



**DEPARTMENT OF
PHYSICAL MEDICINE &
REHABILITATION**

**17TH ANNUAL RESEARCH DAY
JUNE 16, 2005**

**CARDINAL HILL REHABILITATION HOSPITAL
CENTER OF LEARNING
ROOMS CL3 & CL4
LEXINGTON, KENTUCKY**

**UNIVERSITY OF KENTUCKY
DEPARTMENT OF PHYSICAL MEDICINE & REHABILITATION
17TH ANNUAL RESEARCH DAY**

CARDINAL HILL REHABILITATION HOSPITAL
CENTER OF LEARNING, ROOMS CL3 & CL4
JUNE 16, 2005

8:00 a.m. – 8:30 a.m. Continental Breakfast
Sponsored By: Phillip Umbarger, Novartis

8:30 a.m. – 8:40 a.m. Opening Remarks: Nancy Stiles, M.D.

PM&R RESIDENT/GRADUATE STUDENT RESEARCH PRESENTATIONS

8:45 a.m. – 8:55 a.m. Kathleen Dy, M.D.
9:00 a.m. – 9:10 a.m. Tanya Harris, M.D.
9:15 a.m. – 9:25 a.m. Gang Li, M.D.
9:30 a.m. – 9:40 a.m. Harvey Mallory, M.D.
9:45 a.m. – 9:55 a.m. Karen Miller, M.D.
10:00 a.m. – 10:10 a.m. Emese Simon, M.D.

10:15 a.m. – 10:25 a.m. BREAK

10:30 a.m. – 10:40 a.m. Chad Walters, D.O.
10:45 a.m. – 10:55 a.m. Scott Shaffer, P.T.
11:00 a.m. – 11:10 a.m. Scott Shaffer, P.T.

11:15 a.m. – 11:30 a.m. Remarks/Announcements

11:30 p.m. – 1:00 p.m. Lunch ~ Center of Learning, CL3 & CL4
Sponsored By: Jill Phelps, RN, Pfizer Pharmaceuticals

FEATURE SPEAKER

1:00 p.m. – 2:00 p.m. Christopher B. Shields, M.D., Professor & Chairman
University of Louisville, Neurological Surgery
Norton Hospital Chair in Neurological Surgery
Clinical Director, KY Spinal Cord Injury Research Center
“Treatment of Spinal Cord Injury: Past, Present and Future”

POSTER PRESENTATIONS

2:15 p.m. – 3:15 p.m. Jessica Clark, Anatomy & Neurobiology
Laurie Davis, Anatomy & Neurobiology
Sairam Krishnamurthy, Physiology
Vidya N. Nukala, Anatomy & Neurobiology
Y. Deng, Spinal Cord & Brain Injury Research Center
Y. Xiong, Spinal Cord & Brain Injury Research Center
I.N. Singh, Spinal Cord & Brain Injury Research Center

Ravikumar R. Rao, Ph.D., Physical Medicine & Rehabilitation
Sara Salles, D.O., Physical Medicine & Rehabilitation
Diane Snow, Ph.D., Anatomy & Neurobiology

3:15 p.m. – 4:30 p.m. Awards & Closing Remarks
Nancy Stiles, M.D., Physical Medicine & Rehabilitation
Gerald Klim, D.O., Chairman, Physical Medicine & Rehabilitation

SPEAKER PRESENTATION

“Treatment of Spinal Cord Injury: Past, Present and Future”

CHRISTOPHER B. SHIELDS, M.D.

Dr. Shields is currently Professor and Norton Hospital Chair in the Department of Neurological Surgery at the University of Louisville, and clinical Co-director of the Kentucky Spinal Cord Injury Research Center. Dr. Shields was born and grew up in Canada, attending medical school at the University of Toronto, and completing his neurosurgical residency at the University of Manitoba in Winnipeg. He was recruited to Louisville in 1974 following a microvascular fellowship at the University of Vermont. His initial clinical interest was in the field of cerebrovascular surgery, however, over the past 20 years has focused on spinal surgery, and is currently co-chairman of the Kenton D. Leatherman spine center at Norton Hospital in Louisville. Dr. Shields has held numerous prestigious positions in organizational neurosurgery, including President of the Congress of Neurological Surgery, Chairman of the Cerebrovascular section of the American Association of Neurological Surgeons, and President of the Kentucky Neurosurgical Society. His major research interest is in spinal cord regeneration, particularly in neuroprotection, axon regeneration, and translational research. He has authored over 100 scientific papers and 30 book chapters. Over the past 10 years he has been instrumental in creating the Kentucky Spinal Cord Injury Research Center in the Department of Neurosurgery. This group now consists of 6 Endowed Research Chairs in the Department of Neurological Surgery, and there are nearly 55 members in the spinal cord research center.

ORAL PRESENTATIONS

PM&R Residents and Graduate Students

Presenter:

Abstract Presentation:

Kathleen Dy, M.D.

Lateral Antebrachia Cutaneous Nerve Neuropathy After Arteriovenous Fistula Placement: A Case Report

Tanya Harris, M.D.

Juvenile Huntington's Disease: A Family Case Study

Gang Li, M.D.

Recovery of Cardiovascular Control After Spinal Cord Injury

Harvey Mallory, M.D.

The Impact of BMI on Post-operative Recovery in the Pediatric Population

Karen Miller, M.D.

Gait Patterns in Hereditary Spastic Paraplegia

Emese Simon, M.D.

Quantification of Spasticity of the Quadriceps Muscle Group Using 3-D Motion Analysis

Chad A. Walters, D.O.

Does Early PEG Placement in Patients with Severe Dysphagia Impact Acute Rehabilitation Costs, Lengths Of Stay, and Medical Complications

Scott Shaffer, P.T.

