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Morphine administered post-trial induces potent morphine conditioned effects if the context is novel but not if the context is familiar

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ABSTRACT

Morphine administered shortly after exposure to a novel environment induces potent locomotor stimulant conditioning. Environmental novelty is important as pre-exposure (PE) to a stimulus can attenuate the capacity to acquire conditioned stimulus (CS). Here, the importance of environmental novelty for the efficacy of an open-field to become a CS for elicitation of a morphine conditioned response was assessed by comparing the effects of morphine administered post-trial following a 5 min exposure to a novel environment versus a PE environment. Four groups of rats (2 vehicle and 2 morphine groups) were used. Two groups received ten daily 5 min non-drug PEs to an open-field arena and the other two groups were not pre-exposed to the environment. Subsequently, all groups received post-trial injections of either vehicle or morphine immediately after each of five daily 5 min sessions in the open-field. Importantly, on the first day of testing prior to the first post-test morphine administration, the locomotor activity of the novel and PE groups was not different. Over the 5 post-trial morphine treatments, the activity of the PE morphine group, the PE vehicle and the novel environment vehicle groups did not change and were equivalent. In contrast, in the novel environment morphine group, a conditioned hyperactivity response increased with repeated post-trial morphine treatments. For the morphine group it is suggested that the novel environment initiated a post-trial stimulus trace that occurred in temporal contiguity with the post-trial drug response and enabled the trace to become a CS for the morphine unconditioned response. In contrast, PE induced a latent inhibition effect in the PE morphine group, thus the post-trial CS trace was insufficient to become associated to the morphine response and no conditioning occurred. In addition to conventional drug induced Pavlovian delay conditioning, the findings are suggestive of drug induced Pavlovian trace conditioning.

1. Introduction

The use of an environmental context such as an open-field is widely employed in preclinical studies to investigate conditioned and sensitized behavioral stimulant effects induced by drugs such as amphetamine, apomorphine and cocaine (Anagnostaras and Robinson, 1996; Bloise et al., 2007; Braga et al., 2009a; Braga et al., 2009b; Carey and Gui, 1998; Damianopoulos and Carey, 1992; de Matos et al., 2010; Mattingly et al., 1997; Mattingly et al., 1988). In mice and rats, morphine induced locomotor stimulation effects undergo sensitization and conditioning with repeated treatments (Leite Junior et al., 2019; Neisewander and Bardo, 1987; Powell and Holtzman, 2001; Sharf et al., 2010; Scheggi et al., 2000; Tzschentke and Schmidt, 1995; Vanderschuren et al., 1997; Vanderschuren et al., 1999; Vezina and Stewart, 1984).

In general, these drug induced conditioning studies appear to conform to a basic Pavlovian delay conditioning protocol, in which the open-field serves as the contextual conditioned stimulus (CS) that is present in temporal contiguity with the onset of the drug response, which is the unconditioned stimulus/unconditioned response (UCS/UCR). Interestingly, there have been several recent reports (Santos et al., 2015; Santos et al., 2017; Santos et al., 2018) showing that conditioned and sensitized locomotor stimulant effects of apomorphine can also be induced using a post-trial drug treatment protocol in which

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the drugs are administered immediately after removal from a non-drug placement in a novel open-field so that the onset of the drug response (UCS/UCR) occurs outside the open-field and not in temporal contiguity with contextual CS. It was suggested that this post-trial conditioning represented a trace conditioning effect. Furthermore, the magnitude of the conditioned and sensitized locomotor effects using this protocol were comparable to the conditioned and sensitized locomotor effects induced by the same drug dose levels used in conventional Pavlovian delay conditioning protocols, in which the drugs were administered prior to placement in an open-field.

