Transient Receptor Potential Channels and Pain

By Hongzhen Hu, Ph.D.

Abstract: Chronic pain affects millions of American adults to some degree. However, pain management is still a challenging task due to a lack of understanding of the fundamental mechanisms of pain. In the past decade transient receptor potential (TRP) channels have been identified as molecular sensors of tissue injury and inflammation. Activation/sensitization of TRP channels in peripheral nociceptors initiates neurogenic inflammation and signals pain. Pharmacological and genetic studies have affirmed the role of TRP channels in multiple forms of pain conditions. Thus pain-producing TRP channels emerge as promising therapeutic targets for a wide variety of pain and inflammatory conditions.

How to take advantage of inflammation to help repair the brain after intracerebral hemorrhage

By: Jaroslaw Aronowski, Ph.D. and Xiurong Zhao, M.D.

Abstract: Intracerebral hemorrhage (ICH) is an often fatal type of stroke which kills about 30,000 people annually in the USA, for which there is no effective treatment. One of the key pathogenic factors of ICH is toxicity of blood deposited within the brain matter. Although surgical evacuation of blood from the brain showed no health benefit, new emerging studies propose to pharmacologically target phagocytic cells such as microglia or macrophages to help in faster and more efficient clearance of blood clots (hematoma) from brain.

Inflammation within the CNS is an important and immensely complicated process that involves an integrative effort of virtually all brain cell-types as well as hundreds of molecules secreted by these cells. In addition, inflammatory conditions may be externally influenced/regulated by several of the major body organs such as the spleen, lungs, gut or liver. The inflammatory process is a necessary step in alerting and defending the CNS from deleterious effects of various external and internal pathogenic factors. However, at the same time chronic, exces-
NRC Celebrates 20th Anniversary

From the director, John H. Byrne, Ph.D.

In 1992, the Neuroscience Research Center (NRC) was founded as an interdisciplinary “umbrella” organization to strengthen existing programs in the neurosciences. The efforts of the Center coincided with the national initiative designating the 1990s as the “Decade of the Brain”. For 20 years, the NRC has been at the forefront of cutting-edge neuroscience discoveries and public awareness of brain health. Today, the NRC has grown to over 280 neuroscientists from various UTHealth schools and departments. This year, we celebrate our twentieth anniversary by looking toward the future—continuing our tradition of excellence in neuroscience research, education and service to the community.

A snapshot of the NRC’s highlights over the past 20 years includes:

1992 UTHealth received a generous, private donation to create a center that would join together neuroscientists from multiple departments to foster research collaborations and support. Part of the mission included promoting neuroscience education and understanding to the community at large.

Dr. Mortimer Mishkin from NIMH gave the first Distinguished Lecture. Since then, there have been a total of 30 Distinguished Lectures. On February 8th, we welcomed the 2008 Nobel Laureate in Chemistry, Dr. Roger Tsien, Investigator at the Howard Hughes Medical Institute and Professor of Pharmacology and Chemistry & Biochemistry at the University of California, San Diego, to deliver the 30th Distinguished Lecture in the Neurosciences.

1993 The first NRC Poster Session took place at the UTHealth Medical School. Our most recent Poster Session on December 3, 2011 was our largest competition yet, with over 50 abstract submissions and 26 judges from UTHealth, Baylor College of Medicine and Rice University. This year, for the first time, we welcomed graduate students from the Psychology Department at Rice University. Prizes for the top three posters for graduate students and postdoctoral fellows are awarded annually and many attendees walk away with a door prize from our favorite local vendors.

1994 The first NRC Newsletter was published featuring basic and clinical research perspectives on Traumatic Brain Injury. Currently, the Newsletters is distributed to over 4,000 individuals and groups engaged in neuroscience research within the Texas Medical Center, around the country and worldwide.

1995 The Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases was created to study diseases at the genetic, cellular and molecular levels using DNA and protein technologies. NRC Member, Dr. John Hancock, is currently the Interim Director.