The Utilization of Multidirectional Body Weight Support Treadmill Training for Older Adults with Peripheral Nerve Disease: A Single-Subject Design

Scott Shaffer, P.T.

Reliability and Diagnostic Accuracy of Self-Report, History And Clinical Examination Items for the Diagnosis of Polyneuropathy in Adults With and Without a History of Falls

PM&R RESIDENT PRESENTATIONS

Lateral Antebrachial Cutaneous Nerve Neuropathy after Arteriovenous Fistula Placement: A Case Report

Presenter:

Kathleen C. Dy, M.D.

Collaborators:

Robert B. Nickerson, MD

Departmental Affiliations:

University of Kentucky, Department of Physical Medicine and Rehabilitation

Abstract Text:

The lateral antebrachial cutaneous nerve of the forearm (LABC) is the distal terminal branch of the musculocutaneous nerve. Entrapment of or injury to the LABC is uncommon, though it has been reported in some cases as a result of venipuncture, prolonged muscle contraction during windsurfing, heavy exercise, stretch injuries from forced hyperextension of the upper extremity, external compression from carrying objects with the forearm flexed, repair of distal biceps tendon, compression at the point of exit lateral to the biceps tendon or by compression by the superficial antebrachial fascia, or a glomus tumour. This report describes the compression of the LABC after arteriovenous anastomosis and subsequent vessel engorgement. Symptoms included painful dysesthesias and allodynia over the radial aspect of the volar and extensor surfaces of the forearm. To our knowledge, this is the only reported case of isolated LABC neuropathy after arteriovenous fistula placement.

Key Words: Lateral antebrachial cutaneous nerve, musculocutaneous nerve, arteriovenous fistula, neuropathy

PHYSICAL MEDICINE & REHABILITATION RESEARCH DAY 2005

Juvenile Huntington's Disease: A Family Case Study

Presenter:

Tanya Harris, M.D.

Collaborators:

Not Applicable

Departmental Affiliations:

University of Kentucky, Department of Physical Medicine and Rehabilitation

Abstract Text:

Huntington's disease is a degenerative central nervous disorder most known for its jerky and dance-like movement disorder. For this reason, it is also known as Huntington's chorea (Greek for dance). The genetic basis is an altered form of the Huntington gene by way of a long string of repeat CAG codons. Although the disease is inherited, it typically begins its expression in the adult years; hence, the gene is often unknowingly passed on to the next generation.

In many cases, the afflicted person develops the movement disorder in his/her 50s and 60s and has accompanying mental status change which begins as mild but may develop into psychosis.

In the disease spectrum, there is some rare expression among juveniles. It is postulated that these youngsters have earlier expression linked to higher number of CAG repeats. The progression is faster in these youths and is associated with earlier demise.

Often, diagnosis is delayed and the child is exposed to excessive testing because the disease is poorly recognized in this age group.

In this presentation two young brothers in the preschool years who were recently diagnosed with Huntington's disease will be discussed. Indeed, diagnosis may not have been established this early if it was not for the mother who was recently diagnosed some many years after onset of symptoms. We will elucidate the familial history and will discuss their physical manifestations of this disorder in hopes that it may better prepare us for more timely diagnosis of Huntington's disease in others.

Key Words: Huntington's Disease, Juvenile Huntington's Disease, Movement Disorders

PHYSICAL MEDICINE & REHABILITATION RESEARCH DAY 2005

Recovery of Cardiovascular Control After Spinal Cord Injury

Presenter:

Gang Li, M.D.

Collaborators:

Joyce Evans, MS, James Abbas, PhD, Charles Knapp, PhD, Susan McDowell, MD, Robert Nickerson, MD, David Gater, MD, Robert Taylor, MD, PhD, David Randall, PhD, David Brown, PhD

Departmental Affiliations:

University of Kentucky, Department of Physical Medicine and Rehabilitation

Abstract Text:

Problem: Blood pressure regulation is a significant problem after SCI. The problems with cardiovascular regulation in SCI patients are orthostatic hypotension (excessive blood pooling in lower extremities due to disruption in autonomic control), autonomic dysreflexia and blood pressure lability. The conventional therapy is repeated head-up tilt, but underlying adaptations poorly understood, and this is a problem for some patients, especially in the months following injury. **Aim:** to characterize the changes in CV control that occur in the months following SCI, to develop techniques to be used in the clinical setting to assess cardiovascular function in individuals with SCI. **Methods:** 27 subjects (age of 18-35) with C/T SCI of 1-2 wk duration without contraindication for head-up tilt/monitoring devices attachment are in the study, several hemodynamic (BP/CO/SV/EF) and hormonal (epinephrine/PRA/PPP) measurements while the subject undergoes head-up tilt using a standard tilt table are being collected and analyzed using 3 factor ANOVA. A control group of 8 able-bodied individuals are in the study as well. **Results and Conclusions:** In response to head up tilt, compared with AB, SCI demonstrated: decreased ability to regulate BP, decreased sympathetic control of BP/HR, decreased parasympathetic control of HR and increased lability of respiration.

Key Words: *spinal cord injury, tilt table, cardiovascular regulation, orthostatic intolerance*

PHYSICAL MEDICINE & REHABILITATION RESEARCH DAY 2005

The Impact of BMI on Post-operative Recovery in the Pediatric Population

Presenter:

Harvey Mallory, M.D.

