Biomedical Approach: What's Next, Other Options

Autism One Conference
Down Syndrome Track
May 2012

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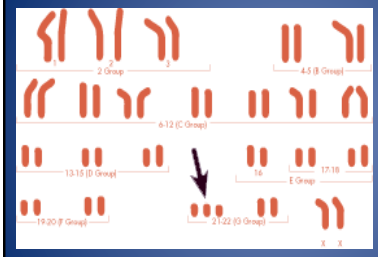
True Health Medical Center
Naperville, Illinois

Disclaimer

- Information is for educational purposes only
- Not to be taken as specific medical advice
- All medical decisions regarding your child's health issues should be discussed with your health care provider
- Medical Director of True Health Medical Center

More than Genetics: Trisomy 21



Goal is raising healthy children regardless of diagnosis.

RAISING A HEALTHY CHILD IN A TOXIC WORLD

With the rise of environmental toxins there has been an increased incidence of children experiencing health challenges such as allergies, digestive problems, difficulty focusing and delayed development.

We Are All Toxic!!

- Each year chemical companies in the US manufacture over 6.5 trillion pounds of 9,000 different chemicals and release 7.1 billion pounds of over 650 chemical pollutants into the atmosphere and water.
- In addition, heavy metals are released from manufacturing and coal combustion, including 48 tons of mercury/year.
- EWG studied 9 healthy individuals with no exposures. 167 chemicals, 76 carcinogens, 94 chemicals with known toxicity to brain and nervous system were found.
- EWG studied 10 newborns. The cord blood contained 200 chemical pollutants including PCBs, dioxins, flame retardants, DDT, pesticides, and mercury.
- NHANES studied 2,540 individuals. They found widespread phthalate metabolites from plastics in 75% of participants.
- CDC studied 400 adults, 95% had bisphenol A (BPA) - a chemical from plastics

Toxins and Children

"It is vitally important to recognize that children are far more susceptible to damage from environmental carcinogens and endocrine-disrupting compounds than adults."

"Ideally, both mothers and fathers should avoid exposure to endocrine-disrupting chemicals and known or suspected carcinogens prior to a child's conception and throughout pregnancy and early life, when the risk of damage is greatest."

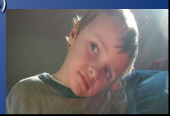
2008-2009 Annual Report Presidents Cancer Panel

Total Body Burden

Mother's Burden
Toxic Metals
Environmental Pollutants
Electromagnetic Fields
Sensory Input
Stress/Internal Conflicts
Dietary Factors
Allergens
Microbial/Biofilm
Immune/Inflammatory Burden

Patient Burden

- Environmental Toxic Exposures
  - Chemicals (remodeling, new house, new furniture, pesticides in home, plastics, pollution, …)
  - Heavy Metals (toys, food, coal burning plant, factories, amalgams…)
  - Dietary
  - Pharmaceutical (antibiotics, acetominophen, anesthesia (MRI)
- Immune Triggers
  - Injected Antigens, Adjuvants, Viruses
  - Allergic (new foods, mold, food sensitivities)
  - Infectious (viral, tic borne, bacteria/strep)
- Stressors, Other
  - Physical
  - Emotional
  - Surgical



Metabolic Aftermath of Body Burdens

Oxidative Stress
- Depletion of Antioxidants, Glutathione, Metallothionein, Cysteine, Vitamins, Minerals, Amino Acids and Phytonutrients
- Impaired Detoxification - Methylation, Sulfation,

Mitochondrial Dysfunction
Immune Dysregulation
Endocrine Disruption
Gastrointestinal Dysfunction
Neurological Issues

Chronic Inflammatory Disorders: Allergies, Asthma, Arthritis, Frequent Infections, Fatigue, Mood, Behavior and Cognitive Issues

Down Syndrome / Autism

- Symptoms
  - Memory
  - Cognition
  - OCD
- Comorbid
  - Thyroid/Endocrine
  - Childhood Leukemia
  - Heart Defects
  - Alzheimers
  - Celiac
  - Sleep Disorder
  - Vision/Hearing
- Metabolic
  - Immune
  - Mitochondria
  - Methylation
  - Oxidative Stress
  - Neurologic

- Symptoms
  - Sterotypical Behavior
  - Language
  - Social
- Comorbid
  - Sleep
  - Seizures
  - Gastrointestinal Issues
- Metabolic
  - Immune
  - Mitochondria
  - Methylation
  - Oxidative Stress
  - Neurologic
  - Endocrine

Neurologic Issues Affecting Memory and Cognition in DS

- Impairment of Neurogenesis, low cerebellar volume and brain volume. (Sonic Hedgehog (SHH) signaling of granule cell precursor (GCP).
- Disrupted Neurosignaling, associated with elevated extracellular GABA causing inhibition.
- APP (amyloid precursor protein) gene overexpression and protein interference leading to degeneration of specific neural cell circuits, particularly forebrain to hippocampus.
- Age related loss of forebrain cholinergic neurons. (also seen in Alzheimers)

MRDD Research Reviews 2007

Hippocampal Dysfunction

- Linked to an imbalance between inhibitory and excitatory pathways.
- Disruption of communication between the basal forebrain and hippocampus.
- Basal forebrain cholinergic neurons (BFCN) utilize acetylcholine as a neurotransmitter.
- BFCN transports NGF (nerve growth factor) produced in the hippocampus back to the basal forebrain to remain active.
- This retrograde transport of NGF is greatly impaired in Ts65Dn mice.

Neurotrophins (NGF and BDNF)

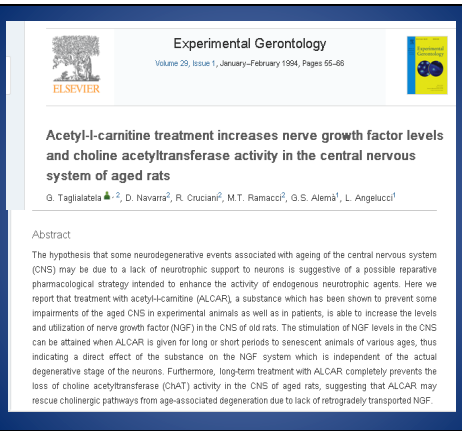
- Function and structure are similar.
- NFG found in peripheral and CNS, promotes expression and growth of Basal Forebrain cholinergic neurons. (BCFN)
- BDNF found globally in the brain, implicated in learning and memory, and long term potentiation.
- Supplementation improves memory in animal models of aging and AD.
- NGF improved cholinergic neuron atrophy as well as size and number.

Physiology and immunology of the cholinergic anti-inflammatory pathway

J Clin Invest. 2007 Feb;117(2):289-96.