1996 In conjunction with the The Dana Alliance for Brain Initiatives’ annual “Brain Awareness Week,” the NRC hosted our first Public Forum on the Brain. Speakers for this event were Drs. James A. Ferrendelli and Robert Guynn. On January 21st, we hosted the 17th Annual Public Forum on Rehabilitation moderated by Dr. Gerard Francisco, one of Congresswoman Gifford’s physicians at TIRR Memorial Hermann, and featured panelists Drs. Marcia O’Malley, Jeff Berliner and Corwin Boake. This event is supported, in part, by the Society for Neuroscience Chapter Award.

1997 W. M. Keck Center for the Neurobiology of Learning and Memory at UTHealth Medical School was established as a hub of research to better understand the physiology and molecular processes underlying learning and memory.

1998 Almost every year, the NRC hosts a Reception at the annual Society for Neuroscience Conference to promote collaborations and scientific exchange amongst attendees. With over 30,000 neuroscientists in attendance at the meetings, this intimate reception is a way to reunite past and present NRC faculty members, postdoctoral fellows, residents, and students. This event also encourages students and postdoctoral fellows from other institutions to explore the diverse array of research opportunities available at the NRC.

1999 The NRC initiated an annual Neurobiology of Disease Course for graduate and medical students. It has since been expanded to include Postdoctoral Fellows, Clinicians and Faculty from UTHealth and other Houston institutions. The first topic was Movement Disorders, and other topics have included the Neurobiology of Addiction, Neurovascular Disease, The Developing Brain, and The Genetic Basis for Brain Diseases.

2001 Brain Night for Kids, a free event held annually at The Health Museum in Houston, is attended by hundreds of children and families from the local community. Brain Night is packed with activity booths aimed to educate children about how the brain works and to spark an
interest in neuroscience at an early age. Demonstration topics ranged from bike-helmet safety, brain reflexes, eye-hand coordination, comparing brains of different species and face-painting. This event is supported, in part, by the Society for Neuroscience Chapter Award.

2002 Staying Sharp: In collaboration with the Dana Alliance for Brain Initiatives and NRTA AARP’s Educator Community, the NRC presented “Staying Sharp: Current Advances in Brain Research.” This event was such a great success it was presented again in 2010 featuring a panel discussion by Drs. James ‘Red’ Duke, Jr., James Ferrendelli and Sharon Ostwald, as well as myself.

2003 The Children’s Learning Institute (CLI) was created through the unification of two nationally recognized centers: the Center for Academic and Reading Skills (CARS) and the Center for Improving the Readiness of Children for Learning and Education (CIRCLE). NRC member, Dr. Susan Landry, is the founder and director of the CLI.

2006 Vivian Smith Neurosurgery Center and Mischer Neuroscience Institute led by NRC Executive Committee Members Dong H. Kim, M.D., and James C. Grotta, M.D., was established. Specialized Centers of Excellence include: Cerebrovascular and Stroke, Neuro Oncology, Restorative Neurosurgery and Neurology, Spine and Neuromuscular, Critical Care and Neurotrauma, Neurorehabilitation and Pediatric Neurology and Neurosurgery.

2009 Dedication of Senator Lloyd and B.A. Bentsen Center for Stroke Research. This center was established as part of The Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases to promote stroke research collaborations.

Opening of the George P. & Cynthia W. Mitchell Center for Research in Alzheimer’s Disease and Related Brain Disorders organized by Dr. Claudio Soto, Professor of Neurology and Director of the Center. This center is devoted to eradicating Alzheimer’s disease and related brain disorders.

2010 Over 50 runners and walkers form the UTHealth Medical School joined together for a student organized “Brain Pumpin’ Fun Run” held in conjunction with the ConocoPhillips Rodeo Run. This event raised over $2,000 for Brain Awareness activities sponsored by the NRC. Look for a similar event in the year to come.

The University-wide Consortium on Aging was established at UTHealth and is led by Dr. Carmel Dyer and Dr. Sharon Ostwald, NRC member. This institute provides support for health care needs of older adults and promotes research to expand the understanding of aging processes.

The selective Scholarly Concentration Program in the Neurosciences was introduced to enrich and supplement medical school neuroscience education through student participation in basic or translational research, teaching opportunities, scientific presentations and course work.

