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Low dose apomorphine induces context-specific sensitization of hypolocomotion without conditioning: Support for a new state dependent retrieval hypothesis of drug conditioning and sensitization

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ABSTRACT

High doses of apomorphine induce sensitization to locomotor stimulant effects whereas low doses induce locomotor inhibition. We examined whether repeated low dose apomorphine induced sensitization and conditioning to the locomotor inhibitory effect. Three doses of the D1/D2 agonist, apomorphine, were used in a Pavlovian conditioning protocol: 0.05 mg/kg (autoreceptor level), 0.5 and 2.0 mg/kg (post-synaptic level). Rats received 5 daily apomorphine treatments paired or unpaired to an open-field environment (conditioning phase) followed by a saline test (conditioning test) and an apomorphine challenge test (sensitization test). Locomotion was measured for 30 min. During the acquisition phase, the 0.05 mg/kg paired treatment decreased locomotion while the high dose paired treatments increased locomotion. The 0.05 mg/kg paired treatment did not induce conditioning but induced inhibitory locomotor sensitization. The post-synaptic paired treatments produced conditioned and sensitized locomotor stimulation. For the low dose results, we propose an expanded contextual stimulus, which includes interoceptive drug cues. In the sensitization test, the same interoceptive drug cues and test environment cues are present as those during acquisition. In the conditioning test, normative dopaminergic activity is present which generates internal cues that may or may not generalize to the drug-induced cues and, permit or prevent retrieval of conditioning.

1. Introduction

Following the initial observations of Pavlov (1927), it has been well established that a variety of physiological and behavioral effects of drugs can become conditioned to drug-associated situational cues (Carey et al., 2003). A drug acts as an unconditioned stimulus (US) and elicits behavioral effects expressed as unconditioned responses (UR). When it is administered several times contiguous with conditioned stimuli (CS) initially neutral with respect to the US, an association between UR and CS (conditioned stimulus) is formed. Accordingly, when a vehicle injection is administered in combination with the CS, a conditioned response (CR) can occur (Möller et al., 1987). This consideration has long been recognised to have importance for drug use phenomena such as tolerance and sensitization and for drug addiction.

It has been long-known that drugs with dopaminergic agonist properties can induce conditioned drug effects (Beninger, 1983; Schiff, 1982). These studies have provided support to the importance of dopaminergic system in learning and memory processes. On the other hand, drugs, which block dopaminergic transmission such as haloperidol, have also been reported to induce conditioned drug effects (Poulos and Cappel, 1991). While drugs such as haloperidol block dopaminergic effects, dopaminergic activity in dopamine neurons, nonetheless, is actually increased (Carey et al., 2000; Chessalet, 1984; Karolewicz et al., 1996; Nowak et al., 1990; Rayevsky et al., 1995). An alternative approach to study the role of the dopaminergic system in drug conditioning is to employ drug treatments, which are selective for dopamine autoreceptors that inhibit dopaminergic neural activity (Aghajanian and Bunney, 1973; Carey et al., 2005; Di Chiara et al., 1977). Consequently, if dopamine neuronal activity is critical for dopamine drug conditioning, then, a selective activation of the dopamine autoreceptors, which would inactivate dopamine neurons, provides an opportunity to test for dopamine involvement in drug conditioning and sensitization processes.

Apomorphine in low doses (<0.1 mg/kg) preferentially activates dopamine autoreceptors, which in turn inactivate dopamine neurons. The behavioral effect of autoreceptor stimulation is that low dose apomorphine (APO) treatments are well-defined unconditioned drug responses, which include suppression of locomotion and rearing (Aghajanian and Bunney, 1973; Carey et al., 2004). Thus, low dose APO treatment, which elicits unconditioned drug responses, provides an opportunity to assess whether inactivation of dopamine neurons

