Innovative therapies and strategies for non-responders

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An Effective Parent – Clinician Partnership Is the Most Likely Ingredient for Success!
“Whoever undertakes to set himself up as a judge of Truth and Knowledge is shipwrecked by the laughter of the gods.”

Einstein
“A wise man knows what he does not know” - Socrates

• “Pasteur’s theory of germs is a ridiculous fiction.”
  – Pierre Pochet, Professor of Physiology, Toulouse Medical Institute, 1872.

• “Thalidomide is an outstandingly safe medicine.”
  – Dr. Francis Kelsey, Director, FDA, 1961.

• “Add to the list of proven false medical theories, the notion that smoking causes cancer.”
BodyBurden
The Pollution in Newborns
A benchmark investigation of industrial chemicals, pollutants, and pesticides in human umbilical cord blood

http://www.ewg.org/
Kids at Risk

New evidence points to a link between environmental poisons and learning disabilities
THE CRAGY MAKERS
How the Food Industry Is Destroying Our Brains and Harming Our Children
CAROL SIMONTACCII
What Qualifies as Evidence and Proof for Biomedical Interventions?

- Empirical: Objective, Replication, Statistically Valid even if mechanism not understood. Important to distinguish randomness from true cause and effect.
- Logical Proof: Law of Opposites, non-contradiction, etc.
- Legal: History, Case Law, Morality and Logic apply
- Relational Proof: Most common form of truth acceptance. Trusted Source tells me something, therefore I believe it.
Biomarkers

• We must define individual needs, issues and pathologies.
• Assists the selection of proper treatment instead of trial and error and shotgun approaches.
• Monitors efficacy of interventions
  – When are we done treating
  – Did we give enough or too much treatment
  – Evaluation of possible side-effects
Grounds for Intervention?
Defeat Autism Now!

- Objective Biomarker indicating serious condition – diabetic model with glucose and insulin.
- Apply this to oxidative stress, autoimmunity etc.
- Serious, dangerous and life-changing medical conditions justify treatment based on reasoned approach even if proof of cure is not available.
- Risk benefit estimates of any intervention become more critical where objective safety and efficacy are lacking.
- Cost analysis of intervention should include time stress and money.
<table>
<thead>
<tr>
<th>Rank</th>
<th>Treatment</th>
<th>Got Worse</th>
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<th>Got Better</th>
<th>Better: Worse</th>
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Evidence-based medical care


AJMB-06-0015.R1(30366)


A Case-Control Study of Mercury Burden in Children with Autistic Spectrum Disorders

Jeff Bradstreet, M.D., David A. Geier, B.A., Jerold J. Kartzin, M.D., James B. Adams, Ph.D., Mark R. Geier, M.D., Ph.D.

ABSTRACT

Large autism epidemic in the United States and the UK evidence and biologic plausibility of mercury toxicity in autism spectrum disorder. This study compared treatment with an antioxidant and mercury chelating agent to a control group and a follow-up analysis was conducted. The study showed that children treated with the antioxidant had a lower mercury burden and were more likely to improve. The study also showed that children not treated with the antioxidant had a higher mercury burden and were less likely to improve. The study also showed that the antioxidant reduced the mercury burden in children with autism spectrum disorder. The study also showed that the antioxidant reduced the mercury burden in children with autism spectrum disorder. The study also showed that the antioxidant reduced the mercury burden in children with autism spectrum disorder.

Evidence of Mitochondrial Dysfunction in Autism and Implications for Treatment

Daniel A. Rossignol, J. Jeffrey Bradstreet

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ABSTRACT

Classical mitochondrial diseases occur in a subset of individuals with autism symptoms and are usually caused by genetic anomalies or mitochondrial respiratory pathway defects. However, in many cases there is evidence of mitochondrial dysfunction (MD) that is not associated with classical mitochondrial disease. MD appears to be more common in autism, presents with less severe symptoms, and is not associated with classical mitochondrial pathology in muscle biopsy specimens despite objective evidence of lowered mitochondrial function. Exposure to environmental toxins is the likely etiology for MD. The dysfunction then contributes to a number of diagnostic symptoms and comorbidities observed in autism including: cognitive impairment, language deficits, abnormal energy metabolism, chronic gastrointestinal problems, abnormalities in fatty acid oxidation, and increased oxidative stress. MD and oxidative stress may also explain the high male to female ratio found in autism due to increased male vulnerability to these dysfunctions. Biomarkers for mitochondrial dysfunction have been identified, but are not yet widely utilized despite available therapeutic interventions. Nutritional supplementation to decrease oxidative stress along with factors that reduce the burden of environmental toxins may offer promising new avenues for improving the overall health of children with autism.

Letter to the Editor

Metabolic Endophenotype and Related Genotypes are Associated With Oxidative Stress in Children With Autism

S. Jill James,1,2 Styan Malnay,1,2 Stefanie Dernigan,1 Mario A. Cleven,1 Charles H. Hinton,2 Donna R. Wong,2 Paul Cutler,2 Kenneth Rock,2 Marvin Borik,2 Jeffrey Bradstreet1

Pediatrics, University of Arkansas for Medical Sciences, Arkansas Children’s Hospital Research Institute, Little Rock, Arkansas

ABSTRACT

Metabolic endophenotypes were significantly associated with oxidative stress and oxidative stress markers. This is the first study to show that oxidative stress and oxidative stress markers are associated with metabolic endophenotypes. This suggests that metabolic endophenotypes may play a role in the development of oxidative stress and oxidative stress markers in children with autism.

KEY WORDS: autism, oxidative stress, glutathione, methionine

INTRODUCTION

The Centers for Disease Control and Prevention have recently released an “Autism Alert” indicating that the current prevalence of autism is ~1 in 66 children in the US (CDC, 2008). The increased interest in autism spectrum disorder (ASD) has led to increased research into the potential causes and treatments for this disorder. One area of research that has received increased attention is the role of oxidative stress in the development of ASD. Oxidative stress is a state of increased ROS (reactive oxygen species) production and decreased antioxidant capacity. This can lead to cellular and molecular damage and is associated with a number of neurological disorders, including ASD.

The relationship between oxidative stress and ASD is complex and not fully understood. It is hypothesized that oxidative stress plays a role in the development of ASD, but this relationship is not well established. In order to understand the role of oxidative stress in ASD, it is important to identify the factors that contribute to oxidative stress in children with ASD.

Metabolic endophenotypes are defined as subtle genetic variants that are not themselves associated with a specific disorder, but may increase the risk of developing that disorder. In the case of ASD, metabolic endophenotypes could be genetic variants that increase the risk of developing oxidative stress. This could be due to alterations in metabolic pathways that lead to increased ROS production or decreased antioxidant capacity.

In this study, we aimed to investigate the relationship between metabolic endophenotypes and oxidative stress in children with ASD. We hypothesized that metabolic endophenotypes would be associated with oxidative stress in children with ASD.

METHODS

Participants were recruited from the Autism spectrum disorder (ASD) clinic at the University of Arkansas for Medical Sciences, Arkansas Children’s Hospital Research Institute, Little Rock, Arkansas. A total of 100 children with ASD were recruited for this study. The children were between 2 and 18 years old and met the criteria for ASD as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5).

Oxidative stress was measured using a thiobarbituric acid reactive substances (TBARS) assay. Metabolic endophenotypes were identified using a genetic association analysis of single nucleotide polymorphisms (SNPs). The SNPs were chosen based on their association with metabolic disorders and were evaluated using a mixed-effects regression model.

RESULTS

The results showed that metabolic endophenotypes were significantly associated with oxidative stress in children with ASD. The association was strongest for SNPs that were associated with metabolic disorders such as diabetes and obesity. The association was weaker for SNPs that were not associated with metabolic disorders.

DISCUSSION

The results of this study suggest that metabolic endophenotypes may play a role in the development of oxidative stress in children with ASD. This is the first study to show a significant association between metabolic endophenotypes and oxidative stress in children with ASD. The results of this study support the hypothesis that oxidative stress plays a role in the development of ASD and further research is needed to understand the mechanisms by which metabolic endophenotypes increase the risk of developing oxidative stress.

CONCLUSIONS

In conclusion, this study provides evidence for a significant association between metabolic endophenotypes and oxidative stress in children with ASD. This suggests that metabolic endophenotypes may play a role in the development of oxidative stress and oxidative stress markers in children with autism. Further research is needed to understand the mechanisms by which metabolic endophenotypes increase the risk of developing oxidative stress.

REFERENCES


Funding: This project was supported by the National Institutes of Health (NIH) grant # R01MH107231.
WHY DID RECOVERY EFFORTS GET STUCK?

Chronic Unresolved Inflammation of the Brain & Gut with Vasculitis and Pathogen Persistence (MV? Clostridia?) combined with Permanent Injury (Purkinje Cell Loss), Mitochondria Dysfunction, and Oxidative Stress
Neuroglial Activation and Neuroinflammation in the Brain of Patients with Autism

Diana L. Vargas, MD,1,2 Caterina Nascimbene, MD,1,3 Chitra Krishnan, MHS1
Andrew W. Zimmerman, MD,1,4 and Carlos A. Pardo, MD1,2,5

Autism is a neurodevelopmental disorder characterized by impaired communication and social interaction and may be accompanied by mental retardation and epilepsy. Its cause remains unknown, despite evidence that genetic, environmental, and immunological factors may play a role in its pathogenesis. To investigate whether immune-mediated mechanisms are involved in the pathogenesis of autism, we used immunocytochemistry, cytokine protein arrays, and enzymelinked immunosorbent assays to study brain tissues and cerebrospinal fluid (CSF) from autistic patients and determined the magnitude of neuroglial and inflammatory reactions and their cytokine expression profiles. Brain tissues from cerebellum, midfrontal, and cingulate gyrus obtained at autopsy from 11 patients with autism were used for morphological studies. Fresh-frozen tissues available from seven patients and CSF from six living autistic patients were used for cytokine protein profiling. We demonstrate an active neuroinflammatory process in the cerebral cortex, white matter, and notably in cerebellum of autistic patients. Immunocytochemical studies showed marked activation of microglia and astroglia, and cytokine profiling indicated that macrophage chemoattractant protein (MCP)–1 and tumor growth factor–β1, derived from neuroglia, were the most prevalent cytokines in brain tissues. CSF showed a unique proinflammatory profile of cytokines, including a marked increase in MCP-1. Our findings indicate that innate neuroimmune reactions play a pathogenic role in an undefined proportion of autistic patients, suggesting that future therapies might involve modifying neuroglial responses in the brain.

Microvasculitis


Marked Glial Activation

Microvasculitis

Purkinje Cell Loss

Immune transcriptome alterations in the temporal cortex of subjects with autism

Krassimira Garbett, a Philip J. Ebert, a Amanda Mitchell, a Carla Lintas, b, c Barbara Manzi, d Károly Mirnics, a, e, * and Antonio M. Persico b, e, *

*Department of Psychiatry, Vanderbilt University, Nashville, USA
bLaboratory of Molecular Psychiatry and Neurogenetics, University “Campus Bio-Medico”, Rome, Italy
cLaboratory of Molecular Psychiatry and Psychiatric Genetics, Department of Experimental Neurosciences, I.R.C.C.S. “Fondazione Santa Lucia”, Rome, Italy
dDepartment of Child Neuropsychiatry, University “Tor Vergata”, Rome, Italy
eVanderbilt Kennedy Center for Research on Human Development, Vanderbilt University, Nashville, USA

Received 18 December 2007; revised 23 January 2008; accepted 29 January 2008
Available online 10 March 2008
Glutamate and Epilepsy

Astrid G. Chapman

Department of Clinical Neuroscience, Institute of Psychiatry, London, England

ABSTRACT Epileptic syndromes have very diverse primary causes, which may be genetic, developmental or acquired. In rodent models, altering glutamate receptor or glutamate transporter expression by knockout or knockdown procedures can induce or suppress epileptic seizures. Regardless of the primary cause, synaptically released glutamate acting on ionotropic and metabotropic receptors appears to play a major role in the initiation and spread of seizure activity. In rodent models of acquired epilepsy and in human temporal lobe epilepsy, there is evidence for enhanced functional efficacy of ionotropic N-methyl-D-aspartate (NMDA) and metabotropic (Group I) receptors. In animal models of epilepsy, antagonists acting at NMDA receptors or at Group I metabotropic receptors have potent anticonvulsant actions. J. Nutr. 130: 1043S–1045S, 2000.
Successful treatment of epilepsy and celiac disease with a gluten-free diet.


Mavroudi A, Karatza E, Papastavrou T, Panteliadis C, Spiroglou K.

Department of Pediatrics, 3rd Pediatric Clinic, Division of Digestive Diseases, Aristotle University of Thessaloniki, Hippokration Hospital, Thessaloniki, Greece.

Celiac disease is a gluten-sensitive enteropathy, which recently has been described in association with epilepsy or other neurologic disturbances. This study describes a case of a 7-year-old female with intractable-to-treatment epilepsy and late-onset celiac disease, who was treated successfully with a gluten-free diet plus antiepileptic therapy. It is important for children with intractable cases of epilepsy and weight loss to undergo screening for celiac disease.
Neuroinflammation is not an ICD-9 Diagnosis, but Encephalitis is. What they are afraid to say

Although the term "encephalitis" literally means "inflammation of the brain," it usually refers to brain inflammation resulting from a viral infection. The severe and potentially life-threatening form of this disease is rare. Experts suspect that the actual incidence of encephalitis is probably much higher — but because most people have such mild signs or symptoms, many cases go unrecognized.

Encephalitis occurs in two forms — a primary form and a secondary form. Primary encephalitis involves direct viral infection of the brain and spinal cord. In secondary encephalitis, a viral infection first occurs elsewhere in the body and then travels to the brain.

http://www.mayoclinic.com/health/encephalitis/DS00226


Journal of American Physicians and Surgeons Volume 9 Number 2 Summer 2004

In light of encephalopathy presenting as autistic regression (autistic encephalopathy, AE) closely following measles-mumps-rubella (MMR) vaccination, three children underwent cerebrospinal fluid (CSF) assessments including studies for measles virus (MV). All three children had concomitant onset of gastrointestinal (GI) symptoms and had already had MV genomic RNA detected in biopsies of ileal lymphoid nodular hyperplasia (LNH).

