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Post-trial induction of conditioned apomorphine stimulant and inhibitory response effects: Evidence for potent trace conditioning of drug effects

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ABSTRACT

The Pavlovian conditioning of drug effects has frequently been demonstrated using protocols that are variants of Pavlovian delay conditioning. We undertook to determine if drug conditioning could be induced using a Pavlovian trace conditioning procedure. Rats were tested in a novel open-field environment for 5 min and in post-trial phase were injected either with vehicle, 2.0 mg/kg or 0.05 mg/kg apomorphine immediately or after a delay of 15 min. The procedure was repeated three times and subsequently a 30 min non-drug test was given. The vehicle and 15 min post-trial apomorphine groups did not differ and in the 30 min test their locomotion scores were equivalent to another vehicle group tested for the first time. The group that received 2.0 mg/kg apomorphine immediately post-trial had a progressive increase in activity over the three sessions and also initially in the 30 min test. The results for the 0.05 mg/kg immediate post-test group were a mirror image of the 2.0 mg/kg apomorphine group. Post-trial apomorphine treatments can induce potent conditioned effects indicative of the efficacy of trace conditioning of drug effects. These finding suggest that trace conditioning may be an important contributor to the potency of conditioned-drug effects in the development of drug addiction.

1. Introduction

It is widely accepted that activation of dopamine systems is a common feature of drugs of abuse. Of major importance for the addictive potency of psychostimulant drugs is the transformation of the contiguous contextual stimuli into conditioned stimuli and incentive stimuli that can motivate and maintain addictive behavior in that the pairing of a drug effect with a specific environment is essentially a Pavlovian drug conditioning protocol, it is not surprising that the contextual cues can acquire conditioned stimulus properties and in a post-treatment non-drug test evoke a conditioned drug response. Many preclinical studies have shown that repeated administration of psychostimulants induces both context specific sensitization and conditioned effects that enhance the drug effects (Borowski and Kuhn, 1991; Mazurski and Beninger, 1991; Heidbrenner and Shippenberg, 1994; Mattingly et al., 1994; Carey and Gui, 1998; Bloise et al., 2007; Braga et al., 2009a, 2009b; Dias et al., 2010; de Matos et al., 2010; Filip et al., 2010). These features of psychostimulant drugs are generally ascribed to the pro-dopamine effects of these drugs such that the association of dopamine activation to contextual cues can transform the associated stimuli into conditioned and incentive stimuli that can promote further drug taking and seeking (Robinson and Berridge, 1993; Beninger and Miller, 1998).

Typically, drug-conditioning protocols differ from the standard Pavlovian conditioning paradigm in that the drug treatment (the UCS) is administered before rather than after the CS. Critically there is extensive UCS and the CS overlap. While the administration of the drug UCS, procedurally, precedes the contextual CS, this arrangement is unlike backward conditioning in that the onset of the psychostimulant UCS drug effect is not followed by an inconsequential stimulus as in conventional conditioning but rather the psychostimulant drug effect induces sensory/motor activation so that the environmental context is transformed into a highly salient stimulus complex by the drug UCS. In this way the CS contextual cues acquire the UCS salience effects elicited by the psychostimulant drug treatment. Another deviation of psychostimulant drug conditioning from conventional Pavlovian conditioning is that the UCS drug treatment can last for a substantial duration and it occurs in a test environment serving as the CS. Consequently, the CS–UCS overlap is considerably longer than for the conventional Pavlovian discrete CS conditioning protocol.

We have found that apomorphine is of particular interest in terms of dopamine drug conditioning in that this drug can have pronounced but opposite effects upon dopamine neurotransmission depending upon dose level. In the low dose range in rats (<0.1 mg/kg) apomorphine can induce a profound inhibition of movement presumably by a

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preferential stimulation of dopamine auto-receptors and can substantially decrease dopamine activity in the brain (Aghajanian and Bunney, 1973; DiChiara et al., 1977; Missale et al., 1998). At higher dose levels (>0.5 mg/kg) apomorphine increasingly stimulates dopamine post-synaptic receptors and is a potent behavioral stimulant and generates hyper-locomotion (Mattingly et al., 1988a, 1988b; Rowlett et al., 1997). In line with the presumed role of dopamine in the formation of stimulus–response associations, the high dose locomotor activation induced by a high dose of apomorphine is readily conditioned to the associated environmental cues (Carrera et al., 2012). In contrast, the low dose apomorphine treatment induces a pronounced hypoactivity; but, even after repeated pairings of this apomorphine inhibitory effect to environmental cues, it does not produce a conditioned inhibitory locomotor response (Braga et al., 2009a, 2009b; de Mello Bastos et al., 2014). This disparity appears consistent with the importance of dopamine in learning and memory in that the behavioral inhibition manifested in response to the low dose apomorphine treatment is reflective of dopamine inactivity wherein both sensory and motor systems are suppressed. This circumstance is seemingly unique to the apomorphine induced hypo-activity in that hypo-activity induced by dopamine postsynaptic antagonists such as haloperidol can be conditioned even though the suppression of locomotion can be severe (Banasikowski and Beninger, 2012a, 2012b). This striking difference may be related to the opposite effects of these drugs on the dopamine neurons. Whereas low dose apomorphine selectively stimulates the dopamine auto-receptors and shuts off the dopamine neurons, the dopamine antagonism by haloperidol occurs at postsynaptic as well as auto-receptor sites and the auto-receptor antagonism increases the activity of the dopamine neurons (Carey and DeVeaugh-Geiss, 1984).

