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Research report

Post-trial low dose apomorphine prevents the development of morphine sensitization

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ABSTRACT

The development of sensitization is one of the hallmarks of addictive drugs. Consistent with this relationship many studies have demonstrated that the highly addictive opioid agonist morphine induces sensitization effects. In this study, we administered morphine (10 mg/kg) (MOR) to induce sensitization. In that sensitization is considered to involve associative processes and that dopamine activity is an important contributor to learning and memory processes, we administered a dopamine inhibitory treatment using apomorphine (0.05 mg/kg) (APO) during memory consolidation following a morphine sensitization treatment protocol. Seemingly, a decrease in dopamine activity during consolidation would impair the salience of the association of the morphine response with the contextual cues during consolidation and interfere with the development of morphine sensitization. In two separate experiments, MOR or vehicle (VEH) were administered pre-trial and either VEH or APO were administered post-trial over 5 and 10 days of treatment, respectively. In both the 5 and 10 drug treatment sessions post-trial experiments, MOR groups given VEH immediately post-trial exhibited strong sensitization effects. These sensitization effects were substantially attenuated in the MOR groups given APO immediately post-trial but not in the MOR groups given APO after a 15 min. post-trial delay. In subsequent conditioning and sensitization challenge tests, the MOR groups that had been given APO immediately post-trial exhibited diminished sensitization and conditioned responses relative to MOR groups that had received VEH or APO delayed post-trial. This MOR-APO interaction effect was unique in that it occurred post-trial so that it was only expressed in a pre-trial test in which only MOR was administered. Seemingly, the inhibitory dopamine effect of APO was incorporated into memory during the post-trial consolidation process suggesting that drug/drug interactions can occur during consolidation.

1. Introduction

The use of drug-induced changes in spontaneous motor behavior as a dependent behavioral variable has been employed in numerous studies to assess conditioned stimulant behavior induced by several different stimulant drugs that have pro-dopamine effects such as amphetamine, cocaine, apomorphine and morphine [1,2,5,7,9,10,13,15–17,22,23,25,35]. These studies have shown in rodents that drug induced locomotor hyper-activity effects undergo conditioning and sensitization with repeated drug/environment pairings. This Pavlovian drug conditioning is well recognized to be of substantial importance for understanding and treating drug abuse and addiction in that cues experienced in association with drug taking can become capable of eliciting a drug-like effect and triggering craving and relapse [20].

The present investigation is focused on morphine induced conditioning and sensitization. Numerous studies have shown that in mice and rats, morphine induces locomotor stimulation effects that undergo sensitization and conditioning with repeated treatments [14,19,24,27–29,31–33]. Recently, we have also reported [12] locomotor conditioning and sensitization effects in rats following repeated morphine (10.0 mg/kg) treatments. After conditioned morphine effects had been induced, we demonstrated [12] that a low dose of apomorphine (0.05 mg/kg) could attenuate the morphine conditioned hyperactivity if it was administered immediately but not delayed by 15 min.

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following a brief five minute conditioning test that elicited a morphine conditioned hyper-activity response. In contrast, the same immediate post-trial apomorphine treatment given to vehicle or unpaired morphine groups had no effects on behavior.

In the present report, we again administered morphine pre-trial to induce sensitization and conditioned morphine effects. Whereas in our previous morphine conditioning study [12] the post-trial low dose (0.05 mg/kg) apomorphine treatments were initiated after the induction of conditioning and sensitization effects. In the present study, we administered the low dose apomorphine treatments post-trial during the morphine induction phase to determine if the post-trial low dose apomorphine treatments would also prevent or attenuate the development of morphine sensitization and conditioning. In two separate experiments, morphine (10.0 mg/kg) pre-trial treatments were administered and the animals were tested for locomotor activity in an open-field arena. In the first experiment, post-trial apomorphine (0.05 mg/kg) treatments were administered either immediately post-trial in order to have the opportunity to occur during the post-trial consolidation period or after a 15 min. post-trial delay, as a control for the post-trial apomorphine effects. In contrast, to conventional drug-drug interaction paradigms the present studies employed a unique paradigm in which the drug-drug interaction was designed to occur during consolidation/re-consolidation of the drug experience. The present repost details the findings of these experiments.

