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Blocking of conditioning to a cocaine-paired stimulus: Testing the hypothesis that cocaine perpetually produces a signal of larger-than-expected reward

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Abstract

According to a recent account of addiction, dopaminergic effects of drugs like cocaine mimic the neuronal signal that occurs when a natural reward has a larger value than expected. Consequently, the drug's expected reward value increases with each administration, leading to an over-selection of drug-seeking behavior. One prediction of this hypothesis is that the blocking effect, a cornerstone of contemporary learning theory, should not occur with drug reinforcers. To test this prediction, two groups of rats were trained to self-administer cocaine with a nose-poking response. For 5 sessions, a tone was paired with each self-administered injection (blocking group), or no stimulus was paired with injection (non-blocking group). Then, in both groups, the tone and a light were both paired with each injection for 5 sessions. In subsequent testing, the light functioned as a conditioned reinforcer for a new response (lever-pressing) in the non-blocking group, but not the blocking group. Thus, contrary to prediction, pre-training with the tone blocked conditioning to the light. Although these results fail to support a potentially powerful explanation of addiction, they are consistent with the fact that most conditioning and learning phenomena that occur with non-drug reinforcers can also be demonstrated with drug reinforcers.
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Redish (2004) recently proposed an account of drug addiction based on the hypothesis (Schultz, 1998; Schultz and Dickinson, 2000; Waelti et al., 2001) that dopamine neurons signal when a reward is stronger than expected. According to this hypothesis, after a certain amount of experience with a conventional reinforcer (e.g., food or water), the expected reward value comes to equal the obtained value, and no further signal is generated. However, drugs of abuse have dopaminergic effects that might mimic this signal. Thus, the drug's effects might continue to be interpreted as a signal of a larger-than-expected reward, leading to an "over-selection" of drug-seeking behavior.

A testable prediction of this hypothesis is that the phenomenon of blocking (Kamin, 1969) should not occur with drug reinforcers. Blocking is a cornerstone of associative theories of conditioning and learning (Mackintosh, 1975; Pearce and Hall, 1980; Rescorla and Wagner, 1972). In the typical blocking procedure, a tone is paired with a reinforcer, such as food. Later, the tone and a light are presented in compound and paired with food. Finally, the light is presented alone to measure its effectiveness as a conditioned stimulus. The usual finding with this procedure is that conditioning to the light is attenuated relative to a control group that only received pairings of food with the compound stimulus. Thus, the tone blocks conditioning to the light because the light is redundant, providing no new information about reinforcement.

With cocaine instead of food as the reinforcer, Redish (2004) predicts that each presentation would be interpreted as a larger-than-expected reward, so blocking would not occur. To test this prediction, we modified the conditioned-reinforcement procedure of DiCiano and Everitt (2004) for use in a blocking design. Thus, self-administered cocaine was initially paired with a tone

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in the blocking group, but not in the non-blocking control group. Then, cocaine was paired with a tone-light compound stimulus in both groups. Following this training, we measured the conditioned-reinforcing effects of the light by presenting it contingent on a new response.

1. Method

1.1. Subjects

Seventeen experimentally-naive, male, Sprague–Dawley rats (Charles River Laboratories, Wilmington, MA), weighing approximately 350–400 g, were individually housed with free access to water. Food was restricted to approximately 15 g/day to maintain stable body weights. Although food restriction can influence the rewarding effects of cocaine and increase dopamine function in reward-related brain areas (Carr, 2002; LeSage et al., 1999), this effect should not have influenced the blocking effect because restriction was consistent across phases of the experiment and should not have affected the groups differentially. Lights in the cage room were on from 1800–0600 h (reversed light cycle), and experiments were conducted between 0900–1500 h. At least 3 days before the beginning of training, each rat was implanted with a catheter in the right external jugular vein under ketamine (60 mg/kg, i.p.) and xylazine (8 mg/kg, i.p) anesthesia (for details of surgical procedure, see Panlilio et al., 1996). The facilities were fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, and all procedures were approved by the Institutional Animal Care and Use Committee of the Intramural Research Program of the National Institute on Drug Abuse and conducted in accordance with the guidelines of the National Research Council (1996).