We have reported previously (Carrera et al., 2012) that low dose apomorphine induced hypoactivity could be conditioned if a post-trial protocol was used in which the low dose apomorphine treatment was administered immediately after removal from an open-field in which the animals had previously been conditioned with the high dose of apomorphine. The same post-trial low dose treatment was ineffective in non-conditioned unpaired animals. We attributed the efficacy of the post-trial conditioning of a low dose of apomorphine response suppression effect selectively in the previously high apomorphine dose conditioned groups to an interaction with the post trial reconsolidation of the memory trace of the conditioned response. While a modification of the re-consolidation of the memory trace is one possibility it is also the case that this result could represent trace conditioning in that the post-trial administration of a treatment after the CS is terminated is also a trace conditioning protocol. In typical trace procedures the CS is a punctate sensory stimulus and the interval between the offset of the CS and the onset of the UCS is brief in the order of a few seconds. In that the conditioning induced by a high dose of apomorphine would generate intense dopamine activation by apomorphine and thereby make the contextual stimuli highly salient it is possible that a brief exposure to the cues evokes a stimulus/response trace that persists post-trial for a sufficient duration to become linked to a post-session drug treatment. This latter analysis comports well with the findings that the post-trial apomorphine treatments generated conditioned responses that matched the unconditioned drug responses induced by apomorphine namely response inhibition for the low dose apomorphine post-trial treatment and response activation for the high dose apomorphine post-trial treatment. In the present report we sought to investigate this possibility further by using a brief exposure to a novel environment to achieve intense sensory/motor arousal to elicit the sensory/motor trace to be paired with the post-trial apomorphine treatments.

Our premise was that a brief exposure to a novel environment would create an intense stimulus trace that could persist for a sufficient duration to become associated with the post-session drug treatment. In that this was the first exposure of the animals to the stimulus complex and there was no re-consolidation to consider. In addition, effects on consolidation would tend to either enhance or retard habituation. On the other hand, trace conditioning of the post-trial apomorphine treatments should generate response suppression (low dose) or response stimulation (high dose). The present report details the effects of high and low dose apomorphine treatments administered following a 5 min exposure to a novel environment.

2. Methods

2.1. Subjects

Male Wistar albino rats provided by the State University of North Fluminense Darcy Ribeiro, initially weighing 200–250 g were housed in individual plastic cages (25 × 18 × 17 cm) until the end of 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 0700 h and off at 1900 h). All experiments occurred between 14:00 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 camera (SONY, model IR575M), 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 and to enhance the contrast between the white subject and dark background of the test chamber. Masking noise was provided by a fan located in the experimental room that 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 (i.e., test chamber).

2.3. Drugs

Apomorphine-HCl (Sigma, St. Louis, MO, USA) was dissolved in 0.1% ascorbate/saline (2.0 mg/ml) and was injected subcutaneously in the nape of the neck at a dose of 2.0 and 0.05 mg/kg. A 0.1% ascorbate/saline solution was used as vehicle for the apomorphine experiments. All doses were administered in a volume of 1.0 ml/kg body weight. Drug solutions were freshly prepared before each experiment.

2.4. Experimental procedure

There were two experimental conditions. In experiment 1, rats received vehicle administration immediately before being placed into the experimental arena for 5 min and locomotion was recorded. Immediately after the end of test session (I-POST), the post-trial treatments were administered. For the post-trial treatments, the rats were equally divided into three groups in which the first group received vehicle (VEH-I-POST; n = 6), the second group received apomorphine 0.05 mg/kg (APO-0.05-I-POST; n = 6) and the third group received apomorphine 2.0 mg/kg (APO-2.0-I-POST; n = 6). These treatments were administered for 3 consecutive days, one trial per day and were named as the immediate post-trial phase. In experiment 2, the same protocol as in experiment 1 was followed, except that the post-trial treatments were administered 15 min after (15′-POST) a 5 min arena session test and was named 15 min post-trial phase. Thus, the final groups from experiment 2 were: VEH-15′-POST (n = 6), APO-0.05-15′-POST (n = 6) and APO-2.0-15′-POST (n = 6). One day after completion of both post-trial phases, a final test was carried out, in which the