The Distinguished Medical Student in the Neurosciences award was created for fourth year M.D. or M.D./Ph.D. students who have demonstrated excellence in research in the neurosciences and plan to follow a medical career in a neuro-related field. This year, the award went to an exceptional candidate and M.D./Ph.D. student, Audrey Nath, who worked with NRC faculty member, Dr. Michael Beauchamp.

2012 In conjunction with our 20-year anniversary, the NRC has initiated the Graduate Student Brain Awareness Outreach Award to honor students for remarkable dedication to brain awareness activities in the community. This year’s award went to Sarah Baum, a third year student in Dr. Michael Beauchamp’s lab.

Overall, it has been a fantastic twenty years. The NRC has been privileged to have had the financial support from members of the community, as well as volunteer support to make each and every event a success. Our events would not be possible without a large group of enthusiastic volunteers which have included NRC faculty members and postdoctoral fellows, as well as medical, graduate and undergraduate students. We have grown so much in the past two decades and are using this anniversary milestone to initiate greater goals for our future. Stay tuned.
Awards

Carmen W. Des-sauer, Ph.D., Professor, UTH ealth Department of Integrative Biology and Pharmacology was recently elected as a AAAS Fellow (American Association for the Advancement of Science). The awards ceremony took place on February 18, 2012 in Vancouver, BC.

Linda Ewing-Cobbs, Ph.D., Director, Dan L. Duncan Neurodevelopmental Clinic and Professor, UTH ealth Departments of Pediatrics and Psychiatry and Behavioral sciences, and colleagues received a five-year grant through the National Institute of Neurological Disorders and Stroke to continue studying effects of traumatic brain injury on a child’s neurodevelopment.

David Marshak, Ph.D., Professor, UTH ealth Department of Neurobiology and Anatomy, along with co-investigators at the University of Utah, received a five-year grant to study the structural neurochemistry of retinal circuits from the National Institutes of Health.

NRC Member Recipients of the 2011-2012 Dean’s Teaching Excellence Awards

Biochemistry & Molecular Biology
Michael R. Blackburn, Ph.D.
Vasanthi Jayaraman, Ph.D.
Henry W. Strobel, Ph.D.

Diagnostic & Interventional Imaging
Chitra Chandrasekhar, M.B., B.S.
Clark W. Sitton, M.D.

Integrative Biology & Pharmacology
Kartik Venkatachalam, Ph.D.
Edgar T. Walters, Ph.D.

Neurobiology & Anatomy
Leonard J. Cleary, Ph.D.
Pramod K. Dash, Ph.D.
Daniel J. Fellemman, Ph.D.
David W. Marshak, Ph.D.
Carla S. Rogers, Ph.D.
Han Zhang, M.D.

Neurology
Andrew D. Barreto, M.D.
James A. Ferrendelli, M.D.
Omotola A. Hope, M.D.
Raymond A. Martin, M.D.
Mya C. Schiess, M.D.
Paul E. Schulz, M.D.
Erin Furr Stimming, M.D.

Ophthalmology & Visual Science
Judianne Kellaway, M.D.
Christophe P. Ribelayga, Ph.D.

Pediatrics
Ian J. Butler, M.B., B.S.
Michael J. Gambello, M.D., Ph.D.
Pedro Mancias, M.D.
Fernando A. Navarro, M.D.
Hope Northrup, M.D.

Physical Medicine & Rehabilitation
Jeffrey C. Berliner, D.O.

Psychiatry & Behavioral Sciences
Jeffrey V. Barr, M.D.
Oscar G. Bukstein, M.D.
Prashant Gajwani, M.B., B.S.
R. Andrew Harper, M.D.
Vimeeth P. John, M.B., B.S.
Svetlana Malkina, M.D.
Cheryl L. Person, M.D.
Teresa A. Pigott, M.D.
Cynthia W. Santos, M.D.
Dawnelle J. Schatte, M.D.
Mujeeb U. Shad, M.B., B.S.

