Resolving Chronic Pain

The body’s own mechanism for dispersing the inflammatory reaction might lead to new treatments for chronic pain.

By Claudia Sommer and Frank Birklein | January 1, 2012

Inflammation is correctly blamed as one of the root causes of both acute and chronic pain—and more. Not only does chronic inflammation underlie disorders such as rheumatoid arthritis, inflammatory bowel disease, and other autoimmune diseases, it has also been implicated in the pathogenesis of cancer, chronic heart failure, and neurological disorders such as Parkinson’s and Alzheimer’s diseases. These conditions affect millions, and carry high health-care and socioeconomic costs. And yet, inflammation is an important physiological response that jump-starts tissue repair and more carefully tunes immune reactions. Without it, we could not fight off infection or heal from injury. Why and how does this powerful ally turn into a foe?

A patient who had consulted us earlier about other problems came in complaining of swelling in her right hand, accompanied by incessant pain that left her unable to move her arm very much. An otherwise healthy 47-year-old, she had worked as a bookseller until slipping on ice and fracturing her wrist a few weeks earlier, experiencing what she described as the worst pain of her life. Surgery had been successful, but as she healed, the swelling in her wrist did not resolve. Instead, the swelling had extended to the whole hand, even increasing after her cast was removed, and the hand had become exquisitely sensitive. It appeared to be permanently swollen, reddish in color, and was usually warmer than her other hand. Because of the pain, she was unable to return to her job or perform any exercise, and needed help with many everyday tasks. X-rays did not reveal any pathology that would explain the pain. Treatment with anti-inflammatory drugs like aspirin was
ineffective; even morphine provided little relief.

Her doctors finally arrived at a diagnosis of complex regional pain syndrome and she began a multicomponent pain treatment program. Treatment included very specific physical and cognitive therapies that resulted in a 90 percent restoration of hand function and a reduction in pain. Today, complex regional pain syndrome is thought to be initiated by an unusually strong and long-lasting inflammatory reaction to trauma, although its treatment is not always so successful.

Although not all cases of chronic pain involve inflammation, the majority do. Therapy options for chronic pain are complicated because of the ongoing nature of the symptom.

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While the causes of chronic pain are many and diverse, the pervasive effect it has on a patient’s life—including inability to work, anxiety, depression, and even post-traumatic stress disorder—is universal. Opiates such as morphine are considered among the best medications for relieving pain, but they carry a risk of tolerance and addiction, especially with long-term use. Many doctors thus prefer to prescribe anti-inflammatory drugs such as cyclooxygenase (COX) inhibitors. COX inhibitors, like aspirin or ibuprofen, however, can cause gastrointestinal bleeding and kidney damage when used at high doses, and selective COX-2 inhibitors such as Vioxx have been shown to increase the risk of cardiovascular disease. In addition, these drugs are most effective for mild and moderate pain; they have a “ceiling” beyond which taking more provides no more relief.

One difference between acute inflammation and the persistent inflammation that leads to chronic pain, is that in the latter, the inflammatory factors are never completely cleared from the system. Recent research has revealed that the clearing of these inflammatory factors is an active process rather than a passive one that simply occurs over time. This insight offers the possibility that we might be able to harness resolution factors that clear inflammation and use them to ameliorate the pain that accompanies chronic inflammation.

Reducing inflammation

In 2000, while looking for bioactive molecules derived from the metabolism of omega-3 fatty acids, Charlie Serhan’s laboratory at Brigham and Women’s Hospital at Harvard Medical School discovered a compound that naturally reduces inflammation after an acute reaction.\(^1\)\(^2\) Omega-3 fatty acids, which can be found in foods such as fish and flaxseed oil, include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These two fatty acids have long been known to have beneficial effects in reducing the risk of several diseases, including atherosclerosis, asthma, heart disease, and cancer. The American Heart Association even recommends the consumption of fish rich in omega-3 fatty acids for cardiovascular disease prevention. However, it was not known whether omega-3 fatty acids actively reduced inflammation. The problem was confounded by the fact that many studies investigating the effects included patients who were also taking aspirin, making it difficult to tease apart the anti-inflammatory contribution of each. The Serhan laboratory set out to analyze the interaction of EPA and DHA with aspirin and to identify molecular components derived from the fatty acids.
First, they analyzed the composition of lipid-based compounds that were present in tissues during the resolution of acute inflammation in the mouse. Mice produced fatty acid metabolites that the investigators dubbed “resolvins” for their ability to reduce the inflammatory reaction. Although these compounds appeared to clear the inflammation, the process was different from active suppression of the immune system. The resolvins did not hinder immune cell action; rather, they reduced the inflammatory activity of specific populations of cells and blocked their production of pro-inflammatory chemokines, while increasing the action of immune cells that clear dead tissue.