Tracey KJ.

- The nervous system, via an inflammatory reflex of the vagus nerve, can inhibit cytokine release and thereby prevent tissue injury and death.
- The efferent neural signaling pathway is termed the cholinergic anti-inflammatory pathway.
- Cholinergic agonists inhibit cytokine synthesis and protect against cytokine-mediated diseases.
- Stimulation of the vagus nerve prevents the damaging effects of inflammatory cytokines.



Experimental Gerontology

Volume 29, Issue 1, January–February 1994, Pages 55–66

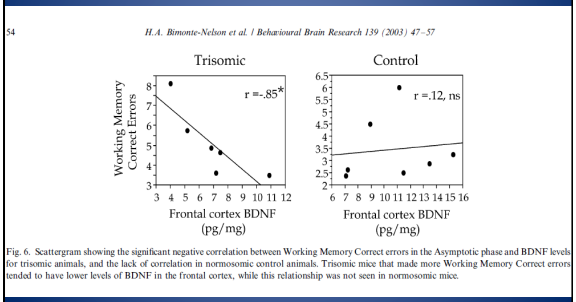
Acetyl-l-carnitine treatment increases nerve growth factor levels and choline acetyltransferase activity in the central nervous system of aged rats

G. Taglialatela[a, 2], D. Navarra[2], R. Cruciani[2], M.T. Ramacci[2], G.S. Alemà[1], L. Angelucci[1]

Abstract

The hypothesis that some neurodegenerative events associated with ageing of the central nervous system (CNS) may be due to a lack of neurotrophic support to neurons is suggestive of a possible reparative pharmacological strategy intended to enhance the activity of endogenous neurotrophic agents. Here we report that treatment with acetyl-l-carnitine (ALCAR), a substance which has been shown to prevent some impairments of the aged CNS in experimental animals as well as in patients, is able to increase the levels and utilization of nerve growth factor (NGF) in the CNS of old rats. The stimulation of NGF levels in the CNS can be attained when ALCAR is given for long or short periods to senescent animals of various ages, thus indicating a direct effect of the substance on the NGF system which is independent of the actual degenerative stage of the neurons. Furthermore, long-term treatment with ALCAR completely prevents the loss of choline acetyltransferase (ChAT) activity in the CNS of aged rats, suggesting that ALCAR may rescue cholinergic pathways from age-associated degeneration due to lack of retrogradely transported NGF.

As BDNF increases in trisomic animals, there is a decrease in memory errors.



54 H.A. Bimonte-Nelson et al. / Behavioural Brain Research 139 (2003) 47–57

Trisomic

Control

Working Memory Correct Errors

r =-.85*

r =.12, ns

Frontal cortex BDNF (pg/mg)

Frontal cortex BDNF (pg/mg)

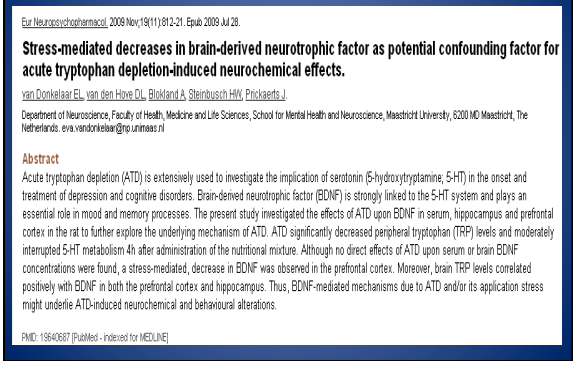
Fig. 6. Scattergram showing the significant negative correlation between Working Memory Correct errors in the Asymptotic phase and BDNF levels for trisomic animals, and the lack of correlation in normosomic control animals. Trisomic mice that made more Working Memory Correct errors tended to have lower levels of BDNF in the frontal cortex, while this relationship was not seen in normosomic mice.

Cortisol Levels During Human Aging Predict Hippocampal Atrophy and Memory Deficits

Lupien, Sonia.
Nature Neuroscience 1998

- Elevated glucocorticoid levels produce hippocampal dysfunction and correlate with individual deficits in spatial learning in aged rats.
- Humans with significant prolonged cortisol elevations showed reduced hippocampal volume and deficits in hippocampus-dependent memory.
- The degree of hippocampal atrophy correlated strongly with both the degree of cortisol elevation over time and current basal cortisol levels.
- Therefore, basal cortisol elevation may cause hippocampal damage and impair hippocampus-dependent learning and memory in humans.

Stress Effects on BDNF



Eur Neuropsychopharmacol. 2009 Nov;19(11):812-21. Epub 2009 Jul 28.

Stress-mediated decreases in brain-derived neurotrophic factor as potential confounding factor for acute tryptophan depletion-induced neurochemical effects.

van Donkelaar EL, van den Hove DL, Blokland A, Steinbusch HW, Prickaerts J.

Department of Neuroscience, Faculty of Health, Medicine and Life Sciences, School for Mental Health and Neuroscience, Maastricht University, 6200 MD Maastricht, The Netherlands. eva.vandonkelaar@np.unimaas.nl

Abstract

Acute tryptophan depletion (ATD) is extensively used to investigate the implication of serotonin (5-hydroxytryptamine; 5-HT) in the onset and treatment of depression and cognitive disorders. Brain-derived neurotrophic factor (BDNF) is strongly linked to the 5-HT system and plays an essential role in mood and memory processes. The present study investigated the effects of ATD upon BDNF in serum, hippocampus and prefrontal cortex in the rat to further explore the underlying mechanism of ATD. ATD significantly decreased peripheral tryptophan (TRP) levels and moderately interrupted 5-HT metabolism 4h after administration of the nutritional mixture. Although no direct effects of ATD upon serum or brain BDNF concentrations were found, a stress-mediated, decrease in BDNF was observed in the prefrontal cortex. Moreover, brain TRP levels correlated positively with BDNF in both the prefrontal cortex and hippocampus. Thus, BDNF-mediated mechanisms due to ATD and/or its application stress might underlie ATD-induced neurochemical and behavioural alterations.

PMID: 19640687 [PubMed - indexed for MEDLINE]

Improving BDNF, reverses hippocampal atrophy, and improves neurogenesis

- Elevated cortisol and chronic stress decrease BDNF.
  - **Phosphatidyl serine and adaptogenic herbs, such as Ashwaghanda help modulate cortisol**
- Fluoxetine (Prozac)
  - **In Ts65Dn mice, fluoxetine treatment restored the expression of 5-HT1A receptors and BDNF and enhances neurogenesis.**
- Lithium
  - **Lithium Restores Neurogenesis in the Subventricular Zone of the Ts65Dn Mouse, a Model for Down Syndrome.**

Improving BDNF, reverses hippocampal atrophy, and improves neurogenesis: possible interventions…

- Diet
- Exercise
- Omega 3 EFA
- Bifidobacterium breve
- Curcumin

Mom's with high fat diets have babies with oxidative stress in the hippocampus, leading to decreased neurogenesis. (mouse model)

FASEB J. 2009 Jun;23(6):1920-34. Epub 2009 Jan 21.

