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Research report

Post-trial dopaminergic modulation of conditioned catalepsy: A single apomorphine induced increase/decrease in dopaminergic activation immediately following a conditioned catalepsy response can reverse/enhance a haloperidol conditioned and sensitized catalepsy response

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HIGHLIGHTS

- Repeated haloperidol treatment produced conditioned and sensitized catalepsy.
- A single Post-trial high dose of apomorphine reversed conditioning and sensitization.
- A single Post-trial low dose of apomorphine enhanced conditioning and sensitization.
- Contextual cues are bi-directionally sensitive to post-trial drug treatment.

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ABSTRACT

Haloperidol can induce catalepsy and this drug effect can be conditioned as well as sensitized to contextual cues. We used a paired/unpaired Pavlovian conditioning protocol to establish haloperidol catalepsy conditioned and sensitized responses. Groups of rats were given 10 daily catalepsy tests following administration of vehicle (n = 24) or haloperidol (1.0 mg/kg) either paired (n = 18) or unpaired (n = 18) to testing. Subsequently, testing for conditioning was conducted and conditioning and sensitization of catalepsy were observed selectively in the paired group. Immediately following a second test for catalepsy conditioning, the groups were subdivided into 4 vehicle groups, 3 unpaired haloperidol groups and 3 paired haloperidol groups and were given one of three post-trial treatments (vehicle, 0.05 mg/kg or 2.0 mg/kg apomorphine). One day later the conditioned catalepsy test 3 was carried out and on the next day, a haloperidol challenge test was performed. The post-trial apomorphine treatments had major effects on the paired groups upon both conditioning and the haloperidol challenge test. The low dose apomorphine post-trial treatment enhanced both the conditioned and the haloperidol sensitized catalepsy responses. The high dose apomorphine post-trial treatment eliminated conditioned catalepsy and eliminated the initial acute catalepsy response to haloperidol that was induced in the vehicle control groups. These results demonstrate the sensitivity of conditioned drug cues to modification by increases/decreases in activity of the dopamine system in the immediate post-trial interval after a conditioning trial. This demonstration that post-trial dopaminergic drug treatments can modify conditioned drug behavior has broad implications for conditioned drug effects.

1. Introduction

Numerous studies have shown that increases/decreases in brain dopamine activity can have potent effects upon learning and memory by increasing/decreasing reward effects [34] and by

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increasing/decreasing the incentive value of stimuli [eg. Refs. [6,7]]. It is also the case that psycho-stimulant drugs such as cocaine and amphetamine, which have strong pro-dopamine effects, can function as unconditioned stimuli and induce conditioned and sensitization effects that are important contributors to the addictive potency of these drugs [1,12,20,30,31].

Locomotor stimulation is a commonly used psycho-stimulant response in the preclinical study of conditioning and sensitization. In general, these investigations conform to a Pavlovian conditioning paired/unpaired paradigm in which the test environment serves as the conditioned stimulus (CS), the drug treatment the unconditioned stimulus (UCS) and the drug induced locomotor response the unconditioned response (UCR). Mostly these investigations have used a Pavlovian delay conditioning protocol in which the drug treatment is administered prior to placement in the test environment so that the drug response occurs in temporal contiguity with the test environment cues. Pavlovian conditioning also can occur with a temporal gap between the termination of the CS and the onset of the UCS. Pavlov had proposed that a central representation or stimulus trace of the CS persists during the temporal gap so that the CS trace becomes contiguous with the onset of the UCS [46,47]. In recent trace conditioning investigations the central representation of the CS trace has been more firmly connected to central nervous system (CNS) activity and linked to CS initiated neural activity in brain structures such as the hippocampus [50,59]. This trace-conditioning paradigm has only recently been applied to psychostimulant drug conditioning [55]. In these studies, the drug is given post-trial once a CS has been established by conventional delay conditioning [11]. While this post CS drug administration fits into a Pavlovian trace conditioning protocol it also can be viewed as a memory re-consolidation paradigm. In fact, substantial evidence has accumulated that some conditioned drug associations can be disrupted by treatments administered shortly after termination of a drug CS. This vulnerability of previously formed association has been most thoroughly investigated with regard to conditioned stimuli induced by addictive drugs.