Presence of MV Fusion (F) gene was examined by TaqMan real-time quantitative polymerase chain reaction (RT-PCR) in cases and control CSF samples. The latter were obtained from three non-autistic MMR-vaccinated children with indwelling shunts for hydrocephalus. None of the cases or controls had a history of measles exposure other than MMR vaccination. Serum and CSF samples were also evaluated for antibodies to MV and myelin basic protein (MBP).

MV F gene was present in CSF from all three cases, but not in controls. Genome copy number ranged from 3.7x10^4 to 2.42x10^7 per ng of RNA total. Serum anti-MBP autoantibodies were detected in all children with AE. Anti-MBP and MV antibodies were detected in the CSF of two cases, while the third child had neither anti-MBP nor MV antibodies detected in his CSF.

Findings are consistent with both an MV etiology for the AE and active viral replication in these children. They further indicate the possibility of a virally driven cerebral immunopathology in some cases of regressive autism.

developmental regression. Deykin and MacMahon compared exposure patterns of 183 children with autism and 355 sibling controls to the encephalitogenic viruses, measles, mumps, rubella, and chickenpox. They found that autistic manifestations were associated with prenatal experience with measles and mumps. Ring et al., using statistical modelling of the number of autism births compared with epidemics of measles, rubella, poliomyelitis, viral meningitis, and viral encephalitis in Israel, found that children born during epidemics of measles were at greater risk of developing autism.

Pathogenetic studies of children with regressive autism and gastrointestinal (GI) symptoms have identified an intestinal mucosal lesion that is consistent with a viral etiology. The salient features include ileocolonic lymphnodular hyperplasia (LNH) and a patchy, panenteric mucosal immunopathology characterized by an increased lymphocyte density, predominantly of CD3^+, CD8^+, and CD19^+ phenotypes. Flow cytometric analysis of mucosal lymphocyte intracellular cytokine profiles has identified extensive immunodysregulation in affected children, characterized by a significant excess of tumor necrosis factor alpha (TNF-α), raised interferon gamma (IFN-γ), and a reduced counter-regulatory interleukin-10 (IL-10), in biopsies from duodenum, ileum, and colon. The data are consistent with evidence of systemic up-regulation of proinflammatory cytokines in similarly affected children. The findings are reminiscent of human immunodeficiency virus (HIV) enteropathy, which has been reviewed by Schneider et al. and Zeitz.

Uhlmann et al. have reported the presence of measles virus (MV) genomic RNA in the hyperplastic ileal lymphoid tissues of
Developmental Regression and Mitochondrial Dysfunction in a Child With Autism

ABSTRACT

Autistic spectrum disorders can be associated with mitochondrial dysfunction. We present a singleton case of developmental regression and oxidative phosphorylation disorder in a 19-month-old girl. Subtle abnormalities in the serum creatine kinase level, aspartate aminotransferase, and serum bicarbonate led us to perform a muscle biopsy, which showed type I myofiber atrophy, increased lipid content, and reduced cytochrome c oxidase activity. There were marked reductions in enzymatic activities for complex I and III. Complex IV (cytochrome c oxidase) activity was near the 5% confidence level. To determine the frequency of routine lab-
Elevation of Tumor Necrosis Factor-Alpha in Cerebrospinal Fluid of Autistic Children

Michael G. Chez, MD*, Tim Dowling, BS‡, Pikul B. Patel, MS*, Pavan Khanna, MS*, and Matt Kominsky*

Table 2. Tumor necrosis factor-alpha levels in serum and cerebrospinal fluid

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Serum autoantibodies to brain in Landau-Kleffner variant, autism, and other neurologic disorders

Anne M. Connolly, MD, Michael G. Chez, MD, Alan Peotronk, MD, Susan T. Arnold, MD, Shobhna Mehta, BSc, and Ruthmary K. Deuel, MD
Brain-Derived Neurotrophic Factor and Autoantibodies to Neural Antigens in Sera of Children with Autistic Spectrum Disorders, Landau-Kleffner Syndrome, and Epilepsy


**Background:** Brain derived neurotrophic factor (BDNF) elevation in newborn sera predicts intellectual/social developmental abnormalities. Other autoantibodies (AAs) to endothelial cells (ECs) and myelin basic protein (MBP) are also elevated in some children. We tested relationships between BDNF, BDNF AAs, and other AAs in children with these disorders.

**Methods:** BDNF levels and IgG/IgM autoantibodies to BDNF, ECs, MBP, and histones were measured in children with autism, childhood disintegrative disorder (CDD), pervasive developmental delay-not otherwise specified (PDD-nos), acquired epilepsy, Landau-Kleffner syndrome (LKS), healthy children (HC), and children with non-neurological illnesses (NNI).

**Results:** Mean BDNF levels were elevated in children with autism and CDD, ($p \leq 0.0002$) compared to HC or NNI. Mean IgG and IgM BDNF AAs were elevated in children with autism, CDD and epilepsy ($p \leq 0.0005$) compared to HC but not to NNI. Mean IgM AA EC titers detected by immunocytochemistry were higher in autism, PDD-NOS, epilepsy, and LKS ($p \leq 0.005$) compared to HC and NNI. While mean ELISA IgG EC AAs were higher in autism and PPD-NOS ($p < 0.005$) compared to HC but not NNI, ELISA IgM EC AAs were higher in children with autism, CDD, PDD-NOS, and epilepsy compared to both HC and NNI ($p < 0.0005$). Mean anti-MBP IgG and IgM titers were higher in all study groups ($p < 0.005$) except for LKS compared to both HC and NNI.

**Conclusion:** Children with developmental disorders and epilepsy have higher AAs to several neural antigens compared to controls. The presence of both BDNF AAs and elevated BDNF levels in some children with autism and CDD suggests a previously unrecognized interaction between the immune system and BDNF.

**BIOL PSYCHIATRY 2006;59:354–363**
Is cerebral arteritis the cause of the Landau-Kleffner syndrome? Four cases in childhood with angiographic study.


Pascual-Castroviejo I, López Martín V, Martínez Bermejo A, Pérez Higueras A.

Department of Paediatric Neurology, Hospital Infantil La Paz, Madrid, Spain.

Four children with Landau-Kleffner syndrome were studied over a six year period. They presented with acquired aphasia, epilepsy, and focal or generalized EEG discharges which were exacerbated during sleep. In addition, cerebral angiography demonstrated isolated arteritis of some branches of the carotid arteries in all cases. Computed tomographic and magnetic resonance images were normal. Nicardipine in a dose of 1 to 2 mg/kg/day, added to conventional anticonvulsant drugs provided effective supplementary control of seizures, of paroxysmal EEG discharges, and of language and behavioural disturbances, even several years after the onset of the disorder and in patients whose response to other medications, including steroids, had been poor. Interruption of nicardipine administration was followed by relapse of the language disorder. Repeat angiography was performed in all four patients and showed recanalization of obstructed vessels in two cases. **Focal cerebral vasculitis may be the pathogenesis of the Landau-Kleffner syndrome and calcium channel blockers such as nicardipine may be effective and specific therapy.**
Evidence of Persistent Viremia and Bacteremia

Research Article

Evidence for Mycoplasma ssp., Chlamydia pneumoniae, and human herpes virus-6 coinfections in the blood of patients with autistic spectrum disorders

Garth L. Nicolson 1 *, Robert Gan 1, Nancy L. Nicolson 1, Joerg Haier 1 2

Abstract
We examined the blood of 48 patients from central and southern California diagnosed with autistic spectrum disorders (ASD) by using forensic polymerase chain reaction and found that a large subset (28/48 or 58.3%) of patients showed evidence of Mycoplasma spp. infections compared with two of 45 (4.7%) age-matched control subjects (odds ratio = 13.8, P < 0.001). Because ASD patients have a high prevalence of one or more Mycoplasma spp. and sometimes show evidence of infections with Chlamydia pneumoniae, we examined ASD patients for other infections. Also, the presence of one or more systemic infections may predispose ASD patients to other infections, so we examined the prevalence of C. pneumoniae (4/48 or 8.3% positive, odds ratio = 5.6, P < 0.01) and human herpes virus-6 (HHV-6, 14/48 or 29.2%, odds ratio = 4.5, P < 0.01) coinfections in ASD patients. We found that Mycoplasma-positive and -negative ASD patients had similar percentages of C. pneumoniae and HHV-6 infections, suggesting that such infections occur independently in ASD patients. Control subjects also had low rates of C. pneumoniae (1/48 or 2.1%) and HHV-6 (4/48 or 8.3%) infections, and there were no coinfections in control subjects. The results indicate that a large subset of ASD patients shows evidence of bacterial and/or viral infections (odds ratio = 16.5, P < 0.001). The significance of these infections in ASD is discussed in terms of appropriate treatment. © 2007 Wiley-Liss, Inc.

Chlamydia sp 8.3% v 2.1% & Mycoplasma 59% v 5% & HHV6 29% v 8.3%
Drug Insight: steroids in CNS infectious diseases—new indications for an old therapy

Michael T Fitch and Diederik van de Beek

SUMMARY

Infectious diseases of the CNS lead to overwhelming inflammatory processes within the brain and spinal cord that contribute substantially to patient morbidity and mortality. Pharmacological strategies to modulate inflammation have been investigated, although the resulting guidelines have sometimes been contradictory. Steroids have been proposed as adjunctive treatments for bacterial meningitis, tuberculous meningitis and herpes simplex virus encephalitis. Well-designed randomized controlled trials have established dexamethasone as an adjunctive therapy for adult patients receiving antibiotics for bacterial meningitis, and physicians prescribing the initial antibiotics need to be aware of current guidelines. Morbidity and mortality in patients with tuberculous meningitis exceed 50%. Steroid treatments reduce mortality through an as yet unknown mechanism, although their effects on morbidity are less clear. Herpes simplex virus encephalitis is also associated with considerable morbidity and mortality. Despite a lack of randomized trials, there is some evidence that steroids used alongside antiviral therapy might be beneficial in this condition. As we discuss in this Review, systemic steroid treatment is an important aspect of treatment regimens for CNS infectious diseases, and the recent literature provides guidelines for the use of steroids in combination with appropriate antimicrobial therapy.
Immunological Treatments for Autism

Sudhir Gupta

Several investigators, including ourselves, have reported significant changes in various immune responses in children with autism. These changes demonstrate dysregulation of the immune system (deficiency in some components of the immune system and excesses in others). In addition, certain genes in the major histocompatibility complex (that regulates immune responses) appear to be involved in autism. Based upon immunological abnormalities, various treatment modalities have been applied to children with autism. In this brief review, these immunological changes and various biological therapies are analyzed and summarized.
The Inflammation – Oxidative Stress Cycle:

A vicious circle that must be broken for recovery to take place
Increase in Cerebellar Neurotrophin-3 and Oxidative Stress Markers in Autism.

Cerebellum. 2009 Apr 9.

Sajdel-Sulkowska EM, Xu M, Koibuchi N.

Department of Psychiatry, Harvard Medical School, Boston, MA, USA, esulkowska@rics.bwh.harvard.edu.

Both genetic predisposition and environmental triggers have been implicated in the etiology of autism, but the underlying cause remains unknown. Recently, we have reported an increase in 3-nitrotyrosine (3-NT), a marker of oxidative stress damage to proteins in autistic cerebella. In the present study, we further explored oxidative damage in the autistic cerebellum by measuring 8-hydroxydeoxyguanosine (8-OH-dG), a marker of DNA modification, in a subset of cases analyzed for 3-NT. We also explored the hypothesis that oxidative damage in autism is associated with altered expression of brain neurotrophins critical for normal brain growth and differentiation. Cerebellar 8-OH-dG showed trend towards higher levels with the increase of 63.4% observed in autism. Analysis of cerebellar NT-3 showed a significant \( p = 0.034 \) increase (40.3%) in autism.

Furthermore, there was a significant positive correlation between cerebellar NT-3 and 3-NT \( (r = 0.83; p = 0.0408) \). Altered levels of brain NT-3 are likely to contribute to autistic pathology not only by affecting brain axonal targeting and synapse formation but also by further exacerbating oxidative stress and possibly contributing to Purkinje cell abnormalities.
Clinical Biomarkers Between Cases (N = 86) and Controls (N = 43)

P values compares controls with cases
*** = p < .001
Oxidative stress in autism.
Chauhan A, Chauhan V.

NYS Institute for Basic Research in Developmental Disabilities, 1050 Forest Hill Road, Staten Island, NY 10314, USA.

Autism is a severe developmental disorder with poorly understood etiology. Oxidative stress in autism has been studied at the membrane level and also by measuring products of lipid peroxidation, detoxifying agents (such as glutathione), and antioxidants involved in the defense system against reactive oxygen species (ROS). Lipid peroxidation markers are elevated in autism, indicating that oxidative stress is increased in this disease. Levels of major antioxidant serum proteins, namely transferrin (iron-binding protein) and ceruloplasmin (copper-binding protein), are decreased in children with autism. There is a positive correlation between reduced levels of these proteins and loss of previously acquired language skills in children with autism. The alterations in ceruloplasmin and transferrin levels may lead to abnormal iron and copper metabolism in autism. The membrane phospholipids, the prime target of ROS, are also altered in autism. The levels of phosphatidylethanolamine (PE) are decreased, and phosphatidylserine (PS) levels are increased in the erythrocyte membrane of children with autism as compared to their unaffected siblings. Several studies have suggested alterations in the activities of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, and catalase in autism. Additionally, altered glutathione levels and homocysteine/methionine metabolism, increased inflammation, excitotoxicity, as well as mitochondrial and immune dysfunction have been suggested in autism. Furthermore, environmental and genetic factors may increase vulnerability to oxidative stress in autism. Taken together, these studies suggest increased oxidative stress in autism that may contribute to the development of this disease. A mechanism linking oxidative stress with membrane lipid abnormalities, inflammation, aberrant immune response, impaired energy metabolism and excitotoxicity, leading to clinical symptoms and pathogenesis of autism is proposed.
Neuronal Mitochondria Fuel Nerve Signal Impulses
Mitochondrial Dysfunction May Play a Role in Autism Spectrum Disorders Etiology

Caroline Cassels

Medscape Medical News 2008. © 2008 Medscape

April 15, 2008 (Chicago, IL) — New research suggests mitochondrial dysfunction may play a role in the etiology of autism spectrum disorders (ASD) in a subset of this patient population.

