REVIEW OF ANTI-OXIDANTS
Genetic and Non-Genetic Ataxias

Susan L. Perlman, M.D.
Clinical Professor of Neurology
David Geffen School of Medicine @ UCLA
Director, Ataxia Center

- **WHAT ARE ANTI-OXIDANTS?**
- **HOW DO ANTI-OXIDANTS RELATE TO THE CAUSES OF ATAXIA?**
- **DO ANTI-OXIDANTS BENEFIT ATAXIA?**
- **ARE ANTI-OXIDANTS SAFE?**
- **Google search “anti-oxidants and ataxia” yielded 1,120,000 hits.**

WHAT ARE ANTI-OXIDANTS?

- **What are free radicals and what causes oxidative stress?**

Mitochondrion

Food carbohydrates, fats, proteins >>> >>>**AcetylCoA**>>>Citric Acid Cycle>>>**2 H+** Betaoxidation

2 H+>>>Respiratory Chain— Complex I & II Flavoproteins

½ O2 Iron-sulfur clusters

Ubiquinone (coenzyme Q)

Complex III Cytochrome b, c1

Iron-sulfur clusters

Cytochrome C

Complex IV Cytochrome a3

Copper

ATP, H2O

Flavoproteins react with oxygen to produce superoxides/free radicals.

Vitamin E, Vitamin C, glutathione, selenium, and three enzymes in solution in the cell (superoxide dismutase, catalase, glutathione peroxidase) scavenge these free radicals to prevent the damage they cause to cells—anti-oxidants.

- Reactive oxygen and nitrogen species, including free radicals, are produced in the human body in both health and disease. In health, they may arise as regulatory mechanisms, intercellular signaling species, or as bacteriocidal agents. Their production is normally controlled by the antioxidant defense mechanisms that include intracellular enzymes--for example, glutathione peroxidase and superoxide dismutase--and low molecular-mass compounds such as vitamin E or ascorbic acid. So some free radicals are necessary.
- Although repair mechanisms exist, some steady-state basal oxidative damage occurs in all individuals. Oxidative stress arises when there is a marked imbalance between the production and removal of reactive oxygen and nitrogen species. This may originate from an overproduction of these substances or from a depletion in the antioxidant defenses. Certain drugs may induce oxidative stress by forming drug-derived radicals that can not only deplete the antioxidant defenses but can also react directly with biomolecules (eg. aminoglycosides, cisplatin).

HOW DO ANTI-OXIDANTS RELATE TO THE CAUSES OF ATAXIA?

- **Genetic Ataxias**
  - **Triplet repeat ataxias**
  - **Friedreich's ataxia**
  - **Mitochondrial ataxias**
- **Non-genetic Ataxias**
  - **Cerebellar neurons under stress**
  - **The mitochondrion as innocent bystander**

TRIPLET REPEAT ATAXIAS

RESEARCH HAS PARALLELED THAT OF HUNTINGTON'S DISEASE

- **Polyglutamine tract of mHtg has toxic gain of function**
  - **>impaired vesicular trafficking**
  - **>disturbed protein transport**
  - **>transcriptional dysregulation**
  - **>activation of apoptotic pathways**
- **Apoptotic pathways trigger programmed cell death**
- **Dying cells stress mitochondria**
- **Stressed mitochondria do not produce energy and allow the build-up of free radicals, which further damage the cell**
- **Dying mitochondria release cytochrome c into the cell, which stimulates more apoptosis**

FRIEDREICH'S ATAXIA

- **GAA repeat in the gene for frataxin prevents production of the frataxin protein.**
- **Frataxin protein is needed in the mitochondrion to assist in the formation of the iron-sulfur clusters used in the respiratory chain.**
- **Without proper iron-sulfur cluster assembly, the mitochondrion cannot make energy or control the level of free radicals. Free iron not bound in the clusters creates more free radicals, worsening the oxidative stress on the mitochondrion and ultimately on the cell.**
- **This triggers cell death pathways.**

