TCOM
Research Notes

Volume 8, Number 5 March 1993

In Search of a Cure for Cocaine Abuse

According to a National Institute on Drug Abuse (NIDA) study, cocaine addicts in America spend more than $80 billion to support their habit. In 1987, one in 10 high school seniors said they had tried cocaine at least once before graduation. A 1991 NIDA report said that almost 24 million Americans admitted to using cocaine at least once in their lifetime.

Through a $1.5 million, four-and-one-half year contract from NIDA, pharmacology faculty members Michael Emmett-Oglesby, Ph.D., and Michael J. Forster, Ph.D., are working on a way to help stem the tide of cocaine abuse. According to Harold W. Keller, Ph.D., research office, their contract is one of the largest research contracts TCOM has ever received.

The researchers will be screening 500 or more compounds to determine their potential to block the effects of cocaine. The substances they're looking for, called cocaine antagonists, will hopefully not only block the euphoric effects of cocaine, but also reduce the craving for the drug.

"Those might be two separate things or they might be one and the same," Emmett-Oglesby says. "Right now, there isn't a drug out there that is acceptable for clinical use because of its side effects."

Their contract is one of two NIDA awards given last year in an effort to find an antagonist for cocaine. Scott Lukas, Ph.D., a professor of psychiatry at Harvard University, will test Forster and Emmett-Oglesby's potential compounds to determine the drugs' effectiveness in primates that self-administer cocaine.

Landing the NIDA Contract

Last year, NIDA contacted about 20 research laboratories around the country and invited them to submit proposals for the cocaine antagonist project. Each invitation for a proposal was based on the laboratory's recognized scientific leadership in the cocaine abuse research field, scientific resources and ability to complete the project.

"When the request for a proposal arrived, we had less than six weeks to complete it," Emmett-Oglesby says. "That was last summer, and I was already committed to be out of the country for two of those weeks. We worked hard to get everything ready."

Emmett-Oglesby asked Forster, who had completed his doctoral work in drug abuse, if he would be interested in participating in the project as a principal co-investigator. Forster's recent research has dealt with the effect of aging on activity in mice.

"One aspect of the NIDA contract was to screen substances using an animal activity model and I already had all the technology in place," Forster says.

Before submitting the proposal, the researchers had to look at the space and available equipment, and determine if the return in dollars was worth the investment.

"This type of research is very time-intensive. But we discussed the advantages and talked it over with our colleagues here and in other research facilities. Everyone said we should go for it," Emmett-Oglesby says.

"TCOM's infrastructure enabled us to be competitive," Forster says. "We were competitive not only scientifically, but in terms of TCOM's support services — the research and budget offices, the vivarium, the low indirect costs — all came together to make our proposal competitive."

Emmett-Oglesby credits the pharmacology department's encouragement for collaboration within the department as a key to the success of much of their research here at the college.

Narrowing the Field

According to Emmett-Oglesby, the theory behind what makes cocaine users "feel good" is that the drug inhibits the retrieval of the neurochemical dopamine in the body's neurons. When dopamine is released in the synapse of neurons, it binds with receptors and causes a

Continued on last page

TCOM Blue Book of Grant Funding 1991-1992 Now Available

College Sets Record in External and Cumulative Awards

This 28-page publication is now available from the Research Office. It contains all of the extramural awards, internal awards such as the Texas Research Enhancement Program, and proposal submissions organized by academic and clinical units. Each award entry has the principal investigator's name, degree, title of project, source of funding, starting and ending dates for the first year of the project, and total dollars awarded. There is also data that measures the external award dollars for sponsored project activity by unit for the four most recent fiscal years. This was a record year for TCOM with 77 external awards that total $5,057,018 for the 1991-1992 fiscal year and active cumulative awards of $17,024,107.

