Discovery could help combat chronic pain in diabetics

June 26 2012, By Kathy Keatley Garvey

(Medical Xpress) -- Researchers at the University of California, Davis, have discovered a class of natural compounds found within the body that may someday lead to pain relief for millions of diabetics and others suffering from chronic pain.

A team of nine entomology, cancer and nutrition researchers, in work published in the June 25th edition of Proceedings of the National Academy of Sciences, found that this new class of drug molecules stabilized the natural molecules and "effectively blocked neuropathic pain" or pain caused by nerve damage. The research, conducted on rodents, is expected to lead to an orally active drug candidate for human clinical trials.

"This discovery offers a promising new approach to controlling chronic pain in diabetics," said lead author and project scientist Bora Inceoglu of the Bruce Hammock lab based in the Department of Entomology. "We were initially looking at anti-inflammatory compounds which regulate a key branch of an inflammatory pathway. These compounds are highly selective and inhibit a key enzyme called soluble epoxide hydrolase. Inhibition of this enzyme successfully blocks pain sensations."

"Our data indicate that this drug candidate is more effective on neuropathic pain caused by diabetes than any of the prescription drugs now on the market," said Hammock, a distinguished professor of entomology who holds a joint appointment with the UC Davis Comprehensive Cancer Center.

The research is significant in that in the United States alone, diabetics total 25.8 million or 8.3 percent of the population, and millions more-estimated at 79 million-are pre-diabetic, according to the American Diabetes Association. The Centers for Disease Control and Prevention tallies the economic burden of diabetes at approximately $170 billion a year.

Professor Daniele Piomelli, director of drug discovery and development at UC Irvine and who holds the Louise Turner Arnold Chair in Neurosciences, said that the study holds promise. He was not involved with the UC Davis research.

"Current medicines do not control well chronic pain produced by damage to the nerves," said Piomelli, professor of anatomy, neurobiology, and biological chemistry. "The study by Hammock and collaborators identifies a new class of chemical compounds that could change this situation. These compounds act by boosting natural signals, produced by the body, which curb both inflammation and pain. Exploiting the body's own 'medicines' is a great approach to creating safer medicines."

Piomelli cautioned that the experiments "were conducted in animals and need therefore to be confirmed by clinical trials."

UC Davis School of Veterinary Medicine anesthesiologist and pain specialist Alonso Guedes, also not involved in the study, said that the research shows that "stabilization of a class of bioactive lipid greatly reduces pain derived from nerve lesions. This novel and emerging knowledge may help fulfill a critical medical need for millions of animals and people afflicted by such pain modalities."

For the study, the UC Davis researchers used a Type I diabetes-induced pain model. "Although Type II diabetes, associated with obesity,

hypertension and metabolic disorders, is more prevalent in humans, to study the analgesic effects we selected Type I diabetes since pain manifests in an accelerated manner," said co-researcher and pharmacology doctoral candidate Karen Wagner. "In Type II diabetes patients, the occurrence of pain is delayed by many years of pre-diabetic or diabetic state, whereas our model affords a very rapid onset of pain."

Team member Fawaz Haj of the Departments of Nutrition and Internal Medicine, a leading nutrition and diabetes expert and a collaborator with the Hammock lab on diabetes, said that "Intriguingly, in this study, acute treatments with soluble epoxide hydrolase inhibitors did not significantly affect the diabetic status of the animals, such as blood glucose levels and responses to insulin, indicating a selective effect on pain sensation. Neuropathic pain is a major co-morbidity of diabetes and an important debilitating factor that reduces the quality of life and this study accomplished a first in showing analgesic effects of soluble epoxide hydrolase inhibitors."

The researchers worked on a physiological pathway that was largely unknown until recently. When the enzyme, soluble epoxide hydrolase, is inhibited, "what happens is that the biological effects of a group of lipid metabolites, that are degraded by this enzyme, accumulate to effective levels," Hammock said.
"It turns out that a major function of these lipid metabolites is to selectively block pain sensation while sparing other types of sensations," Hammock said.

Inceoglu described neuropathic pain as "a debilitating condition and very difficult to treat with available painkillers or analgesics. Most analgesics are ineffective while those that reduce neuropathic pain often come with a variety of side effects that negatively affect the quality of life."

Nerve damage may be the result of trauma and chemotherapy agents or

even diabetes itself. In diabetes, high levels of blood glucose damage the fine endings of sensory neurons that normally transmit pain-related information, the scientists explained. The aberrant signaling from the damaged neurons is interpreted as extreme sensitivity to touch and sometimes insensitivity to heat. "Even an innocuous touch, such as buttoning a shirt or the collar rubbing against the neck, or the vibration of being in a bumpy car ride can result in extreme pain," Inceoglu said.

"Almost half of advanced diabetic patients suffer from this painful condition which worsens as diabetes progresses," Inceoglu said.

Nerve and vascular damage can lead to gangrene and amputation. In advanced stages, the nerve damage leads to life-threatening heart and kidney diseases.

Physicians face a dilemma in selecting the right painkillers for the right conditions and with the least possible side effects, the UC Davis researchers said. Over-the-counter non-steroidal anti-inflammatory drugs (NSAIDs), for example, are completely ineffective for neuropathic conditions, Hammock said. Narcotics, like opium, can be addictive; withdrawal is difficult.

"Therefore, there is a great need to discover new approaches in combating pain," Hammock said. "New medications will effectively increase the number of choices for patients and physicians in treating intractable pain. Our study shows that the novel approach is effective and may not lead to the known side effects of narcotics or anti-depressants."

"It is still too early for these new compounds to reach the stores as analgesic drugs, since FDA approval takes a decade with very thorough evaluations," Inceoglu said. "However, once the feasibility of this approach is demonstrated, hopefully a major hurdle in moving toward

clinical application is overcome."

The research, funded by the National Institutes of Health, supports earlier studies at UC Davis and later at Medical College of Wisconsin that showed the natural epoxy-fatty acids are analgesic molecules. "Although very effective in blocking pain, unlike narcotics, these molecules do not affect coordination skills of animals," Inceoglu said.

The research team included Bora Inceoglu, Karen Wagner, Jun Yang, Nils Schebb, Sung Hee Hwang and Christophe Morisseau, all of the Department of Entomology; Bruce Hammock, Department of Entomology and UC Davis Comprehensive Cancer Center; Ahmed Bettaieb of the Department of Nutrition; and Fawaz Haj of the Departments of Nutrition and Internal Medicine.

"This is an interdisciplinary effort among neurobiologists, diabetes specialists, organic chemics and analytical chemists," said Hammock. "We could not have done this without sophisticated mass spectrometry equipment."

"The emerging mass spectrometric technique allowed us to analyze the tiny amounts of natural bioactive compounds, contributing to this pain discovery," said Yang.

Hammock directs the campuswide Superfund Research Program, the National Institutes of Health Biotechnology Training Program and the NIEHS Combined Analytical Laboratory. He is a Fellow of the Entomological Society of America, a member of the prestigious National Academy of Sciences, and the recipient of the UC Davis Faculty Research Lecture Award in 2001 and the Distinguished Teaching Award for Graduate and Professional Teaching in 2008.

Hammock's initial research involved regulating the development of

insect larvae.

Provided by UC Davis