Embargoed until Oct. 15, 11:30 a.m. CST
Press Room, Oct. 13–17: (504) 670-4630

Contacts: Kat Snodgrass, (202) 962-4090
Todd Bentsen, (202) 962-4086

NEW FINDINGS COULD HELP SPEED RECOVERY, ALLEVIATE PAIN ASSOCIATED WITH SPINAL CORD INJURY

Deep brain stimulation, electric pulses, and social contact emerge as potential aids

NEW ORLEANS — Research released today demonstrates how new scientific knowledge is driving innovative treatments for spinal cord injuries. Spinal cord damage is debilitating and life-altering, limiting or preventing movement and feeling for millions worldwide, and leading to chronic health conditions and pain. The new studies suggest potential therapies for managing the aftermath of pain and pressure sores, repairing nervous system damage, and speeding recovery. The findings were presented at Neuroscience 2012, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

In the United States, approximately 12,000 people are hospitalized for spinal cord injury (SCI) each year, and at least 270,000 people live with it. The initial injury is usually compounded by a wave of immune activity that can extend the initial nervous system damage, and complications of SCI may include pain and pressure sores that compromise the quality of life. New research is tackling all of these dimensions of SCI.

Today's new findings show that:

- Nervous system tracts that are left intact but nonfunctioning following SCI appear to be reactivated through deep brain stimulation, speeding recovery of walking in a rodent model (Brian Noga, PhD, abstract 678.12, see attached summary).
- Painful and sometime life-threatening pressure sores due to immobilizing nervous system injuries may be prevented by underwear wired to deliver tiny electrical currents that contract the paralyzed buttocks muscles, mimicking the natural fidgeting of able-bodied people (Sean Dukelow, MD, PhD, abstract 475.09, see attached summary).
- Carbon monoxide's anti-inflammatory effects appear to accelerate healing in rats with spinal cord injury, possibly by altering the balance of immune cells and limiting the damage caused by molecules called free radicals (Yang Teng, MD, PhD, abstract 450.11, see attached summary).
- Social contact appears to lessen the pain that follows peripheral nerve injury. A new mouse study correlates the healing social behavior with biochemicals in the brain and spinal cord (Adam Hinzey, abstract 786.04, see attached summary).

"While the damage of SCI can appear to be immediate and dramatic, the biological events that lead to extensive nerve and tissue damage are complex, and injuries evolve over time," said press conference moderator Jacqueline Bresnahan, PhD, of the University of California, San Francisco, an expert on nervous system trauma caused by spinal cord injuries. "Today researchers are finding ways to intervene in the cascade of molecular changes that follow SCI. From understanding immune cell responses to the healing power of social contact, researchers are finding new ways to treat and rehabilitate patients."

This research was supported by national funding agencies such as the National Institutes of Health, as well as private and philanthropic organizations.

# # #

Abstract 678.12 Summary

Lead author: Brian Noga, PhD (305) 243-6155
The Miami Project to Cure Paralysis bnoga@miami.edu
University of Miami
Miami, Fla.

Deep Brain Stimulation Restores Locomotion in Rats with Partial Spinal Cord Injuries

Treatment enhances function of uninjured pathways connecting brain and spinal cord

Many cases of paralysis following spinal cord injuries (SCI) could potentially be avoided by deep brain stimulation (DBS), according to a new rodent study. Some 61 percent of new SCI in the United States are "partial," meaning some brain fibers that descend to the nerve cells in the spinal cord that activate the legs, are intact — although they may not be functioning at peak capacity or at all. New research in a rodent model shows that DBS appears to bring some of these fibers back on-line and improve walking. The findings were presented at Neuroscience 2012, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

DBS has been used relatively safely and effectively to treat thousands of patients for movement disorders such as Parkinson's Disease, but has been used rarely after SCI. Now, new study results reported by Brian Noga, PhD, of the University of Miami, show that DBS can enhance the function of uninjured pathways connecting the brain and spinal cord in rodents.

"Undamaged descending nerve pathways appear to be viable targets for improving walking following incomplete SCI," Noga said. "These results are encouraging news, since DBS could be quickly translated into a versatile treatment depending on the nerve pathways affected."

