Adolescence – a time for learning and change

“The fundamental task of adolescence—to achieve adult levels of social competence—requires a great deal of learning about the complexities of human social interactions. Puberty appears to create a neurobehavioral nudge toward exploring and engaging these social complexities.”
Sick kids are stressed out kids! And puberty can make things worse...

- Sleep disruption
- Sensory issues - texture, sound, lights
- Flight or fight response (running or aggression)
- Tantrums/Meltdowns
- Isolation/disengaged
- Anxiety
- Need for sameness/OCD
- Lack of regulation or homeostasis
- Abnormal reaction to stressors

In a Swedish sample of five cases deterioration or severe symptom aggravation at the onset of puberty is described that followed earlier improvement.

Autistic children with pubertal deterioration may constitute a meaningful subgroup of the syndrome.

The matter deserves more attention in future follow-up studies.

Common Medical Issues During Puberty

- Seizures
- *Endocrine/Hormones
  - Adrenal/Thyroid Dysfunction
  - Blood Sugar Issues, Pre-diabetes, PCOS
  - Hormonal Abnormalities (Androgen Excess)
  - Low Cholesterol
  - Poor Detox of Hormones
- *Dysautonomia/ Excitation vs Inhibition
  - Sympathetic vs Parasympathetic
  - Glutamate vs GABA
- Obsessive behaviors / tics / PANS / PANDAS
- Constipation / GI abnormalities/SIBO
- Acne
- Sleep issues
- ADHD / ADD

HHS Public Access

Published in final edited form as:

Surging Hormones: Brain-Behavior Interactions During Puberty

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Abstract

In this paper we discuss the surging hormones of puberty and their influences on adolescent behavior. We describe why these issues represent an interesting and important area of investigation, emphasizing their contributions to a specific set of developmental processes at the heart of the transition from childhood to adolescence. We briefly review the neuroendocrine underpinnings of human puberty. Our review focuses on evidence for behavioral (and neurobehavioral) effects of gonadal hormones, and emphasizes the social and affective dimensions of these hormonal effects. More broadly, we consider how these hormonal events contribute to brain-behavior interactions that can bias early adolescent trajectories in both positive and negative directions, and in ways that may begin as small influences, but can spiral into large-scale effects over time. These influences also appear to play an important role in functional and structural brain development during adolescence. Finally we offer some thoughts on directions for future research in these areas.
Hormonal Surges

• Prepuberty (2-3 yrs prior)
  • Girls 9-10 yrs
  • Boys 10-12 yrs

• Puberty (age 10-25)
  • Girls Average Age 12.5 yrs
  • Boys Average Age 13.5 yrs

• Increases in GnRH, LH, FSH, estrogen, testosterone, DHEA
• Changes in body/physical characteristics
• Changes in behavior
  • Increased aggression, risk taking behavior, more reward dependent, less inhibition
• Changes in brain
  • Social and mood processing, flexibility in cognitive engagement
• Changes in sleep patterns and preferences

Clinical Characteristics of Children with Autism Spectrum Disorder and Co-Occurring Epilepsy

METHODS: Cross-sectional study using four samples of children with ASD for a total of 5,815 participants with ASD.

RESULTS: The average prevalence of epilepsy in children with ASD 2-17 years was 12.5%; among children aged 13 years and older, 26% had epilepsy. Epilepsy was associated with older age, lower cognitive ability, poorer adaptive and language functioning, a history of developmental regression and more severe ASD symptoms. Children age 10 or older had 2.35 times the odds of being diagnosed with epilepsy (p<.001) and for a one standard deviation increase in IQ, the odds of having epilepsy decreased by 47% (p<.001).

Viscidi et al., 2013  PLoS One 8(7): e67797
Evidence points to valproate, lamotrigine and levetiracetam as the most effective and tolerable AEDs with ASD.

Limited evidence supports ketogenic and modified Atkins diets, multiple subpial transections, immunomodulation and neurofeedback treatments.

Limited evidence supports L-carnitine, multivitamins and N-acetyl-L-cysteine in mitochondrial disease and dysfunction.

Folinic acid in cerebral folate abnormalities.

