

For more information, please contact :



Lisa Spellman, UNMC Public Affairs, (402) 559-4353

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UNMC College of Dentistry Scientist Receives \$1.5 million grant from NIH to Continue Multiple Sclerosis Research

Kalipada Pahan, Ph.D., associate professor of biochemistry, oral biology and pharmacology at the University of Nebraska Medical Center College of Dentistry in Lincoln, has received a five-year, \$1.5 million grant from the National Institutes of Health to study potential new anti-neuroinflammatory drugs for multiple sclerosis.

Multiple Sclerosis (MS) is an autoimmune disease that affects the central nervous system (CNS), which consists of the brain, spinal cord, and the optic nerves. Surrounding and protecting the nerve fibers of the CNS is a fatty tissue called myelin, which helps nerve fibers conduct electrical impulses. When myelin or the nerve fiber is destroyed or damaged, the ability of the nerves to conduct electrical impulses to and from the brain is disrupted producing symptoms of MS.

Myelin is synthesized by oligodendrocytes, particular cells in the CNS, which are very much vulnerable to inflammatory insult. Dr. Pahan said understanding how the disease works is important to developing effective drugs that protect the CNS and stop the progression of MS.

NF-kB is a protein present naturally in the body and is involved in the production of different inflammatory molecules. He and his colleagues have found that when multiple sclerosis is present in animal models the amount of NF-kB markedly increases in the brain and spinal cord. In an article published in the July 2004 issue of *Journal of Immunology*, Dr. Pahan's lab found that NBD peptides, peptides shown to block the activation of NF-kB, markedly inhibit the inflammatory disease process of multiple sclerosis in mouse models. These results raise the possibility that NBD peptides as well as other inhibitors of NF-kB may turn out to be anti-neuroinflammatory drugs in MS.

Earlier Dr. Pahan's lab has shown that sodium phenylacetate and sodium phenylbutyrate block the disease process of MS in mice effectively. Sodium phenylacetate and sodium phenylbutyrate are two FDA-approved drugs for children with urea cycle disorders, a genetic disorder caused by a deficiency of one of the enzymes in the urea cycle which is responsible for removing ammonia from the blood stream.

"These two drugs are safe and have several advantages over interferon-b, the approved drug for MS. Such as these drugs are fairly nontoxic and less expensive compared to IFN-b. Instead of taking painful injection of IFN-b, MS patients can take these drugs orally with water or milk," Dr. Pahan said.

At present, sodium phenylbutyrate is being clinically tried on one female MS patient at the Thomas Jefferson University in Philadelphia. The MS clinic at the UNMC campus in Omaha is also trying for a phase-II clinical trial on this drug.

Although the disease is not fatal, it causes weakness, tremors, loss of vision, cognitive changes, depression and other problems. About half of the patients become wheelchair bound within 15 years of

disease onset and during the last stages of the disease patients are bedridden. In Nebraska, about 110 to 140 cases per 100,000 people occur, according to the National Multiple Sclerosis Society. An estimated 1,600 to 1,800 Nebraskans have MS.

According to the National Multiple Sclerosis Society, about 400,000 people in the United States have multiple sclerosis, which is often diagnosed between age 20 and 40. It is more common among caucasians, particularly those of northern European ancestry, and is more common in women than in men. Some of the potential causes of the disease are believed to be viruses, as well as environmental, genetic, and immune system factors.