There have been a number of pre-clinical reports that have used cue activation of conditioned drug responses followed subsequently by post-trial treatments designed to impair the drug-cue association during what is thought to be a memory re-consolidation phase [8,24,25,26,27,35,39,40,44,45,48,49]. This cue-evoked reconsolidation of existing associations has important implications for drug addiction as well as memory modification treatments more broadly, in that the re-activated memory trace can now be modified by post-trial treatments.

In several recent experiments [16–18,55] we have shown that the drug apomorphine given immediately after removal from a psychostimulant paired test environment or a novel test environment has a substantial impact on the subsequent non-drug behavior in the test environment. The impact of post-trial apomorphine depends upon the unconditioned apomorphine drug response. In the low dose range in rats (<0.1 mg/kg) apomorphine preferentially stimulates dopamine auto-receptors and thereby inhibits dopamine activity in the brain, manifested in behavior as a profound response inhibition [2,23,41]. At higher dose levels (>0.5 mg/kg) apomorphine increasingly stimulates postsynaptic dopamine receptors and is a potent behavioral stimulant [36,37,52]. Importantly, we have shown in several reports, in which we first established a conditioned stimulant response to test environment cues [16–18,55], that when the low dose apomorphine treatment is given post-trial immediately following removal from the test environment after a conditioning test then in a subsequent conditioning test session, the test environment no longer elicits a behavioral stimulant effect. If this same protocol is followed with the same low apomorphine treatment that is administered after a delay of 15 min following removal from the test environment, then the conditioned behavioral stimulant response is unaffected in the subsequent conditioning test. In contrast, if a high stimulant dose of apomorphine is administered immediately after removal from the test environment the conditioned behavioral stimulant response evoked by the test environment in a subsequent conditioning test is enhanced. Again, this post-trial facilitative effect of the high dose of apomorphine does not occur if the apomorphine treatment is administered after a delay of 15 min following removal from the test environment. Furthermore, when these same groups are subsequently given a drug sensitization challenge test, the sensitization is either eliminated (immediate post-trial apomorphine low dose) or potentiated (immediate post-trial apomorphine high dose) although not for the groups given the same post-trial apomorphine treatments but after a 15 min post-trial delay.

The present study was undertaken to determine the impact of post-trial low and high dose apomorphine treatments on an opposite conditioned behavioral response namely catalepsy. In preclinical studies using laboratory rats, haloperidol (>0.5 mg/kg) markedly reduces behavioral activity and if the animal is placed in an awkward position it has a diminished capacity to change its position. A common behavioral response used to quantify catalepsy is to place the animal with its forelimbs over a bar and then to record the descent time. Whereas non-drugged animals quickly descend to the floor from this awkward position, animals treated with haloperidol are substantially slower at moving out of this position. Interestingly, with repeated haloperidol treatments, sensitization can occur and furthermore when tested without haloperidol using a saline conditioning test, the rats continue to manifest catalepsy [22,32]. Thus, similar to repeated treatments with dopamine agonist psychostimulant drugs that induce sensitization and conditioned effects, dopamine antagonist drugs with repeated treatments also induce sensitization and conditioned effects albeit in the opposite direction of behavioral inhibition versus behavioral stimulation. In the present study we used a paired/unpaired design and administered ten haloperidol treatments (1.0 mg/kg) to induce sensitization and conditioning of the catalepsy response. In this study we administered (post-test) either a single inhibitory (0.05 mg/kg) or a stimulatory (2.0 mg/kg) apomorphine treatment to the paired, unpaired and vehicle groups following a non-drug test for catalepsy conditioning. This report details the impact of the post-trial apomorphine treatments on subsequent tests for haloperidol conditioned and sensitized catalepsy.

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. The animals were housed individually in consideration of the possible untoward consequences on group behavior of the use of drug treatments that have major effects on behavior. 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 10:00 and 14:00 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.