1.2. Apparatus

Ten sound-attenuated experimental chambers (30×24×29 cm, Coulbourn Instruments, Allentown, PA) were used. During initial training, each chamber had two nose-poke holes in the right wall. During testing for conditioned reinforcement, the nose-poke holes were removed and 2 levers were installed. A shielded light bulb (type 1820, 24 V) on the wall above the nose-poke holes was illuminated at all times, except during certain conditioning phases of training when the light was pulsed at a rate of 5 Hz in association with delivery of cocaine. An 83 dB, 4500-Hz tone (Sonalert; Mallory, model 628) was also pulsed in association with injections in certain phases of training. Cocaine solution was delivered by a syringe pump (MED-Associates, St. Albans, VT) at 3.2 ml/min over approximately 2 s using a 10-ml syringe and tubing that was protected by a metal spring and suspended through the ceiling of the experimental chamber from a single-channel fluid swivel (Instech, Plymouth Meeting, PA). To reduce tension on the catheter, the spring was attached to a 20-mm plastic screw that was mounted on the rat's head during catheterization surgery. Experimental events were controlled by computer using a MED-Associates interface.

1.3. Procedure

All training and testing sessions lasted 2.5 h. Throughout training, each response in one hole (the active hole) produced an injection of cocaine (.3 mg/kg), followed by a timeout period during which responding had no scheduled effect. The injection and timeout lasted a total of 5 s. Responses in the other hole (the inactive hole) had no scheduled effect at any time. Phases of training differed with regard to which stimuli were paired with the injection. For all rats, no stimuli were presented during the initial phase of training (acquisition phase; 3–15 sessions), which continued until the rat self-administered at least 10 injections/session for 3 consecutive sessions. In the second phase of training (blocking phase), rats were randomly assigned to either the blocking group or the non-blocking group. In the blocking phase, the blocking group was trained for 5 sessions with the pulsed tone presented during injection and timeout, and the non-blocking group continued to be trained with no stimulus presentations. In the third and final phase of training (compound-conditioning phase), all rats were trained for 5 sessions with both the tone and light pulsed during injection and timeout. Finally, to test for conditioned-reinforcing effects of the light, there were 3 test sessions in which the nose-poke holes were removed and two levers were installed. During the test, each response on one lever (the active lever) caused the light stimulus to pulse for 5 s. Responses on the other lever (inactive lever) had no scheduled effect. No cocaine was delivered during the test. Rats were trained 5 days/week, and the last day of training and 3 days of testing were always conducted on 4 consecutive days. Over the course of the experiment, 3 rats were lost due to catheter failure, 3 were lost due to illness, and 2 failed to acquire cocaine self-administration, leaving 5 rats in the blocking group and 4 rats in the non-blocking group.

2. Results

During training, self-administration behavior was similar in the blocking and non-blocking groups (see Fig. 1). There were no significant differences between the groups in the number of cocaine injections per session (p's > .62) or the percentage of responses in the active versus inactive nose-poke hole (p's > .9). Although one rat in the non-blocking group had rates of self-administration during the blocking phase that were noticeably higher than those of the other rats in either group, the total number of stimulus-cocaine pairings for this rat during the compound-conditioning phase was similar to that of the other rats.

During testing, the light stimulus was found to be an effective conditioned reinforcer only in the non-blocking group. Statistical analysis of responses on the active and inactive levers over the 3 days of testing (see Fig. 2) revealed a significant main effect of group [$F(1,7) = 7.28$, $p < .05$)] and a significant group × lever interaction [$F(1,7) = 7.83$, $p < .05$]. Although active-lever responding tended to increase over the 3 days of testing in the non-blocking group, the main effect and interactions involving test day were non-significant (p's > .6). Post-hoc comparisons (Tukey–Kramer procedure) confirmed

