Schizophrenia remodelled

By Lois Baker

ILLUSTRATION BY JAMES STEINBERG

New transgenic mouse links structure, function deficits

Schizophrenia researchers have historically aligned themselves into two opposing camps: structuralists and functionalists.

Structuralists have pursued the idea that the brains of schizophrenics show structural changes in the cortex and brain stem. Functionalists have held to the dopamine antagonist theory, which posits that the neurotransmitter dopamine is malfunctioning, causing the disease's characteristic delusions and hallucinations.

"These two camps don't talk to one another," explains Michal Stachowiak, PhD, neuroscientist and senior researcher on a UB team that appears to have broken that stalemate.

He and UB colleague Ewa K. Stachowiak created a transgenic mouse missing a critical brain component called the fibroblast growth factor receptor. The mouse displays the structural and neurochemical changes in dopamine neurons similar to those seen in PET scans of human patients with schizophrenia.

"Our new model has the potential to allow, for the first time, a way to search for new therapeutic treatments that target brain development or compensate for the abnormal structure of dopamine-producing neurons," says Michal Stachowiak. "It provides a new unifying concept of schizophrenia as a neuroanatomical-biochemical disorder.

"The mice display characteristic behavioral symptoms, such as an impaired processing of sensory information, which was reversed by a dopamine receptor antagonist used to treat schizophrenia. In other animal models, behavioral symptoms were induced by manipulating dopamine transmission only, without the underlying structural changes in the dopaminergic neurons.

> "Our new model has the potential to allow, for the first time, a way to search for new therapeutic treatments that target brain development or compensate for the abnormal structure of dopamine-producing neurons."
> —Michal Stachowiak, PhD

The two known conditions inherent in schizophrenics—underdeveloped dopamine-producing regions in their brains, but too much dopamine in their systems—seemed to contradict each other, says Stachowiak.

The crux of the research was proving that the two conditions were interconnected. In a paper published in the June 2006 issue of the *Journal of Neurochemistry,* the researchers describe how they found that both the dopamine-producing regions in the brain and the new cells within those regions were smaller than normal, prompting the neurons to overcompensate and overproduce dopamine.

Consequently, treating schizophrenics with drugs that block dopamine's action only dampens this function, but doesn't control it, Stachowiak notes.

Stachowiak is professor of pathological and anatomical sciences and chemistry, and director of the Molecular and Structural Neurobiology and Gene Therapy Program at UB. Ewa Stachowiak is research instructor in pathology and anatomical sciences and chemistry. Ilona Klejbor, a postdoctoral researcher in Stachowiak's laboratory, now at the Medical University of Gdansk, in Gdansk, Poland, is first author on the paper.

The neurobiology team, along with Robert Miletich, UB clinical associate professor of nuclear medicine, currently is searching for a "fingerprint" that identifies those at risk of developing the disease by looking for common brain symptoms in schizophrenic patients and the animal model.

If such a risk factor could be found, says Stachowiak, children with behavioral problems or from families with a history of schizophrenia could be screened and treatment could be started before the disease becomes full-blown.

Additional authors on the paper are Jason M. Meyers, graduate student; Thomas D. Corso, visiting professor, and Robert Hard, professor, all from the UB Department of Pathology and Anatomical Sciences; Jerry Richards and Kathy Hausknecht, student researchers, both from the UB Research Institute on Addictions; Angelo S. Gambino, a student researcher from Canisius College; Janusz Morys from the Medical University of Gdansk; and Pamela A. Maher from the Salk Institute in La Jolla, Calif.

The research was funded by grants from the March of Dimes and Birth Defects, the John R. Oishei Foundation, the Canisius College Learning Excellence Program and the National Institutes of Health. BP

Symptoms in Obese May Not Mean Asthma

Weight, not inflammation, may be causing breathing problems

By Lois Baker

Pulmonary researchers at UB have created asthma-like symptoms in non-asthmatic volunteers by decreasing their lung volume through simulated obesity.

Volunteers participating in the study wore chest vests with pockets filled with buckshot to mimic the weight distribution associated with various levels of obesity.

The study results, which were published in the September 2006 issue of *Chest,* suggest that the airway hyper-responsiveness seen in obese patients, which often leads to a diagnosis of asthma, may be treated more successfully through weight reduction than by asthma medication.