Collaborators:

C. M. Tylkowski, M.D., R. Meir, M.D., H. Mallory, M.D., Cristin Minter, M.A.

Departmental Affiliations:

Shriners Hospital for Children, Lexington, Kentucky

Abstract Text:

It is well documented recently that pediatric obesity is on the rise and presents a major health concern. It is speculated that one in three children will be on some type of hyperglycemic medication within the next ten years if trends continue as they are now. It is also well known that obesity presents a significant risk factor for adults undergoing surgery. In the obese adults, there are higher rates of infection, DVT, wound issues, skin breakdown, and prolonged hospitalization with prolonged rehabilitation. In this study, we will perform a retrospective chart review of children diagnosed with scoliosis, and who underwent spinal fusion at the Shriners Hospital in Lexington, Kentucky. Factors to be evaluated include BMI, operative time, length of hospital stay, post-operative complications, and long-term outcome. The goal of this study is an attempt to quantify the risk factors of obesity in the pediatric surgical population in an effort to determine the point where surgical risk increases secondary to weight issues.

PHYSICAL MEDICINE & REHABILITATION RESEARCH DAY 2005

Gait Patterns in Hereditary Spastic Paraplegia

Presenter:

Karen Miller, M.D.

Collaborators:

Chester Tytkowski, MD, Hank White, Donna Oeffinger

Departmental Affiliations:

University of Kentucky, Department of Physical Medicine and Rehabilitation
Shriners Hospital for Children

Abstract Text:

Hereditary spastic paraplegic (HSP) is a progressive movement disorder that mainly affects the lower extremities. Common gait patterns of patient with cerebral palsy have been identified. There have been no studies about the gait patterns in patients with HSP. The purpose of this study was to try to identify gait patterns of patients with HSP. The HSP patients not only showed patterns found commonly in cerebral palsy, but also demonstrated a pattern of a knee extension moment with decreasing or plateaued ankle dorsiflexion and a common finding of abnormal downward trunk obliquity, which is not described in subjects with cerebral palsy.

Key Words: Hereditary Spastic Paraplegia, gait

PHYSICAL MEDICINE & REHABILITATION RESEARCH DAY 2005

Quantification of Spasticity of the Quadriceps Muscle Group Using 3-D Motion Analysis

Presenter:

Emese Simon, M.D.

Collaborators:

Chester Tylkowski, M.D. Shriners Hospital for Children, Lexington, KY

Co-Author: Hank White MSPT, Shriners Hospital for Children, Lexington, KY

Departmental Affiliations:

University of Kentucky, Department of Physical Medicine and Rehabilitation

Abstract Text:

Spasticity is a common feature in patients suffering from stroke, cerebral palsy, multiple sclerosis and CNS trauma. There is decreased ability to control motor activity because of spastic paresis.

Resistance to externally imposed movement increases with increasing speed of stretch and varies with the direction of joint movement. Numerous methods are known and used in testing spasticity only some of which can be used as an objective measure.

In our study the Wartenberg pendulum test, an objective, reproducible method was used in children with cerebral palsy to assess spasticity. A group of healthy children with no orthopedic or neurological impairments were tested as a control group. The study was performed in a motion laboratory, using standard Cleveland clinic marker set with surface EMG attached to the quadriceps and hamstring muscles to assess their activity. Ortho Trak software was utilized to analyze kinematic data.

This study, using 3-dimensional motion analysis made it possible to quantify spasticity of the quadriceps muscle group in all three planes, in children with cerebral palsy.

Key Words: Spasticity, Pendulum test, Cerebral palsy

PHYSICAL MEDICINE & REHABILITATION RESEARCH DAY 2005

Does Early PEG Placement in Patients with Severe Dysphagia Impact Acute Rehabilitation Costs, Lengths of Stay, and Medical Complications?

Presenter:

Chad A. Walters, D.O.

Collaborators:

Sara Salles, D.O.

Departmental Affiliations:

University of Kentucky, Department of Physical Medicine and Rehabilitation

Abstract Text:

Many patients in acute rehabilitation facilities suffer from dysphagia. They experience such severe dysphagia that they require an alternate feeding source for maintaining nutritional requirements and medicine administration. Some are fed via a nasogastric feeding tube while others undergo PEG placement during the acute care admission. They are then transferred to acute rehab facilities. Some of the patients with a nasogastric feeding tube require PEG placement while still in the acute rehab setting. The literature clearly shows the risks and benefits of PEG placement and overall quality of life. However, the literature does not show its impact on acute rehab admissions. This study will be a retrospective one which will look at patients that undergo early PEG placement and those who require PEG placement after acute rehab admission in regards to lengths of stay (which will be used as an indirect measure of cost) and medical complications (e.g. Aspiration pneumonia). The anticipated outcome will be that patients with severe dysphagia (as evident on Video Fluoroscopy) and early PEG placement have shorter lengths of stay and fewer complications than those being fed via nasogastric feeding tube.

Key Words: dysphagia, PEG, acute rehabilitation

GRADUATE STUDENT PRESENTATIONS

The Utilization of Multidirectional Body Weight Support Treadmill Training for Older Adults with Peripheral Nerve Disease: A Single-Subject Design.

Presenter:

Scott Shaffer PT¹

Collaborators:

Anne Harrison PT, PhD²,

Departmental Affiliations:

¹ Rehabilitation Sciences Doctoral Program, University of Kentucky,

² Department of Physical Therapy, Rehabilitation Sciences, & Gerontology, University of Kentucky.

Abstract Text:

Falls in the elderly are the consequence of several risk factors. One identified source is the reduction of lower extremity sensation that occurs with peripheral nerve disease (PND). Literature suggests that this is a result of increased medial-lateral postural instability. Researchers have also proposed that interventions that challenge postural stability in multiple directions may enhance outcomes. Multidirectional body weight supported treadmill training (MBWSTT) provides dynamic feedback and is commonly used for the treatment of various neurological disorders. Therefore, the primary objective of this single-subject multiple baseline study is to determine if individuals (N=4-8) with PND exhibit improved balance (Berg Balance Scale, Four Square Step Test), function (self report and gait speed), and confidence of movement (Activities specific Balance Confidence Scale) with MBWSTT. The secondary objective is to assess if variables such as strength, sensation, H-reflex, and posturography assist in explaining any improvements in balance and/or confidence of movement. Subjects will have an electrodiagnostic examination that confirms PND and a history of at least one fall within the past two years. The intervention will consist of a maximum of 30 minutes of MBWSTT conducted 2-3 times a week for a 5-8 week period. Dependent variables will be collected pre-intervention, post-intervention, and 1, 3, 6 months post-intervention. Based on a previous case-study it is postulated that participants will exhibit increased balance, confidence of movement, gait speed, posturography, and hip abduction strength post-intervention. These findings would suggest that hip strength and/or central processing may be responsible for improved balance and confidence of movement.