• RESEARCH AWARDS & GRANT SUBMISSIONS •

RECENT TCOM AWARDS

Rafael Alvarez-Gonzalez, Ph.D., (Department of Microbiology and Immunology), "Chemical and Kinetic Mechanisms of Enzyme Catalyzed Polymerization Reactions," American Chemical Society - Petroleum Research Fund, 03/01/93 - 02/28/94, $10,500.

Robert W. Gracy, Ph.D., (Department of Biochemistry and Molecular Biology), "Molecular Basis for Abnormal Proteins in Aging Cells," National Institutes of Health - National Institute on Aging, 02/01/93 - 01/31/94, $217,431.

Robert W. Gracy, Ph.D., (Department of Biochemistry and Molecular Biology), "Molecular Basis for Abnormal Proteins in Aging Cells," Research Supplement for Underrepresented Minorities, National Institutes of Health - National Institute on Aging, 02/01/93 - 01/31/94, $59,833.

Robert R. Luedtke, Ph.D., (Department of Pharmacology), "Regulation of Dopamine Receptor Subtypes," National Institutes of Health - National Institute of Neurological Disorders and Stroke, $127,904.

Tony Romeo, Ph.D., (Department of Microbiology and Immunology), "Glycogen-Enhanced *E. coli*," ICI Seeds, Inc., 12/29/92 - 12/29/93, $2,500.

Total Awards: $418,168

AWARDS FROM THE TEXAS INSTITUTE FOR RESEARCH AND EDUCATION ON AGING

Zhong Chen, Ph.D., William E. McIntosh, D.O., Walter J. McConathy, Ph.D., (Department of Medicine), "Aging and the Blood-Brain Barrier," $5,000.

RECENT TCOM SUBMISSIONS

Neeraj Agarwal, Ph.D., (Department of Anatomy and Cell Biology), "Possible Mechanism (s) of Photoreceptors Cell Death in Retinal Dystrophies," Life & Health Insurance Medical Research Fund, $49,500.

Neeraj Agarwal, Ph.D., (Department of Anatomy and Cell Biology), "Possible Mechanism of Photoreceptor Cell Death in rds Mutation," Fight for Sight, Inc. - National Society to Prevent Blindness, $12,000.

Rafael Alvarez-Gonzales, Ph.D., (Department of Microbiology and Immunology), "Enzyme Mechanism (s) of Poly(ADP-ribose) Polymerase," National Institutes of Health, $437,701.

William W. Barrow, Ph.D., (Department of Microbiology and Immunology), "Processing of AIDS Related Mycobacterial Antigens," National Institutes of Health - National Institute of Allergy and Infectious Diseases, $907,201.

Michael H. Chaitin, Ph.D., (Department of Anatomy and Cell Biology), "Immunolocalization of CD44 in the Mouse Retina," Fight for Sight, Inc. - National Society to Prevent Blindness, $10,250.

Richard A. Easom, Ph.D., (Department of Biochemistry and Molecular Biology), "Ca^{2+}/Calmodulin-Dependent Protein Kinase II and Insulin Secretion," Juvenile Diabetes Foundation International, $100,000.

Michael W. Emmett-Oglesby, Ph.D., (Department of Pharmacology), "Characterization of Benzodiazepine Dependence," INVEST Program, International Research Fellowship, Alcohol, Drug, Abuse and Mental Health Administration - National Institute on Drug Abuse.

Michael W. Emmett-Oglesby, Ph.D., (Department of Pharmacology), "Dopamine Release During Cocaine Self-Administration," National Institutes of Health - National Institute on Drug Abuse, $679,386.

Andras G. Lacko, Ph.D., (Department of Biochemistry and Molecular Biology), "Structure/Function of Recombinant LCAT," National Institutes of Health - National Heart, Lung, and Blood Institute, $511,653.

Robert R. Luedtke, Ph.D., (Department of Pharmacology), "Age-Associated Autoreactive Antibodies," National Institutes of Health - National Institute on Aging, $461,380.

Peter B. Raven, Ph.D., (Department of Physiology), "Regulation of Blood Pressure During Exercise," National Institutes of Health - National Heart, Lung, and Blood Institute, $693,355.