In the study, the researchers used an electrical implant to stimulate the midbrain locomotor region in rodents in which the spinal cord was injured, but not completely severed. This activated a number of descending nerve fibers that control walking. With the therapy, improvements in speed of locomotion and distance travelled were observed over a 10-week study period in rats with mild-to-moderate contusion injuries. In addition, rats that had been unable to step following injury began walking. The results show that DBS can re-activate anatomically intact pathways that function poorly after injury.

Research was supported with funds from The Christopher and Dana Reeve Foundation, The Craig Neilsen Foundation, and the National Institute of Neurological Disorders and Stroke.

Scientific Presentation: Tuesday, Oct. 16, 4–5 p.m., Hall F-J

678.12, Improvements in locomotor speed and endurance with deep brain stimulation of the mesencephalic locomotor region in animals with contusive spinal injuries
B. R. NOGA, C. O'TOOLE, F. J. SANCHEZ, K. H. LEE, *I. D. HENTALL; Miami Project Cure Paral, Univ. Miami Schl Med., MIAMI, FL; Mayo Clin., Rochester, MN

TECHNICAL ABSTRACT: Stimulation of the mesencephalic locomotor region (MLR) initiates locomotion via descending pathways which activate spinal locomotor generating neurons. Here we examined the use of electrical deep brain stimulation (DBS) of the MLR to acutely facilitate treadmill locomotion in animals with partial spinal cord injuries (SCI). Rats were subject to contusion injury at the 8th thoracic level following implantation of DBS electrodes. With DBS, we found significant improvements in the maximum attainable speed both before and after spinal surgery. In control animals, DBS significantly increased maximum speed: uninjured, by 46.8% from a mean of 42.7±10.3 to 62.7±19.5 SD m/min (n=15, paired samples t-test). One week after mild contusion injury, DBS increased maximum speed by 82.5% from 24±9.4 to 43.8±22.7 m/min (n=6). At 4 weeks, DBS improved locomotor speed by 63.1%, from 42.5±11.9 to 69.3±24.7 m/min (n=4). One week after moderate injury, when locomotor performance was lowest, DBS induced stepping in animals without weight support and a slight increase in stepping, from 9.3±9.02 to 12±11.14 m/min, in animals with weight support. By 4 weeks, when locomotion had improved, DBS increased speed of locomotion from 19.6±10.5 to 26.3±13.8 m/min, a 34.2% improvement (n=3; approaching significance). Endurance tests were conducted at a 15° incline (starting at 10 m/min and increasing 1 m/min every 2 min). DBS significantly increased total distance travelled by 42.8% or by an additional 361.7±208.7 m from baseline levels of 761.9±328.6 m uninjured control animals (n=13). DBS increased total distance by an additional 266.5±94.6 m (n=4; 39.7%) from the baseline level of 689.5±205.3 m, tested at 4 weeks post mild injury. At 10 weeks, DBS increased the total distance traveled by 180.7±136.5 m from the baseline level of 587.7±133.5 m, a 30.7% increase (n=6). Following moderate contusion injury (4 weeks), DBS increased baseline values of 175.5±57.3 m by 85.0±15.6 m (n=2; 48.6% increase with slight increases in overall distance travelled at 10 weeks of injury. Significant improvements in locomotor speed and endurance after spinal injury are observed with DBS of the MLR. These findings indicate the potential usefulness of this method for improving walking in persons with chronic SCI.

Abstract 475.09 Summary

Senior author: Sean Dukelow, MD, PhD (403) 944- 5930
Hotchkiss Brain Institute, University of Calgary sean.dukelow@albertahealthservices.ca
Calgary, Canada

Underwear Wired to Deliver Tiny Electrical Currents Appears to Prevent Pressure Sores

Innovative technology could help end epidemic of painful sores that often follow immobilizing spinal cord injuries

Smart underwear — called Smart-e-Pants — with a built-in electronic system to deliver tiny electrical currents appears to prevent the development of pressure ulcers in patients with immobilizing spinal cord injury. The underwear uses electrodes that convey intermittent electrical stimulation, contracting the buttock muscles. Pressure ulcers are painful open wounds typically over bony areas of the body. The findings were presented at Neuroscience 2012, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Pressure ulcers cause an increased risk of infection, hospitalization, and death. In the United States alone, 60,000 people each year die from complications related to pressure ulcers. The economic cost is also staggering, estimated at $11 billion annually in the United States and $3.5 billion in Canada.