Key Words: Falls, Peripheral nerve disease, Body weight support treadmill training

PHYSICAL MEDICINE & REHABILITATION RESEARCH DAY 2005

Reliability and Diagnostic Accuracy of Self-Report, History, and Clinical Examination Items for the Diagnosis of Polyneuropathy in Adults With and Without a History of Falls

Presenter:

Scott Shaffer PT¹

Collaborators:

Anne Harrison PT, PhD²,

Departmental Affiliations:

¹ Rehabilitation Sciences Doctoral Program, University of Kentucky,

² Department of Physical Therapy, Rehabilitation Sciences, & Gerontology, University of Kentucky.

Abstract Text:

Falls in the elderly are the consequence of several risk factors. One identified source is the reduction of lower extremity sensation that occurs with polyneuropathy (PN). Currently the majority of research conducted on PN and falls has focused on identifying the biomechanical deficits associated with neuropathy. Unfortunately, very few investigators have critically evaluated the clinical variables that are associated with or predictive of PN and falls in older adults. Therefore, the purpose of this study is to assess the reliability and diagnostic accuracy of individual clinical examination items for the diagnosis of PN in older adults with and without a history of falls. Adults between the ages of 40-90 who are referred for lower extremity electrodiagnostic examinations and meet the inclusion/exclusion criteria are eligible to participate. Subjects that qualify will complete self-report forms on pain, activity level, and balance confidence. A history and clinical examination will also be conducted to include such items as strength, sensation, and reflex testing. Finally, functional measurements such as the Berg Balance Scale, Four-Square Step Test, and gait speed will be measured. A portion of these subjects will also undergo repeat testing to assess reliability of clinical items. Reliability will be assessed with a Kappa statistic or intraclass correlation coefficient. Contingency tables (2X2) will be used to calculate sensitivity and specificity for each test item. It is postulated that a number of the self-report, history, and clinical examination items will demonstrate good to excellent intra-rater reliability and specificity/sensitivity.

Key Words: Polyneuropathy, Clinical examination items, Reliability, Validity

POSTER PRESENTATIONS

Graduate Students

Presenter:

Poster Presentation:

Jessica Clark

Possible Contribution of Minnesota Multiphasic Personality Inventory-2 (MMPI-2) Validity Indicators to the Detection of Malingered Neurocognitive Dysfunction

Laurie Davis

Possible Mechanism(s) of Fasting Induced Neuroprotection In Rodent Model of Traumatic Brain Injury

Sairam Krishnamurthy

Influence of Propriospinal Pathways in the Development of Autonomic Dysreflexia Following Spinal Cord Injury

Vidya N. Nukala

Cryopreservation of Brain Mitochondria Using Dimethyl Sulfoxide: A Practical Method for Functional Recovery

Y. Deng

Relationship of Calpain-Mediated Cytoskeletal Degradation And Neurodegeneration in the Mouse Controlled Cortical Impact Traumatic Brain Injury Model

Y. Xiong

Time Course of Oxidative Damage and Cytoskeletal Degradation after Spinal Cord Contusion Injury in Rats

I.N. Singh

Relationship of Oxidative Damage, Mitochondrial Dysfunction And Neurodegeneration in the Mouse Controlled Cortical Impact Traumatic Brain Injury Model

GRADUATE STUDENT POSTERS

Possible Contribution of Minnesota Multiphasic Personality Inventory-2 (MMPI-2) Validity Indicators to the Detection of Malingered Neurocognitive Dysfunction

Presenter:

Jessica Clark

Collaborators:

Thomas Wegman, Lindsey Schipper, David Berry

Departmental Affiliations:

University of Kentucky

Abstract Text:

Although validity indices from the Minnesota Multiphasic Personality Inventory (MMPI-2) have been shown to be fairly accurate for the detection of feigned psychiatric disorder, their ability to identify other types of false symptoms, such as malingered neurocognitive dysfunction (MNCD), has been more controversial. Perhaps the most promising index has been the Lees-Haley Fake Bad Scale (FBS) which has been shown to be effective in the identification of somatic malingering by Larrabee (2004). However, other authors have argued that the FBS scale is invalid for the detection of feigning (Butcher et al., 2003). In the present study, patients undergoing forensic neuropsychological examinations were administered the MMPI-2 as part of the evaluation. The 17 who failed 2 or more standardized motivational tests (TOMM, WMT, CARB, etc.) were assigned to the probable feigning group (PF) whereas the 23 who passed all motivational tests were assigned to the honest group (HON). ROC analyses indicated the following AUC values for the MMPI-2 validity scales: FBS .880, F .775, F(p) .664. Although the PF group scored significantly higher on the FBS and F scales, there was not a significant difference on the F(p) scale. At a cutting score of > 22, FBS had a SN rate of .87 and a SP rate of .88. Stepwise forward logistic regression revealed that only FBS contributed significantly to increased classification rates, rising from .575 without FBS to .825 with FBS. These results suggest FBS may have a role in detection of MNCD.

