

## WHAT WORMS CAN TELL US ABOUT COCAINE

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Cocaine is an illegal and addictive drug. It causes addiction by hijacking small molecules called chemical messengers that the cells in the brain use to communicate and work together. Most scientists have studied how cocaine affects three chemical messengers, called serotonin, dopamine, and norepinephrine, but cocaine may also affect a fourth chemical messenger called acetylcholine. To understand whether cocaine affects acetylcholine, we used the egg-laying “brain” of small worms to determine how cocaine works in humans. We found that cocaine makes these worms lay eggs, but only when the acetylcholine message is working properly. This tells us that cocaine acts in part through acetylcholine. Our study provides a first step in understanding the interaction between cocaine and acetylcholine. Treatments for cocaine addiction depend on our understanding of how the drug works, so learning how cocaine affects acetylcholine could lead to the development of effective treatments for cocaine addiction.

## COCAINE ADDICTION

Drug addiction is a medical condition in which people cannot stop using drugs despite negative consequences, such as poor physical or mental health, financial problems, or unstable relationships [1]. People can become addicted to legal drugs, such as the alcohol in beer, wine, and spirits, or the nicotine in cigarettes and vapes. People can also become addicted to illegal drugs such as cocaine. The causes of cocaine addiction are complex and scientists want to better understand how cocaine acts on the brain, so they can develop more effective treatments for addiction [2]. Use of cocaine and other drugs can change the levels of substances in the brain called **chemical messengers**, and these changes in chemical messengers are an important part of what leads to addiction.

## CHEMICAL MESSENGERS IN THE BRAIN

The brain is made up of microscopic, interconnected cells called **neurons**. The job of neurons is to communicate with each other so that the brain can function properly [3]. Working together, these neurons direct our thoughts, our senses, and our movements. Neurons talk to other neurons by sending out chemical messengers.

The process of sending chemical messengers between neurons can be broken down into four steps that are kind of like sending a snap on Snapchat (Figure 1). First, just like sending a snap requires taking a picture, the neuron must make the chemical messenger. Second, the neuron must release the chemical messenger, which is like sending the snap from your phone. Third, another neuron receives the chemical messenger by capturing it with a special protein on its surface called a receptor. This step is similar to your friend's Snapchat receiving your snap, so that your friend can open it. Finally, just like your friend's Snapchat automatically deletes your snap, the neuron that received the message eventually destroys the chemical messenger.

## COCAINE AND THE CHEMICAL MESSENGER ACETYLCHOLINE

One reason scientists care so much about chemical messengers is that these messengers play an important role in addiction to dangerous drugs like cocaine [2]. Researchers have found that cocaine affects the brain by increasing the amounts of three of its chemical messengers, called dopamine, serotonin, and norepinephrine. There is additional evidence, however, that cocaine may affect a fourth chemical messenger called **acetylcholine** [4]. Acetylcholine plays an important role in several major parts of addiction, including motivation (such as the motivation to seek out drugs) and attention (such as the attention placed on opportunities to use drugs). Studying how cocaine might affect acetylcholine could one day help scientists

### CHEMICAL MESSENGERS

Chemicals that neurons send to each other to communicate.

### NEURONS

Small, interconnected cells that make up the brain. Neurons are specialized to send information to each other.

### ACETYLCHOLINE

A chemical messenger that neurons use to produce motivation and attention.

### Figure 1

Neurons communicating via chemical messengers can be compared to sending a snap. **(A)** Production of chemical messengers (red circles) by the neuron is like taking a Snapchat photo. **(B)** Release of chemical messengers is like sending a snap. **(C)** Capture of chemical messengers by the other neuron is like your friend receiving a snap. **(D)** Eventual destruction of chemical messengers is like the automatic deletion of a snap.

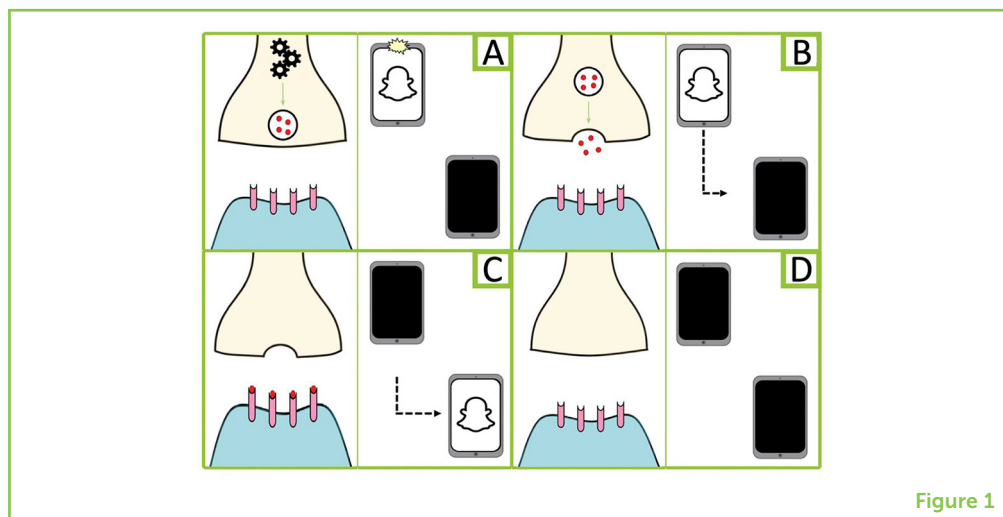


Figure 1

understand and treat cocaine addiction, but cocaine's possible effects on acetylcholine are not yet fully understood.

