Potential Treatment Trials for Gulf War Illness Discussion

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Theories of Gulf War Illness

- Disordered pain processing in CNS
- Mitochondrial dysfunction
- Neuroinflammatory disorder
- neuroendocrine dysfunction
- White matter toxic leukoencephalopathy
- Hypercoagulable state

Mechanism of Illness

- Most hypotheses suggest a neurotoxicant-based mechanism of CNS/immune effects from Acetylcholinesterase inhibitor (AChE) exposures from:
  - Pesticides
  - Anti-nerve gas pills (PB)
  - Sarin exposure

Laetz, CA et al. The synergistic toxicity of pesticide mixtures: Implications for risk assessment and the conservation of endangered salmon. Environ. Health persp. 2009;117:348-353.

- Found synergistic effects of organophosphate pesticides including malathion, diazinon and chlorpyrifos in wild salmon causing much greater effects than individual exposures or even additive effects.
- These same 3 OP pesticides were some of the most widely used during the Gulf War.

Soltaninejad K & Abdollahi M. Current opinion on the science of organophosphate pesticides and toxic stress: A systematic review. *Med Sci Monit*. 2009;15(3):RA75-90.

- Review of experimental & clinical studies evaluating OP toxicity
- Oxidative stress = important mechanism of OP poisoning causing depletion of mitochondrial energy and DNA fragmentation leading to apoptosis.
- Suggest that those overexposed to OPs should be given potent antioxidants.

Myhill et al. Chronic fatigue syndrome and mitochondrial dysfunction. *IntJClinExpMed*. 2009;2:1-16.

- 71 CFS patients (met CDC criteria) underwent “ATP profile” test for mitochondrial functioning which showed:
  - mitochondrial dysfunction of the neutrophils suggesting specific immune system dysfunction in at least some patients with chronic fatigue syndrome.

GWI Treatment Approaches

- **Symptom based treatments**

  - Acupuncture, biofeedback, pain medications, nutritional supplements.

- **Mechanism based treatments**

  - Low Dose Naltrexone (LDN)
  - Mifepristone
  - Carnosine
  - Co-enzyme Q10

Ongoing Treatment Trials

- **Co-enzyme Q10 therapy** – antioxidant
  - To improve mitochondrial functioning and prevent apoptosis or cell death.
  - To improve GWI symptoms of fatigue, muscle pain, cognition.

- **Environmental medicine approach**
  - Housing veterans in hospital clean rooms
  - Eating organic foods and drinking filtered water
  - Vitamin and nutrient supplementation
  - Sauna – detoxification

Ongoing Treatment Trials

- **Mifepristone – glucocorticoid receptor antagonist**
  - Enhanced negative feedback inhibition of HPA axis and lower 24-hour plasma ACTH levels found in GWI.
  - Trial to reverse the neuroendocrine abnormalities in GWI by reducing glucocorticoid sensitivity and improving health.
- **Carnosine therapy – protein**
  - initial study showed decreased protein carnosine in CSF of GWI and CFS patients.
  - Trial gives carnosine supplements to see if GWI symptoms improve including sleep, pain, decreased activity and vitality.

Newly Funded Treatments

- Low Dose Naltrexone and dextromethorphan
  - Used to treat neuroinflammation and pain in GWI by using morphinins through opioid induced immune system regulation.
- Acupuncture
  - Used to treat joint and muscle pain, headaches, fatigue, cognition

Discussion

- New Ideas/avenues for treatment?
  - Flavonoids to reduce neuroinflammation and improve mitochrondrial function (quercetin, luteolin)
  - Glutathione to improve mitochondrial function.
  - Other pharmaceuticals
  - Complementary therapies:
    - Biofeedback
    - Laser acupuncture
    - Low-level Laser light/ LED therapy
    - Hyperbaric oxygen therapy (HBOT)

Flavonoids to improve neuroinflammation and mitochondrial functioning

•Quercetin and luteolin are naturally occurring polyphenolic flavonoids found in apples, onions, celery and green peppers.

•They have antioxidant and anti-inflammatory properties thought to improve mitochondrial functioning and reduce neuroinflammation. Two of the commonly hypothesized mechanisms for GW illness.

Gong et al. Quercetin up-regulates paraoxonase 1 gene expression with concomitant protection against LDL oxidation. *Biochem. Biophys. Res. Commun*. 2009;article in press.

