Pain research may pave the way to understanding and controlling chronic pain

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(PhysOrg.com) -- Researchers at the University of California, Davis have discovered a "cross-talk" between two major biological pathways that involve pain -- research that may pave the way to new approaches to understanding and controlling chronic pain. And they did it with something old, new, practical and basic.

The newly published research reveals that analgesia mediated by inhibitors of the enzyme, soluble epoxide hydrolase (sEH), is dependent on a pain-mediating second messenger known as cyclic adenosinemonophosphate or cAMP.

"The interaction of many complex biological pathways is essential for the development of persistent pain, whether inflammatory or neuropathic," said lead researcher Bora Inceoglou of the Bruce Hammock lab, UC Davis Department of Entomology. Inflammatory pain includes arthritis, and neuropathic pain is linked to diabetes and other diseases, and trauma.

"Pain is a major health concern and painkiller medications or analgesics do different things," Inceoglu said. Painkilling medications may target the pain, but have side effects or lack a broad-spectrum efficacy.

The collaborative study, the work of scientists in the UC Davis Department of Entomology, UC Davis Cancer Research Center, UC Davis School of Medicine and the School of Veterinary Medicine, is published in the March 7th early edition of the *Proceedings of the*

National Academy of Sciences (*PNAS*).

An estimated 9 percent or 30 million adults in the United States suffer from moderate to severe non-cancer related chronic pain, according to the American Pain Society.

The messenger, cAMP, relays responses and mediates the action of many biological processes, including inflammation, and cardiac and smooth muscle contraction.

The research, done on rodents and funded by the National Institutes of Health, confirmed earlier studies at UC Davis that showed stabilization of natural epoxy-fatty acids (EFAs) through inhibition of sEH reduces pain. "However, in the absence of an underlying painful state, inhibition of sEH is ineffective," Inceoglu said.

"This permits normal pain responses that serve to protect us from tissue damage to remain intact, while alleviating debilitating pain," said co-author and pain neurobiologist Steven Jinks, associate professor of anesthesiology and pain medicine, UC Davis School of Medicine.

"Another advantage of inhibition of sEH is that it does not impair motor skills in several tests, unlike other analgesics," said graduate student researcher Karen Wagner of the Hammock lab research team.

While conducting the research, the scientists found something they weren't looking for. "To our surprise, we found that cAMP interacts with natural EFAs and regulates the analgesic or pain activity of sEH inhibitors," Inceoglu said.

"This demonstrates the power of using advance instrumental analysis techniques to better understand the molecular mechanism of biological effects," said Nils Helge Schebb, a postdoctoral researcher from the

Hammock group who worked on the quantification of the oxylipins in this project. Schebb leaves UC Davis this week to accept a position as junior research group leader at the University of Veterinary Medicine, Hannover, Germany.

"This is like something old, something new, something practical and something basic, too," said Hammock, a distinguished professor of entomology who holds a joint appointment with the UC Davis Cancer Research Center.

Old? The research, Hammock said, involves "an old class of drugs known as phosphodiesterase inhibitors that likely exert part of their action by increasing the levels of natural compounds in the body called EETs (epoxyeicosatrienoic acids). Rolipram, Viagra, Theophyline, and Ibudilast are all in the phosphodiesterase-inhibitor class."

New? The Hammock lab previously reported that a new class of experimental drugs called soluble epoxide hydrolase inhibitors (sEHIs) stabilize and also increase EETs.

Practical and basic? "A practical application of this work demonstrated by Bora Inceoglu is that the combination of this old and new class of drugs are highly effective in controlling pain," said Hammock, senior author of the paper. "Of course, the basic aspects of the work include new insights in how EETs, cyclic nucleotides and the enzymes that degrade them interact to regulate a variety of biological functions."

Both the old and the new class of drugs are based on inhibiting enzymes which degrade potent natural chemical mediators.

Inceoglu, Hammock, Jinks, Schebb, and Wagner co-authored the paper with veterinary anesthesiologist Robert Brosnan, associate professor of surgical and radiological sciences, School of Veterinary Medicine; and

Christophe Morisseau, Arzu Ulu, Christine Hegedus and Tristan Rose, Department of Entomology and the Cancer Research Center.

The Jinks lab played a major role in the earlier UC Davis studies that showed a stabilization of EFAs through inhibition of sHE reduces pain. The Hammock lab works closely with the Jinks lab.

The pain discovery would not have been possible without sophisticated mass spectrometry equipment which allowed the analysis of the vanishingly small amounts of natural compounds that control pain and inflammation in the body, the researchers agreed.

Hammock described the potential practical applications of these fundamental discoveries as exciting. "We all have both suffered pain and have friends with unrelenting chronic pain problems," he said. "The possibility of combining members of an old class of drugs with our new sEHI and actually providing relief for pain is very exciting."

From his time as a graduate student, Hammock and his laboratory have focused on xenobiotic metabolism and largely on esterases and epoxide hydrolases. Current projects involve examining the role of esterases in insecticide resistance and human metabolism of pyrethroids. His laboratory is exploiting inhibitors of epoxide hydrolases as drugs to treat diabetes, inflammation, ischemia, and cardiovascular disease.

More information: www.pnas.org/content/early/201 … /1101073108.abstract

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