"True asthma is associated with a chronic inflammation of the airways, which makes the airways susceptible to certain triggers," says Frank J. Cerny, professor emeritus of pediatrics and exercise and nutrition sciences in the School of Public Health and Health Professions.

"We've shown that asthma symptoms seen in people who are overweight may be caused by the obesity-related increased pressure on the chest wall that reduces lung volume and alters the airways; in other words, by mechanics rather than inflammation. This may account for the high incidence of asthma in developed nations where the incidence of obesity is epidemic."

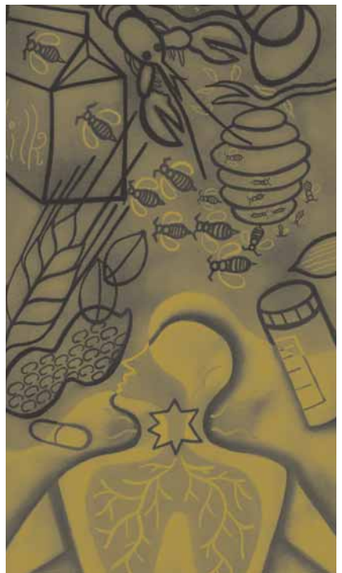

ILLUSTRATION BY AMY BROWNAWELL

The UB study was conducted with eight lean volunteers with a body mass index of BMI≤25 kg/m^2. None of the subjects had a history of asthma, smoking, cardiopulmonary disease, abdominal injury or surgery, and all had normal lung function and healthy airways.

The study was conducted under four conditions: no intervention (normal), which served as the control condition; chest loading to simulate a BMI of around 30, considered borderline obese; thigh and calf compression to create increased lung blood volume that might be experienced at a BMI of 30; and chest loading and leg compression together.

Four volunteers also underwent chest compression equal to a BMI of 42, simulating gross obesity.

Chest loading involved wearing a vest with pockets filled with buckshot to mimic the weight distribution associated with these levels of obesity. Increased lung blood volume was simulated by using a modified antigravity suit similar to those worn by astronauts to prevent blood from pooling in the lower extremities during reentry to the earth's atmosphere.

Under each study condition, volunteers received methacholine, a type of chemical in aerosol form used in airway challenge testing that produces airway constriction in persons with asthma.

Methacholine had no effect on the asthma-free participants during the control condition. However, when lung volume was reduced by chest loading, leg constriction and in combination, participants showed asthma-like symptoms. Those in the simulated BMI of 42 study had stronger reactivity.

"As the severity of simulated obesity increased, lung volume decreased and airways became hyperreactive," reports Cerny. "Decreasing lung volume upsets the regulatory mechanisms that govern the smooth muscle lining the airways and the tethers that control airway responsiveness.

"Both obesity and asthma are on the rise in developed nations and pose a major health challenge," observes Cerny. "Our study implies that, at least in some persons, the changes in airway hyperresponsiveness associated with obesity may not be asthma, which is characterized by chronic airway inflammation, but may simply reflect structural changes in the lung.

"The message to physicians is 'If you have obese patients who have asthma symptoms, it might be a good idea to get them to lose weight before putting them on medication,'" says Cerny.

Li-Ying Wang, a former UB doctoral student now at National Taiwan University, is first author on the study. Other authors, both from UB, are Thomas J. Kufel, MD, clinical associate professor of medicine, and Brydon J. B. Grant, MD, professor of medicine, physiology and biophysics, and social and preventive medicine. BP

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Post-Concussion Syndrome

New treatment pioneered at UB

By Lois Baker

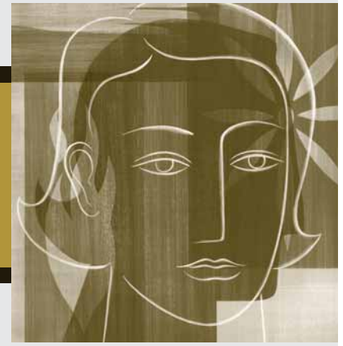


ILLUSTRATION BY SANDRA DIONISI

For unknown reasons, 5 to 10 percent of people who experience a concussion have symptoms that persist beyond the normal 10 to 14 days. Many of these individuals have symptoms that continue for months. Unfortunately, there has been no proven treatment for this lingering condition, which is called post-concussion syndrome (PCS).

Recently, however, researchers in UB's Sports Medicine Institute have developed a new method for treating PCS that, unlike the conventional treatment regimen, allows athletes to maintain conditioning while recovering gradually from the injury.