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which can induce unconditioned responses can also serve as an effective unconditioned stimulus in a Pavlovian drug conditioning protocol to generate a Pavlovian conditioned drug response and context-specific sensitization. At higher dose levels (>0.5 mg/kg) APO also activates post-synaptic dopamine receptors and, in this way, mimics dopaminergic activation. At these higher dose levels, APO induces locomotor hyperactivity (Antoniou and Kafetzopoulos, 1991; Bloise et al., 2007; Mattingly and Gotsick, 1989). The aim of the present study was to evaluate the role of dopaminergic autoreceptor vs. post-synaptic activation in drug conditioning of locomotor responses. Accordingly, three doses of the D2/D1 agonist, APO, were used: a predominantly pre-synaptic low dose (0.05 mg/kg), a post-synaptic moderate dose (0.5 mg/kg) and a post-synaptic high dose (2.0 mg/kg) in a conventional paired/unpaired Pavlovian conditioning protocol. In addition, we assessed whether each of these APO treatments could produce context-dependent sensitization.

2. Materials and methods

2.1. Subjects

Male Wistar albino rats provided by the State University of North Fluminense, initially weighing 300–350 g were housed in individual plastic cages (25×18×17 cm) until the end of the experiment. Food and water were freely available at all times. The vivarium was maintained at a constant temperature (22±2 °C), and a 12/12 h light/dark cycle (lights on at 07:00 h and off at 19:00 h). All experiment occurred between 08:00 h and 18:00 h. For 7 days prior to all experimental procedures each animal was weighed and handled daily for 5 min. All experiments were conducted in strict accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals.

2.2. Apparatus and measurement of behavior

The behavioral measurements were conducted in a black open-field chamber (60×60×45 cm). A closed-circuit video camera (DISISEC, model IR575M), mounted 50 cm above the arena was used to record behavioral data. The complete test procedure was conducted automatically without the presence of the experimenter in the test room. The behavioral data for locomotion (measured as number of crossings) were recorded during a 30 min period in the test environment. For crossing, the experimental arena floor was divided into eight equal-sized squares and the number of times that the rat passed from one square to another with its four paws was recorded. The behavioral activity was analysed by a trained observer who was unaware of the treatment under test. All behavioral testing was conducted under dim red light to enhance the contrast between the white subject and dark background of the test chamber and diminish anxiogenic factors involved in open-field testing under white light conditions (Nasello et al., 1998). Masking noise was provided by a fan located in the experimental room and was turned on immediately prior to placing the animal in the test arena and turned off upon removal of the animal from the test arena.

2.3. Drugs

Apomorphine-HCl (Sigma, St. Louis, MO, USA) was dissolved in 0.1% ascorbate/saline and was injected subcutaneously in the nape of the neck at doses of 0.05, 0.5 or 2.0 mg/kg using a volume of 1.0 ml/kg body weight. Drug solutions were freshly prepared before each experiment.

2.4. Design and procedures

The experiments were conducted following a modified experimental protocol from Damianopoulos and Carey (1992) and Dias et al. (2006). First, all rats received three 30 min test environment acclimation sessions, conducted on consecutive days. The acclimation protocol was conducted so that a baseline of the target behavior could be established and equated among groups prior to the start of the drug treatments. In these three tests, the animals were administered saline and placed in the experimental arena and activity was measured. After completion of the acclimation procedure, the animals were assigned to groups equated on baselines and were submitted to the pharmacological treatments (conditioning phase). For each dose level of apomorphine (APO), there were three treatment groups: a paired group, an unpaired group and a vehicle treatment group. In the paired group, rats received administration of APO (0.05, 0.5 or 2.0 mg/kg) 20 min before being placed into the test environment and vehicle administration 30 min after removal from test environment. In the unpaired group, rats received administration of vehicle 20 min before being placed into the test environment and APO 30 min after being removed from the test environment. The vehicle treatment group was treated the same as the paired group except that it received vehicle 20 min prior to and 30 min after being placed in the experimental arena. The animals were tested for 30 min in the test environment. These treatments were administered for 5 consecutive days, one trial per day and served as the acquisition phase designed to establish a conditioned drug response to test environment cues. After a period of 2 days without injections or behavioral testing (withdrawal period), the animals received an injection of saline rather than vehicle as established by Damianopoulos and Carey (1992), 20 min prior to being placed into the test environment (conditioning test). Following a second withdrawal period (2 days), all groups received a challenge injection of APO prior to test environment placement (senitization test). On the sensitization test day, all groups (except the vehicle group) received a challenge injection of APO (0.05, 0.5 or 2.0 mg/kg according to the dose received during the conditioning phase) 20 min prior to being placed into the test environment.

