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Modafinil Reinstates a Cocaine Conditioned Place Preference Following Extinction in Rats

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Abstract

The current study examined whether modafinil would reinstate an extinguished cocaine conditioned place preference (CPP). Following extinction of a cocaine CPP, rats were administered modafinil (128mg/kg), cocaine (5mg/kg) or vehicle and given a 60-min reinstatement test. While the effect of cocaine was transient, modafinil robustly reinstated a cocaine CPP following extinction, suggesting that modafinil may induce relapse or increase the vulnerability of addicts to the reinforcing effects of environmental triggers.

Keywords

modafinil; cocaine; conditioned place preference; reinstatement

Modafinil [(±)2-(benzylidene-sulfinyl)acetamide] is a psychostimulant that promotes wakefulness, and as such is FDA-approved for the treatment of excessive daytime sleepiness associated with narcolepsy, shift-work sleep disorder, and obstructive sleep apnea in humans. Modafinil has also been investigated for use in other neuropsychiatric disorders, such as cocaine addiction [12,17], and thus it has been important to determine whether the neurochemical and behavioral effects of modafinil are similar to those of other psychostimulants, such as cocaine and amphetamine.

Preclinical work has found that modafinil may partially exert its effects on arousal by interacting with the dopamine transporter (DAT) [15] and subsequently enhancing dopaminergic neurotransmission, similar—but with lower affinity [16]—to the pharmacological action of cocaine [22]. Modafinil's lower affinity for DAT *in vitro* [16] and conflicting behavioral profile [7,21] as compared to conventional psychostimulants [16] was believed to confer on modafinil less abuse potential [7,8,16]. However, Madras et al. [15] reported that modafinil or an active metabolite had a high affinity interaction with the DAT of monkey brain *in vivo*, and inhibited dopamine uptake via DAT in human embryonic kidney (HEK) cells *in vitro*. Furthermore, DAT knock-out mice showed decreased responsiveness

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to the wake-promoting action of modafinil [27], and dopamine β -hydroxylase knockout mice showed increased sensitivity to the wake-promoting action of modafinil [18]. Finally, microdialysis studies have shown prolonged elevations of extracellular dopamine in the canine caudate [27] and rat nucleus accumbens [8,20] after administration of modafinil. Together, these data suggest that modafinil may resemble conventional dopaminergic psychostimulants to a greater degree than was initially believed.

Given the central role hypothesized for dopamine in reinforcement mechanisms [reviewed in 1], these findings of modafinil's dopaminergic effects necessitate the study of its reinforcing properties. Preclinically, Deroche-Gamonet et al. [5] reported that modafinil failed to produce a conditioned place preference, induce self-administration, alter responding during cocaine self-administration, or alter cocaine-induced reinstatement of self-administration following extinction in rats. However, in drug discrimination studies, modafinil has been shown to substitute for the reinforcing and discriminative stimulus effects of cocaine [6,9]. Human studies have found that modafinil may not substitute for cocaine-like discriminative stimulus effects, but may increase some subjective "positive" drug effects [23]. Recently, Volkow et al. [26] reported that in human subjects, modafinil increased dopamine in the nucleus accumbens, an important characteristic of abused drugs.

The current study examined whether modafinil would reinstate an extinguished cocaine CPP in rodents, a preclinical model of drug relapse in humans, which is characterized by a return to drug use following prolonged absence. Reinstatement procedures allow measurement of the ability of drugs like cocaine to induce drug-seeking behaviors following extinction, in which cues previously paired with cocaine are presented repeatedly in the absence of the drug. As a consequence of extinction, preference for cocaine-associated stimuli is no longer observed. However, when cocaine is presented after extinction sessions, the preference for cocaine-associated cues can be reinstated [19]. We hypothesized that, based on recent evidence suggesting that modafinil pharmacology appears to be very similar to conventional dopaminergic psychostimulants such as cocaine, modafinil would also reinstate an extinguished CPP.

Forty-nine male Sprague Dawley rats (Harlan, Indianapolis, Indiana) weighing 300–350gm served as subjects. Subjects were housed two per cage in a temperature-controlled (21°C) environment maintained on a 12hr light-dark cycle (lights on at 6a.m.). Food and water were available *ad libitum*. Experiments were performed in accordance with the National Institutes of Health guidelines for the care and use of laboratory animals and the Institutional Animal Care and Use Committee of the Portland VA Medical Center. All behavioral testing was conducted between 0700h and 1600h.