Limited evidence for a number of novel treatments, particularly magnesium with pyridoxine, omega-3 fatty acids, gluten free /casein-free diet and transcranial magnetic stimulation.
Adrenal Hormones

Adrenal Cortex
Steroid Hormones
- Cortisol (glucocorticoid)
- Aldosterone (mineralocorticoid)
- Progesterone
- DHEA
- Testosterone
- Estrogen

Adrenal Medulla
Catecholamines
- Epinephrine
- Norepinephrine

Adrenal Pathways

Cholesterol ➔ Vitamin D ➔ Pregnenolone

- Progesterone ➔ Hydroxyprogrenolone ➔ Dehydroepiandrosterone
- Deoxycorticosterone ➔ Hydroxyprogesterone ➔ Androstenedione
- Corticosterone ➔ Deoxycortisol ➔ Estrone ➔ Testosterone
- Aldosterone ➔ Cortisol ➔ Estradiol

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Melatonin, mitochondrial homeostasis and mitochondrial-related diseases.

Authors: Gomes, A. and Soares, M.

Abstract: Melatonin, a hormone produced in the pineal gland, has been shown to have various biological effects, including antioxidant properties, regulation of the sleep-wake cycle, and protection against oxidative stress. In the context of mitochondrial homeostasis, melatonin has been suggested to play a role in maintaining mitochondrial function and preventing damage caused by reactive oxygen species (ROS). This review provides an overview of the current understanding of melatonin's effects on mitochondrial homeostasis, with a focus on recent studies that have explored the potential therapeutic applications of melatonin in mitochondrial disorders.

Keywords: Melatonin, mitochondrial homeostasis, oxidative stress, mitochondrial dysfunction.
Melatonin Benefits More Than Sleep

- Antioxidant
- Anti-inflammatory
- Anti-aging
- Mitochondrial Function
- Dental Health
- Neurodegeneration
- Migraine Relief
- Antidepressant
- Thyroid function
- Antiviral, Antibacterial, Antiparasitic

Homeopathic Remedies- Sleep

- Coffea – over active mind, unable to switch off
- Pulsatilla – restless in first sleep, too hot – too cold
- Aconite – restlessness, nightmares, fear
- Chamomile – feeling wide awake and irritable
- Lycopodium – active mind, ruminating, laughs in sleep, awakes around 4am
- Arnica – bed feels hard, overtired, fidgety
- Opium – feels sleepy but unable, sound sensitive, unable to then arouse
- Arsenicum – wakes 12 – 2am, restless, worried
50% of 30 kids with ADD showed an abnormal HPA response.

As measured by an abnormal dexamethasone suppression test (DST) and abnormal diurnal rhythm.

Abstract
Children with Autism often show difficulties in adapting to change. Previous studies of cortisol, a neurobiologic stress hormone reflecting hypothalamic-pituitary-adrenal (HPA) axis activity, in children with autism have demonstrated variable results. This study measured cortisol levels in children with and without Autism: (1) at rest; (2) in a novel environment; and (3) in response to a blood draw stressor. A significantly higher serum cortisol response was found in the group of children with autism. Analysis showed significantly higher peak cortisol levels and prolonged duration and recovery of cortisol elevation following the blood draw stressor in children with autism. This study suggests increased reactivity of the HPA axis to stress and novel stimuli in children with autism.

Adrenal Response to Stress

• Adaptation
  – 3 stages
  • Alarm (increased cortisol, normal DHEA, increased epinephrine, norepinephrine)
  • Resistance (pregnenolone steals cholesterol to make cortisol, but at the expense of sex hormones, increased cortisol, low DHEA)
  • Exhaustion (low cortisol, low DHEA)

Hans Selye, M.D
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Signs and Symptoms of Adrenal Stress

Adrenal Hypofunction
- Cannot stay asleep
- Craves salt
- Slow starter
- Afternoon fatigue
- Dizziness on standing
- Afternoon headaches

Low cortisol
- High epinephrine
- High anxiety
- Low glucose (hypoglycemia)
- Craves sweets
- Irritable if meals missed
- Better with meals

Adrenal Hyperfunction
- Cannot fall asleep
- Perspires easy
- Lots of stress
- Weight gain
- Craves sweets after meals
- Sleepy after meals
- Wakes up tired
- Hyperactivity

High cortisol
- High glucose (hyperglycemia)
- Low melatonin
- Insulin resistance
- High Testosterone (women)
- High Estrogen (men)

Impact of Adrenal Stress Syndrome

Sleep
- Adrenal hypofunction, low cortisol, loss of ability to maintain blood sugar levels at night, causes stress response.
- The stress response causes the medulla to secrete epinephrine and norepinephrine to try to mobilize glucose to compensate for a lack of cortisol.
- Adrenal hyperfunction, Epinephrine and Norepinephrine activate the sympathetic nervous system and cause night time awakening.