The efficacy of systemic administrations of APO to modify unconditioned locomotor activity and to induce a conditioned locomotor response as well as to produce behavioral sensitization was evaluated using 3 different doses of APO. In the first experiment, an autoreceptor dose (0.05 mg/kg) was used and the rats were divided into three groups: APO-0.05-paired ($n=10$), APO-0.05-unpaired ($n=10$) and vehicle ($n=10$) groups. In the second experiment a moderate post-synaptic dose of APO (0.5 mg/kg) was used and the rats were divided into three subgroups: APO-0.5-paired ($n=8$), APO-0.5-unpaired ($n=8$) and vehicle ($n=5$) groups. In experiment 3, a high post-synaptic dose (2.0 mg/kg) was used and the rats were divided in APO-2.0-paired ($n=8$), APO-2.0-unpaired ($n=8$) and vehicle ($n=5$) groups.

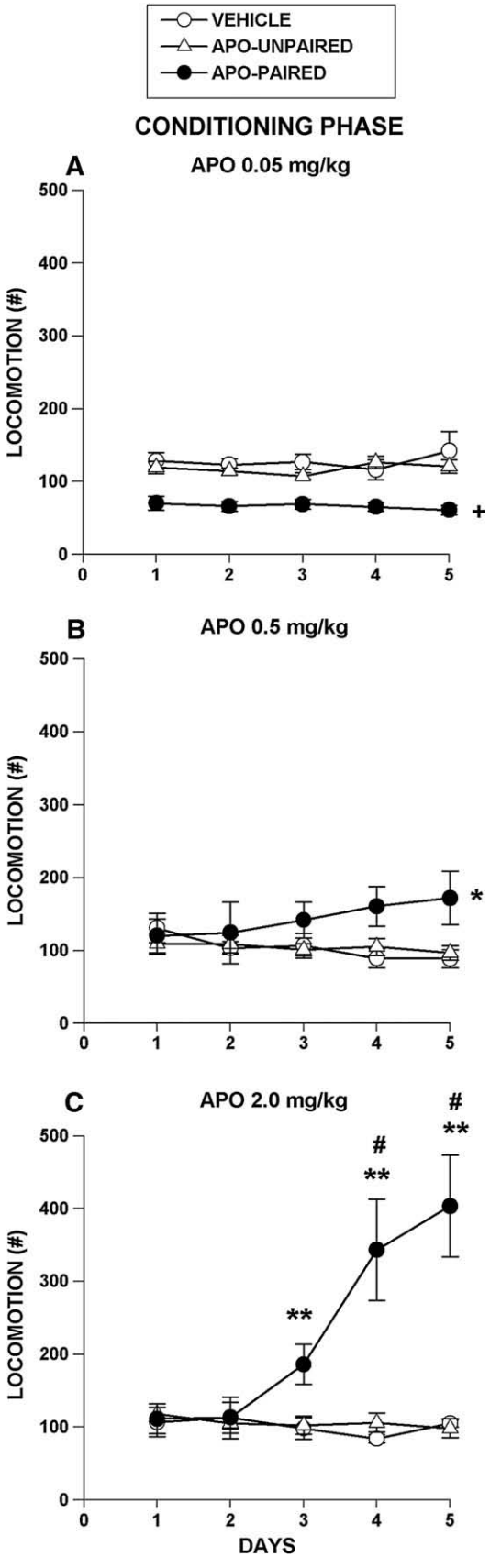
2.5. Statistics

The total number of crossings during 30 min in the test arena was used as the dependent variable measure. In the conditioning induction phase, a two-way analysis of variance (ANOVA) was used to analyse the behavioral data to determine the group effect, day effect, as well as the interactions between these two variables. When a significant effect of group×day interaction was recorded, data were further analysed by one-way ANOVA followed by the Duncan multiple range test with $p<0.05$ used as the criterion for statistical significance. The behavioral data obtained from the conditioning test and sensitization test were analysed by one-way ANOVA. Wherever indicated by the ANOVA (group effects with p-values <0.05), possible differences among groups were analysed by Duncan's multiple range test.

