Mast Cell and Microglial Activation
Implications for ASD

Dr. Anju Usman Singh, MD, FAAFP, ABIHM, Hom-C, FMAPS

Disclaimer

• Information is for educational purposes only
• Not to be taken as specific medical advice
• All medical decisions regarding health issues should be discussed with your health care provider
• Clinical trials have not been done on some treatment approaches discussed
• Ideas and concepts discussed are considered alternative theories and not standard of care yet
• Dr. Usman Singh is Medical Director of True Health Medical Center and Pure Compounding Pharmacy
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Neuroinflammation

- Neuroinflammation is widely regarded as chronic.
- Acute inflammation usually follows injury to the central nervous system immediately, and is characterized by inflammatory molecules, endothelial cell activation, platelet deposition, and tissue edema.
- Chronic inflammation is the sustained activation of glial cells, mast cells and recruitment of other immune cells into the brain.
Causes of Neuroinflammation

- Toxic metabolites
- Autoimmunity
- Allergens
- Aging
- Microbes/Infections
- Viruses
- Traumatic brain injury
- Spinal cord injury
- Air pollution
- Passive smoke
- Mycotoxins
- Stress

The Unresolved Inflammatory Response aka Chronic Inflammation

- The Innate Immune response is activated
- Mast Cells degranulate
- Microglial activated
- Glutamate is released
- Excess Excitation ensues
- Leading to
  - Dysautonomia
  - Mitochondrial dysfunction
  - Protein aggregation (hyper-coaguable state)
  - Oxidative stress
  - Abnormal neuronal connectivity (choking)

Nicolas G. Bazan, ... Ludmila Belayev, in Basic Neurochemistry 2012
Possible Symptoms of Mast Cell Activation

- Atopic or Allergic Symptoms
- Hives (urticaria), Feeting rashes, Flushing
- Angioedema
- Itching
- Nasal Congestion
- Shortness of Breath
- Chest Tightness
- Tachycardia
- High or Low Blood Pressure
- Fatigue
- Musculoskeletal Pain
- Nausea/Vomiting
- Migraine
- Difficulty concentrating
- Memory loss
- Anxiety
Various triggers cause Mast Cells to degranulate and release a variety of inflammatory cells. Mast Cells cause Microglial Activation.

- **Mast cell activators**
  - Receptor-binding agonists
  - IgE + antigen or IgE alone
  - Light chain
  - Complement
  - Neuropeptides
  - Cytokines
  - Chemokines
  - Physical activators
    - Temperature
    - Pressure
  - Cell-cell contact
    - CD40/CD40L
    - CD40L/CD40
    - TCR/MHCII

- **Mast cell molecules**
  - Preformed mediators
    - Histamine
    - Proteases
    - Serotonin
    - Heparin
    - IL-4, TNF, GM-CSF
  - T and B cell ligands
    - PD-1/L, CD40, CD80, CD86, CD95, 4-1BB
  - Newly synthesized mediators
    - Lipid derived: prostaglandins, leukotrienes
    - PAF
    - Cytokines
    - Growth factors
    - Chemokines
    - Free radicals
    - Others: substance P

**TRENDS in Neuroscience**

Acute/chronic neural injury

- Infiltration of macrophages
- Microglial activation

**NEUROINFLAMMATION**

- Mast cell
- Bacteria
- Virus

- Anti-viral effects
- Efferent clearance
- MC mediators
- IL-6
- MCP-1

- MCs are found in microglia, brain parenchyma and nerve.

- MCs activate astrocytes via CD40-CD40 ligand interaction
- Cytokines of astrocytes induce mast cell degranulation

- MCs release neurotrophic factors
- Nerve growth factor (NGF)

- Astrocyte
- Neuron
- Microglia

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Microglia release proinflammatory cells, that cause
Glutamate release from neurons,
Glutamate binds to the NMDA receptor,
Allowing Calcium to flow into cells rapidly
Excess Calcium excites the cells and causes damage to neurons
The principle excitatory receptor, the N-Methyl-D-Aspartate (NMDA) receptor, and its associated calcium (Ca\textsuperscript{2+}) permeable ion channel are activated by glutamate.
“Integrative Approach to Mast Cell/Microglial Activation”