- ♂ rats fed liquid quercetin [10mg/L] for 4 weeks
  - upregulated PON1 gene expression and activity
  - significantly increased protective capacity of HDL against LDL oxidation
  - PON1 is also associated with clearing neurotoxicants from the body. Could increasing PON1 activity potentially help with GW illness?

Davis et al. Quercetin increases brain and muscle mitochondrial biogenesis and exercise tolerance. *Am J Physiol Regul Integr Comp Physiol*. 2009; 296:1071-1077.

- ♂ mice given 12.5-25 mg/kg quercetin daily for 7 days
  - enhanced wheel running activity and maximal endurance capacity.
  - exhibited increased mRNA expression in brain & muscle tissue of mitochondrial DNA and its substrates including:
  - PGC-1α - thought to be the master regulator of mitochondrial biogenesis.
  - SIRT1- which increases PGC-1 activity.
  - Cytochrome *c* - which usually occurs in conjunction with other mitochondrial enzymes of the electron transport chain.
  - Authors suggest that quercetin may enhance exercise tolerance through its activity as an adenosine A1 receptor antagonist in the brain.

Jang et al., Luteolin reduces IL-6 production in microglia by inhibiting JNK phosphorylation and activation of AP-1. PNAS.2008:105;7534-7539.

- Luteolin is a potent anti-inflammatory flavonoid.
- Study showed that luteolin inhibits production of IL-6 in periphery where it plays a role in immunologically mediated fatigue and loss of strength.
- Results suggest that luteolin could be a promising agent for treating neuroinflammation.

Potential white matter volume therapies

- Several studies have shown lower brain white matter volumes in symptomatic GW veterans.
- Many neurotoxicants are lipophilic and can cause demyelination of the white matter tracts.
- The question arises whether GW exposures caused a toxic leukoencephalothy in some GW veterans.
- What therapies might help reduce WM volume loss – pharmaceuticals, stem cells?

Khan et al. Long-term study of brain ^{1}H-MRS study in MS: Effect of glatiramer acetate therapy on axonal metabolic function and feasibility of long-term ^{1}H-MRS monitoring in MS. *J Neuroimaging*. 2008; 18(3):314-319.

- Patients with relapsing-remitting MS treated with glatiramer acetate (copaxone) for up to 4 years
  - showed a significant reduction in relapse rate and neurologic disability.
  - increased NAA/Cr ratio suggesting improved neuronal integrity.
  - Could this therapy be beneficial in other demyelinating disorders?

Riordan et al. Non-expanded adipose stromal vascular fraction (SVF) cell therapy for multiple sclerosis. *J Transl Med*. 2009;7:29.

- Adipose tissue may be an alternative stem cell source.
- Mesenchymal stem cells inhibit innate immune activation by suppressing macrophage activation, dendritic cell maturation and blocking inflammatory signalling.
- Stromal vascular fraction infusions from adipose tissue improved 3 MS patients' symptoms & quality of life suggesting its potential utility in MS and other autoimmune conditions.

Thank You

CDMRP Funding

Department of Defense Gulf War Illness Research Program (GWIRP)
Funding Opportunities for Fiscal Year 2009

The Fiscal Year 2009 (FY09) Defense Appropriations Act provides $8 million to the Department of Defense Gulf War Illness Research Program (GWIRP) The FY09 GWIRP encourages proposals that specifically address critical needs of ill Gulf War veterans in the following areas **(Revised for FY09)**:

FY09 GWIRP program announcements and application instructions, including deadlines, for the following award mechanisms are anticipated to be posted and available on Grants.gov in March 2009.

Award Mechanism	PI Eligibility	Key Mechanism Elements	Funding
Clinical Trial Award	Independent investigators at all academic levels (or equivalent)	• Fund Phase 0, I, or II clinical trials relevant to Gulf War Illness; combinations of phases are permitted • Preclinical data required for all clinical trial proposals • Preproposal is required; proposal submission is by invitation only	• Maximum funding of $750,000 in direct costs (plus indirect costs) • Period of performance should not exceed 4 years • Anticipate 1 award
Investigator Initiated Research Award	Independent investigators at all academic levels (or equivalent)	• Supports basic and clinical research relevant to GWI • Research Strategy and Impact are the most important review criteria • Preliminary data is required, though not necessarily from the field of GWI. Clinical trials are not permitted. • Pre-proposal is required; proposal submission is by invitation only	• Maximum funding of $600,000 for direct costs (plus indirect costs) • Period of performance should not exceed 3 years • Anticipate 3 awards