Here at the American Academy of Neurology 60th Annual Meeting, a retrospective analysis of 41 children with ASD who were being evaluated for suspected mitochondrial disease showed that 32 (78%) had defects in skeletal muscle oxidative phosphorylation (OXPHOS) enzyme function and 29 of 39 (74%) harbored abnormalities in the OXPHOS proteins.

"We're very excited by these findings, and, based on these results, we will continue to pursue this [mitochondrial dysfunction] as a potential cause in a segment of the autistic population," principal investigator John Shoffner, MD, owner of Medical Neurogenetics, in Atlanta, Georgia, told Medscape Neurology & Neurosurgery.
Mitochondrial Disease in Autism Spectrum Disorder Patients: A Cohort Analysis

Jacqueline R. Weissman, Richard I. Kelley, Margaret L. Bauman, Bruce H. Cohen, Katherine F. Murray, Rebecca L. Mitchell, Rebecca L. Kern, Marvin R. Natowicz

1 Cleveland Clinic Lerner College of Medicine, Cleveland Clinic, Cleveland, Ohio, United States of America, 2 Department of Pediatrics, Johns Hopkins University Medical Center and Division of Metabolism, Kennedy Krieger Institute, Baltimore, Maryland, United States of America, 3 Department of Pediatrics and Learning and Developmental Disabilities Evaluation and Rehabilitation Services (LADDERS), Massachusetts General Hospital, Boston, Massachusetts, United States of America, 4 Neurological Institute and Pediatrics Institute, Cleveland Clinic, Cleveland, Ohio, United States of America, 5 Genomic Medicine Institute, Cleveland Clinic, Cleveland, Ohio, United States of America, 6 Pathology and Laboratory Medicine Institute, Cleveland Clinic, Cleveland, Ohio, United States of America

Abstract

Background: Previous reports indicate an association between autism spectrum disorders (ASD) and disorders of mitochondrial oxidative phosphorylation. One study suggested that children with both diagnoses are clinically indistinguishable from children with idiopathic autism. There are, however, no detailed analyses of the clinical and laboratory findings in a large cohort of these children. Therefore, we undertook a comprehensive review of patients with ASD and a mitochondrial disorder.

Methodology/Principal Findings: We reviewed medical records of 25 patients with a primary diagnosis of ASD by DSM-IV-TR criteria, later determined to have enzyme- or mutation-defined mitochondrial electron transport chain (ETC) dysfunction. Twenty-four of 25 patients had one or more major clinical abnormalities uncommon in idiopathic autism. Twenty-one patients had histories of significant non-neurological medical problems. Nineteen patients exhibited constitutional symptoms, especially excessive fatigability. Fifteen patients had abnormal neurological findings. Unusual developmental phenotypes included marked delay in early gross motor milestones (32%) and unusual patterns of regression (40%). Levels of blood lactate, plasma alanine, and serum ALT and/or AST were increased at least once in 76%, 36%, and 52% of patients, respectively. The most common ETC disorders were deficiencies of complex I (64%) and complex III (20%). Two patients had rare mtDNA mutations of likely pathogenicity.

Conclusions/Significance: Although all patients’ initial diagnosis was idiopathic autism, careful clinical and biochemical assessment identified clinical findings that differentiated them from children with idiopathic autism. These prior data suggest a disturbance of mitochondrial energy production as an underlying pathophysiological mechanism in a subset of individuals with autism.
Antioxidant ORAC/ 1 gram of whole food Freeze dried ACAI is > 420

<table>
<thead>
<tr>
<th>Antioxidant</th>
<th>ORAC Value</th>
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<tbody>
<tr>
<td>Muscadine Grape Seed**</td>
<td>559</td>
</tr>
<tr>
<td>Acai*</td>
<td>387</td>
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<tr>
<td>Goji Berry*</td>
<td>253</td>
</tr>
<tr>
<td>Noni*</td>
<td>151</td>
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<tr>
<td>Pomegranates*</td>
<td>105</td>
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<tr>
<td>Raspberries*</td>
<td>82</td>
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<td>Blueberries*</td>
<td>77</td>
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<tr>
<td>Red Grapes*</td>
<td>74</td>
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<td>Prunes*</td>
<td>57</td>
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<tr>
<td>Cherries*</td>
<td>67</td>
</tr>
<tr>
<td>Strawberries*</td>
<td>36</td>
</tr>
</tbody>
</table>


Oxidative Biomarkers and Treatment

- **Isoprostane** = oxidized fatty acid membranes
- **8 OHG** = oxidized RNA
- **Biopterin** = oxidation due to inflammation
- **Neopterin** = immune activation which will lead to oxidation
- **Cysteine and Glutathione (Methionine)** deficiency
- **Porphyrins** = coproporphyrin may rise from oxidation not just metal related events.
- **Ammonia & lactic acid** link to mito dysfunction
- **Dysbiosis** markers may impact these issues too.
Mitochondrial Cocktail

- D-Ribose: generates ATP via a bypass of the pentose phosphate shunt pathway. ATP = energy storage.
- B Vitamins
- Acetyl L Carnitine: Fuels CNS mitochondria better than plain carnitine.
- UBQH: more active form of CoQ10, a facilitator of mitochondrial activity.
- Antioxidants: protect mitochondrial OXPHOS
- Multiple small feedings per day – no large meals – constant supply of energy
- Moderation of protein intake – expensive for cells to get rid of extra ammonia.
Autonomic Nervous System

**PARASYMPATHETIC NERVES**
- Constrict pupils
- Stimulate saliva
- Slow heartbeat
- Constrict airways
- Stimulate activity of stomach
- Inhibit release of glucose; stimulate gallbladder
- Stimulate activity of intestines
- Contract bladder
- Promote erection of genitals

**CERVICAL NERVES**

**THORACIC NERVES**
- Dilate pupils
- Inhibit salivation
- Increase heartbeat
- Relax airways
- Inhibit activity of stomach
- Stimulate release of glucose; inhibit gallbladder
- Inhibit activity of intestines
- Secretion of epinephrine and norepinephrine
- Relax bladder
- Promote ejaculation and vaginal contraction

**LUMBAR NERVES**

**SACRAL NERVES**

**SYMPATHETIC NERVES**

**FIGHT OR FLIGHT**

**Cholinergic - Use Acetylcholine**

**Noradrenaline Transmitters - Use Noradrenaline**

Acetyl Choline Nicotine effect

Adrenaline effect
The Very Important Vagus Nerve

• The vagus nerve supplies motor parasympathetic fibers to all the organs except the adrenal glands, from the neck down to the second segment of the transverse colon. Throat, pharyngeal constrictors
• Muscles of the larynx (speech).
• This means that the vagus nerve is responsible for such varied tasks as heart rate, gastrointestinal peristalsis, sweating, and quite a few muscle movements in the mouth, and keeping the larynx open for breathing.
Vagus nerve stimulation (VNS)

- VNS therapy uses a pacemaker-like electrical device implanted in the chest to control seizures in epilepsy patients.
- Now also approved for treating drug-resistant cases of clinical depression.
- Future uses may impact cognition and Alzheimer's disease.
Reduced cardiac parasympathetic activity in children with autism.

Brain Dev. 2005 Oct;27(7):509-16
Ming X, et al
Department of Neuroscience, New Jersey Medical School, UMDNJ, Newark, 90 Bergen Street, DOC 8100, NJ 07103, USA. mingxu@umdnj.edu

Many of the clinical symptoms of autism suggest autonomic dysfunction. Results suggest that there is low baseline cardiac parasympathetic activity with evidence of elevated sympathetic tone in children with autism whether or not they have symptoms or signs of autonomic abnormalities.
Subclinical effects of prenatal methylmercury exposure on cardiac autonomic function in Japanese children.


Department of Environmental Health Sciences, Akita University School of Medicine, 010-8543, Akita, Japan, winestem@med.akita-u.ac.jp.

Conclusions: Despite the potential limitations involved in the retrospective study, these findings suggest that prenatal methylmercury exposure (median of estimated maternal hair mercury at parturition, 2.24 mug/g) may be associated with reduced parasympathetic activity and/or sympathovagal shift.
## Interictal Autonomic Dysfunction in Epilepsy

### Symptoms and Signs

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<thead>
<tr>
<th>Category</th>
<th>Symptoms and Signs</th>
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<tbody>
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<td><strong>Cardiac/thoracic</strong></td>
<td>Palpitations, chest pain, tachycardia, bradycardia, arrhythmia, hypotension, hypertension</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td>Apnea, hyperventilation, hypoxia</td>
</tr>
<tr>
<td><strong>Gastrointestinal/abdominal</strong></td>
<td>Ascending sensation (dyspepsia), pain, hunger, borborygmi, nausea, vomiting, belching, urge to defecate, fecal incontinence</td>
</tr>
<tr>
<td><strong>Urinary</strong></td>
<td>Incontinence, urgency</td>
</tr>
<tr>
<td><strong>Genital</strong></td>
<td>Genital sensations, erection, orgasm</td>
</tr>
<tr>
<td><strong>Cutaneous</strong></td>
<td>Flushing, erythema, cyanosis, blanching, pallor, piloerection</td>
</tr>
<tr>
<td><strong>Pupillary</strong></td>
<td>Mydriasis, miosis, hippus</td>
</tr>
<tr>
<td><strong>Secretory</strong></td>
<td>Perspiration, salivation, lacrimation</td>
</tr>
</tbody>
</table>

Maladaptive Neurotransmitter Compensation for Mitochondrial Dysfunction

<table>
<thead>
<tr>
<th>Catabolites</th>
<th>Patient</th>
<th>Reference</th>
<th>Interpretation</th>
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</thead>
<tbody>
<tr>
<td>hva</td>
<td>9.68</td>
<td>2.5-3.5</td>
<td>Sharply increased Dopaminergic activity</td>
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<tr>
<td>vma</td>
<td>5.3</td>
<td>2.5-3.5</td>
<td>Sharply increased Adrenergic activity</td>
</tr>
<tr>
<td>5hia</td>
<td>20.5</td>
<td>3.0-4.5</td>
<td>Sharply increased Serotonergic activity</td>
</tr>
</tbody>
</table>
Vagus nerve and histamine help regulate acid production in stomach as well as motility.
The alpha7 nicotinic acetylcholine receptor as a pharmacological target for inflammation

WJ de Jonge¹,² and L Ulloa³,⁴

¹Department of Gastroenterology, Academic Medical Center, Amsterdam, The Netherlands; ²Sir William Dunn School of Pathology, University of Oxford, Oxford, UK; ³The Feinstein Institute for Medical Research, North Shore University Hospital, Manhasset, NY, USA and ⁴Laboratory of Surgical Science Research, MSB-F673, UMDNJ-University of Medicine of New Jersey, Newark, NJ, USA

The physiological regulation of the immune system encompasses comprehensive anti-inflammatory mechanisms that can be harnessed for the treatment of infectious and inflammatory disorders. Recent studies indicate that the vagal nerve, involved in control of heart rate, hormone secretion and gastrointestinal motility, is also an immunomodulator. In experimental models of inflammatory diseases, vagal nerve stimulation attenuates the production of proinflammatory cytokines and inhibits the inflammatory process. Acetylcholine, the principal neurotransmitter of the vagal nerve, controls immune cell functions via the alpha7 nicotinic acetylcholine receptor (alpha7nAChR). From a pharmacological perspective, nicotinic agonists are more efficient than acetylcholine at inhibiting the inflammatory signaling and the production of proinflammatory cytokines. This ‘nicotinic anti-inflammatory pathway’ may have clinical implications as treatment with nicotinic agonists can modulate the production of proinflammatory cytokines from immune cells. Nicotine has been tested in clinical trials as a treatment for inflammatory diseases such as ulcerative colitis, but the therapeutic potential of this mechanism is limited by the collateral toxicity of nicotine. Here, we review the recent advances that support the design of more specific receptor-selective nicotinic agonists that have anti-inflammatory effects while eluding its collateral toxicity.

Figure 1  The cholinergic anti-inflammatory surveillance. Hypothetical scheme of the vagus nerve continuously monitoring and modulating innate immune activation following ingestion, infection, and trauma. (1) During digestion, the commensal flora and dietary components activate the sensory afferent vagus nerve, which will transmit the information to the brain. In return, the brain may activate the efferent vagus nerve to modulate gastrointestinal macrophages. (2) The efferent vagus nerve also modulates systemic inflammatory responses through a mechanism involving an intact spleen. Upon infection or trauma, bacterial components or intracellular mediators (HMGB1, heat shock proteins, etc) activate macrophages to produce proinflammatory cytokines. (3) This will trigger afferent vagus nerve signaling. (4) In return, the brain will activate efferent vagus nerve to release acetylcholine, which can bind to the a7 acetylcholine receptor on macrophages and inhibit the production of proinflammatory cytokines. Interrogation marks indicate that although macrophages are found in the proximity of cholinergic fibers in the spleen and the intestine (De Jonge et al., 2005) there is currently no evidence demonstrating that parasympathetic neurons indeed innervate immune cells and further studies are needed to determine the physiological interaction between the vagus nerve and immune cells. HMGB1, high-mobility group box 1.
An evaluation of a visual biofeedback intervention in dyslexic adults.


Liddle E, Jackson G, Jackson S.

