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TRAUMATIC INJURY RESEARCH WORKING TO IMPROVE THE LIVES OF CITIZENS AND SOLDIERS

New studies consider transgenic mouse as mine-sweeper, test dietary supplement for brain injuries

NEW ORLEANS — New studies presented today offer vivid examples of how advances in basic brain research help reduce the trauma and suffering of innocent landmine victims, amateur and professional athletes, and members of the military. The research was presented today 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.

From the playing field to the battlefield, neuroscientists are gaining better understanding of what happens to the brain when it suffers traumatic injury or repeated hits. While the chronic learning and memory deficits that often accompany such damage have been resistant to treatment, opportunities for effective early intervention to minimize long-term damage may be on the horizon. Scientists are also creatively applying new insights into how our brain senses odors, to better detect landmines and help both soldiers and civilians avoid becoming casualties of war.

Today's new findings show that:

- United Kingdom soldiers who sustained blast-related traumatic brain injuries were more likely to have injuries in the brain stem and cerebellum than were civilian victims of non-blast traumatic brain injuries. Damage to the "white matter" in the brains of both groups could only be detected using an advanced form of magnetic resonance imaging (David Sharp, PhD, MBBS, abstract 315.04, see attached summary).
- Frustrated by the lack of treatments for chronic neurological problems that frequently follow traumatic brain injury, scientists searched the brain for potential therapeutic targets and focused on inflammatory pathways. Now, they may have averted memory problems in brain-injured mice by giving them a widely available dietary supplement derived from tobacco that appears to suppress inflammation (Fiona Crawford, PhD, abstract 315.02, see attached summary).
- Scientists report developing a transgenic mouse with enhanced capacity to smell the explosives used in landmines, with the hopes they can be deployed to detect landmines in affected areas (Charlotte D'Hulst, PhD, abstract 815.09, see attached summary).

Another recent finding shows that:

- Scientists using mice to study the effect of a single encounter with a model of military blast injury found the effects of blast winds alone — which can reach 330 miles per hour — appear sufficient to induce a brain injury. They also discovered that immobilizing the head may help reduce the severity of injury (Ann McKee, MD, see attached speaker's summary).

"These studies are particularly outstanding for how they take some of the most complex and cutting edge science of our time and translate it into practical applications that can have an enormous, visible impact on people's lives," said Jane Roskams, PhD, of the University of British Columbia, an expert on brain repair and neural regeneration. "That one day a mere mouse might save a child from losing a limb while walking across an old mine field, or a simple dietary supplement could make life more bearable for a brain injury victim shows why the field of neuroscience is attracting so much interest these days."

– more –

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

Related Presentation:

Fred Kavli Public Symposium: **The Societal Impact and Biology of the Overt and Hidden Dysfunctions Resulting From Traumatic Brain Injury**
Saturday, Oct. 13, 1:30–4 p.m., New Orleans Theater B
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Abstract 315.04 Summary

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Blast-related Traumatic Brain Injury Appears More Likely to Damage Brain's Motor Control Regions than Non-Blast Brain Injuries

Sophisticated technology captures damage overlooked by conventional imaging

Blast-related traumatic brain injuries appear more likely than non-blast injuries to damage the back lower region of the brain, which is responsible for motor control and other essential life functions. These and similar injuries sustained in the brain's "white matter" cannot be accurately detected by conventional magnetic resonance imaging (MRI), yet they can be devastating. The injuries were found using an advanced form of MRI, known as diffusion tensor imaging (DTI). 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.

Around 60 percent of the injuries to United Kingdom soldiers sustained in Afghanistan have been the result of explosive devices. While exposure to the primary blast wave is a major cause of death and disability, it has been unclear whether injuries caused by blast are distinct from other types of traumatic brain injury (TBI). The study, reported by lead author David Sharp, PhD, MBBS, of the Computational, Cognitive and Clinical Neuroimaging Laboratory at the Imperial College London, compared blast-related traumatic brain injuries sustained by U.K. soldiers in Afghanistan to non-blast traumatic brain injuries in civilians.

