Embargoed until Nov. 15, 3:15 p.m. EST
Press Room, Nov. 12–16: (202) 249-4080

Contacts: Kat Snodgrass, (202) 962-4090
Melissa Malski, (202) 962-4051

BRAIN, REPAIR THYSELF: STUDIES HIGHLIGHT BRAIN'S RESILIENCY TO DAMAGE

Findings suggest new treatments to limit damage from stroke, very premature birth

Washington — New research released today demonstrates the brain's remarkable capacity to repair itself. The animal studies, which propose ways to prevent or limit damage after blood and oxygen deprivation and blood clots, were presented at Neuroscience 2011, the Society for Neuroscience's annual meeting and the world's largest source of emerging news about brain science and health.

Stroke is the number one cause of long-term disability and the third leading cause of death in the developed world. Limiting the damage caused by stroke would improve patient prognosis.

Today's new findings report:

- Sensory stimulation protects against stroke damage if administered within the first two hours of stroke onset, whether animals were awake or anesthetized (Ron Frostig, PhD, abstract 781.15, see attached summary).
- An animal study suggests that auditory stimulation delivered soon after a stroke protects from damage (Ron Frostig, PhD, abstract 781.14, see attached summary).
- An animal study identifies a cellular mechanism that blood vessels use to clear their own clots (Jaime Grutzendler, MD, abstract 891.17, see attached summary).

Other recent findings discussed show that:

- Oxygen deprivation in very premature babies born before their lungs are fully developed can interfere with myelin, the fatty protective structures surrounding nerve cells. Animal studies discussed today define cellular changes that lead to white matter damage in preemies, and molecular pathways that can be potentially targeted to promote repair (Vittorio Gallo, PhD, see attached speaker summary).
- A human study identifies that a protein called AXIN2 is affected by white matter injuries in infants. Further research showed that mice given a drug preventing AXIN2 destruction repaired myelin faster than other mice, suggesting AXIN2 may be an important therapeutic target (David Rowitch, MD, PhD, see attached speaker summary).

"The brain is remarkably robust," said press conference moderator Mark Paul Goldberg, MD, a neurologist at the University of Texas Southwestern Medical Center and an expert in brain injury. "Many of the brain's systems have mechanisms that allow it to protect or repair itself. With the help of further research we can better understand these mechanisms and find new applications for treating brain injuries."

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

Related Presentation:

Symposium: **Neurobiology of Perinatal Brain Injury**
Wed., Nov. 16, 8:30–11 a.m., Ballroom A

# # #

Abstract 781.15 Summary

Senior author: Ron Frostig, PhD (949) 824-2883
University of California rfrostig@uci.edu
Irvine, Calif.

Sensory Stimulation Protects from Stroke Damage in Awake Animals

First time effect is shown without anesthesia

Exploring an engaging, novel environment soon after a stroke protects rats from brain damage, according to new research presented at Neuroscience 2011, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. The findings suggest that sensory stimulation benefits stroke recovery whether the victim is anesthetized or awake.

Previous studies, led by Ron Frostig, PhD, of the University of California, Irvine, found that anesthetized rats undergoing an ischemic stroke could be protected from brain damage if they received sensory stimulation within two hours of stroke onset. The current study found rats were also fully protected if immediately awakened from anesthesia after ischemic stroke and placed in an "enriched environment" replete with buried treats, tunnels, and toys. Conversely, rats revived from anesthesia three hours following the stroke and placed in the same environment suffered damage.

"A phrase commonly heard in stroke treatment is 'time is brain,'" said Frostig. "It may be possible to develop a stroke treatment strategy that could be initiated by a friend, loved one, or first responder prior to arrival at a treatment facility," he said.

Research was supported by the National Institute of Neurological Disorders and Stroke.

Scientific Presentation: Wednesday, Nov. 16, 10–11 a.m., Halls A–C

781.15, Active exploration completely protects rodent cortex from ischemic stroke following permanent MCA occlusion
C. C. LAY, Q. VU, M. F. DAVIS, C. H. CHEN-BEE, **R. D. FROSTIG**; Neurobio. & Behavior, Univ. of California, Irvine, Irvine, CA

TECHNICAL ABSTRACT: Using a rodent model of ischemic stroke (permanent middle cerebral artery occlusion; pMCAO), our laboratory previously demonstrated that mechanical single whisker stimulation treatment delivered under an anesthetized condition within two hours of ischemic onset confers complete protection from impending infarct. Rats that received the identical treatment three hours following ischemic onset lost neuronal function and sustained a substantial infarct. The present study examined, using functional imaging and histological analysis, whether cortical activation is also protective in behaving, unrestrained rats that actively explore an enriched environment. Rats were revived from anesthesia either immediately or three hours after pMCAO - at which point they were allowed to freely explore the enriched environment. Rats that explored immediately after ischemic onset maintained normal neuronal function and were histologically equivalent to sham-pMCAO controls (animals that underwent surgery without occlusion of MCA). Rats that were revived three hours post-pMCAO exhibited eliminated cortical activity and sustained ischemic infarct. Thus, early active exploration following pMCAO results in neuroprotection from ischemic infarct, and this result was independent of anesthetic effect. If applicable to humans, the study of neuroprotective cortical activation via sensory stimulation may lead to innovative treatment strategies that help protect the human brain from stroke.