"The most common approach by physicians is to recommend no exercise and prescribe antidepressants," says Barry Willer, PhD, professor of psychiatry and rehabilitation sciences and lead author on a paper describing the new method, published in the September 2006 issue of *Current Treatment Options in Neurology.*

"Most people with PCS have symptoms of depression," says Willer, "so antidepressant treatment makes sense. However, antidepressants do little more than relieve some of the depression symptoms. We were interested in a treatment that didn't just treat the symptoms, but actually improved the patient's brain function."

The researchers call their new treatment "regulated exercise." The approach consists of determining the ideal exercise program for each athlete based on a number of individual physiological indicators at baseline.

> "Their regimen is based on the hypothesis that the regulatory system responsible for maintaining cerebral blood flow, which may be dysfunctional in people with a concussion, can be restored to normal by controlled, graded symptom-free exercise.

Patients are tested every two to three weeks with specialized equipment at the sports medicine clinic to determine their progress, and a new program is developed based on those results.

Willer and coauthor John Leddy, MD '85, clinical associate professor of orthopaedics and rehabilitation sciences, note that it is too early to call the treatment a cure, but they are optimistic about the results so far.

"This treatment is not only for athletes but would also have application to other patients who have PCS, as well," says Leddy.

The researchers described the treatment method in September at the 2006 Brain Injury Conference of the Americas in Miami, where the response was very favorable, according to Willer.

"Professionals at the meeting were delighted that our approach to treatment of post-concussion syndrome doesn't involve any medications and is very cost-efficient," he says. "We were surprised to learn that we are among only a few investigators interested in people with symptoms that won't go away.

"There is no other known treatment specifically for PCS, which we define as persistent symptoms of concussion past the time they should have cleared, usually around three weeks," adds Willer. "As far as we can determine, there is only one other group in North America that is using regulated exercise as part of the treatment for PCS."

Willer and Leddy have used regulated exercise successfully with people who were as much as six months post-concussion. Their regimen is based on the hypothesis that the regulatory system responsible for maintaining cerebral blood flow, which may be dysfunctional in people with a concussion, can be restored to normal by controlled, graded symptom-free exercise.

"The treatment program is well tolerated by patients" Willer explains. "Just being able to exercise often reduces the depressive symptoms. But it's imperative that the patient not go beyond the exercise limits.

"After the first three weeks of regulated exercise, we reassess the patient to see if there has been any change in physiology. The exercise program then is realigned successively to respond to the changes. In our experience thus far, symptoms disappear within several months for at least some of the patients," he reports.

The researchers have worked with a small number of patients to date. They have included a UB soccer player who has returned to play and now is one of the team's leading scorers. Another young athlete was able to return to cross-country running and attend school full-time. BP

A 40-year-old woman in good health falls and hits her head while visiting her roommate at her workplace.

After a trip to the emergency department, her roommate takes her home with limited instructions. Two days later she finds her dead in her bedroom from a brain hemorrhage.

Mild Brain Injury

Hospital discharge instructions faulty

By Lois Baker

ILLUSTRATION BY PATRICIA BARRY LEVY

This tragic, but true, vignette illustrates the problem of patients leaving emergency departments after suffering a concussion or mild traumatic brain injury without clear and thorough information about the signs of impending complications.

In a study published in the August 2006 issue of *Brain Injury,* researchers at the University at Buffalo found that discharge sheets from 14 of 15 hospitals that were reviewed lacked at least one important sign of a possible hemorrhage. Ten of the hospitals were located in Western New York; five were located in southern Ontario, Canada.

In addition, most instruction sheets were written at too high a reading level. Furthermore, some suggestions for concussion management were simply wrong, says Michael Fung, MD, a Canadian physician serving a fellowship in UB's Sports Medicine Institute and the study's lead author.

"We looked at information given to patients from hospitals on both sides of the U.S.-Canadian border in order to determine if the information provided was consistent with the research evidence on signs of hemorrhage," explains Fung.

"We found no difference between the countries, but major differences between hospitals. In fact, not one hospital had all of the information needed in a simple, easy-to-understand format. We were especially surprised that the designated trauma hospitals in both countries had such inadequate discharge information sheets."

The study authors include a proposed evidence-based emergency department discharge form they hope will result in universal discharge instructions for patients with mild traumatic brain injury.

