New study brings medicine closer to non-addictive painkillers

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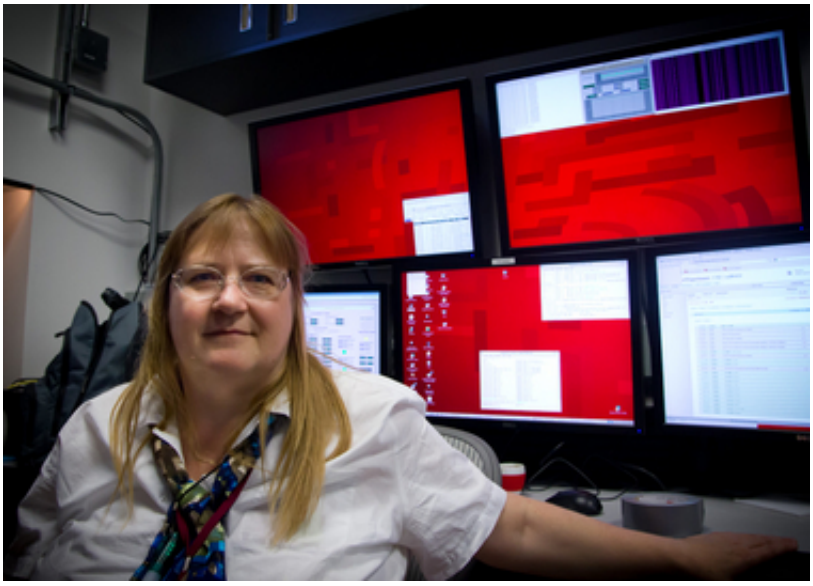

Petra Fromme directs the Biodesign Institute's Center for Applied Structural Discovery. The current project involves the use of serial femtosecond crystallography to examine opioid receptors and chemicals that bind with them, alleviating pain. The work provides key insights that could lead to improved analgesics and techniques of pain management. Credit: The Biodesign Institute at Arizona State University

Powerful opiate drugs are a mainstay in modern medicine, alleviating pain in both acute and chronic forms. These charms however, bear a curse. Users quickly develop tolerance to their effects, requiring ever-increasing doses of the drug. Further, such opioid compounds lead to

drug dependence, owing to their notoriously addictive qualities.

In a first-of-its-kind study, Petra Fromme, a researcher at Arizona State University's Biodesign Institute, joins an international team using techniques of X-ray crystallography with high-speed lasers to home in on the detailed structure of opioid receptors and synthetic drugs that bind to these sites.

Their efforts pave the way for the development of powerful new analgesics, capable of blocking pain without generating tolerance or dependency. Their research findings appear in the current issue of the journal *Nature Structural and Molecular Biology*.

The international research group was led by Gustavo Fenalti (formerly of the Scripps Research Institute, now with Celgene Corporation, San Diego, California) and includes researchers from the laboratory of Raymond C. Stevens with the University of Southern California, as well as members of the SLAC National Accelerator Laboratory; Center for Free Electron Laser Science; Deutsches Elektronen-Synchrotron (DESY)-Hamburg, Germany; and others.

Fromme, director of the Biodesign Institute's newly established Center for Applied Structural Discovery, highlights the importance of the present study: "Serial femtosecond crystallography permits detailed examination of vital biochemical details that have long eluded proper study. In this case, revealing the subtle interaction of a human opioid receptor with a binding peptide is a critical step for understanding the pharmacological profile of opioid drugs. The research opens the door to a new generation of improved treatments for pain."

Ancient friend and foe

Opioids figure among the oldest known drugs, their therapeutic uses

dating to prehistory. Such compounds are structurally similar to morphine and other natural alkaloid derivatives of the opium poppy. They work by binding to various opiate receptors, located primarily in the central and peripheral nervous systems and the gastrointestinal tract. While this much is known, many mysteries remain regarding their precise mode of action (and their troublesome side-effects).

Opioid receptors belong to a large protein family known as G protein-linked receptors. These sensing molecules outside of cells trigger a cascade of cellular responses that affect the brain.

When an opioid binding agent, called a ligand, binds with a receptor, the result is a dramatic attenuation of pain, often accompanied by a sense of intense euphoria, (a fact accounting for the popularity of opioid drugs, including opium and heroin, for recreational use and abuse).

Fromme's group has a led a major initiative to better understand this protein family using a powerful new X-ray laser technology.

Three primary opioid receptors are known to bind with various naturally-occurring opioids produced by the body. A more thorough understanding of these naturally-occurring opioids and their receptors is essential for drug discovery of new pain analgesics with more desirable properties.

Researchers hope to create synthetic opiate ligands, capitalizing on their powerful analgesic properties while reducing or eliminating side-effects. The current study examines a particular opioid ligand which has already shown considerable promise as a tolerance-free, dependence-free analgesic.

X-ray vision

X-ray crystallography has been a vital tool for revealing the structure and

function of a wide variety of biological molecules, including drugs, vitamins, proteins and nucleic acids, such as DNA. The technique remains a primary method for characterizing the atomic structure of new materials and their properties – key ingredients in the eventual design and validation of new pharmaceutical drugs.

One shortcoming of traditional X-ray crystallography is that X-rays can damage or destroy the delicate crystal structures under investigation. The current study used a pathbreaking method known as serial femtosecond crystallography using a device known as an X-ray Free Electron Laser (XFEL).

The use of XFEL allows much smaller crystals to be used, capturing critical structural information before the sample is destroyed.

In the current study, the team used serial femtosecond crystallography to observe peptide-receptor interactions essential for developing a complete pharmacological profile of opioid peptides, and development and refinement of improved analgesic drugs.

The XFEL method provided unprecedented structural details revealing new molecular determinants of peptide interaction and identifying a key structure contributing to a particular ligand's activity.

Analysis of that ligand presents a platform for the examination of numerous peptides with pharmacological properties, including new ligands for the management of pain.

In addition to her appointment at the Biodesign Institute, Fromme is a professor at ASU's Department of Chemistry and Biochemistry.

More information: "Structural basis for bifunctional peptide recognition at human δ-opioid receptor." *Nature Structural & Molecular*

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