Findings could lead to treatments for chronic pain caused by nerve damage

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Non-narcotic treatments for chronic pain that work well in people, not just mice, are sorely needed. Drawing from human pain genetics, an international team led by Boston Children's Hospital demonstrates a way to break the cycle of pain hypersensitivity without the development of addiction, tolerance or side effects.

Their findings, reported June 17 in the journal *Neuron*, could lead to treatments for chronic pain conditions caused by nerve damage, such as diabetic peripheral neuropathy (DPN) and post-herpetic neuralgia (PHN), as well as chronic inflammation, like rheumatoid arthritis. Current treatments provide meaningful pain relief in only about 15 percent of patients.

"Most pain medications that have been tested in the past decade have failed in phase II human trials despite performing well in animal models," notes Clifford Woolf, MD, PhD, director of Boston Children's F.M. Kirby Neurobiology Center and a co-senior investigator on the study with Michael Costigan, PhD. "Here, we used human genetic findings to guide our search from the beginning."

In 2006, Costigan, Woolf and colleagues showed in Nature Medicine that people with variants of the gene for GTP cyclohydrolase (GCH1)--about 2 percent of the population--are at markedly lower risk for chronic pain. GCH1 is needed to synthesize the protein tetrahydrobiopterin (BH4), and people with GCH1 variants produce less BH4 after nerve injury. This suggested that BH4 regulates pain sensitivity.

"We wanted to use pharmacologic means to get the same effect as the gene variant," says Alban Latremoliere, PhD, also of Boston Children's Kirby Center, who led the current study along with Woolf and Costigan.

In a "reverse engineering" approach, the researchers modeled the human biology in mice. They first showed that mice with severed sensory nerves produce excessive BH4, churned out both by the injured nerve cells themselves and by macrophages--immune cells that infiltrate damaged nerves and inflamed tissue. Mice engineered to make excess BH4 had heightened pain sensitivity even when they were uninjured, suggesting that BH4 is sufficient to produce pain. On the flip side, mice that were genetically unable to produce BH4 in their sensory nerves had decreased pain hypersensitivity after peripheral nerve injury.

"We then asked, if we could reduce production of BH4 using a drug, could we bring about reduction of pain?" says Latremoliere.

The answer was yes. The researchers blocked BH4 production using a specifically designed drug that targets sepiapterin reductase (SPR), a key enzyme that makes BH4. The drug reduced the pain hypersensitivity induced by the nerve injury (or accompanying inflammation) but did not affect nociceptive pain--the protective pain sensation that helps us avoid injury.

Fine-tuning pain relief

Because BH4 is active all over the body, with important roles in the brain and blood vessels, the goal of any treatment would be to dial down excessive BH4 production, but not eliminate it entirely. Latremoliere and colleagues showed that blocking SPR still allowed minimal BH4 production through a separate pathway and reduced pain without causing neural or cardiovascular side effects.

"Our findings suggest that SPR inhibition is a viable approach to reducing clinical pain hypersensitivity," says Woolf. "They also show that human genetics can lead us to novel disease pathways that we can probe mechanistically in animal models, leading us to the most suitable targets for human drug development."

Source:
Boston Children's Hospital
