

Advancements in Options for Treating Neurodegenerative Diseases

Research at the School of Pharmacy offers new insight into neurologic disease

by Allison Motszko

Dr. Jeffery Johnson is the director of the Molecular and Environmental Toxicology PhD program and director of the Pharmacology and Toxicology Bachelor of Science program at the UW School of Pharmacy. In addition, he serves as an associate professor in the Pharmaceutical Sciences Division at the School of Pharmacy. Johnson's research is on the cutting edge of developing treatments for neurodegenerative diseases. He and his graduate students have generated astonishing advancements in this area and are expanding the potential options for patients suffering from these diseases.

Johnson has a long list of publications and his incredibly active and successful laboratory has investigated treatments for several neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, Huntington disease and amyotrophic lateral sclerosis (ALS). Johnson focuses on the molecular neuropharmacology/neurotoxicity of these diseases. Although his research is the first phase of drug development, and many more steps must be completed to introduce a treatment onto the market, he has discovered several compounds that have a high potential for leading to newly designed drugs.

Each of these neurodegenerative diseases is similar in that they are considered to be partially caused by some type of oxidative damage. Johnson directs his research at determining the antioxidant response element (ARE) in each of these disease states. He uses animal models to monitor where the ARE pathways are most prevalent and how different molecules and procedures modulate the animal's response to oxidative stress or damage via the ARE. The majority of the current drug therapy for neurodegenerative diseases is focused



UW's Dr. Jeff Johnson's research is on the cutting edge of developing treatments for neurodegenerative diseases.

on increasing the release, increasing the reception or decreasing the degradation of neurotransmitters. These drugs may be effective, but they are not able to significantly slow or stop the progression of disease.

ALZHEIMER'S DISEASE

Alzheimer's disease is characterized by brain lesions of aggregated beta-amyloid proteins called neuritic plaques and hyperphosphorylated tau deposits called neurofibrillary tangles and a significant loss of neurons. These lesions result in a decreased release of acetylcholine in the brain. Johnson has been focusing on a preventive approach to Alzheimer's disease. When the amyloid precursor protein (APP) in the brain is cleaved,

beta-amyloid proteins can be formed. The protein can be cleaved in two ways. Cleavage first by a beta-secretase then by a gamma-secretase leads to the production of beta-amyloids, whereas, cleavage by an alpha-secretase then by a gamma-secretase does not. In addition, Johnson's lab has found evidence that alpha-secretase-cut proteins can increase the amount of transthyretin (TTR) in the brain which has been shown to bind to beta-amyloids and prevent them from aggregating. Using a mouse model, Johnson's lab has developed a four amino acid compound that mimics the alpha-secretase protein. This small peptide, like the alpha-secretase, cuts the APP in a different location than the beta-secretase and prevents the formation of beta-amyloid, thus blocking the aggregation of neuritic plaques.

HUNTINGTON DISEASE

Huntington disease is clearly linked to genetic mutations, making this neurodegenerative disease much different from many other neurodegenerative diseases where a genetic component often is not evident. In the genetic make-up of these patients, tri-nucleotide (cytosine-adenine-guanine) repeats are found on chromosome 4 causing the gene to encode Huntington protein which gathers in detrimental clumps in brain cells.¹ Clinically these patients display progressive chorea (involuntary, unpredictable movements) and dementia.² This unfortunate disease has few medication options for treating symptoms and no therapy for decreasing the progression of the disease. In many neurodegenerative diseases, an underlying problem is that the mitochondria in the neurons are damaged by oxidative processes. By increasing the Nrf-2 stimulation of the ARE pathway, the mitochondria will be "buffed up,"

continued on page 44

ment of Biomedical Engineering where he plans to develop novel, stimulisensitive biomaterials for tissue engineering and biosensors. Furgeson and his wife Katherine have three children and are avid runners who look forward to participating in their first Mad City Marathon. Furgeson admits to being a life-long Dungeons and Dragons player. "It's a bit geeky," he says, but counters it with the fact that he also enjoys college football and basketball.



MELGARDT M. DE VILLIERS grew up in the small town of Oudtshoorn (the ostrich capital of the world) in South Africa. He received his BPharm, MSc and PhD from

the Potchefstroom University for Christian Higher Education. Both graduate degrees are in pharmaceuticals. After serving on the faculties of North-West University in South Africa and the University of Louisiana at Monroe and a sabbatical year at the University of Iowa, he joined the UW School of Pharmacy faculty in July 2005, replacing Prof. Judy Thompson in the Pharmaceutical Sciences Division and teaching the compounding and dispensing courses. De Villiers also plans to continue his research program which focuses on developing innovative nano and micro particulate drug delivery systems for treating and preventing communicable and chronic diseases. He is married to Mei-Ling Chau, special education teacher in the Madison school district.