MITOCHONDRIAL DISORDERS GENETIC AND NON-GENETIC

- **Genetic mitochondrial disorders result from mutations in the genes that produce the components of the mitochondrion.**
- **These could be genes located within the mitochondrion (mitochondrial DNA) or outside the mitochondrion.**
- **Lack of proper components results in mitochondria that cannot perform their functions—energy is not produced and free radicals are not policed.**
- **This causes oxidative stress in the mitochondrion and in the cell, leading to cell death.**
- **Cell death (apoptosis) stresses the mitochondria that may still be functioning, even if they are genetically normal.**
- **The unknown stressors that cause non-genetic ataxia contribute to the vicious cycle of cell death and mitochondrial dysfunction.**

DO ANTI-OXIDANTS BENEFIT ATAXIA?

- **Studies of vitamin E, coenzyme Q10, and idebenone have been undertaken in Friedreich's ataxia, showing improvement in the cardiomyopathy, but not the ataxia. Higher dose studies of idebenone and studies of anti-oxidants (mitoQ) and iron chelators targeted to the mitochondrion are being planned.**
- **36 Huntinton's disease patients treated with vitamin E showed a trend toward slowing of early stage motor decline.**
- **170 Huntington's disease patients treated with coenzyme Q10 300 mg per day showed a trend toward slowing in total functional decline (13%) over 30 months. A higher dose study is being planned.**
- **Creatine given at 5 grams per day to patients with HD did not show benefits, but a higher dose study is being planned.**
- **A study of EPA (omega fish oil) is being completed in patients with HD and may show benefit.**

- **N-acetylcysteine in Unverricht-Lundborg disease improved blood levels of glutathione and reduced seizures, but did not help ataxia.**
- **In vitro work with N-acetylcysteine and with lipoic acid suggest benefit in Ataxia telangiectasia, as does NAC in SCA1.**

- **None of the HD work or work with NAC has yet been replicated in patients with SCA.**

DESIGNING ANTI-OXIDANT TRIALS

- Cochrane Database Syst Rev. 2004 Oct 18(4):CD002829.

Antioxidant treatment for amyotrophic lateral sclerosis / motor neuron disease.

Orrell R, Lane J, Ross M.

This meta-analysis found 21 studies of anti-oxidants for ALS, but only 3 were randomized and carried on for at least 12 months.

Vitamin E, acetylcysteine, and a combination of E, selenium, and methionine were used. No beneficial or adverse effects were seen.

Concerns were raised about study sizes, outcome measures, and study durations.

"The high tolerance and safety, and relatively low cost of vitamins C and E, and other considerations related to the lack of other effective treatments for amyotrophic lateral sclerosis, explain the continuing use of these vitamins by physicians and patients. While there is no substantial clinical trial evidence to support their clinical use, there is no clear contraindication."

ON THE OTHER HAND, CAN YOU HAVE TOO MUCH OF A GOOD THING?

- **Ann Intern Med. 2004 Nov 10 [Epub ahead of print]**

  Meta-Analysis: High-Dosage Vitamin E Supplementation May Increase All-Cause Mortality.

  Miller ER 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E.

  This meta-analysis looked at 135,967 participants in 19 studies of the use of vitamin E for various chronic conditions, including heart disease and cancer, at doses from 16.5 – 2000 IU per day.

  The risk of dying from any cause was greater in participants taking "high-dose" vitamin E (>/= 400 IU per day), although the effect was small (39 excess deaths per 10,000 people) and the study subjects were all over the age of 60 and had chronic illnesses.

  Similar concerns were raised in an earlier studies of lung cancer and cardiovascular disease with beta-carotene.

  "High-dosage (>/=400 IU/d) vitamin E supplements may increase all-cause mortality and should be avoided."

ARE ANTI-OXIDANTS SAFE?

- **Ann Intern Med. 2004 Nov 10 [Epub ahead of print]**
  Meta-Analysis: High-Dosage Vitamin E Supplementation May Increase All-Cause Mortality.
  Miller ER 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E.

- **Cochrane Database Syst Rev. 2004 Oct 18(4):CD004183.**
  Antioxidant supplements for preventing gastrointestinal cancers.
  Bjelakovic G, Nikolova D, Simonetti R, Gluud C.