Key Words: Minnesota Multiphasic Personality Inventory-2 (MMPI-2), malingered neurocognitive dysfunction, Fake Bad Scale

PHYSICAL MEDICINE & REHABILITATION RESEARCH DAY 2005

Possible Mechanism(s) of Fasting Induced Neuroprotection in Rodent Model of Traumatic Brain Injury

Presenter:

Laurie Davis¹

Collaborators:

Dr. Patrick Sullivan¹, Dr. Jong Rho²

Departmental Affiliations:

¹Anatomy and Neurobiology, SCoBIRC University of Kentucky;

²Barrow Neurological Institute, Phoenix, AZ

Abstract Text:

Mitochondria are responsible for the majority of energy production within the cell and play a pivotal role in the regulation of cell death cascades. Thus, maintaining mitochondrial homeostasis following traumatic brain injury (TBI) would predict improved neuronal survival and behavioral outcome. Previously we demonstrated that fasting animals after TBI reduces neuronal tissue damage. However, it is unclear which of the fasting-induced metabolic changes (decreased blood glucose, increased ketone levels, or upregulation of mitochondrial uncoupling proteins [UCPs]) is(are) responsible for this neuroprotective effect. In the present study, we have attempted to elucidate the neuroprotective mechanism(s) by modulating blood glucose levels and ketone levels independently following controlled cortical impact in adult male Sprague-Dawley rats. Additionally, we investigated the modulation of neuronal mitochondrial UCPs using free fatty acids (FFA) of varying chain lengths. Blood glucose levels were modulated with a 10 unit dose of insulin administered at various times post-injury to mimic fasting-induced hypoglycemia. Ketone levels were elevated by using subcutaneously implanted osmotic mini pumps to deliver β HB (beta-hydroxybutyrate) post-injury (1.6 mM/Kg/day). Blood glucose and ketone levels were monitored throughout both experiments. Our preliminary data indicate that the neuroprotective effects of fasting are not mediated via hypoglycemia, but that increasing ketone levels post-injury is neuroprotective. This is demonstrated by a significant increase in cortical tissue sparing (15%) and improved cognitive function compared to vehicle-treated animals. Additionally several FFA with chain lengths > 14, which are also known to be increased by fasting and ketosis, proved to be significantly effective in activating mitochondrial UCPs.

Key Words: Fasting, Glucose, Beta-hydroxybutyrate, Free Fatty Acids (FFA), Uncoupling Proteins (UCP)

PHYSICAL MEDICINE & REHABILITATION RESEARCH DAY 2005

Influence of Propriospinal Pathways in the Development of Autonomic Dysreflexia Following Spinal Cord Injury.

Presenter:

Dr. Sairam Krishnamurthy, Alexander Rabchevsky

Collaborators:

S. Krishnamurthy, A.A. Cameron, L.E. Schwindel, T.S. Lyttle, K.M. Carrico and A.G. Rabchevsky

Departmental Affiliations:

Spinal Cord & Brain Injury Research Center (SCoBIRC)

Department of Physiology, University of Kentucky, Lexington, KY 40536-0509

Abstract Text:

Spinal cord injuries, whether clinically complete or incomplete, are frequently characterized by a serious hypertensive condition, autonomic dysreflexia. Autonomic dysreflexia is typically elicited by noxious stimuli below the injury level, and can result in hypertension producing cerebral and spinal subarachnoid hemorrhage, seizures, and pulmonary edema (see **III**). It is believed that this condition arises in the injured cord following interruption of bulbo-spinal inhibition, combined with injury-induced increases in growth factors that result in structural and electrical changes in both primary afferent fibers and spinal interneurons. Although the effects nerve growth factor (**NGF**) has been extensively studied, little attention has been focused on the role of propriospinal neurons (spinal interneurons), which are known to constitute up to 97% of all spinal neurons. Interneurons are regulated by descending bulbo-spinal pathways, in turn playing an essential role in controlling the flow of information between primary afferents and sympathetic preganglionic neurons of the intermediolateral cell column (**IML**) in both the developing and adult spinal cord. Dysregulation of this intraspinal reflex control mechanism following injury is one way in which sacral afferent signals from the bladder or bowel might be able amplify the synchronous discharge of sympathetic preganglionic neurons in multiple thoracolumbar spinal segments (see **IX**). We have over-expressed NGF with recombinant adenovirus to augment CGRP+ fiber sprouting and identified critical lumbosacral segments in the spinal injured rat that convey colorectal afferent signals to magnify spinal sympathetic reflexes (see **VII**). Conversely, over-expression of C-fiber growth-inhibitory semaphorin 3A (**Sema3a**) reduced CGRP+ fiber sprouting and mitigated dysreflexic hypertension. To investigate the contribution of propriospinal plasticity in the development of autonomic dysreflexia after injury, we are currently establishing whether lumbosacral interneurons relay sensory input from colorectal afferents to sympathetically-correlated interneurons in thoracolumbar levels. *Supported by grants from ISRT #STR063, KSCHIRT #3-11 and NIH/NINDS R01 NS049901-01*

PHYSICAL MEDICINE & REHABILITATION RESEARCH DAY 2005

Cryopreservation of Brain Mitochondria Using Dimethyl Sulfoxide: A Practical Method for Functional Recovery

Presenter:

Vidya N. Nukala^{1,2}

Collaborators:

Indrapal N. Singh^{1,2}, Laurie M. Davis^{1,2}, Melanie L. McEwen^{1,2}, Doug A. Price³, Steve S. Scheff^{2,3} and Patrick G. Sullivan^{1,2}

Departmental Affiliations:

¹Spinal Cord and Brain Injury Research Center, ²Department of Anatomy and Neurobiology, ³Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY 40536

Abstract Text:

Mitochondrial function is typically analyzed using mitochondria isolated from fresh tissues and cells as they are tightly coupled; whereas those from frozen samples can consist of broken mitochondria and membrane fragments. This prevents serial usage and/or long-term batch storage of isolated mitochondria for functional studies. To overcome these limitations, we conducted experiments to establish optimum methods to cryopreserve mitochondria with preserved bioenergetics. In the present study, we used adult Sprague-Dawley rats; total (synaptic and non-synaptic) cortical mitochondria were isolated using digitonin and further purified with discontinuous percoll gradient. Dimethyl sulfoxide (DMSO) is considered to be an effective cryopreservative agent because it is membrane-permeable and prevents ice formation. Therefore, we added DMSO (10% v/v) to mitochondria of various purities, allowed them to cool at a uniform rate of ~1°C/min and kept them frozen at -80°C. They were reanimated after a week and assessed for structural integrity and bioenergetics by electron microscopy and oxygen consumption respectively. The mitochondria cryopreserved with DMSO showed significant functional recovery compared to the mitochondria cryopreserved without DMSO. There is no significant difference in bioenergetics between mitochondria cryopreserved before or after percoll purification. Electron microscopy of such mitochondria revealed that they all have preserved inner and outer membrane structures. We conclude that DMSO (10% v/v) could be successfully used to cryoprotect rat brain mitochondria. This will considerably expand the range of biochemical, molecular and metabolic studies without the constraints of mitochondrial longevity *ex vivo*.

Key Words: Brain, Cortex, Mitochondria, Digitonin, Percoll, Cryopreservation, DMSO, Respiration, Electron Microscopy

PHYSICAL MEDICINE & REHABILITATION RESEARCH DAY 2005

Relationship of Calpain-Mediated Cytoskeletal Degradation and Neurodegeneration in the Mouse Controlled Cortical Impact Traumatic Brain Injury Model

Presenter:

Y. Deng

Collaborators:

Y. Deng, B.M. Thompson, T.R. Gibson and E.D. Hall

Departmental Affiliations:

Spinal Cord & Brain Injury Research Center, University of Kentucky Chandler Medical Center

Abstract Text:

Recent studies in our laboratory have evaluated the time course of post-traumatic neurodegeneration after a severe focal injury (controlled cortical impact, CCI) in mice using the deOlmos silver staining technique (Hall et al.; J. Neurotrauma 22:252-265, 2005). Neurodegeneration-related silver staining was observed as early as 6 hrs post-injury, but the damage did not peak until 48 hrs. The presently reported study has examined the time course of cytoskeletal degradation in terms of the breakdown of the 280 kD protein α -spectrin by either calpain (145 kD product) or calpain and or caspase 3 (150 kD product) triggered by an injury-induced increase in intracellular calcium. The time course of degradation was then compared to the previously determined time course of neurodegeneration. The injured mice displayed a significant increase in the 150 kD product by 1 hr post-injury in both the ipsilateral cortex and the underlying hippocampus. This was followed by an increase in the calpain-specific 145 kD product at 3 hrs. This appearance of cytoskeletal damage precedes the onset of post-traumatic neurodegeneration. Both spectrin products peaked in both brain areas at 24 hrs after injury, which again preceded the peak in neurodegeneration at 48 hrs in the CCI model. The calpain-specific 145 kD product showed a higher magnitude suggesting that calpain is perhaps the major player in the post-traumatic cytoskeletal degradation. The magnitude of the spectrin degradation waned progressively after 24 hrs although an ongoing degradation was still observed as late as 72 hrs after injury. As we have shown before in the mouse diffuse TBI model (Kupina et al., Exp. Neurol. 180:55-72, 2003), the largely calpain-mediated spectrin degradation precedes the time course of neurodegeneration (silver staining) after CCI suggesting that cytoskeletal damage is perhaps a final common pathway leading to neuronal death. Furthermore, a comparison of the time courses of spectrin degradation and neurodegeneration in the previously studied diffuse model with the time courses currently reported for the focal CCI model indicates that both the therapeutic window and needed duration of treatment for pharmacological inhibition of calpain-mediated cytoskeletal damage is significantly different between the two types of TBI.

PHYSICAL MEDICINE & REHABILITATION RESEARCH DAY 2005

Time Course of Oxidative Damage and Cytoskeletal Degradation after Spinal Cord Contusion Injury in Rats

Presenter:

Y. Xiong

Collaborators:

Y. Xiong, A.G. Rabchevsky, T. Lyttle, B.M. Thompson and E. D. Hall

Departmental Affiliation:

Spinal Cord & Brain injury Research Center, University of Kentucky School of Medicine

Abstract Text:

Traumatic injury to the spinal cord triggers secondary effects, including oxidative damage, calcium disruption and compromised energy metabolism. Although the important role of reactive oxygen-induced oxidative damage has been strongly supported by previous work, the time course of oxidative damage and its relationship to post-traumatic neurodegeneration in the injured spinal cord have been incompletely defined. In the present study, we used immunoblotting techniques to determine the time course of peroxynitrite-derived oxidative damage and calpain-mediated cytoskeletal degradation after spinal cord contusion injury in rats. Peroxynitrite (ONOO⁻), formed by nitric oxide synthase generated NO• radical and •O₂⁻, is believed to play a key role in oxidative damage because its decomposition products possess potent free radical characteristics. Our results showed 3-nitrotyrosine (3-NT), a specific biomarker for peroxynitrite, rapidly accumulated at early time points (1hr, 3hr) after SCI and the high level was sustained to 1week post injury. Peroxynitrite can also initiate oxidative damage by lipid peroxidation and protein carbonylation. 4-Hydroxynonenal (HNE), a major reactive product formed following lipid peroxidation was elevated significantly at 1, 3, 24, 48 and 72hrs and 1week post injury. The time course of protein carbonylation showed a similar pattern. The level of protein carbonyl rapidly increased at 1hr post injury and was maintained to 72hrs and began to wane after 1week. Oxidative damage to cellular components results in intracellular calcium overload, which activates cytosolic protease calpain leading to cytoskeletal protein (α -spectrin) degradation. Spectrin breakdown analysis revealed rapid onset of cytoskeletal degradation following SCI. The 145kd fragments of α -spectrin, which are specifically generated by calpain, were dramatically increased at 1hr, 3hrs, 6hrs, 24hrs, 48hrs, 72hrs and decreased back toward control levels at 1week post injury. The peak of oxidative damage was shown at 3hrs post injury while the peak increase in spectrin degradation was observed at 72hrs post injury, indicating that oxidative damage precedes cytoskeletal degradation. These results suggest that the peroxynitrite-mediated oxidative stress is an important factor in secondary SCI causing cellular damage by lipid peroxidation, protein oxidation and nitration. This oxidative damage most likely promotes an increase in intracellular calcium and calpain-mediated cytoskeletal degradation by inhibition of neuronal calcium homeostatic mechanisms.