Strakis. Neuroendocrinology and pathophysiology of the stress response. 1995

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Impact of Adrenal Stress Syndrome

Gastrointestinal Function

• High cortisol suppresses secretory Immunoglobulin A (sIg A)
• High cortisol contributes to dysbiosis
• High cortisol causes thinning of the GI lining
• Food allergies/sensitivities activate the GALT and place the body in an alarm pattern, further stimulating the LHPA Axis
• High cortisol decreases gastric and colonic motility causing GERD and constipation

Cunningham-Rundies. 1978. 1979
Guhad. Salivary IgA as a marker of social stress in rats. 1996.
Soderholm. Stress and the gastrointestinal tract. 2001

Impact of Adrenal Stress Syndrome

Thyroid Underconversion

• High cortisol has a suppressive effect on 5’deoiodinase which converts T4 (inactive) to T3(active).
• T4 is converted to T3, reverse T3, T3 sulfate and T3 acetic acid.
• If T4 is normal, T3 is low, and TSH is low, think of adrenal stress.
• High cortisol suppresses TSH and LH and increases rT3

Geuchot. Physiological and pathological variations in saliva cortisol. 1982
LoPresti. Thyroid response in critical illness.1997

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Impact of Adrenal Stress Syndrome

Blood Sugar Imbalances
- High cortisol
  - Leads to insulin receptor insensitivity, and excess insulin production. This results in insulin resistance and hyperglycemia which leads to leptin resistance
  - Insulin resistance causes elevated testosterone in women (PCOS) and elevated estrogen in men
- Low cortisol
  - Affects liver’s ability for gluconeogenesis and glycogenolysis
  - Causes hypoglycemia

Insulin Resistance/Insulin Receptor Insensitivity
- 25-35% of population
- Increased insulin
- Increased sodium retention, increased BP, increased coagulation
- Increased HMG CoA reductase
- Increased incidence
  - Diabetes
  - Cardiovascular disease
  - Sleep Apnea
  - Hormonal imbalances
  - Obesity
Symptoms of Insulin Resistance (IR)

- Fatigue
- Cravings for sugar and simple carbs
- Constant hunger
- Fatigue after meals
- Belly fat (central obesity)
- Increased waist to hip ratio
- Gynecomastia (boys)
- Hirsuitism (girls)

Signs of Insulin Resistance (IR)

- IR prevents glucose from entering the cells and decreases oxidative phosphorylation
- Messages sent back to increase glucose to improve ATP production causing a vicious cycle
- Elevated fasting or post-prandial glucose
- Elevated fasting or post-prandial insulin
- Elevated triglycerides
- Cholesterol:Triglycerides ratio>1
- Insulin upregulates HMG –CoA reductase
- Low HDL, High LDL
- Elevated uric acid
- Elevated BP
Female Hormones and Blood Sugar

PCOS (Polycystic Ovarian Syndrome) (4-10%):
- less than 6 periods/yr (chronic anovulation)
- ovarian cysts
- elevated testosterone, elevated estrogen, increased androstenedione, increased DHEA, increased LH, increased 17 OH progesterone
- insulin receptor sensitivity decreased by androgens
- unwanted hair growth, weight gain, mood swings
- insulin up regulates 17, 20 lyase and decreases sex hormone binding globulin

PCOS Treatment

- Traditional: Oral contraceptives suppress secretion of hormones and decrease androgens, but inhibit the natural HPO feedback loop, and affects the gut microbiome
- Other Traditional Rx: Ketoconazole, metformin, spironolactone
- Natural options
  - Diet
  - Exercise
  - Support insulin receptor sensitivity
  - Microbiome rebalance
Symptoms of Elevated Androgens

- Anxiety
- Obsessive compulsive tendencies
- Excess facial body hair
- Aggression towards self or others
- Masturbation/playing with self
- Acne
- Adult type body odor

