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BRAIN RESEARCH FINDINGS IDENTIFY NEW TREATMENTS AND KNOWLEDGE ABOUT PREEMIE AND NEWBORN BRAIN FUNCTION

Researchers increasingly see brief 'window of opportunity' to protect and repair the infant brain

Washington, DC — Research released today offers new evidence of the highly vulnerable state of the newborn brain and creates potential for evaluating current or new neonatal medical interventions. The findings, presented at Neuroscience 2008, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news on brain science and health, report on new opportunities to diagnose potential long-term brain disorders and mitigate dangers of anesthesia use on newborns, and signal potential problems with a steroid treatment currently used to manage premature birth that may cause brain cell death in infant mice.

Findings such as these contribute to a greater understanding of the brain early in development and hold potential to improve neonatal outcomes, especially for the growing number of premature infants who survive due to recent research and medical progress.

Today's new findings:

- Animal research suggests that keeping a neonate cool may help prevent a potential side effect of anesthetics commonly used for early newborn therapeutic and diagnostic interventions (Catherine Creeley, abstract 355.6, see attached summary). Recent evidence has shown that anesthetic drugs can trigger programmed brain cell death in infant animals — hypothermia has been found to reduce this nerve cell death in infant mice.
- Following a lack of oxygen or blood in the newborn brain, a new brain scan technique may create a diagnostic yardstick to evaluate the severity of the injury and improve the quality of prognosis (Jacqueline Coats, 553.27, see attached summary). Crucial differences in the scan results may tell parents how likely a child is to recover and whether there may be structural brain injury.
- In an animal study, steroid treatments given to some women in preterm labor and to some premature infants with breathing difficulties caused brain cell death in infant mice — leading to damage in the developing cerebellum (Kevin Noguchi, abstract 355.13, see attached summary).

Other recent findings discussed show that:

- The excitability and amazing plasticity of the infant brain make it both more vulnerable to assault and more capable of repair. The newborn brain provides a potential window of opportunity in which doctors can help protect and repair the infant brain to a greater extent than previously recognized (see attached speaker's summary).

"The brain is the body's most complex organ, and early wiring success, or failure, has long-lasting implications," said press conference moderator Donna Ferriero, MD, of the University of California, San Francisco. "We are learning a great deal about the potential to identify, reverse, or treat neonatal brain disorders. With more research, we will make more progress for these vulnerable patients — and even improve outcomes by leveraging the newborn brain's tremendous potential to recover."

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Related Presentation:

Special Lecture: **Imaging Selective Vulnerability in the Newborn Brain**
Saturday, November 15, 2–3 p.m., Washington Convention Center, Hall D
# # #

Abstract 355.6 Summary

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Hypothermia Prevents Brain Cell Death Caused by Anesthesia in Infant Mice

Findings may aid in the development of safer anesthetics

Hypothermia reduces normal nerve cell death and prevents nerve cell death due to anesthesia in infant mice, according to new research presented at Neuroscience 2008, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. The findings may aid the development of anesthetics that are safer for use in human infants.

"For human infants requiring surgical treatment, it has been widely assumed that the benefits of anesthesia are achieved without adverse consequences," said study co-author John Olney, MD, from the Washington University School of Medicine. "However, this assumption has been called into question by recent evidence that anesthetic drugs can trigger neuroapoptosis — programmed death of nerve cells — in the brains of infant animals," Olney said.

Olney and colleagues found that in infant mice incubated at normal or high temperatures, the anesthetic drug isoflurane increased neuroapoptosis. However, low-temperature incubation blocked neuroapoptosis caused by isoflurane and also reduced the low level of neuroapoptosis that normally occurs during brain development.

"These results suggest that temperature regulation may be an effective means of ensuring that anesthetic drugs will not delete nerve cells from the developing brain," said Olney. "In addition, our findings have potentially important implications for preventing neuroapoptosis associated with other pathological processes affecting the developing human brain."

The research was supported by the U.S. National Institutes of Health. Olney has a patent pending on methods for protecting the developing brain derived from separate findings.

