



Reflected in the Eyes

Glaucoma assessment tool can track MS activity

MAGNETIC RESONANCE IMAGING (MRI) of the brain is the gold standard for monitoring the progression of multiple sclerosis (MS), but it is expensive and comes with limitations, one of which is the inability to assess fully the extent of loss of neurons.

NEW RESEARCH by neurologists at UB has shown that a technique called optical coherence tomography, or OCT, a simple and inexpensive measure employed currently to assess glaucoma, also could be used as a surrogate marker of disease status in MS and to assess the effectiveness of new and current MS treatments.

BY
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“This organization is advantageous,” she says, “because changes in the structure of the retinal-nerve-fiber layer principally represent axonal damage, whereas the myelin wrapping

around the axons into the optic nerve begins behind the eye. Consequently, the retina can be used to focus on the neuronal and axonal components of MS pathological changes.”

The study involved a retrospective review of scans of 30 patients with relapsing-remitting MS (characterized by acute attacks with full or partial recovery) who were seen at the Baird Multiple Sclerosis Center, the clinical section of the JNI. All patients had received OCT, and 18 were analyzed also by MRI. All scans were analyzed at the Buffalo Neuroimaging Analysis Center (BNAC), also part of UB’s JNI.

Results showed that the thickness of the retinal-nerve-fiber layer (RNFL) as assessed by OCT was strongly associated with MRI findings of brain atrophy and lesion volume, says Weinstock-Guttman.

“Furthermore, we found a negative correlation between average RNFL thickness (average of both eyes) and disability, as assessed by the Expanded Disability Status Scale, the gold standard measure used in MS.

“The results demonstrate that OCT can be an excellent patient monitoring technique, because the decrease in RNFL thickness reflects inflammatory and neurodegenerative components of MS,” she



OPTICAL COHERENCE TOMOGRAPHY MAY BE HELPFUL IN MONITORING DISEASE PROGRESSION, BUT ALSO COULD REPRESENT A POTENTIAL SENSITIVE TOOL OR OUTCOME MEASURE FOR FUTURE TRIALS USING NEUROPROTECTIVE THERAPEUTIC INTERVENTIONS.



explains. “Further studies are needed to assess and validate OCT measures versus MRI measures and to delineate the role of OCT in patients with relapsing and progressive forms of MS. **BP**”

Erica Grazioli, MD, UB clinical instructor of neurology, was first author on the paper. Additional contributors were Robert Zivadinov, MD, PhD, director of the BNAC and UB associate professor of neurology; Norah Lincoff, MD, UB clinical professor of ophthalmology; Jan Rang Wong; David Hojnacki, MD, clinical instructor of neurology; Sara Hussein; Jennifer Cox, PhD, assistant professor neurology and director of clinical imaging at the BNAC; Murali Ramanathan, PhD, UB associate professor of neurology and pharmaceutical sciences; and Monica Baier, PhD, from the University of Alabama. This study was funded in part by a grant from “Jog for the Jake.”

Premature Birth, an Age-Old Problem

Research attempts to shed new light on causes

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IN THE 21ST CENTURY, human tissue can be generated from stem cells and severed limbs are successfully reattached, while the physiological processes governing life’s most fundamental event, childbirth labor, remain a medical mystery.

MORE THAN 500,000 BABIES, or one of every eight infants born in the U.S., were born prematurely in 2004, the most recent year for which statistics are available. The causes of 30 to 50 percent of preterm births are unknown.

Glenna Bett, PhD, assistant professor of gynecology and obstetrics in the School of Medicine and Biomedical Sciences, hopes to shed new light on this age-old problem. Supported by grants totaling \$438,500 from the National Institutes of Health and March of Dimes, she is investigating the basic cellular mechanics that instigate the muscle contractions of labor.

Her work is aimed at developing drugs that can prevent the premature onset of those contractions.

“Identifying the molecular bases of changes in uterine muscle activity during pregnancy offers opportunities for rational drug design for the pharmacological treatment of preterm labor,” says Bett. “Therapeutic interventions that target earlier steps in parturition should prove more effective in

Uterine contraction, like all smooth-muscle contraction, is primarily an electromechanical event. Although hormonal and biochemical changes play a vital role in regulating and developing conditions leading to labor, she says, the speed and coordination of a process called excitation-contraction coupling in uterine muscle tissue indicates that the short-term signals for contraction are carried by ion channels.

