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Cocaine-induced behavioral sensitization and conditioning in male Japanese quail

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Abstract

Repeated intermittent cocaine treatment often results in behavioral sensitization or an augmented response to cocaine. Cocaine-induced behavioral sensitization may be an important contributor to cocaine addiction and abuse. Some studies have also shown that conditioned drug effects may play a role in behavioral sensitization. The current experiment utilized a simplified discrimination paradigm to investigate behavioral sensitization and the role of conditioning in an avian species. Male Japanese quail received alternating injections of cocaine (10 mg/kg ip) paired with a context and saline injections paired with a different context. They were later given a cocaine challenge followed by and a saline challenge in the drug-paired context. Results showed that birds that received cocaine paired with one context also demonstrated behavioral sensitization to a cocaine challenge given after a withdrawal period and they developed conditioning to the drug-paired context. A saline control and a control group that received cocaine that was not paired with the test context failed to demonstrate sensitization or conditioning. The findings demonstrate visual discrimination learning and implicate the role of Pavlovian conditioning in behavioral sensitization.
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Chronic pre-exposure to cocaine may lead to a progressive and enduring enhancement of a motor stimulant effect, a phenomenon referred to as behavioral sensitization (e.g., Kalivas et al., 1998; Robinson and Berridge, 2001). Sensitization refers to the augmentation of a behavioral response to drugs of abuse that occurs with repeated administration and persists long after drug use is discontinued (e.g., Robinson and Becker, 1986). It is considered to be an important contributor to the addictive potency of cocaine (Robinson and Berridge, 1993). Cocaine-induced behavioral sensitization has been well documented in rats (e.g., Kalivas and Duffy, 1993; Post and Rose, 1976). Although less well documented, studies with avian species have demonstrated similar results. Hughes and McCormick (1993) found a dose-dependent increase in cocaine-induced locomotor activity and vocalizations in cockerels. More recent studies with Japanese quail have also demonstrated cocaine behavioral sensitization (Levens and Akins, 2001, 2004), including similar dose-dependent and temporal effects as those found in rodents (Geary and Akins, 2007).

Pavlovian conditioned drug effects appear to play an important role in behavioral sensitization. A number of studies have demonstrated the importance of conditioning in the development and expression of sensitization (Hinson and Poulos, 1981; Keller et al., 2002; Pert et al., 1990; Siegel et al., 1987; Wynne and Delius, 1995). The findings of these experiments indicate that when drugs are administered in association with a unique environment, contextual cues acquire the properties of a conditioned stimulus (CS), with the drug acting as the unconditioned stimulus (US). After pairing of the CS with the US, the CS (context) alone comes to elicit drug-like effects. When drugs serve as the US, the conditioned response resembles the unconditioned response, the drug-like response (Anagnostaras and Robinson, 1996; Hiroi and White, 1989; see

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also Martin-Iverson and Fawcett, 1996 for review). Several studies have demonstrated context specific conditioned locomotor activity to drugs (Beninger and Hahn, 1983; Hinson and Poulos, 1981; Levens and Akins, 2004; Post et al., 1981; Weiss et al., 1989).

The present experiment utilized a simplified drug discrimination procedure to assess behavioral sensitization and contextual conditioning. A typical drug discrimination procedure involves the use of an interoceptive drug cue to signal or "set the occasion" for when a CS will be reinforced (positive feature) or the use of the absence of a drug cue to signal or "set the occasion" for when that CS will not be reinforced (negative feature) (e.g., Holland, 1983; Rescorla, 1993). Previous research has shown that drugs can serve as positive features (Palmatier et al., 2004, 2005; Palmatier and Bevins, 2007) or negative features (Troisi and Akins, 2004; Bevins et al., 2006). The present experiment does not involve using the drug cue as an occasion setter but rather context appears to function as the CS and the cocaine drug state as the US.