Recipient of the Graduate Student Brain Awareness Outreach Award, Sarah Baum (left,) and the Distinguished Medical Student in the Neurosciences Award, Dr. Audrey Nath (right), with Director of the NRC, Dr. Jack Byrne. Recipients received their awards at the 2012 Public Forum on January 21st.
Publications


Books


The NRC is able to host events free to the public because of the continued support and generosity of individuals in the community. Please support us by making a tax-deductible donation online at: http://giving.uthouston.org/nrc
great strides have been made to understand the molecular mechanisms of pain in the past decade, treatment of pain still remains a major challenge in clinical practice. The most commonly used pain medicines, opioids and non-steroidal anti-inflammatory drugs (NSAIDs), suffer from serious side effects. Therefore, there is an urgent need to develop novel and safer pain medicines to meet the needs of patients.

Pain results from complex processing of neural signals at multiple levels. Primary sensory neurons residing in dorsal root, trigeminal and vagal sensory ganglia detect environmental changes through peripheral nerve endings in the skin and visceral organs and inform the CNS of thermal, mechanical and chemical conditions through action potential firing and release of neurotransmitters to activate neurons in the spinal cord. Noxious conditions such as extreme temperatures, tissue damage, or noxious chemicals are detected by a subpopulation of sensory neurons, the so-called nociceptors, which upon excitation signal pain and induce neurogenic inflammation.

Ion channels play critical roles in the pain pathway. In the past decades, transient receptor potential (TRP) channel family has been identified in the primary sensory neurons. About 28 TRP channels have been identified so far with different numbers of splicing variants in each group. TRP channels are calcium permeable non-selective cation channels. The widespread expression of TRP channels in neuronal and non-neuronal tissues suggests that they may play important roles in many cellular and physiological functions. TRP channelopathies are part of important mechanisms in a variety of diseases such as inflammatory bowel disease, epilepsy, diabetes mellitus, neurodegenerative disorders, and cancer.

Several members of the TRP family (TRPV1-4, TRPM8 and TRPA1, “ThermoTRPs”) are involved in the detection of temperature changes, thus acting as the molecular thermometers of our body. In addition, TRP channels, especially TRPV1 and TRPA1, are polymodal detectors integrating painful stimuli and play central roles in pain sensation under physiological and pathological conditions including inflammation and neuropathy. TRPV1 is the first cloned prototypical vanilloid TRP channel expressed primarily in small-diameter dorsal root ganglion (DRG) neurons and by both peptidergic and non-peptidergic primary afferents. TRPV1 is activated by a variety of physical and chemical stimuli including capsaicin, noxious heat (>43°C), low pH (5.2), voltage, bioactive lipids and other pungent natural compounds. TRPV1-immunoreactive fibers were increased in inflamed human skin and vulva, which correlates with inflammatory hyperalgesia. Interestingly, application of selective TRPV1 blocker such as A-425619, SB-705498 and AMG9810 reduced both hyperalgesia and allodynia in rodent models of pathological nociception and inflammatory pain. Consistent with TRPV1 being a pain initiator, TRPV1 knockout (KO) mice lacked vanilloid-evoked pain but had normal response to noxious mechanical stimulation. More importantly, the thermal hypersensitivity in inflammation was dramatically decreased in TRPV1 KO mice. Therefore, it is clear that TRPV1 is required for inflammatory thermal hyperalgesia.

TRPA1 is expressed in a subset of mammalian sensory ganglion neurons that also express TRPV1. TRPA1 is a polymodal sensor, able to integrate actions of many exogenous and endogenous noxious stimuli, such as the natural pungent compound allyl isothiocynate (AITC), environmental irritant acrolein and oxidative oxygen radicals. The recent finding that a gain-of-function mutation in TRPA1 causes familial episodic pain syndrome in human provides compelling evidence for the involvement of TRPA1 in pain sensation. TRPA1 expression is increased in DRG by Freund’s complete adjuvant-induced inflammation or nerve injury. TRPA1 KO mice show reduced thermal and mechanical pain responses to intraplantar injection of bradykinin or AITC. The TRPA1 antagonist AP18 also attenuated mechanical hyperalgesia in Freun’d complete adjuvant model of inflammatory pain and in the spinal nerve ligation model of neuropathic pain. Interestingly, AP18 also attenuated mechanical hyperalgesia produced by intra-articular injection of Freund’s complete adjuvant, suggesting that TRPA1 might directly mediate inflammatory and arthritic pain.