Diet-induced obesity in female mice leads to peroxidized lipid accumulations and impairment of hippocampal neurogenesis during the early life of their offspring.

Tozuka Y, Wada E, Wada K.

Department of Degenerative Neurological Diseases, National Institute of Neuroscience, National Center of Neurology and Psychiatry, 4-1-1 Ogawahigashi, Kodaira, Tokyo 187-8502, Japan.

Abstract

Maternal obesity may affect the child's long-term development and health. However, there is little information about the involvement of maternal obesity in the brain development of offspring. Here, we investigated the effects of maternal obesity on the hippocampal formation of offspring. Adult female mice were fed either a normal diet (ND, 4% fat) or a high-fat diet (HFD, 32% fat) 6 wk before mating and throughout pregnancy and the majority of lactation. We found that infants from HFD-fed dams (HFD offspring) showed obesity and hyperlipidemia during suckling. In HFD offspring, lipid peroxidation was promoted in serum and the hippocampal dentate gyrus, where neurogenesis takes place throughout postnatal life. Using a BrdU-pulse labeling study, we showed that malondialdehyde, a product of peroxidized lipids, reduced the proliferation of hippocampal progenitor cells in vitro and that neurogenesis in HFD offspring during postnatal development was similarly lowered relative to the ND animals. These results indicated that maternal obesity impairs hippocampal progenitor cell division and neuronal production in young offspring possibly due to metabolic and oxidative changes.

PMID: 19158155 [PubMed - indexed for MEDLINE] Free full text

Offspring of Mom's with a high fat diet, had increased oxidative stress, less BDNF, less neurogenesis, and decreased cognitive function. (mouse model)

Neurochem Int. 2010 Oct;57(3):235-47. Epub 2010 Jun 9.

Maternal obesity impairs hippocampal BDNF production and spatial learning performance in young mouse offspring.

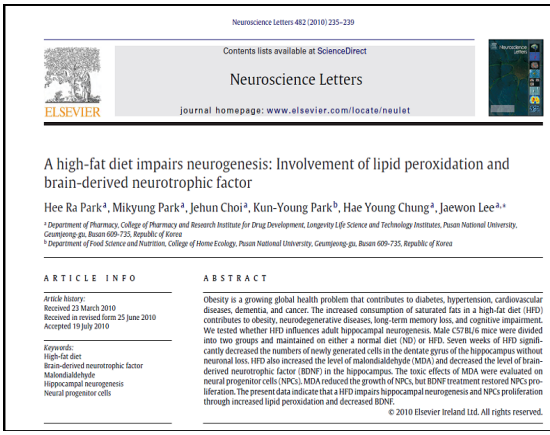
Tozuka Y, Kumon M, Wada E, Onodera M, Mochizuki H, Wada K.

Department of Degenerative Neurological Diseases, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Tokyo, Japan.

Abstract

Maternal obesity may affect the child's long-term development and health, increasing the risk of diabetes and metabolic syndrome. In addition to the metabolic and endocrine systems, recent reports have indicated that maternal obesity also modulates neural circuit formation in the offspring. However, this not yet been fully investigated. Here, we examined the effect of diet-induced maternal obesity on hippocampal development and function in the mouse offspring. Adult female mice were fed either a normal diet (ND, 4% fat) or a high-fat diet (HFD, 32% fat) before mating and throughout pregnancy and lactation. After weaning, all offspring were fed with a normal diet. We found that HFD offspring showed increased lipid peroxidation in the hippocampus during early postnatal development. HFD offspring had less brain-derived neurotrophic factor (BDNF) in the hippocampus than ND offspring. BDNF has been shown to play crucial roles in neuronal differentiation, plasticity and hippocampus-dependent cognitive functions such as spatial learning and memory. Using retroviral labeling, we demonstrated that dendritic arborization of new hippocampal neurons was impaired in the young HFD offspring. Finally, we evaluated cognitive function in these offspring using hippocampus-dependent behavioral tasks. The Barnes maze test demonstrated that HFD offspring showed impaired acquisition of spatial learning in the young but not adult period. This study, using a mouse model, indicates that diet-induced maternal obesity impairs hippocampal BDNF production and spatial cognitive function in young offspring, possibly due to their metabolic and oxidative changes.

PMID: 20538025 [PubMed - indexed for MEDLINE]



Neuroscience Letters 482 (2010) 235–239

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ELSEVIER

A high-fat diet impairs neurogenesis: Involvement of lipid peroxidation and brain-derived neurotrophic factor

Hee Ra Park[a], Mikyung Park[a], Jehun Choi[a], Kun-Young Park[b], Hae Young Chung[a], Jaewon Lee[a,*]

[a] Department of Pharmacy, College of Pharmacy and Research Institute for Drug Development, Longevity Life Science and Technology Institutes, Pusan National University, Geumjeong-gu, Busan 609-735, Republic of Korea
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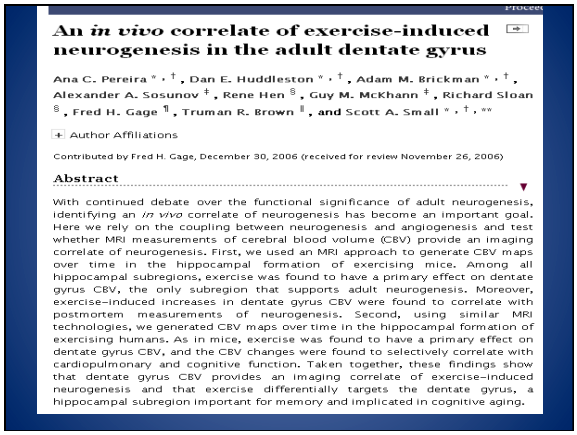
Hippocampal neurogenesis
Neural progenitor cells

ABSTRACT

Obesity is a growing global health problem that contributes to diabetes, hypertension, cardiovascular diseases, dementia, and cancer. The increased consumption of saturated fats in a high-fat diet (HFD) contributes to obesity, neurodegenerative diseases, long-term memory loss, and cognitive impairment. We tested whether HFD influences adult hippocampal neurogenesis. Male C57BL/6 mice were divided into two groups and maintained on either a normal diet (ND) or HFD. Seven weeks of HFD significantly decreased the numbers of newly generated cells in the dentate gyrus of the hippocampus without neuronal loss. HFD also increased the level of malondialdehyde (MDA) and decreased the level of brain-derived neurotrophic factor (BDNF) in the hippocampus. The toxic effects of MDA were evaluated on neural progenitor cells (NPCs). MDA reduced the growth of NPCs, but BDNF treatment restored NPCs proliferation. The present data indicate that a HFD impairs hippocampal neurogenesis and NPCs proliferation through increased lipid peroxidation and decreased BDNF.



