Specialized compound could lead to chronic pain relief without the use of opioids

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Purdue researchers have discovered a compound that could lead to the treatment of chronic pain without the need for patients to rely on opioids.

A team led by Val Watts, associate head and professor of medicinal chemistry and molecular pharmacology in Purdue's College of Pharmacy, said the compound shows unparalleled selectivity in inhibiting the adenylyl cyclase 1 (AC1).

Adenylyl cyclases are enzymes that organize the production of cyclic adenosine monophosphate, an important biological messenger in numerous organisms. There are 10 isoforms of adenylyl cyclases found in humans. Numerous studies have suggested that AC1 could be used as a drug target for chronic pain.

The compound identified at Purdue has shown selectivity for inhibiting AC1 versus the other nine isoforms.

"With the AC1 technology, there's a chance to treat chronic pain directly or through reducing the side effects of the opioids," said team member Richard van Rijn, assistant professor of medicinal chemistry and molecular pharmacology in Purdue's College of Pharmacy. "There's an issue with misuse of opioids used to treat chronic pain. They are good as a short-term analgesic for acute pain, but don't address the underlying issues of chronic pain."

Opioids are a class of drugs that include the illicit drug heroin as well as prescription pain relievers oxycodone, hydrocodone, codeine, morphine, fentanyl and others. They interact with opioid receptors on nerve cells in the brain and nervous system to produce pleasurable effects and relieve pain.

According to the Centers for Disease Control and Prevention, overdose deaths involving prescription opioids have quadrupled since 1999. From 1999 to 2015, more than 183,000 people have died in the United States from overdoses related to prescription opioids.

The Watts group is the first to identify a compound that is selective for AC1 only.

Findings from the study are published in a research paper by Watts' group that recently appeared in *Science Signaling*. There is also a recent news feature about the research in *Science*.

While the research is still in its early stages, another potential application for the compound is the possibility of reducing opioid dependence. Separate research has shown that completely deleting the AC1 enzyme reduces the signs of dependence.

"If you decrease the physical symptoms of withdrawal, that could help reduce psychological dependence," Watts said. "You might also be able to stop relapse."

More information: Tarsis F. Brust et al. Identification of a selective small-molecule inhibitor

of type 1 adenylyl cyclase activity with analgesic properties, *Science Signaling* (2017). DOI: 10.1126/scisignal.aah5381

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