

Scientists Seek Biochemical Roots of Pain

Linda Carroll

As scientists take a closer look at the biochemistry of chronic pain, they are beginning to see changes at the molecular level that may aid in the search for better treatments for the condition.

In two studies presented at the 2008 annual meeting of the American Society of Anesthesiologists, in Orlando, Fla., Minnesota researchers reported finding measurable changes in certain compounds in patients with low back pain and facial arthromyalgia.

In one study (abstract 1549), researchers compared the pH of spinal fluid extracted by lumbar puncture from 12 patients with back pain severe enough to warrant surgery with the pH of spinal fluid taken from 30 control subjects with no history of low back pain.

All 42 patients had magnetic resonance imaging of their lumbar spines. The scans revealed moderate to severe disk degeneration in 82% of those experiencing severe pain and 40% of those who were free of pain.

Even after adjusting the data for degree of disk degeneration, sex and age, the researchers found that patients' level of pain and cerebrospinal fluid pH were positively associated, and those with the most intense pain had the highest spinal fluid pH.

"There is a body of literature that talks about the activation of pain-sensing fibers by acidic pH," said study co-author Lois Kehl, DDS, PhD, assistant professor of anesthesiology at the University of Minnesota Medical School, in Minneapolis. "There is a specific family of receptors involved—acid-sensing ion channel receptors. And these are known to be present in the spinal cord and are important for pain transmission."

Most of what is known about the role of these ion channels in pain is based on acute studies done in animal models or in cultured nerve cells, Dr. Kehl said. "In these studies, acid pH activates pain-sensing neurons. However, this preliminary finding from patients with long-term pain suggests that the opposite may be true in individuals with chronic pain, possibly due to some type of compensatory mechanism or other associated factors. More work needs to be done to evaluate whether these pH changes may be great enough to affect the activity of spinally administered drugs in patients with chronic pain."

In the second study (abstract 1550), Dr. Kehl and colleagues looked at patients with pain related to temporomandibular joint (TMJ) disk displacement. The researchers included only patients with pain related to their masseter muscle and TMJ, as this is the most common clinical presentation for the disorder. They biopsied the most tender areas of masseter muscle and collected samples of TMJ synovial fluid in 16 patients with persistent pain, 14 people with TMJ disk displacement but no pain and 13 people with neither pain nor TMJ disk displacement. Plasma samples were also collected from all three groups.

Other research has suggested that the levels of certain pronociceptive compounds are up- or downregulated in plasma, muscle and synovial fluid when people experience musculoskeletal pain. Dr. Kehl and her colleagues focused on the levels of nerve growth factor (NGF), which is released from peripheral tissues in response to injury and is known to promote hyperalgesia when it is administered to both humans and animals. The latest study showed for the first time that endogenous levels of NGF within muscle are elevated in association with musculoskeletal pain in humans.

NGF: Marker and Target?

The researchers found a negative association between pain intensity and plasma NGF and a positive association between pain and NGF levels in samples from the masseter muscle. Ultimately, NGF may not only serve as a marker for pain, but also as a target for drug therapies, Dr. Kehl said. An antagonist to NGF may mitigate muscle pain.

In future research, Dr. Kehl and her colleagues plan to use the samples collected for their current analyses to examine the levels of several other pronociceptive compounds: bradykinin, substance P, prostaglandin E₂, leukotriene B₄ and F₂-isoprostane. Right now it's too early to say which of these substances plays the leading role in persistent musculoskeletal pain, Dr. Kehl said.

Other pain researchers called the NGF findings intriguing.

TMJ pain is very common and tends to be intractable, said Eric S. Hsu, MD, associate clinical professor of anesthesiology at the David Geffen School of Medicine at the University of California, Los Angeles, and director of education at the UCLA Pain Management Center. "This study is really interesting because it suggests that there could be a possible future treatment using an NGF antagonist," Dr. Hsu said.

Doris K. Cope, MD, professor and vice-chair of pain medicine at the University of Pittsburgh Medical Center, agreed. "NGF is one of about 30 compounds in a soup of metabolic mediators," Dr. Cope said. "They all work together. They also mediate depression, fatigue and sleeplessness."

Dr. Cope said the study was particularly compelling because it involved human subjects. "Most studies are done in animals and experimental models," she said, "because it's very hard to get a clean study in human subjects."

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