The mini-muscle contractions generated by the underwear mimics the subconscious fidgeting of able-bodied individuals, stimulating blood flow and redistributing pressure away from the sitting bones. Sean Dukelow, MD, PhD, of the University of Calgary reported that, of the 33 clinical care patients who wore the underwear, none developed pressure ulcers during the two-month study period. The underwear delivered muscle-contracting stimulation for 10 seconds every 10 minutes, 12 hours a day, and four days per week for up to two months.

"Pressure ulcers can be terribly debilitating. Their incidence has not changed since the 1940's, indicating that the current methods of prevention simply are not working," Warwaruk Rogers said. "Our hope is that this innovative, clinically friendly system will eventually make a difference in the lives of millions of people." Researchers plan to follow up with further efficacy studies.

Research was supported with funds from Alberta Innovates – Health Solutions.

Scientific Presentation: Monday, Oct. 15, 1–2 p.m., Hall F-J

475.09, Smart-e-Pants: A novel neural prosthetic device for the prevention of deep tissue injury in spinal cord injury and other neurological disorders
R. A. WARWARUK ROGERS, A. AHMETOVIC, D. SCHNEPF, R. SOMMER9, L. KAWASAKI, G. ISSACSON9, V. MUSHAHWAR, M. CHAN, ***S. P. DUKELOW**, Clin. Neurosciences, Hotchkiss Brain Inst., Fac. of Med., Univ. of Calgary, Calgary, AB, Canada; Ctr. for Neurosci., Dept. of Pharmacol., Dept. of Cell Biol., Fac. of Med. and Dent., Univ. of Alberta, Edmonton, AB, Canada; Allen Gray Continuing Care Ctr., Edmonton, AB, Canada; 9Glenrose Rehabil. Hosp., Edmonton, AB, Canada

TECHNICAL ABSTRACT: Pressure ulcers (PU), specifically deep tissue injury (DTI) are a common complication in people with reduced mobility such as those with spinal cord injury. DTI originates in the muscle layer around a bony prominence, resulting from unrelieved loading causing sustained mechanical deformation and ischemia to the underlying tissue. PUs decrease health status, mobility, increase pain, and may require invasive surgical reconstruction procedures of the affected area and can be fatal. Despite advances in pressure relieving strategies, DTI continues to impact patient health negatively and contributes substantial costs to the healthcare system.
In this study, we examined the safety and feasibility of a novel prevention system for DTI: Smart-e-Pants. The Smart-e-Pants system is a neural prosthetic device that involves a stimulator designed to deliver intermittent electrical stimulation (IES) via electrodes placed directly on the skin or through an engineered garment. The electrodes are applied over the motor point of the gluteus maximus muscle. Simulation causes contraction of the gluteus maximus to mimic the subconscious fidgeting movements of able bodied people. Previous studies in animals have demonstrated significant increases in tissue oxygenation and pressure redistribution in response to IES. The aim of the Smart-e-Pants device is to prevent the development of DTI in individuals with spinal cord injury and others with immobility. In the present study the Smart-e-Pants system was tested in a variety of patient care settings. Subjects with immobility (n=23) wore Smart-e-Pants and received IES for 12 hours a day, 4 days per week, for 4 weeks to induce muscle contractions in the gluteus maximus. The system administered stimulation for 10 seconds at 10 minute intervals during periods when subjects wore the garment. We assessed the system for safety and feasibility during periods of garment application and removal by quantifying patient and healthcare staff responses to measures of time demands for application and removal, acceptability for participant and caregiver, skin irritation, and muscle contraction stability. Smart-e-Pants received positive ratings from both patients and healthcare staff. The system was generally safe and the time demands were reasonable for application and removal. No one in the present study developed a PU during the experimental period. Our results suggest that IES may be an acceptable method for the prevention of PU's, but further efficacy studies are necessary.

Abstract 450.11 Summary

Senior author: Yang D. Teng, MD, PhD (617) 525-8676
Harvard Medical School and yang_teng@hms.harvard.edu
Veterans Affairs Boston Healthcare System
Boston, Mass.