Excitation-contraction coupling is a term used in muscle physiology that describes the

process of converting an electrical stimulus (a nerve impulse) to a mechanical response (muscle-fiber contraction), Bett explains, and ion channels are proteins that act as pores in a cell membrane, permitting selective passage of potassium, sodium and calcium molecules in and out of the cell. This process of ion exchange produces and regulates electrical current.

“Spontaneous premature labor must therefore result from a perturbation in the normal timing and regulation of the electromechanical profile of the uterus,” says Bett.

“Efficient and well-timed excitation-contraction requires two equally important components: an excitatory action to initiate an influx of ions into nerve cells and subsequently contraction, and a relaxing action to return the membrane to the resting state, allowing ions to exit. This whole process is called repolarization.

“Without adequate and timely repolarization,” notes Bett, “the excitation-contraction coupling sequence will become dysfunctional, leading to abnormal contraction.”

Bett has shown in preliminary data that ion channel expression changes 150-fold during gestation. She will study these changes during pregnancy by comparing uterine muscle tissue obtained from non-pregnant women through hysterectomy with uterine tissue from women whose babies were delivered by Caesarean section. **BP**



“IDENTIFYING THE MOLECULAR BASES OF CHANGES IN UTERINE MUSCLE ACTIVITY DURING PREGNANCY OFFERS OPPORTUNITIES FOR RATIONAL DRUG DESIGN FOR THE PHARMACOLOGICAL TREATMENT OF PRETERM LABOR.”

delaying birth than currently used agents, which have only limited effectiveness.

“A fundamental problem in developing therapeutic interventions for preterm labor,” Bett continues, “is that the molecular bases of the mechanisms involved in parturition are unknown.”



Adverse Effects

Popular arthritis drug may disrupt heart rhythm

CELEBREX, a popular arthritis drug that blocks pain by inhibiting an enzyme known as COX-2, has been shown in laboratory studies to induce arrhythmia, or irregular beating of the heart, via a novel pathway unrelated to its COX-2 inhibition.

IN A STUDY published in the January 18, 2008, edition of the *Journal of Biological Chemistry*, UB researchers led by Satpal Singh, PhD, associate professor of pharmacology and toxicology, report that they discovered this unexpected finding while conducting basic research on potassium channels.

They found that low concentrations of the drug, corresponding to a standard prescription, reduced the heart rate and induced pronounced arrhythmia in fruit flies and the heart cells of rats.

The drug inhibited the normal passage of potassium ions into and out of heart cells through pores in the cell membrane known as delayed rectifier potassium channels, the study showed.

“The adverse effects of drugs like Celebrex and Vioxx based on their selective inhibition of COX-2 currently are a topic of intense discussion in the medical community,” notes Singh, who was senior author on the study. (Vioxx was withdrawn from the market in September 2004.)

“We now have shown an important new effect of Celebrex through a totally different pathway, one that is unrelated to the drug’s effect as a pain reducer,” he adds. “The adverse effect arising from this unexpected mechanism definitely needs to be studied

more closely because the potassium channels inhibited by the drug are present in heart, brain and many other tissues in the human body.”

By
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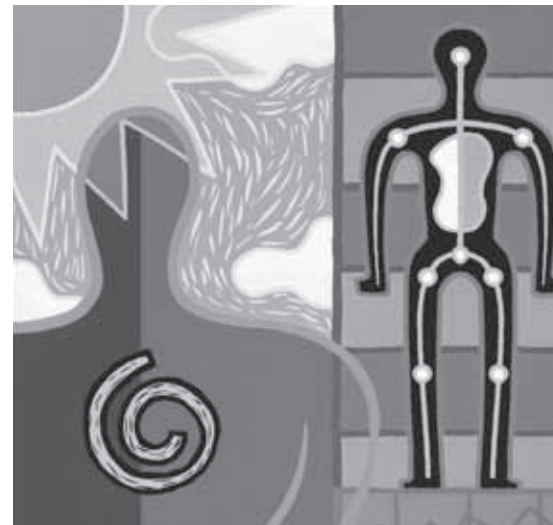
The research was supported by grants from the National Science Foundation to Singh and Randall D. Shortridge, PhD, UB assistant professor of biological sciences, to analyze the basic properties of potassium channels.