Serhan’s team also showed that these resolving molecules were naturally derived from omega-3 fatty acids—and that aspirin enhanced this conversion. When they then administered the resolvins to animal models of acute and chronic inflammation such as peritonitis, colitis, or asthma, they saw an accelerated return to homeostasis.

The study demonstrated how aspirin could increase the production of the body’s own natural inflammation mediators by catalyzing the metabolism of the touted omega-3 fatty acids into chemical forms that diminish inflammation. In addition, it appeared that these newly discovered mediators permitted the aggressive acute inflammation stage to occur, which is so physiologically important, before then subduing the reaction and returning the body to homeostasis. But it was not yet clear whether the reduction in inflammation would also reduce pain.

Inflammation includes a number of processes, not all of which are associated with pain. For example, while systemic infections, like the flu or a cold, spur strong inflammatory reactions, they are only occasionally associated with pain. Pain only occurs when inflammatory cytokines are released near nociceptive, or damage-signaling, nerve fibers. Damaged tissues release their contents during injury or inflammation, flooding the surrounding tissues with prostaglandins (PGs) and bradykinin, which activate the secretion of histamines. Together, these chemicals make blood vessels leaky enough to permit immune cells to enter the damaged tissue from the circulation, releasing PGs creating the swelling that is a cardinal symptom of inflammation. When this process occurs in richly innervated tissues, the inflammatory mediators also cause nearby nociceptors to fire, conveying the sensation of pain.

**Resolving the pain**

Given that resolvins are derived from omega-3 fatty acids—that is, from essential nutritional factors—and that they are endogenous anti-inflammatory substances, it seemed a likely hypothesis that they would also have an effect on inflammation-related pain. In 2010, the lab of Ru-Rong Ji at Brigham and Women’s Hospital in Boston, in collaboration with Serhan, explored this question.3
Using an animal model of pain, investigators injected the paws of mice with formalin, which produces two phases of pain: an immediate reaction, relayed by the peripheral nerves; and a delayed-onset reaction, mediated by inflammation and by spinal cord neurons. The first phase is characterized by mice licking the injected foot for about five minutes after injection. Then, after a lag of 20–30 minutes, the second phase begins with another bout of foot licking. The researchers administered two different resolvin (Rv) molecules, RvD1 and RvE1, to test their ability to reduce this pain behavior, and found both molecules to be effective when injected either into the paw or directly into the spinal canal. They noted that RvE1 diminished swelling and reduced markers of the inflammatory response, and that, compared to either morphine or COX-2 inhibitors, a much lower dose of the resolvin effectively halted pain behavior. Interestingly, only the second phase of pain behavior—mediated by spinal cord mechanisms that are often associated with chronic pain—was attenuated, indicating that RvE1 and RvD1 were likely acting via a receptor known as ChemR23, a G protein–coupled receptor found on nociceptive neurons in the dorsal root ganglia and the dorsal horn of the spinal cord. These neurons also express the transient receptor potential vanilloid 1 (TRPV1), which is the receptor for the inflammation-producing irritant found in chili pepper, capsaicin. In living mice, RvE1 was able to block the pain induced by capsaicin.

The same researchers looked at another model of inflammatory pain induced by the injection of carrageenan, which also initiates two phases of pain, but is thought to more closely mimic standard muscle pain than the formalin model. When the mice were given RvE1 or RvD1 in the hindpaw before a carrageenan injection, the pretreatment markedly reduced inflammation: the mice showed diminished swelling, fewer immune effector cells called neutrophils infiltrating the damaged tissue, and a reduced level of pro-inflammatory cytokines. Just like morphine, RvE1 did not dull the ability to sense “normal” pain. In other words, the mice did not experience numbing, but rather a more specific alleviation of the pathologic pain associated with inflammation.

Recently, researchers have begun to investigate whether chronic persistent pain might be the result of a learning response in neurons of the spine. Neurons change shape when they are actively involved in learning, both in terms of the number of physical connections between cells and the number of receptors at the synapses of those connections. Researchers have proposed that when pain persists, the neuronal connections relaying that pain strengthen, making it easier to transmit the response—thus lowering the threshold at which something feels painful.

