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Aldo Badiani (right) at the University of Sussex, UK, discussing an electrophysiology experiment.

ADDICTION

A slippery target

To help solve the opioid epidemic, researchers must understand what makes these drugs so addictive.

BY LAUREN GRAVITZ

The latest edition of the *Diagnostic and Statistical Manual of Mental Disorders* recognizes only two types of addiction: gambling and substance-use disorders. Lumping together addictive substances into one category implies that they all affect the same neural pathways in the brain. But that might actually be wrong.

The manual lists 11 distinct diagnostic criteria for a substance-use disorder, including a strong craving for the substance, or an inability to stop or cut down on taking it. A diagnosis requires only two or more of these criteria to be met. "There are hundreds of different ways of being addicted," says Aldo Badiani, an addiction researcher at the University of Sussex in Brighton, UK. "So it doesn't stand to reason that the same mechanisms are involved in all of these different combinations."

Unified theories of drug addiction assume that the same brain circuits are involved in all substance-use disorders. But in the past decade, studies have begun to emerge that counter this narrative and suggest that alcohol addiction shouldn't be lumped in with nicotine, and that nicotine shouldn't be lumped in with cannabis or cocaine. What's more, none of those should be lumped together with addiction to opioid drugs, the most lethal of all. Only by understanding what gives opioids their unique grasp on the brain and the body can scientists begin to understand how to release that hold.

OPIOID BIOLOGY

In a similar way to other addictive substances, opioids hijack the brain's reward pathway and impair decision-making. Unlike the others, however, opioids such as morphine target their own class of cell-surface receptor with great specificity. These μ-opioid receptors are found mainly in the brain and spinal cord, but are also present in the gut, which explains why opioids can induce constipation.

One of the biggest differences between opioids and other drugs is opioids' ability to cause people who take them to develop a strong physical dependency. "The withdrawal is so intense and terrible that it promotes continued drug use," says pharmacologist Ellen Unterwald, who conducts research on substance abuse at the Lewis Katz School of Medicine at Temple University in Philadelphia, Pennsylvania. After only a few weeks of opioid use, withdrawal symptoms begin to hit users just eight hours after their last dose — something that is unique to this family of drug. "Someone who's dependent on opiates has to take them several times a day just to feel normal," Unterwald says. Otherwise, they begin to get symptoms that can include intense diarrhoea, nausea, vomiting and muscle pain. No other addictive substance takes hold with such ferocity. After these physical symptoms subside, people must also then deal with the longer-term brain changes that opioids share with other substance addictions, which can cause depression, anxiety and anhedonia — the inability to derive pleasure from life.

But the most dangerous aspect of opioids is not that they are more addictive than other drugs. Rather, researchers say, it's that they are more deadly. This is because there are different classes and concentrations of μ-opioid receptor across the body — and each area becomes tolerant of opioids at its own pace.

"Tolerance isn't a bad thing," says pharmacologist Hamid Akbarali at Virginia Commonwealth University in Richmond, Virginia. "The problem is that you develop tolerance to different effects of opioids at different rates. You develop tolerance to the pain-relieving and euphoric effects a lot faster than you do to the respiratory depression." With cocaine, death often occurs in people who haven't used the drug for a while, and then start taking it again at their habitual dose — they have lost their tolerance for the drug, which renders fatal a previously comfortable dose. Although this also happens with opioids, death can also occur as a result of the user's more tolerant reward pathway demanding more of the drug than their respiratory pathway can cope with, which causes breathing and the heart to slow or stop.

This tolerance mismatch remains poorly understood. Some of Akbarali's work implicates bacteria that live in the gut, known collectively as the gut microbiota. "Chronic opioids change the gut bacteria," he says. The drugs cause a breakdown of the epithelial barrier, which is the layer of cells that lines the digestive tract. As that layer degrades, bacteria move into the gut wall, which increases inflammation and, for reasons that are unclear, increases tolerance to opioids.

In animal models, eliminating gut bacteria seems to negate opioid tolerance, which in turn decreases reward-seeking behaviour. Akbarali and his colleagues found that when they gave opioid-tolerant mice antibiotics before administering morphine, the animals were able to withstand much more pain than they could without antibiotics[1] — their tolerance for morphine had decreased, so they felt its effects more strongly.

Anna Taylor, a pharmacologist at the University of Alberta in Canada, went one step further. When she gave antibiotics to opioid-naive mice, the animals showed symptoms similar to opioid withdrawal[2]. "Gut microbes communicate with the brain to affect brain behaviour. People have shown this in schizophrenia, depression and anxiety. Patients with these diseases have a different gut microbiome," Taylor says.

The gut is crowded with opioid receptors, which helps to explain some of the most severe symptoms of both drug use and withdrawal, she adds. Opioid use slows down the gut, causing severe constipation, whereas cessation speeds things up. And changes in gut motility affect its resident microorganisms. This confluence prompted Taylor to look at how the composition of the gut microbiota changes during opioid exposure and withdrawal[2]. "We found it changed twice: it changed when you first gave the opioid, but then it changed again when they went through a period of withdrawal."

Taylor and her colleagues refined their experiments to work out what was happening. The researchers took mice that had never been exposed to morphine and gave them antibiotics to kill their gut microbiotas. They then transplanted gut microorganisms from the faeces of mice that were undergoing morphine withdrawal. Recipient mice exhibited behaviour that was consistent with opioid withdrawal. The researchers are now trying to manipulate the gut of mice undergoing withdrawal, in an attempt to improve their symptoms.