Natural Anti- Androgens

- Saw Palmetto- decrease production of DHT
- Black Cohosh- increase estrogens
- Vitex/Chasteberry – increase estrogens
- Licorice- phytoestrogens
- Rosemary- phytoestrogens
- Lavender- phytoestrogens
  - (careful with phytoestrogens in males)
- White Peony- balance TH1/TH2
- Spearmint Tea
- ECGC /Green Tea
Male Hormones and Blood Sugar

- Increased insulin, Increased Cortisol, Decreased Progesterone
- Increased Androstendione, Decreased DHEA
- Decreased Testosterone
- Increased Aromatase enzyme activity, causes Testosterone to Estrogen
- Prostate hypertrophy
- Osteopenia
- Increased body fat, can not initiate lipolysis
What do you think is going on?

GLUCOSE TOLERANCE TEST.
2 SPECIMENS (7MG)
FASTING SPECIMEN
115
2 HOUR SPECIMEN
83
American Diabetes Association

INSULIN
109.2 M
2.0-19.6 uIU/mL
This insulin assay shows strong cross-reactivity for
some insulin analogs (lispro, aspart, and glargine)
and much lower cross-reactivity with others (detemir,
glulisine).

PROLACTIN
2.2 L
ng/mL.

Stages of Puberty (Tanner Stages)

<table>
<thead>
<tr>
<th>Female Observed</th>
<th>Male Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range (ng/mL)</td>
<td>Range (ng/mL)</td>
</tr>
<tr>
<td>Stage I: 3.6 - 12.0</td>
<td>&lt; OR = 10.0</td>
</tr>
<tr>
<td>Stage II - III: 2.6 - 18.0</td>
<td>&lt; OR = 6.1</td>
</tr>
<tr>
<td>Stage IV - V: 3.2 - 20.0</td>
<td>2.8 - 11.0</td>
</tr>
</tbody>
</table>

INSULIN, 2 HOUR
104.9 M
5.0-58.0 uIU/mL
This insulin assay shows strong cross-reactivity for
some insulin analogs (lispro, aspart, and glargine)
and much lower cross-reactivity with others (detemir,
glulisine).

The Role of Gut Microbiota on Insulin Resistance

Andrea M. Caccialanza and Mario J. A. Saad

Abstract

The development of obesity and insulin resistance has been extensively studied in the last decades, but the
mechanisms underlying these alterations are still not completely understood. The gut microbiota has been
identified as a potential contributor to metabolic diseases. It has been shown that obese individuals present
different proportions of bacterial phyla compared to lean individuals, with an increase in Firmicutes and
Actinobacteria and a decrease in Bacteroidetes. This alteration seems to interfere with intestinal
permeability, increasing the absorption of lipopolysaccharide (LPS), which reaches circulation and initiates
activation of Toll-like receptor (TLR) 4 and 2 and LPS receptor CD14, leading to increased activation of
inflammatory pathways. With these activations, an impairment of the insulin signaling is observed, with
decreased phosphorylation of the insulin receptor, insulin receptor substrate (IRS) and Akt, as well as
increased inhibitory serine phosphorylation of IRS-1. Altered proportions of bacterial phyla have also been
demonstrated to interfere with host’s biochemical pathways, increasing energy extraction and depot in
adipose tissue. Therefore, understanding the mechanisms by which the alteration in the gut microbiota
produces different signaling activations and phenotype changes may offer an interesting opportunity for the
treatment of obesity and type 2 diabetes.
Prebiotics improve glucose metabolism and change gut microbiota in parallel

Prebiotics strengthen the hypoglycemic effects of metformin through the gut microbiota in mice

Recent research has found that the gut microbiota may play an important role not only in the development of type 2 diabetes mellitus (T2DM), but also the therapeutic actions of the widely prescribed antidiabetic drug metformin. Although dietary fiber has documented effects on preventing T2DM and improving glucose metabolism in diabetic individuals, little is known about whether prebiotics could have an impact on the hypoglycemic effects of metformin.

A new study, led by Dr. Jinsong Shi from the Key Laboratory of Carbohydrate Chemistry and Biotechnology at the School of Pharmaceutical Sciences at Tsinghua University in China, has found...
Detoxification of Hormones

- Methylation
  - COMT ++ (V158M, H62H)
- Glucuronidation
  - UGT
- Sulfation
  - SULT
- Phase 1 Detox
  - CYP1A2, CYP1B1

- Supplements that help with Detox of Hormones
  - Sulforaphane- Broccoli Sprout Extract
  - DIM (di- indole methane) or Indole 3-carbinol
  - Ca-D- glucarate

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Sulforaphane treatment of autism spectrum disorder (ASD).