An *in vivo* correlate of exercise-induced neurogenesis in the adult dentate gyrus

Ana C. Pereira [*, †], Dan E. Huddleston [*, †], Adam M. Brickman [*, †], Alexander A. Sosunov [‡], Rene Hen [§], Guy M. McKhann [‡], Richard Sloan [§], Fred H. Gage [¶], Truman R. Brown [‖], and Scott A. Small [*, †, **]

Author Affiliations

Contributed by Fred H. Gage, December 30, 2006 (received for review November 26, 2006)

Abstract

With continued debate over the functional significance of adult neurogenesis, identifying an *in vivo* correlate of neurogenesis has become an important goal. Here we rely on the coupling between neurogenesis and angiogenesis and test whether MRI measurements of cerebral blood volume (CBV) provide an imaging correlate of neurogenesis. First, we used an MRI approach to generate CBV maps over time in the hippocampal formation of exercising mice. Among all hippocampal subregions, exercise was found to have a primary effect on dentate gyrus CBV, the only subregion that supports adult neurogenesis. Moreover, exercise–induced increases in dentate gyrus CBV were found to correlate with postmortem measurements of neurogenesis. Second, using similar MRI technologies, we generated CBV maps over time in the hippocampal formation of exercising humans. As in mice, exercise was found to have a primary effect on dentate gyrus CBV, and the CBV changes were found to selectively correlate with cardiopulmonary and cognitive function. Taken together, these findings show that dentate gyrus CBV provides an imaging correlate of exercise–induced neurogenesis and that exercise differentially targets the dentate gyrus, a hippocampal subregion important for memory and implicated in cognitive aging.

Omega 3 supplementation improved BDNF levels in rats with oxidative stress after trauma.

J Neurotrauma. 2004 Oct;21(10):1457-67.

Dietary omega-3 fatty acids normalize BDNF levels, reduce oxidative damage, and counteract learning disability after traumatic brain injury in rats.

Wu A, Ying Z, Gomez-Pinilla F.

Department of Physiological Science, University of California at Los Angeles, 90095, USA.

Abstract

Omega-3 fatty acids (i.e., docosahexaenoic acid; DHA) regulate signal transduction and gene expression, and protect neurons from death. In this study we examined the capacity of dietary omega3 fatty acids supplementation to help the brain to cope with the effects of traumatic injury. Rats were fed a regular diet or an experimental diet supplemented with omega-3 fatty acids, for 4 weeks before a mild fluid percussion injury (FPI) was performed. FPI increased oxidative stress, and impaired learning ability in the Morris water maze. This type of lesion also reduced levels of brain-derived neurotrophic factor (BDNF), synapsin I, and cAMP responsive element-binding protein (CREB). It is known that BDNF facilitates synaptic transmission and learning ability by modulating synapsin I and CREB. Supplementation of omega-3 fatty acids in the diet counteracted all of the studied effects of FPI, that is, normalized levels of BDNF and associated synapsin I and CREB, reduced oxidative damage, and counteracted learning disability. The reduction of oxidative stress indicates a benevolent effect of this diet on mechanisms that maintain neuronal function and plasticity. These results imply that omega-3 enriched dietary supplements can provide protection against reduced plasticity and impaired learning ability after traumatic brain injury.

Maternally seperated rats have increased cortisol and increased BDNF.
Bifidobactrium replacement improves hippocampal BDNF, but not in maternally seperated rats.

Benef Microbes. 2011 Sep;2(3):199-207.

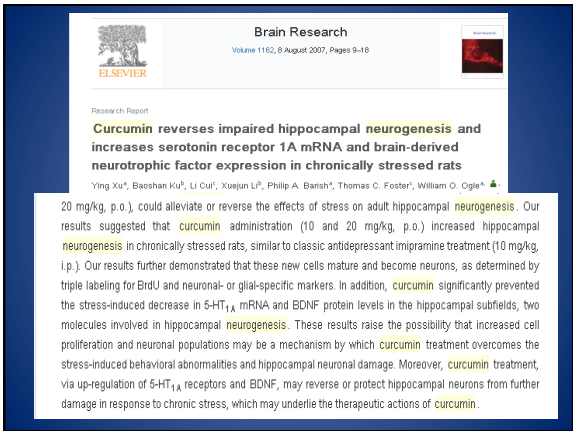
BDNF expression in the hippocampus of maternally separated rats: does Bifidobacterium breve 6330 alter BDNF levels?

O'Sullivan E, Barrett E, Grenham S, Fitzgerald P, Stanton C, Ross RP, Quigley EM, Cryan JF, Dinan TG.

University College Cork, Alimentary Pharmabiotic Centre, College Road, Cork, Ireland.

Abstract

Brain-derived neurotrophic factor (BDNF) is of interest because of its putative role in stress and psychiatric disorders. Maternal separation is used as an animal model of early-life stress and of irritable bowel syndrome (IBS). Animals exposed to the paradigm show altered gut function together with heightened levels of arousal and corticosterone. Some probiotic organisms have been shown to be of benefit in IBS and influence the brain-gut axis. Our objective was to investigate the effects of maternal separation on BDNF under basal conditions and in response to the probiotic Bifidobacterium breve 6330. The study implemented the maternal separation model which we have previously described. Polymerase chain reaction and in situ hybridisation were performed to measure the effect of maternal separation on both BDNF total variants and BDNF splice variant (exon) IV in the hippocampus. Maternally separated and non-separated rats were treated with B. breve 6330, to investigate the effect of this probiotic on BDNF total variant and BDNF exon IV expression. Maternal separation increased BDNF total variants ($P<0.01$), whilst having no effect on BDNF exon IV. B. breve 6330 increased BDNF total variants ($P<0.01$), and decreased BDNF splice variant IV, in non-separated rats ($P<0.01$). B. breve 6330 did not alter BDNF levels in the maternally separated rats. Maternal separation caused a marked increase in BDNF in the hippocampus. While B. breve 6330 influenced BDNF in normal animals, it had no significant effect on BDNF in those which were maternally separated. We have demonstrated that an orally administered probiotic can influence hippocampal BDNF.