To test whether resolvins might prevent the formation of this learned pain reaction in the spine, researchers took slices of mouse spinal cord and tested how the transmission between neurons changed in the presence and absence of resolvins. Resolvins blocked an increase in the action of tumor necrosis factor-alpha (TNF-α)—a cytokine thought to increase the frequency of synaptic transmission, and thus possibly the likelihood of forming a “pain memory”—without blocking the normal levels of transmission. Then, the authors showed that RvE1 also inhibited glutamate release—required for some types of neuronal learning—by a pathway
dependent on the extracellular signal-regulated kinase (ERK). Additionally, RvE1 changed the activity of the glutamate N-methyl-D-aspartic acid receptor (NMDAR), also via the ERK pathway, supporting the concept that blocking the ERK pathway could be a promising therapeutic target for the treatment of pain.

Since the publication of the first paper by Ji and colleagues describing the analgesic effect of resolvins, others have followed. These new studies described positive effects in other pain models, and have uncovered additional mechanisms by which resolvins can diminish pain. For example, RvD1 was shown to reduce, prevent, and transiently attenuate pain associated with operation trauma in a rat model. In this study, an oversensitivity to pain, in which a touch that is normally benign feels painful, was reduced or prevented by 20 to 40 nanograms of RvD1 injected into the spinal cord up to 2 days after the surgical trauma. However, if RvD1 was given on postoperative day 9 or 17, the reversal of pain was only transient and incomplete.

In a model of pain that mimics inflammatory arthritis in rats, RvD1 reduced an increased sensitivity to pain. The effect was partially mediated by a decrease in TNF-α and interleukin-1β—cytokines that drive inflammation and are also thought to increase pain hypersensitivity in the central nervous system. In this model, systemic injection, rather than spinal administration, of the resolvins was shown to be effective, providing a much more feasible clinical application, as spinal injections themselves are associated with significant pain. Furthermore, in cell culture, RvD1 inhibited other members of the TRP family of receptors. Subsequent in vivo experiments demonstrated that injecting RvD1 under the skin was sufficient to attenuate pain caused by direct activation of these TRP receptors in the mouse.

A clearer picture for the future

From the animal data summarized above, it appears that resolvins may be ideal candidates for novel analgesics. Because they are derived from lipid molecules normally produced in the body, resolvins counteract inflammation in a physiological way. Their precursors, the omega-3 fatty acids, have been tested with some success in treating pain conditions, although a recent meta-analysis did not show a definitive effect. However, resolvins appear to show effects at concentrations about 10,000 times lower than effective doses of omega-3 fatty acids—an advantage for drug development.

Intriguingly, one of the mechanisms that Ji and colleagues identified for the analgesic action of the resolvins is that they block various TRP receptors (particularly TRPV1) indirectly by blocking the TRPV1-dependent release of glutamate. This is particularly interesting inasmuch as it may provide a better avenue for blocking TRPV. In fact, recently developed TRPV1 antagonists that have been tested in humans resulted in serious side effects such as high fever. The reason for this side effect is most likely that TRPV1 not only conveys information about pain, but also about temperature. Complete blockade of this receptor, therefore, would also block information about fever from reaching the brain, which would be unable to respond by initiating cooling mechanisms such as sweating. Since resolvins block glutamate rather than directly acting on TRPV1, they might avoid such life-threatening side effects.

Side effects of blocking TRP might be reduced even more with the use of resolvins that act specifically on certain TRP receptors, as recently demonstrated in vitro and in vivo with RvD1, which appears to be specific for TRPV3. This receptor specificity may potentially pave the way to a more tailored treatment for individual pain symptoms such as thermal or mechanical pain hypersensitivity. A further potential advantage of resolvins is that they may have a dual function as both an analgesic and an inflammatory disease-modifying drug. In fact, a number of molecules with this potential have already been investigated, including nerve growth factor and its antagonists in the treatment of nerve lesions, neuropathic pain, or osteoarthritis; erythropoietin in diabetic neuropathy; and cytokine inhibitors in rheumatoid arthritis. Unfortunately, of these, currently only the cytokine inhibitors have made it to clinical application.
The challenge now, as it is for every promising molecule at the preclinical stage of investigation, will be to develop resolvins into a clinically applicable form. Many of the experimental applications have been via spinal injection, which would limit the use in humans. As drugs, these molecules would need to be stable—so that they could be taken orally, for example—and long-acting. Because they act on the immune system, they might have unwanted side effects, which will need to be investigated further. In addition, although the results reported by Ji and others are impressive and reasonable, the size of the effect on pain behavior in the animals is moderate. Other analgesic drugs, which had even stronger effects than the resolvins in animal models, have failed in human clinical trials because their impact was not sufficiently different from that of placebos. The reason might be that human pain still differs significantly from even the best and most elaborate animal pain models. With all these caveats, testing resolvins in clinical trials will be the best way to determine if alleviating chronic low-grade inflammation, a factor underlying not only pathogenic pain but diseases ranging from cancer to obesity, could reduce morbidity and mortality.

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