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SPINAL CORD INJURY BC

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Engineering Success

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pain relief

Purdue University researcher Dr. Riyi Shi is shedding light on the role of a common neurotoxin in SCI neuropathic pain—and how a safe and effective blood pressure medication could be repurposed to neutralize it.

Regular readers of *The Spin* know that we like to write about pain. Life with any type of level of SCI is no picnic, but to have severe neuropathic pain as a constant companion to paralysis, as is the case for many of our readers, just seems like a gross injustice. That's why we're always on the lookout for promising research in this area.

Late last year, we learned about some fascinating results from a decade-old research effort led by Dr. Riyi Shi, a professor of neuroscience and biomedical engineering in Purdue University's Department of Basic Medical Sciences, School of Veterinary Medicine and Weldon School of Biomedical Engineering. The results were published in the November 29th issue of the Journal of Neurochemistry.

The essence of Shi's work is that a well-known neurotoxin called acrolein appears to be one of the culprits behind the

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LEFT: Dr. Riyi Shi at work in his laboratory (photo courtesy of Purdue University). BELOW: A conceptual drawing showing the molecular structure of the neurotoxin acrolein.

often excruciating neuropathic pain that many people with SCI live with. Additionally, and perhaps more importantly, a drug already approved by the FDA neutralizes this neurotoxin, reduces the neuropathic pain, and is therefore a potential treatment.

A word of caution: as with a great deal of SCI research, this body of work has been conducted only in animal studies. But it's still promising, and because the drug involved is already being used successfully and safely for other conditions, it may be possible to move it quickly into human clinical studies for a neuropathic pain application.

So what is acrolein? It's a highly toxic compound that can be found all around us in the environment, and also inside of us. For example, it's produced when many foods such as vegetable oils and animals fats are heated, and it's also in cigarette smoke and vehicle exhaust. Industrially, it's actually produced in large quantities, often for use as a herbicide to control water-based weeds and algae.

Scientists have also known for some time that acrolein is produced inside the body as the result of a process called oxidative stress.

We couldn't live without oxygen—our bodies combine it with the food we digest to essentially power vital life functions. But where there is oxygen, there is also the possibility of oxidation. When you see rusting iron, for example, you're actually viewing oxidation in action—the process by which free oxygen radicals "steal" electrons from the iron atoms and damage them in the process. This process also occurs in our bodies throughout our lifetime—it's one reason why we age. Inside our bodies, we refer to this process as oxidative stress.

Oxidative stress is largely kept in check in a healthy person by antioxidants. But it can be accelerated by elevated levels of free radicals. When this happens, it can have devastating results. Research to date implicates oxidative stress as a contributing factor in more than 70 well-known diseases, including heart disease, cancer, Parkinson's, diabetes, and Alzheimer's. And there's long been an acknowledgement that elevated levels of oxidative stress increase the severity of an SCI in the days and weeks that follow the initial trauma, which leads us to Shi's research.

"It's well known that oxidative stress and free radicals are important pathological mechanisms related to SCI," says Shi. "However, strategies aimed at reducing free radicals alone have only demonstrated marginal benefits. This is why we were motivated to identify more important targets for therapies in oxidative stress."

Shi and his team knew that acrolein was produced by a specific type of oxidative stress known as lipid peroxidation. Lipids are molecules that our bodies use for a variety of purposes, including forming cell membranes. During lipid peroxidation, free radicals "steal" electrons from lipids in cell membranes. Not only does this cause damage to the cells, it results in the production of acrolein.