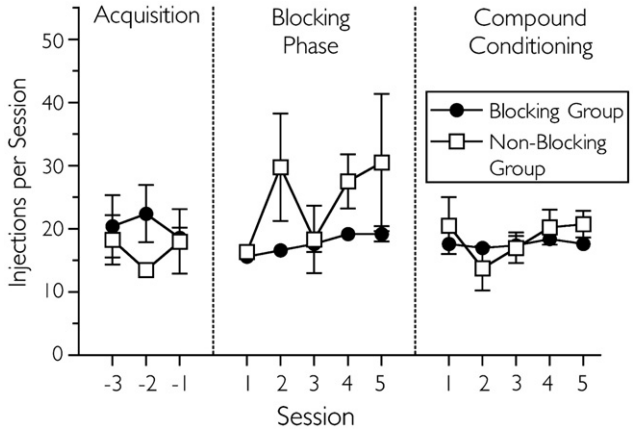

Fig. 1. Rates of cocaine self-administration (mean injection/session+s.e.m.) by the blocking (*filled circles*) and non-blocking (*open squares*) groups during training in the acquisition phase (when both groups learned to self-administer cocaine with no exteroceptive stimulus), the blocking phase (when the tone was paired with each self-administered injections in the blocking group), and the compound-conditioning phase (when the tone and light were paired with each self-administered injection for both groups). Self-administration behavior and the number of conditioning trials were comparable between the groups during training. All rats responded mainly in the active nose-poke hole during these respective phases, with the percentage (mean±s.e.m.) of responses in the active hole being 93.4±4.5, 93.4±2.9, and 93.8±5.3 for the blocking group and 91.9±5.1, 94.0±3.8, and 97.0±1.0 for the non-blocking group. For the acquisition phase, data are shown for the last 3 days only.

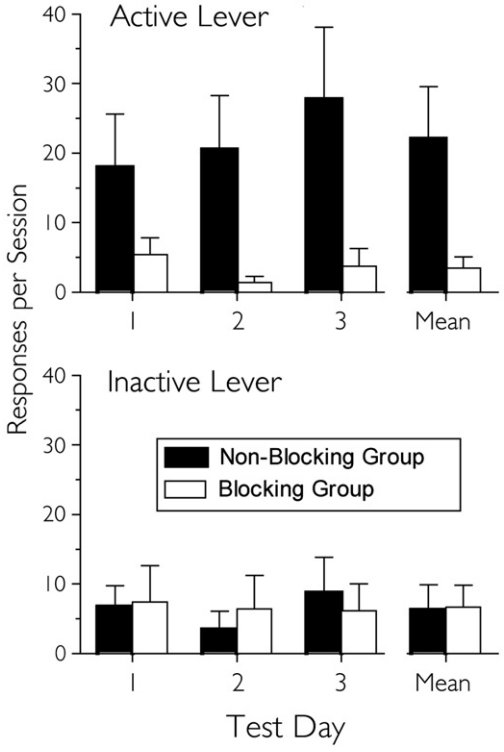

Fig. 2. Response rates (mean responses/session+s.e.m.) on the active (*upper panel*) and inactive (*lower panel*) levers during each of the 3 days of testing for conditioned reinforcement by the light. Means for the entire test are shown in the *far right* bars in each panel. Conditioning to the light was blocked in rats that had received cocaine paired with tone for 5 days before receiving cocaine paired with tone and light for 5 days.

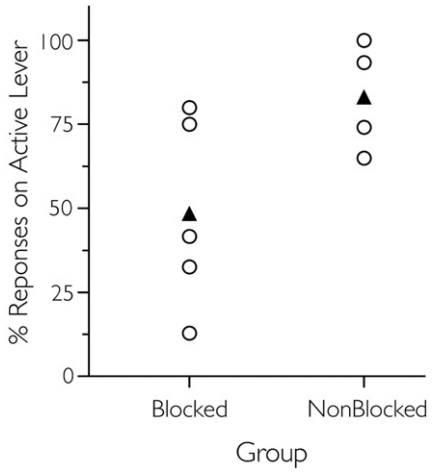

Fig. 3. Percentage of responses on the active lever by individual rats during the conditioned-reinforcement test. Data were combined for the 3 days of testing. Individual data are shown as *open circles*, and group means are shown as *filled diamonds*. The entire distribution for the non-blocking group was well above 50%, but the distribution for the non-blocking group was scattered around 50%.