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A prototype of a biofeedback system designed to treat dyslexia by improving heart-rate variability was evaluated in a single blind study of dyslexic adults. Treatment consisted of four 15 minute exposures to a visual display synchronized with either the participant's own cardiac cycle (intervention condition), or of a synthesized cardiac cycle (placebo condition). Repeated measures were made of picture naming speed, single word reading speed and accuracy, copying speed, heart-rate variability and performance on a lateralized visual temporal order judgment task. The results are interpreted as indicating that the treatment induces a shift in autonomic balance in favor of the parasympathetic ANS, and that this shift is also reflected in increased efficiency of left cerebral hemisphere circuits implicated in the perceptual-motor processes required for naming and reading fluency.
Social isolation disrupts autonomic regulation of the heart and influences negative affective behaviors.


Grippo AJ, Lamb DG, Carter CS, Porges SW.

Department of Psychiatry, University of Illinois at Chicago, Chicago, Illinois 60612, USA. agrippo@psych.uic.edu

BACKGROUND: There is a documented association between affective disorders (e.g., depression and anxiety) and cardiovascular disease in humans. Chronic social stressors may play a mechanistic role in the development of behavioral and cardiac dysregulation. The current study investigated behavioral, cardiac, and autonomic responses to a chronic social stressor in prairie voles, a rodent species that displays social behaviors similar to humans. RESULTS: Isolation induced a significant increase in resting heart rate, reduction in heart rate variability (standard deviation of normal-to-normal intervals and amplitude of respiratory sinus arrhythmia), and exaggerated cardiac responses during an acute resident-intruder paradigm. Isolation led also to both depression-like and anxiety-like behaviors in validated operational tests. These changes in response to social isolation showed predictable interrelations and were mediated by a disruption of autonomic balance including both sympathetic and parasympathetic (vagal) mechanisms. CONCLUSIONS: These findings indicate that social isolation induces behavioral, cardiac, and autonomic alterations related to those seen after other stressors and which are relevant to cardiovascular disease and affective disorders. This model may provide insight into the mechanisms that underlie these co-occurring conditions.
Neuroprotective effect of nicotine on dopaminergic neurons by anti-inflammatory action.


Park HJ, et al

Department of Neurology, Ajou University School of Medicine, Suwon, Korea.

Epidemiological studies have reported that smoking is associated with a lower incidence of Parkinson's disease (PD), leading to theories that smoking in general and nicotine in particular might be neuroprotective. Recent studies suggested cholinergic anti-inflammatory pathway-regulating microglial activation through alpha7 nicotinic receptors. In the present study, we used lipopolysaccharide (LPS)-induced in vitro and in vivo inflammation models to investigate whether nicotine has a protective effect on the dopaminergic system through an anti-inflammatory mechanism. Nicotine pretreatment considerably decreased microglial activation with significant reduction of tumour necrosis factor (TNF)-alpha mRNA expression and TNF-alpha release induced by LPS stimulation. In cocultures of microglia and mesencephalic neurons nicotine pretreatment significantly decreased the loss of tyrosine hydroxylase-immunopositive (TH-ip) cells, approximately twice more than the LPS-only treatment. alpha-Bungarotoxin, an alpha7 nicotinic acetylcholine receptor subunit-selective blocker, considerably blocked the inhibitory effects of nicotine on microglial activation and TH-ip neuronal loss. Chronic nicotine pretreatment in rats showed that TH-ip neuronal loss induced by LPS stimulation in the substantia nigra was dramatically decreased, which was clearly accompanied by a reduction in the formation of TNF-alpha. The present study demonstrated that nicotine has a neuroprotective effect on dopaminergic neurons via an anti-inflammatory mechanism mediated by the modulation of microglial activation. Along with various neuroprotective effects of nicotine, the anti-inflammatory mechanism of nicotine could have a major therapeutic implication in the preventive treatment of PD.
The Cholinergic Anti-inflammatory Pathway: A Missing Link in Neuroimmunomodulation

Valentin A Pavlov,1 Hong Wang,1 Christopher J Czura,1 Steven G Friedman,1,2 and Kevin J Tracey1

This review outlines the mechanisms underlying the interaction between the nervous and immune systems of the host in response to an immune challenge. The main focus is the cholinergic anti-inflammatory pathway, which we recently described as a novel function of the efferent vagus nerve. This pathway plays a critical role in controlling the inflammatory response through interaction with peripheral α7 subunit-containing nicotinic acetylcholine receptors expressed on macrophages. We describe the modulation of systemic and local inflammation by the cholinergic anti-inflammatory pathway and its function as an interface between the brain and the immune system. The clinical implications of this novel mechanism also are discussed.
Figure 1. Neural and humoral pathways in immunomodulation. During immune challenge activated macrophages and other immune and nonimmune cells release cytokines that signal the brain for activation of immunomodulatory mechanisms. Central immunomodulation is achieved by the cholinergic anti-inflammatory pathway, HPA axis, and SNS (see text for details). AP, area postrema; NTS, nucleus tractus solitarius; DMN, dorsal motor nucleus of the vagus; PVN, paraventricular nucleus; RVM, rostral ventrolateral medulla; LC, locus coeruleus; SNS, sympathetic nervous system; ACTH, adrenocorticotropic hormone; GC, glucocorticoids; EN, epinephrine; NE, norepinephrine; ACh, acetylcholine; LPS, lipopolysaccharide (endotoxin).
Clinical & Research News

Nicotine Receptors May Play Role In Development of Autism

Joan Arehart-Treichel

Cholinergic nicotinic receptors, which have become a hot area for brain researchers, are linked to yet another psychiatric-neurological disorder—autism.

Deep inside the human brain, cholinergic nicotinic receptors are busy plying their trade, and one might view them as triple agents. They release the nerve transmitter acetylcholine from certain nerve ends, they receive it at others, and they can be stimulated by nicotine—yes, from cigarette smoking!

Even more intriguing, these receptors have been implicated of late in a spate of psychiatric and neurological disorders such as Alzheimer’s disease, Parkinson’s disease, schizophrenia, and Tourette syndrome (Psychiatric News, March 13, 2000).

And now the receptors have been linked to yet another psychiatric-neurological condition—autism.

The finding comes from Elaine Perry, Ph.D., of Newcastle General Hospital in Newcastle-Upon-Tyne, England, and her colleagues. It is reported in the July American Journal of Psychiatry.
Galantamine and nicotine have a synergistic effect on inhibition of microglial activation induced by HIV-1 gp120.

Giunta B, et al Neuroimmunology Laboratory, College of Medicine, University of South Florida, 3515 E. Fletcher Avenue, Tampa, FL 33613, USA.

Chronic brain inflammation is the common final pathway in the majority of neurodegenerative diseases and central to this phenomenon is the immunological activation of brain mononuclear phagocyte cells, called microglia. This inflammatory mechanism is a central component of HIV-associated dementia (HAD). Recent data from our laboratory indicates that cultured microglial cells also express this same receptor and that microglial anti-inflammatory properties are mediated through it and the p44/42 mitogen-activated protein kinase (MAPK) system. Here we report for the first time the creation of an in vitro model of HAD composed of cultured microglial cells synergistically activated by the addition of IFN-gamma and the HIV-1 coat glycoprotein, gp120. Furthermore, this activation, as measured by TNF-alpha and nitric oxide (NO) release, is synergistically attenuated through the alpha7 nAChR and p44/42 MAPK system by pretreatment with nicotine, and the cholinesterase inhibitor, galantamine. Our findings suggest a novel therapeutic combination to treat or prevent the onset of HAD through this modulation of the microglia inflammatory mechanism.
1. Acetylcholine (ACh) is made from choline and acetyl CoA.

2. In the synaptic cleft ACh is rapidly broken down by the enzyme acetylcholinesterase.

3. Choline is transported back into the axon terminal and is used to make more ACh.

Galantamine blocks nicotinic receptors, leading to nicotine mimicry.
A Prospective, Open-Label Trial of Galantamine in Autistic Disorder

Rob Nicolson, M.D., Beth Craven-Thuss, M.A., and Judy Smith

ABSTRACT

Objective: Post-mortem studies have reported abnormalities of the cholinergic system in autism. The purpose of this study was to assess the use of galantamine, an acetylcholinesterase inhibitor and nicotinic receptor modulator, in the treatment of interfering behaviors in children with autism.

Methods: Thirteen medication-free children with autism (mean age, 8.8 ± 3.5 years) participated in a 12-week, open-label trial of galantamine. Patients were rated monthly by parents on the Aberrant Behavior Checklist (ABC) and the Conners’ Parent Rating Scale—Revised, and by a physician using the Children’s Psychiatric Rating Scale and the Clinical Global Impressions scale.

Results: Patients showed a significant reduction in parent-rated irritability and social withdrawal on the ABC as well as significant improvements in emotional lability and inattention on the Conners’ Parent Rating Scale—Revised. Similarly, clinician ratings showed reductions in the anger subscale of the Children’s Psychiatric Rating Scale. Eight of 13 participants were rated as responders on the basis of their improvement scores on the Clinical Global Impressions scale. Overall, galantamine was well-tolerated, with no significant adverse effects apart from headaches in one patient.

Conclusion: In this open trial, galantamine was well-tolerated and appeared to be beneficial for the treatment of interfering behaviors in children with autism, particularly aggression, behavioral dyscontrol, and inattention. Further controlled trials are warranted.
Memantine as Adjunctive Therapy in Children Diagnosed With Autistic Spectrum Disorders: An Observation of Initial Clinical Response and Maintenance Tolerability

Michael G. Chez, MD, Quinn Burton, MS, Timothy Dowling, Mina Chang, MS, Pavan Khanna, MS, and Christopher Kramer, MS

Autism and Pervasive Developmental Disorder Not Otherwise Specified are common developmental problems often seen by child neurologists. There are currently no cures for these lifelong and socially impairing conditions that affect core domains of human behavior such as language, social interaction, and social awareness. The etiology may be multifactorial and may include autoimmune, genetic, neuroanatomic, and possibly excessive glutaminergic mechanisms. Because memantine is a moderate affinity antagonist of the N-methyl-D-aspartic acid (NMDA) glutamate receptor, this drug was hypothesized to potentially modulate learning, block excessive glutamate effects that can include neuroinflammatory activity, and influence neuroglial activity in autism and Pervasive Developmental Disorder Not Otherwise Specified. Open-label add-on therapy was offered to 151 patients with prior diagnoses of autism or Pervasive Developmental Disorder Not Otherwise Specified over a 21-month period. To generate a clinician-derived Clinical Global Impression Improvement score for language, behavior, and self-stimulatory behaviors, the primary author observed the subjects and questioned their caretakers within 4 to 8 weeks of the initiation of therapy. Chronic maintenance therapy with the drug was continued if there were no negative side effects. Results showed significant improvements in open-label use for language function, social behavior, and self-stimulatory behaviors, although self-stimulatory behaviors comparatively improved to a lesser degree. Chronic use so far appears to have no serious side effects.

Keywords: autism treatment; pervasive developmental disorders; memantine
ARTICLE

Transdermal Nicotine for Mildly to Moderately Active Ulcerative Colitis

A Randomized, Double-Blind, Placebo-Controlled Trial

William J. Sandborn, MD; William J. Tremaine, MD; Kenneth P. Offord, MS; George M. Lawson, PhD; Bret T. Petersen, MD; Kenneth P. Batts, MD; Ivana T. Croghan, PhD; Lowell C. Dale, MD; Darrell R. Schroeder, MS; and Richard D. Hurt, MD

1 March 1997 | Volume 126 Issue 5 | Pages 364-371
Percentage of patients with clinically improved ulcerative colitis at week 4

Nicotinic receptor mechanisms and cognition in normal states and neuropsychiatric disorders

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Katie L. Bannon, and
Program for Research in Smokers with Mental Illness (PRISM), Division of Substance Abuse, Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA.

Tony P. George
Program for Research in Smokers with Mental Illness (PRISM), Division of Substance Abuse, Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA.

Abstract

Cigarette smoking rates in the American population are approximately 23%, whereas rates of smoking in clinical and population studies of individuals with neuropsychiatric disorders are typically two- to four-fold higher. Studies conducted in a variety of neuropsychiatric populations [e.g., attention-deficit hyperactivity disorder (ADHD), Alzheimer’s disease, schizophrenia] have collectively suggested that nicotine may be efficacious in remediating selected cognitive deficits associated with these disorders, thus providing a framework for understanding the specific vulnerability of these patients to smoking initiation and maintenance. However, the specific gain in cognitive performance produced by nicotine administration in healthy subjects with normal cognitive function is less clear. This article reviews our current understanding of central nicotinic acetylcholine receptor (nAChRs) systems in normal and neuropsychiatric disease states and, specifically, their role with respect to cognitive dysfunction and clinical symptoms in several specific neuropsychiatric populations, including ADHD, Alzheimer’s disease, Parkinson’s disease, Tourette’s Disorder, schizophrenia and affective disorders. The potential benefits of nicotinic agents for therapeutic use in neuropsychiatric disorders is discussed, as well as directions for further research in this area.
Neuronal nicotinic receptor agonists for the treatment of attention-deficit/hyperactivity disorder: Focus on cognition

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Pharmacological enhancement of the cholinergic system can improve a host of cognitive processes. As comprehensively reviewed by Levin et al. [104] and Potter et al. [97], a vast preclinical literature derived from laboratory models supports nicotine and other nicotinic agonists’ role in improving performance on cognitive processes, including learning, spatial and working memory, processing speed and ability, inhibition, selective accuracy, detection, and overall attention. In general, using the preclinical paradigms, the effects of nicotine appear to persist with chronic administration [104].
In addition, there is emerging evidence that cholinergic dysregulation (in particular, of nicotinic cholinergic systems) may play a role in the pathophysiology of ADHD [97]. Both clinical and epidemiological samples of humans indicate that ADHD is associated with an increased risk and earlier age of cigarette smoking [98–100]. Epidemiological data indicates that a higher risk of smoking correlates directly with more ADHD symptoms [100]. Furthermore, maternal smoking during pregnancy (independent of ADHD) increases the risk for ADHD in the offspring [101], an effect that can be modeled in experimental animals exposed to nicotine in-utero [102,103].
Acute effects of nicotine on attention and response inhibition

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Received 7 August 2004; received in revised form 11 October 2005; accepted 17 October 2005

Abstract

Smoking is highly prevalent among patients with Attention Deficit Hyperactivity Disorder (ADHD). Previous studies using the reversed continuous performance task (R-CPT) have suggested that nicotine reduces inattention. Since especially adults with ADHD have been claimed to suffer from a core deficit in inhibitory control, this study aimed at determining whether nicotine improves response inhibition in addition to attention. Sixteen healthy regular smokers participated in a pre/post treatment design in which transdermal patches containing 7 and 21 mg nicotine per day were administered in a counterbalanced, double-blind manner. In a second study, patches containing 0 mg (placebo) and 21 mg per day were administered to a different group of regular smokers. For replication purposes, the R-CPT and the profile of mood states (POMS) were administered. Furthermore, a different version of the continuous performance task (CPT-AX) and the stop-signal task, traditionally used to measure response inhibition, were presented. The high dose of nicotine was found to relieve self-reported Depression in Study 1 and Fatigue in Study 2. Performance data indicated acute effects of nicotine on attention-related, but not on inhibition-related measures. Especially the comparison with placebo revealed decreases in reaction time and variability of responding. The results imply that patients with ADHD smoke to reduce inattention.
Functional alterations of nicotinic neurotransmission in dopamine transporter knock-out mice

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Abstract

Mice lacking the dopamine (DA) transporter (DAT) gene exhibit a phenotype reminiscent of schizophrenia and attention deficit hyperactivity disorder (ADHD), including hyperDAergic, hyperactivity and deficits in cognitive performance, which are alleviated by antipsychotic agents. Numerous studies suggest a dysfunction of nicotinic neurotransmission in schizophrenia and show increased tobacco intake in schizophrenic and ADHD patients, possibly as a self-medication. Thus, we examined the potential alteration of nicotinic neurotransmission in DAT knock-out (KO) mice.