The study imaged the brains of 20 U.K. soldiers recently exposed to blast, 40 civilian TBI patients not exposed to blast, and 40 age-matched controls. All patients had moderate-to-severe brain injuries. The study specifically looked at injury to the brain's white matter, that part of the brain that contains axons, nerve cell projections that transmit messages between cells and regions in the brain.

Brain images collected using DTI revealed extensive white matter injury following both blast TBI and non-blast TBI. The damage occurred in both the orbitofrontal cortex (involved in cognition and decision-making) and the posterior fossa (containing the brain stem and cerebellum, two areas critical for motor control and other essential life functions). However, white matter damage in the posterior fossa was more likely to be found in blast victims of traumatic brain injury.

Research was supported with funds from The Medical Research Council (UK) and the Royal Centre for Defence Medicine.

Scientific Presentation: Monday, Oct. 15, 8–10:30 a.m., Room 288

315.04, Traumatic axonal injury after exposure to blast: A comparison of white matter damage in blast and non-blast traumatic brain injury (Blast Injury Outcome Study in Armed forces Personnel - BIOSAP)

*__D. J. SHARP__, R. LEECH, T. E. HAM, P. J. HELLYER, A. MISTLIN, A. BENNETT, N. KITCHEN, M. MIDWINTER, D. BAXTER,; Div. of Neurosci. and Mental Hlth., Imperial Col. London, London, United Kingdom; Div. of Brain Sci., Computational, Cognitive and Clin. Neuroimaging Lab., Imperial College London, United Kingdom; Defence Med. Rehabil. Ctr., Headley Court, London, United Kingdom; Academic centre for Musculoskeletal and Rehabil. Med., Leeds University, United Kingdom; Inst. of Neurol. and Neurosurgery, Univ. Col. London, London, United Kingdom; Royal Ctr. for Defence Med., Birmingham, United Kingdom

TECHNICAL ABSTRACT: *Introduction*: Around 60% of the injuries to UK soldiers sustained in Afghanistan have been the result of explosive devices. Exposure to the primary blast wave is a significant cause of morbidity and mortality. However, it is unclear whether blast causes brain injury that is distinct from other types of TBI. Traumatic axonal injury (TAI) is an important cause of poor clinical outcome after traumatic brain injury (TBI). Diffusion tensor imaging (DTI) can be used to quantify TAI, A recent study of mild blast traumatic brain injury (bTBI) found evidence for TAI in the middle cerebellar peduncles and orbitofrontal white matter that was felt to be specific for bTBI (Mac Donald et al., New Eng J Med 11). Here we extend this work by: 1) studying the pattern of white matter damage following moderate and severe bTBI; and 2) comparing bTBI with a group of non-blast civilians (nb) TBI with injuries of similar severity.

Methods: We studied 20 UK soldiers recently exposed to blast in Afghanistan, 40 civilian TBI patients not exposed to blast and 40 age-matched controls. All patients had moderate-to-severe TBI (Mayo criteria). High resolution T1 and gradient-echo (T2*) imaging and sixty-four direction DTI was collected. Voxelwise analysis of the fractional anisotropy (FA) was carried out using tract based spatial statistics (TBSS) in FSL. Additional region-of-interest analysis focused on areas studied by Mac Donald and colleagues.
Results: Evidence for extensive TAI (low FA) was observed in the bTBI group compared to non-TBI controls. Multiple white matter tracts were affected, including within the posterior fossa and orbitofrontal cortex. This white matter injury was not observed with standard MRI imaging. Extensive damage was also observed in the nbTBI group compared to non-TBI controls. A direct whole-brain comparison of bTBI and nbTBI showed no group differences. In a subgroup of patients with contusions (n = 9 bTBI and 10 nbTBI) region-of-interest analysis showed significantly greater white matter abnormality in the middle cerebellar peduncle, as well as the anterior limb of the internal capsule.
Conclusions: Standard structural MRI imaging does not reveal the full extent of white matter pathology following bTBI. In contrast, DTI is able to demonstrate extensive white matter injury after both moderate/severe blast and non-blast TBI. Over most of the brain the pattern of WM damage observed in blast TBI was similar to non-blast injury. However, in a subgroup of bTBI, greater white matter damage was seen within the white matter of the posterior fossa. This provides further evidence that bTBI produces greater white matter damage within the posterior fossa.