• Dietary Interventions
  - Anti-inflammatory Diet: CF/GF/ grain-free, low glutamate, avoid excitotoxins
  - Consider low lectin diet- night shade free and legume free
  - FAILSAFE Diet
  - Antioxidant, phytonutrient, high carotenoid diet
• Treat potential underlying cause!!!!!!- Toxin, Infection, Allergen
  *Address Mast Cell Activation/Microglial Activation
  *Address Glutamate Excitation (Calcium driven)
  *Address Dysautonomia /Vagal Nerve Dysfunction
• Improve circulation and hyper-coagulation/*HBOT
• Cell Membrane Support- Omega 3’s EPA/DHA- high dose , PC, PS
  *Other Anti-inflammatory agents
    • Spices
    • Foods
    • Herbs
    • Essential Oils

Consider Mast Cell Activation with these Conditions

• ASD
• Acute Regressions
  • Seasonal Regressions
• Allergic Disorders
• Reactions to Food, Chemicals, Temperature, Stress
• Asthma
• Eczema (rashes)
• Multiple Chemical Sensitivities
• Ehlers Danlos Syndrome
Laboratory Workup Immune: Infectious Triggers

- Bacterial- Lyme, Bartonella, Babesia, Mycoplasma/Chlamydia pneumoniae, ASO Titer, AntiDNAse B Ab
- Parasitic- Toxoplasmosis Ab
- Fungal
- Viral Titers- EBV, CMV, HHV6
- Vaccine Titers- MMR, VZ
- Organic Acid Test (OATS) Clostridia
- Stool Test- bacteria, yeast, parasites

Laboratory Workup Immune: Inflammatory Markers

- CBC
- CRP, Sedimentation Rate, Platelet Count
- Fecal calprotectin, lactoferrin, lysozyme
- Oxidative Stress Markers
  - 8OH Deoxyguanosine, Lipid Peroxides, Malondialdehyde
- Total Immunoglobulin Profile
  - (total IgE, IgM, IgA, IgA and IgG subclasses)
- T Lymphocyte Panel- CD4/CD8
- Natural killer cell, CD 57
Work-Up Inflammation

Diagnosis of Inflammation

Blood

Pro-inflammatory
- IL-1β, IL-6, IL-8, IL-17, IL-33, TNF

Anti-inflammatory
- IgA, IgG, IgM
- IL-10
- TGFβ
- Alpha,-antitrypsin
- Alpha2-macroglobulin
- C1-esterase inhibitor
- Granzyme

Diagnosis of Atopic Diseases

Blood
- IgE, IgG1
- Anti-IgE receptor antibody (Basophil activation test)
- Immune IgE (RAST for alpha-gal, casein, gluten, dust mites, fungi, grass, pollen)
- Chromogranin A
- IgG1/IgG4 (Food Intolerance Panel)
- PGD2
- Tryptase

Urine 24 hours (must be kept and sent cold)
- Methylhistamine or MIA
- PGD2
- 17βPGF2α

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### Laboratory Workup Immune: Autoantibodies and Allergy

- Autoantibody tests (e.g. myelin basic protein antibodies, antidopamine Ab, antiganglioside Ab)
- Other Autoimmune Ab- NMDA, GAD65 Ab
- ANA
- Celiac Panel
- Mycotoxin Panel
- IgE RAST or skin testing for inhalants, food, mold
- IgG ELISA testing for food sensitivities

### Natural Agents to Decrease Microglial Activation

- Resveratol- neuroprotective
- Pycnogenol- antioxidant
- Gastrodia elata- brain injury neuroprotective
- Pipera kadsura (Japanese pepper)- PGE2 inhibitor
- Ganoderma lucidum (Reishi Mushroom)- immune modulatory
- Epimedium brevicornum (Horny Goat Weed)- improves blood flow
- Fisetin- anti aging
- PQQ (pyrroloquinoline quinone)- PGE2 and COX-2 inhibitor
Natural Agents to Decrease Microglial Activation

- Luteolin - mast cell stabilizer
- PEA (palmityl ethanolamide)
- Resveratol - neuroprotective
- Pycnogenol - antioxidant
- Gastrodia elata - brain injury neuroprotective
- Pipera kadsura (Japanese pepper) - PGE2 inhibitor
- Ganoderma lucidum (Reishi Mushroom) - immune modulatory
- Epimedium brevicornum (Horny Goat Weed) - improves blood flow
- Stephania tetrandra - Ca channel blocker
- Fisetin - anti-aging
- Benfotiamine/Biotin
- Vinpocetine - PDE inhibitor, Ca regulation
- PQQ (pyrroloquinoline quinone) - PGE2 and COX-2 inhibitor
Stress and the Autonomic Nervous System