Brain Research

Volume 1162, 8 August 2007, Pages 9–18

Research Report

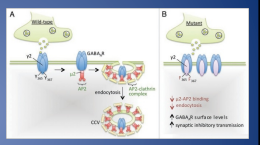
Curcumin reverses impaired hippocampal neurogenesis and increases serotonin receptor 1A mRNA and brain-derived neurotrophic factor expression in chronically stressed rats

Ying Xu[a], Baoshan Ku[b], Li Cui[c], Xuejun Li[b], Philip A. Barish[a], Thomas C. Foster[c], William O. Ogle[a].

20 mg/kg, p.o.), could alleviate or reverse the effects of stress on adult hippocampal neurogenesis. Our results suggested that curcumin administration (10 and 20 mg/kg, p.o.) increased hippocampal neurogenesis in chronically stressed rats, similar to classic antidepressant imipramine treatment (10 mg/kg, i.p.). Our results further demonstrated that these new cells mature and become neurons, as determined by triple labeling for BrdU and neuronal- or glial-specific markers. In addition, curcumin significantly prevented the stress-induced decrease in 5-HT_{1A} mRNA and BDNF protein levels in the hippocampal subfields, two molecules involved in hippocampal neurogenesis. These results raise the possibility that increased cell proliferation and neuronal populations may be a mechanism by which curcumin treatment overcomes the stress-induced behavioral abnormalities and hippocampal neuronal damage. Moreover, curcumin treatment, via up-regulation of 5-HT_{1A} receptors and BDNF, may reverse or protect hippocampal neurons from further damage in response to chronic stress, which may underlie the therapeutic actions of curcumin.

No FDA Approved Meds

- First potential therapy designed to improve cognition and adaptive behavior in individuals with Down's syndrome.



Clinical Trials are underway:

Theory:

- $GABA_a$ receptor not being able to be pulled into the cell due to 2 genes. DYRK1A and Synaptojanin.
- The GABA system is the inhibitory system and inhibits LTP (long term potentiation) ie. Memory.
- Synaptic plasticity is measured by changes in LTP.
- $GABA_a$ receptor antagonist in mice model (Ts65Dn) showed enhancement of normal LTP.

$GABA_a$ Antagonists and Hippocampal Function

- At high doses, can trigger seizures.
- At doses far below those used to induce seizure showed long term improvement in MWM (morris water maze), "object recognition" and "alternating T maze".
- These experimental tests are used to assess hippocampal function.
- Decreased hippocampal function is associated with an imbalance of excitatory (norepinephrine) and inhibitory (GABA) circuits in the DS mouse model.

Bilobalides from Ginkgo Biloba

- Antagonist of $GABA_a$ receptor
- Antioxidant, Anticoagulant, Vasodilator
- Used in Chinese medicine for over 5000 yr
- Safe, caution in patients on anticoagulants
- Researched
  - Memory, cognition
  - Cerebral insufficiency
  - Alzheimers

"The ginkgo biloba extract (EGb 761) protects hippocampal neurons against cell death induced by β-amyloid" European Journal of Neuroscience. 2000

Oxidative stress: A bridge between Down's syndrome and Alzheimer's disease (review)

Neurobiology of Aging Volume 28, Issue 5, May 2007

- The genetic, biochemical and neuropathological analogies between Down's syndrome (DS) and Alzheimer's disease (AD), there is ample evidence of the involvement of oxidative stress (OS) in the pathogenesis of both disorders.
- Oxidative Stress occurs decades prior to the signature pathology and manifests as lipid, protein and DNA oxidation, and mitochondrial abnormalities
- For Down's Syndrome, no scientifically proven diet or drug is yet available.
- In the future, a balanced up-regulation of endogenous antioxidants, together with multiple exogenous antioxidant supplementation, may be expected to be one of the most promising treatment methods.

Oxidative stress and Alzheimer disease

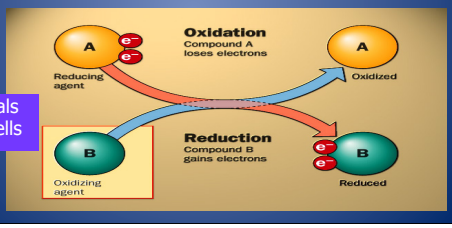
American Journal of Clinical Nutrition, Vol. 71, February 2000

- Aging is the most obvious risk factor for AD. Free radicals are involved. Neurons are extremely sensitive to attacks by destructive free radicals.
- Lesions are present in the brains of AD patients that are typically associated with attacks by free radicals (eg, damage to DNA, protein oxidation, lipid peroxidation, and advanced glycosylation end products), and metals (eg, iron, copper, zinc, and aluminum) are present.
- ß-Amyloid is aggregated and produces more free radicals in the presence of free radicals. ß-amyloid toxicity is eliminated by free radical scavengers.
- AD has been linked to mitochondrial anomalies affecting cytochrome *c* oxidase.
- Finally, many free radical scavengers (eg, vitamin E, selegeline, and *Ginkgo biloba* extract EGb 761) have produced promising results in relation to AD.

Oxidative Stress and Free Radicals

- Free radicals are unstable oxygen atoms that cause oxidation in our bodies, which brings about aging.
- An increase in free radicals can be caused by such things as pollution, pesticides, and contaminated food and water.

Free radicals damage cells



ORAC: Oxygen Radical Absorbance Capacity

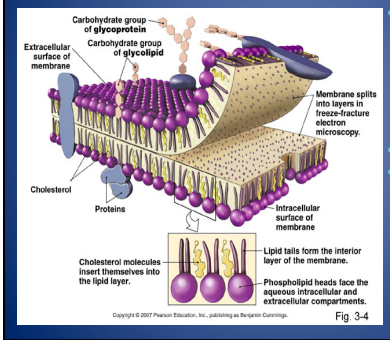
Measures the ability of foods to act as antioxidants, the higher the ORAC the greater reducing capacity

Fats/Lipids are good for your brain!

- Fats, are an integral part of all cell membranes, and are vulnerable to destruction through oxidation by free radicals.
- Fat Soluble Vitamins and Antioxidants are uniquely suited to pass thru the blood brain barrier and alleviate oxidative stress in the lipid(fat) portion of the brain.
  - 70% of the Brain is made up of fat.
  - 25% of our Cholesterol resides in the brain.
  - The mylein sheath is predominantly fat.

- Most neurotoxins, like mercury, are fat soluble and damage lipid membranes thru lipid peroxidation or oxidative stress.