that active-lever responding by the non-blocking group was significantly greater than active-lever responding by the blocking group ($p<.05$). Active-lever responding by the non-blocking group was also significantly greater than inactive-lever within the same group ($p<.05$). Thus, the rats in the non-blocking group not only responded more during the test, they exhibited a consistent preference for the active lever, as shown in Fig. 3. All of the rats in the non-blocking group emitted more than 50% of their responses on the active lever, but the distribution of responses for the blocking group was evenly dispersed around 50%.

3. Discussion

The non-blocking group showed a robust conditioned-reinforcement effect, but the blocking group showed no evidence of conditioned reinforcement. Thus, these results do not support the prediction by Redish (2004) that blocking should not occur when exteroceptive stimuli are paired with cocaine.

The procedures used in this study were well suited for testing this prediction concerning the learning processes that occur during drug self-administration. Drug self-administration in rats parallels many of the features of drug self-administration in humans, providing a highly valid animal model of drug abuse and the conditioning factors involved. The conditioned-reinforcement procedure used here, developed and extensively validated by DiCiano and Everitt (2004), is highly sensitive to the reinforcing effects of stimuli paired with self-administered cocaine. The blocking procedure, which compares a blocked group with a non-blocked control group, has been studied extensively with non-drug reinforcers (e.g., see Gray and Appignanesi, 1973; Holland and Gallagher, 1973; Holland and Fox, 2003; Kim et al., 1998; Rauhut et al., 1999), and the results obtained here with cocaine are quite consistent with this body of work.

There is ample reason to expect that blocking should have been prevented when cocaine was the reinforcer. First, the firing patterns of dopamine neurons during training with appetitive, non-drug reinforcers under a wide variety of behavioral procedures are consistent with these cells providing a "prediction-error signal" when a reward is larger than expected (Schultz, 1998; Schultz and Dickinson, 2000). Second, when monkeys were trained with a blocking procedure using a non-drug reinforcer, conditioning was only blocked when this error signal failed to occur during compound conditioning (Waelti et al., 2001). Third, certain effects of self-administered cocaine — phasic changes in dopamine levels and the firing of nucleus accumbens/striatal cells located post-synaptic to dopamine cells — might mimic this error signal (Carelli, 2004; Peoples and West, 1996). These cocaine-induced phasic changes might be especially salient because the background rate of firing is preferentially decreased, enhancing the signal-to-noise ratio (Peoples and Cavanaugh, 2003). Finally, there is evidence that amphetamine can prevent the blocking effect when given i.p. before conditioning sessions involving non-drug reinforcers (Crider et al., 1982; O'Tuathaigh et al., 2003; cf. Ohad et al., 1987; see also Crider et al., 1986). However, in these amphetamine studies, it is not clear whether i.p. amphetamine: (1) had tonic effects on dopamine that overwhelmed the phasic dopaminergic effects of the non-drug reinforcers by decreasing the signal-to-noise ratio; or (2) had the opposite effect, amplifying the phasic dopamine signal of the non-drug reinforcers. The latter, but not the former, would be consistent with the hypothesis that blocking results from there being no prediction-error signal during the blocking phase.

It should be noted that this experiment tested only one of the predictions of the hypothesis proposed by Redish (2004). It is not clear why the prediction was not supported, but the possibility remains that it might be supported under some other set of experimental conditions (e.g., with different training parameters, measures of conditioning, dosing regimens, levels of food restriction, or conditioned stimuli). Nonetheless, the present study clearly demonstrates that the blocking effect can occur with self-administered cocaine as the reinforcer. Although it is disappointing that these results fail to support a potentially powerful explanation of addiction, they are consistent with the fact that most of the conditioning and learning phenomena that occur with non-drug reinforcers have also been demonstrated with cocaine and other drugs of abuse.

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