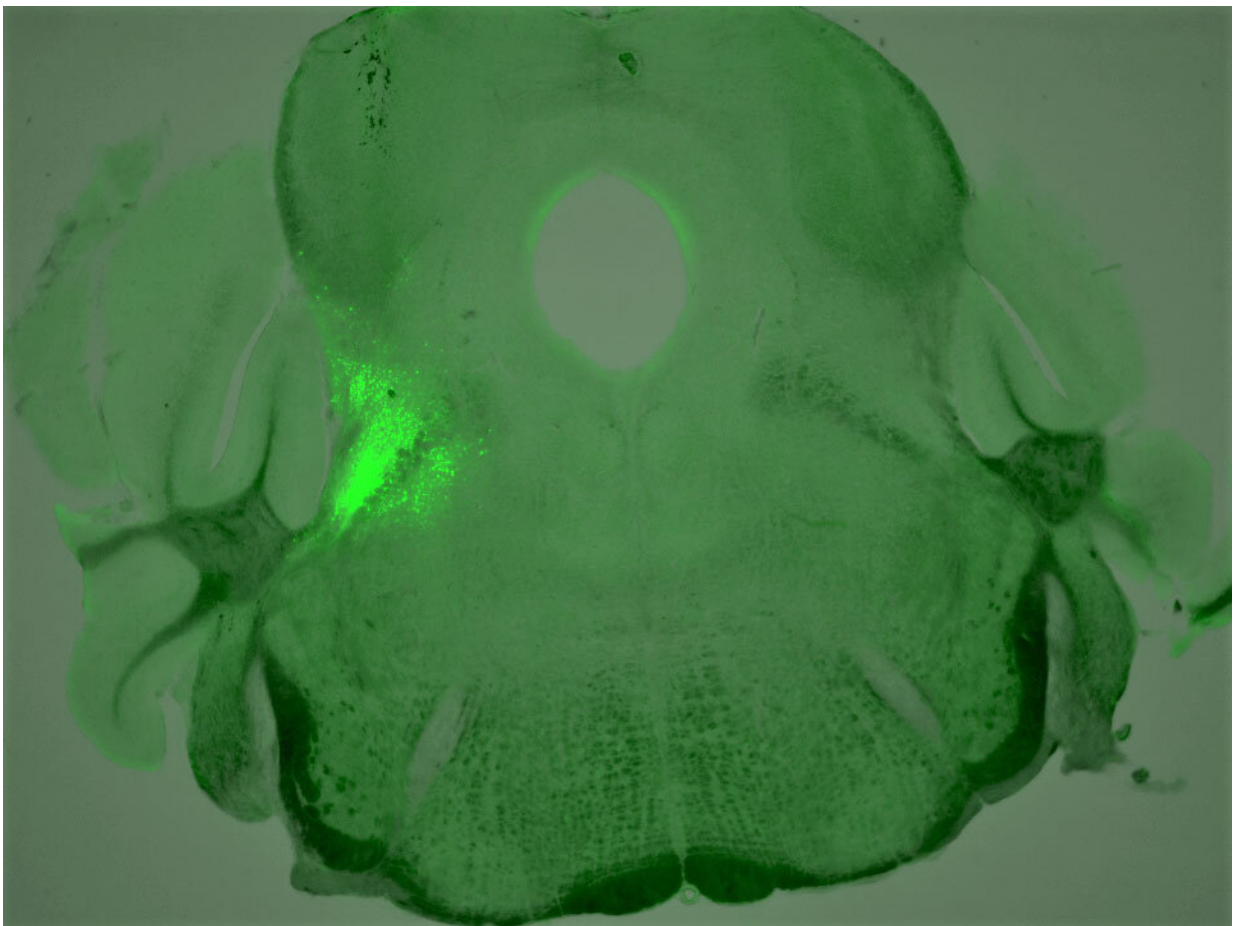


Scientists show how blocking opioid receptors in specific neurons can restore breathing during an overdose

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In this image of a mouse brain cross-section, a cluster of neurons that play a critical role in regulating breathing during an opioid overdose is highlighted in bright green. Credit: Salk Institute

It's long been known that opioid overdose deaths are caused by disrupted breathing, but the actual mechanism by which these drugs suppress respiration was not understood. Now, a new study by Salk scientists has identified a group of neurons in the brainstem that plays a key role in this process.

The findings, published June 8 in the journal *Proceedings of the National Academy of Sciences*, show how triggering specific receptors in these neurons causes opioid-induced respiratory depression, or OIRD, the disrupted breathing that causes overdose deaths. It also shows how blocking these receptors can cause OIRD to be reversed.

"The underlying mechanism of why opiates slow down and depress the breathing rhythm has not been fully characterized," says senior investigator Sung Han, assistant professor in Salk's Clayton Foundation Laboratories for Peptide Biology. "This knowledge can provide a stepping stone to better treatment options for OIRD."

The U.S. saw more than 93,000 overdose deaths in 2020, of which an estimated 60 percent were attributed to opioids like fentanyl. Opioids work by binding to proteins on [nerve cells](#) (neurons) called opioid receptors and subsequently inhibiting their activity. Currently, naloxone is the only medication known to block the effects of opioids and reverse an overdose. But naloxone has limitations, including a short duration that requires it to be administered multiple times. It also works systemically, blocking opioid receptors throughout the entire body, including those that control pain.

To develop strategies to rescue OIRD with more specificity, Han's team set out to search for the breathing neurons in the brain that also carry opioid receptors. In the new study, the researchers identified a group of neurons that express a certain type of opioid receptor (the mu opioid receptor) and are located in the brainstem breathing modulation center;

they then characterized these neurons' role in OIRD.

They found that mice that were genetically engineered to lack [opioid receptors](#) in these neurons didn't have their breathing disrupted when exposed to morphine, as mice in the [control group](#) did. The researchers also found that, without introducing opioids, stimulating these receptors in control mice caused symptoms of OIRD.

The team then looked at ways to reverse the process by treating the overdosed mice with [chemical compounds](#) targeted to other [receptors](#) on the same neurons, which play an opposite role as the [opioid](#) receptor (activating rather than inhibiting them).

"We discovered four different chemical compounds that successfully activated these [neurons](#) and brought back the breathing rate during OIRD," said first author Shijia Liu, a graduate student in the Han lab. Recovery in overdosed mice was close to 100 percent, which surprised the team.

The researchers next plan to look at whether other cell groups also play a role in OIRD. Further study would also examine the connection between breathing regulation and pain perception in the brain, potentially opening the door to developing more targeted treatments for OIRD.

"We hope to explain the pain-breathing segregation at the molecular or microcircuit level," says Han, who holds the Pioneer Fund Development Chair. "By doing that, we can try to restore [breathing](#) without touching analgesic effects of opioids."

Other authors on the study are Dong-Il Kim, Tae Gyu Oh, Gerald M. Pao, Jong-Hyun Kim, Kuo-Fen Lee and Ronald M. Evans of Salk; Richard Palmiter of the University of Washington; and Matthew R. Banghart of the University of California San Diego.

More information: Shijia Liu et al, Neural basis of opioid-induced respiratory depression and its rescue, *Proceedings of the National Academy of Sciences* (2021). [DOI: 10.1073/pnas.2022134118](https://doi.org/10.1073/pnas.2022134118)

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