PHYSICAL MEDICINE & REHABILITATION RESEARCH DAY 2005

Relationship of Oxidative Damage, Mitochondrial Dysfunction and Neurodegeneration in the Mouse Controlled Cortical Impact Traumatic Brain Injury Model

Presenter:

I.N. Singh

Collaborators:

I.N. Singh, P.G. Sullivan, K.M. Day, T.R. Givson, Y. Deng, L.H. Mbye and E.D. Hall

Departmental Affiliations:

Spinal Cord & Brain Injury Research Center, University of Kentucky Chandler Medical Center

Abstract Text:

Recent efforts in our laboratories have been aimed at a more detailed description of the neurodegenerative time course in the mouse controlled cortical impact-induced focal traumatic brain injury (CCI-TBI) [Hall, ED et al *J. Neurotrauma* **22**; 252-265, 2005]. These studies indicated that by 6 hrs, neurodegeneration was apparent in all layers of the ipsilateral cortex at the epicenter of the injury. A time-dependent increase in cortical and hippocampal neurodegeneration was observed between 6 and 72 hrs post-injury. In the present work, the time course of post-traumatic mitochondrial dysfunction in the ipsilateral cortex and hippocampus was assessed at 30 min, 1,3,6, 12, 24, 48, & 72 hrs after a moderate (0.5 mm), and a severe (1.0 mm) injury in young adult male CF-1 mice. A significant decrease ($p < 0.0001$) in mitochondrial oxygen consumption, was observed between 3 h and 12 h (approx. 50 to 60% decrease) post-injury followed by recovery at 24 h both in ipsilateral cortical and hippocampal regions. This reduction in mitochondrial oxygen consumption was very well correlated with the functional state of mitochondrial oxidative phosphorylation. A significant decrease ($p < 0.05$) in complex I-driven (pyruvate and malate as substrates) respiratory rate in state III was observed both in cortical and hippocampal mitochondria. Based on this time course profile, we performed measurement of oxidative damage in mitochondrial proteins (3-nitrotyrosine, 3-NT; protein carbonyl) and lipids (4-hydroxynonenal, HNE) by slot blots at selected time points, sham (3 h), 30 min, 3 h, and 12 h post-injury. Lipid peroxidation was significantly ($p < 0.05$) elevated at 30 min and 12 h post-injury in cortical mitochondria and at 3 h post-injury in hippocampal mitochondria compared to sham. Interestingly, a significant increase in protein carbonyl was noticed at 30 min post-injury in cortical mitochondria ($p < 0.0006$) and this increase was much more pronounced at 3h in injured hippocampal mitochondria compared to sham. Structural integrity of Percoll-purified mitochondria at 30 min, 3h, 12h, and sham (3 h) CCI-TBI were also examined by electron microscopy. The EM pictures revealed mitochondrial matrix condensation at 3h and 12h post-injury. These findings show that increased mitochondrial dysfunction as a consequence of complex-I inhibition leads to generation of oxidative markers and alterations in mitochondrial function and morphology as a function of time post-injury. The results suggest that the window for antioxidant mitochondrial protection may be 3 h or less.

POSTER PRESENTATIONS

Faculty

Presenter:

Abstract Presentation:

Ravikumar R. Rao, Ph.D.

Post-Treatment with the Cyclosporin Derivative NIM811 Reduces Cytochrome C Release and Cell Death, and Increases White Matter Sparing Following Spinal Cord Injury

Sara Salles, D.O.

Inpatient Rehabilitation After Deep Brain Stimulator Placement: A Case Series

Diane Snow, Ph.D.

Chondroitinase-Secreting Astrocytes Mitigate Axon Inhibition by Chondroitin Sulfate Proteoglycans

PHYSICAL MEDICINE & REHABILITATION RESEARCH DAY 2005

Post-Treatment with the Cyclosporin Derivative NIM811 Reduces Cytochrome C Release and Cell Death, and Increases White Matter Sparing Following Spinal Cord Injury

Presenter:

Ravikumar Rangaswamy Rao, Ph.D.