Published online 2010 May 21. doi: [10.1073/pnas.1005139107]
PMCID: PMC2899043
PMID: 20496091

Vinpocetine as a potent antiinflammatory agent
Alexandre E. Medina

Chronic inflammatory processes are related to conditions as distinct as atherosclerosis, amyotrophic lateral sclerosis, asthma, systemic lupus, Alzheimer’s disease, and Parkinson’s disease. The continuous use of antiinflammatory agents is required to treat these conditions. However, the long-term use of these drugs creates an additional challenge: the high frequency of severe side effects. For instance, the long-term use of corticosteroids and cyclooxygenase (COX) inhibitors can dramatically increase the risk for cardiovascular problems and diabetes (1). Currently, there are great efforts to discover antiinflammatory drugs that can be used for long periods with minimal side effects. In PNAS, Jeon et al. (2) show that vinpocetine, a phosphodiesterase (PDE) inhibitor known for its minimal side effects (3–4) and great potential in cognitive enhancement (5–8), also has potent antiinflammatory action. Surprisingly, the anti-inflammatory action of vinpocetine is caused by a direct inhibition of the IκB kinase complex (IKK) rather than PDE blockade.

Pyrroloquinoline quinone (PQQ) inhibits lipopolysaccharide induced inflammation in part via downregulated NF-κB and p38/JNK activation in microglial and attenuates microglia activation in lipopolysaccharide treatment mice.
Yong C1, Xu J1, Kang S2, Ma G2, Zhang J3, Zhu G1, Zhu J1, He D2.

Abstract
Therapeutic strategies designed to inhibit the activation of microglia may lead to significant advancement in the treatment of most neurodegenerative diseases. Pyrroloquinoline quinone (PQQ) is a naturally occurring redox cofactor that acts as an essential nutrient, antioxidant, and has been reported to exert potent immunosuppressive effects. In the present study, the anti-inflammatory effects of PQQ were investigated in LPS treated primary microglial cells. Our observations showed that pretreatment with PQQ significantly inhibited the production of NO and PGE2 and suppressed the expression of pro-inflammatory mediators such as iNOS, COX-2, TNF-α, IL-1β, IL-6, MCP-1 and MIP-1α in LPS treated primary microglial cells. The nuclear translocation of NF-κB and the phosphorylation level of p38, pJNK and JNK MAPK kinase pathways were also inhibited by PQQ in LPS stimulated primary microglial cells. Further a systemic LPS treatment acute inflammation murine brain model was used to study the suppressive effects of PQQ against neuroinflammation in vivo. Mice treated with PQQ demonstrated marked attenuation of neuroinflammation based on Western blotting and immunohistochemistry analysis of IκBα against antibody in the brain tissue. Indicated that PQQ protected primary cortical neurons against microglia-mediated neurotoxicity. These results collectively suggested that PQQ might be a promising therapeutic agent for alleviating the progress of neurodegenerative diseases associated with microglia activation.

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Benfotiamine attenuates inflammatory response in LPS stimulated BV-2 microglia.

Abstract

Microglial cells are resident immune cells of the central nervous system (CNS), recognized as key elements in the regulation of neural homeostasis and the response to injury and repair. As excessive activation of microglia may lead to neurodegeneration, therapeutic strategies targeting its inhibition were shown to improve treatment of most neurodegenerative diseases. Benfotiamine is a synthetic vitamin B1 (thiamine) derivative exhibiting potentially anti-inflammatory effects. Despite the encouraging results regarding benfotiamine potential to alleviate diabetic microangiopathy, neuropathy and other oxidative stress-induced pathological conditions, its activity and cellular mechanisms during microglial activation have yet to be elucidated. In the present study, the anti-inflammatory effects of benfotiamine were investigated in lipopolysaccharide (LPS)-stimulated murine BV-2 microglia. We determined that benfotiamine remediates activated microglia to acquire the shape that is characteristic of non-stimulated BV-2 cells. In addition, benfotiamine significantly decreased production of pro-inflammatory mediators such as inducible form of nitric oxide synthase (iNOS) and NO-cyclooxygenase-2 (COX-2), heat-shock protein 70 (Hsp70), tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), whereas it increased anti-inflammatory interleukin-10 (IL-10) production in LPS stimulated BV-2 microglia. Moreover, benfotiamine suppressed the phosphorylation of extracellular signal-regulated kinases 1/2 (ERK1/2), c-Jun N-terminal kinase (JNK) and protein kinase B Akt/PKB. Treatment with specific inhibitors revealed that benfotiamine-mediated suppression of NO production was via JNK1/2 and Akt pathway, while the cytokine suppression includes ERK1/2, JNK1/2 and Akt pathways. Finally, the potentially protective effect is mediated by the suppression of translocation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) in the nucleus. Therefore, benfotiamine may have therapeutic potential for neurodegenerative diseases by inhibiting inflammatory mediators and enhancing anti-inflammatory factor production in activated microglia.

