Putting a block on neuropathic pain before it starts

October 9 2012

Using tiny spheres filled with an anesthetic derived from a shellfish toxin, researchers at Boston Children's Hospital and the Massachusetts Institute of Technology have developed a way to delay the rise of neuropathic pain, a chronic form of pain that arises from flawed signals transmitted by damaged nerves.

The method could potentially allow doctors to stop the cascade of events by which tissue or nerve injuries evolve into neuropathic pain, which affects 3.75 million children and adults in the United States alone.

The researchers, led by Daniel Kohane, MD, PhD, of Boston Children's Department of Anesthesia and Robert Langer, ScD, of MIT, reported the results of animal studies online the week of October 8 in the Proceedings of the National Academy of Sciences.

Neuropathic pain can be long lasting and debilitating. Caused by shingles, nerve trauma, cancer and other conditions, it arises because damaged nerves send unusual signals to the spinal cord and the brain. The constant signaling effectively reprograms the central nervous system to react to any stimulus to the affected area, or even no stimulus at all, by triggering unpleasant sensations ranging from tingling and numbness to shooting, burning pain.

"Currently neuropathic pain is treated with systemic medications, but there has been significant interest in using powerful local anesthetics to block aberrant nerve discharges from the site of injury to prevent the

onset of neuropathic pain," said Kohane. "Others have tried with varying degrees of success to do this in animal models using a variety of methods, but if applied clinically, those methods would require surgical intervention or could be toxic to tissues. We want to avoid both of those concerns."

The team's method combines saxitoxin, a powerful local anesthetic, and dexamethasone, which prolongs saxitoxin's effects. The two are packaged in liposomes—lipid spheres about 5.5 micrometers wide, or a bit smaller than a red blood cell—for nontoxic delivery to the site of nerve or tissue damage.

To assess whether the anesthetic-loaded liposomes (called SDLs for saxitoxin dexamethasone liposomes) might work as a potential treatment for neuropathic pain, Kohane and Langer—along with Sahadev Shankarappa, MBBS, MPH, PhD (a fellow in the Kohane lab) and others—attempted to use them to block the development of signs of neuropathy in an animal model of sciatic nerve injury. They found that a single injection of SDLs had a very mild effect, delaying the onset of neuropathic pain by about two days compared to no treatment. Three injections of SDLs at the site of injury over the course of 12 days, however, delayed the onset of pain by about a month.

The signal blockade mounted by the SDLs also appeared to prevent reprogramming of the central nervous system. The team noted that astrocytes in the spine, which help maintain the pain signaling in neuropathic patients, showed no signs of pain-related activation five and 60 days after injury in animals treated with SDLs.

"Ultimately we'd like to develop a way to reversibly block nerve signaling for a month with a single injection without causing additional nerve damage," Kohane explained. "For the moment, we're trying to refine our methods so that we can get individual injections to last longer

and figure out how to generalize the method to other models of neuropathic pain.

"We also need to see whether it is safe to block nerve activity in this way for this long," he continued. "We don't want to inadvertently trade one problem for another. But we think that this approach could be fruitful for preventing and treating what is really a horrible condition."

Provided by Children's Hospital Boston