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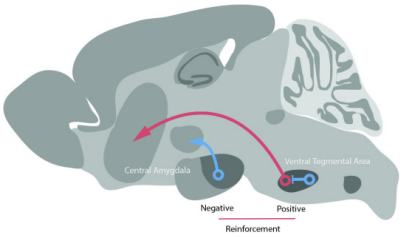
The double face of fentanyl: the neuronal basis of opioid addiction

UNIGE Scientists have discovered that fentanyl leads to the activation of two distinct cell populations in the brain, first when the drug is taken and then during withdrawal, suggesting a novel model for opioid addiction.



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Cells with mu-opioid receptors are activated in the ventral tegmental area during positive reinforcement, and in the central amygdala during negative reinforcement

High resolution pictures

Fentanyl is a particularly powerful synthetic opioid. Diverted from its original medical use, it has become a deadly drug responsible for three-quarters of overdose deaths in the United States. Yet, our knowledge of the impact of opioids on the brain remains incomplete. By deciphering the neuronal mechanisms involved, a team from the University of Geneva (UNIGE) has discovered that this substance exerts two distinct effects through same cell receptor in two different regions of the brain. One triggers the acute euphoric effect of the drug, and the other the aversive state during withdrawal. This could explain why individuals not only take the drug to get high, but also to avoid withdrawal, and why opioids are more addictive than other drugs. These results, published in the journal *Nature*, call into question current models of addiction and open up an original avenue for improving substitution treatments and developing painkillers with fewer side effects.

When injected intravenously, Fentanyl, which is 20 to 40 times more powerful than heroin and 100 times more potent than morphine, works in less than ten seconds. Like other opioids, it induces a massive feeling of well-being. After repeated use, the absence of the drug manifests itself with very unpleasant withdrawal symptoms. «We talk about positive reinforcement when the pleasurable sensation leads to repeated use of the drug, and about negative reinforcement when the drug is taken to avoid the extremely painful withdrawal syndrome», explains Christian Lüscher, Full Professor in the Department of Basic Neurosciences at the UNIGE Faculty of Medicine and at the Synapsy Centre for Neuroscience Research in Mental Health, who led this research. «Withdrawal, which appears a few hours after the last dose is taken, manifests itself both physically with a tremor, excessive sweating and pain, and psychologically with a state of intense uneasiness that does not exist with other drugs.»

Not one, but two brain areas involved

The product triggers the activation of the dopamine neurons in the mesolimbic system (also known as the reward system), which includes the ventral tegmental area and the nucleus accubens. The neurons then release a large quantity of dopamine. Normally, dopamine neurons are under the control of inhibitory GABA cells. However, opioids block GABA neurons, which makes dopamine neurons more active, inducing a euphoric phase. The key to understanding is the «mu» opiate receptor.

«Until now, it was thought that the mechanisms of both positive and negative reinforcements takes place in the same brain area, the

mesolimbic system. Conversely, our hypothesis suggests that the origin of negative reinforcement is to be found in cells that express the mu receptor elsewhere in the brain», explains Fabrice Chaudun, postdoctoral fellow in Christian Lüscher's laboratory and first author of this work.

The scientists used a series of behavioural and neuronal observation experiments to test their hypothesis. The first step was to suppress the mu receptor in the ventral tegmental area of mice addicted to fentanyl. If positive reinforcement disappeared, withdrawal remained unchanged. «By reproducing the experiment in different neuronal networks, we managed to identify a population of as yet unknown cells that express the mu receptor in another brain region, the central amygdala, known to be linked to fear and anxiety», says Fabrice Chaudun. «By suppressing the mu receptor in the cells found there, withdrawal symptoms disappear, but positive reinforcement does not.»

Selectively activating and deactivating neurons

Thanks to the collaboration with the teams of Brigitte Kiefer and Emanuel Valjent (Universities of Strasbourg and Montpelier) and to two mouse lines enabling the mu receptor to be deleted in selected cells, the scientists could mimick the neuronal mechanisms of opioids with a degree of precision never achieved before. «This is the whole complexity of brain research», sums up Christian Lüscher. «Pharmacological substances activate numerous networks indiscriminately. To understand the links between a substance, the activation of a neuronal circuit, and behaviour, we had to combine different techniques to manipulate neurons and networks.»

To confirm their results, the scientists used optogenetics, a technique that enables them to act on individual cells. Stimulating cells in the central amygdala to mimic fentanyl withdrawal triggered the same symptoms and behaviour in the mice as withdrawal. In addition, a device allowed the mice to press a lever to stop the neuronal stimulation: mice that had not taken fentanyl did so, while those on the drug did not, confirming that the product acts on the same networks.

Pain-relieving effect without harmful consequences?

These results radically change the model for understanding opioid addiction. As positive and negative reinforcements are mediated by two different networks, this could explain the exceptionally high addiction potential of these substances: the two mechanisms combine to drive people even further towards irrational consumption. Moreover, these discoveries will make it possible to refine substitution treatments and advance research into analgesics without addiction liability.

contact

Christian Lüscher
Full Professor
Department of Basic Neurosciences
Faculty of Medicine UNIGE
+41 22 379 54 23
Christian.Luscher@unige.ch

Fabrice Chaudun
Postdoctoral Fellow
Department of Basic Neurosciences
Faculty of Medicine UNIGE
Fabrice.Chaudun@unige.ch

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UNIVERSITÉ DE GENÈVE
Communication Department
24 rue du Général-Dufour
CH-1211 Geneva 4

Tel. +41 22 379 77 17

media@unige.ch
www.unige.ch