Singh K¹, Connors SL², Macklin EA³, Smith KB⁴, Fahey JW⁵, Taalav P⁶, Zimmerman AW⁷.

Author information

Abstract

Autism spectrum disorder (ASD), characterized by both impaired communication and social interaction, and by stereotypic behavior, affects about 1 in 68, predominantly males. The medico-economic burdens of ASD are enormous, and no recognized treatment targets the core features of ASD. In a placebo-controlled, double-blind, randomized trial, young men (aged 13-27) with moderate to severe ASD received the phytochemical sulforaphane (n = 29)—derived from broccoli sprout extracts—or indistinguishable placebo (n = 15). The effects on behavior of daily oral doses of sulforaphane (50-150 μmol) for 18 wk, followed by 4 wk without treatment, were quantified by three widely accepted behavioral measures completed by parents/caregivers and physicians: the Aberrant Behavior Checklist (ABC), Social Responsiveness Scale (SRS), and Clinical Global Impression Improvement Scale (CGI-I). Initial scores for ABC and SRS were closely matched for participants assigned to placebo and sulforaphane. After 18 wk, participants receiving placebo experienced minimal change (<3.3%), whereas those receiving sulforaphane showed substantial declines (improvement of behavior): 34% for ABC (P < 0.001, comparing treatments) and 17% for SRS scores (P = 0.017). On CGI-I, a significantly greater number of participants receiving sulforaphane had improvement in social interaction, abnormal behavior, and verbal communication (P = 0.015-0.007). Upon discontinuation of sulforaphane, total scores on all scales rose toward pretreatment levels. Dietary sulforaphane, of recognized low toxicity, was selected for its capacity to reverse abnormalities that have been associated with ASD, including oxidative stress and lower antioxidant capacity, depressed glutathione synthesis, reduced mitochondrial function and oxidative phosphorylation, increased lipid peroxidation, and neuroinflammation.

Comment


Uncommon use of common measures in sulforaphane trial. [Proc Natl Acad Sci U S A. 2015]
Hormone Testing Options

- **Serum**
  - Measures total hormone (free and bound)
  - 99% protein bound, prevents activation
  - 1% free fraction, “biologically active”
  - Good test to rule out tumors

- **Urine**
  - Measures metabolites, relies on renal and hepatic clearance
  - Ex. 2 OH Estradiol is protective, 16 OH and 4 OH are proliferative

- **Saliva**
  - Measures free fraction
  - Enzymes in saliva cleave protein bound portion

Endo Lab Options

- Fasting and post prandial insulin and glucose (75 gms of glucose)
- HbA1C
- Cortisol - salivary
- DHEA, DHEA-Sulfate, Testosterone total and free, Androstendione
- Progesterone
- Estradiol
- Total Cholesterol/Triglycerides
- Vitamin D 25 OH
- TSH, free T3, free T4, reverse T3, Thyroid Peroxidase Ab, Thyroglobulin Ab
- Leptin
Smith Lemli Opitz Syndrome and Low Cholesterol

Benefits of cholesterol feeding in SLOS

- Beginning to walk
- Starting to run
- Growth improvement
- Less infections
- Less UV light sensitivity
- Increased alertness
- Head banging stops
- Decreased tactile defensiveness
- Increased sociability
- Behavior improves
- Talking started in adults

Tierney 2006

Kelley RT. Inborn errors of cholesterol biosynthesis. Adv Pediatric 2000;47

Autism: The role of cholesterol in treatment

ALKA ANEJA & ELAINE TIERNEY

Department of Psychiatry and Behavioral Sciences, Division of Child and Adolescent Psychiatry, Johns Hopkins University School of Medicine, and Department of Psychiatry, Kennedy Krieger Institute, Baltimore, MD, USA