TRP channels are also extensively expressed in the gastrointestinal tract and serve as important regulators of gastrointestinal motility and visceral hypersensitivity. Patients with inflammatory bowel diseases had three times more TRPV1-positive nerve fibers compared to control subjects. Both TRPV1 and TRPV4 were expressed in visceral sensory neurons and responded to physiological mechanical stimuli. They also contributed to visceral mechanical hyperalgesia.

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persensitivity in chemically-induced rodent colitis models. TRPA1 was also expressed in visceral afferent neurons and played an important role in sensory transduction, particularly in the context of visceral inflammation and pain in both gastrointestinal and urinary tracts.

The identification of the TRP channels, particularly TRPV1 and TRPA1, in the pain pathway has shed light on the molecular basis of pain signaling during inflammatory conditions. TRPV1 and TRPA1 thus are considered as potential targets in the treatment of inflammatory pain because of their ability to be activated by nociceptive signals and sensitized by pro-inflammatory mediators. Although development of selective inhibitors targeting pain-initiating TRP channels on peripheral nociceptors appears promising, the first generation TRPV1 antagonists carry an undesired on-target side effect of hyperthermia, making them unsuitable for further development into pain management drugs.

Our recent work has identified the transition metal zinc as a novel TRPA1 activator. Zinc excites nociceptive somatosensory neurons and causes acute nociception in mice through direct activation of TRPA1. Zinc activates TRPA1 through a novel mechanism that requires zinc influx through the constitutively active TRPA1 channels and subsequent activation via specific intracellular cysteine and histidine residues. These findings identify TRPA1 as a major target for the sensory effects of zinc, and support an emerging role for zinc as a signaling molecule that can modulate sensory transmission. Interestingly, our current work found that exogenously applied zinc desensitized currents activated by the TRPA1 agonist AITC in nociceptors following initial activation and suppressed AITC-evoked nocifensive behavior in mice. Zinc also suppressed current and nocifensive behavior in response to the TRPV1 agonist capsaicin. Zinc inhibition of TRPV1 requires co-expressed TRPA1 which mediates entry of zinc into nociceptors. Our findings provide mechanistic insight into zinc inhibition of two critical pain-producing TRP channels and offer a novel approach that is potentially devoid of the systemic effects and safety concerns associated with most TRPV1 antagonists.

Another efficient method of targeting TRPV1 to elicit antihyperalgesia is to use potent analgesics, which act through the desensitization of TRPV1. For instance, topical creams and oral compounds containing capsaicin have been used to treat pain. However, the administration of capsaicin causes a burning pain sensation which limits its application in patients. Our lab is currently searching for novel TRPV1 ligands that possess capsaicin-induced therapeutic effects with little or no pungency using medium-to-high throughput chemical screens.

In summary, TRP channels function as molecular sensors of environmental stimuli and initiate pain during tissue damage and inflammation. TRP channels are emerging as promising drug targets for the management of both acute and chronic pain conditions. Targeting TRP channels present on primary nociceptors is a novel and attractive approach to provide safe and effective relief to millions of patients living with either acute or chronic pain.

About the Author
Hongzhen Hu, Ph.D. is an Assistant Professor in the Department of Integrative Biology and Pharmacology at the University of Texas Medical School at Houston. He received his Ph.D. from the Integrated Biomedical Science Graduate Program (IBGP) at The Ohio State University. He performed his postdoctoral studies at The Genomics Institute of the Novartis Research Foundation (GNF) and The Scripps Research Institute (TSRI) in San Diego, CA. His laboratory at UT-Houston utilizes electrophysiological and pharmacological techniques in combination with molecular biology, mouse genetics and mouse behavioral methods to investigate roles of ion channels in sensory neurons under physiological and pathophysiological conditions.

