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Ryan Horvath, right, and his mentor, Joyce DeLeo, revealed that glial cells play a key role in signaling pain.

Insight into how opioids sometimes worsen pain

The nervous system's glial and microglial cells were once thought to play only a bit part in the body. But they're proving to be integral players in pain signaling, opioid tolerance, and chronic pain, according to findings from the lab of Joyce DeLeo, Ph.D.

Ions: Their role is "more complicated" than originally thought, says DeLeo, the chair of pharmacology and toxicology at DMS. In addition to providing nutrients for neurons and regulating extracellular ions and metabolites, glial cells also warn the body of danger by sensing injury and triggering protective reflexes. If activated, the cells release molecules like proinflammatory cytokines, which may sensitize neurons and "provoke, enhance, or maintain pain," explains DeLeo.

The findings, published in the journal *Neuroscience*, were largely the work of Ryan Horvath, an M.D.-Ph.D. student in her lab. He wanted to explore the concept of glial cell priming and its contribution to morphine tolerance, in which more of the drug is needed to get the same effect. Exposing glia to an insult or drug and later reexposing them can elicit different responses. Horvath wondered how this might make opioids—such as morphine, methadone, or oxycodone—less effective if they are taken over a longer time.

Opioids have been the gold standard for pain relief after surgery, but as chronic opioid use and abuse have exploded in recent years, doctors have become concerned about tolerance. Those who abuse opioids or use opioids consistently for a long period to treat pain may find that their pain actually worsens and that the drugs become ineffective at treating acute episodes of pain. Scientists have recognized for about 10 years that opioid tolerance and chronic pain share many of the same mechanisms, but the relationship has become a hot topic just recently. Until now, the role of glial cells in this process was unknown.

Long-term opioid use can cause acute pain to become chronic.

Incision: Horvath performed surgery on rats to model a postoperative incision. Some of the rats received morphine for seven days before the surgery, while others did not. Horvath noticed behavioral changes in the two groups of animals. The rats that had been given morphine before surgery experienced postoperative hypersensitivity to stimuli for a longer time than the other group of rats.

Based on their previous studies, Horvath and DeLeo expected to see increases in two classic glial marker proteins called Iba1 and GFAP. But no changes in either were apparent, leaving the researchers puzzled.

But "Ryan did not give up," observes DeLeo. Instead, "he said, 'Let me look at a few other things.'"

A big surprise, explains Horvath, came when they zeroed in on certain signaling molecules that can produce pain—mitogen activated protein (MAP) kinases, found in microglia—and saw higher levels of these molecules in the microglia of the rats that had received morphine before surgery.

Relay: Horvath also identified a relationship between how long an animal was exposed to opioids and whether the glial cells expressed particular cytokines. These cytokines can amplify the release of neurotransmitters, which relay pain signals between neurons, thus worsening the pain.

Through most of the 20th century, physicians opposed the widespread use of opioids because they feared patients would become addicted. Gradually opinion shifted, and physicians came to realize that opioids were very effective and could be prescribed safely even for chronic pain. But consensus is now growing that the pendulum has swung too far. Opioid prescriptions increased an estimated 350% from 1991 to 2007, from 40 million to 180 million, according to the National Institute on Drug Abuse.

Doctors now know that long-term exposure to opioids can lead to tolerance, and researchers like DeLeo and Horvath are showing that such tolerance can cause acute postoperative pain to become chronic, thanks in part to the action of glial cells.

Chronic: It may be a decade before the finding can be turned into a treatment for human pain. In the meantime, says Horvath, "physicians can stop chronic pain before it starts" by being careful whom they prescribe opioids to. "That would be best," he adds.

Horvath, who is beginning his third year of medical school, will soon enough be making such decisions himself. KRUPA PATEL