Cell Membranes are Mostly Fat



- Phospholipids
  - Choline
  - Serine
  - Inositol
  - Ethanolamine
- Cholesterol
- Glycolipids

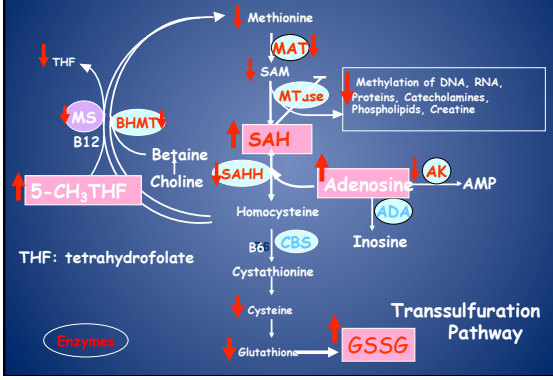
Cholesterol

- Cholesterol is abundant in the tissue of the brain and nervous system.
- Myelin, which covers nerve axons to help conduct the electrical impulses that make movement, sensation, thinking, learning, and remembering possible, is over one fifth cholesterol by weight.
- Even though the brain only makes up 2% of the body's weight, it contains 25% of its cholesterol.
- Cholesterol was found to be the most important factor in the formation of synapses, the basis of our learning and memory.
- Cholesterol is a precursor to vitamin D.
- The human body uses cholesterol to synthesize bile acids, which are important for the digestion of fats.
- Cholesterol is the precursor to all steroid hormones.

Good Fats become Bad Fats if oxidized, antioxidants and Vitamin E prevent this....

- Fats are vulnerable to destruction through oxidative stress.
- Antioxidants and fat-soluble vitamins are uniquely suited to intercept free radicals and thus prevent a chain reaction of fat oxidation or lipid peroxidation.
- Fatty acid oxidation in the brain leads to poor cell to cell communication, microglial activation, glutamate excitotoxicity, methylation/sulfation deficits, glutathione depletion, mitochondrial dysfunction and chronic inflammation! !!!

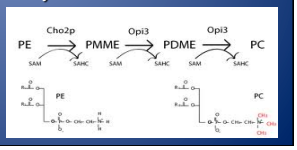
Impact of Oxidative Stress on Methionine Metabolism



Phospholipid Methylation

Richard Deth, PhD

- D4 receptor on cell membranes associated with attention.
- Methylation of Phospholipids (Phosphoethanolamine to Phosphatidylcholine) causes an increase in membrane fluidity.
- Membrane fluidity is important for proper signaling and flow of information and nutrients in and out of cells.
- Dopamine stimulated PLM (phospholipid methylation) requires 4 steps in which a new methyl group is provided by methylfolate or SAMe when methylfolate is low.

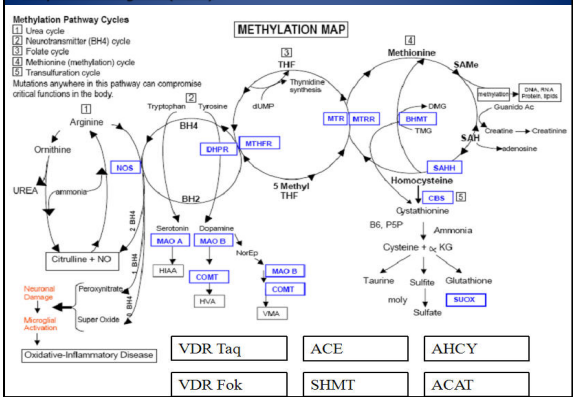


Phosphatidyl Serine

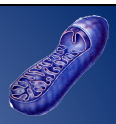
- Supports the function of many vital enzymes.
- Acts as an antioxidant, and quells inflammation in the brain.
- In Europe and Japan, phosphatidylserine is sold as a prescription drug to treat memory and learning dysfunction.
- Aged rats with cognitive deficits have demonstrated decreased phosphatidylserine in the hippocampus.
- Helps with stress induced damage in the brain.

- Ulmann L. *Brain and hippocampus fatty acid composition in phospholipid classes of aged-relative cognitive deficit rats.* Prostaglandins Leukot Essent Fatty Acids. 2001 Mar;64(3):189-95.
- Lomnitski L. *Distinct alterations in phospholipid metabolism in brains of apolipoprotein E-deficient mice.* J Neurosci Res. 1999 Nov 15;58(4):586-92.
- Suzuki S. *Oral administration of soybean lecithin transphosphatidylated phosphatidylserine improves memory impairment in aged rats.* J Nutr. 2001 Nov;131(11):2951-6.
- Castilho JC. *Phosphatidylserine: an antidepressive or a cognitive enhancer?* Prog Neuropsychopharmacol Biol Psychiatry. 2004 Jul;28(4):731-8.
- Pepeu G. *Nootropic drugs and brain cholinergic mechanisms.* Prog Neuropsychopharmacol Biol Psychiatry. 1989;13 Suppl:S77-S88.
- Schreiber S. *An open trial of plant-source derived phosphatydilserine for treatment of age-related cognitive decline.* Isr J Psychiatry Relat Sci. 2000;37(4):302-7.

Amy Yasko Diagram (2005)



Oxidative Stress and Mitochondrial Dysfunction



- The inner membrane of the mitochondria contains a large amount of antioxidants including:
  - Glutathione
  - Vitamin C
  - Vitamin E
  - Anti-oxidant enzymes such as superoxide dismutase
- Oxidative stress impairs mitochondrial function
- The brain is very sensitive to oxidative stress because of its high energy demands, its limited capacity to use substrates other than glucose for ATP synthesis, abundant lipid content, and relatively low antioxidant levels compared to other organs.

Adv Exp Med Biol. 2012;724:291-9.

Oxidative stress and mitochondrial dysfunction in Down syndrome.

Pagano G, Castello G.

Cancer Research Center, Mercogliano, Italy. gbpagano@tin.it

Abstract

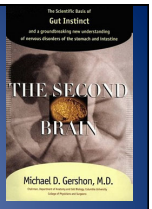
Down syndrome (DS) or trisomy 21 is the genetic disease with highest prevalence displaying phenotypic features that both include neurologic deficiencies and a number of clinical outcomes. DS-associated neurodegeneration recalls the clinical course of Alzheimer disease (AD), due to DS progression toward dementia and amyloid plaques reminiscent of AD clinical course. Moreover, DS represents one of the best documented cases of a human disorder aetiologically related to the redox imbalance that has long been attributed to overexpression of Cu,Zn-superoxide dismutase (SOD-1), encoded by trisomic chromosome 21. The involvement of oxidative stress has been reported both in genes located else than at chromosome 21 and in transcriptional regulation of genes located at other chromosomes. Another well documented hallmark of DS phenotype is represented by a set of immunologic defects encompassing a number of B and T-cell functions and cytokine production, together prompting a proinflammatory state. In turn, this condition can be directly interrelated with an in vivo prooxidant state. As an essential link to oxidative stress, mitochondrial dysfunctions are observed whenever redox imbalances occur, due to the main roles of mitochondria in oxygen metabolism and this is the case for DS. Ultrastructural and biochemical abnormalities were reported in mitochondria from human DS patients and from trisomy 16 (Ts16) mice, to be reviewed in this chapter. Together, in vivo alterations of mitochondrial function are consistent with a prooxidant state as a phenotypic hallmark in DS.