PMID: 23060433  PMCID: PMC4330065  DOI: 10.1371/journal.pone.0118372

Regulation of immunological and inflammatory functions by biotin.

Abstract

Biotin is a water-soluble B-complex vitamin and is well-known as a co-factor for 5-indispensable carboxylases. Homo- and carboxylase synthase (HCS), catalyzes the transamination of carboxylases and other proteins, whereas biotinidase catalyzes the release of biotin from biotinylated peptides. Previous studies have reported that nutritional biotin deficiency and genetic defects in either HCS or biotinidase induce cutaneous inflammation and immunological disorders. Since biotin-dependent carboxylases involve various cellular metabolic pathways including gluconeogenesis, fatty acid synthesis, and the metabolism of branched chain amino acids and odd-chain fatty acids, metabolic abnormalities may play important roles in immunological and inflammatory disorders caused by biotin deficiency. Transcriptional factors, including NF-κB and Sp1/3, are also affected by the status of biotin, indicating that biotin regulates immunological and inflammatory functions independently of biotin-dependent carboxylases. An in-vivo analysis with a murine model revealed the therapeutic effects of biotin supplementation on arthritis. The novel roles of biotinylated proteins and their related enzymes have recently been reported. Non-carboxylase biotinylated proteins induce cytokine production. HCS is a nuclear protein involved in epigenetic and chromatin regulation. In this review, comprehensive knowledge on the regulation of immunological and inflammatory functions by biotin and its potential as a therapeutic agent is discussed.
Stress and the Autonomic Nervous System

Icarin, a major constituent of flavonoids from Epimedium brevicornum, protects against cognitive deficits induced by chronic brain hypoperfusion via its anti-amylloidogenic effect in rats.

Natural and Pharmaceutical Agents for Mast Cell Activation

- Stinging Nettles
- Quercetin
- Luteolin- mast cell stabilizer, anti IL-6
- PEA (palmityl ethanolamide)
- Black Cumin Seed Oil
- NRF2 signaler /Antioxidants: sulforaphane, DIM, EGCG
- H1 blockers: diphenhydramine, chlorpheniramine, cyproheptadine, hydroxyzine
- H2 blockers: ranitidine, cimetidine, famotidine
- Mast Cell Stabilizers: ketotifen, rupatadine, cromolyn sodium

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Avoid Dietary Excitotoxins

- Caffeine
- MSG
- NutraSweet
- Red/yellow food dyes
- Nitrites
- Sulfites
- Glutamates
- Propionates
- Benzoates
- Limit intake of phenolics (apples, grapes, bananas, strawberries,...)
Limit Dietary Glutamate

• Glutamate
  • Monosodium Glutamate (MSG)
  • Hydrolyzed Protein
  • Modified Food Starch
  • Natural Flavors
  • Peas, Mushrooms, Tomatoes
  • Parmesan Cheese
  • Excess Protein

Glutamate Modulators

• Magnesium
• P5P
• Lithium
• Leucine
• Isoleucine
• Lysine
• L-Theanine
• Taurine
• Hypotaurine
• Oxaloacetate
• GABA
• PQQ
• Memantine/Namenda Rx
• Dextromethorphan/Nudexta Rx
Glutamate Modulators

- Calcium Modulation
  - Vitamin D3
  - Vitamin K2
  - Vinpocetine
  - Stephania tetranda