GLYNIS C. KINNEY earned her PharmD from Butler University in 2003 and completed her residencies at Aurora Health Care in Milwaukee and UW Hospital and

Clinics in Madison. Kinney plans to continue her practice at UW Hospital while she takes advantage of the opportunity to expand her teaching skills at the School of Pharmacy. She is a clinical instructor who coordinates pharmacotherapy labs and lectures for the DPH-3 students. In her free time, Kinney enjoys Thai cooking and ballroom and international dancing. ●

Neurodegenerative Diseases

continued from page 42

they will be stronger and will work better, thus preventing cell death.

With this pathway in mind, Johnson's approach to Huntington disease is to transplant neuro-protective cells into the brain of the animal model. These neuro-protective cells (not neurons), called astrocytes, are loaded with extremely high levels of Nrf-2 which activate the ARE pathway and cause the cells to secrete a neuro-protective substance (the nature of this substance is unknown). Thus far, the transplanted animals have experienced complete and long-lasting neuro-protection against the disease.

AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis is a motor neurodegenerative disease that may be partially caused by high levels of glutamate which damage neurons in the body.³ As the disease progresses, patients will suffer severe muscle atrophy, but usually mental function remains intact. Currently there is one FDA-approved drug available which can increase a patient's lifespan by at least a few months. It is thought that riluzole (Rilutek[®]) works by protecting the nerve cells from over-stimulation of glutamate. Again looking for a medication to prevent or treat the disease, Johnson has focused on Nrf-2 and found that it is of importance in ALS as well as Huntington disease. Once targeted as an activator of the ARE pathway, Nrf-2 has been a focus for drug design. Using an ALS mouse model, Johnson's goal is to find a compound that will imitate Nrf-2, thus decreasing oxidative damage in the motor neurons and slowing the progression of ALS. There are hundreds of small molecule compounds that activate the ARE pathway that have already been approved by the FDA for other uses. The next step is to determine if any of these compounds can be delivered effectively and efficiently to the target site, and Johnson's lab is well on its way in that investigation.

PARKINSON'S DISEASE

Parkinson's disease is a slowly progressive disease that results in the degeneration of dopaminergic neurons in the substantia nigra of the brain.² The overall impact is

decreased cortical excitation resulting in a loss of alpha-motor neuron control. Medications for Parkinson's disease, like the treatments for Alzheimer's disease, mainly address the symptoms of the disease and do not affect its progression. Parkinson's disease is the most recent neurodegenerative disease that Johnson has added to his research. He recently received a five-year grant from the Michael J. Fox Foundation. Currently Johnson is looking at a treatment approach that may work by first damaging the neurons in the substantia nigra even further. This particular damage augments stressed cells to regenerate as healthy cells which produce adequate amounts of dopamine. His lab will begin studies in primate models soon.

Johnson's research has been going tremendously, but he is modest. As he says, "Great things in mice have not worked in humans, and great things in humans have not worked in mice. One must be careful how much he or she assumes from an animal study." However, if his research, as well as research being conducted in several other laboratories, continues at this successful rate, treatment for neurodegenerative diseases will likely change dramatically within the next ten years. It is possible that a new line of medications focused on prevention and disease modification, rather than symptomatic treatment, will be on the market within one to two decades. Along with these new treatment discoveries, there is intensive research in the area of diagnostics. The hope is to have imaging techniques, most likely using tracers, which could detect small lesions/deposits before symptoms become evident. This would further facilitate the use of the desired new medications by offering early detection and thus earlier medication use and disease prevention. ●

Allison Motsko is a third-year PharmD student at the UW School of Pharmacy. This article was written as part of an independent study project.

REFERENCES

1. Viken R. Huntington disease. In: Griffith's 5-Minute Clinical Consult - 13th Ed. Last updated 7/5/2005. Accessed on 11/15/2005 at: <http://online.statref.com/document.aspx?fxid=31&docid=851>
2. Aminoff MJ. Pharmacologic management of parkinsonism and other movement disorders. In: Katzung, BG. Basic and Clinical Pharmacology 9th Ed. New York, NY: McGraw-Hill Companies Inc; 2004. p 447-461.
3. Bamford CR. Amyotrophic lateral sclerosis. In: Griffith's 5-Minute Clinical Consult - 13th Ed. Last updated 7/5/2005. Accessed on 11/15/2005 at: <http://online.statref.com/document.aspx?fxid=31&docid=94>