### WHY STUDY THE EFFECT OF COCAINE ON WORMS?

Studying effect of cocaine on acetylcholine with human participants would take a long time, would be very expensive, and would be hard to do safely, so we need another way to know if cocaine affects acetylcholine. There is a small worm called *Caenorhabditis elegans*, and even though it does not look much like a human, it has neurons that work very similarly to those of humans. Some of the worms' neurons use acetylcholine to communicate with each other, like human neurons do, so these worms provide an efficient **model** for human neurons.

In fact, worms are a particularly good model because we can observe whether cocaine is affecting their neurons without needing a fancy microscope. Because neurons control behavior, we can observe changes to neuronal activity by looking at changes in worm behavior. Specifically, we chose to study the effect of cocaine on the egg-laying behavior of worms because egg laying is controlled by a very small "brain" that uses acetylcholine messages [5]. Since the neurons and chemical messengers involved in worm egg laying are very similar to those in humans, we can use the egg laying "brain" as a model for how cocaine affects neurons in people.

### COCAINE AND ACETYLCHOLINE INTERACT TO CAUSE WORM EGG LAYING

In our first experiment, we investigated how cocaine affects worm egg laying. To do so, we put hundreds of worms in tiny baths of cocaine or sugar water (sugar does not affect egg laying) and let them swim in the baths for 1 h (Figure 2). We found that the worms in cocaine baths

### MODEL

A simplified version of a complicated scientific problem that helps scientists study that problem more easily, or without causing harm to people.

laid about six eggs, while those in sugar water rarely laid any eggs. This experiment showed us that cocaine causes worms to lay eggs.

### Figure 2

In our first experiment, we tested the effect of cocaine on worm egg laying. The worms were placed in either sugar water baths or cocaine baths for 1 h. During that time, the worms in cocaine baths laid about 6 eggs each, whereas the ones in sugar water almost never laid eggs. This tells us that cocaine causes worms to lay eggs.

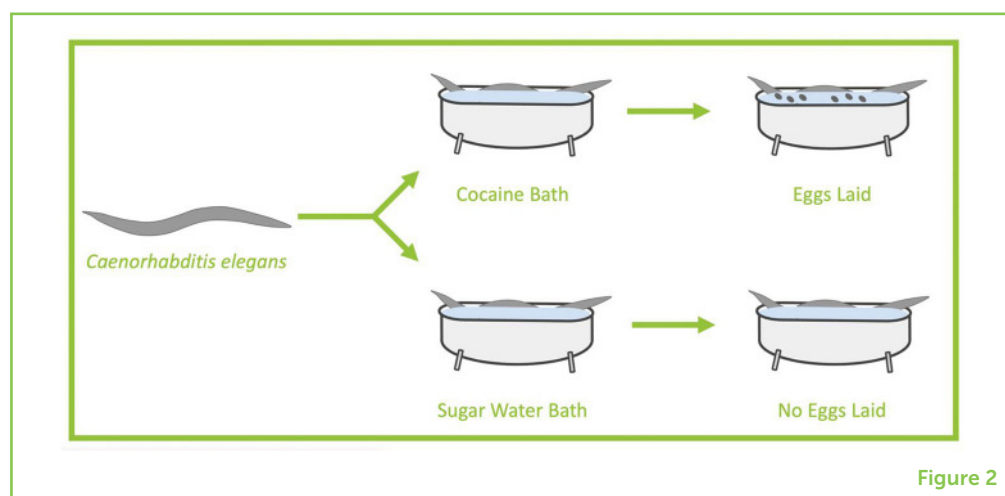


Figure 2

### KNOCKOUT EXPERIMENT

Removing an important piece of a system or organism to figure out what that piece normally does.

### HYPOTHESIS

A possible explanation for something that happens in the world. It is typically the starting point for scientific research.

Next, we checked whether acetylcholine is *necessary* for cocaine to cause worms to lay eggs. To do this, we used a series of **knockout experiments**. In this type of experiment, we take something away from an animal to see what that thing normally does. Imagine you want to find out what the strings on a tennis racket normally do. You have a **hypothesis**, or scientific guess, that they are involved in hitting a ball. To test your hypothesis, you could cut or “knock out” the racket’s strings. If you tried to hit a ball with this racket, you would soon realize that, without good strings, you cannot properly hit the ball—so the strings must be important for hitting a tennis ball. In our knockout experiments, rather than damaging the strings on a tennis racket to see how they normally interact with a tennis ball, we damaged the worms’ acetylcholine communication, to see how it normally interacts with cocaine (Figure 3).