- Herbs
  - Gingko biloba
  - Silymarin
  - Rosemary
  - Lemon Balm
  - Chamomile
  - Skull Cap
  - Bacopa
  - Pycnogenol

Address Dysautonomia

Down-regulate Sympathetic
- Adaptogenic Herbs- Ginseng, Ashwaganda, Bacopa, Tulsi
- Beta Blockers- Propranolol
- Alpha 2 adenoreceptor agonists- Clonidine, Guafacine
- NMDA receptor antagonists- Memantine, Dextromethorphan
- Upregulate inhibitory neurotransmitters- GABA, L-theanine, Taurine, Glycine
- Benfotiamine

Up-regulate Parasympathetic
- Acetylcholine (phosphatidylcholine, phosphatidylserine)
- Acetylcholinesterase Inhibitors (galantamine, huperzine A, piracetam)
- Vagus Nerve Stimulation (TENS unit)

Address Gut Issues- especially SIBO
- Nemecheck Protocol
The Polyvagal Theory:
Phylogenetic Contributions to Social Behavior
Stephen W. Porges

New conceptualization of the role of Vagus

- Vagal regulation of heart rate and heart rate variability
- Vagal brake = modulates the visceral state
  - enables the individual to rapidly engage and disengage with objects and other individuals and to promote self-soothing behaviors and calm behavioral states
  - The vagal brake is obviously compromised in autism.

Polyvagal Theory Cont’d

- The Vagus is involved in the regulation of the HPA axis.
- Vagal afferents exhibit an inhibitory influence on HPA axis and reduce cortisol secretion.
- The afferent Vagus mediates behavioral depression.
- Vagus nerve and Acetylcholine help to mediate gastrointestinal inflammation.
- Loss of vagal tone to the heart causes increased sympathetic tone and release of cortisol. High cortisol causes suppressed immune function.
Adaptogens

- Panax Ginseng
- Siberian Ginseng
- Holy Basil
- Licorice/Glycyrrhizin
- Rhodiola rosea
- Ashwaganda
- Bacopa
- Gotu Kola
- Moringa oleifera
- Schisandra

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

Why Use Herbal Medicine?

http://naturehacks.com/3-common-mistakes-made-when-taking-herbal-remedies/
Medicinal Herbs

- Used traditionally by all cultures for healing
- Complex structures
- Numerous qualities
- Multiple components
- Available as dried herb, tinctures, decoction, oils
- Can be eaten in foods or as teas
- Careful with drug and vitamin interactions
- Careful with phenol and oxalate issues
- I recommend to rotate and pulse when using long term
- Many drugs today are originally derived from herbs
Licorice/Glycyrrhizin

- Prevents breakdown of cortisol to cortisone
- Increases half life of cortisol
- Selective estrogen receptor modulator
- Immune
  - Antiviral
  - Isoflavinoid: antimicrobial, antifungal
- Prevent ulcer formation
- Stimulates healing of mucosa

Holy Basil (Tulsi)

- Adaptogenic herb
- Antianxiety
- Blood sugar regulation
- Antibacterial, antiviral
- Anti-inflammatory
- Helps with headaches
- Reduces fever
- Good source of Vitamin K
- Active compounds: eugenol, rosmarinic acid, apigenin, myretenal, luteolin, β-sitosterol, and carnosic acid
Ashwaganda
Withania somnifera

- Anti-inflammatory
- Antitumor
- Antistress
  - Modulates cortisol
- Exercise intolerance
- Fatigue
- Antioxidant
  - Brain lipid peroxidation
- Immunomodulatory
  - Mobilization and activation of peritoneal n of the lysosomal enzymes
- Hemopoetic


Buhner Herbs (anti-inflammatory)

- Polygonum cuspidatum (Japanese Knotweed) – protects the endothelial lining
- Scutellaria baicalensis (Chinese Skullcap)- inhibits cytokine cascade
- Salvia miltiorrhiza (Red Sage/Danshen)- inhibits cytokine cascade
- Immune Modulators
  - Cordyceps
  - Reishi
  - Rhodiola
  - Scutellaria baicalensis (Chinese Skullcap)
  - Unicaria tomentosa (Cat’s claw)
  - Eleutherococcus senticosus (Siberian Ginseng)
  - Withania somnifera (Ashwaganda)
Effect of Propranolol on Verbal Problem Solving in Autism Spectrum

Neurocase: The Neural Basis of Cognition 2008, Beversdorf

• Drugs decreasing noradrenergic activity are beneficial in ASD.
• Beneficial for difficult network flexibility-dependent problems.
• Benefits performance for simple problems.
• Decreased flexibility of access to networks in ASD.
• ASD subjects benefited from propranolol on simple anagrams, whereas control subjects were impaired by propranolol.

