Chemical compound shows promise as alternative to opioid pain relievers

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A drug targeting a protein complex containing two different types of opioid receptors may be an effective alternative to morphine and other opioid pain medications, without any of the side effects or risk of dependence, according to research led by the Icahn School of Medicine at Mount Sinai. The findings are published in July in the journal *Proceedings of the National Academy of Sciences*.

Morphine is still the most widely-used pain reliever, or analgesic, in people with severe pain, but chronic use can lead to addiction and negative side effects such as respiratory issues, constipation, or diarrhea.

In a previous study published in *Science Signaling* by Lakshmi Devi, PhD, Professor of Pharmacology and Systems Therapeutics at Mount Sinai, researchers identified a therapeutic target called a GPCR heteromer, which is a protein complex that is made up of two opioid receptors called mu and delta. They also showed that the heteromer is abundant in the area of the brain that processes pain, and is the likely cause of morphine tolerance and side effects.

In the current study, Dr. Devi carried out high throughput screening in collaboration with researchers at the National Institutes of Health (NIH) to identify which small molecules might act on the signaling pathway associated with this protein complex. Researchers found one compound called CYM51010 that was as potent as morphine, but less likely to result in tolerance and negative side effects. Dr. Devi's team is currently developing modified versions of this compound that may have potential

as analgesics with reduced side effects.

"GPCR heteromers have been suggested to represent powerful targets for improved, novel therapeutics with reduced adverse effects in people with severe pain," said Dr. Devi. "However, there are presently no chemical tools that allow us to investigate their role in vivo. Our work represents a promising step in this direction, providing results that pave the way towards a new understanding of the function and pharmacology of opioid receptor heteromers."

Dr. Devi and her team are currently working with co-author Marta Filizola, PhD, Associate Professor of Structural and Chemical Biology at Mount Sinai, to learn how CYM51010 binds to the protein complex. Armed with this information, they hope to modify the compound to treat pain without the development of dependency. They also plan to restrict their benefit to the gastrointestinal system and treat diarrhea associated with irritable bowel disease that is unresponsive to existing therapies.

More information: Identification of a ?-? opioid receptor heteromer-biased agonist with antinociceptive activity, *PNAS*, Published online before print July 1, 2013, doi: 10.1073/pnas.1222044110

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