Scientific Presentation: Monday, November 17, 9–10 a.m., Washington Convention Center, Hall A-C

355.6, Hypothermia prevents spontaneous and anesthesia-induced neuroapoptosis in the infant mouse brain
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TECHNICAL ABSTRACT: Drugs that suppress neuronal activity, including many anesthetics, trigger neuroapoptosis in the developing rodent brain. If suppression of neuronal activity *per se* is sufficient to cause apoptosis of developing neurons, it is interesting to consider what would happen if all of the neurons in the brain were suppressed at the same time, for example, by lowering the temperature of the brain. And, what if neuronal activity were suppressed by exposure to an anesthetic drug at the same time that it is being suppressed by hypothermia? To address these questions, 4 day-old infant mice (n = 10 per gp) were exposed to room air or to isoflurane (0.75%) for 4 hrs at a low (24.5°C), intermediate (30°C) or high (36.5°C) ambient temperature. The pups were euthanized 1 hr after cessation of isoflurane and the brains evaluated quantitatively for neuroapoptotic profiles, as revealed by activated caspase 3 immunohistochemical staining. We found that all of the infants exposed to isoflurane at high temperature had a robust neuroapoptotic response several-fold greater than in controls exposed to the same high temperature, whereas all of the pups exposed either to air or to isoflurane at low temperature had very few apoptotic neurons anywhere in the brain. In addition, in controls at low temperature, the rate of neuroapoptosis was suppressed to a level below the rate in controls at either the intermediate or high temperatures, signifying that this degree of hypothermia suppressed spontaneous neuroapoptosis that occurs naturally in the brain, while also totally eliminating the neuroapoptosis response to isoflurane. Similar effects of temperature were observed in experiments pertaining to other anesthetic drugs (e.g., ketamine and propofol). Thus, warming of the immature brain is conducive to a maximal expression of either spontaneous or anesthesia-induced neuroapoptosis, and cooling markedly suppresses both of these apoptotic processes. Supported by HD 37100, DA 05072 , T32 MH14677.

Abstract 553.27 Summary

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Imaging Differences May Predict Consequences of Neonatal Brain Injury

Findings may help improve accuracy of long-term prognoses for injured infants

Brain scans may help predict the consequences of neonatal brain injury, according to a meta-analysis presented at Neuroscience 2008, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. The study identified differences between brain scans of injured infants who went on to develop normally and those who experienced long-term neurological disability. These findings may help clinicians improve the accuracy of long-term prognoses for injured infants.

A temporary lack of blood or oxygen in the neonatal brain can result in hypoxic-ischemic injury (HII). Severe HII can cause long-term disabilities and brain disorders, including cerebral palsy and epilepsy. "Informing parents about their child's prognosis is very important, as many children will need special medical and nursing care, different forms of therapy, and medications to treat associated conditions," said Andre Obenaus, PhD, of Loma Linda University, a co-author of the study.

Obenaus and colleagues examined published imaging data on healthy newborns and those that experienced HII. The reports used an imaging technique called diffusion weighted imaging, which shows the movement of water in brain tissue. In injured regions of the brain, water movement is restricted early after HII.

Compared with healthy newborns, the researchers found that HII infants that went on to have long-term problems (poor outcomes) showed reductions in water diffusion in several brain regions. In contrast, HII infants who went on to develop normally (good outcomes) were similar to healthy newborns.

HII infants with good and poor long-term outcomes showed differences in one brain region — the occipital cortex, which is primarily involved in vision. According to Obenaus, changes in water diffusion in HII infants with poor outcomes may indicate structural injury to the brain.

These data may support the diagnostic use of brain imaging in infants that experience HII. "Such imaging information can be used to help better understand whether a particular newborn with HII has mild, moderate, or severe injury and whether there may be long-term disability," Obenaus said.

The research was supported by the Pediatric Research Fund and an anonymous donation to the Loma Linda University School of Medicine.

