

The relationship between dopamine and cocaine seeking

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Abstract

Dopamine levels in the brain appear to have a direct link to cocaine addiction because dopamine levels increase rapidly and substantially when cocaine is consumed (consummatory phase). It is unknown whether dopamine is involved in cocaine seeking (appetitive phase). To investigate the role of dopamine to cocaine seeking, a rat conditioned to self-administer was fitted with a stimulating electrode, a reference electrode, a microsensor, a canula, and a wireless telemetry pack. Once activated, the pack transmitted dopamine levels while the rat moved freely in the experiment area. When the rat pressed the bar, it received a cocaine reward for 6 seconds through the canula from the telemetry pack. Audio-visual cues were presented for 20 seconds following a bar press. A rapid and substantial increase in dopamine concentration was observed approximately 30 seconds after the rat received the cocaine reward (consummatory phase). Approximately 5 seconds before a bar press, there was a small increase in dopamine levels, followed by a large and rapid increase that occurred just before and following a bar press (appetitive phase). These findings support the hypothesis that dopamine is involved in cocaine seeking.

Introduction

Drug addiction, like sexual behavior, is a kind of motivated behavior. There are two phases of motivated behavior. During the appetitive phase, motivated behavior consists of those behaviors related to “approaching” the goal. The consummatory phase of motivated behavior represents the actual “consuming” of the goal. This experiment will investigate how cocaine acts on dopamine in the brain of a rat seeking and then consuming cocaine.

Cocaine is a drug of abuse. It is an artificial reward because cocaine supports conditioned placed preference and will be self-administered by a rat.

What role does dopamine play in the neurobiology of cocaine use in rats? It is known that when cocaine is consumed (consummatory phase), it blocks dopamine transporters in the nucleus accumbens, which

causes a rapid and substantial increase in dopamine levels. What is unknown is whether dopamine plays a role when a rat is engaged in cocaine seeking behavior (appetitive phase). The hypothesis being tested in this experiment is this: *Dopamine is involved in cocaine-seeking behavior*. If dopamine is involved in cocaine-seeking behavior, we predict that dopamine levels will increase prior to the rat pressing the bar. And if dopamine is involved in cocaine-seeking behavior, then dopamine may hold the key to understanding the neurobiology of persistent drug addiction.

Methodology

The rats involved in this study had already been trained to self-administer cocaine. Fast-scan cyclic voltammetry was chosen as the best method for measuring dopamine levels during both the appetitive and consummatory phases of cocaine-

seeking behavior. This method requires performing surgery on a rat to implant the electrodes that are necessary for measuring dopamine levels.

To prepare an animal for surgery, a rat was selected and weighed. The anesthesia was a pre-mixed cocktail of ketamine and xylazine, a common anesthetic of laboratory rodents. The correct amount of anesthesia to administer was 1ml/kg (e.g., .3 ml for a 300g rat). The anesthesia was injected into the peritoneal cavity. The anesthetized rat was then placed on a heating pad, its scalp was prepared for surgery, a canula was implanted into the jugular vein, and then it was secured in the stereotaxic apparatus.

Three holes were drilled through the skull – one for each of the three electrodes. Three additional holes were drilled into the skull. A surgical screw was inserted into each of those holes (to act as anchors for the cement cap). Using a manipulator arm on the stereotaxic apparatus, a reference electrode was lowered into the superficial cortex through the left anterior hole, and then a hub for the sensing electrode was inserted into the right anterior hole. After cementing both the reference electrode and the hub to the skull, the reference electrode was connected to recording equipment. A microdrive armed with a sensing electrode was secured in the hub and the sensing electrode was connected to recording equipment. The sensing electrode was then lowered into the nucleus accumbens. A stimulating electrode was lowered into the remaining hole using a manipulator arm. After being

connected to stimulating equipment, a train of pulses was sent through the stimulating electrode. It was lowered incrementally until the sensing electrode in the nucleus accumbens recorded a dopamine signal. Once it was, the stimulating electrode and the remainder of the skull were cemented. The animal was released from the stereotaxic apparatus, placed in postoperative care on the heating pad, then returned to its housing for recovery.

After it had recovered from surgery, the rat was used to test dopamine levels during cocaine seeking and consumption.

