Federal Health Matters

VA Researchers Link Brain Antioxidant Deficiency to Neurodegeneration

Researchers at the San Francisco VA Medical Center, San Francisco, CA have identified a protein that may play an important role in protecting neurons from oxidative stress, a toxic process linked to neurodegenerative illnesses such as Alzheimer disease and Parkinson disease. The protein—known as excitatory amino acid carrier 1 (EAAC1) in mice—appears to be the main mechanism through which the amino acid cysteine is transported into neurons. Cysteine bonds with glutamate and glycine to form the tripeptide glutathione, which serves as a reductant in a highly oxidizing environment such as the brain.

In their study, titled "Neuronal Glutathione Deficiency and Age-Dependent Neurodegeneration in the EAAC1 Deficient Mouse" and published by the journal *Nature Neuroscience*, the researchers observed behavioral differences between mice that were deficient in the EAAC1 gene and normal, "wild type" mice. After approximately 11 months, the EAAC1-deficient colony exhibited signs of senility, while the wild type did not. In addition, postmortem examination showed that the brains of the deficient colony had abnormally enlarged ventricles (a common feature of Alzheimer brains), fewer hippocampal neurons, and signs of oxidative stress in all neurons in the hippocampus and cortex.

The researchers then compared brain slices of younger mice in both groups and found that, when exposed to the powerful oxidant hydrogen peroxide, the EAAC1-deficient mice were 10 times more vulnerable to oxidative stress than the wild type mice. They also observed that the neurons of EAAC1-deficient mice contained lower levels of glutathione.

The researchers discovered, however, that these defects were reversible. When treated with N-acetylcysteine, an oral form of cysteine that's readily taken up by neurons, the EAAC1-deficient mice experienced normalization of their glutathione levels, their ability to withstand hydrogen peroxide toxicity, and their response to oxidative challenges.

According to the study report, these results "suggest that EAAC1 is the primary route for neuronal cysteine uptake and that EAAC1 deficiency thereby leads to impaired neuronal glutathione metabolism, oxidative stress, and age-dependent neurodegeneration." They also support the theory that oxidative stress contributes to aging. If it is determined that EAAC1 expression is altered in human neurodegenerative illnesses, EAAC1 manipulation may be an approach for treatment.

2006 VA Budget Approved

On November 18, Congress passed H.R. 2528, the Military Quality of Life and Veterans Affairs Appropriations Act for Fiscal Year 2006, which allocates just over $70 billion for the VA—an increase of 18% over the past two years. Of the total appropriations, $22.5 billion are designated for medical services. President Bush signed the bill into law on November 30.

The bill earmarks an unprecedented $1.2 billion specifically for mental health care and doubles the funding for mental health care research. Included in these special provisions is the creation of three VA Centers of Excellence devoted to advancing research and treatment for mental health issues that affect veterans, particularly post-traumatic stress disorder. On December 8, VA Secretary R. James Nicholson announced the locations for these centers: Waco, TX; San Diego, CA; and Canandaigua, NY.

Also included in the 2006 VA budget is an additional $15 million per year for five years to be used for Gulf War Illness (GWI) research. Most current data indicate that veterans of Operation Desert Shield and Operation Desert Storm experience a combination of aliments (including fatigue, respiratory problems, sleep disturbances, skin rashes, and persistent headaches) to a greater degree than other veterans, but there remain major gaps in our understanding of this apparent syndrome. With the increased funding, the VA can expand on 12 research projects scheduled to begin in 2006 that are designed to enhance understanding and treatment of GWI and to address the potential long-term health effects of Gulf War-related exposures. The bill also provides for new GWI research and treatment centers and a pilot program for studying GWI that partners the VA with the University of Texas Southwestern Medical Center in Dallas.

Other highlights of H.R. 2528 include the Prosthetics and Integrative Health Care Initiative, which aims to help treat soldiers returning from Iraq and Afghanistan who have lost limbs in combat by designating $412 million for medical and prosthetic research; an additional $40 million allocated to the Veterans Benefits Administration to facilitate disability claims processing; and $1.2 billion for VA information technology. To prevent a recurrence of the budget shortfall that occurred this year, the bill also requires the VA to brief Congress

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about its financial situation on a quarterly basis and includes an emergency fund of $1.2 billion for medical services.

DoD Updates Uniform Formulary

William Winkenwerder, MD, assistant secretary of defense for health affairs and director of the TRICARE Management Activity, has approved changes to the TRICARE Uniform Formulary (UF) recommended by the DoD's Pharmacy and Therapeutics (P&T) Committee. These changes include the addition of medications in three therapeutic classes (alpha-blockers for benign prostatic hypertrophy and angiotensin converting enzyme [ACE] inhibitors and calcium channel blockers for cardiovascular disease) and the transfer of 16 medications to nonformulary status over the next few months.

In accordance with UF procedures, the P&T Committee's recommendations, made in August 2005, were subjected to review and comment by the DoD's Beneficiary Advisory Panel, which is comprised of representatives of active duty families and retirees, civilian health care professionals, and TRICARE contractors. This panel expressed concern about the designation of the ACE inhibitor ramipril as a nonformulary agent. But though the P&T Committee agreed that this drug plays an important role in treating some high risk patients with a history of cardiovascular disease, it ultimately determined that the ACE inhibitors available on the formulary are equally effective in most cases.

TRICARE beneficiaries currently taking ramipril—or other drugs that will become nonformulary agents this year—should consult with their providers to determine whether switching to a formulary alternative would be appropriate or whether there is a medical necessity to continue using the nonformulary drug. When a health care provider demonstrates medical necessity for a nonformulary agent, beneficiaries may qualify to obtain the drug at the copayment used for formulary brand name medications ($9 from a TRICARE Retail Network Pharmacy or from the TRICARE Mail Order Pharmacy), rather than that usually required for nonformulary drugs ($22). Active duty beneficiaries who fill their prescriptions at a military medical treatment facility pay no copayment, but they cannot receive nonformulary medications unless their provider demonstrates medical necessity.

More information about the formulary changes, a formulary search tool, and a chart displaying formulary alternatives for certain nonformulary medications along with links to medical necessity forms are all available at the pharmacy portion of the TRICARE web site (www.tricare.osd.mil/pharmacy). ●