The study notes that the signs accepted by brain specialists as associated most consistently with hemorrhage or equally dangerous swelling in the brain following a blow to the head are: vomiting, a worsening headache, amnesia or short-term memory loss, worsening mental status, loss of motor function or vision or speech and seizure.

The idea for the study originated with a web site managed by the Ontario Brain Injury Association that allows people to submit questions to concussion experts. Barry Willer, PhD, professor of psychiatry and rehabilitation sciences in the UB School of Medicine and Biomedical Sciences, is author of the Web site and a coauthor on the study.

"One of the most frequently asked questions is 'Why do I have to wake my child every three hours?'" says Willer. "In an attempt to answer this question, we did a thorough review of research on factors predicting hemorrhage and found that waking your child has no real value in predicting serious consequences.

"Instead, parents should be told to watch for unusual sleepiness, increasing headache, decreasing memory or increasing irritability. Parents also should be told not to allow their child to participate in any activity that places them at risk for a second concussion until a physician gives the okay."

One hospital suggested that patients could take aspirin. "Aspirin is a blood thinner that could increase the risk for hemorrhage," says Willer. "We think doctors should be cautious about allowing patients to take any medications, at least for the first 24 hours, to avoid masking symptoms like worsening headache. A worsening headache may be a major indicator that the brain is bleeding internally."

Douglas Moreland, MD, UB clinical associate professor of pathology and anatomical sciences, and John J. Leddy, MD '85, UB clinical associate professor of orthopaedics, rehabilitation sciences and family medicine and associate director of the UB Sports Medicine Institute, also were study coauthors. BP

Medical Imaging, the Next Generation

Multiple-contrast systems to provide complementary information

By Ellen Goldbaum

> Once injected with these multimodal nanoparticles, the patient can undergo several imaging tests, the results of which will be combined to provide more comprehensive and complementary information, such as correlations between molecular and morphological changes at the cellular level.

Since X-rays were discovered more than a century ago, triggering a revolution in medical imaging, clinicians have sought more powerful ways to "see" into the human body.

In keeping with this tradition, researchers in UB's Institute for Lasers, Photonics and Biophotonics are applying their expertise in nanomedicine to the development of new, nanoparticle-based multi-probe systems, spurring development of a new generation of medical imaging technologies.

Their efforts were recently given a boost by a $1.1 million grant from the John R. Oishei Foundation, which will support research aimed at combining two or more medical imaging techniques to provide complementary information.

These nanoparticle systems—part of a new field called nanobiotechnology—are being designed by the UB scientists to contain multiple contrast agents for different imaging medical techniques.

The goal is to diagnose cancer and other diseases in their earliest stages by providing far more comprehensive data to clinicians.

"Ultimately, clinicians want the most complete data possible that they can gather from medical images, ranging from tissue structure to metabolic processes to molecular markers," says Paras Prasad, PhD, executive director of the Institute for Lasers, Photonics and Biophotonics and SUNY Distinguished Professor of Chemistry.

"We are aiming to provide them with such data by developing nanoparticle platforms capable of carrying multiple contrast agents for complementary medical imaging techniques in the same nano-sized package," he explains.

Once injected with these multimodal nanoparticles, the patient can undergo several imaging tests, the results of which will be combined to provide more comprehensive and complementary information, such as correlations between molecular and morphological changes at the cellular level.

The result is a far more sensitive and comprehensive method of detecting the presence or progression of a disease.

"At the same time, these imaging agents will provide pharmaceutical researchers and clinicians with powerful tools for more precise monitoring and tracking of drug action in real-time," explains Prasad.

The multimodal platforms underway in Prasad's group are based on versatile nanoparticles that the UB researchers have developed with previous Oishei Foundation funding that have been shown to be effective in a broad range of therapeutic applications.

ILLUSTRATION BY JOEL NAKAMURA

"The fields of nanomedicine in which Dr. Prasad and his teams are working are developing extremely rapidly, and they are at the forefront," says Thomas E. Baker, president of the foundation. "The work of these grants has tremendous potential for significantly improving both the diagnostic capabilities of physicians and the clinical outcomes of patients."

The research also is being conducted with partial funding from UB's New York State Center of Excellence in Bioinformatics and Life Sciences, a major supporter of the nanomedicine program at the Institute for Lasers, Photonics and Biophotonics. Prasad is affiliated with the Bioengineering/Tissue Engineering Team at the Center of Excellence.