Collaborators:

R. Ravikumar^{1,2}, M.L. McEwen^{1,2}, C.L. Searce^{1,2}, P.C. Waldmeier³, P.G. Sullivan², & J.E. Springer^{1,2}

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Abstract Text:

Cyclosporin A (CsA) is a potent immunosuppressive drug that inhibits mitochondrial permeability transition (mPT). Although clinical trials examining CsA in traumatic brain injury are currently underway, CsA is highly neurotoxic and appears to have limited neuroprotective actions in experimental spinal cord injury (SCI). NIM811 is a non-immunosuppressive CsA derivative that inhibits mPT following SCI and has significantly less cytotoxicity than CsA. Therefore, in the present experiment, we investigated the effects of NIM811 post-treatment on cytochrome c release, the presence of apoptosis-related mono- and oligonucleosomes, and white matter sparing following SCI in rats. Using a randomized, blinded study design, rats received a spinal cord contusion at T10, and were treated with 20mg/kg NIM811 (n=7) or vehicle (n=10) by oral gavage at 15 min post-injury. These animals were sacrificed 1, 4, or 24 hr later for examination of apoptotic cell death markers in spinal cord homogenates. ELISA procedures revealed that the levels of cytosolic cytochrome c and apoptosis-specific mono- and oligonucleosomes were significantly reduced, indicating a reduction in apoptotic cell death. A second set of rats was used for histological analysis and received an additional dose of NIM811 (n=8) or vehicle (n=7) 24hr post-injury. These animals were perfused 7 days post-surgery and the amount of spared white matter was determined using stereological techniques. Control groups included rats that received sham surgery (laminectomy only) or no surgery (normal). In this histological study, NIM811 post-treatment increased the amount of white matter spared at the injury epicenter, as well as adjacent rostral and caudal regions at 7 days post-SCI, relative to rats post-treated with the vehicle. The experimental findings demonstrate that NIM811-mediated inhibition of mPT significantly reduces apoptotic cell death and increases white matter tissue sparing. We propose that the use of CsA derivatives, such as NIM811 has clinically relevant potential as an acute treatment strategy in SCI. Supported by NIH Grant NS046380, the Kentucky Spinal Cord and Head Injury Research Trust, and the Cardinal Hill Endowed Research Program.

PHYSICAL MEDICINE & REHABILITATION RESEARCH DAY 2005

Inpatient Rehabilitation After Deep Brain Stimulator Placement: A Case Series

Presenter:

Sara S. Salles, D.O.

Collaborators:

Devi Nampiaparampil, M.D., Sara S. Salles, D.O.

Departmental Affiliations:

Physical Medicine & Rehabilitation, Cardinal Hill Hospital

Abstract Text:

Deep brain stimulation (DBS) of the subthalamic nucleus or the globus pallidus internus is an evolving treatment in the management of Parkinson's Disease (PD). DBS is a neurosurgical procedure that involves delivering continuous electrical stimulation to the brain through implanted electrodes connected to an internalized neurostimulator that is programmable in amplitude, pulse width, and frequency. DBS is used in patients who have severe motor fluctuations or dopa-induced dyskinesias, to improve function and decrease medication dosages. This case series describes the inpatient rehabilitation of two patients with PD who had undergone DBS placement. One patient had the stimulator, generator, and leads placed simultaneously. He required multiple adjustments of the stimulator, which often led to worsening dysarthria and dysphagia. This resulted in his having variable functional abilities and therefore, multiple modifications of his weekly functional goals. The second patient had a previous left pallidotomy but because of difficulty managing freezing episodes and frequent dyskinesia, underwent DBS placement. He had a staged procedure where he experienced mild improvement after stimulator placement and additional improvement after generator placement. The patient made increasing functional gains and at one month post-discharge, was not experiencing any "off" phenomena. Both patients' medications were weaned dramatically. This suggests that the inpatient rehabilitation of patients after DBS placement may very considerably and may require periodic reassessments of functional goals.

PHYSICAL MEDICINE & REHABILITATION RESEARCH DAY 2005

Chondroitinase-Secreting Astrocytes Mitigate Axon Inhibition by Chondroitin Sulfate Proteoglycans.

Presenter:

Diane Snow, Ph.D.

Collaborators:

Snow, DM*, Kohler, K., Jin, Y, Caggiano AO, and Smith, GM,

Departmental Affiliations:

Anatomy & Neurobiology and Physiology, University of Kentucky
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Abstract Text:

Spinal cord injury (SCI) is a devastating condition that affects a quarter of a million individuals nationally and results in paralysis below the level of the injury. Chondroitin sulfate proteoglycans (CSPGs) are up-regulated by astrocytes in the glial scar following SCI and contribute to failed regeneration. To this end, we have engineered astrocytes to produce a modified form of the bacterial enzyme chondroitinase AC (ChAC), which can be secreted from mammalian cells. This enzyme normally cleaves and removes glycosaminoglycan (GAG) side chains from the CSPG protein core. Both *in vitro* and *in vivo*, such enzymatic GAG chain elimination enhances the ability of axons to ignore CSPG-induced inhibition and regenerate through the glial scar. Cultures of U373 human astrocytoma cells were transfected with adenovirus encoding ChAC and subsequently induced with doxycyclin to secrete ChAC. Conditioned media from these cultures was collected and concentrated at a minimum ratio of 25:1. In controlled experiments, chicken dorsal root ganglion (DRG) explants and dissociated neurons growing on laminin (25µg/ml) were inhibited by a mixture of CSPGs (Sigma, #CC117; 100 µg/ml) that was adsorbed to the culture dish in a striped pattern. In contrast, cultures treated with conditioned media from chondroitinase-secreting astrocytes showed neurite outgrowth into and across CSPG-adsorbed stripes. Further, injection of adenoviral-encoding ChAC into the lesioned spinal cord in rats showed active enzymatic activity, as identified by staining with antibody 3B3 (ICN, #69636). These studies *in vitro* and *in vivo* show that using endogenous astrocytes transfected to secrete CSPG-degrading enzymes to diminish the inhibitory character of the glial scar can provide a more physiologic approach to treating spinal cord injuries and promises to be of greater clinical relevance than contemporary methods. *Support: Kentucky Spinal Cord and Head Injury Research Trust Grants: # 0-8 (DMS) and #2-16 (GMS)*

PHYSICAL MEDICINE & REHABILITATION RESEARCH DAY 2005

The Department of Physical Medicine & Rehabilitation would like to acknowledge our appreciation to those who have made the 17th Annual Research Day a success.

CARDINAL HILL REHABILITATION HOSPITAL

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