The present experiment utilized an avian model to study discriminative learning and the role of Pavlovian conditioning in behavioral sensitization. The use of avian models to investigate drug effects may have additional relevance to human drug abuse because these studies involve using visual cues that may become conditioned to later elicit craving. Several studies have demonstrated that drug cues may become associated with a drug state through Pavlovian conditioning and that, in the absence of the drug, these cues may come to elicit conditioned physiological and subjective responses. These responses may initiate craving and trigger relapse (Childress et al., 1986, 1999; O'Brien et al., 1988).

In the present experiment, male Japanese quail were given alternating injections of cocaine in a chamber with distinct visual cues and saline in another. One control group received alternating injections of saline in each distinct chamber and another control group received alternating injections of cocaine and saline in their home cage. Later a cocaine challenge and a saline challenge were administered to assess cocaine sensitization and conditioning, respectively.

1. Methods

1.1. Subjects

Twenty male Japanese quail (*Coturnix japonica*) approximately 6–12 months old served as subjects. Quail was hatched (from eggs purchased from GQF Manufacturing; Savannah, GA) and raised at the University of Kentucky. After hatching, chicks were housed together in a heated brooder until sexual differentiation, 28–30 days posthatch. After sexual differentiation, males were individually housed in metal cages (50.8 × 25.4 × 21.4 cm). The birds were maintained on a 16:8 light/dark schedule with food and water available ad libitum. The experimental protocol for this experiment was approved by the University of Kentucky IACUC for the use of animal subjects and the procedures are in compliance with NIH "Guide for Care and Use of Laboratory Animals".

1.2. Apparatus

Sixteen standard locomotor activity chambers (28.6 long cm × 21.2 wide cm × 21.2 cm deep; Med Associates; Georgia, VT) were used to quantify locomotor activity. All chambers had wire mesh floors covered with brown paper and clear plastic ceilings. Half of the chambers had green and yellow alternating stripes on the walls (the colored context) and the other half had white walls (the white context). Thus, the two chambers were distinct. Each chamber had six photobeams that were approximately 6.4 cm apart and 3.2 cm above the floor. A Med Associates program (Georgia, VT) was used to collect photobeam breaks in 5 min increments.

1.3. Drugs

Cocaine hydrochloride (National Institute for Drug Abuse; Bethesda, MA), was mixed with saline (0.9% NaCl) at a volume of 3 ml/kg. (This volume was chosen to better control the precision of mixing and injecting since Japanese quail weigh less than rodents.) Cocaine was injected intraperitoneally (ip) at a dose of 20 mg/kg.

2. Procedure

Birds were randomly assigned to one of three groups: Paired Cocaine (PC), Saline (S), and Unpaired Cocaine (UC), with *n*s of 7, 6, and 7, respectively, and the experiment was conducted in two replications. Birds were given 1 day of habituation during which they were exposed to a white and a green and yellow striped context for 30 min each. Presentation of white and striped contexts was counterbalanced within each group. During discrimination training, group PC received alternating injections of cocaine and saline in either the striped or white context. Cocaine was paired with one of the contexts throughout training. Treatment was counterbalanced with context such that half of the birds received cocaine paired with the striped context and the other half had cocaine paired with the white context. Group S received the same treatment as group PC but was injected with saline and placed in the white context on alternating days with the striped context. The UC group received no injection prior to each locomotor session, but received alternating days of cocaine and saline administration in their home cage 2 h after the locomotor session. The purpose of this group was to determine whether cocaine injections in the home cage would result in sensitization to a cocaine challenge given in a context that was never paired with cocaine. Each session was 60 min. A total of 20 injections were given, one per day for 20 days. Photobeam breaks were collected for all groups during the locomotor sessions.

Following discrimination training, birds remained in their home cages for a 14-day withdrawal period. A cocaine challenge (10 mg/kg ip) was given to all groups. Group PC received the cocaine challenge in their previously trained cocaine-paired context. Half of groups UC and S received cocaine in one context and the other half in the other context. The challenge dose was half of the original training dose

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