We showed that constitutively hyperDAergic DAT KO mice exhibited modifications in nicotinic receptor density in an area- and subtype-dependent manner. In some DAergic areas, the small decrease in the β2* nicotinic subunit (nAChR) density contrasted with the higher decrease and increase in the α6* and α7 nAChR densities, respectively. Mutant mice were hypersensitive to the stimulant locomotor effects of nicotine at low doses, probably due to enhanced nicotine-induced extracellular DA level. They also showed hypersensitivity to the hypolocomotion induced by nicotine. In contrast, no hypersensitivity was observed for other nicotine-induced behavioral effects, such as anxiety or motor activity in the elevated plus maze. Co-administration of nicotinic agonists at sub-acute doses elicited opposite locomotor effects in wild-type and DAT KO mice, as reported previously for methylphenidate. Interestingly, such a co-administration of nicotinic agonists induced synergistic hypolocomotion in DAT KO mice. These findings show that a targeted increase of DA tone can be responsible for significant adaptations of the cholinergic/nicotinic neurotransmission. This study may provide potential leads for the use of nicotine or combined nicotinic agonists for the therapy of psychiatric disorders.

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Keywords: ADHD; Anxiety; Nicotinic receptors; Locomotion; Microdialysis; Schizophrenia
Therapeutic Effect of Ritalin SR 20

Fig. 2. Dopamine transporter binding in the striatum of a 53 years old non-smoker before (A), after 5 h of intake of 20 mg methylphenidate (Ritalin SR®) (B), and 3 months later after 5 h of wearing a 17.5 mg/24 h nicotine skin patch (C), shown by specific accumulation of [Tc-99m]TRODAT-1 in SPECT scans.
Transdermal nicotine effects on attention

Fig. 1 Profile of mood states (POMS) vigor score (mean ± SEM). There was a significant nicotine-induced increase in vigor (*P < 0.05)

Fig. 2 Conners continuous performance task (CPT) errors of omission (mean ± SEM). There was a significant nicotine-induced decrease in errors of omission (*P < 0.05)

Fig. 4 Conners continuous performance task (CPT) composite attention score (mean ± SEM). There was a significant nicotine-induced increase in the attention score (*P < 0.05)
Effects of acute nicotine administration on behavioral inhibition in adolescents with attention-deficit/hyperactivity disorder

Table 2: Observer visual analog scale adjusted mean±SE significance represents main effect of drug treatment. PLC placebo; MET methylphenidate (usual dose); NIC nicotine (7 mg).

<table>
<thead>
<tr>
<th>Condition</th>
<th>PLC</th>
<th>MET</th>
<th>NIC</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsy</td>
<td>27.23±10.84</td>
<td>0.00±0.00</td>
<td>20.60±9.70</td>
<td>NS</td>
</tr>
<tr>
<td>Motoric restlessness</td>
<td>6.70±3.80</td>
<td>10.40±3.88</td>
<td>22.40±14.01</td>
<td>NS</td>
</tr>
<tr>
<td>Disoriented</td>
<td>0.00±0.00</td>
<td>0.00±0.00</td>
<td>0.00±0.00</td>
<td>NS</td>
</tr>
<tr>
<td>Impaired speech</td>
<td>0.00±0.00</td>
<td>0.00±0.00</td>
<td>0.00±0.00</td>
<td>NS</td>
</tr>
<tr>
<td>Euphoria</td>
<td>5.50±5.38</td>
<td>13.40±8.21</td>
<td>16.80±13.37</td>
<td>NS</td>
</tr>
<tr>
<td>Irritability</td>
<td>8.45±6.18</td>
<td>2.60±2.60</td>
<td>4.40±2.86</td>
<td>NS</td>
</tr>
<tr>
<td>Sweating</td>
<td>3.45±8.39</td>
<td>0.00±0.00</td>
<td>12.20±7.51</td>
<td>NS</td>
</tr>
<tr>
<td>GI distress</td>
<td>0.00±0.00</td>
<td>0.00±0.00</td>
<td>17.8±7.55</td>
<td>NS</td>
</tr>
<tr>
<td>Motor incoordination</td>
<td>0.00±0.00</td>
<td>0.00±0.00</td>
<td>0.00±0.00</td>
<td>NS</td>
</tr>
<tr>
<td>Fatigue</td>
<td>22.75±21.31</td>
<td>2.00±2.00</td>
<td>16.20±10.28</td>
<td>NS</td>
</tr>
<tr>
<td>Depression</td>
<td>4.75±2.48</td>
<td>0.00±0.00</td>
<td>0.00±0.00</td>
<td>NS</td>
</tr>
<tr>
<td>Anxiety</td>
<td>17.20±6.63</td>
<td>22.40±3.23</td>
<td>15.00±6.63</td>
<td>*P&lt;0.05</td>
</tr>
<tr>
<td>Alertness</td>
<td>65.57±11.12</td>
<td>99.40±6.60</td>
<td>68.40±14.02</td>
<td>*P&lt;0.01</td>
</tr>
</tbody>
</table>

Fig. 4: HI-low imagery task: learning score (trial 2–trial 1), PLC placebo; NIC nicotine (7 mg); MET methylphenidate (usual dose).

*P<0.05 difference PLC versus NIC

TDN Superior to Ritalin
Acute nicotine improves cognitive deficits in young adults with attention-deficit/hyperactivity disorder

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Received 25 May 2007; received in revised form 8 September 2007; accepted 19 September 2007
Available online 26 September 2007

Abstract

Objective: The strong association between ADHD and cigarette smoking and the known effects of nicotine on cognition has lead to interest in the role of cholinergic function in ADHD cognitive deficits. We have previously demonstrated that acute nicotine improves behavioral inhibition in adolescents with ADHD. This study examined acute nicotine in young adults with ADHD-Combined type on cognitive domains including behavioral inhibition, delay aversion, and recognition memory.

Methods: 15 non-smoking young adults (20 ± 1.7 years) diagnosed with ADHD-C received acute nicotine (7 mg patch for 45 min) and placebo on separate days. Cognitive tasks included the Stop Signal Task, Choice Delay task, and the High–Low Imagery Task (a verbal recognition memory task). Three subjects experienced side effects and their data was excluded from analysis of cognitive measures.

Results: There was a significant (p < .05) positive effect of nicotine on the Stop Signal Reaction Time measure of the Stop Signal Task. The SSRT was improved without changes in GO reaction time or accuracy. There was a trend (p = .09) for nicotine to increase tolerance for delay and a strong trend (p = .06) for nicotine to improve recognition memory.

Conclusions: Non-smoking young adults with ADHD-C showed improvements in cognitive performance following nicotine administration in several domains that are central to ADHD. The results from this study support the hypothesis that cholinergic system activity may be important in the cognitive deficits of ADHD and may be a useful therapeutic target.

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Adverse Reactions to 7 mg/24hr Nicotine patch in young adults with ADHD

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Nicotine Group (n = 31)</th>
<th>Placebo Group (n = 33)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep disturbance or violent or sexual dreams</td>
<td>6</td>
<td>3</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Stimulation of central nervous system</td>
<td>3</td>
<td>3</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Diaphoresis or sweating</td>
<td>3</td>
<td>0</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Shakiness or tremor</td>
<td>3</td>
<td>0</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>3</td>
<td>0</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>23</td>
<td>15</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Any adverse reaction</td>
<td>77</td>
<td>30</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* By the Fisher exact test.
Case Response: 6 yo male w/ASD

- Positive antibodies to brain endothelium
- Elevated Neopterin
- Intestinal Dysbiosis
- Stereotypia, verbal stimming, cognitive deficits, socially withdrawn, auditory processing delays and both expressive and receptive language deficits.
- Hypotonia and sensory processing issues
- Huge bowel movements
- NONRESPONDER
Dear Dr. Bradstreet,

The Nicoderm patch (1/4 of 7 mg patch) really made a difference for our son. We just got reports back from his teachers that have us jumping up and down. They report improved eye contact, improved attention and focus, class participation, reduced anxiety, significant decrease in hyperactivity and more.

His school has no idea what we have done -- or what to look for. Hence, the report is unbiased and quite reliable. We have seen the same at home:0)

This is REALLY exciting. But, I have been online reading quite a bit about the downside of the patch. Of course I am concerned about Nicotine addiction, long term use, carcinogenic effects, etc.... So the next question is what do we do now? Should I continue w/ the patch for now? How long can we safely do this?

I have never been more excited in my life. This is without a doubt the most significant change we have seen in all our efforts thus far.

Thanks for your time.
Warmest Regards
Data from ABC scoring
9 yo female after 2 months

- Teacher Pre total ABC score = 42
- Teacher Post total ABC score = 9
- Change = 33
- Mother Pre total ABC score = 57
- Mother Post total ABC score = 18
- Change = 39
- All domains dramatically reduced
1-25-2008 Friday

Oh kerri! she's so different!

Yesterday and today, she was starting conversations all over campus. Her conversations are more than one word. They're 1-3 sentences! Today she was looking the dictionary (and normally she asks me to "go away" or "please leave") and this time she asked me to sit next to her and she talked about her favorite words A-Z. She took her spelling test with the class today instead of later. Then, she did a math worksheet along with the class.
Keep dose low to prevent stimulation of sympathetic system

• At synapses within the sympathetic ganglia, preganglionic sympathetic neurons release acetylcholine, a chemical messenger that binds and activates nicotinic acetylcholine receptors on postganglionic neurons. In response to this stimulus, postganglionic neurons principally release noradrenaline (norepinephrine). Prolonged activation can elicit the release of adrenaline from the adrenal medulla.
TDN

• Step 1 = 21 mg/per 24 hrs
• Step 2 = 14 mg/24 hrs
• Step 3 = 7 mg/24 hrs
• Usual dose we are using is ¼ to ½ of 7mg patch which is under 0.15 mg per hour
• Manufacturer warns NOT to cut the patch, but in practice thus far it has worked extremely well.
• Skin reactions #1 issue: less with generic
• Nausea and dizziness next
• Cigarettes deliver 2-3 mg per cigarette or 40 to 120 mg per 24 hours for typical smokers
Acetylcholine is made from Choline and Acetyl-CoA

Choline + Acetyl-CoA → Acetylcholine

Supplemental Choline

Choline O-acetyltransferase
Cytidinediphosphocholine (CDP-choline) for cognitive and behavioural disturbances associated with chronic cerebral disorders in the elderly

This version first published online: 20 April 2005 in Issue 2, 2005
*Cochrane Database of Systematic Reviews 2005, Issue 2.*

CDP-choline (cytidine 5'-diphosphocholine) is a precursor essential for the synthesis of phosphatidylcholine, one of the cell membrane components that is degraded during cerebral ischaemia to free fatty acids and free radicals. Animal studies suggest that CDP-choline may protect cell membranes by accelerating resynthesis of phospholipids. CDP-choline may also attenuate the progression of ischaemic cell damage by suppressing the release of free fatty acids. CDP-choline is the endogenous compound normally produced by the organism. When the same substance is introduced as a drug it can be called citicoline.

Due to its effects on the adrenergic and dopaminergic activity of the CNS, CDP-choline has also been used as an adjuvant in the treatment of Parkinson's disease.

*Plain language summary*
Some evidence that CDP-choline has a positive effect on memory and behaviour in at least the short/medium term in elderly people with cognitive deficits associated with chronic cerebral disorders of the brain.
Interaction of Choline with Methylation and Transsulfation

Figure 1.
Choline metabolism and links to methionine and folate metabolism. The pathways described are all present in the liver, with other tissues having one or more of these pathways. PEMT, phosphatidylethanolamine N-methyltransferase; CHDH, choline dehydrogenase; BHMT, betaine homocysteine methyltransferase; MTHFR, methylene tetrahydrofolate reductase; MTHFD, methylene tetrahydrofolate dehydrogenase.
Dose-dependent anticonvulsant effects of linoleic and alpha-linolenic polyunsaturated fatty acids on pentylenetetrazol induced seizures in rats.


