

Do Antioxidants Have Potential To Treat MS?

The health benefits attributed to antioxidants are growing daily. These substances may help to prevent cancer, heart disease, cataracts, and more. What about multiple sclerosis? In fact, scientists are investigating the role of “oxidants” – molecules targeted by antioxidants – in MS damage. Based on this research, studies of antioxidants in animal models, and even clinical trials in people with MS, are underway.

Oxidative Stress in MS

Each molecule within a cell contains pairs of electrons. Molecules that are missing electrons may “steal” them from other molecules, causing instability and damage in the cell. These bandits are known as free radicals or oxidants. Cells have antioxidant mechanisms to defend against this damage, but if free radical production exceeds defenses, oxidation can kill the cell.

The immune attack on the brain and spinal cord that occurs in MS increases the production of oxidants such as nitric oxide, superoxide, and peroxynitrite. This may damage the nervous system in several ways, say Kenneth J. Smith, PhD, and Hans Lassmann, MD (*The Lancet Neurology*, August 2002):

- Oxidative stress may kill cells that make nerve-insulating myelin, and damage myelin proteins.
- Nitric oxide has been shown to block nerve impulse conduction, particularly in nerve fibers without myelin, indicating a possible role in MS symptoms.
- Free radicals may disrupt the blood-brain barrier, weakening this protective lining and escalating the immune attack.

Researchers have found much evidence linking oxidants to damage in MS and MS-like disease. While a Harry Weaver Neuroscience Scholar of the National MS Society, Anne H. Cross, MD (Washington University in St. Louis) reported the presence of nitric oxide in the spinal cords of mice with EAE, an MS-like disease (*The Journal of Experimental Medicine*, August 1993).

This observation has held for persons with MS. Society-funded grantee John W. Rose, MD (University of Utah, Salt Lake City) analyzed 13 tissue samples from people with MS in which inflammation and myelin damage was actively occurring (*Journal of Neuroimmunology*, June 2004). Rose found substantial amounts of iNOS – an enzyme that produces nitric oxide – in immune and brain cells, and associated with chemicals that damage myelin.

Konrad Rejdak, MD (Medical University in Lublin, Poland) and colleagues examined the spinal fluid of 51 people with different types of MS. Nitric oxide products were increased specifically in people with MS who had mild disabilities and active inflammation as shown on imaging scans. They concluded that nitric oxide production is increased in early, active MS. (*Neurology*, October 26, 2004).

D. Craig Hooper, PhD (Thomas Jefferson University, Philadelphia) has extensively investigated the actions of peroxynitrite, an oxidant that is a product of nitric oxide and superoxide. With funding from the Society, he reported that peroxynitrite can trigger changes in the blood-brain barrier to allow immune cells to infiltrate the nervous system (*The FASEB Journal*, April 2000). Hooper recently reported that peroxynitrite is toxic to nerve cells (*Journal of Neurotrauma*, September 2004).

Antioxidant Strategies in MS-Like Disease

The evidence for oxidative activity in MS damage raises possibilities for battling this activity with antioxidants. However, nitric oxide seems to have certain benefits in the immune system, such as inhibiting activation and proliferation of immune cells; blocking it could have a negative impact. Smith and Lassmann suggest that therapeutic strategies that restrain only superoxide or peroxynitrite may be more helpful.

Hooper has studied antioxidants that specifically target peroxynitrite. One such agent is uric acid, a naturally occurring antioxidant that inhibits peroxynitrite. Interestingly, people with MS have lower uric acid levels than siblings who do not have MS (*Multiple Sclerosis*, June 2001). When Hooper raised uric acid levels in mice, it protected them from EAE, and administering the antioxidant promoted recovery (*Proceedings of the National Academy of Sciences*, January 1998).

Dennis Bourdette, MD, and colleagues (Oregon Health and Science University) administered the antioxidant alpha lipoic acid (ALA) to mice induced with EAE. When given after disease onset, ALA decreased the extent of myelin damage and nerve fiber injury. When given before onset, ALA reduced the number of immune cells infiltrating the spinal cord (*Journal of Neuroimmunology*, October 2002).

Clinical Studies of Antioxidants

Small, early studies of antioxidant agents have also been conducted in people with MS. Hooper and colleagues administered both uric acid and inosine – a naturally-occurring substance that increases uric acid levels – to 11 people with MS in a Society-funded study. Uric acid was destroyed by bacteria in the intestine. Among 11 people taking inosine for 10 or 15 months, however, neurological exams showed some clinical improvement in three patients, and stability in 8 patients. Some areas of myelin damage seen on MRI in two patients

could not be detected after treatment (*Multiple Sclerosis*, October 2001). Based on these findings, a larger study is underway at the University of Pennsylvania, comparing inosine to placebo in 30 people with relapsing-remitting MS.

Gordana Toncev, MD (Clinical Hospital Center Kragujevac, Yugoslavia) and colleagues studied the effectiveness of inosine in secondary-progressive and relapsing-remitting MS. They administered oral inosine to 32 people daily for 24 months, and compared the results to 32 untreated controls. People treated with inosine had no adverse effects, lower rates of MS relapses, and lower scores on the EDSS, a measure of disease activity (Abstract #P06.091, American Academy of Neurology [AAN] Annual Meeting, 2004). Further study is needed to confirm these early results.

Bourdette and colleagues recently reported on a small safety study of alpha lipoic acid. Thirty volunteers with relapsing or progressive MS received one of two doses of ALA or placebo for two weeks. This study did not test for a clinical benefit, but the treatment seemed to be well tolerated, and blood samples indicated that some participants who took ALA had lower levels of an enzyme (MMP-9) that may help T cells enter the brain and spinal cord (Abstract #S29.003, AAN, 2004).

What does this research mean for the wealth of vitamins (A, C, E) and supplements on the market with antioxidant properties? It's important to consider that antioxidant vitamins stimulate the immune system. In MS, an overactive immune system is part of the disease process and stimulation may be dangerous.

A reasonable amount of antioxidants can be obtained by eating 2-4 servings of fruits and 3-4 servings of vegetables daily. For more information, the Society's brochure, "Vitamins, Minerals, and Herbs in MS," is available online at <http://www.nationalmssociety.org/Brochures-Vitamins.asp>, or from your local chapter.

The early, interesting findings on the potential of antioxidant strategies need to be confirmed in larger, longer-term studies before such agents can be considered safe, effective treatments for people with MS.