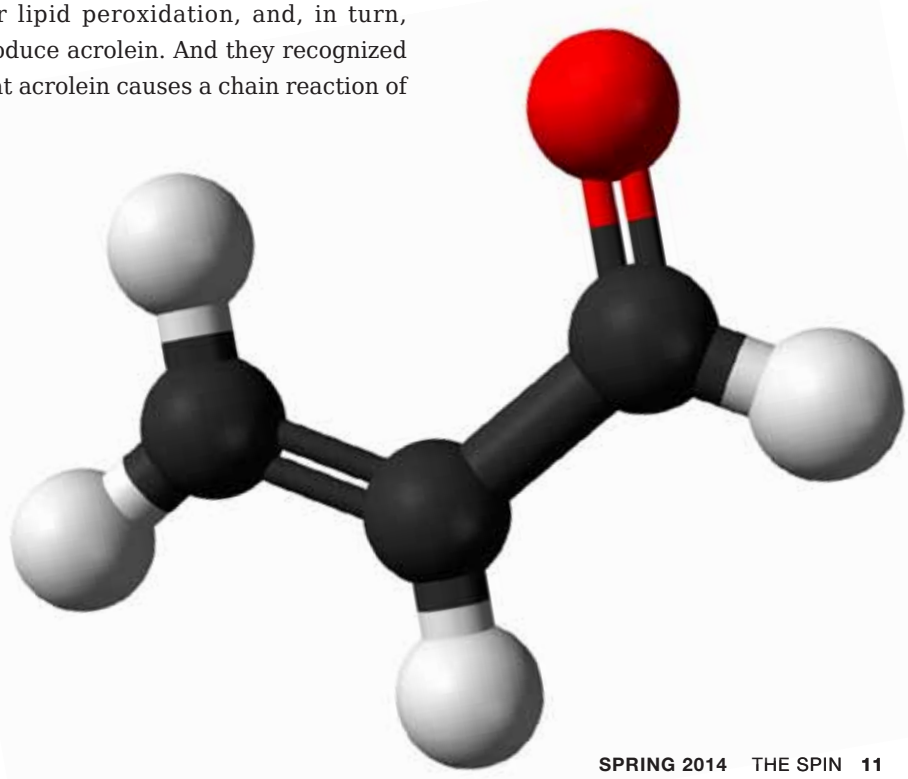
They also knew that trauma to nerve cells has been demonstrated to trigger lipid peroxidation, and, in turn, produce acrolein. And they recognized that acrolein causes a chain reaction of biochemical events thought to worsen the injury's severity, perpetuate the oxidative stress, and produce even more acrolein—truly a vicious biochemical circle. Therefore, they set their sights on better understanding the role of acrolein in SCI.

In a series of experiments with rats, they confirmed that the quantity of acrolein present in the body increases by an astonishing 300 percent immediately following SCI. But they discovered much more.

"It turns out that acrolein is a very important compound behind neuropathic pain," Shi says.

Their findings suggest that the increased levels of acrolein bind to and activate pain receptors called TRPA1, which are contained in pain-sensory nerve fibers of dorsal root ganglia located alongside the spine. In fact, the elevated levels of acrolein after SCI resulted in a three-fold increase in the number of TRPA1 channels.

"The amplification of pain can be exacerbated in SCI due to acrolein's direct activation of pain receptors, as well as acrolein-induced inflammation that further intensifies pain sensation," Shi says. "Sometimes you have pain even without stimulation. You can have excruciating pain just sitting there."



With new evidence that acrolein is at least in part responsible for neuropathic pain following SCI, Shi and his team then moved on to finding some way of limiting it after injury. They focused on hydralazine, a drug that was already known to be an "acrolein scavenger."

"The reason we tried hydralazine is because other scientists have already shown it could bind and neutralize acrolein, particularly in liver cells," Shi explains. "It turned out to work very well."

Shi's work with hydralazine involved measuring a treated rat's reaction to stimulation, and demonstrated a significant reduction in neuropathic pain that corresponded with the reduction in acrolein. And there's more—they also discovered that hydralazine treatment also resulted in significant reduction of post-SCI tissue damage and motor deficits.

All of this might sound like hydralazine is effective only in the short period of time after injury—the acute phase of injury. But Shi says it also has promise as a treatment for neuropathic pain in people who have been injured for some time.

