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Technological Breakthroughs Transform the Future of Neuroscience

Promising devices and drugs shed light on diagnosis and treatment of brain diseases

WASHINGTON, DC — As major research projects around the globe such as the BRAIN Initiative push forward the development of new technologies to better understand the brain, researchers at Neuroscience 2014 today unveiled remarkable advances in bioimaging and nanotechnology. Innovations in bioimaging allow scientists to observe and even manipulate neurons deep within the brain, leading to important findings about the neurological mechanisms underlying eating disorders, Parkinson's disease, and other brain conditions. In addition, advances in nanotechnology — including a "nanodrug" that reverses some of the features of Parkinson's disease in a mouse model — are pointing to exciting possibilities for the treatment of various brain diseases.

These findings were presented at Neuroscience 2014, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Today's new findings show that:

- Nanoparticles derived from a rare earth metal can slow down some of the brain-cell degeneration in a mouse model of Parkinson's disease, suggesting that these nanoparticles may offer a potential treatment for the disease (Beverly Rzigalinski, PhD, abstract 199.01, see attached summary).
- Using hair-thin visual probes and high-resolution fluorescence microscopes, scientists have identified separate groups of cells deep within the brains of mice that play key roles in hunger and eating, which could offer new insights into self-destructive eating disorders such as anorexia and bulimia (Garret Stuber, PhD, abstract 178.09, see attached summary).
- Using a technology called optogenetics, researchers have demonstrated in mice that the brain chemical dopamine plays a crucial role in enabling the body to move, thus helping to explain how the motor-system symptoms of Parkinson's and other movement disorders develop (Joaquim Alves Da Silva, PhD, abstract 633.15, see attached summary).

"These and other innovative technologies are truly transforming the field of neuroscience," said David Van Essen, PhD, of Washington University in St. Louis, Mo., an expert in brain mapping and a past president of SfN. "They're providing us with an unprecedented ability to monitor and control the nervous system, and are therefore helping us to devise better ways to treat or potentially prevent brain disorders that currently devastate so many lives."

This research was supported by national funding agencies such as the National Institutes of Health as well as other private and philanthropic organizations. Find out more about advances in neuroscience-related technologies at *BrainFacts.org*.

Related Neuroscience 2014 Presentation:
Minisymposium: *In Vivo* Reprogramming for Brain Repair
Monday, Nov. 17, 8:30–11 a.m., Ballroom B, WCC

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Abstract 199.01 Summary

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'Nanodrug' Shows Promise in Animal Model of Parkinson's Disease

Mice brains showed improvement after single dose

Nanoparticles derived from a rare earth metal called cerium increased dopamine circulation and cell survival in a mouse model of Parkinson's disease, according to research released today at Neuroscience 2014, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"Our research demonstrates for the first time that cerium oxide nanoparticles have the potential of slowing down, halting, or even reversing the progression of Parkinson's disease after the disease has developed," said Beverly Rzigalinski, PhD, of the Virginia College of Osteopathic Medicine in Blacksburg.

Cerium oxide nanoparticles are part of a new generation of drugs called "nanopharmaceuticals." These very, very small particles are 10 nanometers wide — a human hair is 80,000 nanometers wide. Cerium oxide nanoparticles have been shown to scavenge free radicals that cause oxidative stress. Cerium oxide nanoparticles are also thought to protect mitochondria, the cellular powerhouses that fuel neuron activity. Both oxidative stress and mitochondrial damage are believed to occur early in the development of Parkinson's disease.

An estimated 7 million to 10 million people are living with Parkinson's disease worldwide, a number that is expected to double within the next couple of decades. There are currently no effective treatments for slowing, halting, or reversing the disease's progression.

In the study released today, the researchers found that a single dose of cerium oxide nanoparticles was associated with a 50 percent improvement in the animals' dopamine levels (a brain chemical that declines in Parkinson's disease) and an 84 percent improvement in the number of healthy dopamine-producing neurons in brain areas damaged by Parkinson's. In addition, the animals' brains showed evidence of reduced oxidative stress. Together, these findings suggest that cerium oxide nanoparticles may offer a potential treatment for the disease.

Research was supported with funds from the Michael J. Fox Foundation.

Scientific Presentation: Sunday, Nov. 16, 1–4:30 p.m., Room 206

199.01. Cerium oxide nanoparticles as a disease-modifying therapy for Parkinson's disease
B.A. RZIGALINSKI, A.S. FREY, B. LOCKLER, M.J. BILLINGS, K.S. HOCKEY, C.A. SHOLAR; Dept Pharma, Virginia Col. Osteo. Med., Blacksburg, Va.