Figure 1: Diagram of zinc regulation of TRP channels in the primary afferent neurons and its implication in neurogenic inflammation and pain.
sive or aberrant inflammatory process may predispose the CNS tissue to disease (e.g., atherosclerosis in cerebrovascular diseases) or directly mediate acute or chronic damage via deleterious cytokines, oxidative processes and the proteolytic degradation of cellular components and extracellular matrices.

Following ischemic stroke (brain vessel occlusion) or hemorrhagic stroke (leakage of blood out of vessels to brain parenchyma; referred to as intracerebral hemorrhage or ICH); septic inflammation is triggered by the damage-associated molecular pattern (DAMPs) molecules (e.g., ATP, urea acid, DNA, high-mobility group box 1 or heat-shock proteins) released from cells following tissue injury in response to stroke. This early signaling activates the brain’s resident macrophages, microglia, which in turn by generating a battery of signaling molecules, initiate a systemic reaction leading to infiltration of hemogenous white blood cells; first neutrophils and then 1 to 3 days later monocytes into the brain parenchyma. In animal models of stroke, early (within hours after the onset of stroke) inhibition of some of the inflammatory processes including microglia activation (e.g., with the tetracycline antibiotic, minocycline), blocking endothelial transmigration of neutrophils (e.g., by neutralization of adhesion molecules) or neutralization of pro-inflammatory cytokines such as interleukin-1-β (IL-1β) or tumor necrosis factor-α (TNFα) (e.g., with IL-1β receptor antagonist or TNFα neutralizing antibody) has been demonstrated to reduce brain injury and neurological deficit after stroke. These therapeutic profiles have solidified a present notion that the early pro-inflammatory responses, which are controlled by the transcription factor NF-κB, adversely affect pathogenesis of stroke.

Although the detrimental effects of inflammation are well-described, it certainly needs to be recognized that selected inflammatory processes play an important role in the inhibition of perpetuated inflammatory processes at later stages of inflammation (self-inhibition) and that one of the key functions of several types of inflammatory cells is the cleanup of death/injured tissue (via phagocytosis), wound healing and ultimately brain tissue repair. The cell types which primarily participate in the brain cleanup process are microglia and blood-derived macrophages. Microglia represent an abundant cell population and account for approximately 10% of all the brain cells. These cells are distributed throughout the brain but are more abundant in gray matter. It appears that the origin of the microglial cell is not from a postnatal hematopoietic progenitor as generally assumed, but instead from a primitive myeloid progenitor cell population present early in brain development prior to the closure of the blood brain barrier and the establishment of a mature functional blood circulation in the CNS. Thus, it is likely that functionally microglia and blood-derived macrophages are indeed different. Nevertheless, following stroke both hemogenous macrophages and locally activated microglia in the injured brain assist in cleanup of cellular debris, apoptotic cells and extravasated red blood cell (RBCs) (in case of intracerebral hemorrhage). This cleanup is mediated by a phagocytic process that is mediated through the cell surface scavenger receptors (e.g., CD36, SR-AI, SR-AII or CD91).

The cleanup of blood clots (hematoma) from the brain after ICH appears to be of unique importance. RBCs represent the majority of the mass of brain hematoma. RBCs lyse, releasing over time, highly cytotoxic hemoglobin which consequently breaks down into heme and iron. These molecules can produce extensive cytotoxicity through Fenton’s reaction, generating highly-reactive hydroxyl radicals (Figure). Thus, timely phagocytosis-mediated removal of RBCs may effectively prevent this deleterious event. However, phagocytosis and the subsequent oxidative degradation of the engulfed cellular debris in phagosomes can also generate destructive oxygen and nitrogen oxidants, in addition to cytokines and proteolytic enzymes that eventually can collectively spread secondary injury events to surrounding normal brain tissues. In fact, when using a primary tissue culture system to mimic the brain’s environment after intracerebral hemorrhage, we showed that microglia involved in phagocytosis of RBCs are more likely to produce damage to adjacent neurons in the microglia-neuron co-culture system.

