Scientists learn to block pain at its source

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A substance similar to capsaicin, which gives chili peppers their heat, is generated at the site of pain in the human body. Scientists at The University of Texas Health Science Center at San Antonio have discovered how to block these capsaicin-like molecules and created a new class of non-addictive painkillers.

The findings were published April 26 in the Journal of Clinical Investigation. The senior investigator was Kenneth Hargreaves, D.D.S., Ph.D., professor and chair of the Department of Endodontics in the Dental School at the UT Health Science Center. Amol M. Patwardhan, M.B.B.S., Ph.D., a graduate of the Health Science Center's Department of Pharmacology who worked under Dr. Hargreaves' supervision, is the lead author.

"Nearly everyone will experience persistent pain at some point in their lifetime," Dr. Hargreaves said. "Our findings are truly exciting because they will offer physicians, dentists and patients more options in prescription pain medications. In addition, they may help circumvent the problem of addiction and dependency to pain medications, and will have the potential to benefit millions of people who suffer from chronic pain every day."

A 'complex epidemic'

Pain has been called a "complex epidemic" in the United States. Nearly 50 million Americans live with chronic pain caused by disease or injury. Few physicians or dentists specialize in the field of pain medicine. With

pain medication options largely limited to opioids (such as morphine) and aspirin-like drugs, some patients become addicted or dependent upon these drugs, or suffer side effects such as kidney or liver damage.

Researchers at the UT Health Science Center found a new family of fatty acids, produced by the body itself, that play an important role in the biology of pain.

"Capsaicin is an ingredient in hot chili peppers and causes pain by activating a receptor called transient potential vanilloid 1 (TRPV1). We started out seeking the answer to the question "Why is TRPV1 consistently activated in the body upon injury or painful heat? We wanted to know how skin cells talk to pain neurons," Dr. Hargreaves said. "What we found was much more surprising and exciting. We have discovered a family of endogenous capsaicin-like molecules that are naturally released during injury, and now we understand how to block these mechanisms with a new class of non-addictive therapies."

The hot chili pepper effect

Researchers used flaps of skin from laboratory mice that were heated in a water bath at temperatures greater than 43 degrees Celsius. The degree of heat used was significant because the human body normally begins to feel discomfort and pain at 43 degrees Celsius and higher, Dr. Hargreaves noted.

TRPV1 resides on the membranes of pain- and heat-sensing neurons. When a person eats a hot chili pepper, for example, he immediately feels a burning sensation because the capsaicin, the primary ingredient in the chili pepper, has activated the TRPV1 protein in the pain neurons. In high concentrations, capsaicin can also cause a burning effect on other sensitive areas of the skin.

The fluid from the heated skin was then applied to sensory neurons cultured from two sets of laboratory mice, including one set of animals in which a gene was deleted or "knocked out." Neurons from the wild type (non-altered) mice were sensitive to capsaicin, the main ingredient in chili peppers. The neurons of the knockout mice, in which the TRPV1 gene was deleted, were not sensitive to capsaicin and were used as the control.

"We found that in the skin flaps heated at greater than 43 degrees Celsius, the cells' pain neurons showed tremendous activity in the wild type, but not in neurons from mice that lacked TRPV1," Dr. Hargreaves said. He indicated that this novel phenomenon was taking place because the cells, in response to the heat, began to create their own natural endogenous capsaicins, which they later identified as a series of compounds or fatty acids called oxidized linoleic acid metabolites (OLAMs).

Linoleic acid is one of the most abundant fatty acids in the human body. Under conditions such as inflammation, low blood pressure and some other illnesses, linoleic acid is rapidly oxidized to form biologically active metabolites. However, little else is understood about these substances. The metabolites that were consistently seen in increased amounts in the mouse skin biopsies exposed to heat temperatures greater than 43 degrees Celsius are called 9- and 13-HODE (hydroxyoctadecadienoic acid).

'Major breakthrough'

"This is a major breakthrough in understanding the mechanisms of pain and how to more effectively treat it," Dr. Hargreaves said. "These data demonstrate, for the first time, that OLAMs constitute a new family of naturally occurring capsaicin-like agents, and may explain the role of these substances in many pain conditions. This hypothesis suggests that

agents blocking either the production or action of these substances could lead to new therapies and pharmacological interventions for various inflammatory diseases and pain disorders such as arthritis, fibromyalgia and others, including pain associated with cancer."

The research has led Dr. Hargreaves' team to develop two new classes of analgesics using drugs that either block the synthesis of OLAMs or antibodies that inactivate them. These drugs could eventually come in the form of a topical agent, or a pill or liquid that could be ingested, or in the form of an injection. Both approaches have the potential to block pain at its source, unlike opioid narcotics that travel to the brain and affect the central nervous system.

Provided by University of Texas Health Science Center at San Antonio

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