2. Materials and methods

2.1. Subjects

Male Wistar albino rats provided by the State University of North Fluminense Darcy Ribeiro, initially weighing 200 − 300 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 experiments occurred between 8:00 and 12:00 h. For 7 days prior to all experimental procedures, each animal was weighed and handled daily for 5 min. All experiments were performed in compliance with Brazilian Council for Animal Experimentation (CONCEA), which are based on the US National Institutes of Health guide for the care and use of laboratory animals (NIH Publications No. 8023, revised 1978).

2.2. Drugs

Morphine sulfate (Cristalia, São Paulo, Brazil) was used from 10 mg ampoules (1 ml) and was injected subcutaneously in the nape of the neck at a dose of 10 mg/kg [12,21,30,32]. Apomorphine-HCl (Sigma, St. Louis, MO, USA) was dissolved in 0.9 % saline solution and was injected subcutaneously in the nape of the neck at a dose of 0.05 mg/kg. A 0.9 % saline solution was used as vehicle. All doses were administered in a volume of 1.0 ml/kg body weight. Drug solutions were freshly prepared before each experiment.

2.3. Apparatus and behavioral measurements

The behavioral measurements were conducted in a black open field chamber (60 × 60 × 45 cm). A closed-circuit camera (IKEGAMI, model ICD-49) mounted 60 cm above the arena was used to record behavioral data. Locomotion, measured as distance traveled (m), was automatically analyzed using EthoVision (Noldus, The Netherlands). The complete test procedure was conducted automatically without the presence of the experimenter in the test room. All behavioral testing was conducted under dim red light to avoid the possible aversive quality of white light [18] and to enhance the contrast between the white subject and the dark background of the test chamber. A fan in the experimental room provided masking noise. The fan was turned on immediately prior to placing the animal in the experimental arena and turned off upon removal of the animal from the experimental arena.

2.4. Experimental procedure

Two separate experiments were conducted following a modified protocol from Carrera and co-workers [6]. Prior to the start of each experiment, all animals received an acclimation protocol that entailed one week of extensive handling and saline injections. Next, all the animals were given three 30 min. vehicle (VEH) tests in the open-field arena to familiarize the animals to the test arena. Two separate experiments were conducted and in each experiment, the procedure consisted of three phases: An induction phase, a conditioning test phase and a sensitization challenge test phase. In the induction phase, the groups were injected with either VEH or MOR (morphine 10 mg/kg) immediately prior to a 5 min. placement in the test arena. In the first experiment, the induction phase entailed 5 daily five min. test sessions and in the second experiment the induction phase was extended to 10 daily five min. test sessions. In each experiment, the induction phase was followed two days later by a five min conditioning test in which all groups received VEH before testing but no injections post-trial. The conditioning test was followed two days later by a five min. MOR sensitization challenge test in which all groups received MOR prior to testing except for VEH groups that received VEH to control for possible changes in the behavioral baseline response level.

In the first experiment eight groups (n = 7 animals per group) were used and in the second experiment four groups (n = 5–6 animals per group) were used. In the first experiment, four groups received VEH and four groups received MOR immediately prior to the five min. placement in the test arena. Post-trial, the groups received either VEH or APO. The post-trial treatments were administered either immediately upon removal from the test arena or 15 min. after removal from the arena. The designation of groups based on the induction treatments is as follows: The two VEH groups that received VEH immediately or delayed 15 min. post-trial are (VEH/VEH-I) and (VEH/VEH-D), the remaining two VEH groups received APO either immediately post-trial (VEH/APO-I), or 15 min. post-trial (VEH/APO-D). The two MOR groups that received VEH post-trial are (MOR/VEH-I and MOR/VEH-D). The two MOR groups that received APO post-trial are (MOR/APO-I and MOR/VEH-D).

The second experiment was conducted as a replication and extension of the immediate post-trial experiment. The objective of the extension was to increase the number of induction sessions from 5 to 10 in an effort to achieve asymptotic performance levels. In this experiment four groups were used (n = 5–6 animals per group) and only the immediate post-trial treatment protocol was used. The group designations are as follows (VEH/VEH, VEH/APO, MOR/VEH and MOR/APO). In all other aspects, the test protocol was the same as that of the immediate post-trial five induction sessions experiment except there were ten induction sessions.