Breathing Carbon Monoxide Could Accelerate Healing from Spinal Cord Injuries

Gas given to rodents appears to limit nerve damage caused by inflammation

Research with rodents shows that carbon monoxide (CO) inhalation treatment can improve walking and reduce damage caused by a spinal cord injury (SCI). The treatment appears to work by interfering with the body's inflammatory response to the injury. While all the CO doses were low in this experiment, the larger the CO dose inhaled, the stronger the recovery. The findings were presented at Neuroscience 2012, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

The damage caused by SCI comes in two phases: the instant damage caused by mechanical insults, and a second phase during which the body's defense response generates small molecules that can continuously kill nerve cells far from the primary injury. The new research, first authored by Inbo Han, MD, a neurosurgeon and research fellow in the Laboratory of Yang (Ted) Teng, MD, PhD, appears to improve recovery from SCI by reducing the harmful effects of the inflammatory response.

"Effective treatment for acute spinal cord injury remains an unmet medical demand, and the need for an answer is obvious," Teng said. "We explored the possible use of CO as a therapy based on prior research showing that it readily crosses the blood-brain barrier, and has a protective effect on cells in the lungs."

In the study, four groups of rats with induced spinal cord injuries were housed inside exposure chambers that contained 100, 250, or 500 parts per million (ppm) CO, or normal room air. The rats underwent one hour of exposure to CO or room air inhalation treatment daily for 12 days. The rats receiving 500 ppm CO inhalation exposure showed the most improvement in walking, reduction in nerve lesion volume, and survival of motor neurons. In addition, molecular analysis found a shift in the balance of macrophages (a type of immune system cell), limiting the damage caused to still-living nerve cells.

Research was supported with funds from Center for Integration of Medicine and Innovative Technology —Department of Defense, Veterans Affairs Research & Development, and Massachusetts SCI Cure Research Fund.

Scientific Presentation: Monday, Oct. 15, 3–4 p.m., Hall F–J

450.11, Neuroprotection resulting from low-dose carbon monoxide inhalation in rat spinal cord injury
*I. HAN, E. IFEDIGBO, D. YU, A. E. ROPPER, H. HARAGOPAL, S.-W. KIM, A. M. K. CHOI, **Y. D. TENG**;
Dept. of Neurosurg., Div. of Pulmonary and Critical Care Med., Harvard Med. School/Brigham & Women's Hosp., Boston, MA; Div. of Spinal Cord Injury Res., VA Boston Healthcare Syst., Boston, MA; Dept. of Neurosurg., CHA University, CHA Bundang Med. Ctr., Seoungnam, Kyeunggido, Korea, Republic of; Div. of Periodontology, Harvard Sch. of Dent. Med., Boston, MA; Dept. of PM&R, Harvard Med. School/Spaulding Rehabil. Hosp., Boston, MA

TECHNICAL ABSTRACT: Background and Object: Inflammation plays major roles in the pathogenesis after spinal cord injury (SCI). Carbon monoxide (CO) confers anti-inflammatory protection in rodent models or clinical cases of lung injury when applied at low concentration. We investigated the effects of low dose CO ventilatory exposure with a special focus on their effect on macrophage activation after SCI.
Methods: SCI was produced by 35 g weight compression for 5 minutes at the level of T9-T10 in female Sprague-Dawley rats. Immediately following recovery from general anesthesia (3-4h post surgery), four groups of rats were randomly housed inside whole body exposure chambers that contained 100, 250 and 500 ppm CO (n=7/each group) or control air (n=7/group), respectively. The rats underwent 1hour of CO exposure each day for 12 consecutive days. Locomotor function recovery was evaluated, spinal cord samples were analyzed for measurement of lesion volume, white matter sparing, and motor neuron survival; we used immunohistochemistry and Western blot analyses to examine the anti-inflammatory effect of CO on the injured spinal cord.
Results: SCI rats treated with low concentration CO inhalation demonstrated a dose-dependent therapeutic effect for neural recovery, with those receiving 500ppm exposure manifesting most significantly improved hind limb locomotion recovery, decreased lesion volume, and increased white matter and motor neuron sparing, compared with control treatment of room air ventilation. The neuroprotective outcome is associated with increased numbers of alternatively activated macrophages (M2 phenotype: arginase-1 or CD206-positive) and decreased numbers of classically activated macrophages (M1 phenotype: iNOS or CD86-positive).Conclusions: Our data suggests that 500 ppm CO inhalation can markedly modify the inflammatory environment by shifting the macrophage phenotype from M1 to M2. CO inhalation treatment, with its capacity of selective activation of macrophages plus other known effects of impeding oxidative damage, may provide a novel neuroprotection therapy for traumatic SCI and neurodegenerative diseases.

