Science Education Collection

Self-administration Studies

URL: https://www.jove.com/science-education/5427

Abstract

Behavioral reinforcement induced by the rewarding feelings following substance use sometimes leads to addiction, which is demonstrated by increased self-administration. Drug self-administration studies in rodents model human behavior during drug abuse. These models are useful in understanding the neurobiological behavior of addiction in order to help scientists discover new treatments for drug dependence.

This video reviews the concepts underlying self-administration studies. A general protocol of self-administration is discussed, which includes description of necessary equipment and different routes of administration commonly employed. Some modified protocols used to model more complex aspects of addiction, such as progressive ratio schedule and extinction, are also explained. Finally, experiments conducted in current addiction research labs will be examined.

Transcript

Drug self-administration studies in rodents model human behavior of reward seeking and addiction. Compulsive drug-taking behavior is a major societal concern, and therefore scientists are trying to decode the neurobiology underlying drug dependence and addiction. Rodents' responses to addictive drugs are similar to humans, and they demonstrate many of the hallmarks of addictive behavior, such as withdrawal and increased self-administration.

This video will cover some of the concepts underlying self-administration studies, review a basic experimental protocol, and look at some experiments being conducted in addiction labs today.

Let's start by discussing what is currently known about addiction, and how self-administration in rodents can be used to study this behavioral phenomenon.

Drug-taking behavior is often initiated and continued because of the substance-induced feelings of pleasure mediated by brain reward pathways. The major reward pathway is dopaminergic, and runs from the ventral tegmental area to the nucleus accumbens. Additionally, the amygdala, pre-frontal cortex and hippocampus are also activated in response to a reward. They are suggested to be involved in drug-related emotional processing, planning, and memory.

The behavioral reinforcement induced by these rewarding feelings often leads to addiction, demonstrated by increased self-administration. Rodents can be trained to self-administer using the operant chamber, where a lever press can be rewarded with a drug infusion. Animals often learn to associate the behavior with the reward, and this learning can be used to test addiction potential of compounds.

Now that you have learned about addiction, let's look at a general self-administration protocol.

As mentioned before, drug self-administration studies are performed in an operant conditioning box. To limit external stimuli, the box is housed inside a sound-attenuating chamber. Various components, such as cue lights, speakers and a home light, can be used as part of the experimental setup. Typically, two levers are available in the box, one "active" that triggers reward delivery, and the other "inactive" that provides no response.

Determining the route of drug administration is a critical first step. Intravenous administration is the most common method because this route provides rapid uptake and near immediate induction of reward. It also mimics the most common way of administering narcotic drugs in humans. Another commonly used route is intracranial, which also leads to rapid drug effects and can be used to target specific brain regions. Insertion of the drug catheter for both the above-mentioned routes must be performed in such a way that the animal can still move freely. For drugs like alcohol, oral methods of administration have also been employed.

Self-administration studies typically involve an acquisition paradigm. One example of this paradigm can involve food-deprivation for 20-24 hours followed by training sessions. During these sessions, the animal is placed in the box, where it receives food pellets in response to pressing the "active" lever. This action can be accompanied by activation of a cue light, which signals a time-out period where no food is delivered, irrespective of active lever pressing. Food is typically delivered on a fixed-ratio one or "FR1" schedule, which simply means that one lever press results in reward delivery. During the acquisition phase, the number of active lever presses should rise with each session before stabilizing, and training is considered complete once this equilibrium is reached.

For drug self administration, surgeries are often performed that typically allow for intravenous infusion of a drug like cocaine. Once the animal has recovered and is allowed to acclimatize to the testing environment the total active and inactive lever responses are recorded during a testing session, in which a 3 second infusion of cocaine is delivered after an active lever press. A time-out period similar to the one described in the acquisition session for food is employed here to prevent animal overdosing. Just as before, training is considered complete when active lever presses for infusions are seen to plateau.

Now that we've reviewed a general self-administration protocol, let's look at some modified protocols used to model more complex properties of addiction.

For example, instead of testing on an FR1 schedule, scientists test animals on a progressive ratio schedule. This requires increasing numbers of lever presses for reinforcement, which means first the reward is delivered after one active lever press, but the second time, the reward is delivered after two lever presses. The third time requires four lever presses, and so on, until the animal reaches a break-point, which is defined as the number

of active lever presses at which time the animal gives up and ceases self-administration. The breakpoint is known to correlate with the reinforcing strength of a drug.

Another modified protocol involves second-order schedules, which builds on fixed or progressive ratios schedules. These experimental paradigms include a pairing of a second-set of cues, such as light, sound, or both with drug delivery, and then study the animal's response following presentation of the cue. This type of schedule can model how environmental cues affect drug-seeking behavior.

Lastly, scientists use extinction and reinstatement schedules to model relapse behaviors. Here, the acquisition step is performed using drug as the reward. This is followed by extinction training, where all variables remain the same, but drug delivery is discontinued following active lever pressing. This eventually leads to the "extinction" of the trained lever-pressing behavior. Relapse can then be studied following administration of a "priming" dose of the addictive compound, followed by examination of active lever responses during the reinstatement session.

After looking at how self-administration studies are performed, let's see how they are being applied in the field today.

Scientists study various behaviors that occur with increased drug self-administration. Here, scientists examine vocalization, which is an indicator of emotional response during cocaine self-administration. By using special ultrasonic microphones, researchers demonstrated correlation between vocalization and cocaine administration.

Drug-taking behavior is often associated with environmental cues stored in an animal's memory. Here, researchers use the conditioned place preference test combined with cocaine self-administration to test memory associated with drug taking. Animals were conditioned by performing cocaine self-administration in one environment and saline self-administration in another. Testing involved animals freely exploring both chambers, followed by evaluation of environmental preference.

Finally, scientists are interested in identifying factors that affect relapse. In this study, researchers examined the effect of food restriction on heroin relapse. For 14 days after acquisition with heroin, one group of rats was given free access to food, while another group was fed a food-restricted diet. Then, animals were tested for heroin seeking. The results of this experiment demonstrate that food-restricted rats showed greater heroin seeking behavior.

You've just watched JoVE's video on drug self-administration studies. This technique allows researchers to study behavior and neurobiology associated with reward seeking in humans, and scientists can adapt this protocol in numerous ways to understand different facets of addiction. As always, thanks for watching!