In both experiments the induction phase, conditioning test and sensitization challenge test sessions lasted five minutes. This brief test session was used during induction to increase the likelihood that the subsequent immediate post-test treatments occurred during consolidation of the drug treatment/context association. In addition, the previous study [12], showed that the sensitization effects of morphine pre-trial treatments manifested in the initial five minutes of the induction session mirrored the sensitization effects observed for the thirty min. induction session. Thus, a five min. induction session was sufficient to generate sensitization effects.

2.5. Statistics

In the morphine induction protocol, a repeated two-factor analysis of variance (ANOVA) was used to determine the treatment, days, and interaction effects. When a significant effect of treatment group versus induction day interaction was obtained, data were further evaluated by

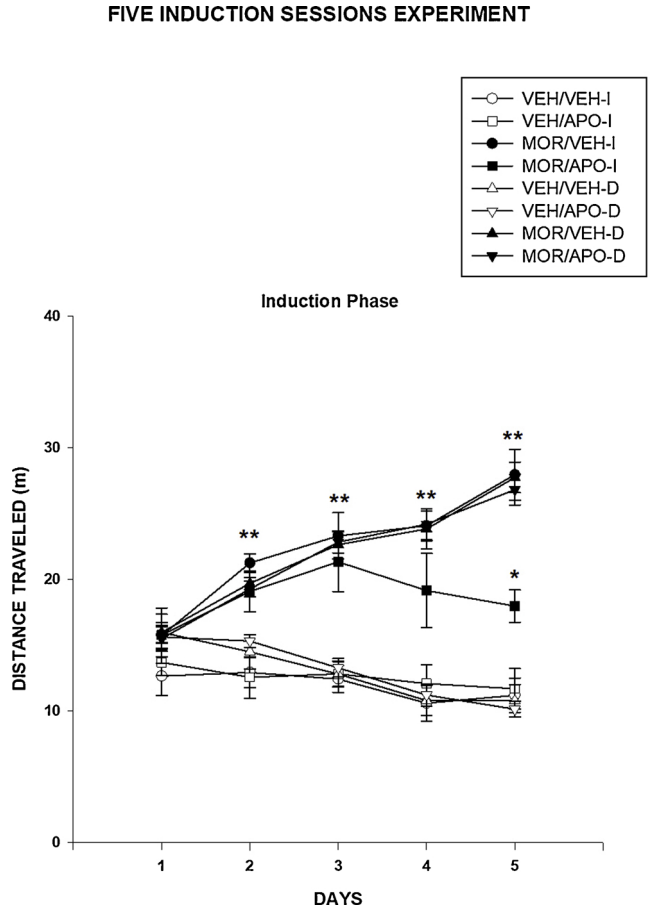

Fig. 1. The Means and SEMs for distance scores (m) during the five induction sessions in which the post-trial treatments of VEH or APO were administered immediately post-trial. ** $p < 0.05$ vs. all groups, * $p < 0.05$ vs. all vehicle groups.

one-way ANOVA followed by Tukey post-hoc tests using $p < 0.05$ as the criterion for statistical significance. The behavioral data obtained from the conditioning and sensitization tests were evaluated using a one-way ANOVA. Wherever indicated by the ANOVA (group effects with p-values < 0.05), possible differences among groups were further analyzed using the Tukey test. Statistical analyses were performed using SPSS Statistics 21 (IBM).

3. Results

3.1. Five induction sessions experiment

Fig. 1 presents the locomotor activity over the course of induction days 1-5. A repeated two-factor treatment by day ANOVA showed a treatment group X day interaction effect [$F(28, 192) = 10.23$; $p < 0.01$], an effect of groups [$F(7, 48) = 23.45$; $p < 0.01$] and an effect of days of treatment [$F(4, 192) = 11.09$; $p < 0.01$]. One-way ANOVAs followed by Tukey test to further analyze the interaction of group X days showed that on day 1 there were no differences among the groups [$F(7, 48) = 1.02$; $p > 0.05$]. On day 2 [$F(7, 48) = 10.0$; $p < 0.01$], day 3 [$F(7, 48) = 16.20$; $p < 0.01$] and day 4 [$F(7, 48) = 17.62$; $p < 0.01$], however, there were differences among the experimental groups and the Tukey test showed that all MOR groups except the MOR/APO-I group had higher locomotion distance scores than all VEH groups ($p < 0.05$). On day 5 [$F(7, 48) = 39.0$; $p < 0.01$], the MOR/VEH-I, MOR/VEH-D and MOR/APO-D groups had higher locomotion than all groups ($p < 0.05$). The MOR/APO-I group had higher locomotion than all VEH groups ($p < 0.05$).