Abstract 786.04 Summary

Lead author: Adam Hinzey (614) 688-4665
Ohio State University adam.hinzey@osumc.edu
Columbus, Ohio

Social Contact Unleashes Molecules that Lessen Pain in Nerve-Injured Mice

Changes silence inflammatory chemicals in the brain and spinal cord

The pain that follows peripheral nerve injury — sometimes weeks or months after the original injury — can be devastating. Mouse studies show that social interaction can reduce the severity of some types of nerve-injury related pain, and a new study suggests it may do so through altering the production of inflammatory molecules in the brain and spinal cord. The findings were presented at Neuroscience 2012, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Chronic pain harms the quality of life of millions of people and costs an estimated $560 billion through direct health-care costs and lost wages in the United States. Now, Adam Hinzey, a graduate student at Ohio State University, reports on a mouse study that reveals a possible biological mechanism behind the apparently pain-soothing impact of social contact.

"Our research shows that the company of another mouse can alleviate pain associated with a type of nerve damage in which even a light touch can be painful," Hinzey said. "We've identified a shift in two important molecules involved in the inflammatory response to nerve injury. Further investigation could lead to treatments that decrease the pain in peripheral nerve injury patients."

In both chronically stressed and non-stressed nerve-injured mice, the researchers found that social contact through pair-housing increased the animals' ability to withstand a greater force of touch before they feel pain. Furthermore, the researchers identified two immune-system molecules linked to inflammation — IL-1β and IL-6 — found in the brain and/or spinal cord, which appear to be involved in the chemical pathways that are altered by social contact.

Research was supported with funds from the National Institute of Nursing Research.

Scientific Presentation: Wednesday, Oct. 17, 11 a.m.–12 p.m., Hall F–J

786.04, Social interaction reduces allodynia response to peripheral nerve injury
A. HINZEY, B. JARRETT, K. A. STULLER, *A. C. DEVRIES; Neurosci., Ohio State Univ., COLUMBUS, OH

TECHNICAL ABSTRACT: Peripheral nerve injury often leads to allodynia, pain arising from typically innocuous stimuli, which in turn can become a debilitating disorder, extending the recovery period from trauma and significantly decreasing quality of life after injury. Social interaction and stress have been shown to significantly affect the development of allodynia after spared nerve injury (SNI) in mice. While stress exacerbates allodynia after SNI, pair housing decreases SNI-induced allodynia, as compared to socially isolated controls. We sought to identify potential physiological mediators of these effects in the brain and spinal cord among pair-housed versus isolated mice in our model of spared nerve injury (SNI). We hypothesized that social interaction, as compared to isolation, would be able to attenuate stress-induced hypersensitivity to mechanical stimuli following nerve injury. Male mice were pair housed with an ovariectomized female or socially isolated for 1 week prior to SNI, and also exposed to chronic stress or no stress for 3 days prior to SNI. Chronic restraint stress exacerbated the development of mechanical allodynia, and by day 7 post-SNI pair housed animals showed significantly less hypersensitivity to mechanical stimulation in both the stressed and non-stressed experimental groups. In addition, pair housing resulted in a significant decrease in mRNA expression of IL-1B, a proinflammatory cytokine, in both spinal cord and right prefrontal cortex in non-stressed SNI animals, offering insight into the possible mechanisms through which social interaction may mediate its effects on development of the neuroinflammatory response to SNI. We also observed a significant decrease in proinflammatory IL-6 mRNA expression in the spinal cord in stress versus non-stressed animals. Together these results demonstrate that social interaction is capable of reducing the severity of allodynia following SNI, and suggest that alterations in neuroinflammation in the brain and spinal cord may underlie the observed behavioral effects.