Abstract

Cholesterol is essential for neuroactive steroid production, growth of myelin membranes, and normal embryonic and fetal development. It also modulates the oxytocin receptor, ligand activity and G-protein coupling of the serotonin-1A receptor. A deficit of cholesterol may perturb these biological mechanisms and thereby contribute to autism spectrum disorders (ASDs), as observed in Smith-Lemli-Opitz syndrome (SLOS) and some subjects with ASDs in the Autism Genetic Resource Exchange (AGRE). A clinical diagnosis of SLOS can be confirmed by laboratory testing with an elevated plasma 7β-HC level relative to the cholesterol level and is treatable by dietary cholesterol supplementation. Individuals with SLOS who have such cholesterol treatment display fewer autistic behaviours, infections, and symptoms of irritability and hyperactivity, with improvements in physical growth, sleep and social interactions. Other behaviours shown to improve with cholesterol supplementation include aggressive behaviours, self-injury, temper outbursts and trichotillomania. Cholesterol ought to be considered as a helpful treatment approach while awaiting an improved understanding of cholesterol metabolism and ASD. There is an increasing recognition that this single-gene disorder of abnormal cholesterol synthesis may be a model for understanding genetic causes of autism and the role of cholesterol in ASD.
Association of Serum Cholesterol and History of School Suspension Among School-age Children and Adolescents in the United States

In the Third National Health and Nutrition Examination Survey (1988-1994), serum total cholesterol was measured in 4,852 children aged 6-16 years.

- Psychosocial development was evaluated by interviewing the mother regarding the child's history of school suspension or expulsion and difficulty in getting along with others.

- Non-African-American children with a serum total cholesterol concentration below the 25th percentile (<145 mg/dl) were almost threefold more likely to have been suspended or expelled from schools than their peers with total cholesterol at or above the 25th percentile (odds ratio = 2.96, 95% confidence interval: 1.55, 5.64).

Zhang et al., 2005 Am J Epidemiol 161(7): 691-9

Dysautonomia/Vagal Nerve Dysfunction

- Malfunction of the Autonomic Nervous System
- "Autonomic or Automatic" function not functioning optimally
- Imbalance between the sympathetic and parasympathetic nervous system
- In ASD- too much sympathetic tone, not enough parasympathetic or vagal tone
- ASD: Theory= lack of vagal brake

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The Polyvagal Theory: Phylogenetic Contributions to Social Behavior
Stephen W. Porges

New conceptualization of the role of the Vagus

Vagal regulation of heart rate and heart rate variability

Functionally, the vagal brake, by modulating the visceral state, enables the individual to rapidly engage and disengage with objects and other individuals and to promote self-soothing behaviors and calm behavioral states.

These behaviors are obviously compromised in autism.

Polyvagal Theory Cont’d

• The vagus is involved in the regulation of the HPA axis. Vagal afferents exhibit an inhibitory influence on HPA axis and reduce cortisol secretion.

• The afferent vagus mediates behavioral depression, but not fever, in response to peripheral immune signals following abdominal inflammation.

• Mobilization strategies resulting in a withdrawal of vagal tone to the heart, increased sympathetic tone and release of cortisol have been associated with suppressed immune function.
Symptoms of Dysautonomia

- Excessive fatigue, sleep disruption
- Excessive heat or cold
- Loss of sweating or excessive sweating
- Excessive urination and thirst, salt cravings
- Lightheadedness, dizziness, orthostatic hypotension, syncope
- Rapid or slow heart rate
- Noise and Light Sensitivity
- Tremulousness, Dysequilibrium
- Feelings of anxiety or panic
- Headaches, nerve pain, numbness
- Facial flushing
- Constipation, Diarrhea, Nausea, Reflux, Dysmotility
- Seizures

Pupillatory response can measure ANS function

Larger tonic pupil size in young children with autism spectrum disorder.
Anderson C.L., Colonnesi J.
Department of Psychology, Schiefelbusch Institute for Life Span Studies, University of Kansas, Dole Human Development Center, 1000 Sunnyside Avenue, Room 1052, Lawrence, Kansas 66045-7995, USA; cander@ku.edu

Abstract
The symptoms of Autism Spectrum Disorder (ASD) have been suggested to manifest from atypical functioning of the autonomic nervous system (ANS), leading to altered arousal and atypical processing of salient stimuli. Coherent with this, persons with ASD show heightened autonomic activity, sleep difficulties, and structural and neurochemical alterations within the ANS. Recently, we observed decreased pupil responses to human faces in children with ASD. In the current study, we found differences in baseline (tonic) pupil size, with the ASD group exhibiting a larger pupil size than age-matched controls. Pupil responses are sensitive and reliable measures of ANS functioning, thus, this finding highlights the role of the ANS, and may provide clues about underlying neuropathology.