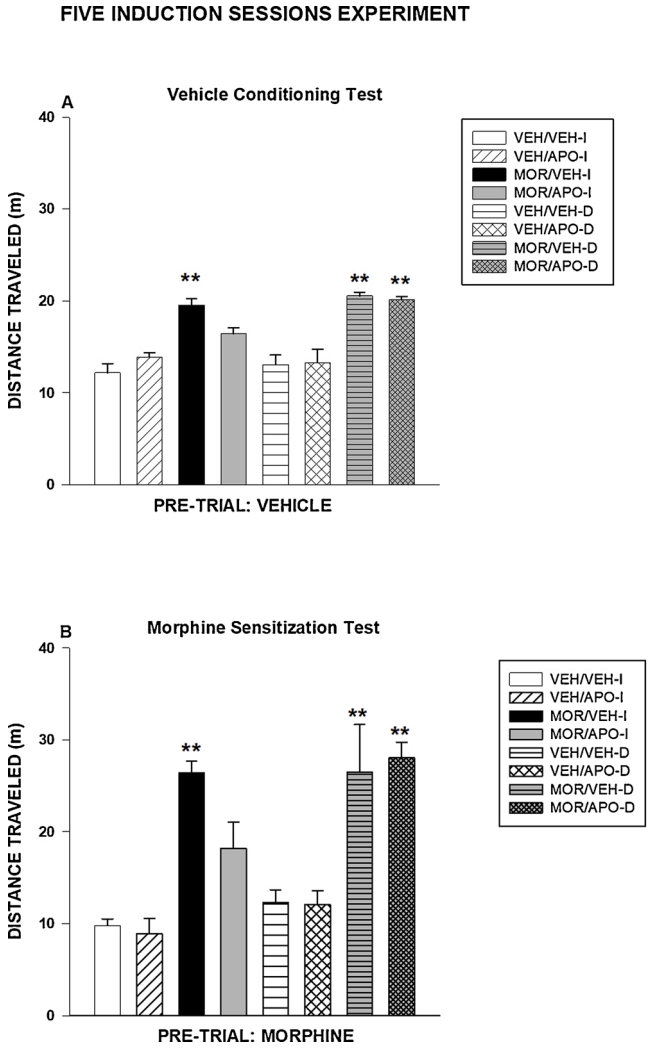

Fig. 2. A. The Means and SEMs for distance scores during the conditioning test in which all groups received vehicle before testing. **B.** The Means and SEMs for distance scores during the sensitization test in which groups received morphine 10 mg/kg before testing. ** $p < 0.05$ vs. all groups.

The results for the conditioning test are presented in Fig. 2**A**. A one-way ANOVA [$F(7, 48) = 17.41$; $p < 0.01$] indicated statistically significant differences among groups and specific group comparisons using the Tukey test showed that the MOR/VEH-I, MOR/VEH-D and MOR/APO-D groups had higher locomotion than all groups ($p < 0.05$). The results of morphine sensitization test are presented in Fig. 2**B**. The one-way ANOVA showed that there were differences among the experimental groups [$F(7, 48) = 22.60$; $p < 0.01$] and individual group comparisons using Tukey test showed that the MOR/VEH-I, MOR/VEH-D and MOR/APO-D groups had higher locomotion than all groups ($p < 0.05$).