Rouel S. Roque, M.D., (Department of Anatomy and Cell Biology), "Mechanisms of Photoreceptor Cell Death: The Role of the Retinal Microglia," Fight for Sight, Inc. - National Society to Prevent Blindness, $11,570.

Rouel S. Roque, M.D., (Department of Anatomy and Cell Biology), "Glial Cells in the Diabetic Retina," Juvenile Diabetes Foundation International, $100,000.

Harold Sheedlo, Ph.D., (Department of Anatomy and Cell Biology), "Inhibition of Retinal Vascular Proliferation by Astrocyte Transplants in RCS Rats," Fight for Sight, Inc. - National Society to Prevent Blindness, $11,750.

Phillip C. Slocum, D.O., (Department of Medicine), "Educating Primary Care Physicians in Tuberculosis Control," National Institutes of Health - National Heart, Lung, and Blood Institute, $586,343.

James E. Turner, Ph.D., (Department of Anatomy and Cell Biology), "A Study of the Mechanism and Treatment of Diabetic Retinopathy," Juvenile Diabetes Foundation International, $49,500.

James E. Turner, Ph.D., (Department of Anatomy and Cell Biology), "Study of the Mechanisms and Treatment of Retinal Neovascularization," Alcon Laboratories, Inc., $58,800.

Thomas Yorio, Ph.D., (Department of Pharmacology), "Cellular Mechanisms in Adrenergic Ocular Hypotension," National Institutes of Health - National Eye Institute, $1,016,281.

Total Funding Requested: $5,696,670

RECENT TCOM RESEARCH ACTIVITIES

Ben G. Harris, Ph.D., (Department of Biochemistry and Molecular Biology), attended the Keystone Symposium entitled "Molecular Helminthology an Integrated Approach" in Tamarron, Colorado and gave a paper entitled "Biochemistry and Molecular Biology of Glycolytic Enzymes." He also recently witnessed the launch of his experiment aboard the space shuttle Columbia from Cape Canaveral, Florida. His research, which uses enzymes that come from roundworms found in the intestinal tracts of pigs, may hold the key to destroying parasitic roundworms in humans. This experiment was designed to grow crystals of malic enzyme at zero gravity. The gravitational pull on earth prevents the crystals from growing large enough for x-rays to reveal their inner workings and, thus, the weightlessness of space is an ideal environment for conducting this experiment.

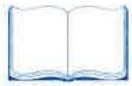
Ming-chi Wu, Ph.D., (Department of Biochemistry and Molecular Biology), recently was invited to his native country of Taiwan to consult with pharmaceutical companies and present a two-day lecture series on "Hematological Growth Factors as Therpaeutic Agents" at Taitung Enterprise Corp. He also presented seminars entitled "Expression of Cytokines in Insect Cells by Baculovirus Vectors" to the Development Center for Biotechnologies and "Macrophage Colony-Stimulating Factor: Structure, Function and Clinical Applications" to the Taiwan Hematology Society and National Taiwan University College of Medicine.

Robert W. Gracy, Ph.D., Professor and Chairman, and **Ümit Yüksel, Ph.D.** (Department of Biochemistry and Molecular Biology), met with a team of researchers in Mexico City headed by Dr. Armando Gomez-Puyou, head of the Instituto de Fisiologia Celular at the Universidad Nacional Autonoma de Mexico. This research team has been collaborating for several years on how proteins wear out and how certain proteins accumulate in aging cells and tissues. This research collaboration has resulted in scientists from the Mexico City laboratories spending several months at TCOM conducting research and *vice versa*.

Paul F. Cook, Ph.D., Professor and Chairman, (Department of Microbiology and Immunology), recently gave a guest lecture entitled "Use of Isotope Effects to Determine Enzyme Mechanism" to the Department of Biochemistry, School of Medicine, at the Universidad Nacional Autonoma de Mexico in Mexico City. He also presented a seminar entitled "Mechanism of O-acetylserine Sulhydrylase: An Enzyme Involved in Cysteine Biosynthesis" to students and faculty in the Division of Medicinal Chemistry and Pharmaceutics at the University of Kentucy.