Trace conditioning was first demonstrated by Pavlov (1927) and was attributed to a central representation of a trace of the stimulus that persisted after its termination, enabling a contiguous association of the stimulus with the UCR. In line with the stimulus trace proposal of Pavlov, a number of recent studies (Cheng et al., 2008; Cox et al., 2013; Tam and Bonardi, 2012; Wilmot et al., 2019; Zhang et al., 2019) using well-established Pavlovian conditioning protocols including eye blink conditioning, have demonstrated central nervous system activity in brain structures such as the hippocampus during the temporal gap between the termination of the CS and the onset of the UCR. Importantly, these are brain areas implicated in memory and association processes. In this regard a recent report by Menezes et al. (2015), found that immediately after removal from a novel open-field, there is activation in rat brain areas such as the hippocampus as well as dopamine release that persists for a brief period, pointing to a possible stimulus trace that potentially could become associated with the immediate post-test drug treatment used in post-drug conditioning studies (Santos et al., 2015; Santos et al., 2017; Santos et al., 2018). Furthermore, the additional finding (Santos et al., 2015, Santos et al., 2017, Santos et al., 2018) that the same drug treatments administered after a 15 min delay following removal from the novel environment showed that no conditioning occurred, indicating that the trace was no longer present, is also consistent with a trace conditioning effect. The temporal trace parameters for this type of contextual trace conditioning while < 15 min, remain to be determined but is clearly longer than for auditory stimuli used in eye-blink conditioning, which is < 1 s but substantially shorter than for taste conditioning in which the UCS can be delayed by several hours (Garcia et al., 1974; Riley et al., 1984). Another key element of conditioning is the novelty of the stimulus in that repeated pre-exposure to the stimulus to be used as a CS substantially diminishes the efficacy of the stimulus to acquire CS properties. In drug studies using auditory stimuli as the CS, this pre-exposure effect has been labeled as latent inhibition (Lubow and Moore, 1959) and this has been utilized to investigate effects of drugs on attention (Feldon and Weiner, 1991). While latent inhibition has been studied in delay drug conditioning protocols, it has not been investigated with drugs in contextual trace conditioning. A seemingly straightforward way to assess latent inhibition effects in post-test drug conditioning using the novel environment protocol is to compare the conditioning induced by the post-test drug treatments given after exposure to a novel open-field versus after exposure to the same open-field environment following repeated pre-exposure so that it is no longer novel and consequently evoking a less effective post-trial trace. The post-trial conditioning studies mentioned above make for an interesting test for latent inhibition (Santos et al., 2015; Santos et al., 2017; Santos et al., 2018). These studies used brief (5 min) test sessions in order increase the likelihood that the post-test trace process initiated by the novel environment exposure continues to be ongoing after removal from the novel environment, so that the drug treatments would have the opportunity to occur in temporal contiguity with the trace. Interestingly, the repeated brief 5 min tests used in these studies have also revealed that the 5 min locomotor activity levels remain essentially unchanged in vehicle groups even with numerous repeated tests. Using repeated 5 min non-drug exposures to an initially novel open-field to attenuate the novelty of the open-field would not be manifested in a change in the dependent variable of locomotor activity. Therefore, the presumptive loss of novelty would indeed be latent.

Previously, it has been reported (Oliveira et al., 2019) that morphine (3, 5, 10 mg/kg) administered shortly after a brief 5 min exposure to a novel environment induces dose linked persistent morphine conditioned hyper-locomotor activity. The present study compares the induction of conditioning of morphine hyper-activity by administering morphine following a 5 min exposure to a novel open-field versus a 5 min exposure to the same open-field following ten 5 min pre-exposures. Furthermore, this study provides a unique variation on the conventional paired/unpaired drug conditioning design in that the pre-exposure and novel groups would both receive the morphine treatment immediately after the same open-field exposure but the pairing versus non-pairing would depend on whether or not the pairing occurs in conjunction with an open-field environment induced post-test trace.

2. 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 h/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. This process included being placed in a transport cage and taken to the injection administration bench located in an anteroom adjacent to the experimental testing room. The animals were given VEH injections. In this way, the animals were familiarized with the handling and injection aspects of the testing protocol. All the 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. 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 travelled (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 (Nasello et al., 1998) 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

Four groups were used (n = 7 per group). Two novel environment groups (the NOVEL groups) that received no prior arena tests before initiating the drug treatment phase. Two pre-exposure groups (the PRE-

EXP groups) were given 10 daily 5 min sessions in the open-field arena prior to the start drug treatment phase. One day after completion of this pre-exposure testing, each of the four groups received a 5 min test in the open-field arena. Immediately prior to each 5 min test each group received vehicle (VEH) injections. Immediately following each 5 min test, one PRE-EXP group and one NOVEL group received vehicle injections (VEH) and the other PRE-EXP and NOVEL groups received morphine 10.0 mg/kg (MOR) injections immediately post-test. Five post-trial treatments were administered after each of five successive daily 5 min open-field test sessions. For the post-trial treatments, the animal was removed from the open field, placed in a transport cage, taken to an injection administration bench in an adjacent room, injected with either VEH or MOR and then placed back in the transport cage and returned to the vivarium. The whole process required approximately 15–20 s.

