UNIVERSITÉ DE GENÈVE

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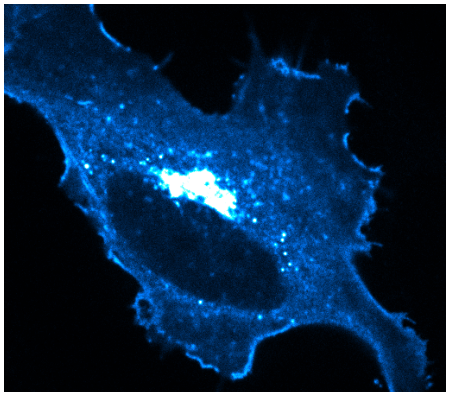
How opioid drugs get into our cells

Unlike natural opioids, opioid drugs penetrate our cells, which explains both their high efficacy and their side effects, reveals a UNIGE team.

The human body naturally produces opioid-like substances, such as endorphins, which block the perception of pain and increase the feeling of well-being. Similarly, opioid drugs, including morphine or fentanyl, are widely used for alleviating severe pain. However, their use is associated with a high risk of dependence and addiction, and their excessive misuse causes over 350,000 annual deaths worldwide. Researchers from the University of Geneva (UNIGE) have compared the action of natural and therapeutic opioids. The latter penetrate inside the cells to activate opioid receptors, whereas natural opioids are unable to enter cells and activate only receptors located on the cell surface. The location of the activated receptors could therefore explain why opioid drugs trigger very different physiological responses from those induced by natural opioids. The results, to read in *Science Advances*, could help to develop safer and more effective medications that better mimic natural opioids.



Activation of opioid receptors inside a cell.

High resolution pictures

Opioids consist of a broad group of painkiller drugs, highly powerful but with potentially severe side-effects. The human organism's response to these medications is governed by opioid receptors that belong to a large family of membrane receptors called GPCRs, which are present in all our cells and mediate a wide range of physiological functions, from vision and smell to brain function. Opioid drugs activate these receptors in neurons, thereby inducing signals that block the sensation of pain.

But why do the effects of different opioids vary? And why do they trigger so severe side-effects? "We had previously discovered that some opioids not only interact with receptors present at the surface of cells, but also have the ability to enter inside the cells to activate intracellular receptors," summarises Miriam Stoeber, assistant professor in the Department of Cell Physiology and Metabolism at the UNIGE Faculty of Medicine, who led this research. "Does this have any implication on how the body reacts to natural and therapeutic opioids? This what we wanted to ascertain. Furthermore, as a third of all currently existing drugs target GPCRs, understanding the exact role of intracellular receptors could have very wide therapeutic implications."

Localisation is crucial to defining a response

Taking advantage of new molecular tools they developed, the researchers studied the functioning of opioid receptors at unprecedented spatial resolution. "Instead of observing changes

occurring at whole-cell scale, we were able to detail what happens at different locations inside the cells," explain Arthur Radoux and Lucie Oberhauser, researchers in Miriam Stoeber's laboratory and co-first authors of the study. "To do so, we developed biosensors that allowed us to detect in living cells whether receptors present at specific locations in or on the cells are activated and able to initiate a response." Combining these new tools with analyses of gene expression and protein regulation, the scientists were able to demonstrate that the location of GPCRs activation modifies the response triggered by opioids, and consequently the signals involved in pain relief.

The key role of membrane lipids

In a second step, the researchers wanted to determine the mechanisms responsible for these different responses and teamed up with Prof. Francesco Gervasio and Dr. Simone Aureli from the School of Pharmaceutical Sciences at the Faculty of Science of the UNIGE for their studies. "We focused specifically on membrane lipids, as recent research has shown that they can interact with certain signalling proteins and modify the responses receptors trigger," clarifies Miriam Stoeber. And indeed, the types of lipids surrounding the GPCR influence the responses they transmit. This crucial role of lipids might also explain the variations in the effects of opioid drugs. "We hope now to discover if changes in membrane lipids occurring in metabolic diseases, such as diabetes, can influence the efficacy and the unwanted effects of GPCR drugs," adds Miriam Stoeber.

The fact that the localization of receptors changes the cellular responses could explain differences of effects and side-effects triggered by natural and therapeutic opioids. "To confirm that hypothesis, we are planning in vivo experiments, with the ultimate aim to design better targeted therapeutics with improved efficacy and reduce side-effects," concludes Miriam Stoeber.

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