Abstract 315.02 Summary

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Study in Mice Finds Using Dietary Supplement for Traumatic Brain Injury May Help Retain Memory Skills

Widely available dietary supplement is derived from tobacco

Each year traumatic brain injury (TBI) inflicts long-term neurological disabilities on thousands of people, including a large number of U.S. military personnel, yet there are no effective drugs for treating their chronic problems. But in a new study, scientists report spatial memory loss in mice suffering from TBI appears to have been averted by treating them with an anti-inflammatory dietary supplement derived from tobacco leaves.

The findings were presented today 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.

"We began with extensive efforts to understand what happens in the brain after TBI and found that inflammatory pathways are significantly affected," said Fiona Crawford, PhD, the study's senior author. "We wanted to see if inhibiting these inflammatory responses might have an impact on the memory problems that frequently develop after TBI."

The scientists are particularly interested in the widely available dietary supplement anatabine (made from tobacco plants), which is known for its anti-inflammatory properties. Crawford and her colleagues studied a group of 96 mice, half of which had suffered TBI and half of which had not. Among the injured mice, half received a placebo and half received either a compound derived from an experimental Alzheimer's drug or the dietary supplement anatabine. After two weeks, the injured mice that received either the drug or the dietary supplement performed as well as the uninjured mice on a test that evaluates spatial memory. The injured mice that got the placebo performed significantly worse.

Research was supported with funds from the Department of Defense and the Roskamp Foundation.

Scientific Presentation: Monday, Oct. 15, 8–10:30 a.m., Room 288

315.02, TBI-induced spatial memory loss is averted by treatment with the dietary supplement anatabine
S. FERGUSON, B. MOUZON, J.-O. OJO, A. BISHOP, G. CRYNEN, J. REED, D. PARIS, V. MATHURA, M. MULLAN, **F. CRAWFORD**; Roskamp Inst., Sarasota, FL; James A Haley Veterans' Hosp., Tampa, FL; The Open Univ., Milton Keynes, United Kingdom

TECHNICAL ABSTRACT: According to the Centers for Disease Control, 1.5 million people in the United States experience a traumatic brain injury (TBI) each year, with 80,000 survivors suffering long-term disability. There are currently no therapeutic compounds approved for use which can prevent or reduce the long-term neurobehavioral sequelae of TBI. A previous study by our group examined the proteomic response to TBI by mice transgenic for either human APOE3 or APOE4 across multiple timepoints and injury severities. ApoE isoforms are known to be important in determining relative outcome from injury, thus genotype-specific differences in response may be related to differential outcome from injury. In particular, we noted differences in the response of NF-kB related proteins following TBI. Our current study examined the effectiveness of treatment with the dietary supplement Anatabine after TBI, as we have previously shown this to be a potent NF-kB inhibitor and anti-inflammatory compound. For the administration of TBI, 48 male C57BL/6J mice received either a sham (craniectomy only) or controlled cortical impact (CCI) surgery (2mm diameter tip, 1.8mm depth, 5m/s). Mice were treated with PBS (placebo) or Anatabine (2mg/kg) by IP injection 30 minutes after surgery, and thereafter the treatment group received Anatabine treated water (estimated dose 20mg/kg/day). All mice were pre-trained on the Rotarod 1 day before surgery (3 acclimation trials at 5 rpm for 3 min, followed by 3 trials at 5-50 rpm over 5 min). Post-surgery testing on the Rotarod occurred 1, 3, 5, and 7 days after surgery at an accelerating speed of 5-50 rpm over 5 min, 3 trials per day. Barnes maze testing began on day 8. Mice were given 4 trials per day for 6 days starting from one of 4 random cardinal points. A single probe trial was administered on day 7 with the target box removed. Anatabine treated mice showed no loss of spatial memory retention after TBI during the probe trial as measured by latency to the target or adjacent hole (10.2 seconds), whereas PBS treated TBI mice had a significantly higher latency to the target or adjacent hole (20 seconds) than sham mice. Anatabine treatment appeared to completely prevent the loss of spatial memory retention following severe TBI. Further study of this promising treatment is warranted and will include treatment in a mild closed head injury model as well as long term outcome from injury. Dietary supplementation for reducing secondary injury after TBI offers an easy path to clinical application and simplifies the administration of the therapeutic. Pre-administration of the supplement to at-risk individuals participating in high contact sports or engaged in combat operations is also possible.