The first test session was essentially a VEH test session for all groups in that the morphine injections were not administered until after the first test session. In order to assess the effect of the fifth post-trial morphine injections, a sixth test session was conducted in that the effects on behavior in the open field induced by the post-trial morphine injections are expressed in the open field test on the following day. No injections were administered after the sixth test session.

2.5. Statistics

For the pre-exposure and post-test conditioning protocols 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 one-way ANOVA followed by Tukey post-hoc tests using $p < 0.05$ as the criterion for statistical significance.

3. Results

Fig. 1 presents the results of the 10 non-drug habituation test sessions for the two groups that underwent the pre-exposure protocol. A repeated two-way ANOVA showed that there was no effect of groups [$F(1, 12) = 0.01$; $p > 0.05$], no effect of days of treatment [$F(9, 108) = 0.80$; $p > 0.05$] and no interaction group × day [$F(9, 108) = 0.35$; $p > 0.05$].

Fig. 2 shows the locomotion during day 1 of the induction phase. This test session was a VEH test day for all groups in that the morphine injections were not administered until the test session was completed. A one-way ANOVA showed that there was no difference among the experimental groups [$F(3, 24) = 0.21$; $p > 0.05$].

Fig. 3 shows the locomotion for days 2–6. A repeated two-way ANOVA showed that there was group × day interaction [$F(12, 96) = 2.10$; $p < 0.05$], an effect of groups [$F(3, 24) = 7.0$; $p < 0.01$] but no effect of days of treatment [$F(4, 96) = 1.20$; $p > 0.05$]. A one-way ANOVA followed by Tukey tests to further analyze the interaction group × days showed that on day 2 (Fig. 3A) [$F(3, 24) = 1.72$; $p > 0.5$] there was no statistically significant difference among the groups. On day 3 (Fig. 3B) [$F(3, 24) = 3.51$; $p < 0.05$], the NOVEL MOR group had higher locomotion scores than all groups as well as on day 4 (Fig. 3C) [$F(3, 24) = 5.51$; $p < 0.01$], day 5 (Fig. 3D) [$F(3, 24) = 12.0$; $p < 0.01$] and day 6 (Fig. 3E) [$F(3, 24) = 8.43$; $p < 0.01$].

4. Discussion

The present finding that a conditioned hyper-locomotion response was induced by post-trial 10 mg/kg morphine treatments administered following exposure to a novel environment is consistent with a previous report (Oliveira et al., 2019). This hyper-locomotion effect can be considered as a conditioned response in this post-test treatment protocol in that all testing is conducted in the non-drug state 24 h after the post-test morphine treatment. On the other hand, it could be argued that this hyper-activity was not a conditioned response but simply a morphine withdrawal effect. This possibility is ruled out by the absence of a hyper-activity response in the pre-exposure morphine group. That is, the pre-exposure morphine group was given the same 5 min test in the same open-field environment, administered with the same dose of morphine immediately post-test and tested at the same time post morphine injection but yet did not exhibit hyper-activity and furthermore, its locomotor behavior was indistinguishable from vehicle treated groups. In view of this similarity in testing and treatment, the response of the novel environment group cannot be attributed to a non-specific effect of the morphine treatment per-se.