That the human gut has many more opioid receptors than it has receptors for any other addictive drug leads Taylor to conclude that the connection between the gut microbiota and symptoms of opioid addiction and withdrawal will probably be stronger than that of other drugs. And, she notes, something as simple as tailored probiotics could be used to help treat people with opioid-use disorder.

BRAIN AND BEHAVIOUR

The environment in which users prefer to take drugs represents another crucial difference between opioids and other addictive substances, and researchers are beginning to take note. The long-held assumption that all such drugs act on the same reward pathways in the brain, Badiani says, overlooks important nuances. Both rodents and people show a preference for taking opioids in familiar living spaces[3]. Social settings, by contrast, prompt a demand for stimulants such as cocaine. "It's very difficult to think that two drugs act in the same manner when you tend to prefer one drug in one context and another drug in another," Badiani says. Delineating those differences could help to explain which brain pathways are activated by opioid use.

When people use addictive drugs outside those preferred contexts, they often experience an extreme negative reaction. The reason for this, Badiani thinks, is that there is a mismatch between the environmental setting of drug use and the drugs' actions. "The effects of drugs are broader and don't just affect the brain but the rest of the body." As an example, he points to cocaine, which not only produces euphoria but also increases users' heart rate, breathing, muscle tension and other responses that are similar to those elicited by exposure to stress[4]. At home or in a safe place, the emotional centre of a person's brain processes such effects as a mismatch between those it expects to encounter in that environment, which decreases the reward response. Opioids have the inverse effect: the drugs decrease heart rate, breathing and muscle tension, but such relaxation feels inappropriate in an intense, stimulating environment.

"The problem is that you develop tolerance to different effects of opioids at different rates."

No one has yet identified any neural circuits in the brain that are dedicated to specific drugs. For instance, all known opioid-responsive regions are also affected by cocaine. In fact, brain-imaging studies indicate a number of similarities. "Findings for addictions, across the board, were strikingly similar," says Rita Goldstein, who studies the neuroscience of addiction at the Icahn School of Medicine at Mount Sinai in New York City. By reviewing imaging studies[5], Goldstein and her colleagues found that people who were exposed to drug-related cues showed increased activation of drug-responsive brain regions and decreased activation in regions that were not. There was no difference in how the brain was activated by various addictive substances.

Under another lens, however, discrepancies between addictions to specific substances begin to emerge. Sarah Yip, a neuroscientist at Yale School of Medicine in New Haven, Connecticut, has shown that conventional imaging of single brain regions is not sensitive enough to reveal such differences. Yip has been looking at addiction in terms of whole-brain connectivity by using the brain's connectome — neural networks that stretch across regions of the brain.

She and her colleagues used functional magnetic resonance imaging to scan the brains of cocaine[6] and opioid[7] users before and after they received treatment for addiction to see how various brain regions interact with each other during reward-anticipation and cognitive tasks. Then, the researchers analysed those scans using a machine-learning approach that could identify the connections between brain regions that seemed to be responsible for specific addiction behaviours (see 'Addiction prediction').

The team found that patterns of interactions between brain regions could accurately predict who would take cocaine or opioids during treatment. More telling, she says, is that the patterns for opioids, as well as the specific brain regions that are involved, differ completely from those of cocaine. "These neural networks involve much more distributed brain regions than we ever hypothesized," Yip says. "The hope is that by identifying the connections, we could identify treatment targets."

Researchers are beginning to capitalize on these findings in their quest for potential interventions. Badiani is developing a smartphone application that encourages people who are experiencing a craving to change their environment in such a way that would reduce their desire to use drugs. "Say you're at home and, in theory, more vulnerable to relapsing to heroin. I will tell you to go out. If you're a cocaine user, maybe it would be better to stay home," he says. "It doesn't work with everybody, but it might reduce the probability of relapse." It's a start.

"Eighty per cent of opioid addicts relapse within the year, so our current methods for treating opioid addiction are pretty bad," Taylor says. "There's room for improvement — and some of that might come from better, more targeted approaches based on the understanding of the underlying neurobiology of opioid addiction." ■

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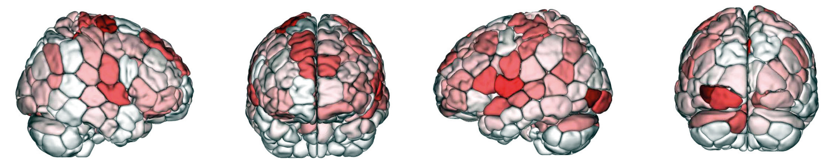
ADDICTION PREDICTION

Addiction to opioids involves neural networks in dozens of locations in the brain. Connectivity between those regions can be mapped to show which areas have more (dark red) or fewer (light red) connections in relation to abstaining from drugs. The resulting patterns can be used to predict whether someone will respond to treatment.



S. LICHENSTEIN, D. SCHEINOST, M. POTENZA, K. CARROLL & S. YIP, DATA IN PREPARATION. IMAGES GENERATED USING BIOIMAGE SUITE; BIOIMAGESUITE.ORG

CORRECTION

This article (*Nature* **573**, S20–S21; 2019) mischaracterized the differences in causes of death between cocaine and opioid users.