Abstract 815.09 Summary

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Scientists Developing Mice Able to Detect Hidden Landmines

Genetic modification could increase capacity to smell TNT by 500 fold

Inspired by a widely acclaimed program that has deployed specially trained rats to sniff out landmines, scientists are now working to develop transgenic mice with the capacity to smell landmine explosives amplified by 500 fold. The results of the new effort, The MouSensor Project, to build a "biosensor" for landmine detection were presented today 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.

Landmines affect 66 countries and 7 territories around the world, posing a structural barrier to development and economic growth. Landmine removal is costly and dangerous. Giant African pouched rats (HeroRats), with their acute sense of smell, have proven to be effective at detecting landmines, yet small enough not to detonate them.

"The rats are very effective but mice have some advantages as mine detectors because they are cheaper to manage and house, and easier to breed," said lead author Charlotte D'Hulst, Ph.D. in the laboratory of Dr. Paul Feinstein at Hunter College, City University of New York. "Most importantly, it is relatively easy to genetically manipulate odorant receptors in mice."

Odorant receptors give mammals the ability to distinguish one odor from another. A specific receptor for identifying a particular smell is typically found in 1 out of every 1,000 olfactory neurons, the cells in the nose that process activity from odorant receptors and transmit these signals to the brain. Recently, other U.S. scientists identified the specific rodent odorant receptor that detects a chemical known as 2,4-dinitrotoluene, or DNT, which is essentially the same as TNT. Feinstein and his colleagues were able to genetically modify a mouse so that the odorant receptor for DNT now occurs at much greater proportions in the mouse's nose. Follow-up imaging and behavioral tests will measure their sensitivity to DNT.

Research was supported with funds from the National Institutes of Health.

Scientific Presentation: Wednesday, Oct. 17, 8 –9 a.m., Hall F-J

815.09, Generating a biosensor for the detection of landmines
***C. D'HULST**, M. SAPARAUSKAITE, P. FEINSTEIN; Biol. Sci., Hunter College/Cuny, New York, NY

TECHNICAL ABSTRACT: Detection of landmines is difficult, dangerous, costly and time-consuming (http://www.apopo.org). Considering the critical need to develop a biosensor for the detection of explosives found in landmines, our goal is to generate a transgenic mouse strain that is hypersensitive to 2,4-dinitrotoluene (DNT), a mimic for the explosive TNT. Currently, a Belgian NGO, APOPO, trains giant African pouched rats (HeroRats) to identify the scent of explosives in landmines. The rats have an acute sense of smell and are small enough not to detonate the mines. Every time they detect TNT, the rats make a clicking sound and receive a bite of banana as a reward. Although this approach has proven to be effective (two of APOPO's mine detection rats, working with two human handlers, can cover 300 square meters of land in one hour. In comparison, two manual deminers using metal detectors, will need two full days to cover the same area), it takes nine months of painstaking on-and-off field training for a rat to be deployed for mine detection. Therefore, we engineered an innovative biological approach to challenge this global health problem. We generated a transgenic mouse model that over expresses a newly identified odorant receptor (OR) that can report the presence of 2,4-dinitrotoluene (DNT), an explosive residue mimic (Radhika et al., 2007 & Fukutami et al., 2011). Usually, a specific OR is expressed in 1/1000 neurons with a limited detection of the specific odorant as a consequence; our technique allows us to amplify the detection limit of a specific odor of interest 500-fold, which may be even further amplified by higher cortical areas of the brain. A first analysis of these transgenic animals showed that glomeruli (the first relay station in the brain, which allows for synaptic activity of an activated odorant receptor to be registered), which are tagged with a red fluorescent protein, are formed in the olfactory bulb. We are currently testing these genetically modified mice for their sensitivity to DNT using in vivo imaging techniques and behavioral tests such as the go/no go discrimination test. This is the first time that a mouse with a monoclonal nose', in which greater than 50% of the sensory neurons express a single odorant receptor gene, hypersensitive to a mimic for the explosive TNT has been created.