A Prospective, Open-Label Trial of Galantamine in Autistic Disorder

Dr. Rob Nicolson, Beth Craven-Thuss, and Judy Smith. Journal of Child and Adolescent Psychopharmacology

• Thirteen children with autism (mean age, 8.8 ± 3.5 years) participated in a 12-week, open-label trial of galantamine.
• Results: Patients showed a significant reduction in parent-rated irritability and social withdrawal on the ABC.
• Significant improvements in emotional lability and inattention on the Conners’ Parent Rating Scale—Revised.
• Clinician ratings showed reductions in the anger subscale.
• 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.

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Phosphadityl Serine

- Lowers cortisol
- Increases cellular metabolism
- Antioxidant
- Improves mood
- Improves motivation
- Decreases anxiety
- Improves memory and cognition
- Prevents hippocampal damage from high cortisol

Phosphatidyl Serine

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

Hyperbaric Oxygen Reduces Neuroinflammation

Hyperbaric Oxygen Alleviates the Inflammatory Response Induced by LPS Through Inhibition of NF-κB/MAPKs-CCL2/CXCL1 Signaling Pathway in Cultured Astrocytes.

Abstract
The purpose of this study was to investigate the inhibitory mechanisms of hyperbaric oxygen therapy (HBOT). Primary astrocytes were incubated with lipopoly saccharide (LPS) after which they underwent HBOT and separate administration of inflammatory cytokine inhibitors. The respective expression of inflammatory factors was then detected. Results showed that LPS significantly induced increases in the expression levels of chemokine (C-X-C motif) ligand 1 (CXCL1), chemokine C-C motif ligand 2 (CCL2), phospho-nuclear factor-kappa B (p-NF-κB), phospho-e-NOS-Terminal kinase (p-JNK), phospho-extracellular signal-regulated kinase (p-ERK), and phospho-p38 (p-p38) in cultured astrocytes and peaked at 3 h. HBOT downregulated the expression of some inflammation mediators including CXCL1 and CCL2. Furthermore, HBOT inhibited the expression of some up-stream regulators of inflammation mediators including NF-κB, p-JNK, p-p38 (at 3 and 9 h), and p-ERK (3 h). Inhibitors of NF-κB, ERK, and JNK (BAY117082, PD98059, and SP600125) significantly suppressed the expression of CXCL1 and CCL2 that were induced by LPS for 3 h. However, the p38 inhibitor, SB203580, had no obvious effect on expression levels of CXCL1 and CCL2. In conclusion, we found that HBOT inhibits neuroinflammation via regulation of the LPS-induced NF-κB/mortal protein kinases (MAPKs, JNK, and ERK)-CCL2/CXCL1 signaling pathways.

KEYWORDS: CCL2; CXCL1; LPS; astrocytes; hyperbaric oxygen

DOI: 10.1053/j.jn.2011.05.005

HBOT Decreases Neuroinflammation in Rat Model of TBI
(2.8 ATA, 2 sessions for 45 min each)


Hyperbaric oxygen therapy reduces neuroinflammation and expression of matrix metalloproteinase-9 in the rat model of traumatic brain injury.

Abstract
The acute inflammatory response plays an important role in secondary brain damage after traumatic brain injury (TBI). Neutrophils provide the main source of matrix metalloproteinases (MMPs) which also play a deleterious role in TBI. Numerous preclinical studies have suggested that hyperbaric oxygen therapy (HBOT) may be beneficial in various neurological and cerebral inflammatory diseases. The goal of this study was to evaluate the effects of HBOT on inflammatory infiltration and the expression of MMPs in correlation with secondary cell death in the rat model of dynamic contusion deformity (DCD). Twenty animals underwent DCD with subsequent HBOT (2.8 ATA, two sessions of 45 min each); 10 animals: DCD and normobaric oxygenation (1 ATA), 10 animals: not treated after DCD. Cell death was evaluated by TUNEL. Neutrophils were revealed by myeloperoxidase staining. Immunohistochemical staining for MMP-2 and -9 and tissue inhibitors of matrix metalloproteinase (TIMP-1) and -2 was also performed and the results were quantitatively evaluated by image analysis. In the animals treated by HBOT, a significant decrease in the number of TUNEL-positive cells and neutrophil inflammatory infiltration was seen in comparison with non-treated animals and those treated by normobaric oxygen. The expression of MMP-9 was also significantly lower in the treated group. Staining for MMP-2 and TIMP-2 did not change significantly. Our results demonstrate that HBOT decreased the extent of secondary cell death and reactive neuroinflammation in the TBI model. The decline of MMP-9 expression after HBOT may also contribute to protection of brain tissue in the peripheral area. Further research should be centered on the evaluation of long-term functional and morphological results of HBOT.