TECHNICAL ABSTRACT: Cerium oxide nanoparticles (CeONP) are highly efficient mitochondrial protectants and regenerative free radical scavengers. Our prior work in the MPTP-mouse model of Parkinson's disease found that administration of CeONP prior to MPTP challenge could completely protect mice from dopaminergic loss. In the present work, we tested the hypothesis that CeONP may be a disease-modifying therapy for Parkinson's disease when delivered after development of the disease. C57Bl/6 mice were treated with 20 mg/kg MPTP given in 4 injections spaced 2 hrs apart. CeONP (0.05-5.0 micrograms/g) was delivered intravenously in a single dose, 12 hrs after the last MPTP injection. Seven days later, mice were euthanized and dopamine content in the striatum was measured. Dopaminergic neurons in the substantia nigra were stained and sterotaxically counted. Lipid peroxidation levels in the brain were also measured. We found that: • CeONP increased the levels of TH+ neurons in the substantia nigra, when delivered alone (No MPTP) • CeONP preserved striatal dopamine by approximately 50%, when delivered after development of the disease. • CeONP preserved dopaminergic neurons in the substantia nigra to 84-87% of controls when delivered after development of the disease • CeONP decreased basal levels of lipid peroxidation in the cortex. These results suggest that CeONP may halt or slow disease progression. Further, the ability of CeONP to promote growth of neurons in the substantia nigra suggests the potential to reverse PD.

Abstract 178.09 Summary

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Advanced Imaging Technique Offers New Opportunities for Understanding Addiction and Eating Disorders

Research identifies specific brain cells involved in feeding and reward

Using advanced bioimaging technology, researchers have identified separate groups of cells deep within the brains of mice that play key roles in hunger and eating, a discovery that offers new prospects for understanding the neurological underpinnings of anorexia, bulimia, and other self-destructive behaviors. The findings were presented today at Neuroscience 2014, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"The area of the brain we focused on — the lateral hypothalamus — is known to be involved in elements of eating, including hunger and consumption," said Garret Stuber, PhD, of the University of North Carolina at Chapel Hill. "Until now, however, we didn't know which particular cells within that area of the brain contribute to each of those behaviors."

To identify those cells, Stuber and his colleagues introduced fluorescent proteins that can detect changes in neural activity into neurons in the lateral hypothalamus, the region of the brain critical to a range of functions, including feeding and controlling reward processes. They also implanted thin visual probes called microendoscopes directly above these cells. When coupled with very high-resolution fluorescence microscopes, these devices enable scientists to observe and record how cells function while animals are in action and engaged in complex behaviors.

The researchers found that different neurons within the lateral hypothalamus became activated when the mice consumed food compared to when the mice worked to gain access to food, although the processes were highly intertwined. This finding suggests that some of the symptoms of eating disorders may derive from the haywire activity of specific groups of cells within the lateral hypothalamus. Learning how to regulate the activity of those cells may offer promising avenues for treatment.

Research was supported with funds from the Klarman Family Foundation and the National Institute on Drug Abuse.

Scientific Presentation: Sunday, Nov. 16, 8–9 a.m., Halls A-C

178.09, Deep-brain calcium imaging of distinct lateral hypothalamic neuronal ensembles reveals a precise neural signature for motivation
G. D. STUBER[1], J. H. JENNINGS[1], R. L. UNG[1], A. M. STAMATAKIS[1], K. VELETA[1], K. SHILLING-SCRIVO[1], W. GAO[2], K. DEISSEROTH[3], *C. RAMAKRISHNAN[4], S. OTTE[5]; [1]Psychiatry, [2]Radiology, [4]Bioengineering, [3]Univ. of North Carolina at Chapel Hill, Chapel Hill, N.C.; [5]Inscopix, Palo Alto, Calif.

TECHNICAL ABSTRACT: An organism's need for nutrients is a fundamental requirement of survival and is satisfied through discrete components of feeding, including motivation and consumption. Delineating the neural underpinnings of each feeding element may help explain how maladaptive hedonic and anhedonic behaviors manifest in conditions associated with overeating, addiction, and depression. Given that more than 50 neuronal products in the brain have experimental consequences on feeding behavior, uncovering the precise neural representation that is unique to both features of feeding has remained a major challenge. The lateral hypothalamus (LH), a well-conserved neurosubstrate, is thought to regulate both motivational and consummatory aspects of feeding, since gross activation of the structure can elicit feeding and promote positive reinforcement behavior. However, the LH is comprised of numerous molecularly defined neuronal populations that possess various neural and peripheral inputs, thus the discrete nodes within the LH that selectively compute specific aspects of feeding remains poorly understood. Therefore, we aimed to monitor and modulate the activity patterns within genetically defined LH neuronal ensembles during various behavioral tasks, where hungry animals work to obtain calories. To accomplish this, we implanted microendoscopes directly into the LH and interfaced the lens with a mini-epiflourescence microscope to image inhibitory LH neurons expressing the engineered calcium indicator (GCaMP6m) in freely behaving mice. We resolved somatic calcium dynamics from ~100 inhibitory LH neurons per freely moving mouse. Calcium transients from individual cells were tracked across several behavioral assays in order to determine if their activity patterns are altered as a function of behavioral demand. By monitoring large-scale network activity in vivo, we discovered discrete motivation-coding ensembles within the LH that displayed time-locked calcium transients during motivational responses. Complimentary to these findings, optogenetic activation of these inhibitory LH neuronal populations promotes positive reinforcement behavior. We also plan to activate these neurons during motivational feeding tasks with chemogenetic approaches. In addition, cell-type specific ablation of inhibitory LH neurons demonstrated the necessity of these neurons for regulating energy balance. Collectively, these data reveal that precise motivation-coding ensembles within the LH coordinate feeding and positive reinforcement behavior, suggesting that alterations of this motivation-coding scheme might underlie overeating and addiction-related disorders.