3. Results

Prior to the start of experimentation, the animals underwent to a three-day habituation procedure. The statistical analyses using a one-

way ANOVA indicated a significant effect of days ($F_{2,213}=19.70$; $p<0.01$). The Duncan's test showed that day 1 had higher locomotor activity than day 2 and day 3 ($p<0.05$) (data not shown) and day 2 had higher locomotor activity than day 3 ($p<0.05$) (data not shown).



For all experimental animals, the locomotor activity declined with repeated testing ($p<0.05$) as expected for the development of habituation to a novel environment (Cerbone and Sadile, 1994). Importantly, prior to the initiation of the conditioning protocol, there were no differences among the treatment groups ($p>0.05$) in any experiment.

Fig. 1 shows the mean locomotor activity scores obtained for the conditioning induction phase for all three APO doses. For the 0.05 mg/kg APO dose (Fig. 1A), a two-way ANOVA indicated that there was a significant effect of group ($F_{2,135}=86.70$; $p<0.01$), no effect of the days of testing ($F_{4,135}=0.63$; $p>0.05$) and no interaction group *versus* days ($F_{8,135}=0.66$, $p>0.05$). Duncan's multiple test showed that the APO-0.05-paired group had a lower locomotor activity than the vehicle and APO-0.05-unpaired groups ($p<0.05$). For the 0.5 mg/kg APO dose (Fig. 1B), the results showed that there was a significant effect of group ($F_{2,90}=6.68$; $p<0.01$) and Duncan's multiple test showed that the APO-0.5-paired group had higher locomotion than the vehicle and APO-0.5-unpaired groups ($p<0.05$). There was no effect of the days of testing ($F_{4,90}=0.13$; $p>0.05$) and no interaction group *versus* days ($F_{8,90}=0.66$, $p>0.05$). For the locomotion induced by 2.0 mg/kg APO (Fig. 1C), the two-way ANOVA indicated interaction group *versus* days ($F_{8,90}=4.44$, $p<0.01$), a significant effect of groups ($F_{2,90}=18.30$; $p<0.01$) and a significant effect of days of testing ($F_{2,90}=3.14$; $p<0.01$). To further analyse the interaction, a one-way ANOVA followed by Duncan's multiple test was performed. The results showed that from the third day of administration until the end of conditioning induction phase the APO-2.0-paired group showed a higher locomotor activity than the other groups ($p<0.05$) and that for the APO-2.0-paired group the locomotor activity on the 4th and 5th days were higher than the 1st, 2nd and 3rd days ($p<0.05$).

Fig. 2 shows the mean total locomotor activity obtained over a 30 min period during the conditioning test (left panel) and during sensitization test (right panel) for all three APO doses. For the 0.05 mg/kg APO dose during the conditioning test (Fig. 2A), the results showed that there were no statistical differences among groups (one-way ANOVA; $F_{2,27}=0.03$; $p>0.05$). However, during the sensitization test (Fig. 2B), there were differences among the groups (one-way ANOVA; $F_{2,27}=18.40$; $p<0.01$) and the APO-0.05-paired group had a lower locomotor activity than the vehicle and APO-0.05-unpaired groups ($p<0.05$). Also, the APO-0.05-unpaired group had lower locomotor activity than the vehicle group ($p<0.05$). For the 0.5 mg/kg APO dose, the results showed differences among groups during the conditioning test ($F_{2,18}=5.28$; $p<0.01$; Fig. 2C) and Duncan's test showed that the APO-0.5-paired group had significantly higher locomotor activity than the other groups ($p<0.05$). The locomotor activity level for the paired group was also higher than the unpaired group during the first test session, indicating that the paired treatment did not simply block habituation effects ($p<0.05$). For the sensitization test, the results showed there were differences among the experimental groups ($F_{2,18}=7.53$; $p<0.01$; Fig. 2D) and Duncan's test showed that the APO-paired group showed higher locomotor activity than the other groups ($p<0.05$). For the 2.0 mg/kg APO dose, there were statistical differences during conditioning test ($F_{2,18}=9.22$; $p<0.01$; Fig. 2E) and Duncan's test showed that the APO-2.0-paired group had a significantly higher locomotor activity than the other groups ($p<0.05$). These activity scores for the paired group were also higher than the unpaired group on the first test ($p<0.05$). For the sensitization test (Fig. 2F), the results showed that there was a difference for the groups ($F_{2,18}=8.30$; $p<0.01$) and the