Harbans Lal, Ph.D., Professor and Chairman, and **Michael J. Forster, Ph.D.,** (Department of Pharmacology), recently attended the American College of Neuropsychopharmacology meeting in San Juan, Puerto Rico and gave the presentation entitled "A Paradigm for Assessment of Pharmacological Enhancement of Cognition in Individual Aging Mice." He also attended the Gerontological Society of America and gave the following presentations coauthored with M. J. Forster, "Longitudinal Analyses of Decline of Recent Memory in Aging C57BL/6NNia Mice" and Dietary Restriction Delays Age-related Declines in Recent Memory Capacity of Aging B6D2F1/NNia Mice."

Recent TCOM Publications



Gracy, R. W. 1992. Effects of Aging on Proteins. pp. 119-145, In: *Stability of Protein Pharmaceuticals, Part B: In Vivo Pathways of Degradation and Strategies for Protein Stabilization*. T.J. Ahern and M.C. Manning, Eds., Plenum Press, New York.

Lacko, A.G. and P.H. Pritchard. 1992. Reverse Cholesterol Transport and Coronary Heart Disease. pp. 45-57. In: The Proceedings of the 14th International Symposium of Kyungpook National University.

TCOM Faculty Research Grants

Application forms for the 1993-1994 Academic Year Faculty Research Grants are available from the Research Office, Med. Ed. 1, Room 860. **Grant applications are due by 5 p.m., June 1, 1993.** Any faculty member who holds a tenure track position is eligible to apply for support of an individual research project. Non-tenure track personnel who hold a doctorate may also apply. Faculty members on tenure track will be given preference when all other considerations are equal.

Funds for internally sponsored research projects are extremely limited. In addition, both the competition for the funds and the sophistication of the projects has increased dramatically in the last few years. For these reasons, the Faculty Research Committee believes that further restrictions on funding should apply and the following guidelines on projects with equal scientific merit will be utilized in this year's competition: a high priority will be given to new investigators with little external funding; a high priority may also be given to senior investigators who have experienced a temporary hiatus in funding; all investigators with external funding greater than $50,000 per year will receive a lower priority for funding unless the project represents a major change in research direction; a priority will be given to collaborative efforts between basic sciences and clinical sciences faculty; and proposals which overlap with externally funded projects must clearly identify the need for faculty research funds and provide appropriate justification.

American Heart Association 1994-1995 Research Programs Available

Application forms are available in the Research Office for the following programs: Clinician Scientist Award-deadline June 1, 1993; Grant-in-Aid, Research Investigator Program, July 1, 1993; International Research Fellowship, June 1, 1993; Minority Scientist Development Award, June 1, 1993; Medical Student Research Fellowship, June 1, 1993.

Cocaine *continued from front page*

euphor-ic feeling. After dopamine is released, a protein retrieves it and brings it back into the cell. But cocaine blocks the protein's retrieving ability.

"The theory is that all the drugs, and perhaps all the events that make you feel good, work this way," Emmett-Oglesby says. "One of the problems is trying to find a substance that blocks the effect of dopamine without it causing someone to lose interest in everything else pleasurable in life. Drugs like that are available, but they are unacceptable."

Forster says that the neural organization of basic emotional states like pleasure or fear is similar in mice, rats, primates and humans.

The first step of their research deals with a mouse's response to cocaine. In the experiment, a mouse is injected with cocaine and put into an specially designed plastic cage about the size of a college dorm room refrigerator. Photocells, spaced about two centimeters apart, line the walls, floor and ceiling of the cage. The animal's activity in three-dimensional space (horizontal movement, the number of times an animal rears, and 22 other measurements) is recorded by a computer.

"We call the mouse's spontaneous movements locomotor activity," Forster says. "The specific pattern of locomotor activity elicited by a dose of cocaine is different from normal activity."