PMID: 22411251 [PubMed - indexed for MEDLINE]

Mitochondria, Methylation, Fatty Acids and Carnitine connection

- Carnitine biosynthesis is initiated by methylation of lysine.
- The only firmly established function of carnitine is its function as a carrier of activated fatty acids and activated acetate across the inner mitochondrial membrane.
- Choline and carnitine supplementation lowers lipid peroxidation, and promotes conservation of retinol and alpha-tocopherol .

Gut Brain Axis



- A bidirectional communication system between the brain and gastrointestinal systems.
- Communication occurs along immunologic, neural, and biochemical pathways.
- Gut microbiota can effect both brain development and behavior.
- Stress also can alter the composition of Gut microbiota.

100 trillion bacteria in the gut

70% of immune system lies in the gut

Early disruption of gut flora, affects later immune function, potential allergies and autoimmunity

Aids with digestion of carbohydrates and fiber to form SCFA which in turn fuels enterocytes

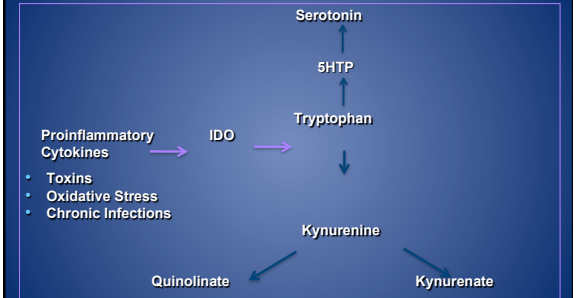
Microbial Flora

- pH balance
- Modulation of the immune system
- Digestion, Energy Production, Metabolism, Vitamin Production
- Destruction of toxins and mutagens
- Repression of pathogenic microbial growth
- Preventing allergy
- Preventing inflammatory bowel disease and inflammation
- Alleviate anxiety, improve mood

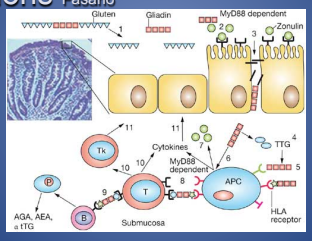
- The Colon has an obligate need for bacterial fermentation products (SCFA- short chain fatty acids)

"Composition and Metabolic Activities of Bacterial Biofilms Colonizing Food Residues in the Human Gut" (Macfarlane Sept 2006)

Tryptophan and IDO



Human Zonulin a Potential Modulator of Intestinal Tight Junctions Fasano



Mechanisms of Disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases
Nature Clinical Practice Gastroenterology & Hepatology (2005) **2**, 416-422
Alessio Fasano 50

Leaky Gut Theory (Fasano)

- Gluten causes leaky gut by releasing zonulin.
- The Paracellular Pathway – space between cells in the gut is impermeable to large molecules.
- Zonulin release causes cytokine and chemokine activation (CXCR-3 , ligands CXCL 9, 10, 11) and migration of pathological Th1 cells.
- Gluten causes wbc(neutrophil) recruitment
- Impaired intestinal barrier is involved in Chronic INFLAMMATION!!!
- MS, strokes, asthma, cardiomyopathy, IDDM, thyroiditis, celiac disease, rheumatoid arthritis, inflammatory bowel disease and Autism.

51

Basic Strategy

- History and Physical Examination
- Laboratory Testing
- Clean Up
  - Environmental Controls
  - Dietary Interventions
  - Address Gastrointestinal Health
- Foundational Nutrients
- Alleviate Oxidative Stress
- Support Neurogenesis and GABA balance
- Support Mitochondrial Function
- Support Methylation Pathways
- Detoxification
- Hyperbaric Oxygen Therapy

Clean up the Child's Environment

- Use natural, biodegradable and perfume free detergents and cleaning agents, do not dry clean clothes.
- Avoid chlorine: use water filters, limit pool and hot tubs.
- Wear 100% cotton clothes, avoid flame retardants. (Sb)
- Use fluoride-free toothpaste (tin,titanium).
- Use an air purifier, especially in the bedroom.
- Avoid prolonged exposure to batteries (light up shoes, lap tops, cell phones, head phones).
- Check for recalled TOYS with lead.
- Use aluminum-free salt, baking powder, deodorant. Do not cook in aluminum foil or drink from aluminum cans.
- Avoid use of herbicides or pesticides or mosquito repellants, on lawns, garden, or self(remove shoes when home).
- Use natural shampoos, soaps, and make-up (lipstick-Pb/Al)
- Avoid sources of electrosmog/(EMF), especially in the bedroom. (cordless phones, wi-fi, baby monitors)

Clean up the Diet

- Casein-free/Gluten-free/Soy-free/Diet Trial for 3-6 months.
- Avoid sugar and refined starch, replace with whole grains
- Maximize antioxidants and phytonutrients (colorful foods)
- Limit processed and preserved foods; organic is best.
- Avoid excitotoxins (ex. Caffeine, MSG, NutraSweet, red/yellow food dyes, nitrites, sulfites, glutamates, propionates, benzoates).
- Limit intake of phenolics (apples, grapes, strawberries…).
- Drink plenty of filtered water.
- Never microwave in plastics or Styrofoam, do not store food in plastic or foil, or cook on Teflon coated pans.
- Eliminate seafood.
- Add good fats (avocado, olive, coconut, flax). Avoid fried foods, hydrogenated, trans-fats and esterified fats.
- Buy hormone-free, antibiotic-free, grass fed organic meat and eggs.
- Add fermented foods (kefir, kombucha, cabbage…).