Scientific Presentation: Tuesday, November 18, 10–11 a.m., Washington Convention Center, Hall A-C

553.27, MRI meta-analysis of the newborn brain
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TECHNICAL ABSTRACT: ***Introduction***: Global blood flow reduction in the term neonate can cause hypoxic-ischemic injury (HII) to the brain. The resultant bilateral lesions are visible on MRI using diffusion weighted imaging (DWI) techniques. The apparent diffusion coefficient (ADC) is a quantitative measure of free water diffusion (Brownian motion) in biological tissues and is calculated from DWIs. ADC measurements in HII lesions can quantify injury severity when compared to normative ADC values. Although DWI is the clinical standard for diagnosis of newborn HII, currently there are no definitive data for normative ADC values in the term newborn brain. We performed a meta-analysis to establish normative ADC standards for the term newborn brain and compared them with those from term HII newborns.

Methods: We reviewed 59 published studies and excluded 45 based on our meta-analysis parameters. ADC measurements from the remaining 14 primary studies were grouped and then stratified into three levels of increasing anatomical specificity: tissue type (n = 3; gray matter (GM), white matter (WM), cerebellum), tissue distribution (n = 6; e.g. cortex, WM tracts) and anatomical structures (n = 14; e.g., basal ganglia (BG), posterior limb of internal capsule (PLIC)). HII data were dichotomized into good and poor outcome groups. Data were analyzed using the random-effects meta-analysis model.
Results: Normative data: The 95% CIs for normative ADCs in the newborn brain are presented. ADCs were the lowest in the PLIC and the highest in frontal WM. HII data: In both outcome groups GM and WM tissue ADCs were significantly lower than the normative values. In the poor outcome group ADCs were significantly lower than normative values in the GM, cortex, WM tracts, BG and PLIC.
Conclusion: Normative ADC values were lower in deep brain structures compared to cortical regions and may reflect the level of tissue maturation and WM myelination. Based on the differences observed between the normative and HII poor outcome groups, reduced ADC values in the BG and PLIC suggest pathologies that might be associated with increased risk of neurological sequelae. Further research should elucidate the relationship between ADC measurements and neurological outcomes. Most importantly, these differences support clinical experience and provide a matrix for future investigations of HII in the newborn brain.
Supported by the Pediatric Research Fund and an anonymous donation to the School of Medicine.

Abstract 355.13 Summary

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Animal Study Finds that Corticosteroids, Used to Speed Lung Development in Preemies, Cause Brain Cell Death in Mice

Findings may impact treatment guidelines in humans

A range of corticosteroid hormones that are used to prevent lung collapse in premature infants appear to cause brain cell death in infant mice, according to new research. The study was presented at Neuroscience 2008, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Synthetic corticosteroid hormones, like betamethasone and dexamethasone, are given to premature infants and women at risk of premature birth to accelerate fetal lung maturation. "However, this study creates possible concern about the use of these agents, as clinical evidence has shown that neonatal exposure may produce permanent neuromotor and cognitive deficits," said Kevin Noguchi, PhD, at Washington University, who led the study.

To address the mechanism behind these adverse effects, the researchers treated one-week-old mice — thought to be similar developmentally to premature human infants — with a single dose of one of several different corticosteroids. They found that every corticosteroid tested caused a similar pattern of nerve cell death, or apoptosis, in the cerebellum, a brain region involved in motor control and cognition. This effect was reduced by a drug that blocks glucocorticoid receptors.

In a related study presented elsewhere at the meeting, the researchers found that these corticosteroid treatments in infant mice appear to cause behavioral deficits later in life. If the same result is found in humans, doctors might need to weigh the life-saving ability of corticosteroid drugs against their potential effects in the brain.

"Ultimately, these findings raise new questions about the safety of corticosteroids at a time when the rates of premature birth have risen dramatically," Noguchi said.

The research was supported by the U.S. National Institutes of Health.