CPP was assessed using an unbiased design [4] in four automated one-compartment place conditioning chambers (modified from San Diego Instruments, San Diego, CA). Each chamber consists of a clear acrylic test cage (70cm $\times$ 23cm $\times$ 38.5cm) with removable floors composed of interchangeable halves (left/right) of two distinct floor types. A GRID floor consists of 2.3mm stainless steel rods mounted 13mm apart. A HOLE floor consists of perforated black acrylic with 13mm round holes on 19mm staggered centers [modified from 3]. Pilot experiments have demonstrated that rats show approximately equal preference for the two floor types. Position in the chamber (left/right side) and general activity (number of beam interruptions) are assessed by computer software (San Diego Instruments, San Diego, CA) that records and analyzes beam interruptions from 16 infrared photocell emitter/detector pairs (8 evenly-spaced pairs per left/right side) located along the long axis of the chamber, 1.5cm above the chamber floor. Place conditioning chambers are housed in sound-attenuated, black acrylic enclosures (Flair Plastics, Portland, OR) designed to eliminate noise from the external

environment. Inside each chamber, a fan provides ventilation and a low level of masking noise. The apparatus was cleaned with 10% isopropanol between trials.

Rats were randomly assigned to one of three groups representing drug treatment during reinstatement: vehicle (VEH; $n=16$), cocaine (COC; $n=17$), and modafinil (MOD; $n=16$), and received place conditioning involving the following phases: habituation, conditioning, testing, and reinstatement. A 2-day break separated the first four and second four conditioning sessions, as well as the first and subsequent tests of preference. During habituation, rats were injected with intraperitoneal (IP) saline and placed in the apparatus without floors for 25 min.

For conditioning, rats in each drug treatment group were randomly assigned to one of two conditioning subgroups (cocaine on GRID floor = GRID+; cocaine on HOLE floor = GRID-; $n=7-9$ /subgroup) and exposed to a Pavlovian discrimination conditioning procedure [4]. On alternate days over eight conditioning sessions (four cocaine/four saline), rats in the GRID+ subgroup received 20mg/kg IP cocaine (dissolved in 0.9% NaCl for 1ml/kg injection; Sigma, St. Louis, MO) immediately prior to 25-min conditioning trials on the GRID floor and saline (1ml/kg IP) immediately prior to 25-min trials on the HOLE floor. Rats in the GRID- subgroup received cocaine on the HOLE floor and saline on the GRID floor. During conditioning trials, the order of cocaine/saline treatment exposure was counterbalanced within each GRID+ and GRID- subgroup, and left and right floor types were identical so that rats access to both sides of the apparatus [4].

For Test 1, rats received a saline injection (1ml/kg IP) immediately prior to placement into the apparatus with half GRID floor and half HOLE floor for a 25-min preference test. Position of the floors (left vs. right) was counterbalanced within each GRID+ and GRID- subgroup, and magnitude of the place preference was determined by comparing the amount of time spent on the GRID floor between the GRID+ and GRID- conditioning subgroups [4], a between-subjects comparison that controls for any floor bias that may be present in the experiment. Identical tests (2-5) were designed to extinguish the CPP seen during Test 1. Data were analyzed for the first 15 min of each test for comparison to 15-min intervals of the 60-min reinstatement test.

For reinstatement testing, rats received vehicle, cocaine (5mg/kg), or modafinil (128mg/kg) immediately prior to a 60-min preference test. Modafinil (Sigma) was dissolved in 22% (2-hydroxypropyl)- β -cyclodextrin (w/v) for IP injection (6ml/kg) and administered at 128mg/kg. This dose of modafinil was chosen because it has been shown not to induce a conditioned place preference on its own [5], and is considered to be a behaviorally relevant, yet high, dose [6]. Cocaine [5mg/kg; dissolved in 22% (2-hydroxypropyl)- β -cyclodextrin (w/v), identical to modafinil vehicle] and vehicle injections were administered at 6ml/kg. Cocaine (5mg/kg) was used as a positive control for reinstatement as this dose has previously been shown to reinstate an extinguished cocaine conditioned place preference [19].

Statistical analyses were conducted with SPSS software (Chicago, IL). Place preference was analyzed using two-way ANOVA (Drug Treatment $\times$ Conditioning Subgroup). Student's t -tests were used to compare GRID+/GRID- subgroups within each drug treatment group (Bonferroni-corrected $\alpha/3 = 0.017$). Activity data were analyzed using one-way ANOVA (Drug Treatment), followed by post-hoc comparisons using Fisher's PLSD test. Significance was set at $p < .05$.

Rats in each group (VEH, COC, and MOD) showed a CPP during Test 1 (Figure 1A). There was a reliable main effect of Conditioning Subgroup [$F(1,43) = 43.4$, $p < .001$] and no significant interaction ($F < 1$). Student's t -tests confirmed that groups VEH [$t(14) = 3.0$, $p < .017$], COC [$t(15) = 4.1$, $p < .001$] and MOD [$t(14) = 4.8$, $p < .001$] all showed significant

cocaine-induced CPP during Test 1. Locomotor activity during Test 1 did not differ between groups VEH(1654.6 ± 90.0), COC(1637.4 ± 65.0), and MOD(1545.0 ± 60.7)($F < 1$).