Pupil responses are sensitive and reliable measures of ANS functioning. ASD show heightened autonomic activity, sleep difficulties, and neurochemical alterations within the ANS.
Children tended to use self-stimulatory activities in order to calm hyperresponsive sympathetic activity. Autistic children use overt behavior to control a malfunctioning autonomic nervous system.
Vagus Nerve Cools Gut Inflammation

Mice exposed to sodium dextran sulfate to simulate inflammatory bowel disease.

Mice with intact vagus nerve exhibit less inflammation in the gut.

Mice with vagus nerve cut produced heightened inflammation in the gut.

The vagus nerve by releasing Acetylcholine stimulates T regulatory cells that lower inflammation.


Dorsal Vagal Complex (DVC)

• The DVC (dorsal vagal complex) is comprised of 2 structures- area postrema (AP) and nucleus solitarius (NTS) – which lie on either side of the dorsal motor vagal nucleus (DMV).

• DMV nucleus is the orgination point of the efferent portion of the vagus nerve.

• Preferential toxicity due to ease of entry.

• NTS – Secretin, Social function, Anxiety, Pain, Seizure
The Vagus nerve inherently communicates with the splenic nerve to suppress TNF alpha production by macrophages in the spleen and modulate immune function. (Dr. Rosas-Ballina)

- Parasympathetic
- Efferent or Motor
- Afferent or Sensory (80%)
  - Back to the brain from the ear, tongue, larynx, GI
- Dorsal Vagal Nucleus
  - Motor to Pharynx, Larynx, GI..
- Releases ACh (acetylcholine)
  - Nicotinic Receptors
  - Muscarinic Receptors

Physiology and Immunology of the Cholinergic Anti-inflammatory Pathway

- 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 antiinflammatory pathway.
- Cholinergic agonists inhibit cytokine synthesis and protect against cytokine-mediated diseases.
- Stimulation of the vagus nerve prevents the damaging effects of inflammatory cytokines.

Address Dysautonomia

Down-regulate Sympathetic (high NE, Epi)
- Adaptogenic Herbs- Ginseng, Ashwaganda, Bacopa, Tulsi
- Beta Blockers- Propranolol
- Alpha 2 adenoreceptor agonists- Clonidine, Guafacine
- NMDA receptor antagonists- Memantine, Dextromethorphan
- Upregulate inhibitory neurotransmitters- GABA, L-theanine, Taurine, Glycine
- Epigenetic Modulation- COMT, MAOa

Up-regulate Parasympathetic
- Acetylcholine (phosphatidylcholine, phosphatidylserine)
- Acetylcholinesterase Inhibitors (galantamine, huperizine A, piracetam)
- Vagus Nerve Stimulation (TENS, singing, humming, hippo-therapy...)

Salt

Address Gut Issues- especially SIBO

Adaptogens
plant compounds that have a normalizing impact on the HPA axis under times of stress, help with blood sugar regulation, anxiety, immune modulation

- Panax Ginseng- lowers cortisol
- Siberian Ginseng
- Holy Basil- anticonvulsant properties
- Licorice/Glycyrrhizin- increases cortisol
- Rhodiola rosea
- Ashwaganda- blood sugar regulation
- Bacopa
- Gotu Kola
- Moringa oleifera- anti-inflammatory
- Schisandra
Propranolol on Verbal Problem Solving in Autism Spectrum

- Some studies suggest drugs decreasing noradrenergic activity are beneficial in ASD.
- In individuals without neurodevelopmental diagnoses, propranolol is beneficial only for difficult network flexibility-dependent problems.
- However, in populations with altered noradrenergic regulation, propranolol also benefits performance for simple problems. Due to decreased flexibility of access to networks in ASD, we wished to examine the effect of propranolol on NF in ASD.
- ASD subjects benefited from propranolol on simple anagrams, whereas control subjects were impaired by propranolol.

• Neurocase: The Neural Basis of Cognition 2008 Beversdorf
5m/kg divided BID improved aggression, SIB and anxiety. Mechanism is reported to be due to minimal sedation and NMDA modulation.