For our second experiment, we again put hundreds of worms in tiny baths of cocaine or sugar water, but this time, some of the worms were “knockouts,” missing the proteins needed to do one of the four steps of sending acetylcholine messages. We found that all worms lacking proper acetylcholine signaling laid fewer eggs in the cocaine baths compared to normal worms in cocaine baths. This suggests that acetylcholine signaling is needed for cocaine to produce egg laying. Understanding this interaction between cocaine and acetylcholine in worms may help us better understand the interaction of cocaine and acetylcholine in the human brain as well.

### OUR FINDINGS COULD HELP COCAINE ADDICTION RESEARCH

Effective treatments for cocaine addiction have not been developed because scientists still do not fully understand how cocaine affects the chemical messengers in the human brain [2, 6]. The role of the

### Figure 3

In our second experiment, we tested cocaine's interaction with acetylcholine. This can be compared to testing a tennis ball's interaction with racket strings. The example hypothesis is that the strings interact with the ball to produce a great shot. We could confirm this hypothesis by showing that, without strings, there is no great shot. Our actual hypothesis was that acetylcholine interacts with cocaine to cause egg laying. We confirmed our hypothesis by "knocking out" acetylcholine and showing that the acetylcholine message is in fact needed for cocaine to cause egg laying.

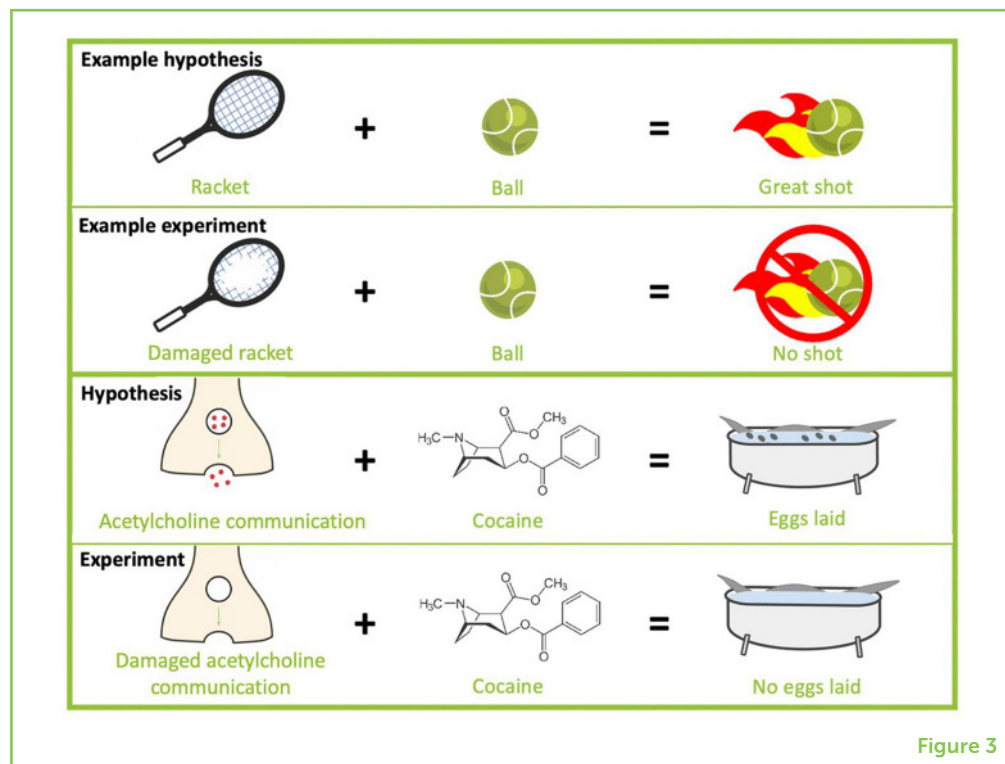


Figure 3

chemical messenger acetylcholine in cocaine addiction particularly needs more study [4]. In our experiments, we used the egg laying "brain" of small worms as a model for how cocaine affects acetylcholine, and our experiments showed that cocaine changes acetylcholine messages.

Our use of the worm egg laying "brain" establishes a new model to investigate how cocaine affects acetylcholine. Our finding that cocaine interacts with acetylcholine could contribute to the development of new treatments for cocaine addiction. Scientists have tried to develop cocaine addiction treatments that block other chemical messengers, including serotonin, dopamine, and norepinephrine, but these treatments have not been very effective [6]. It is possible that blocking cocaine's effect on acetylcholine could be a new way to treat cocaine addiction, which is currently an undertreated condition that affects many people.

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## ORIGINAL SOURCE ARTICLE

Emerson, S., Hay, M., Smith, M., Granger, R., Blauch, D., Snyder, N., et al. 2021. Acetylcholine signaling genes are required for cocaine-stimulated egg laying in *Caenorhabditis elegans*. *G3*. 11:jkab14. doi: 10.1093/g3journal/jkab143

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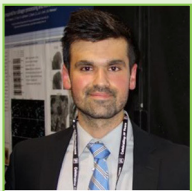
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I play chess competitively and I am on a rock climbing team. My favorite subject in school is physics. When I can not be outside with my dog I like to play drums.

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