Rats in each group showed extinction of CPP by Test 5 (Figure 1B). There was no significant main effect of Conditioning Subgroup or interaction ($F_s < 1$). Locomotor activity during Test 5 did not differ between groups VEH(1490.1 ± 93.5), COC(1559.9 ± 60.3), and MOD(1421.0 ± 72.0)($F < 1$).

Rats in the COC group showed a transient reinstatement of cocaine CPP that was evident only during the first 15 min of the 60-min test for reinstatement. In contrast, the MOD group showed a robust, persistent reinstatement of preference that was evident during both the first and last 15 min of the test. During the first 15 min of the 60-min reinstatement test, the MOD and COC groups showed a significant CPP, but VEH did not (Figure 2A). There was a reliable main effect of Conditioning Subgroup [$F(1,43) = 12.3, p < .005$] and no significant interaction [$F(2,43) = 2.6, p = .086$]. Student's *t*-tests confirmed that group VEH [$t(14) = 0.14, p > 0.80$] did not show a significant preference during the first 15 min, whereas groups COC [$t(15) = 4.2, p < .001$] and MOD [$t(14) = 3.0, p < .01$] did show reinstatement. However, the preference seen in the COC group was no longer significant by the second, and during the third, 15 min interval ($p_s > 0.17$) of the 60-min test, while the MOD group ($p_s < .005$) continued to show a preference during both of these intervals (*data not shown*). Figure 2B shows that mean activity differed in groups VEH, COC, and MOD during the first 15 min of the 60-min test of reinstatement [$F(2,46) = 9.2, p < .001$]. Post-hoc comparisons revealed that the VEH group differed in locomotor activity from the COC and MOD groups ($p_s < .005$) during the first 15 min of the reinstatement test, whereas the COC and MOD groups did not differ ($p > 0.90$).

Figure 3A shows that during the last 15 min of the 60-min reinstatement test, the MOD group continued to show a significant CPP, but the COC group continued to show no preference. There was a reliable Drug Treatment X Conditioning Subgroup interaction [$F(2,43) = 3.6, p < .05$], suggesting differences in magnitude of preference during this interval. Follow-up ANOVAs revealed a significant Drug Treatment X Conditioning Subgroup interaction between the VEH and MOD groups [$F(1,28) = 7.3, p < .05$], suggesting reliable differences in magnitude of preference between the VEH and MOD groups, as well as significant main effects of both Drug Treatment and Conditioning Subgroup [$F_s(1,28) > 4.9, p_s < .05$]. Between the VEH and COC groups, there was no significant Drug Treatment X Conditioning Subgroup interaction or significant main effects ($F_s < 1$). Between the COC and MOD groups, there was a significant Drug Treatment X Conditioning Subgroup interaction [$F(1,29) = 4.5, p < .05$], suggesting reliable differences between these two groups in magnitude of preference, and a significant main effect of Conditioning Subgroup [$F(1,29) = 5.1, p < .05$]. Student's *t*-tests for each of the three groups revealed that only group MOD [$t(14) = 3.6, p < .005$] showed a significant preference (VEH and COC: $p_s > 0.70$). Figure 3B shows activity differences during the last 15 min of the 60-min reinstatement test ($F(2,46) = 20.7, p < .001$). Post-hoc comparisons revealed that groups VEH and COC did not differ in locomotor activity during the last 15 min of the test for reinstatement ($p > 0.65$), while the MOD group was significantly higher than both the VEH and COC groups during this interval ($p_s < .001$). Previous studies have found that higher levels of activity serve as a competing behavior that impedes preference [11], so our ability to detect a robust place preference under these conditions underscores the magnitude of modafinil-induced reinstatement.

Using a preclinical model of relapse in humans, the current study found that modafinil reinstated a CPP following extinction. This effect was seen throughout the 60-min reinstatement test. In contrast, in animals pretreated with low-dose cocaine, the reinstatement effect was transient, lasting only during the first 15 min of the 60-min reinstatement test.