"This new imaging work represents an exciting and timely extension of our existing nanomedicine portfolio that will be particularly important for the Center of Excellence initiatives in neurodegenerative disease and cancer," says Bruce A. Holm, PhD, UB senior vice provost and executive director of the Center of Excellence. "This research not only crosses a variety of UB 2020 Strategic Strength areas, but holds enormous promise for commercialization potential as well."

The UB institute's new emphasis on application of nanobiotechnology to medical imaging also distinguishes it from other nanotechnology research centers throughout the U.S., while enriching its current collaborations with The Johns Hopkins University, Roswell Park Cancer Institute and others.

The nanoprobes are being developed for use with:

- Optical imaging techniques, especially those in which fluorescence and Raman scattering can probe the intracellular distribution of molecular events that are early signals of disease or responses to drugs
- Magnetic resonance imaging (MRI), in which fluorine nuclear probes would be developed using the nanoparticles, providing more selective targeting of specific biological sites
- Positron emission tomography (PET), in which radioisotopes are incorporated inside nanoparticles as contrast agents for more sensitive assessments of drug efficacy during therapy
- Computed tomography (CT) and single photon emission computer tomography (SPECT), in which radio-opaque ions are incorporated inside nanoparticles as contrast agents for improved in vivo imaging.

The Oishei grant, "Developing New Advances in Medical Imaging through Nanotechnology," will be used in part to recruit and support a research professor to provide expertise in ultrasound imaging, as well as postdoctoral fellows and graduate students who will focus on the development of multimodal nanoprobes for medical imaging.

In addition to Prasad, other key personnel involved in the research from the Institute for Lasers, Photonics and Biophotonics are E. J. Bergey, PhD, deputy director of biophotonics; Dinish Sukumaran, PhD, director of UB's magnetic resonance center; Indrajit Roy, PhD, postdoctoral associate; Tymish Y. Ohulchanskyy, PhD, postdoctoral associate; Haridas E. Pudivar, PhD, research assistant professor and Aliksandr Kachynski, PhD, research scholar, all in the Department of Chemistry. Also involved are Richard V. Mazurchuk, PhD, director of the preclinical magnetic resonance imaging facility, and Ravindra K. Pandey, PhD, professor of biophysical sciences at Roswell Park Cancer Institute; Hani A. Nabi, MD, PhD, professor and chair of nuclear medicine at UB; and Benjamin Tsui, PhD, at Johns Hopkins.

The John R. Oishei Foundation is committed to enhancing the quality of life for Buffalo-area residents by supporting education, health care, scientific research and the cultural, social, civic and other charitable needs of the community. The foundation was established in 1940 by John R. Oishei, founder of Trico Products Corporation, one of the world's leading manufacturers of windshield wiper systems. BP

ILLUSTRATION BY MARK STEPHEN

Online Resource Expands

Regional Knowledge Network adds health, human services

By Rachel M. Teaman

Which neighborhoods in the City of Buffalo have the highest percentage of disabled elderly? What is the distribution of lung cancer across Western New York? How does the rate of HIV mortality in Southern Ontario compare to that of Western New York?

Answers to these and other key questions on health in the binational Buffalo-Niagara region now can be found at the Regional Knowledge Network (RKN), an online information resource developed by UB's Institute for Local Governance and Regional Growth.

Launched in its first phase in March 2006, RKN (rkn.buffalo.edu) is designed to inform regional decision-making by providing access to data, maps, lists and resources on 10 topics for the region spanning Western New York and Southern Ontario. The latest enhancement to RKN is the addition of 79 data variables and dynamic mapping capacities for the Health and Human Services topic, a development supported by a major grant from the John R. Oishei Foundation.

"RKN is an integral component of the institute's mission to promote regional progress by building understanding on challenging topics," says Kathryn A. Foster, director of the institute. "The addition of these data and maps is an important step in RKN's development, and will help to shed light on timely health and human services policy issues."

The 79 Health and Human Services data variables cut across the categories of disability, disease, mortality, health behaviors, mental health, child health and social needs. Some patterns in regional health revealed by RKN include high rates of motor-vehicle fatalities in Western New York's rural counties, Chautauqua County as the top per-capita spender on Medicaid, and a mean of one to three years as the number of years a foster child is in foster care in Western New York.

For five of the 10 topic areas (Population and Demographics, Government, Economy, Education and Schools, and now Health and Human Services), RKN users may download data, produce customized maps or view reference maps, sort and download lists of other topical information and link to related resources. Lists and resources also are available for the other five topic areas, with data and maps in progress.

