



VA Research Currents

Sugar-breakdown byproduct may halt neuron death after diabetic coma

Pyruvate, a natural, nontoxic byproduct of glucose metabolism, may prevent brain-cell death and cognitive impairment in diabetics following an episode of severely low blood sugar, according to researchers at the San Francisco VA Medical Center (SFVAMC).

In studies with rats, senior investigator Raymond A. Swanson, MD, and lead author Sang Won Suh, PhD, demonstrated the effectiveness of pyruvate, a naturally-occurring end-product of the breakdown of glucose, when administered along with glucose after 30 minutes of diabetic coma. The therapy prevented brain damage and subsequent memory and learning

impairment far better than treatment with glucose alone.

The findings, appearing in the May issue of *Diabetes*, have direct implications for the treatment of diabetic patients in hypoglycemic coma, say the researchers.

Glucose is a sugar that serves as the body's main fuel. People with diabetes do not metabolize it properly, and thus have too much glucose in the blood. Treatment with sugar-lowering drugs or insulin—the main glucose-metabolizing hormone—helps keep sugar levels in check, but can sometimes result in hypoglycemia, or abnormally low blood

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Gulf War solicitation

ORD is seeking to fund new research on adverse health outcomes linked to military service in the Persian Gulf in 1990 and 1991. To date, VA and the Department of Defense have funded 274 such projects. This latest VA solicitation will support fully developed and pilot studies, with an emphasis on epidemiologic, clinical and laboratory research with the potential to contribute significantly to the understanding and treatment of Gulf War-related health conditions.

June 30 is the proposal deadline. For full details on this and other current solicitations, visit www.va.gov/resdev/funding/solicitations.

Update from the Office of Research and Development...

OMB performance ratings: What they mean for VA investigators

By Stephan D. Fihn, MD, MPH, acting chief research and development officer

The president's Office of Management and Budget (OMB) has established effective government as one of its FY 2006 budget priorities. As a tool to help programs achieve their expected results and continue to improve performance, OMB has initiated its Budget and Performance Integration Initiative. In its communications to federal departments, OMB emphasizes that demonstrating, or not demonstrating, effective accountability may affect a program's budget over time.

To assess and improve the performance of all major federal government programs, OMB introduced the Performance Assessment Rating Tool (PART) in 2002. Approximately 20 percent of federal programs are evaluated each year in a formal PART assessment. While a

PART assessment considers several aspects of each program, the category of "Results/Accountability" has the largest weight in the final scoring.

The president and OMB take the PART assessment seriously in the budget process. OMB clearly states, "A key principle of the PMA [President's Management Agenda] is that performance should significantly influence policy-making." The FY 2006 budget reflects this in that programs that are identified as "Effective" in the PART assessment tend to fare better in the President's budget than do programs that receive a lesser assessment. (For a chart that illustrates this point, go to www.john-mercero.com/omb_part.htm)

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VA funds 10 new Research Enhancement Award Programs

The Office of Research and Development recently announced funding for 10 new Research Enhancement Award Programs (REAPs) at eight VA medical centers. Each REAP award provides up to \$1.25 million in funding over five years for a multidisciplinary group of VA investigators to study a medical issue of concern to veterans. Important REAP goals are to train new investigators and promote innovative research integrating basic and clinical science.

Here are brief descriptions of the new REAPs:

Posttraumatic stress disorder (PTSD)—Murray Raskind, MD, at the VA Puget Sound Health Care System, will lead a REAP addressing PTSD and secondary drug abuse. The goals of the research are to develop better treatments for PTSD by using animal models of PTSD to identify important circuits and chemicals in the brain; evaluate World War II veterans to identify changes that occur in the brains of patients experiencing PTSD over a long period of time; and review the symptoms and characteristics of patients with PTSD who also abuse drugs.

Nonalcoholic fatty liver disease (NAFLD)—This REAP, at Puget

Sound, will investigate the causes of nonalcoholic fatty liver disease (NAFLD), now the most common cause of liver cirrhosis, after hepatitis and alcohol abuse. The group, headed by Sum Lee, MD, PhD, will investigate the relationship among insulin resistance, diabetes, obesity and chronic liver disease, as well as between NAFLD and metabolic syndrome.