3.2. Ten induction sessions experiment

Fig. 3 shows the locomotor activity over the course of days 1–10 for the 10 days of induction. A repeated two-factor treatment by day ANOVA showed a treatment group X day interaction effect [$F(27, 171) = 4.0$; $p < 0.01$], an effect of treatments [$F(3, 19) = 25.0$; $p < 0.01$] and an effect of days of treatment [$F(9, 171) = 6.0$; $p < 0.01$]. One-way ANOVAs with p values of $p < 0.05$ were followed by Tukey tests to identify specific group differences. The one-way ANOVAs showed that on day 1 there were no differences among the groups ($p > 0.05$). On day 2 through day 10, the one-way ANOVAs

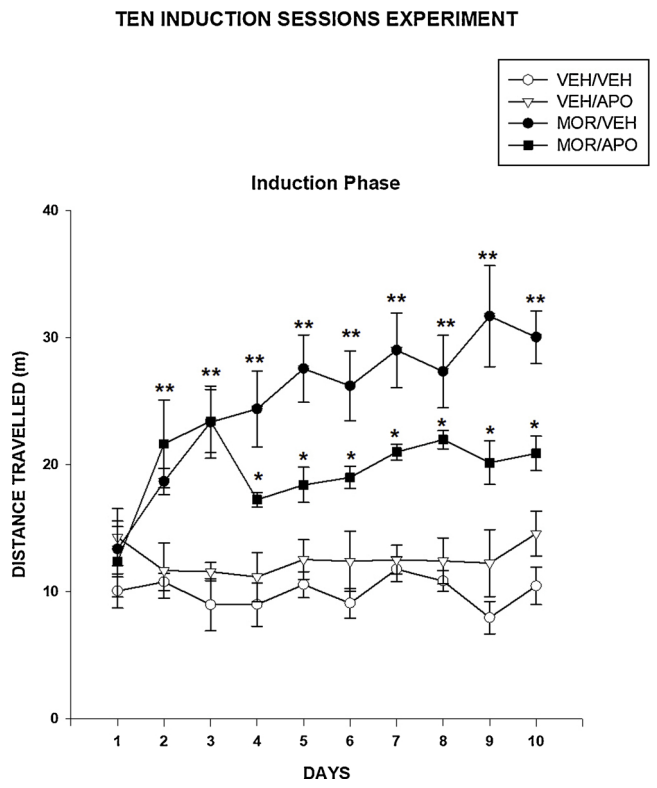

Fig. 3. The Means and SEMs for distance scores during the ten induction sessions in which the post-trial treatments of VEH or APO were administered immediately post-trial. ** $p < 0.05$ vs. all groups, * $p < 0.05$ vs. all VEH groups.