Abstract 781.14 Summary

Senior author: Ron Frostig, PhD (949) 824-2883
University of California rfrostig@uci.edu
Irvine, Calif.

Sound Stimulation Prevents Stroke Damage in Animal Model

Stimulating blood-deprived regions of the brain may be protective

Auditory stimulation applied soon after stroke reduces brain damage, according to new animal research presented at Neuroscience 2011, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. If these findings translate to humans, they could help develop a stroke treatment that could be applied even before an ambulance arrives.

Previous research showed that stimulating a rat's whisker within two hours of an interruption of blood flow to the brain prevented brain damage. The whisker stimulation activated a part of the rat's brain that was deprived of blood. A team led by Ron Frostig, PhD, of the University of California, Irvine, asked whether stimulating blood-deprived brain regions in other ways might produce similar results.

Instead of stimulating whiskers, the team played intermittent sounds to activate the auditory cortex, part of the brain affected by this stroke. The auditory stimulation prevented damage completely in some rats and decreased damage by up to 90 percent in the rest.

"This evidence suggests that the activation of blood deprived brain regions by sensory stimulation may be enough to protect from stroke damage," said Frostig. "If these results hold for humans, it may aid the development of non-invasive, non-pharmacological interventions for stroke victims that could be administered by informed friends and family," he said.

Research was supported by the National Institute of Neurological Disorders and Stroke.

Scientific Presentation: Wednesday, Nov. 16, 9–10 a.m., Halls A–C

781.14, Stimulation of auditory cortex following permanent MCA occlusion confers complete or near complete protection from ischemic stroke in the adult rat
M. F. DAVIS, C. C. LAY, C. H. CHEN-BEE, **R. D. FROSTIG**; Neurobio. & Behavior, UC Irvine, IRVINE, CA

TECHNICAL ABSTRACT: Previous research in our lab has demonstrated that when delivered within 2 hours following ischemic onset, single whisker stimulation can completely protect from impending cortical stroke following a permanent middle cerebral artery occlusion (pMCAO) in an adult rat model. In the current study we sought to determine whether another type of sensory stimulation, auditory stimulation, could also be protective following pMCAO. To test this we delivered auditory stimulation (5 Hz white noise delivered in the same pattern and over the same period as in our previous whisker stimulation model) immediately post-pMCAO in a new experimental group (n=10). Intrinsic signal optical imaging was used to record evoked functional activity before occlusion, during the stimulation treatment period, and on the following day and 2,3,5-triphenyltetrazolium chloride (TTC) staining was used to assess infarct at 24 hours post occlusion. Auditory stimulation delivered immediately following pMCAO resulted in complete or near complete cortical protection compared to untreated (no stimulation) pMCAO controls. Six of ten animals were completely protected by auditory stimulation. These results demonstrate that protective cortical activity is not limited to activation in somatosensory cortex. The 4 animals that did sustain injury had extremely small infarct (mean=5.4mm3 +2.3mm3) located in a region of the endangered area most distant from auditory cortex (in the anterior extent of the ischemic region). These infarct data are interesting given the differences in location of cortical activation for whisker versus auditory stimulation in relation to the area jeopardized by pMCAO. In the previous study, whisker stimulation, which activates an area central to the ischemic region, completely protected all animals from infarct. In contrast, in the current study, auditory stimulation, which activates cortex towards the posterior extent, at the periphery of the ischemic region, does not always confer complete protection and occasionally results in a small amount of infarct in the anterior most region of the jeopardized cortex. This suggests that while the proximity of cortical activation to the ischemic region is relevant, the protective effect does not require cortical activity to be central to the ischemic tissue. Understanding the limitations and requirements for this sensory stimulation induced protection is critical should this work have translational potential.

Abstract 891.17 Summary

Senior author: Jaime Grutzendler, MD (312) 503-5298
Yale University School of Medicine jaime.grutzendler@yale.edu
New Haven, Conn.