"RKN can tell provocative stories about regional issues," Foster adds. "It is our hope that RKN becomes a go-to tool for researchers, government officials, news media, and citizens in search of the most up-to-date information on Buffalo Niagara."

A new user-friendly Web interface also has been added to RKN as part of the latest round of developments. Funding from the Oishei Foundation will enable the institute to fully develop RKN by May 2008, with data and maps for all 10 topic areas and new information tools for pin-mapping, enhanced searches and advanced data charting and analysis. On tap for the addition of data and maps are the Regional Assets and Public Safety topic areas.

A major research and public service unit of UB, the Institute for Local Governance and Regional Growth plays a vital role in addressing key policy and governance issues for regions, with focused analysis of the Buffalo-Niagara region. An affiliate of the UB Law School, the institute leverages the resources of the university and binational community to pursue a wide range of scholarship, projects and initiatives that frame issues, inform decisions and guide change. BP

"The 79 Health and Human Services data variables cut across the categories of disability, disease, mortality, health behaviors, mental health, child health and social needs."

Pathway for Treating Mental Disorders

New critical drug target revealed

By Lois Baker

In their continuing search for promising targets for treating mental disorders, a group of neuroscientists in the School of Medicine and Biomedical Sciences has identified a pathway critical to the functioning of antidepressants, antipsychotic drugs and drugs for anxiety disorders.

In their research—the results of which were published in the November 13, 2006 issue of *Proceedings of the National Academy of Sciences*—the scientists focus on the noradrenergic system in the brain's prefrontal cortex. This is a region responsible for many high-level functions, such as cognitive processing, working memory and control of emotions.

"Abnormal operation of the α-adrenergic system, one type of noradrenergic receptor in the prefrontal cortex, is strongly linked to many neuropsychiatric disorders, including depression, anxiety, ADHD and schizophrenia," says Zhen Yan, PhD, a senior author on the study, along with Jain Feng, PhD.

Both researchers are associate professors of physiology and biophysics and members of the Neurodegenerative Disease Group in UB's New York State Center of Excellence in Bioinformatics and Life Sciences.

"Many antidepressant, anti-anxiety and antipsychotic drugs target the α-adrenergic system," Yan continues. "Until now it has been unclear how α-adrenergic receptors perform the complicated functions carried out by the prefrontal cortex."

The research team revealed that a critical target of α-adrenergic receptors is the NMDA-type glutamate receptor channel, which also is a pivotal player in cognition and emotion. Glutamate is a neurotransmitter normally involved in learning and memory, but under certain circumstances it can be toxic and may cause nerve cell death in a variety of neurodegenerative disorders.

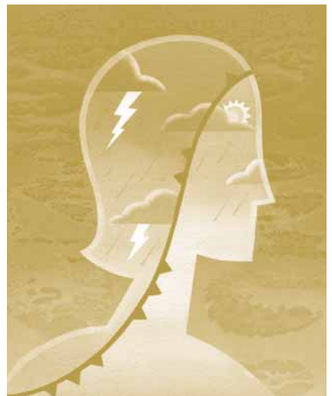
"We found that different α-adrenergic receptors regulate the activities of NMDA receptor channels by activating specific intracellular signaling cascades," says Yan. "Moreover, we have identified two important players that influence critically the regulatory effects of α-adrenergic receptors, known as RGS4 and spinophilin, which are involved in schizophrenia and depression, respectively.

"Modifying α-adrenergic signaling has been considered one of the key therapeutic actions of many current drugs," notes Yan. "To understand the functional role of α-adrenergic receptors, we needed to know their cellular targets. The NMDA receptor channel has been implicated in both normal cognitive processes and mental disorders, which makes it a potentially important target by which α-adrenergic receptors may regulate prefrontal cortex functioning.

Insights gained from this discovery eventually may provide new drug targets for various neuropsychiatric diseases, Yan says.

Wenhua Liu, PhD, and Eunice Y. Yuen, PhD, postdoctoral associates in Yan's laboratory performed the experiments. Also contributing to the research were Patrick B. Allen from the Yale University School of Medicine, and Paul Greengard from Rockefeller University.

The work is supported by grants awarded to Yan from the National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, the National Institute of Aging and the National Alliance for Research on Schizophrenia and Depression. BP



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