Opioid Peptide Theory

- Casein/gluten peptides are broken down by the enzyme DPPIV (dipeptidyl dipeptidase 4). This enzyme can be inhibited by toxic metals and yeast.
- If DPPIV is not optimal dairy and gluten protein are not digested and partially broken down proteins or peptides accumulate. These peptides act as false neurotransmitters and have an opiate effect, creating problems with behavior, focus, attention, mood regulation, and processing info. Other symptoms include high pain tolerance, dilated pupils, addiction to dairy and gluten products.
- High levels of opioid peptides (gliadorphin and caseomorphine) found in urine of autistics. (Reichelt, 1997)
- Casein-free, Gluten-free diet may be an effective intervention (Whiteley,1999)

Clean Up the Gut

- Address Maldigestion
  - Add Digestive Enzymes
- Address Malabsorption
  - Add Probiotics and Prebiotics, Essential Fats, Biotin
  - Address Fat Soluble Vitamin Deficiencies (A, D, E, K)
- Start Foundational Nutrients
- Address Dysbiosis
- Diagnose and Treat Immune Dysregulation
  - Address Food Allergies and Hypersensitivities
  - Treat Immunodeficiencies
  - Treat Chronic Inflammation
- Address Motility/Constipation

Foundational Nutrients

- Minerals
  - Zinc
  - Magnesium
  - Selenium
- Antioxidants
  - Vitamin C
  - Vitamin E
  - Vitamin D
- Good Fats
  - Omega 3 EFA
  - Coconut oil
  - Phosphatidyl Choline/Serine
- Vitamins
  - Vitamin D3
- Epsom Salts Baths

57

Abstract

Children affected with Down syndrome (DS) show deficient growth, immunodeficiency—especially concerning T-cell population—and low plasma zinc levels. New growth charts have been recently proposed, and zinc supplementation to the diet the diet has been reported to improve transiently the efficiency of the immune system. The aim of this study was to evaluate if in DS children zinc sulphate therapy could improve the growth rate and affect some endocrine parameters. We studied 22 patients (16 males and 6 females) who received zinc sulphate for 6 to 9 months. Fifteen of 22 patients studied reached a higher centile in their growth rate, whereas the remaining seven showed no change, at least to date. The average heighty velocity changed from 23.84 ± 7.98 mm/6 months t 40.80 ± 7.68 mm/6 months. Growth hormone serum level mwas 5.94 ± 4.89 ng/ml compared with 7.49 ± 6.75 ng/ml before and after therapy, respectively. Somatomedin serum level was 160.27 ± 68.88 after therapy, respectively. In conclusion, zinc sulphate therapy of patients with DS affects not only the immune system, as previously reported, but can also accelerate growth.

Behavioral and Brain Functions Biomed Central

Mercury exposure, nutritional deficiencies and metabolic disruptions may affect learning in children

Renee Dufault

- Nutritional deficiencies, including deficiencies in the long chain polyunsaturated fatty acids eicosapentaenoic acid and docosahexaenoic acid, methionine, zinc and selenium, have been shown to influence neuronal function and produce defects in neuronal plasticity, as well as impact behavior in children with attention deficit hyperactivity disorder.
- Nutritional deficiencies and mercury exposure have been shown to alter neuronal function and increase oxidative stress among children with autism.
- High fructose corn syrup has been shown to contain trace amounts of mercury and its consumption can also lead to zinc loss.
- Consumption of certain artificial food color additives has also been shown to lead to zinc deficiency.
- Dietary zinc is essential for maintaining the metabolic processes required for mercury elimination.

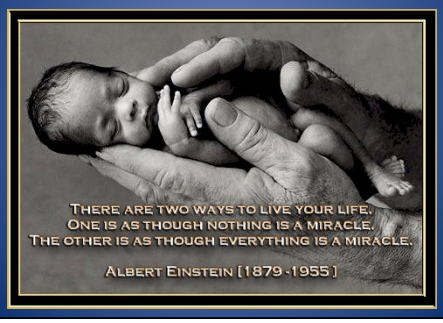
The Oxford-Durham Study: A Randomized, Controlled Trial of Dietary Supplementation With Fatty Acids in Children With Developmental Coordination Disorder

Alexandra J. Richardson

PEDIATRICS Vol. 115 No. 5 May 2005, pp. 1360-1366

- Mounting evidence suggests that a relative lack of certain polyunsaturated fatty acids (PUFA) may contribute to related neurodevelopmental and psychiatric disorders such as dyslexia and attention-deficit/hyperactivity disorder.
- No effect of treatment on motor skills was apparent, but significant improvements for active treatment versus placebo were found in reading, spelling, and behavior over 3 months of treatment in parallel groups.
- After the crossover, similar changes were seen in the placebo-active group, whereas children continuing with active treatment maintained or improved their progress.

Laboratory testing options are varied and based on the individual.



Basic Biomedical Blood Testing

- CBC
- Comprehensive Metabolic Panel
- Serum Copper
- Plasma Zinc
- Thyroid profile
- Blood Lead
- Iron, blood
- Celiac panel
- Ammonia, blood
- Vitamin D 25 OH
- Carnitine Panel
- Lactic Acid
- Reduced Glutathione
- Total Cholesterol/Triglycerides

Biomarkers: Oxidative Stress

- 8 OH deoxyguanosine
- 8 OH guanosine
- Isoprostane F2 alpha
- Malondialdehyde (urine)
- Lipid Peroxides
- Reduced Glutathione

Antioxidants

- Vitamin E
- Vitamin A, vitamin K
- Vitamin C
- Selenium, Zinc
- Reduced Glutathione (r-GSH)
- Bioflavinoids (catechins) and Carotenoids
- Superfruits (noni, goji, acai, mangosteen…)
- Kangen water

Support Neurogenesis and GABA Balance

- Diet, Low oxidized fats/trans fats
- Exercise
- Omega 3
- Cholinergics
  - Phosphatidyl choline/serine
  - Acetylcholinesterase inhibitors
- Bifidobacterium breve
- Curcumin
- Gingko biloba

65

Address Adrenal Balance

- Keep stressors to a minimum
- Plenty of sleep
- Limit sugar and refined carbs
- Adaptogenic herbs
  - Ashwaghanda
  - Ginseng
  - Holy Basil
- Vitamin C

66

Support Methylation

- Methylation
  - DMG
  - TMG
  - Hydroxy B12
  - Folinic Acid
  - Methyl Folate

67

Support Mitochondrial Function

- Vitamin B1, B2, B3, B5, and Biotin
- Antioxidants
  - Glutathione
  - Alpha Lipoic Acid- careful
  - Coenzyme Q10
- L-Carnitine
- Magnesium

Hyperbaric treatment for children with autism: a multicenter randomized, double blind, controlled trial

BMC Pediatr. 2009 Mar 13;9(1):21.
Rossignol DA, Rossignol LW, Smith S, Schneider C, Logerquist S, Usman A, Neubrander J, Madren EM, Hintz C, Grushkin B, Mumper EA.

Children with autism who received hyperbaric treatment at 1.3 atm and 24% oxygen for 40 hourly sessions had significant improvements in overall functioning, receptive language, social interaction, eye contact, and sensory/cognitive awareness compared to children who received slightly pressurized room air.

PMID: 19284641

Thank You for opening your minds and hearts to learning to help heal our kids.

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