While appreciating the yin and yang nature of the cleanup process; the benefits of phagocytosis-mediated brain cleanup vs. the potential risks associated with this process, we initiated studies aimed at modifying microglia function, so that they could be converted into better phagocytes while generating less oxidants and pro-inflammatory cytokines.
Through several years efforts working with two ubiquitous transcription factors, PPARγ (peroxisome proliferator-activated receptor gamma) and Nrf2 (NF-E2-related factor 2), we knew that one of their common gene targets is the multifunctional scavenger receptor CD36, a transmembrane protein present on macrophages with the role of recognition and phagocytosis of apoptotic cells, senescent neutrophils, as well as engulfment of RBCs. Since ICH pathogenesis is directly linked to RBC toxicity, we predicted that activation of PPARγ or Nrf2 in microglia would lead to an upregulation of CD36 and improve RBCs phagocytosis/removal from the brain parenchyma, thus limiting the toxic impact of RBCs on surrounding brain cells. In fact, this turned out to be the case. Microglia in culture exposed to various PPARγ agonists (e.g., pioglitazone, rosiglitazone, or endogenous prostaglandin D2 metabolite 15-deoxy-Δ12, 14-prostaglandin J2) or an inducer of Nrf2 activity (e.g., sulforaphane), showed increased expression of CD36 and exhibited greater efficiency in engulfing RBCs. To confirm that this process involves CD36, we showed that CD36 neutralizing antibodies or a deficiency in CD36 expression inhibited the ability of microglia to phagocytose RBCs.

Now that we have learned how to increase the phagocytic function of microglia, the next step was to learn how to modify microglia so that they do not generate toxic levels of cytokines and free radicals during phagocytosis. It turns that this task was easier than we expected. PPARγ and Nrf2 are involved in glucose/lipid metabolism and detoxification processes, respectively, and as such control expression of numerous anti-oxidative enzymes such as catalase, superoxide dismutase, glutathione S-transferase, thioredoxin, glutathione peroxidase as well as others. We anticipated that the pharmacological activation of PPARγ or Nrf2 in microglia within the rodent brain would not only improve phagocytic function via CD36 express/activity, but simultaneously enhance the anti-oxidative status of the phagocyte. Indeed, when microglia in culture or injured animals were treated with pioglitazone or sulforaphane, we observed a substantial upregulation of anti-oxidative enzymes at both the mRNA and protein levels. This treatment not only bolstered cellular anti-oxidative stress defense mechanisms, but also substantially reduced the oxidative modification protein and lipids (key targets of oxidative stress-mediated damage). Furthermore, this treatment remarkably reduced the generation of pro-inflammatory molecules such as IL-1β, TNFα, MMP-9 or the enzyme, iNOS, responsible for production of toxic levels of nitric oxide by microglia during the phagocytosis of RBCs. Since PPARγ and Nrf2 have both direct and indirect inhibitory effects on the transcription factor NF-κB, a master regulator of inflammatory responses, this anti-inflammatory effect is likely through NF-κB inhibition. Most importantly, microglia pre-treated with pioglitazone or sulforaphane demonstrated less toxicity toward neurons in a co-culture system.

Encouraged by our results with PPARγ and Nrf2 agonists in cultured microglia, our next step was to use the rodent model of ICH to study the clinical relevance of this approach. We intracerebrally injected autologous blood into the rodent brain to mimic human ICH and used pioglitazone or sulforaphane as the experimental therapy. Our hypothesis was that these treatments would activate microglia and macrophages within rodent brain and improve the hematoma cleanup process, reduce neurological deficits and facilitate the recovery process. Once again, in agreement with the hypothesis and in vitro data, treatment of rodents with PPARγ or Nrf2 activators, for up to 24h after the onset of ICH, resulted in: (1) increased CD36 expression which was associated with faster hematoma clearance, (2) reduced oxidative stress in brain areas surrounding the hematoma, and (3) overall reduced production of pro-inflammatory cytokines and (4) improved functional recovery.

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Brain Awareness Week 2012

With support from the Society for Neuroscience, Partners in Education Program in the Neurosciences and the TIRR Foundation & Mission Connect, the NRC hosted two events in association with Brain Awareness Week 2012.

17th Annual Public Forum - Jan. 21, 2012
“Rehabilitation: Recovery, Restoration and Re-integration”

From Left to Right: Drs. Jeffrey Berliner, Corwin Boake, Gerard Francisco, Marcia O’Malley and Jack Byrne.