These results are consistent with findings in rats and nonhuman primates that modafinil can substitute for cocaine in drug discrimination tasks [6,9]. Furthermore, in humans, oral modafinil has been shown to produce some pleasurable effects [23] and like abused psychostimulants increases dopamine in the nucleus accumbens [26]. Our results are also consistent with work demonstrating the ability of other dopaminergic psychostimulants to reinstate an extinguished cocaine conditioned place preference. These include methylphenidate [14], which like cocaine [22] exerts its action on dopaminergic transmission through DAT binding [24], as well as the dopamine D1 receptor agonist SKF 81297 [10]. Thus, modafinil may be sufficiently reinforcing or stimulant-like to trigger relapse in vulnerable stimulant abusers. Similarly, in human studies, dopamine agonists and antagonists have been reported to increase and decrease, respectively, responsivity to environmental cues in cocaine abusers [2]. Our finding that modafinil induces reinstatement in a conditioning paradigm suggests that modafinil may increase responsivity to stimulant cues, which can precipitate relapse in humans.

Our prolonged behavioral effects are consistent with the comparatively prolonged neurochemical effects of modafinil in microdialysis studies [20,27]. Together, these studies show that modafinil has much more pronounced and prolonged dopamine agonist-like behavioral and neurochemical effects than anticipated by earlier *in vitro* studies [16]. These prolonged effects, as well as the demonstration that at clinically relevant doses modafinil interacts with 100% of DAT [15], raise serious concerns about potential adverse interactions of modafinil with dopaminergic psychostimulants. Dopaminergic psychostimulants have a steep lethality curve such that small changes in dosage can lead to large changes in lethality [13]. It is therefore imperative to assess modafinil's effects on the lethality curve for dopaminergic psychostimulants.

In summary, we have shown that modafinil, like cocaine, reinstated a cocaine CPP following extinction. In fact, modafinil's behavioral effect in the conditioned place preference paradigm was more prolonged than cocaine. This increases concern about abuse potential. It also raises concerns about an adverse proconvulsant or potentially lethal interaction of modafinil with abused stimulants and commonly prescribed dopamine agonists, such as bupropion, which is approximately equally potent with cocaine as an inhibitor of dopamine uptake [25]. Preclinical and human laboratory interaction studies are needed, as well as human laboratory assessments of modafinil's ability to increase responsivity of cocaine addicts to environmental cues. Even if modafinil lacks abuse potential, this mechanism could increase the vulnerability of addicts to drug-seeking produced by common environmental triggers.

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Figure 1.

CPP during Test 1 and Test 5. (A) Cocaine induced a CPP following conditioning. Data represent mean (+SEM) time spent on GRID floor for the GRID+ and GRID- subgroups during the first 15 min of the 25-min drug-free test. All groups showed a significant preference for the cocaine-paired floor. (B) Cocaine CPP was absent following extinction. Data represent mean (+SEM) time spent on GRID floor for the GRID+ and GRID- subgroups during the first 15 min of the 25-min drug-free test. All groups demonstrated extinction of preference, failing to show a preference for the cocaine-paired floor. VEH=Vehicle, COC=Cocaine, MOD=Modafinil; * $p < .017$ (Bonferroni-corrected $\alpha/3$), ** $p < .001$.

Figure 2.

Modafinil- and cocaine-induced reinstatement of an extinguished cocaine CPP during the first 15-min interval of the 60-min reinstatement test. (A) Modafinil- and cocaine-treated rats show a significant reinstatement of preference. Data represent mean (+SEM) time spent on GRID floor for the GRID+ and GRID- subgroups during the first 15 min of the 60-min test. Rats that received modafinil or cocaine showed a significant cocaine CPP during the 15-min interval, while vehicle-treated rats failed to show a preference. (B) Activity levels during the first 15-min interval. Data represent mean (+SEM) activity counts during the first 15 min of the 60-min test. Modafinil- and cocaine-treated rats show significantly higher activity than vehicle-treated rats. VEH=Vehicle, COC=Cocaine, MOD=Modafinil; * $p < .017$ (Bonferroni-corrected $\alpha/3$), ** $p < .001$, ^a $p < .001$ (vs. VEH), ^b $p < .005$ (vs. VEH).

Figure 3.

Modafinil-induced reinstatement of an extinguished cocaine CPP during the last 15-min interval of the 60-min test. (A) Modafinil-treated rats show a significant reinstatement of preference. Data represent mean (+SEM) time spent on GRID floor for the GRID+ and GRID – subgroups during the last 15 min of the 60-min test. Rats that received modafinil showed a significant cocaine CPP during the 15-min interval, while vehicle- and cocaine-treated rats failed to show a preference. (B) Activity levels during the last 15-min interval. Data represent mean (+SEM) activity counts during the last 15 min of the 60-min test. Modafinil-treated rats show significantly higher activity than vehicle- or cocaine-treated rats. VEH=Vehicle, COC=Cocaine, MOD=Modafinil; * $p < .005$ (Bonferroni-corrected $\alpha/3 = .017$), ^a $p < .001$ (vs. VEH/COC).