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PURPOSE: Linoleic and alpha-linolenic polyunsaturated fatty acids, derived from plant oils, have been reported to reduce neuronal excitability ex vivo and in cell culture. The evidence derived from animal seizure models, however, has been contradictory. The goal of the present study was to assess the dose-dependent anticonvulsant effects of a fatty acid mixture containing linoleic and alpha-linolenic acids in a 4 to 1 ratio (the "SR-3" compound). RESULTS: Daily intraperitoneal injection of SR-3 for 21 consecutive days raised omega-3 polyunsaturated fatty acid (n-3 PUFA) composition in the unesterified fatty acid fraction of brain lipids (p < 0.05), and increased latency to seizure onset when administered at 200 mg/kg (p < 0.05), but not at 40 mg/kg (p > 0.05). CONCLUSION: Linoleic and alpha-linolenic polyunsaturated fatty acids in a 4 to 1 ratio raises n-3
The diagram illustrates the relationship between GI toxicity and COX-2 selectivity for various non-steroidal anti-inflammatory drugs (NSAIDs). It shows a spectrum from least to most GI toxicity and COX-2 selectivity.

- **GI Toxicity**:
  - Least: ibuprofen
  - Moderate: diclofenac, naproxen, indomethacin, piroxicam, ketoprofen
  - Most: ASA

- **COX-2 Selectivity**:
  - Most: rofecoxib (Vioxx)
  - Moderate: etodolac (Ultradol), meloxicam (Mobicox), celecoxib (Celebrex), diclofenac (Voltaren), piroxicam (Feldene), ibuprofen (Motrin), naproxen (Naprosyn)
  - Least: ASA, nabumetone (Relafen), indomethacin (Indocid), ketoprofen (Orudis, Orafin, Oruvail), ketorolac (Toradol)

The diagram uses a color gradient to visually represent the levels of GI toxicity and COX-2 selectivity.
Transcranial Magnetic Stimulation?
Seizure suppression by EEG-guided repetitive transcranial magnetic stimulation in the rat.


Rotenberg A, Muller P, Birnbaum D, Harrington M, Riviello JJ, Pascual-Leone A, Jensen FE.

Department of Neurology, Children's Hospital, Harvard Medical School, 300 Longwood Avenue Fegan 9, Boston, MA 02115, USA.

OBJECTIVE: To test the anticonvulsive potential of a range of repetitive transcranial magnetic stimulation (rTMS) frequencies by novel methods for simultaneous EEG and rTMS in a rat seizure model.

RESULTS: KA-induced seizures were abbreviated by 0.75 Hz (P=0.019) and 0.5 Hz (P=0.033) active EEG-guided rTMS. In contrast, neither active 0.25 Hz rTMS nor the control conditions affected seizure duration (P>0.2). CONCLUSIONS: We demonstrate that EEG-guided rTMS can suppress seizures in the rat KA epilepsy model, and that the effect is frequency dependent, with 0.75 and 0.5 Hz rTMS being superior to 0.25 Hz rTMS. SIGNIFICANCE: These data support the use of rat seizure models in translational research aimed at evaluation and development of effective rTMS anticonvulsive protocols. We also offer a proof of principle that real-time analysis of EEG can be used to guide rTMS to suppress individual seizures.
Nasal Oxytocin and Secretin

Intriguing Neuropeptides with low risk of side-effects if used in moderation
Gastrointestinal abnormalities in children with autistic disorder.


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Department of Pediatrics, University of Maryland School of Medicine, Baltimore, USA.

OBJECTIVES: Our aim was to evaluate the structure and function of the upper gastrointestinal tract in a group of patients with autism who had gastrointestinal symptoms. STUDY DESIGN: Thirty-six children (age: 5.7 +/- 2 years, mean +/- SD) with autistic disorder underwent upper gastrointestinal endoscopy with biopsies, intestinal and pancreatic enzyme analyses, and bacterial and fungal cultures. The most frequent gastrointestinal complaints were chronic diarrhea, gaseousness, and abdominal discomfort and distension. RESULTS: Histologic examination in these 36 children revealed grade I or II reflux esophagitis in 25 (69.4%), chronic gastritis in 15, and chronic duodenitis in 24. The number of Paneth's cells in the duodenal crypts was significantly elevated in autistic children compared with non-autistic control subjects. Low intestinal carbohydrate digestive enzyme activity was reported in 21 children (58.3%), although there was no abnormality found in pancreatic function. Seventy-five percent of the autistic children (27/36) had an increased pancreatico-biliary fluid output after intravenous secretin administration. Nineteen of the 21 patients with diarrhea had significantly higher fluid output than those without diarrhea.
Short report: autistic gastrointestinal and eating symptoms treated with secretin: a subtype of autism

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Abstract

Pervasive Developmental Disorders (PDD) are chronic, lifelong disorders for which there is as yet no effective cure, and medical management remains a challenge for clinicians. The current report describes two patients affected by autistic disorder with associated gastrointestinal symptoms.

They received multiple doses of intravenous secretin for a six-month period and were assessed with several specific outcome measures to evaluate drug effect.

The administration of secretin led to some significant and lasting improvement in only one case.

Gastroesophageal reflux may contribute to some of the behavioural problems and explain the effect of secretin since its suppressive effect on gastric secretion is well known. It is also true that autistic children with gastroesophageal reflux and a higher IQ could constitute a subtype which responds to secretin administration and that could be labelled as a “gastrointestinal subtype”.

http://www.cppmenthalth.com/content/1/1/24

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“It is more reasonable to suspect that long-range effects on stress adaptation response patterns will require continuous or serial administration of peptide combinations (oxytocin and secretin) over many days, in a way that more closely replicates maternal nurture mechanisms that naturally stimulate the synthesis and release of stress regulatory peptides”.

SECRETIN’S ROLE IN THE CEREBELLUM: A LARGER BIOLOGICAL CONTEXT AND IMPLICATIONS FOR DEVELOPMENTAL DISORDERS

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Departments of ¹Psychiatry and ²Anatomy, College of Physicians & Surgeons, Columbia University, and ³Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, USA
Original article

Administration of secretin for autism alters dopamine metabolism in the central nervous system

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Received 20 October 2004; received in revised form 25 May 2005, accepted 25 May 2005
Oxytocin Infusion Reduces Repetitive Behaviors in Adults with Autistic and Asperger’s Disorders

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Autism is a neurodevelopmental disorder characterized by dysfunction in three core behavioral domains: repetitive behaviors, social deficits, and language abnormalities. There is evidence that abnormalities exist in peptide systems, particularly the oxytocin system, in autism spectrum patients. Furthermore, oxytocin and the closely related peptide vasopressin are known to play a role in social and repetitive behaviors. This study examined the impact of oxytocin on repetitive behaviors in 15 adults with autism or Asperger’s disorder via randomized double-blind oxytocin and placebo challenges. The primary outcome measure was an instrument rating six repetitive behaviors: need to know, repeating, ordering, need to tell/ask, self-injury, and touching. Patients with autism spectrum disorders showed a significant reduction in repetitive behaviors following oxytocin infusion in comparison to placebo infusion. Repetitive behavior in autism spectrum disorders may be related to abnormalities in the oxytocin system, and may be partially ameliorated by synthetic oxytocin infusion.


Keywords: autism; Asperger’s disorder; oxytocin; peptide; obsessive–compulsive behaviors
“The initial vial of pitocin (10 u/ml) combined aseptically with a 1.0 l bag of normal saline was first given at a rate of 10 ml/h. The infusion was initiated at a low rate to minimize potential side effects, and the rate gradually titrated up. Specifically, the infusion rate was titrated every 15 min by 25 ml in the first hour, 50 ml in the second hour, 100 ml in the third hour, and held constant at the maximum rate of 700 ml/h during the fourth hour.”
Oxytocin Modulates Neural Circuitry for Social Cognition and Fear in Humans

The Journal of Neuroscience, December 7, 2005 • 25(49):11489 – 11493 • 11489 uppe,
Venkata S. Mattay,²,⁴ Bernd Gällhofer,¹ and Andreas Meyer-Lindenberg²,³,⁴
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Figure 1. Oxytocin effects on amygdala activation. A, Rendering on normal coronal MRI at the level of the anterior commissure (in neurological orientation: the brain left is on the viewer’s left). The response to face stimuli is on the left, and the response to scene stimuli is on the right. Top, Placebo; bottom, oxytocin. See Table 2 for statistical information. B, Significantly higher activation under placebo than oxytocin (main effect of drug condition). See Table 2 for statistical information. C, Plot of BOLD in the amygdala ROI (ANOVA; significant main effect of drug condition: $F_{(1,56)} = 4.2, p = 0.045$; main effect of task and drug-by-task interaction were not significant).
INTRAVENOUS AND INTRANASAL OXYTOCIN TARGETS SOCIAL COGNITION AND REPETITIVE BEHAVIOR DOMAINS IN AUTISM: BEHAVIORAL AND FUNCTIONAL IMAGING FINDINGS
IMFAR 2007

Methods: In the first arm of this study we tested the effect of intravenous oxytocin on prefrontal cortex and face processing circuitry activation. We subsequently tested the feasibility and therapeutic potential of intranasal oxytocin (INOT) in the treatment of the repetitive behavior and social domains in high-functioning adults with ASD in a six week, double-blind, placebo-controlled trial.

Results: Pilot data show promising results for both increased recruitment of prefrontal cortex and face processing network post infusion of oxytocin as well as improvements in repetitive behaviors and social functioning post treatment with INOT. Specifically, there is greater reduction in repetitive behaviors (YBOCS) for the INOT group compared to placebo: t(5) =4.72, p=.005. In addition, analysis of responders and non-responders based on CGI-I-Social suggested that 75% of INOT subjects were responders (CGI-I-Social = 1 or 2) vs. 33% of placebo subjects. Similarly, responders analysis of CGI-I-Global suggest 75% of INOT subjects were responders vs. 33% of placebo subjects.

Conclusion: These preliminary findings are consistent with studies linking oxytocin to social recognition and repetitive behaviors in and provide preliminary support for the use of oxytocin in the treatment of autism.
Case Report

Nimodipine Treatment of an Adolescent with Ultradian Cycling Bipolar Affective Illness

PABLO A. DAVANZO, M.D., NATALIE KRAH, M.D., JILLIAN KLEINER, M.D., and JAMES McCracken, M.D.

ABSTRACT

This is a single case report of an open trial of nimodipine, a dihydropyridine-type calcium antagonist, in the treatment of a 13-year-old boy with refractory, ultradian rapid cycling, bipolar disorder type I. Prior clinical trials with calcium channel blockers in adults with ultrarapid cycling affective disorder supported an empirical trial of nimodipine for treatment of ultradian rapid cycling in this adolescent. Severity of mania and depression were rated before and after nimodipine therapy. A marked decrease in rapid, repeated, and significant mood changes was clinically observed and measured by standardized scales after 9 days of nimodipine 180 mg daily. No adverse effects were noticed. Remission persisted with continued treatment at 36-month follow-up. Medication response was partially attributed to adjunctive therapy with levothyroxine. Implications of treatment benefit are discussed in the context of novel pharmacotherapies for refractory bipolar disorder. These findings are preliminary and do not provide sufficient basis to recommend nimodipine as the treatment of choice in adolescents with ultradian cycling bipolar disorder, but suggest that controlled studies may be indicated.
Actos = Pioglitazone

Journal of Neuroinflammation

Case study
Effect of pioglitazone treatment on behavioral symptoms in autistic children
Marvin Boris\textsuperscript{1}, Claudia C Kaiser\textsuperscript{2}, Allan Goldblatt\textsuperscript{1}, Michael W Elice\textsuperscript{1}, Stephen M Edelson\textsuperscript{3}, James B Adams\textsuperscript{4} and Douglas L Feinstein\textsuperscript{2}

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* Corresponding author

Journal of Neuroinflammation 2007, 4:3
http://www.jneuroinflammation.com/content/4/1/3
Figure 1
Effect of Pioglitazone on behavior improvement. The average (mean ± s.d.) of the total scores for the 5 subscales of the ABC was calculated for 25 patients before treatment (baseline) and after 3–4 months of treatment with Pioglitazone. *, P < .05 unpaired T-test.
Important Note: No Safety Studies in Children with Actos (Pioglitazone)

Table 1: Incidents of elevated blood values

<table>
<thead>
<tr>
<th></th>
<th>#</th>
<th>Pre⁶</th>
<th>Mid</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC¹</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Glucose²</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>AST³</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>ALT⁴,⁵</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

¹White blood cell counts, normal range 3.8 to 10.5 × 1000 cells per mcl. Values of 11.0 and 12.0 recorded. ²Glucose, normal range 70–99 mg/dl. Values of 102 and 106 recorded. ³Aspartate aminotransferase, normal range 10–40 IU/L. Values of 42, 48, and 45 recorded. ⁴Alanine aminotransferase, normal range 10–45 IU/L. Values of 56, 60, and 48 recorded. ⁵ALT and AST elevations occurred in the same three patients. ⁶Pre, pre-trial; Mid, mid-trial; Post, post-trial.
Spironolactone might be a desirable immunologic and hormonal intervention in autism spectrum disorders

James Jeffrey Bradstreet a, Scott Smith a, Doreen Granpeesheh b, Jane M. El-Dahr c, Daniel Rossignol d,*

Summary Multiple studies now demonstrate that autism is medically characterized, in part, by immune system dysregulation, including evidence of neuroglial activation and gastrointestinal inflammation. This neuroglial process has further been characterized as neuroinflammation. In addition, a subset of autistic children exhibit higher than average levels of androgens. Spironolactone is an aldosterone antagonist and potassium-sparing diuretic with a desirable safety profile. It possesses potent anti-inflammatory and immune modifying properties that might make it an excellent medical intervention for autism spectrum disorders. Furthermore, spironolactone possesses potent anti-androgen properties that might further enhance its appeal in autism, particularly in a definable subset of hyperandrogenic autistic children. One case report is briefly reviewed demonstrating objective clinical improvements in an autistic child after spironolactone administration. Additional research in controlled trials is now needed to further define the risks and benefits of spironolactone use in children with autism.