Blood Vessel Cells Have a Mechanism To Clear Their Own Clots

Newly discovered mechanism may remove materials that block small blood vessels

Blood vessel cells may be capable of removing blockages from small blood vessels, according to animal research presented at Neuroscience 2011, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. The findings suggest a natural system works to clear clots in the smallest blood vessels.

Blockages in small blood vessels lead to many brain pathologies, like stroke and age-related cognitive decline. To study small vessel clots, scientists, led by Jaime Grutzendler, MD, of Yale University School of Medicine infused fluorescently labeled clots into mouse arteries and observed the blood vessels' reaction.

The study found that within one day, blood vessel cells engulfed the nearby clots. Within three days, the vessels pushed the clots to the space outside of the vessel. Researchers term this mechanism "angiophagy." Their study also showed that clot-busting enzymes, whether produced by the body or given as a treatment, are inefficient at clearing clots in small vessels.

"Our results suggest a new physiologic mechanism to be studied and understood in the context of both normal health and disease," said Grutzendler. "Better understanding of angiophagy may lead to improved clinical outcomes for many conditions in which small blood vessels become obstructed," he said.

Research was supported by the National Institutes of Health.

Scientific Presentation: Wednesday, Nov. 16, 1–2 p.m., Halls A–C

891.17, Endothelial engulfment of emboli is a fundamental mechanism of cerebral microvascular recanalization
B. HINER, C. K. LAM, T. YOO, **J. GRUTZENDLER**; Neurol., Northwestern Univ., Chicago, IL

TECHNICAL ABSTRACT: Embolic events in the cerebral microcirculation are a relatively common phenomenon and may play a role in many pathological and iatrogenic processes. Apart from the fibrinolytic system no other physiologic mechanism for re-establishing microvascular patency following embolic occlusion has been identified. We have delineated the natural course and consequences of cerebral microvascular occlusions by using high resolution confocal, transmission electron, and two-photon microscopy of microemboli in post-mortem tissues and the living mouse brain. Emboli that failed to be washed out or lysed within 24 hours were found to translocate outside the vessel lumen leading to complete re-establishment of blood flow and vessel sparing. Recanalization occurred by previously unknown mechanisms of microvascular plasticity involving the enveloping of emboli by endothelial processes followed by their translocation into the brain parenchyma which we term "angiophagy". Microvascular occlusion in young mice was not associated with perivascular cell death or persistent synaptic injury. However, in aged mice, angiophagy was markedly delayed resulting in tissue hypoxia, synaptic damage and cell death. Alterations in angiophagy efficiency may have important implications in stroke recovery, vascular dementia and other microvascular pathologies.

Speaker's Summary

Speaker: Vittorio Gallo, PhD (202) 476-4996
Children's National Medical Center vgallo@cnmcresearch.org
Washington, DC

Enhancing oligodendrogenesis and white matter function after perinatal brain injury: molecular and cellular targets (736.03)

Symposium: Neurobiology of Perinatal Brain Injury

Wednesday, Nov. 16, 9:10–9:45 a.m., Washington Convention Center, Ballroom A

A significant pediatric and adult public health concern is the growing population of very preterm infants. Chronic neurological disabilities - including neurodevelopmental and cognitive delays - occur with increased frequency in premature infants of very low birth weight, as do behavioral disorders, epilepsy, and cerebral palsy. Most of these infants have premature lungs at birth, resulting in a failure to oxygenate (hypoxia). Although premature infants experience severe respiratory problems, most of them survive and demonstrate progressive neurodevelopmental improvement by adolescence. Major causes of chronic disability in survivors reflect morphological and structural changes in the brain, with main disturbances in the white matter. Sustained neurodevelopmental and sensorimotor impairments correlate with diffuse white matter injury, commonly identified in premature infants by brain neuroimaging. Diffuse white matter injury is now considered as a major cause of delay in brain development in premature infants and there are currently no specific targeted therapies available.

Myelin is an electrically insulating material that forms a layer around the axons of neurons. The production of the myelin sheath is called myelination, a crucial developmental process that occurs in the brain predominantly during infancy and continues through the adolescent stages of life. Timely myelination has been associated with proper locomotor and cognitive development in children. Alterations in white matter development due to perinatal brain damage are usually associated with significant disruption of myelination. As oligodendrocytes are the cells responsible for myelination, understanding the cellular and molecular mechanisms of oligodendrocyte development and maturation in white matter following hypoxia in vivo is essential for developing therapeutic strategies to prevent neurodevelopmental deficits associated with this pathology in premature infants.