Dextromethorphan (d-3-methoxy-N-methylmorphinian) is an antitussive preparation that is the d-isomer of the codeine analog levorphanol. Unlike the l isomer, it has no analgesic or addictive properties and does not act through opioid receptors. Although not indicated as a psychotropic agent, reports have emerged of its psychotherapeutic properties in persons with neurodevelopmental disorders.

12-week uncontrolled, open-label study (LOE 4) of galantamine in 13 children with autism (mean age 8.8 ± 3.5 years)

Improvement in aggression, dyscontrol, and inattention.
Catecholamine -O- Methyl Transferase (COMT V158M and H62H)

- Enzyme transfers methyl groups to catecholamines, (dopamine, NE, and Epi)
- Enzyme involved in neurotransmitter and estrogen breakdown
- Cofactors include Magnesium, B3, B2
- If enzyme is weak (COMT +/+), methyl groups are not used effectively may accumulate
- If enzyme is efficient (COMT -/-), methyl groups are used up rapidly and SAMe is depleted
- In both cases, methylation and neurotransmission is impaired
- My experience COMT++ patient’s may have increased hyperactivity, anxiety and rage. Also have more issues with detoxification of “amines”, phenols, and hormones.
  Avoid methyl donors
- Avoid quercetin and curcumin, which inhibit COMT.

Monamine Oxidase (MAO A) warrior gene

- Monoamine oxidase A (MAO-A) is an enzyme in the brain that breaks down neurotransmitters such as noradrenaline, adrenaline, serotonin, and dopamine
  - If we have high levels of this enzyme, it means we’ll have less neurotransmitters, more likely to have depression, sleep disturbance and increased risk of suicide
  - If we have low levels of this enzyme, we’ll have more neurotransmitters, more likely to be aggressive, impulsive, antisocial and risk takers
  - Rs2064070 – Males with: rs909525 (G), rs6323 (G) and rs2064070 (A) had higher scores on the scale measuring expression of anger outwards. Females with TT allele reported higher “spontaneous aggression.”
  - Rs6323 (MAOA R297R Gene) – The G or GG allele indicates higher levels of the enzyme, while the T allele indicates lower levels (T is the ‘risk’ allele). In females, the G allele was associated with higher outward anger and it seems like G allele also causes aggression in males. G=More Aggression.
  - Modulate with Riboflavin (B2), and Progesterone and Respen A
Figure 2. Effects of progesterone and metabolites on monoamino oxidase, catechol-O-methyl transferase activity, γ-aminobutyric acid receptor A (GABA<sub>A</sub>) and serotonin.

Other Possible Biomedical Causes of Aggression/Rage

- Environment
- Diet
- Low Zinc/High Copper Ratio
- Metal Burden- Lead
- *Gut Issues
  - High Ammonia
  - Dysbiosis/Clostridia/*SIBO
  - Constipation/Dysmotility
  - GI Pain/Inflammation/IBD
  - GERD
- *Persistent Infections
  - PANS/PANDAS
  - Lyme/Co-infections/Bartonella
  - Parasitic Infections
- Neuroinflammation
- Headaches/ PAIN
- Immune/Autoimmune/AE
- *Mast Cell Activation Disorder
Special Environmental and Dietary Considerations

- Environmental Controls: Avoid endocrine disruptors especially pesticides, plasticizers, BPA, phthalates, organophosphates...
- Dietary Interventions
  - Anti-inflammatory Diet: CF/GF/ limit grains
  - Consider low lectin diet- night shade free and legume free
  - Antioxidant, phytonutrient, high carotenoid diet
  - Low glycemic, Limit sugar and carbs
  - Protein and fiber with meals and snacks
- Avoid hormones- in meat, eggs, and dairy products
- Avoid excitotoxins in food- MSG, nutrasweet, dyes, HFCS, caffeine, sulfites, nitrates/nitrites
- Limit phenolics- apples, bananas, grapes...

Integrative Approach to Aggression

- Treat potential underlying cause!!!!!!
- Address Blood Sugar and Hormonal Imbalances
- Address Dysautonomia
- Address Gut Issues/Dysmotility
- Address Mast Cell Activation/Microglial Activation/Neuroinflammation
We must accept finite disappointment,
But never give up infinite hope!
MLK, Jr.

Never, never, never give up HOPE