Prostate Cancer—Under the direction of Rajvir Dahiya, PhD, investigators at the San Francisco VAMC will develop strategies for early detection of prostate cancer, such as through biomarkers, and will evaluate treatment strategies. For example, the researchers will attempt to identify mutations in certain genes that can be used for early detection and for predicting response to therapy. They will also aim to identify genes that become active and lead to prostate cancer when the diet is high in fat.

Hepatitis C—Teresa Wright, MD, will lead an investigation of HCV infection at the San Francisco VAMC to better understand and predict the occurrence of complications such as arthritis, kidney disease, diabetes and liver damage among patients with HCV infection. The REAP will also investigate how treatment with interferon causes nerve damage; test the effectiveness of Remicade (often used for rheumatoid arthritis) in treating HCV liver disease; and work to develop an animal model for testing HCV vaccines.

Chronic obstructive pulmonary disease (COPD)—Jeffrey Curtis, MD, will head a research team at the Ann Arbor VAMC to study how exposure to tobacco smoke leads to repeated lower respiratory-tract infections and decreased lung function. The group will use a mouse model to

study how the interaction of tobacco smoke with immune responses contributes to chronic lung diseases and lower respiratory-tract infections caused by the bacteria *haemophilus influenzae*.

Amyotrophic lateral sclerosis (ALS/Lou Gehrig's disease)—Paul Fishman, MD, PhD, will lead a REAP at the Baltimore VAMC to develop therapies for ALS and other neurodegenerative diseases. His team will explore methods to rapidly screen potential new drug therapies and investigate the use of adult stem cells to replace lost nerve cells. The team will also study genetically modified stem cells as a vehicle for delivering novel therapies—for example, growth factors—and work to develop new imaging techniques to monitor the survival and function of injected stem cells.

Type 2 diabetes—Led by Steven Elbein, MD, a REAP team at the Little Rock VAMC will identify genes involved in fat metabolism; examine derangements of fat metabolism in patients with metabolic syndrome and pre-diabetes; and identify the processes that predispose to insulin resistance and diabetes. Other goals are to determine if there is an increased amount of fat in the cardiac muscle of people with diabetes or metabolic syndrome, and to examine the benefits of drugs that enhance insulin sensitivity.

Kidney Disease—Principal investigator John Raymond, MD, and his REAP team at the Charleston, S.C., VAMC will attempt to identify urinary proteins that predict the development of kidney disease and explore new treatments for acute and chronic

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Career milestones

Kristin Nichol, MD, MPH, MBA, a clinician-researcher at the Minneapolis VA Medical Center, is the first recipient of the Dr. Charles Merieux Award from the National Foundation for Infectious Diseases. Nichol was cited for her “extensive research in behavior and cost-effectiveness in adult vaccination against influenza and pneumococcal disease ... and contributions to the development of national and global programs aimed at improving vaccination rates.” The award is named for a French humanist and vaccine-manufacturing pioneer who lived at the turn of the last century.

Neena Abraham, MD, of the Houston VA Medical Center and VA’s Houston Center for Quality of Care and Utilization Studies, received a 2005 Crystal Award from the American Society of Gastrointestinal Endoscopy for her contributions to the field. Her current research focuses on promoting safer prescription of nonsteroidal antiinflammatory drugs.

Rory Cooper, PhD, director of the Human Engineering Research Laboratories at the Pittsburgh VAMC, was inducted into the “Hall of Fame” of the National Spinal Cord Injury Association for lifetime contributions to wheelchair technology and related areas on behalf of those with spinal cord injury. More information on the award is available at the association’s website: www.spinalcord.org. ■

REAPs (cont. from pg. 2)

kidney disease. The group will also seek to understand how various risk factors affect kidney function and study drugs that might slow the progression of kidney disease.

Multiple Sclerosis (MS)—Arthur Vandenberg, PhD, of the Portland VAMC will direct a REAP aimed at studying whether adult stem cells that have been modified to produce growth factors can protect nerve fibers. Disease progression will be monitored by a new MRI technique. The researchers will also study alpha-lipoic acid and testosterone as potential therapies, and investigate the role of specific types of immune cells in protecting and repairing nerve fibers.