We are using a mouse model of chronic perinatal hypoxia, which closely mimics the global alteration in brain development evident in infants born prematurely, to investigate cellular and molecular mechanisms responsible for diffuse white matter injury. The goal of our studies is to define the cellular changes that occur in white matter and in oligodendrocytes after hypoxia that are responsible for death of these cells and for delayed myelination. We also want to identify molecular pathways that are active in the developing white matter that can be targeted to promote oligodendrocyte repair after hypoxia. Oligodendrocytes originate from immature cells called oligodendrocyte progenitor cells; therefore we are particularly interested in targeting these cells to promote oligodendrocyte regeneration under pathological conditions.

Our studies demonstrate that - similar to the human brain - exposure of mice to hypoxia a few days after birth exerts a biphasic effect on white matter development, resulting in myelination delay and chronic functional impairment. In particular, hypoxia induced oligodendrocyte death during a critical developmental time window, causing long-term alterations in functional myelination. In order to identify molecular targets that promote timely oligodendrognesis after hypoxia, we analyzed the cell cycle pathways involved in oligodendrocyte progenitor cell proliferation and differentiation in white matter after hypoxia. We identified two molecular targets, cyclin-dependent kinase-2 (Cdk2) and $p27^{Kip1}$ as crucial regulators of timely oligodendrocyte regeneration after hypoxia. In conclusion, our studies demonstrate long-term effects of perinatal hypoxia in white matter development and function. We also identify Cdk2 and $p27^{Kip1}$ as main regulators of oligodendrocyte differentiation under hypoxic conditions, and as potential therapeutic targets to promote oligodendrogensis and restore timely myelination in diffuse white matter injury in premature infants.

Research was supported by the National Institute of Neurological Disorders and Stroke, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Speaker's Summary

Speaker: David Rowitch, MD, PhD (415) 476-7242
University of California, San Francisco rowitchd@peds.ucsf.edu
San Francisco, Calif.

Promoting myelin repair in human newborn brain injury (736.04)
Symposium: Neurobiology of Perinatal Brain Injury
Wednesday, Nov. 16, 9:45–10:20 a.m., Washington Convention Center, Ballroom A

Over 60,000 very low birth weight (<1.5 kg) preterm neonates are born yearly in the United States. Such infants suffer from a range of neurological impairments such as damage to the white matter of the brain leading to cerebral palsy, learning and behavioral problems. Although the mechanisms of such injuries are poorly understood, new research in Dr. Rowitch's laboratory at the University of California, San Francisco has identified a new molecular player, and shows how such injuries might one day be treated. The study used human brain tissue and mice to explore the function of cells called oligodendrocytes. These cells make myelin sheaths, the fatty structures that surround nerve cells and help them send their signals more effectively.

In pre-term babies born before their lungs are fully developed, as well as full term infants with difficult deliveries, lack of oxygen can disrupt the brain's ability to make myelin. Without myelin, brain cells are dysfunctional and may die, leaving children vulnerable to neurological deficits. We have become very good at keeping these premature babies alive, but we have no strategy to prevent the long-term neurological consequences that can occur in them," says Vittorio Gallo, a neuroscientist at the Children's National Medical Center in Washington DC.

The research done by Rowitch and colleagues at the University of Cambridge, UK, point the way towards such a strategy. By studying the brains of babies who had died after incurring brain injuries caused by a lack of oxygen, they discovered that a gene called AXIN2 was expressed in infants with white-matter brain injuries. The AXIN2 protein interacts with proteins in the Wnt signaling pathway, which is involved in controlling many cellular processes, including development.

The investigators went on to study young mice with white-matter nerve damage similar to that seen in premature babies. When the researchers injected myelin-deficient regions in the mice with a drug that prevents destruction of the AXIN2 protein, the mice grew myelin sheaths faster than untreated mice, repairing the damage. There's a lot of work needed before we want to seriously propose that this is going to be a therapeutic avenue," says Rowitch. "But this is the first evidence that this pathway can be manipulated therapeutically. Dr. Stephen Fancy, a postdoc working with Rowitch, says that the work could be very important for multiple sclerosis. Although treatments are available for the disease, they do not repair the damage to nerve cells. "This is going to be important in the future, both for multiple sclerosis and different types of newborn white-matter injury," Fancy says.

This type of animal and cellular research is crucial for understanding the biology of disease and can identify chemicals that may be worth testing in humans. More animal research will be needed to determine whether the chemical used in this study or similar chemicals appear to be effective and safe enough for testing in human trials. Such research takes time, and not all chemicals that show promise in animals are effective or safe in humans. However, the finding offers a new avenue of exploration for potential treatments for diseases such as multiple sclerosis and like pre-term white matter injury.

Research was supported by the National Institutes of Health, Howard Hughes Medical Institute, and the National Multiple Sclerosis Society.