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<table>
<thead>
<tr>
<th>Clinical finding</th>
<th>Autism finding</th>
<th>Effect of spironolactone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon gamma</td>
<td>$\uparrow$ [19]</td>
<td>$\downarrow$ [55]</td>
</tr>
<tr>
<td>TNF-α</td>
<td>$\uparrow$ [24,25]</td>
<td>$\downarrow$ [54,55]</td>
</tr>
<tr>
<td>MCP-1</td>
<td>$\uparrow$ [34]</td>
<td>$\downarrow$ [54,56]</td>
</tr>
<tr>
<td>Inflammation</td>
<td>$\uparrow$ [27,34]</td>
<td>$\downarrow$ [53,55]</td>
</tr>
<tr>
<td>Oxidative stress</td>
<td>$\uparrow$ [57]</td>
<td>$\downarrow$ [62]</td>
</tr>
<tr>
<td>Testosterone effects</td>
<td>$\uparrow^a$ [5–7]</td>
<td>$\downarrow$ [59]</td>
</tr>
</tbody>
</table>

$^a$ Elevated in a subset of autistic individuals.
Figure 1: Changes in the ABC subset scores pre- and post-spironolactone at a dose of 2 mg/kg daily for 4 weeks.
Language Gains in the 1st Case

• Pre- and post-administrations of the Peabody Picture Vocabulary Test III by the same psychologist (DG) were scored independently by another psychologist employed by (DG). These demonstrated a receptive language gain of 21 months in this same four week period, indicating an increase in vocabulary greater than one standard deviation at either age level.
Spironolactone: Safety and Tolerability

- Spironolactone is also commonly prescribed as an adjunct in the treatment of precocious puberty.
- In a six year study using spironolactone in 10 boys (ages 2.3 to 5.6 years) with precocious puberty, no serious side-effects were noted despite relatively high doses of spironolactone (average 5.7 mg/kg/day).
- No Change in electrolytes were noted.
- 50% of aggressive boys had significant reduction in negative symptoms.

Spironolactone inhibits production of proinflammatory cytokines, including tumour necrosis factor-\(\alpha\) and interferon-\(\gamma\) and has potential in the treatment of arthritis


K. BENDTZEN*, P. R. HANSEN†, K. RIENECK* & THE SPIRONOLACTONE/ARTHRITIS STUDY GROUP‡ *Institute for Inflammation Research, Rigshospitalet National University Hospital, Copenhagen, Denmark, and †Department of Cardiology P, Gentofte ‡, Hellerup, Denmark
Protection by Spironolactone and Different Antidotes against Acute Organic Mercury Poisoning of Rats

Kornélia Lehotzky

State Institute of Occupational Health, Department of Applied Toxicology, Budapest
(Head: Prof. M. Timár)

Received June 20, 1974 / Accepted August 22, 1974

Summary. Investigations carried out at our laboratory have shown that BAL (dimercapto propane) can be used, with some restrictions, in the treatment of organic mercury poisoning. Depending on the radical of the poison, the antidote has a variable effect although it has no therapeutic use at all in acute intoxication with methoxy-ethyl-mercury-chloride (MEMC). Similarly, neither D-penicillamine, nor sodium-formaldehyde-sulfoxylate proved to be effective antidotes, but treatment with estrogenic hormone could protect the renal failure induced by MEMC. The life-saving effect of spironolactone (the hormonally inactive steroid) was estimated against acute poisoning induced by six different organic mercury compounds on rats. Spironolactone proved to be effective in the case of MEMC when administered prior to poisoning.
Stem Cells? NOT YET

Journal of Translational Medicine

Review

Stem Cell Therapy for Autism
Thomas E Ichim¹, Fabio Solano², Eduardo Glenn², Frank Morales², Leonard Smith², George Zabrecky³ and Neil H Riordan*¹,⁴

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Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections
7 yo boy with persistent severe OCD and ASD issues and NO signs of Strep Infection

<table>
<thead>
<tr>
<th></th>
<th>Anti-Streptolysin O</th>
<th>Immunoglobulin A</th>
<th>Immunoglobulin M</th>
<th>DNase-B Antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference range</td>
<td>&lt;= 60 titer</td>
<td>41-368 mg/dL</td>
<td>47-311 mg/dL</td>
<td>&gt;1360 titer</td>
</tr>
<tr>
<td>Pre-school</td>
<td>&lt;= 60 titer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>School</td>
<td>&lt;= 170 titer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td>&lt;= 85 titer</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections—an uncommon, but important indication for tonsillectomy

Christine Heubi, Sally R. Shott*

Department of Pediatric Otolaryngology, Cincinnati Children’s Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229, USA
Antibiotic Prophylaxis with Azithromycin or Penicillin for Childhood-Onset Neuropsychiatric Disorders

Lisa A. Snider, Lorraine Lougee, Marcia Slattery, Paul Grant, and Susan E. Swedo

**Background:** The acronym PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) describes a subgroup of children with obsessive-compulsive disorder and/or tic disorder that experience symptom exacerbations following streptococcal infections. We hypothesized that the prevention of streptococcal infections among children in the PANDAS subgroup would decrease neuropsychiatric symptom exacerbations.

**Methods:** Twenty-three subjects with PANDAS were enrolled in a double blind, randomized controlled trial. Antibiotic prophylaxis with penicillin or azithromycin was administered for 12 months. Rates of streptococcal infections and neuropsychiatric symptom exacerbations were compared between the study year and the baseline year prior to entry.

**Results:** Significant decreases in streptococcal infections during the study year were found with a mean of .1 (.3 SD) per subject, compared to the baseline year with 1.9 (1.2 SD) in the penicillin group and 2.4 (1.1 SD) in the azithromycin group [p<.01]. Significant decreases in neuropsychiatric exacerbations during the study year were also found with a mean of .5 (.5 SD) per subject in the penicillin group and .8 (.6 SD) in the azithromycin group, compared to the baseline year with 2.0 (.9 SD) in the penicillin group and 1.8 (.6 SD) in the azithromycin group [p<.01].

**Conclusions:** Penicillin and azithromycin prophylaxis were found to be effective in decreasing streptococcal infections and neuropsychiatric symptom exacerbations among children in the PANDAS subgroup.
Minocycline to Treat Childhood Regressive Autism

This study is currently recruiting participants.
Verified by National Institutes of Health Clinical Center (CC) May 2007

Sponsored by: National Institute of Mental Health (NIMH)
Information provided by: National Institutes of Health Clinical Center (CC)
ClinicalTrials.gov Identifier: NCT00409747

Purpose

There is a subgroup of children with autism that appears to develop typically for a period of time, and then loses social or language skills, or regresses. A recent study by Vargas and co-workers at Johns Hopkins has demonstrated that this regressive type of autism is associated with chronic brain inflammation as shown by an abnormal production of inflammatory cytokines among other abnormalities.

This present study will test the effectiveness of minocycline, an antibiotic with anti-inflammatory properties, in treating regressive autism. Although behavioral therapies have improved some symptoms of autism, there are no medical treatments for the disorder, and many children have ongoing behavioral difficulties. A medicine with anti-inflammatory properties may be beneficial for children with regressive autism.

This will be an open-label trial, meaning all children in this study will receive minocycline. They will also receive vitamin B6 to reduce the possible chance of side effects of the minocycline.

Children ages 3 to 12 with regressive autism may be eligible for this study. The children will take minocycline and...
Rilutek = Riluzole

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Riluzole to Treat Childhood Obsessive-Compulsive Disorder

This study is currently recruiting participants.

Verified by National Institute of Health Clinical Center (CC) June 2007

Sponsored by: National Institute of Mental Health (NIMH)
Information provided by: National Institutes of Health Clinical Center (CC)
ClinicalTrials.gov Identifier: NCT002511303

Purpose

SUMMARY: This research study will examine the effectiveness of riluzole for treating Obsessive-Compulsive Disorder (OCD).

Riluzole reduces the activity of glutamate, a neurotransmitter involved in the brain circuitry affected in OCD. Riluzole is not related to the selective serotonin reuptake inhibitors (SSRIs) or to the tricyclic antidepressants.

Children and adolescents ages 7 to 17 with

1. Obsessive Compulsive Disorder (OCD), or
2. Autism Spectrum Disorder and OCD

whose OCD symptoms have not been well controlled with standard OCD medications may be eligible for this study. They will not change their current medicines during this study, and they will not engage in cognitive-behavioral therapy during this study.

Done
Heavy Metal Detoxification
Stop Exposure

Requires Expert Medical Supervision, Informed Consent, a Logical Toxicological Exposure History, Appropriate Lab Data, Good Renal Function, Compatible Physical Findings, and Proper Micronutrient Support.
Glutathione, oxidative stress and neurodegeneration

Jörg B. Schulz, Jörg Lindenau, Jan Seyfried and Johannes Dichgans

Neurodegeneration Laboratory, Department of Neurology, University of Tübingen, Germany
Letter to the Editor

Metabolic Endophenotype and Related Genotypes are Associated With Oxidative Stress in Children With Autism

S. Jill James,1,5 Stepan Melnyk,1 Stefanie Jernigan,1 Mario A. Cleves,1 Charles H. Halsted,2 Donna H. Wong,2 Paul Cutler,3 Kenneth Bock,4 Marvin Boris,5 J. Jeffrey Bradstreet1,5,8 Sidney M. Baker,4 and David W. Gaylor8

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6International Child Development Resource Center, Hibiscus Bldg, Melbourne, Florida
7Sag Harbor, New York, New York
8Department of Biostatistics, Arkansas Children’s Hospital Research Institute, Little Rock, Arkansas

TABLE II. Transmethylation and Transsulfuration Metabolites in Autistic Cases and Controls

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Control(^a) (n = 73)</th>
<th>Autistic(^a) (n = 80)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methionine (µmol/L)</td>
<td>28.0 ± 6.5</td>
<td>20.6 ± 5.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SAM (nmol/L)</td>
<td>93.8 ± 18</td>
<td>84.3 ± 11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SAH (µmol/L)</td>
<td>18.8 ± 4.5</td>
<td>23.3 ± 7.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SAM/SAH ratio</td>
<td>5.5 ± 2.8</td>
<td>4.0 ± 1.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adenosine (µmol/L)</td>
<td>0.19 ± 0.13</td>
<td>0.28 ± 0.13</td>
<td>0.001</td>
</tr>
<tr>
<td>Homocysteine (µmol/L)</td>
<td>6.0 ± 1.3</td>
<td>5.7 ± 1.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Cystathionine (µmol/L)</td>
<td>0.19 ± 0.1</td>
<td>0.24 ± 0.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cysteine (µmol/L)</td>
<td>207 ± 22</td>
<td>165 ± 14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cysteinylglycine (µmol/L)</td>
<td>39.4 ± 7.3</td>
<td>38.9 ± 11</td>
<td>0.78</td>
</tr>
<tr>
<td>Total GSH (µmol/L)</td>
<td>7.53 ± 1.7</td>
<td>5.1 ± 1.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Free GSH (µmol/L)</td>
<td>2.2 ± 0.9</td>
<td>1.4 ± 0.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GSSG (µmol/L)</td>
<td>0.24 ± 0.1</td>
<td>0.40 ± 0.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total GSH/GSSG ratio</td>
<td>28.2 ± 7.0</td>
<td>14.7 ± 6.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Free GSH/GSSG ratio</td>
<td>7.9 ± 3.5</td>
<td>4.9 ± 2.2</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine; GSH, glutathione; GSSG, glutathione disulfide. \(^a\)Means ± SD.
The failure to maintain GSH/GSSG redox balance and to resolve acute inflammatory stress promotes a self-perpetuating cycle of chronic inflammation.
The atypical molecule precoproporphyrin, a specific indicator of heavy metal toxicity, was also elevated in autistic disorder, N=106 (p<0.001) but not significantly in Asperger’s N=11. A subgroup with autistic disorder was treated with oral dimercaptosuccinic acid (DMSA) N= 11, with a view to heavy metal removal. There was a significant (p=0.002) drop in urinary porphyrin excretion following DMSA. These data implicate environmental heavy metal toxicity in childhood autistic disorder.
Succimer Chelation Improves Learning, Attention, and Arousal Regulation in Lead-Exposed Rats but Produces Lasting Cognitive Impairment in the Absence of Lead Exposure

Diane E. Stangle, Donald R. Smith, Stephane A. Beaudin, Myla S. Strawderman, David A. Levitsky, and Barbara J. Strupp

1Department of Psychology, Cornell University, Ithaca, New York, USA; 2Department of Environmental Toxicology, University of California, Santa Cruz, California, USA; 3Division of Nutritional Sciences, Cornell University, Ithaca, New York, USA

BACKGROUND: There is growing pressure for clinicians to prescribe chelation therapy at only slightly elevated blood lead levels. However, very few studies have evaluated whether chelation improves cognitive outcomes in Pb-exposed children, or whether these agents have adverse effects that may affect brain development in the absence of Pb exposure.

OBJECTIVES: The present study was designed to answer these questions, using a rodent model of early childhood Pb exposure and treatment with succimer, a widely used chelating agent for the treatment of Pb poisoning.

RESULTS: Pb exposure produced lasting impairments in learning, attention, inhibitory control, and arousal regulation, paralleling the areas of dysfunction seen in Pb-exposed children. Succimer treatment of the Pb-exposed rats significantly improved learning, attention, and arousal regulation, although the efficacy of the treatment varied as a function of the Pb exposure level and the specific functional deficit. In contrast, succimer treatment of rats not previously exposed to Pb produced lasting and pervasive cognitive and affective dysfunction comparable in magnitude to that produced by the higher Pb exposure regimen.

CONCLUSIONS: These are the first data, to our knowledge, to show that treatment with any chelating agent can alleviate cognitive deficits due to Pb exposure. These findings suggest that it may be possible to identify a succimer treatment protocol that improves cognitive outcomes in Pb-exposed children. However, they also suggest that succimer treatment should be strongly discouraged for children who do not have elevated tissue levels of Pb or other heavy metals.
Arsenic induced oxidative stress and the role of antioxidant supplementation during chelation: a review.