Fig. 1. Means and S. E. M. of locomotor activity for 0.05 mg/kg (A), 0.5 mg/kg (B) and 2.0 mg/kg (C) APO doses during the 5 days of the conditioning phase. * denotes higher locomotor activity than the other groups. $^{+}$ denotes lower locomotor activity than the other groups. ** denotes higher locomotor activity than the other group during the same day of administration. $^{\#}$ denotes that for the APO-2.0-paired group the locomotor activity on the 4th and 5th days was higher than on the 1st, 2nd and 3rd days ($p<0.05$; ANOVA followed by Duncan's multiple range test).

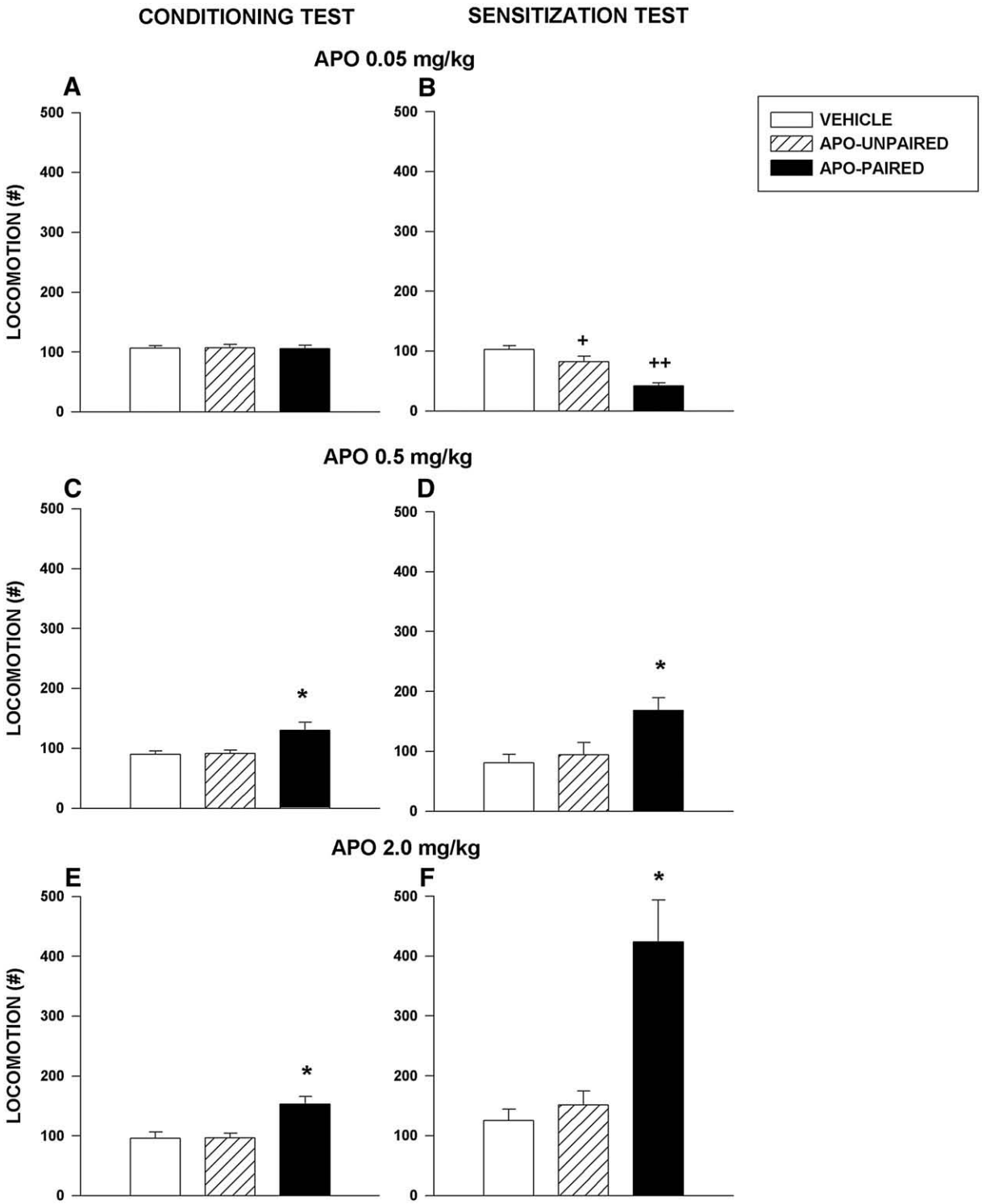


Fig. 2. Means and S. E. M. of locomotor activity following administration of three doses of APO during conditioning and sensitization tests. (A) 0.05 mg/kg: conditioning test; (B) 0.05 mg/kg: sensitization test; (C) 0.5 mg/kg: conditioning test; (D) 0.5 mg/kg: sensitization test; (E) 2.0 mg/kg: conditioning test; and (F) 2.0 mg/kg: sensitization test. * denotes higher locomotor activity than the other groups. $^{++}$ denotes lower locomotor activity than the other groups. $^{+}$ denotes lower locomotor activity than the vehicle group ($p<0.05$; ANOVA followed by Duncan's multiple range test).

APO-2.0-paired group had significantly higher locomotor activity than the other groups ($p<0.05$).

4. Discussion

In agreement with extensive literature, APO in the present study had a bidirectional effect upon locomotion activity depending upon dose level. An autoreceptor preferring dose (Aghajanian and Bunney, 1973) substantially and reliably suppressed locomotor activity; whereas, the higher dose levels, which stimulate both pre and post-synaptic DA receptors, generated a hypermotility effect. The important issue addressed in this study was whether the anti-dopaminergic behavioral inhibitory effects of low autoreceptor level of APO would generate conditioned and context-specific sensitization effects that

occur with agonistic dopaminergic effects elicited by high dose stimulant APO treatments. Consistent with the literature (Bloise et al., 2007; Braga et al., 2009; Damianopoulos and Carey, 1993; Möller et al., 1987), the high dose APO treatment (0.5 and 2.0 mg/kg) produced conditioned as well as context-specific sensitization. With the low dose APO treatment, however, there was