Furthermore, the present study extends the earlier morphine post-trial conditioning report (Oliveira et al., 2019) in pointing up the key role of the novelty of the environment in the efficacy of morphine induced conditioning by the post-trial administration of morphine. Importantly, in the first test session prior to the initiation of the post-trial morphine protocol, the novel environment group and the pre-exposure group had essentially equivalent locomotor activity scores so the subsequent differential in post-test effects on locomotor effects were not related to pre-treatment activity levels. It was also interesting that after the ten 5 min pre-exposures to the open-field test arena, activity levels did not change from when the open-field environment was novel. In that the pre-exposures ostensibly would increase familiarity to the test arena so that it was no longer novel, we have interpreted this as a latent inhibition effect such that the post-test after-effects induced by the novel environment that are necessary for post-test drug conditioning trace were made insufficient by the pre-exposure protocol. While the occurrence of post-test trace effects generated by a novel environment can be inferred from the induction of a morphine conditioned effect only after exposure to the open-field when it is novel, the question becomes what is the trace. We have suggested (Santos et al., 2015; Santos et al., 2017; Santos et al., 2018) that the novel environment neurobiological study by Menezes et al. (2015) is relevant for post-test drug conditioning studies using drugs with significant dopaminergic activity. These investigators (Menezes et al., 2015) found that following removal from a novel environment, there is activation in rat brain structures linked to brain activity in associative systems such as the hippocampus along with the release of dopamine that persists for a time post-test, that is sufficient to generate behavioral stimulant effects. This dopamine release may be relevant to the conditioned hyperactivity induced by post trial morphine in that there is substantial evidence that morphine also increases dopaminergic activity (Chen et al., 2015; Liu et al., 2014; Mori et al., 2016; Vanderschuren et al., 1999). Thus, formulating this post-trial conditioning of morphine in terms of dopamine, suggests that the elicitation of the conditioned morphine hyper-activity response seemingly could represent a summation of the novel environment elicited dopamine response plus the morphine dopamine response elicited by the conditioned morphine drug association. Thus, the transformation of the open-field into a morphine drug response CS may elicit an amplified dopamine response. Assessment of this possibility however, clearly awaits further neurobiological investigations.

In the present study, the latent inhibition protocol appeared highly effective in preventing the post-test conditioning of the morphine response. Of course, it is possible that with additional post-test trials the latent inhibition effect could eventually be reversed. While latent inhibition is readily reversible in delay conditioning protocols (Cheng et al., 2008; Cox et al., 2013; Leite Junior et al., 2019; Tam and Bonardi, 2012; Wilmot et al., 2019; Zhang et al., 2019) it is also the case that in delay conditioning the stimulus subjected to latent inhibition is always presented in association with the unconditioned stimulus. Evidently, this pairing of the stimulus with the unconditioned stimulus (UCS) is able to reverse the latent inhibition. Latent inhibition effects remain to be investigated in conventional eyelid trace conditioning protocols. It is not known if an auditory stimulus subjected to latent inhibition is able to elicit a stimulus trace sufficient to serve as a CS. If

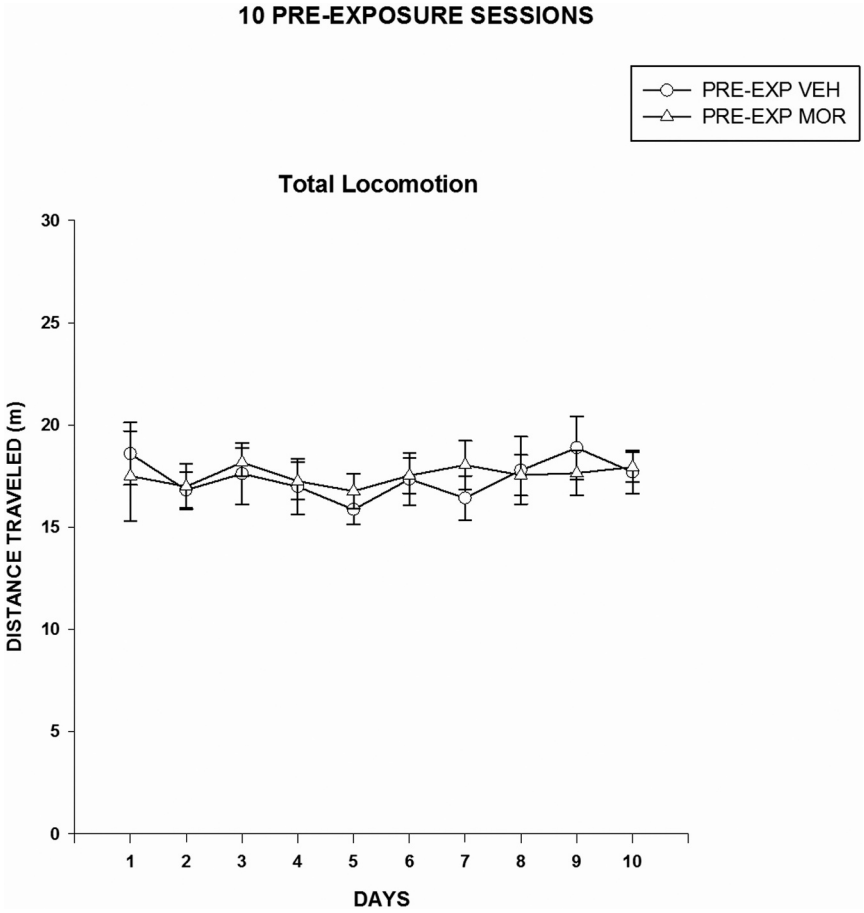

Fig. 1. Means and S. E. M.s for distance travelled (m) during pre-exposure to 10-successive daily 5 min tests for total locomotion in the open-field arena.