UTHealth Neuroscience Programs graduate students Stuart Red and Heather Turner discussed how the brain works with members of the audience at a special reception following the Forum.

Welcome New Executive Committee Members!

The NRC would like to welcome Ruth Heidelberger, M.D., Ph.D. of the UTHealth Department of Neurobiology and Anatomy, Min Li, Ph.D., of the UTHealth Department of Neurosurgery, and George M. Stancel, Ph.D., Dean of the UTHealth Graduate School of Biomedical Sciences and UTHealth Executive Vice President for Academic and Research Affairs.

The NRC would like to thank Drs. Dong H. Kim, Louvenia Carter-Dawson, and Peter J. Davies for their years of dedicated service to the NRC Executive Committee.

11th Annual Brain Night for Kids
March 15, 2012
The Health Museum

Sarah Baum, student in Michael Beauchamp’s laboratory, and Dr. Timothy Ellmore explain to children and parents how the brain works using real human brains.

Representing the TIRR Foundation & Mission Connect, Cynthia Adkins and Dr. Pramod Dash

Audience members attentively listening as panelists describe current rehabilitation techniques.
The 20th Distinguished Lecture Series
February 8, 2012

The 20th Distinguished Lecture Series was held on February 8, 2012. Dr. Roger Y. Tsien, Nobel Laureate and Investigator at the Howard Hughes Medical Institute and Professor at the University of California San Diego, delivered an outstanding lecture on “Breeding and building molecules to image and control action potentials and synapses”.

A group of high school students from the WRAP program (Worth- ing Rice Apprentice Program) and Dr. Steve Cox from Rice University take a tour of the Byrne laboratory in the UTHealth Department of Neurobiology & Anatomy.

The NRC hosted a reception at the Annual meeting of the Society for Neuroscience in Washington, DC on November 15, 2011 at Hill Country BBQ. Former and current UTHealth students, postdoctoral fellows, faculty and colleagues attended.

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This pre-clinical study provided the basis for ongoing NIH-funded clinical study directed by Dr. Nicole Gonzales, M.D., Assistant Professor of Neurology, Stroke Program at UT-Health Houston, evaluating pioglitazone as potential treatment for ICH in humans.

About the Authors

Jaroslaw (Jarek) Aronowski received his medical degree in clinical pharmacology from the Warsaw Medical School and Doctor of Philosophy degree from the Polish Academy of Sciences for work on regulation of protein phosphorylation after global brain ischemia. He completed postdoctoral training at the Texas Research Institute of Mental Sciences at Houston and then University of Texas Health Science Center Departments of Neurobiology and Anatomy and Neurology. Dr Aronowski joined the faculty of the Department of Neurology in 1993. He is currently a Professor of Neurology and the Director of Research, Cerebrovascular Program and is affiliated with the Senator Lloyd and B.A. Bentsen Center for Stroke Research.

Xiurong Zhao received her MD from Shang Dong Medical University in China. She worked as a Research Instructor at the Anti-epidemic Center of Jinan in China. She moved to Houston in 1992 to work with the Neurosurgery group at University of Texas – Health Science Center at Houston to study traumatic brain injury. Dr. Zhao is now an Associate Professor of Neurology in the Cerebrovascular Program.
Questions? Comments?
Contact us at 713-500-5538
or E-mail: nba-nrc@uth.tmc.edu

Check out our Neurofax calendar of neuroscience events online! The Neurofax includes seminars, grand rounds, research colloquia, symposia, and local or national conferences that are sponsored by UTHealth, the Texas Medical Center, and Houston area universities and research institutions. To submit your event to this calendar, please send an email to nba-nrc@uth.tmc.edu and include Event Name, Event Contact, Date, Time and Location.

This Newsletter is distributed by mail to individuals and groups engaged in neuroscience research within the Texas Medical Center and worldwide and features research, neuroscience accomplishments and outreach efforts performed at UTHealth. Past issues are available on the NRC Website. If you would prefer to receive a digital copy through email, please send an email to nba-nrc@uth.tmc.edu with your information.