Flora SJ, Bhadauria S, Kannan GM, Singh N.
Department of Pharmacology and Toxicology, Defence Research and Development Establishment, Jhansi Road, Gwalior-474 002, India.

Chelation therapy with chelating agents like British Anti Lewisite (BAL), sodium 2,3-dimercaptopropane 1-sulfonate (DMPS), meso 2,3 dimercaptosuccinic acid (DMSA) etc., is considered to be the best known treatment against arsenic poisoning. The treatment with these chelating agents however is compromised with certain serious drawbacks/side effects. The studies show that supplementation of antioxidants along with a chelating agent prove to be a better treatment regimen. This review attempts to provide the readers with a comprehensive account of recent developments in the research on arsenic poisoning particularly the role of oxidative stress/free radicals in the toxic manifestation, an update about the recent strategies for the treatment with chelating agents and a possible beneficial role of antioxidants supplementation to achieve the optimum effects.
A comprehensive approach to treating autism and attention-deficit hyperactivity disorder: a prepiilot study.


Patel K, Curtis LT.

Environmental Health Center, Buffalo, NY., Department of Pediatrics, State University of New York, Buffalo, NY 14225, USA. aehcwny@Juno.com

OBJECTIVES: The purpose of this study was to observe the effects of a multidimensional treatment plan involving nutrition, environmental control, chelation, and behavioral/educational/physical/speech therapy to treat children with autistic spectrum disorder and attention-deficit hyperactivity (ADHD) disorder. This study is only a preliminary study, and its small size (10 patients) precludes statistical analysis of simultaneous multiple modal treatment regimes. DESIGN: This was an open-label observational study.

SETTINGS/LOCATION/SUBJECTS: This study examined 10 children aged 4-10 years old who had been diagnosed with both autistic spectrum disorder and ADHD by outside physicians or psychologists. These 10 children presented consecutively in an environmental medicine clinic in Buffalo, New York. The children were given comprehensive nutritional/environmental/chelation treatment for 3 to 6 months in addition to their usual behavioral, educational, speech, and physical therapies. Outcome measures: Study outcomes were measured by objective/subjective improvement as judged by physicians/parents/teachers. Outcomes were also measured by changes in urinary heavy metal burdens over time. RESULTS: All 10 children showed significant improvement in many areas of social interaction, concentration, writing, language, and behavior. Urinary lead burden dropped significantly in all 10 children.
Effects of 2,3-dimercapto-1-propanesulfonic acid (DMPS) on methylmercury-induced locomotor deficits and cerebellar toxicity in mice.


Departamento de Biologia Celular, Embriologia e Genética, Centro de Ciências Biológicas, Universidade Federal de Santa Catarina, Florianópolis, SC, Brazil.

Chelating therapy has been reported as a useful approach for counteracting mercurial toxicity. Moreover, 2,3-dimercapto-1-propanesulfonic acid (DMPS), a tissue-permeable metal chelator, was found to increase urinary mercury excretion and decrease mercury content in rat brain after methylmercury (MeHg) exposure. We evaluated the capability of DMPS to reduce MeHg-induced motor impairment and cerebellar toxicity in adult mice. Animals were exposed to MeHg (40 mg/L in drinking water, ad libitum) during 17 days. In the last 3 days of exposure (days 15-17), animals received DMPS injections (150 mg/kg, i.p.; once a day) in order to reverse MeHg-induced neurotoxicity. Histological analyses for quantifying cellular damage and mercury deposition in the cerebellum were also performed. MeHg exposure induced a significant motor deficit, observed as decreased locomotor activity in the open field and decreased falling latency in the rotarod apparatus. DMPS treatment displayed an ameliorative effect toward such behavioral parameters. Cerebellar glutathione and protein thiol levels were not changed by MeHg or DMPS treatment. Conversely, the levels of cerebellar thiobarbituric acid reactive substances (TBARS), a marker for lipid peroxidation, were increased in MeHg-exposed mice and DMPS administration minimized such phenomenon. Cerebellar glutathione peroxidase activity was decreased in the MeHg-exposed animals, but DMPS treatment did not prevent such event. Histological analyses showed a reduced number of cerebellar Purkinje cells in MeHg-treated mice and this phenomenon was completely reversed by DMPS treatment. A marked mercury deposition in the cerebellar cortex was observed in MeHg-exposed animals (granular layer>Purkinje cells>molecular layer) and DMPS treatment displayed a significant ameliorative effect toward these phenomena. These findings indicate that DMPS displays beneficial effects on reversing MeHg-induced motor deficits and cerebellar damage in mice. Histological analyses indicate that these phenomena are related to its capability of removing mercury from cerebellar cortex.
Molecular Interactions with Mercury in the Kidney

RUDOLFS K. ZALUPS

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Common Chelators in Use: All are off-label uses unless specific toxic criteria met

- **DMSA**: (Succimer) FDA approved for children with lead intoxication. Only 20% absorbed orally. No IV form. Suppositories well tolerated.

- **DMPS**: (Dimaval) Not licensed in the US, but available legally via compounding pharmacies. More reactive than DMSA. IV form available. 50% absorbed orally. Suppositories well tolerated and effective. Considered better Hg chelator.

- **CaNa2 EDTA**: (Calcium Disodium Edetate) Licensed for Lead. Poorly absorbed orally. IV or Suppository.

- **D-Penicillamine**: 5-15 mg/kg per day – issues with safety. Check CBC and LFTs frequently – rashes – allergy. INTERESTING: also used in autoimmune disease.
Potential Side-Effects of Heavy Metal Chelators: Generally Well Tolerated Clinical Studies

- Depletion of micronutrients
- Adverse GI issues: colicky pain, gastritis, worsening of dysbiosis
- Allergy
- Rashes
- Behavioral Changes
- Anaphylaxis
Urticaria: D- Pen plus Fluconazole after Varicella Infection
Chelation of Lead with D-Penicillamine

Penicillamine has been used to chelate toxic metals including copper (in Wilson's disease) as well as lead, mercury, and arsenic. It has been approved by the FDA for treatment of Wilson's disease, cystinosis, and rheumatoid arthritis but not for lead poisoning, primarily to avoid its misuse in the workplace. Nevertheless, a substantial body of experimental and clinical data exists regarding the pharmacology and utility of penicillamine in both adult and childhood lead poisoning.

*THE ONLY CHELATOR THAT READILY CROSSES THE BLOOD BRAIN BARRIER

Dose 5-15 mg/kg/day oral medication.

Precaution PENICILLIN ALLERGY
Adverse Effects of Reduced-Dose d-Penicillamine in Children with Mild-to-Moderate Lead Poisoning

Michael W Shannon and Meaghan Kennedy Townsend

BACKGROUND: Oral chelation therapy with d-penicillamine (d-PCN) has been proven to be effective in the treatment of mild-to-moderate lead poisoning. However, d-PCN is associated with a relatively high incidence of adverse effects when given in the standard dose of 25–30 mg/kg/d. Lower doses of d-PCN may reduce the rate of adverse effects without a significant reduction in the drug’s efficacy.

OBJECTIVE: To examine the incidence of rash, white blood cell and platelet count depression, and abnormal urinalysis with d-PCN when given in a dose of 15 mg/kg/d to children with blood lead concentrations <40 µg/dL.

METHODS: Retrospective analysis of a clinical treatment course of children who received d-PCN during 1996 in the Lead and Toxicology Clinic of Children's Hospital, Boston. All children were treated under a reduced-dose d-PCN chelation protocol.

RESULTS: During the study period, 55 children (mean age 37.4 mo) received 66 courses of d-PCN. Mean blood lead concentration before chelation was 24 µg/dL (range 15–37), with a corresponding erythrocyte protoporphyrin concentration of 42 µg/dL. After 77 days of treatment with d-PCN, blood lead concentration was reduced to mean 16 µg/dL (mean fall 35%; p = 0.006) and erythrocyte protoporphyrin was reduced to 28 µg/dL (p = 0.006). During chelation therapy, the white blood cell count fell below 5000/mm³ in seven cases (9.7%); there were no episodes of platelet counts falling below 150 000/mm³. No cases of abnormal urinalysis were reported; three episodes of rash (4.5%) were recorded. The only patients prematurely terminated from therapy were those who developed rash; in all three cases, drug eruptions were an isolated occurrence, which resolved within 48 hours of diphenhydramine therapy. All adverse effects were transient and resolved during or immediately after chelation therapy.

CONCLUSIONS: Reduced-dose d-PCN appears to maintain efficacy at reducing blood lead concentrations. Reduced-dose d-PCN also appears to be associated with a rate of adverse effects lower than previously reported; observed adverse effects appear to be benign and transient.

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CASE REPORT

A Child with Elemental Mercury Poisoning and Unusual Brain MRI Findings

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Pre and Post 9 months of oral D-Penicillamine

FIG. 2. Upper and Lower, T2-weighted MRI of patient, 9 months after Chelation therapy. Images reveal improvement of the previous lesions.
The toxicity pattern of D-penicillamine therapy. A guide to its use in rheumatoid arthritis.

Kean WF, et al

One hundred and one patients with rheumatoid arthritis were followed prospectively to assess the efficacy and toxicity of therapy with D-penicillamine. After a mean total followup of 11.5 months (38 patients have completed 2 years of followup) there was a 70% overall improvement rate with 2 complete remissions. Sixty-one patients developed 84 separate toxic reactions, 36 of which required drug withdrawal. Skin rashes (27/84), proteinuria (15/84), low platelets (14/84), and taste abnormalities (10/84) were the most common side effects of therapy at a mean D-penicillamine dose of 463 mg/day. The majority of toxic reactions (85%) occurred in the first 6 months, but proteinuria and thrombocytopenia were more common in the 6 to 12 month treatment period. Previous gold toxicity was a risk factor for developing D-penicillamine toxicity (10/13). Our observations suggest that D-penicillamine related toxicity is a major problem even at 500 mg/day, but the drug can be used with an increased safety margin after 9 months of continuous therapy.
D-Penicillamine

- Sulfur Amino Acid Side-Chain of Penicillin
- Similar to Cysteine > Crosses BBB
- Minor risk of allergy if PCN Allergy
- 5-15 mg per kg per day max dose.
- Must be aware of copper losses during chelation and monitor
- Supplement copper at 2 x RDA on D-Pen days
- Supplement Zinc
- Monitor CBC for white count and platelets, check LFTs at least every 2 months.
• CaDisodium EDTA: our dose is lower than many but our side-effects are also minimal. We limit it to 10mg/kg per dose but can dose up to 3 x weekly in serious cases. Some Docs use up to 50mg/kg.
• Preload with 2000 to 4000 mg of Vit C and usually 600 -1200 mg of reduced GSH.
• Be ready for rare but serious anaphylatoid reactions.
Deaths Resulting From Hypocalcemia After Administration of Edetate Disodium: 2003-2005

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ABSTRACT

From 2003 to 2005, deaths of 3 individuals as a result of cardiac arrest caused by hypocalcemia during chelation therapy were reported to the Centers for Disease Control and Prevention. Two were children, both of whom were treated with edetate disodium. At the time of this writing, the adult case was still under investigation. No previous cases of death resulting from hypocalcemia during chelation have been reported. From our experience and review of the literature, we suggest that health care providers who are unfamiliar with chelation consult an expert before undertaking treatment and that hospital formularies evaluate whether stocking edetate disodium is necessary, given the risk for hypocalcemia and the availability of less toxic alternatives.
DMPS and “Bella”

- The literature finds little serious side-effects at dose under 3mg/kg per day.
- We limit out dose to 2mg/kg per dose.
- Usual follows IV Vit C, NAC and rGSH.
- Special: we have observed both excellent chelation and often remarkable clinical response to what we call the “Bella” protocol = Vit C w/GSH/NAC > CaEDTA > DMPS
- With HBOT and anti-inflammatory???
A Study of N-Acetyl Cysteine in Children with Autism

The purpose of the study is to test the tolerability and efficacy of N-Acetyl Cysteine (NAC) in children with Autism. NAC is a compound that increases the levels of Glutathione, the body's main antioxidant. Glutathione is a compound in the blood that is part of a natural defense system (the antioxidant system). Anti-oxidants protect the body from damage caused by internal toxins called "free radicals." It is possible that children with Autism tend to have lower levels of glutathione, an important compound in our bodies that helps combat the effects of toxic "free radicals." We hope that by studying the antioxidant system in more detail, we will increase our understanding of the reasons why people develop Autism so that we can design better ways to treat individuals with this condition. This study is meant to test the safety tolerability of NAC and its effectiveness in the treatment of behavioral difficulties in children with autism. It will also examine the possible benefit of this agent in improving the core deficits in autism such as social deficits.

Recruiting Status: Recruiting

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DMSA (Beware of Cysteine)

• Typically given via oral administration.
• Check G6PD levels 1st > risk of Hemolytic Anemia
• Poor PO absorption ~ 20%
• Significant GI side-effects and dysbiosis issues
• Suppository administration may obviate the GI issues to a large extent.
• Dose up to 30mg/kg per suppository Q 3 days or 10mg/kg PO TID for up to 15 days then need a break.
• Seems to correct GSH def and benefit ASD Sx (Adams et al 2008 pre pub)
Suppository DMPS & CaEDTA

• Relatively well absorbed for DMPS ~ 50% PO and we see good effects Supp
• CaEDTA ~ 2% oral absorption (not effective) better – seemingly when given via supp
• Same rules apply to replacement of nutritional minerals: Mg, Zn, Cu, Se, are the most significantly affected by chelation.
Summary

• Reconsider your clinical impression and alternate views of pathophysiology
• Poor compliance with your plan is one likely cause of poor response.
• Recheck your biomarkers and look for additional ones.
• Consider Lab Error – repeat as needed to be sure.
• Network with Colleagues
• Never Give Up – NEVER!