

PERSPECTIVES & OPINIONS

Michael W. Salter

AN ALTERNATE
VIEW OF
CHRONIC PAIN

Finn O'Hara

Scientists whose work challenges conventional wisdom often toil for years before their ideas catch on—if ever. But Michael W. Salter, an HHMI international research scholar at Toronto’s Hospital for Sick Children, managed in just 6 years to prove that the traditional thinking behind chronic pain was, if not wrong, at least not completely right.

Pain is usually a warning. It alerts us to injuries or potential damage to the body. But sometimes the nervous system itself is the cause of pain. Such “neuropathic” pain, which occurs when peripheral nerves are damaged from surgery, disease, or infection, can render people so sensitive to normal stimuli that everyday activities—wearing shoes, for example—can be excruciating. Sadly, modern medicine does not have much to offer these patients. Current therapies offer relief to fewer than half of patients, and their pain is usually reduced by no more than 25 percent.

Until recently, the accepted dogma was that malfunctioning neurons were completely responsible for neuropathic pain. My colleagues and I have now shown that while neurons are indeed involved, they have co-conspirators: the spinal cord’s microglial cells. It turns out that, among their many jobs in immune surveillance in the nervous system, microglia serve as signaling cells that provide information to neurons. We’ve demonstrated this relationship by proving its inverse: by inhibiting a receptor, called P2X4, on the microglia, we were able to alleviate induced neuropathic pain in rats.

Unfortunately, the agent we used to block the receptor was not sufficiently stable to be a good candidate for a therapeutic agent for humans. But knowing that microglia are key to neuropathic pain gives us other approaches to pursue. Once activated, this pain pathway is like a set of dominoes. When the first one falls, it knocks down the next one, and so on, until reaching the pain networks in the brain, which is when the hurt begins.

So, our theory is that neuropathic pain would be eased if we could pharmacologically interfere with just one of those myriad intermediate steps—the dominoes—in the spinal cord between the beginning of the pathway (activation of the P2X4 receptor on the microglia) and the end (suppression of a transporter known as KCC2 on spinal-cord neurons that send the pain signals on to the brain). Sorting out this relationship between microglia and neurons is the current emphasis of our research.

We have already experimented with some attractive targets. One of them is brain-derived neurotrophic factor (BDNF). Our team has shown that activation of microglia’s P2X4

receptors causes the release of BDNF, which then mediates the signaling between the microglia and neurons that leads to pain hypersensitivity. To interfere with this process, we have used antibodies that successfully block the action of BDNF. But they have to be injected directly into the spinal cord—a less-than-practical approach.

Another potential target is the KCC2 transporter on spinal-cord neurons. One of the characteristics of chronic pain is an increased concentration of chloride ions in neurons, which causes them to fire in a hyperexcited manner. Because a normal-functioning KCC2 removes chloride from the cells, something happens in chronic pain that causes the KCC2 to down-regulate and allow for a rise in chloride concentration. We’ve shown that both the activation of P2X4 and the rise in intracellular chloride concentrations are necessary for maintaining chronic pain.

In addition to finding new approaches to treating chronic pain, we need better ways of diagnosing it. Individuals with intractable pain often stop talking about their problem because few people believe them. It’s no surprise, then, that many patients with this condition become depressed and may even begin to prefer the thought of death to living with their intense pain. An objective diagnostic test would allow people with neuropathic pain to say “my microglia cells are activated” or “the chloride concentration in my spinal neurons is too high,” much as we cite cholesterol or glucose readings now. Being able to point to a physiological difference would allow patients suffering from chronic pain to gain legitimacy and, as a consequence, merit higher priority among medical practitioners, researchers, and the public.

The work in our lab might help with that problem. By quantifying the physiological changes involved in chronic pain, we may be able to create assays to measure microglia activation or a change in chloride-ion concentration.

Our goal is that this research will ultimately lead to viable therapeutic options as well.

INTERVIEW BY AMY STONE. *A physician-scientist, Michael Salter received his M.D. from the University of Western Ontario and his Ph.D. from McGill University.*