"Even if we delay administration of hydralazine we can still reduce the pain, meaning not only acute but chronic pain might be reduced by acrolein-scavenging treatment," Shi says. "In addition to the elevated acrolein level immediately following SCI, the expression (activity) of the TRPA1 is elevated long after the injury. This means that the sensory neurons remain sensitive to acrolein. So acrolein may produce neuropathic pain even after the acrolein level is normalized. Therefore, it's likely that acrolein can not only contribute to pain in acute SCI, but also to chronic pain in SCI long after the acute stage. One piece of evidence to support this is the very fact that, in our animal experiments, treatment with hydralazine not only reduced pain in the acute stage post-SCI, but also in sub-acute and chronic stages post-SCI."

All of this leads us to ask, "So what is hydralazine?" It's a drug known as a "smooth muscle relaxant" that has long been approved by the U.S. Food and Drug Administration to treat high blood pressure, or hypertension. In this role, it works by relaxing blood vessels so blood can flow through the body more easily. Its ability to "scavenge" acrolein has been known for some time, but it's only recently that studies like Shi's are finding specific applications for this ability.

"We are making efforts to push hydralazine to the clinical usage," says Shi. "It is FDA approved, so there is a history of several decades of safety data regarding hydralazine. Meanwhile, the dosage to lower acrolein is at least a magnitude lower than that needed for reducing blood pressure, making it safe to use in SCI. Since it is FDA approved, this will be a repurposing drug, just like aspirin was repurposed from a pain medication to a blood thinner. So we could likely skip phase I trials to test safety, and go directly to phase II clinical trials, to see if it is effective in humans. This would significantly expedite the approval process."

As for side effects of hydralazine, the most concerning is hypotension, or a dangerous drop in blood pressure. "However," says Shi, "since the dosage to scavenge acrolein would be lower than that used for hypertension, the risk of hypotension will be minimal. In addition, in the animal studies, the dosage at which hydralazine could effectively lower acrolein did not cause any significant hypotension."

Interestingly, we did find someone in a popular online SCI consumer forum who claims to have recently started taking hydralazine for neuropathic pain. When we told Shi that, he understandably expressed concern.

"At this point, I need to make it clear that hydralazine has not been approved for SCI or as an analgesic medication," he cautions.

Shi is also researching the role of acrolein in multiple sclerosis, where he believes it is one of the agents responsible for the breakdown of myelin, the protective sheath found around neurons. Watch future issues of *The Spin* for developments about hydralazine and Shi's research as they become available. ■

The Changing Face of SCI

The number of serious traumatic spinal cord injuries is on the rise in the USA, and the leading cause no longer appears to be motor vehicle crashes, but falls.

That's the verdict from a recent Johns Hopkins research report, recently published in the *Journal of Neurotrauma*.

The same research also confirms a trend seen here in Canada that the average age of people when injured is quickly rising, with more and more seniors acquiring SCIs.

"We have demonstrated how costly traumatic spinal cord injury is and how lethal and disabling it can be among older people," says Shalini Selvarajah, M.D., M.P.H., a postdoctoral surgical research fellow at the Johns Hopkins University School of Medicine and leader of the study. "It's an area that is ripe for prevention."

The researchers analyzed a nationally representative sample of 43,137 adults treated in hospital emergency rooms for SCI in the United States between 2007 and 2009. While the incidence among those aged 18 to 64 dropped from 52.3 per million in 2007 to 49.9 per million in 2009, the incidence per million in those 65 and older increased from 79.4 in 2007 to 87.7 in 2009.

At 41.5 percent, falls were the leading cause of injury over the three-year study period, followed by motor vehicle crashes at 35.5 percent.

The average age of adults at time of injury of adults is now 51. The average age of injury was 41 in a study that covered the years 2000 to 2005.

While the researchers say they can't pinpoint the exact reason that falls have surpassed car crashes as a cause of traumatic SCI, they believe it may be a combination of the general aging of the population, the more active lifestyles of many Americans over 65, and airbags and seatbelt laws that allow drivers and passengers to survive crashes.

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