To prepare the rat for the experiment, the telemetry pack was loaded with cocaine and the canula tube was connected to the wireless cocaine administration equipment in the telemetry pack. A microdrive armed with a sensing electrode was secured to the hub, then the sensing electrode was connected to the wireless transmitting equipment. The telemetry pack was secured to the rat and the rat was then placed in a cage attached to a bar-press machine. The cage contained a light bulb for the visual cue and a speaker for the audio cue. All the equipment was checked. To initiate the session and to record the data, the researchers turned on the bar press machine. When the rat pressed the bar, it received a cocaine reward for 6 seconds and the audio-visual cues were presented for 20 seconds. The monitor displayed 10 seconds of data. The data included the dopamine level, whether the cocaine was being administered, and whether the audio-visual cues were being presented. The researchers

collected data for 10 minutes. They observed the relationship between the rat's cocaine-seeking behavior (bar presses) and dopamine levels, as well as the relationship between the dopamine levels, cocaine release, and the audio-visual cues.

Data, Analysis, and Conclusion

From the data, the researchers found that dopamine levels rise very rapidly and substantially approximately 36 seconds after a bar press and 30 seconds after the cocaine reward was administered (see **Figure 1**).

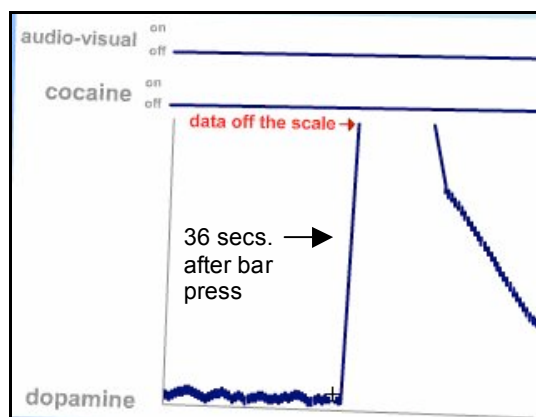


Fig. 1: The magnitude of the spike was so substantial that its apex could not be recorded. Dopamine levels returned to normal after a rapid then gradual decrease over approximately 10 seconds.

These findings are consistent with other studies where it was shown that dopamine levels increase rapidly and substantially when cocaine is consumed (consummatory phase). The researchers conclude that this substantial spike is caused by cocaine arriving in the nucleus accumbens, blocking dopamine transporters.

From the data, the researchers found that approximately 5 seconds

before a bar press, there was a small increase and then decrease in dopamine levels. This was followed by a large and rapid increase that occurred just before and following a bar press (see **Figure 2**).

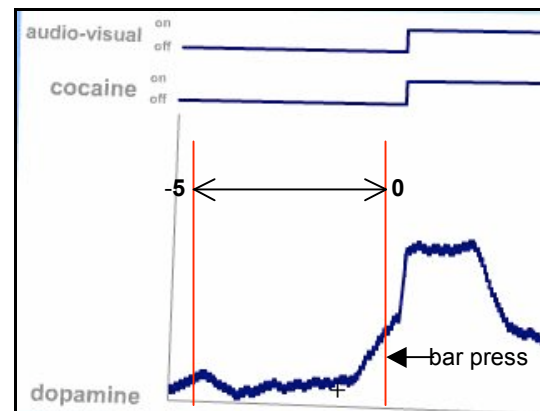


Fig. 2: At approximately 5 seconds before a bar press, there is a small increase in dopamine levels. Dopamine levels increased gradually until approximately 2 seconds before a bar press, then there was a rapid and large increase that peaked for approximately 3 seconds, and then decreased. Dopamine levels returned to normal approximately 10 seconds after a bar press.

Because dopamine levels rise before the rat receives its cocaine reward but while engaged in cocaine seeking behavior, the data supports our hypothesis that dopamine plays a role in cocaine seeking (appetitive phase). Why might this occur? The researchers conjecture that before the cocaine-addicted rat receives cocaine, it "thinks" about its need for cocaine. When the rat anticipated receiving it by pressing the bar, dopamine levels increased.

Thus, by observing dopamine levels and cocaine seeking behavior, the brain of a cocaine-addicted rat responds not only to the physical presence of cocaine in the brain, it

also responds to the activity of cocaine seeking.

Rat brains are similar to human brains. Since the brain of a cocaine-addicted rat responds not only to the physical presence of cocaine in its brain but also to the activity of cocaine seeking, it is possible that the brain of a human cocaine addict will react to cocaine-seeking behavior with a spike in dopamine levels. If so, then breaking the

addiction to cocaine will be more difficult for addicts who spend time in activities and locations associated with past “cocaine seeking” behavior.

Future experiments will include working with more rats, comparing these findings to rats not trained to self-administer cocaine, and exploring any possible relation between audio-visual cues and dopamine levels.

References

Phillips, P. E., G. D. Stuber, M. L. V. Helen, R. M. Wightman, & R. M. Carelli (2003): Subsecond dopamine release promotes cocaine seeking. **Nature**. Vol 422 (April): 614-618.