  May also increase risk of overall mortality.

- **Arch Intern Med. 2004 Jul 26;164(14):1552-6.**
  Randomized trials of vitamin E in the treatment and prevention of cardiovascular disease.
  Eidelman RS, Hollar D, Hebert PR, Lamas GA, Hennekens CH.

"The use of agents of proven lack of benefit, especially those easily available over the counter, may contribute to under use of agents of proven benefit and failure to adopt healthy lifestyles."

- **There is so much as yet unknown about the influence of lifestyle and environmental factors on the health of the brain facing genetic stress or non-genetic stress, that we should not rule out the potential beneficial impact of lifestyle modification on the occurrence and progression of cerebellar disease.**
- **The National Ataxia Database may help answer some of these questions.**

CAN ANTI-OXIDANTS INTERFERE WITH EACH OTHER?

- J Nutr. 2002 Nov;132(11):3400-4.

  Excess dietary vitamin E lowers the activities of antioxidative enzymes in erythrocytes of rats fed salmon oil.
  Eder K, Flader D, Hirche F, Brandsch C.

  Megadoses of vitamin E lowered the activities of antioxidative enzymes in the red blood cells and lowered the concentration of glutathione in rats fed a diet with a high proportion of polyunsaturated fatty acids.

- **Vitamins C and E taken together result in increased blood levels of both.**
- **Vitamin E and Coenzyme Q10 taken together result in increased blood levels of both, although vitamin > 1000 IU reduces the blood level of coQ10.**

RISKS OF ANTI-OXIDANTS THAT CAN BE SEEN IN INDIVIDUALS

- **Vitamin E can potentiate the blood-thinning effects of aspirin and warfarin.**
- **Some herbal supplements may cause serious heart arrhythmia, and many supplements significantly interact with warfarin (garlic, gingko, ginseng) and digoxin (St. John's wort).**
- **Coenzyme Q10 levels are decreased by cholesterol lowering medications, and coQ10 supplements may interfere with cholesterol lowering medications.**

Perspective on Antioxidants and Metabolic Stimulators

- **Alpha lipoic acid 150–1800 mg/day. No particular concerns to monitor.**
- **Coenzyme Q10 400–1200 mg/day Check LFTs, cholesterol, PT/PTT.**
  Mild GI changes.
  May interfere with cholesterol-lowering medications or oral anticoagulants.
- **Creatine 5–10 g/day. Lower doses are recommended in patients on cimetidine, diuretics,NSAIDs, probenecid, and trimethoprim.**
  Check creatinine.
  Should not be used in patients with kidney disease. Avoid dehydration.
- **L-carnitine (D-carnitine should not be taken) 250–1250 mg/day.**
  Check chemistry panel, carnitine levels. Mild GI changes.

- **N-acetylcysteine 60 mg/kg/day. Mild GI changes.**

- **Omega 3 fish oil/EPA (eicosapentanoic acid) 2 g/day. Bruising/bleeding.**

- **Selenium 50–100 ug/day (not to exceed 400 ug/day). Diarrhea, hair/nail/skin changes, fatigue, neuropathy.**

- **Vitamin E (d-alpha tocopherol succinate) 300–1200 IU/day. Check PT/PTT in patients on oral anticoagulants. Diarrhea, abdominal pain, bruising/bleeding, possible blood clots in patients on estrogens.**

PARTNERS IN CLINICAL ATAXIA RESEARCH

- **Daniel Geschwind, M.D., Ph.D.**
- **Ming Guo, M.D., Ph.D.**
- **Joanna Jen, M.D., Ph.D.**
- **Susan L. Perlman, M.D.**
- **Patricia Cardenas--coordinator (310/794-1195)**
- **Lyndsay Elliott—Friedreich's ataxia research coordinator (310/794-1225)**
- **Sakena Patterson—Ataxia database coordinator (310/794-1225)**
- **Joyce Bryan, M.S.W.--social work coordinator (562/537-8420)**
- **Michelle Fox, M.S.--genetics counsellor (310/206-6581)**
- **New Patient Appointments--310/794-1195**