a divergence in conditioned and context-specific sensitization effects. The low dose treatment failed to induce a conditioned locomotor inhibitory effect but did induce a locomotor context-specific drug sensitization effect. Thus, this result provides evidence for a clear dissociation between conditioned drug effects and context-specific sensitization effects.

The relationship of Pavlovian conditioned drug effects and context-specific sensitization has been a long-standing issue in behavioral pharmacology. The Pavlovian conditioning process has been related to the development of context-specific behavioral sensitization (Carey and Damianopoulos, 2006). context-specific sensitization is a well-known phenomenon with respect to repeated usage of several psychostimulant drugs (Bedingfield et al., 1996; Cornish and Kalivas, 2000; Crombag et al., 2000; Erb et al., 2004; Pert et al., 1990; Zavala et al., 2000). In such studies, context has been manipulated using complex environmental stimuli; while less recognized, it is also the case that the drug state in which the psychostimulant drug is experienced can be a critical component of the contextual cue. In the study of conditioning, it has been shown that drugs can function as conditioned stimuli as well as unconditioned stimuli. The fact that drugs can serve as CS as well as US is not surprising in that the stimulus properties of centrally active drugs are well-known (Overton et al., 1999). The use of drugs as CS in operant as well as Pavlovian conditioning is well-established (Bevins and Peterson, 2004; Järbe et al., 1981; Lal and Bennet, 1989; Overton, 1977; Siegel, 1977, 1988). Furthermore, a drug cue can be an effective CS even when another drug cue is used as an effective US (Carey, 1989, 1991; Greeley et al., 1984; Revusky, 1985; Revusky and Reilly, 1990a,b; Taukulis, 1986, 1996). Drugs have also been used as CSs in open-field test paradigms in which drugs as diverse as buspirone, dizocilpine (MK-801) (Carey et al., 1999) acquire CS properties to elicit cocaine locomotor stimulant effects. Interoceptive drug cues and their specific function in the non-drug and drug states of post-treatment tests are relevant to the present findings in determining the elicitation of conditioned drug effects as well as context-specific sensitization.