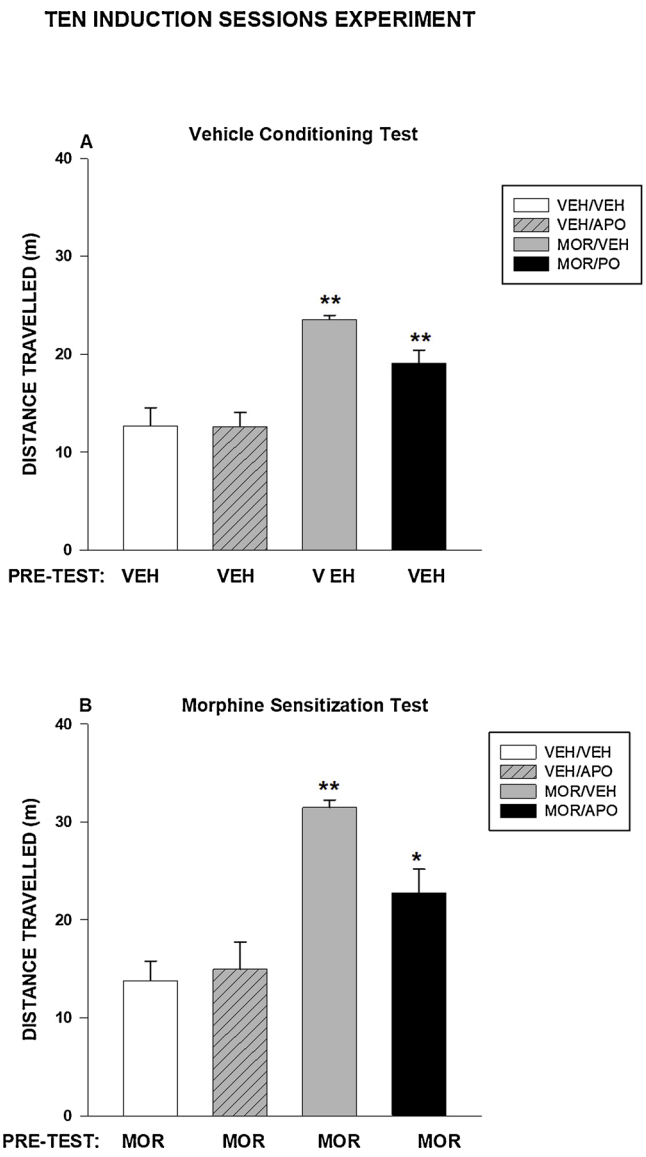

Fig. 4. A. The Means and SEMs for distance scores during the conditioning test in which all groups received vehicle before testing. ** $p < 0.05$ vs. all groups. **B.** The Means and SEMs for distance scores during the sensitization test in which all groups received morphine 10 mg/kg before testing. ** $p < 0.05$ vs. all groups, * $p < 0.05$ vs. all vehicle groups.

had p values < 0.01. On day 2 and day 3 the Tukey test showed that both groups that received MOR regardless of post-trial treatment had higher locomotion distance scores than the groups that received VEH ($p < 0.05$). From day 4 until the end of induction phase, the MOR/VEH group had higher locomotion than all groups ($p < 0.05$). The MOR/APO had higher locomotion than the VEH groups ($p < 0.05$) and there were no differences between VEH groups ($p > 0.05$). As was observed in the 5 session induction experiment, in which a decline in activity level for the MOR/APO-I group on day 4 was suggested in this 10-treatment session experiment, the reduction in activity level on day 4 was more apparent and statistically significant.

The conditioning test results are presented in Fig. 4**A**. A one-way ANOVA [$F(4, 29) = 15.10$; $p < 0.01$] showed that there were statistically significant differences among groups. Specific group comparisons were made using the Tukey test and showed that the MOR/VEH and the MOR/APO groups had higher locomotion than the VEH groups ($p < 0.05$). The VEH groups did not differ from each other ($p > 0.05$). The results of the sensitization challenge test are shown in Fig. 4**B**. The one-way ANOVA indicated statistically significant differences among groups [$F(3, 15) = 15.7$; $p < 0.01$]. Individual group comparisons using Tukey test indicated that the MOR/VEH group had higher locomotion distance scores than all groups ($p < 0.05$) and that the MOR/APO group had distance scores greater than the VEH groups ($p < 0.05$) that did not differ from each other ($p > 0.05$).

4. Discussion

In both the 5 and 10 MOR induction experiments, a strong MOR sensitization effect was evident in the immediate MOR/VEH groups that were attenuated in the immediate MOR/APO groups. In both experiments the MOR/VEH-I and MOR/APO-I groups performances were indistinguishable over the first three test sessions but diverged on session four and by session 5 the sensitization effects in the MOR/APO-I groups in both experiments were substantially reduced. Furthermore, when APO treatments were delayed 15 min. post-trial in the MOR/APO-D group, robust sensitization was generated comparable to the MOR/VEH-I groups. This result affirmed the critical significance of the post-trial treatment interval for the post-test APO effect and is in line with an effect related to the consolidation process. It has been long established that post-trial events during consolidation can have major effects on the incorporation of an association into memory [11]. On the other hand, the same immediate post-test APO treatment did not modify the activity level for the VEH/APO-I groups in either the immediate 5 or the immediate 10 induction session experiments. We have previously reported similar null effects for VEH/APO immediate post-trial treatment groups [12]. The consistent element for the absence of an immediate post-trial APO inhibitory effect in VEH animals is that the animals were extensively habituated to the test environment prior to the low dose APO post-trial treatment protocol. However, the same immediate post-trial APO treatment administered following exposure to a novel