PMID: 16496602

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

BMC Pediatr. 2009

Children with autism who received hyperbaric treatment at 1.3 atm and 24% oxygen for 40 hourly sessions had significant improvements in overall functioning, receptive language, social interaction, eye contact, and sensory/cognitive awareness compared to children who received slightly pressurized room air.
PMID: 19284641
### Anti-inflammatory Herbs, Spices and Foods

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<td>- Fenugreek</td>
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<td>- Oregano</td>
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### Common Anti-inflammatory Herbs

#### Curcumin - Turmeric
- COX-2 inhibitor, anti-prostaglandin
- Similar to ibuprofen
- Antimicrobial
- Breaks down biofilms
- Prevents blood clots
- Helps joint pain
- NRF2 stimulator
- Poor oral absorption
- Inhibits COMT and MAOa genes

#### Boswellia – Indian frankincense
- 5-LOX (lipoxxygenase inhibitor)
- TNF alpha inhibitor
- Antibacterial
- Helps with joint pain
- Improves spatial memory
Other Anti-inflammatory Herbs

- Cat’s claw / Samento (Unicaria tomentosa)
  - Natural Calcium Channel Blocker
  - Antiviral, Antibacterial
  - Immune modulator
  - Protects DNA from damage
- Milk Thistle (Silymarin)
  - Increases SOD and increases glutathione production
  - Protects liver and kidney
- Ginger
  - Inhibits NO, COX-2, and PGE2
  - Helps with nausea

www.2bucketscleaning.com/2017/12/5-useful-essential-oils/
Essential Oils

- Use goes back to ancient civilizations 2000 BC
- Used by all cultures, traditionally as perfumes, cosmetics and for medicinal properties
- Volatile aromatic compounds
- Change state quickly from liquid to gas at room temperature
- Lipophilic, fat soluble compounds, can penetrate tissue and cells
- Potent, may cause irritation to skin and mucosa
- Extracted from fruits, plants, herbs, flowers, stems, leaf, seed, root or bark by steam distillation

Egyptian Medicinal Essential Oil Formulas
Using Essential Oils Safely

- **Topical** - May be applied in small quantities with a carrier oil
  - Accupuncture Points
  - Reflexology Points
  - Massage
  - Trigger points
  - Careful with citrus oils, may cause photosensitivity

- **Aromatic** - May be inhaled, diffused or nebulized

- **Internal** - Some oils can be consumed (teas, water) and used in cooking
  - Less is more
  - Rotate various oils
  - Avoid prolonged use of the same oil
  - Read labels regarding use

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Neuroprotective and Anti-Aging Potentials of Essential Oils from Aromatic and Medicinal Plants

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The use of essential oils (EOs) and their components is known since long in traditional medicine and aromatherapy for the management of various diseases, and is further increased in the recent times. The neuroprotective and anti-aging potentials of EOs and their possible mechanism of actions were evaluated by numerous researchers around the globe. Several clinically important EOs and their components from Agasthi sassa, Azadirachta indica, Lavandula angustifolia, Eucalyptus globulus, Mentha piperita, Rosmarinus officinalis, Jasminum sambac, Piper nigrum and so many other plants are reported for neuroprotective effects. This review article was aimed to summarize the current finding on EOs tested against neurodegenerative disorders like Alzheimer disease (AD) and dementia. The effects of EOs on pathological targets of AD and dementia including amyloid deposition (Aβ), neurodegenerative tangles (NFTs), cholinergic hypofunction, oxidative stress and glutamatergic abnormalities were focused. Furthermore, effects of EOs on other neurological disorders including anxiety, depression, cognitive hypofunction epilepsy and convulsions were also evaluated in detail. In conclusion, EOs were effective on several pathological targets and have improved cognitive performance in animal models and human subjects. Thus, EOs can be developed as multi potent agents against neurological disorders with better efficacy, safety and cost effectiveness.