Speaker's Summary

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Spectrum of Chronic Traumatic Encephalopathy in Athletes and Military Veterans (2.04)
Fred Kavli Public Symposium — The Societal Impact and Biology of the Overt and Hidden Dysfunctions Resulting From Traumatic Brain Injury
Saturday, October 13, 1:30–4 p.m., New Orleans, Theater B

Chronic traumatic encephalopathy, or CTE, is a neurodegenerative disease found in athletes who experience multiple concussive or subconcussive traumatic brain injuries (TBI), including amateur and professional football players, ice hockey players, rugby players, boxers, and wrestlers. CTE has also been found in marines, soldiers and sailors from World War II, Vietnam, and the Gulf War who experienced repetitive concussive impacts related to combat. Recently, we found CTE neuropathology in the brains of US military personnel from Iraq and Afghanistan who were exposed to blast from improvised explosive devices that was indistinguishable to the CTE neuropathology observed in the brains of young athletes. In CTE, the spectrum of tau pathology ranges in severity from focal perivascular clusters in mild disease to severe tauopathy affecting widespread brain regions in advanced disease. Axonal injury is apparent in all stages of CTE, ranging from multifocal, often perivascular, axonal varicosities in the cortex and subcortical white matter in early stages to severe, diffuse axonal loss in the cortex and white matter in late stage disease. Symptoms in early stage CTE include headache, loss of attention and concentration, depression, explosivity and short-term memory loss. As the disease advances, executive dysfunction, word-finding difficulty, aggression, cognitive impairment, and dementia may develop. Suicidal ideation and completed suicide are common; in our large series of CTE, over 25% of subjects diagnosed with pure CTE either expressed suicidal ideations at some point during their course or died from suicide. It is likely that axonal dysfunction and loss, as well as hyperphosphorylated tau pathology, neuronal and synaptic loss contribute to the production of clinical symptoms of CTE. Although the data suggest that CTE produces slowly progressive neurodegeneration, the axonal and tau-linked neurodegeneration may not progress at the same rate in all persons and some individuals may be genetically resilient. Establishing the genetic determinants for susceptibility or resilience to CTE is an important future direction of the research.

Recently, we developed a mouse model of blast neurotrauma that mimics typical blast conditions associated with military blast injury and discovered that blast-exposed mice also demonstrate CTE neuropathology, including deposition of abnormal tau protein, axonal injury, microvascular damage, chronic neuroinflammation, and neurodegeneration. Surprisingly, the blast-exposed mice developed CTE neuropathology within 2 weeks after exposure to a single blast. The neuropathology was accompanied by functional deficits, including slowed axonal conduction, reduced activity-dependent long-term synaptic plasticity, and impaired spatial learning and memory that persisted for 1 month after exposure to a single blast. We demonstrated that blast winds with velocities of more than 330 miles/hour-- greater than the most intense wind gust ever recorded on earth -- induced oscillating head acceleration of sufficient intensity to injure the brain. These blast-induced learning and memory deficits in the mice were reduced by immobilizing the head during blast exposure. Our findings provide a direct connection between blast injury and CTE and indicate a primary role for blast wind - induced head acceleration in blast-related neurotrauma and its aftermath. This novel new blast neurotrauma mouse model will be essential for developing new diagnostics, therapeutics, and rehabilitative strategies for treating blast-related TBI, concussive TBI as well as CTE.