In attempting to account for the dissociation between conditioned and context-specific sensitization effects for low dose APO treatment, the contribution of drug state dependent effects appear relevant (Carey and Damianopoulos, 1994; Stephens et al., 2000; Overton, 1991). The low dose APO treatment produces a marked inhibition of locomotor behavior and is associated also with decreased arousal and drowsiness (Kropf et al., 1992; Kropf and Kuschinsky, 1991). The low arousal, dopaminergic inactivation state contrasts to the non-drug state in which there is a high level of arousal and normative dopaminergic activity. Consequently, when testing for conditioning is conducted in the non-drug state, the association made in the low arousal quiescent behavioral state is not available for retrieval; and, therefore, no conditioning is manifested. In contrast, when the drug test for context-specific sensitization is conducted, the low arousal state is present and, thus, the association made during this drug-induced state is available for retrieval. Low arousal states are not incompatible with learning as indicated by learning acquired under the pentobarbital drug state (Reilly and Revusky, 1992; Siegel, 1988).

When drug conditioning is evaluated in a non-drug state, the external cues (test environment) remain constant but the internal (drug state) cues are absent. As a consequence, in a non-drug state conditioning test, the presence or absence of non-drug conditioning becomes linked to the degree of comparability of internal cues between the drug state and the non-drug state. In the present study, the low dose drug state and the non-drug states are dissimilar, so no conditioning is manifested. With the high dose APO treatment, there is a high level of dopaminergic activation and in the non-drug state there is also dopaminergic activation albeit at a reduced level so that some overlap of contextual internal cues between the APO drug state and non-drug state is possible. Seemingly, the degree of separation between the conditioned and drug-induced context-specific sensitization effect provides an indication of an overlap. In this report, the magnitude of the context-specific sensitization effect for high dose APO was much greater (approximately 300 crossings) vs. the non-drug conditioned response (approximately 50 crossings) so the comparability was fairly weak. For the 0.5 m/kg dose, however, the differential between the conditioned response and the context-specific sensitization drug response was much smaller (approximately 40 vs. 70 crossings indicating a greater degree of comparability between the non-drug and the drug state. With high doses of APO, however, the drug state and the non-drug state cues can be so dissimilar that no conditioning is evident in a non-drug test (Damianopoulos and Carey, 1994; Mattingly et al., 1997).

In the schema implicit in this argument, context-specific sensitization represents a Pavlovian conditioned drug effect in which external and internal drug cues are present, whereas, for conditioning in which testing is conducted in the non-drug state, the external cues are present but the acquisition internal drug cues may or may not generalize to the non-drug state internal cues. In this way, conditioned drug effects and context-specific drug sensitization effects are not viewed as involving different learning mechanisms but, rather, different cue conditions. Certainly, drugs which block dopamine activity would appear incapable of generating conditioned drug effects in a non-drug test since the non-drug test would typically involve robust dopaminergic activity. This internal state would be incompatible with the internal cues of the anti-dopaminergic drug state present during acquisition. Thus, the present finding of an absence of conditioning of hypolocomotion in the non-drug test for low dose APO could lead to an inference that dopamine activity is critical to drug conditioning. Rather, it could simply be that the internal cues generated by dopaminergic activity in the non-drug state are so dissimilar to the conditioned internal drug cues that conditioning is not manifested.

The context-specific sensitization and drug conditioning perspective developed in this paper ascribes the lack of conditioning in low dose APO levels to the different internal cues present in the non-drug conditioning test *versus* acquisition. In that dopamine activity is present in the non-drug test but not in the drug test, the dopamine activity has a critical role, but it is one of interfering with or blocking retrieval of the drug-induced conditioning. In conclusion, the proposed incorporation of drug cues into the contextual stimulus provides an integrative framework to link context-specific drug sensitization and drug conditioning into a common learning process differentiated by the presence or absence of necessary drug cue stimuli.

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