environment produces a strong inhibitory effect [21]. We have suggested [12] for animals well acclimated to the test environment that the immediate post-trial interval is not a consolidation event and that familiarization with the test environment is analogous to a latent inhibition effect [26,34] whereas, the novel environment experience evokes a consolidation event. Although the MOR/APO groups were also habituated to the test environment prior to the start of the induction protocol, this was their first experience with the MOR plus test environment stimulus complex. In this regard, the test environment in the induction protocol can be considered a novel experience and therefore one more likely to initiate a consolidation process. In that the MOR/APO post-test drug effect seemingly occurs during consolidation, it creates the possibility that the APO effect can become incorporated into the MOR/test environment consolidation process. While this analysis overall is consistent with the present findings, the results are more complex and raise additional questions. First of all, the immediate MOR/APO-I and MOR/VEH-I treatment groups did not differ in their MOR response until test session 4. In terms of the APO treatments, session 4 represents the effect of the third APO post-test treatment that followed induction session 3. A possible clue as to why there was a delay in the efficacy of the low dose APO post-test treatment until the third post-test APO treatment is suggested by the MOR response shown in the induction results in Figs. 1 and 3. First of all, there was no apparent effect of the MOR versus VEH treatments on day 1 so, from the consolidation perspective stated above, there would be no expectation for a post-trial consolidation event after session 1 that could then impact session 2. This finding is not surprising in that test environment familiarization has been shown to prevent the acute locomotor stimulation effects induced by other indirect agonists such as cocaine [4,3]. By day 2 however, there was an effect of the MOR/VEH-I treatments. Seemingly, this MOR response represented the start of a sensitization effect and the initiation of a re-consolidation process following induction day 2. While a MOR effect was initiated on day 2 the influence of the post-trial APO-I treatments was not manifested until induction day 4. The day 4 effect represents the impact of the MOR/APO-I treatment following induction day 3. Whether the inhibitory post-trial APO treatment inhibitory effect required 2 post-trial treatments (post-trial session 2 and post-trial session 3) to be effective or whether the magnitude of the MOR sensitization effect needed to activate a re-consolidation process requires up to 3 treatments at this dose and in this testing protocol remains to be experimentally addressed. Seemingly if the latter is the case then a group that receives its first post-trial APO treatment after the third or fourth MOR treatment would have the same inhibitory effect on the fourth or fifth MOR induction treatment as a group that receives the same APO treatments after every MOR treatment as was the case in the present study.

The conditioning and sensitization challenge test results are another interesting facet of the findings obtained in the present study. In the 5 day induction experiment, the post-trial MOR/APO-I conditioned and sensitization effects were reduced and did not reach statistical significance when compared to the VEH groups. In the 10 day experiment, a conditioned response was observed in the MOR/APO-I group but the sensitization response in the challenge test was diminished relative to the sensitization response in the MOR/VEH-I group. Seemingly, the partial sensitization response in the MOR/APO-I over the course of the 10 treatment sessions was sufficient to generate a conditioned response.

The finding in the present report that a low dose APO treatment given immediately post-trial to MOR treated animals substantially attenuated the sensitization response induced by MOR is consistent with our earlier report [12] in which the same low dose APO treatment administered immediately post-trial during the re-consolidation of a MOR conditioned response markedly diminished the conditioned response. While the importance of dopamine in motor behavior has been long known, Beninger (1983) [8] demonstrated that dopaminergic stimulant drugs do not simply increase movement but also enhance the salience and incentive value of the environmental stimuli. Consequently, a dopaminergic inhibitory treatment induced by the low dose of apomorphine used in the present study would seemingly decrease the salience and incentive value of the contextual cues present during consolidation. Guided by this framework, the dopamine inhibitory effect of the APO during consolidation on salience and incentive value would decrease the motivational significance of the association. The unusual feature of this algebraic summation in the present study is that it occurs post-trial and is incorporated in memory and that the algebraic summation is manifested in a subsequent MOR test without the APO treatment.

In conclusion, the present findings raise several important issues regarding the sensitization/conditioning relationship and suggest a number of new protocols pertinent to this issue. For example, how the post-trial MOR/APO interaction compares to the pretrial MOR/APO interaction will be important to determine. That is, after the completion of an induction protocol, would the response of the pre versus post-trial MOR/APO groups differ in a VEH conditioning test, a MOR sensitization challenge test as well as a test in which APO is administered pretrial. This assessment will allow for a determination as to whether the associative drug/drug interaction effect that occurs in the presence of contextual stimuli is different from when the drug-drug interaction occurs post-trial. Thus, the present study suggests several new methodological directions for the investigation of drug interactions relevant to drug conditioning and sensitization

Acknowledgements

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