- Keywords: essential oils, Alzheimer’s disease, cholinesterase inhibitors, antidepressants, anxiety, NFTs, dementia, BACE1

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Anju Usman, M.D.
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Neuroprotective Oils

- Cholinesterase Inhibitors
  - Polygonum hydropiper – Marshpepper knotweed
  - Rumex hastatus - Arrowleaf dock
  - Narcissus poeticus - Daffodil
  - Salvia leviolfa - sage family
  - Marlierea racemose - Bidi Leaf Tree
  - Cistus family - Rock Rose

- Sustained Attention
  - Eucalyptus globulus
  - Lavandula augustifolia
  - Rosemarinus officinalis
  - Metha peperita
  - Jasmine

Antioxidant Oils

- Lavender – increase GSH
- Thyme
- Coriander - increase GSH in hippocampus
- Clove
- Eucalyptus
- Cinnamon
- Juniper
- Basil – anticonvulsant, helps with sleep
- Chamomile
- Cumin
- Coriander
- Thyme
- Oregano
- Common Yarrow
- Salvia multicaulis
**Antioxidant and Anti-Inflammatory Activities of Essential Oils: A Short Review**

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**Abstract:** Essential oils are complex mixtures isolated from aromatic plants which may possess antioxidant and anti-inflammatory activities of interest in the food and cosmetic industries as well as in the human health field. In this work, a review was done on the most recent publications concerning their antioxidant and anti-inflammatory activities. At the same time a survey of the methods generally used for the evaluation of antioxidant activity and some of the mechanisms involved in the anti-inflammatory activities of essential oils are also reported.
Antimicrobial, Antioxidant and Anti-Inflammatory Activity of Essential Oils

- Eucalyptus Oil
- Lemongrass Oil
- Thyme Oil
- Lindernia Oil
- Geranium Oil
- Tea Tree Oil

- Antimicrobial
  - E. Coli - All
  - Staphylococcus - All
  - Gram Neg bacteria - not geranium
  - Candida - lemon grass, thyme, lindernia
  - Pseudomonas - none
- Decreased TNF-alpha – not geranium
- Decreased LOX-5
- Decreased IL-1 Beta
- Decreased IL -8
- Decreased NO
- Lemon grass most potent antimicrobial
- Thyme most potent antioxidant
Bitters/HOPS in Beer Have an Anti-inflammatory Effect in Alzheimer’s Mice

Iso-a-acids, Bitter Components of Beer, Prevent Inflammation and Cognitive Decline Induced in a Mouse Model of Alzheimer’s Disease.

Abstract

Alongside the rapid growth in aging populations worldwide, prevention and therapy for age-related memory decline and dementia are in great demand to maintain a long, healthy life. Here we found that iso-a-acids, hop-derived bitter compounds in beer, enhance microglial phagocytosis and suppress inflammation via activation of the peroxisome proliferator-activated receptor γ. In normal mice, oral administration of iso-a-acids led to a significant increase both in CD11b and CD40 double-positive anti-inflammatory type microglia (p < 0.05) and in microglial phagocytosis in the brain. In Alzheimer’s model SxFAD mice, oral administration of iso-a-acids resulted in a 21% reduction in amyloid-β in the cerebral cortex as observed by immunohistochemical analysis, a significant reduction in inflammatory cytokines such as IL-1β and chemokines including macrophage inflammatory protein-1α in the cerebral cortex (p < 0.05) and a significant improvement in a novel object recognition test (p < 0.05), as compared with control-fed SxFAD mice. The differences in iso-a-acid-fed mice were due to the induction of microglia to an anti-inflammatory phenotype. The present study is the first to report that amyloid-β deposition and inflammation are suppressed in a mouse model of Alzheimer’s disease by a single component, iso-a-acids, via the regulation of microglial activation. The suppression of neuroinflammation and improvement in cognitive function suggests that iso-a-acids contained in beer may be useful for the prevention of dementia.

Consider incorporating more herbs and oils in your daily routine drinking, eating, sleeping, bathing...