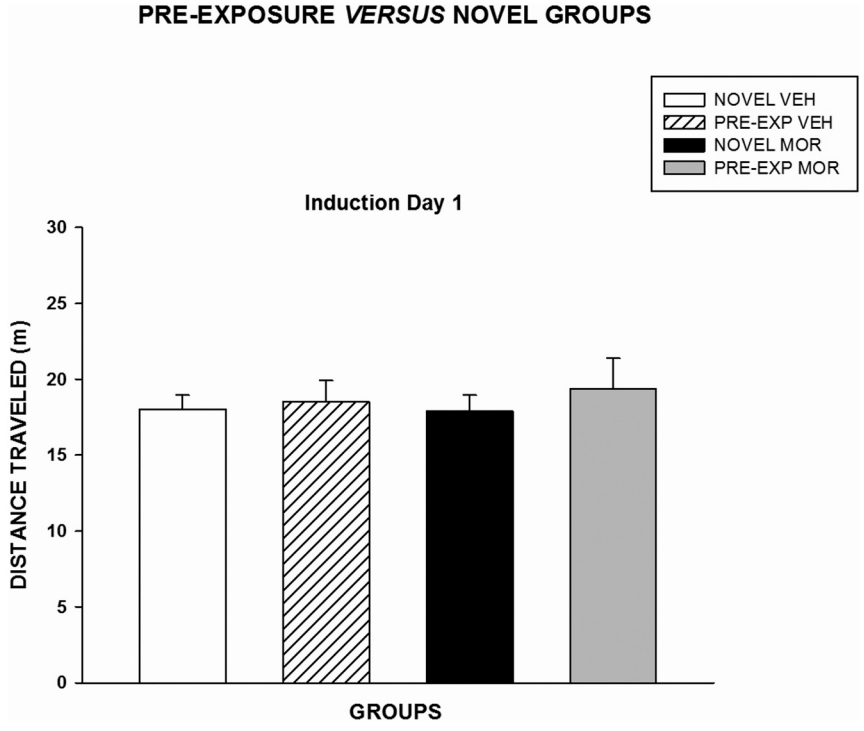

Fig. 2. Means and S. E. M.s for distance travelled (m) during the 5 min test on induction day 1.

