

## Study may help explain addictive nature of synthetic opioid drugs

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By *Pete Farley* [1]



Findings from a new UCSF study may one day allow scientists to create new types of opioid-based pain medications that have a lower risk for addiction.

A new study led by UC San Francisco scientists shows that brain cells, or neurons, react differently to opioid substances created inside the body — the endorphins responsible for the “natural high” that can be produced by exercise, for example — than they do to morphine and heroin, or to purely synthetic opioid drugs, such as fentanyl. The researchers say their findings may help explain why the use of synthetic opioids can lead to addiction.

Since both synthetic opioids and the natural, “endogenous” opioids produced in the brain bind to and activate opioid receptors on the surface of nerve cells, scientists have long

assumed that both types of molecules target the same cellular systems. But the new research reveals that these molecules also activate opioid receptors inside cells, and that the locations of these activated intracellular receptors differ between natural and synthetic opioids.

In the new study, published in the May 10, 2018 issue of *Neuron* [2], the researchers report that this difference could help explain why the effects of synthetic opioid drugs are more rewarding than those produced by endogenous opioids.

## **Body's natural opioids affect brain cells differently than morphine**

There has been no evidence so far that opioid drugs do anything other than what natural opioids do, so it's been hard to reconcile the experiences that drug users describe that opioid drugs are more intensely pleasurable than any naturally rewarding experience that they've ever had," said Mark von Zastrow, MD, PhD [3], a professor of psychiatry at UCSF and senior author on the new paper. "The possibility that these opioid drugs cause effects that natural opioids cannot is very intriguing because it seems to parallel this extremely rewarding effect that users describe."



Mark von Zastrow, MD,  
PhD [3]

Researchers in von Zastrow's lab collaborated with Aashish Manglik, MD, PhD [4], assistant professor of pharmaceutical chemistry, to create a "biosensor" that binds to the opioid receptors along with an opioid drug or natural opioid. The tool allowed the scientists to see what's happening inside cells, giving them a closer look than ever before at opioids' effects. "It's a way of sniffing out where these receptors are active in the particular types of neurons in which opioids work," explained von Zastrow, a member of the UCSF Weill Institute for Neurosciences [5].

It has generally been thought that all opioid molecules, natural or synthetic, impart their signal only from receptors on the surface of the cell. Opioid-bound receptors are then taken inside the cell to compartments called endosomes, but receptors were thought not to signal from this location. Overturning this long-held view, the research team discovered that receptors actually remain active in endosomes and they use the endosome to sustain the signal within cells.

But in the most intriguing twist, the research team discovered that morphine and synthetic opioids activate receptors in yet another internal location called the Golgi apparatus, where

endogenous opioids are unable to produce any activation at all.

“It really surprised us that there was a separate location of activation for drugs in the Golgi apparatus that could not be accessed by endogenous opioids,” said first author Miriam Stoeber, PhD [6], a postdoctoral researcher in von Zastrow’s lab. “Drugs, which we generally thought of as mimics of endogenous opioids, actually produce different effects by activating receptors in a place that natural molecules cannot access.”

Moreover, morphine and synthetic opioids crossed cell membranes without binding receptors or entering endosomes. They traveled directly to the Golgi apparatus, reaching their target much more quickly than endogenous opioids got into endosomes, taking only 20 seconds compared to over a minute. This time difference could be important in the development of addiction, the researchers said, because typically the faster a drug takes effect, the higher its addictive potential.

## A potential pathway to less addictive medications

The scientists hope to apply their findings to create new types of opioid-based pain medications that have a lower risk for addiction. They also plan to screen other existing medications to see if they act more like natural or synthetic opioids.

“We’re very excited about the possibility of leveraging these principles to develop better or more selective drugs that have the ability to get into the brain, but then differ in their activities at internal locations within individual neurons,” says von Zastrow. “This is an area that hasn’t been explored in drug development because people haven’t been thinking about it, but the potential is there.”

Other authors on the study were Damien Jullie, PhD [7], and Braden Lobingier, PhD [8], of the UCSF Department of Psychiatry; Toon Laeremans, PhD [9], and Jan Steyaert, PhD [10], of Vrije Universiteit Brussel, in Brussels, Belgium; and Peter Schiller, PhD [11], of the Clinical Research Institute of Montreal, in Canada.

The research was supported in part by funding from the National Institute of Drug Abuse, the Canadian Institutes of Health Research, and the Swiss National Science Foundation.

## Read the research article

- **Neuron:** A genetically encoded biosensor reveals location bias of opioid drug action [2]

## Further coverage

- **National Institutes of Health:** Study upends conventional view of opioid mechanism of action [12]
- **Genetic Engineering & Biotechnology News:** Opioid drugs rush in where natural opioids fail to activate [13]

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## About UCSF Psychiatry

The UCSF Department of Psychiatry [14] and the Langley Porter Psychiatric Institute are

among the nation's foremost resources in the fields of child, adolescent, adult, and geriatric mental health. Together they constitute one of the largest departments in the UCSF School of Medicine and the UCSF Weill Institute for Neurosciences, with a mission focused on research (basic, translational, clinical), teaching, patient care and public service.

UCSF Psychiatry conducts its clinical, educational and research efforts at a variety of locations in Northern California, including UCSF campuses at Parnassus Heights, Mission Bay and Laurel Heights, UCSF Medical Center, UCSF Benioff Children's Hospitals, Zuckerberg San Francisco General Hospital and Trauma Center, the San Francisco VA Health Care System and UCSF Fresno.

## **About the UCSF Weill Institute for Neurosciences**

The UCSF Weill Institute for Neurosciences <sup>[15]</sup>, established by the extraordinary generosity of Joan and Sanford I. "Sandy" Weill, brings together world-class researchers with top-ranked physicians to solve some of the most complex challenges in the human brain.

The UCSF Weill Institute leverages UCSF's unrivaled bench-to-bedside excellence in the neurosciences. It unites three UCSF departments—Neurology, Psychiatry, and Neurological Surgery—that are highly esteemed for both patient care and research, as well as the Neuroscience Graduate Program, a cross-disciplinary alliance of nearly 100 UCSF faculty members from 15 basic-science departments, as well as the UCSF Institute for Neurodegenerative Diseases, a multidisciplinary research center focused on finding effective treatments for Alzheimer's disease, frontotemporal dementia, Parkinson's disease, and other neurodegenerative disorders.

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UC San Francisco (UCSF) <sup>[16]</sup> is a leading university dedicated to promoting health worldwide through advanced biomedical research, graduate-level education in the life sciences and health professions, and excellence in patient care. It includes top-ranked graduate schools of dentistry, medicine, nursing and pharmacy; a graduate division with nationally renowned programs in basic, biomedical, translational and population sciences; and a preeminent biomedical research enterprise. It also includes UCSF Health, which comprises top-ranked hospitals — UCSF Medical Center <sup>[17]</sup> and UCSF Benioff Children's Hospitals in San Francisco <sup>[18]</sup> and Oakland <sup>[19]</sup> — and other partner and affiliated hospitals and healthcare providers throughout the Bay Area.

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