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# New drug promises relief for inflammatory pain

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Pain from inflammation sidelines thousands of Americans each year. Many face a tough choice: deal with the pain, take a potentially addictive opioid or use a nonsteroidal anti-inflammatory drug that may increase risk for cardiovascular disease or gastrointestinal bleeding.

Now, researchers at the Stanford University School of Medicine have discovered a compound thought to be nonaddictive and safe for the heart and gastrointestinal system that reduces inflammatory pain in mice and rats. They call the compound Alda-1.

"Finding a new pain medication is important because we need a safer drug; there are 17,000 deaths from prescription opiate overdoses a year alone," said Daria Mochly-Rosen, professor of chemical and systems biology.

A paper describing the researchers' findings will be published Aug. 27 in *Science Translational Medicine*. Mochly-Rosen is senior author of the paper, and former Stanford postdoctoral scholars Vanessa Zambelli, PhD, and Eric Gross, MD, PhD, are the lead authors.

The researchers have been working with Alda-1 for more than five years. They discovered it while searching for the reason that moderate drinkers have less-severe heart attacks than nondrinkers or heavy alcohol drinkers. They found that alcohol increases the activity of an enzyme called aldehyde dehydrogenase 2. This enzyme breaks down a byproduct of alcohol called acetaldehyde, forming free radicals that can damage

cells. The enzyme also breaks down additional toxic aldehydes that are formed in the body because of oxidative stress, such as that occurring during a heart attack. Alda-1, an abbreviation for aldehyde dehydrogenase activator 1, kicks the enzyme into high gear, allowing it to break down toxic aldehydes more quickly and leaving less time for them to cause damage. (Coincidentally, Alda is also the name of Mochly-Rosen's 87-year-old mother.)

Now, Alda-1 has shown its prowess as a painkiller.

Mochly-Rosen and her team knew that inflammation causes toxic aldehyde accumulation. But no one had asked whether the enzyme aldehyde dehydrogenase 2, which breaks down these aldehydes, regulates inflammatory pain.

"We made what may appear as a crazy leap," Mochly-Rosen said.

The researchers conducted a series of experiments to illuminate the enzyme's role in the perception of inflammatory pain. First, they demonstrated that mice and rats with an inflamed paw felt less pain when they received Alda-1. Yet the underlying condition, the inflammation, remained unchanged after Alda-1 treatment.

Then, Che-Hong Chen, PhD, a senior research scientist and co-author of the paper, bioengineered a mouse with a mutation in aldehyde dehydrogenase 2 that mimics a mutation found in more than a third of Han Chinese, a group that makes up 8 percent of the world population. In humans, this mutation causes flushing after alcohol consumption because of excess acetaldehyde accumulation.

In mice, the mutation increased sensitivity to inflammatory pain. The researchers then demonstrated increased pain response by injecting the mutant mice with aldehydes and comparing their reactions to those of

normal mice. The mice with the mutated enzyme licked and flicked their paws longer than normal mice. When treated with Alda-1, both groups of mice appeared to feel less pain.

Mochly-Rosen said her team plans to investigate whether humans with the mutated enzyme are also more sensitive to pain.

She said the findings demonstrate the importance of basic research.

"I'm not a pain expert, and pain was never a research focus of my lab," Mochly-Rosen said. "We focused our research on this enzyme for a completely different reason, and because we are in academia, we could follow a serendipitous finding and develop a new research interest. Hopefully, this finding will translate into helping people who have inflammatory pain."

Gross is now an instructor of anesthesiology, perioperative and pain medicine at Stanford. Researchers at the Butantan Institute in Brazil also contributed to the study.

**More information:** "Aldehyde dehydrogenase-2 regulates nociception in rodent models of acute inflammatory pain," by V.O. Zambelli et al. stm.sciencemag.org/lookup/doi/ … scitranslmed.3009539

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