Scientific Presentation: Monday, November 17, 8–9 a.m., Washington Convention Center, Hall A-C

355.13, Acute exposure to multiple corticosteroids can induce selective apoptotic cell death in the neural progenitor cells of the developing cerebellum of neonatal mice
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TECHNICAL ABSTRACT: There has been a growing concern regarding the safety of corticosteroid therapy to treat respiratory dysfunction associated with prematurity as mounting clinical evidence has shown neonatal exposure produces permanent neuromotor and cognitive deficits in humans. We have previously reported that neonatal dexamethasone (a synthetic corticosteroid) exposure at clinically relevant doses can induce selective apoptosis in the neural progenitor cells of the developing mouse cerebellum and produce permanent reductions in cerebellar neuronal cell counts. (Noguchi et al. SFN 2006). In addition, we have found that exposure to this same drug can induce permanent behavioral deficits consistent with neuromotor dysfunction (Fortenbury et al., SFN 2008). Questions exist about dexamethasone's blood-brain permeability and whether its CNS effects are due to a direct stimulation of CNS glucocorticoid receptors or are due to dexamethasone's suppression of endogenous glucocorticoid release, resulting in decrease stimulation of CNS glucocorticoid receptors. Here we show that a single exposure to one of a variety of endogenous and synthetic corticosteroids (e.g. betamethasone, corticosterone) can produce an identical pattern of cerebellar apoptotic death in PND7 ICR mouse pups. In addition to this, we show that the glucocorticoid antagonist mifepristone (RU-486) can reduce this corticosteroid induced neural progenitor cell apoptosis. Taken as a whole, these results suggest that the selective stimulation of glucocorticoid receptors is responsible for the cerebellar toxicity seen following corticosteroid exposure.

Speaker's Summary

Speaker: Donna Ferriero, MD **(415) 502-1099**
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Special Lecture: **Imaging Selective Vulnerability in the Newborn Brain**
Saturday, November 15, 2–3 p.m., Washington Convention Center, Hall D

Stress on the newborn brain due to lack of oxygen or blood supply can have devastating consequences. For example, stroke in a newborn occurs in 1 in 2500 births, a figure comparable to stroke in the elderly. The newborn who survives may have lifelong disabilities such as epilepsy, cerebral palsy, mental retardation and learning and behavioral problems.

Images of the newborn brain show patterns of injury to the brain after a stroke that are somewhat predictable, depending on the age of the baby when the injury occurred and on the severity and type of injury. In a baby who is born very prematurely, this type of injury will affect the pathways contained in the white matter of the brain and can result in severe motor and visual handicaps. In a baby born at term, the injury will more likely be seen in the gray matter of the brain - the nerve cells themselves. If it is severe, this type of injury is much more devastating. These children are more likely to have severe cerebral palsy, seizures and epilepsy, and severe mental retardation.

By understanding how these injuries occur and develop, we can devise therapies that may either prevent, rescue or repair the damaged tissue.

We know that the newborn brain lacks antioxidant enzymes. These enzymes could help counteract the stress that is created in situations where the brain doesn't receive enough blood supply or oxygen. However, there are also enzyme systems that can generate toxic molecules that prevent the brain from responding well to this stress.

We also know that the newborn brain is very "excitable" (easily triggered into action.). It is rich in receptors that allow for rapid conduction of messages, but this same system allows the brain to send harmful messages as well. The newborn brain is set up so that over 50% of nerve cells will die a programmed cell death. This is necessary for the brain to develop appropriately and make the right connections. However, this same mechanism allows the brain to increase its rate of cell death in situations like stress caused by lack of blood supply.

The best feature of the newborn brain is that it has plasticity, or the ability to recover and develop after these stresses. Capitalizing on this phenomenon of plasticity, new therapies are being tested in human newborns. For example, we know that reducing body temperature can be used as a treatment in a full-term newborn who has suffered from lack of oxygen during birth. This treatment will reduce both the risk of death and the extent of permanent disabilities. The search continues for additional therapies that may not only rescue the brain but actually promote repair. Studies in animals using the drug erythropoietin, a hormone that makes new red blood cells, show an increase in the number of new neurons after a newborn stroke.

Images of the human newborn brain show that the injury suffered after an initial stress event at birth can continue to develop over weeks. Therefore, the window of opportunity to protect and repair the brain is actually quite large. The future brings much hope for these challenged babies.