Abstract 633.15 Summary

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Recent Technology Helps Explain Decrease in Motion Seen in Parkinson's Disease

Dopamine brain cells linked directly to body's ability to initiate movement

Using a recently developed technique called optogenetics, researchers have demonstrated in mice that the brain chemical dopamine plays a crucial role in enabling the body to initiate physical movement. This finding promises to help scientists develop a better understanding of how changes in the brain's production of dopamine lead to specific motor-system symptoms in Parkinson's disease and related movement disorders. The research was presented today at Neuroscience 2014, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"It's long been known that the destruction of dopamine-producing neurons is a hallmark of Parkinson's disease, but until now, the connection between the loss of those neurons and the inability to initiate movement, a symptom of Parkinson's, wasn't clear," said Joaquim Alves da Silva of the Champalimaud Center for the Unknown in Lisbon, Portugal. "Our research indicates that dopamine neurons are critical to initiate movement, thus supporting a link between the loss of these neurons and the decrease in motion associated with Parkinson's disease."

To study the role that dopamine plays in initiating movement, Alves da Silva and his colleagues turned to freely moving mice and a technology called optogenetics, which uses light to manipulate neurons with a genetically modified sensitivity to light. The researchers found that inhibiting dopamine neurons in a midbrain structure called the substantia nigra in freely moving mice increased the amount of time the animals took to initiate movement. Using the high temporal resolution of optogenetics, researchers could determine that this decrease in motion was due to an impairment in movement initiation without an increased tendency to stop or disturb ongoing movements. Conversely, activating dopamine neurons in mice when they were immobile promoted the animals' movement.

Although the study involved healthy mice, the findings offer a new hypothesis for how dopamine changes may lead to motor-system symptoms in Parkinson's disease and other movement disorders. This new understanding may provide insight into opportunities for treatment for the estimated 6.3 million people worldwide who have Parkinson's disease, including 1 million living in the United States.

Research was supported with funds from European Research Council and Gulbenkian Advanced Medical Programme.

Scientific Presentation: Tuesday, Nov. 18, 3–4 p.m., Halls A-C

633.15. Substantia nigra dopaminergic neurons are critical for the initiation of self-paced actions

J. ALVES DA SILVA[1], F. TECUAPETLA[2], V. PAIXÃO[1], R. M. COSTA[1]; [1]Champalimaud Neurosci. Programme, Champalimaud Ctr. for the Unknown, Lisbon, Portugal; [2]Inst. de Fisiología Celular, Univ. Nacional Autónoma de México, Mexico City, Mexico

TECHNICAL ABSTRACT: We frequently initiate new actions and transitions between actions. Although vital to our survival, most of the time we are not aware of this orchestration of action sequences. However, for people with Parkinson's disease, initiating movement when they want becomes especially daunting. Among other changes in the brain, these patients present with a loss of substantia nigra compacta (SNC) dopaminergic neurons. Recently, phasic activity of these same neurons has been found to be correlated with the start and stop of a learned action sequence. However, it is still not clear if this activity is necessary for action initiation. We are using an optogenetic approach to evaluate the role of SNC dopaminergic neurons in the initiation of self-paced movement in mice. This strategy enables us to specifically inhibit or activate dopaminergic neurons, with millisecond resolution, while analyzing mice behavior using 3-axis accelerometers and video recordings. We have found that inhibiting SNC dopaminergic neurons while mice were exploring an open field, lead to a decrease in motion and an increase in the time spent immobile. However, if the mice were moving before inhibition started, their motion did not change until they stopped for the first time. Likewise, the latency to stop was not different during inhibition. On the other hand, if the mice were not moving before the inhibition, they stayed immobile or in a low acceleration state during the period of inhibition. Mice were also trained in a self-paced operant task and developed a particular sequence of actions to obtain an outcome. We found that inhibiting SNC dopaminergic neurons just before action initiation delayed the start of the action sequence. However, if the inhibition started immediately after the action sequence was initiated, the performance of the action remained unchanged. In preliminary experiments, a very brief activation of SNC dopaminergic neurons was sufficient to promote movement when the mice were immobile in the open field. These observations suggest that SNC dopamine neurons are specifically necessary for the initiation of movement but not for the maintenance of ongoing movements. To corroborate these findings, we are recording the activity of genetically identified dopamine neurons during movement/action initiation.