living Your Potential - All Your Life!

Enabling Full Participation For People With Developmental Disabilities

Creatine Deficiency Syndrome in ASD Study in Toronto

- Contact Person: Research co-ordinator, Melanie Fenwick,
melanie.fenwick@surreyplace.on.ca
416 925 5141, ext 2527
- Principal Investigators: Andreas Schulze, Alvin Loh
- Co-Investigators: E. Anagnostou, W. Roberts, S. Scherer



Living Your Potential - All Your Life!

Enabling Full Participation For People With Developmental Disabilities