For example, while cocaine generally speeds up movement, it also causes a qualitative change in the type of movements. The effect of cocaine on activity is similar in mice, rats and primates, Forster says.

A cocaine-injected mouse is given a particular substance that might have the potential to block cocaine's effect, and its locomotor activity is recorded. If there is a change in the cocaine-induced activity, the drug might be a candidate for the next step in the experiment.

This "top-of-the-funnel" experiment narrows the field of potentially useful substances. Forster will test about 150 compounds on some 1,250 mice a year to find 100 substances that have a potential for blocking locomotor activity.

"The reason this is at the top of the funnel is we're assuming that if a drug blocks the locomotor stimulus response of cocaine, it might block the euphoric and reinforcing effects of the drug," Forster says.

But, that might not be the case. "Drugs that block locomotor activity may not block the euphoric effect of cocaine," Emmett-Oglesby says. "The assumption is that if a certain drug blocks locomotor activity, then we can choose from those drugs for our next step."

The second step in the experiment — called drug discrimination — trains rats to recognize the effects of cocaine compared to other substances.

"We'll train the rats to use the drug as a cue to decide which of two levers should be pressed to get sugar pellets," Emmett-Oglesby explains. "We'll inject them with either cocaine or saline. The cocaine will serve as a cue to press the right lever; the saline will be the left lever."

The researchers will train the rats 40-60 times to recognize cocaine. After that time, they expect the subjects will learn to distinguish cocaine and begin to push the correct lever corresponding to their injection nine or 10 times in a row. Next, the researchers will begin to reduce the dose of cocaine. Low cocaine doses should attract the rats to the saline lever, with high doses causing a cocaine lever response. "Medium" doses are expected to produce a mixed response.

"During this part of the experiment, the rats should be so drug-sophisticated that if they're injected with a powerful drug like morphine, they should push the saline lever. That's because the rat has learned that only cocaine injections should lead to responses on the cocaine lever," Emmett-Oglesby says.

At this point, Emmett-Oglesby will test the substances Forster narrowed down as likely candidates for blocking cocaine's effects.

"An effective blocking drug will diminish the subjective effects of cocaine and should cause the rat to push the saline lever. To shift the curve back to the cocaine side, it should take bigger doses of cocaine," he says.

Emmett-Oglesby says that the key feature of this cocaine discrimination is that it provides an animal model of cocaine's subjective effects. If a potential therapeutic drug blocks the effects of cocaine in these experiments, it is likely that it will block the euphoric effects of cocaine in humans.

The NIDA contract requires Forster and Emmett-Oglesby to test 500 or more compounds over the next four and one-half years, and to submit the candidates to the principal investigator of the primate study at Harvard. The institute's goal is to narrow the field of potential cocaine antagonists by 1995.

Laying the Groundwork

Forster and Emmett-Oglesby's paths to becoming scientists were taken early in their lives. "I've wanted to be a scientist since I was 12 years old," Forster says. "My first influence was my father who was a physicist working at Bell Telephone Laboratories. In the '60s, scientists were portrayed as heros who helped save the world. I've always been interested in the most difficult problem of all: why people do what they do." Later, an undergraduate professor at Muhlenberg College in Allentown, Pa., encouraged Forster to use his knack for investigating what made things tick. "Dr. Silas White convinced me that behavioral science was the route for me to go. I did research in his laboratory on weekends, during the summer — all the time. As an educator, he really pushed me."

Emmett-Oglesby also had an undergraduate professor who helped fan his scientific spark. "Lewis Seiden at the University of Chicago influenced me as an undergraduate," he says. "I took his behavioral pharmacology class as an undergraduate, served as a teaching assistant for him during the next year and came back to work in his laboratory as a postdoctoral fellow. The observation that tiny quantities of a chemical could profoundly modify behavior hooked me for a life in the world of behavioral pharmacology."

Research Notes is published by the Research Office,
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