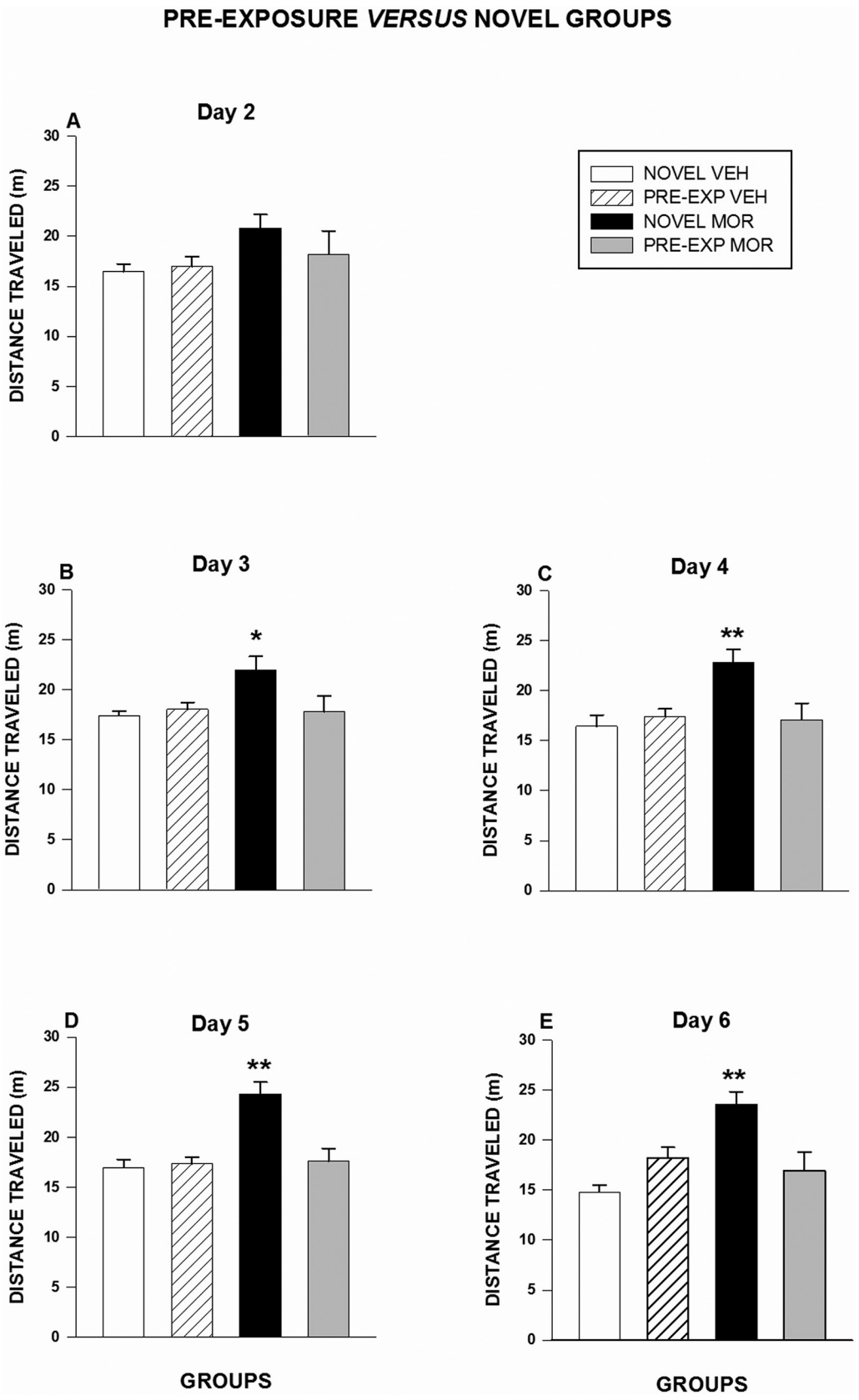

Fig. 3. Means and S. E. M.s for distance travelled (m) during day 2 (A), day 3 (B), day 4 (C), day 5 (D) and day 6 (E). ** $p < 0.01$ and * $p < 0.05$ versus all other groups (repeated ANOVA followed by Tukey test).

the stimulus is no longer able to evoke an adequate stimulus trace then the UCS would not interact with the stimulus and repeated pairings would only serve to increase latent inhibition. Not only are direct comparisons in behavioral conditioning studies of interest wherein a stimulus is subjected to latent inhibition and then assessed in a delay versus a trace conditioning protocol using the same UCS but, in addition, neurobiological studies are needed. The neurobiological investigations are needed to compare the central nervous system (CNS) impact of a stimulus that is to be used as a CS when it is novel and after a latent inhibition protocol. While an attenuated CNS response to the onset of the stimulus is to be expected, as it is used in delay conditioning paradigms, it is unknown as to whether the stimulus subjected to latent inhibition is able to evoke a trace after the termination of the stimulus as it is used in a trace-conditioning paradigm.

Similarly in the open-field drug conditioning model used in the present study, the findings in this latent inhibition investigation indicate it would be critical to measure post-trial changes such as activity in the hippocampus and dopamine release after the initial 5 min exposure to the open-field when it is novel versus after repeated 5 min pre-exposures to the open-field. This would be a particularly important with regard to latent inhibition in the contextual conditioning model used in the present study in that locomotor activity levels did not change with pre-exposure so that the measurement of neurobiological changes following removal from the test environment would not simply be secondary to the animal being less active as is typically the case in standard behavioral habituation protocols which lead to a decrease in behavioral activity.

In conclusion, the present study is consistent with the putative role of a post-trial trace induced by a novel environment for the induction of post-trial morphine conditioning. The experiment also suggests methodological advantages for using brief test sessions that do not decrease activity for the study of latent inhibition in psycho-stimulant post-trial trace conditioning. Furthermore, the impact of latent inhibition on the stimulus trace evoked by a stimulus is of importance to trace conditioning more broadly.

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