Aware that COX-2 inhibitors had been shown to produce cardiovascular side effects, the researchers first tested whether Celebrex would affect the heart in fruit flies, a good animal system for studies on the human heart.

“When we found an effect on the fly heart, we began looking for the underlying mechanism,” recounts Singh. “We searched the fly genome and were surprised to find that these flies don’t have cyclooxygenases, the enzymes targeted by Celebrex.”

“Because the main effect of the drug in our study was induction of arrhythmia, and arrhythmia is often the result of ion-

Roman V. Frolov, a doctoral student working in Singh’s lab, is first author on the paper described above. Ilya G. Berim, MD, research scientist in the UB Department of Medicine, also is a study author, and Malcolm Slaughter, PhD, UB professor of physiology and biophysics and ophthalmology, made significant contributions to the research.



channel dysfunction,” he continues, “we examined the drug’s effect on potassium channels and other ion channels in their models and were struck by the strong inhibition of the potassium channels.”

The researchers now are examining the underlying molecular mechanisms responsible for the drug’s action and its effect on other ion channels that play a prominent role in setting the rhythm of the heart.

“We are trying to determine whether the drug binds directly to the channels or to some other molecule, and if it acts by blocking the pore of the channel through which potassium ions travel or by some other mechanism,” Singh says. **BP**

Tracking Tinnitus

Study explores where phantom auditory sensations originate

FOR THE MORE THAN 50 million Americans who experience the phantom sounds of tinnitus—ringing in the ears that can range from annoying to debilitating—certain well-trained rats may be their best hope for finding relief.

UB RESEARCHERS have studied the condition for more than 10 years and have developed these animal models, which can “tell” the researchers if they are experiencing tinnitus.

These scientists now have received a \$2.9 million, five-year grant from the National Institutes of Health to study the brain signals responsible for creating the phantom sounds, using the animal models, and to test potential therapies to quiet the noise. The research will take place at the Center for Hearing and Deafness, part of the Department of Communicative Disorders and Sciences in the College of Arts and Sciences. Richard Salvi, PhD, director of the center, is principal investigator. Scientists from the Department of Nuclear Medicine and from

Roswell Park Cancer Institute are major collaborators on portions of the project.

Tinnitus is caused by continued exposure to loud noise, by normal aging and, to a much lesser extent, as a side effect of taking certain anticancer drugs. It is a major concern in the military, as 30 percent of Iraq and Afghanistan combat veterans suffer from the condition.

“For many years it was thought that the buzzing or ringing sounds heard by people with tinnitus originated in the ear,” Salvi says. “But by using positron emission tomography [PET scanning] to view the brain activity of people with tinnitus at UB, we’ve been able to show that these phantom auditory sensations originate somewhere in the brain, not in the ear. This

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Salvi and colleagues discovered that when the brain’s auditory cortex begins receiving diminished neural signals from the cochlea (the hearing organ) due to injury or age, the auditory cortex “turns up the volume,” increasing weak neural signals from the cochlea. Increasing the volume of these weak signals may be experienced as the buzzing, ringing or hissing characteristic of tinnitus. Currently there is no drug or treatment that can abolish these phantom sounds.

Over the past decade, Salvi’s team has developed the animal models, allowing the researchers to explore the neurophysiological and biological mechanisms associated with tinnitus, the major focus of this new study. Ed Lobarinas, PhD, and Wei Sun, PhD, in the Department of Communicative Disorders and Sciences, developed the models.

One of the major goals of the project is to try to identify the neural signature of tinnitus—what aberrant pattern of neural activity in the auditory cortex is associated with the onset of tinnitus. In another study phase, the researchers will assess neural activity throughout the entire brain using a radioactive tracer, fluorodeoxyglucose (FDG), which is taken up preferentially into regions of the brain that are highly active metabolically.

The third phase of the study involves the use of potential therapeutic drugs to suppress salicylate or noise-induced tinnitus. In early studies, the researchers were able to modulate some ion channels with one unique compound and were able to completely eliminate aspirin-induced tinnitus using the highest doses of the compound. This phase involves collaboration with scientists at NeuroSearch Pharmaceuticals in Denmark. **BP**

By LOIS BAKER