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PERFORMANCE (cont. from pg. 1)

In FY 2005, VA’s Office of Research and Development (ORD) received a rating of “Results Not Demonstrated.” This rating reflected VA’s failure to have a limited number of specific annual and long-term “performance measures that focus on outcomes and meaningfully reflect the purpose of the program.” In response to this initial rating, VA leadership, ORD staff, and OMB personnel have recently worked to develop performance measures to assess the effectiveness of VA ORD’s research efforts. These measures are:

- number of publications within the fiscal year, as determined by a VA identifier in the affiliation of the **first author** in a PubMed citation;
- number of patent disclosures within the fiscal year;
- percentage of clinicians who remain a paid VA employee at least three years after the completion of their career development award; and
- multi-site clinical trial patient accrual rate.

These measures are by no means perfect. They are neither nuanced, nor do they capture the full impact of VA research. These imperfections are offset by the fact that they are measurable without developing new reporting mechanisms. OMB’s reassessment of VA research and development is currently underway, and preliminary

indications are that we will see a very substantial improvement in this fiscal year’s PART score.

Although there is a role for ORD management in reaching our annual and long-term performance targets, VA investigators and research administrators will ultimately determine whether we meet OMB’s and the public’s expectations. Several items are crucial to improving ORD’s PART score:

- Investigators who conduct VA research must acknowledge their VA affiliation.
- Investigators who invent new technologies must disclose them to VA.
- Career development programs must be tailored to meet not only the needs of young faculty and university affiliates, but also the long-term clinical needs of VA.

If individual VA scientists neglect these obligations, meeting the PART targets becomes difficult, if not impossible and ultimately, the ORD budget could be negatively affected. Working to improve how we report, disclose and design our career development programs will be crucial to the future of ORD and VA’s role in improving the health of both America’s veterans and the population at large. The Washington jargon is to move a score away from red and toward green. Your efforts can help us to show a score in the “green” when we provide an update of the FY 2006 rating. ■

PYRUVATE (cont. from pg. 1)

glucose. Severe hypoglycemia can cause coma. As many as 15 percent of those with diabetes will suffer at least one episode of diabetic coma.

“Anybody who’s worked at a busy emergency room has seen a patient like this,” said Swanson, chief of the neurology and rehabilitation service at SFVAMC and professor of neurology at UCSF.

Standard treatment for severe hypoglycemia is glucose alone. This restores consciousness right away, but may not always prevent the subsequent death of neurons and possible cognitive impairment, said Swanson.

In an earlier paper, Swanson and Suh showed the cause of this brain cell death: hypoglycemia triggers the activation of an enzyme called PARP-1, which in turn prevents neurons from metabolizing glucose into pyruvate, which is used to power cells. Deprived of pyruvate, the neurons starve and die. In the new study, Swanson and Suh discovered they could circumvent the action of PARP-1 and keep neurons alive by administering pyruvate directly.

The researchers induced hypoglycemia and subsequent diabetic coma in rats by administering insulin. After 30 minutes of coma—determined by electroencephalogram (EEG)—one group of rats was restored to consciousness with glucose and pyruvate, while a second group received glucose alone. Control mice were given insulin but then treated immediately with glucose to stop coma from occurring.

Six weeks later, the rats were tested for memory and learning using a maze. Rats that had received only glucose showed significant impairment of learning and memory compared to the controls. By contrast, the pyruvate-plus-glucose rats showed no significant cognitive deficit compared to the control group. Follow-up examination of the rats’ brain tissue revealed that the rats given glucose plus pyruvate had 70 to 90 percent less neuronal death than the rats treated only with glucose.

The research was funded by the Juvenile Diabetes Research Foundation, VA and the National Institutes of Health. ■

REAPs (cont. from pg. 3)

Depression —Joel Gelernter, MD, will lead a REAP team at the VAMC in West Haven, Conn., that will use state-of-the-art imaging tools to identify differences in brain structures between patients with depression and healthy controls, and between twins with and without depression. The researchers will also seek to identify genetic changes associated with depression, and gain insight into how antidepressants work.

More information about REAP funding can be found at www.va.gov/resdev.

Next ORD Field Conference Call:
Monday, June 20, 2005 • 1:30 pm EDT
 1-800-767-1750, code 17323

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