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Research report

Interactions between modafinil and cocaine during the induction of conditioned place preference and locomotor sensitization in mice: Implications for addiction

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HIGHLIGHTS

- We tested whether modafinil could induce place preference and sensitization in mice.
- High dose modafinil induced place preference while low dose modafinil did not.
- Modafinil showed little or no locomotor sensitization at low or high doses.
- Low dose modafinil was sufficient to express sensitization in cocaine-trained mice.

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ABSTRACT

Modafinil is a wake-promoting drug effective at enhancing alertness and attention with a variety of approved and off-label applications. The mechanism of modafinil is not well understood but initial studies indicated a limited abuse potential. A number of recent publications, however, have shown that modafinil can be rewarding under certain conditions. The present study assessed the reinforcing properties of modafinil using conditioned place preference and locomotor sensitization in mice. Experiment 1 examined a high dose of modafinil (75 mg/kg) as well as its interactions with cocaine (15 mg/kg). Cocaine alone and modafinil co-administered with cocaine induced sensitization of locomotor activity; modafinil alone showed little or no locomotor sensitization. Animals given modafinil alone, cocaine alone, and modafinil plus cocaine exhibited a strong and roughly equivalent place preference. When tested for sensitization using a low challenge dose of modafinil, cross-sensitization was observed in all cocaine-pretreated mice. Experiment 2 examined a low dose of modafinil that is similar to the dose administered to humans and has been shown to produce cognitive enhancements in mice. Low dose modafinil (0.75 mg/kg) did not produce conditioned place preference or locomotor sensitization. Together, these results suggest that modafinil has the potential to produce reward, particularly in cocaine addicts, and should be used with caution. However, the typical low dose administered likely moderates these effects and may account for lack of addiction seen in humans.

1. Introduction

Modafinil is a wake-promoting psychostimulant approved by the US FDA for the treatment of narcolepsy, sleep apnea/hypopnea, and shift work sleep disorder [1,2]. The drug is also widely prescribed off-label to help patients with attention deficit disorder, excessive daytime sleepiness, dementia, and depression [3]. In addition, some academic doping has emerged because modafinil may enhance memory and attention [4–9]. Recently, modafinil has been implicated as a therapeutic for cocaine addiction [10–14]. Modafinil is attractive because it has low addictive and cardiovascular risk compared to amphetamine or methylphenidate, and could serve as a weak or slow-onset agonist in the manner that buprenorphine has been used in the treatment of opioid addiction [14].

Initial studies on modafinil indicated a minimal abuse potential. Gold and Balster [15] found that modafinil could not substitute for cocaine in rats but was able to act as a reinforcer in cocaine-experienced rhesus monkeys. In addition, Deroche-Gamonet and colleagues [16] found little evidence of reinforcing effects of modafinil in naïve and cocaine-experienced rats. They found that modafinil (32–256 mg/kg, i.p.) did not induce a place preference for a drug-paired compartment, was not self-administered (0.28–1.7 mg/kg/infusion), and did not alter cocaine self-administration. Modafinil (64 mg/kg) did, however, enhance

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the reinstatement of cocaine self-administration. Together, these studies indicated that modafinil alone was not reinforcing, but could elicit reward in cocaine-experienced animals. Despite these early findings there was some evidence that modafinil alone could be rewarding. Modafinil increases dopamine activity in the accumbens [17–20] and human patients "self-administer" the drug in a "modified progressive ratio procedure" [21]. Indeed, two independent studies have contradicted earlier reports and indicated that modafinil can indeed produce place preference at high doses (64–300 mg/kg) in mice [22,23]. Furthermore, locomotor sensitization to modafinil has also been observed in mice [23,24]. Together, these recent findings indicate that modafinil, even when taken alone, may have addictive potential.

Despite its profile as a modest reinforcer there are no published case reports of addiction to modafinil, and several studies have reported that modafinil lacks a drug-induced "high" [25–28]; for review see [28]. This may be because modafinil is used orally, and has a relatively slow peak time (2–4 h) and long half-life (10–12 h), compared to the stimulants of abuse (i.e., smoked or snorted cocaine and methamphetamine). The possibility remains that high doses of modafinil, especially if it were given via a rapid route of administration, such as inhalation, might be addictive. In human subjects, however, only oral ingestion of modafinil has been studied.

Modafinil's mechanism of action is not well understood. Modafinil has been shown to induce changes in dopamine, norepinephrine, serotonin, glutamate, and GABA transmission (for review, see [29]). Emerging evidence suggests the primary action of modafinil is through dopaminergic neurotransmisson [30–33]. Positron emission tomography (PET) imaging revealed that modafinil binds to over 50% of dopamine transporters and 44% of norepinephrine transporters in rhesus monkey striatum [30]. Furthermore, a recent PET study in humans indicated that modafinil (200–400 mg, p.o.) binds to dopamine transporters and increases extracellular dopamine in the nucleus accumbens [20]. Overall, this profile fits with the characterization of modafinil as a modest reinforcer.

The current study uses two popular rodent models of addiction: behavioral sensitization and conditioned place preference (CPP). Behavioral sensitization is an increase in response to a drug after repeated pairings [34,35]. It is hypothesized to contribute to addiction by enhancing the incentive (rewarding) salience of the drug, and cues associated with drug use, moderating the transition from casual use to compulsive drug seeking [36,37]. CPP is a paradigm used to model drug seeking behavior. With addictive drugs, rodents show a strong preference for the drug-paired context indicating that the drug confers a conditioned reward.

Although recent reports have indicated that modafinil can be rewarding, several points remain unclear. First, it is unclear how high dose modafinil interacts with cocaine in the formation of conditioned place preference and locomotor sensitization. Experiment 1 examines this interaction by training animals on a combined behavioral sensitization and conditioned place preference (CPP) paradigm using modafinil alone, cocaine alone, or co-administered modafinil and cocaine. Second, it remains unclear if modafinil is rewarding at doses actually used by people. Thus, Experiment 2 examined whether an ultra-low dose of modafinil (that produces cognitive enhancement [4]) also produces CPP and locomotor sensitization.

2. Methods and materials

2.1. Subjects

Experiments were conducted using male and female (balanced across groups) F1 hybrid C57B6 × 129T2SvEms/J (129B6, stock from The Jackson Laboratory, West Sacramento, CA) mice at least 10 weeks old before testing. Mice were group-housed with unrestricted access to food and water under a 14:10 light/dark cycle. Animal care and experimental procedures were approved by the UCSD IACUC, in accordance with the NRC Guide for the Care and Use of Laboratory Animals.

2.2. Experiment 1: examining the rewarding effects of high dose modafinil and its interaction with cocaine

2.2.1. Drugs

All drugs were administered intraperitoneally (i.p.) in a volume of 10 ml/kg. Modafinil (Sigma–Aldrich, St. Louis, MO) was suspended in 0.9% saline with 10% Tween 80 [4]. Cocaine HCl (Sigma–Aldrich) was dissolved in saline. Modafinil + Cocaine was a combined mixture suspended in 0.9% saline with 10% Tween 80. Because modafinil and cocaine were dissolved in different vehicles, control animals received 0.9% saline alone.

2.2.2. Conditioning context apparatus

Four mice were tested concurrently, in individual chambers housed in a windowless room. Chambers (59-cm wide, 29-cm high, 29-cm deep) consisted of two distinct sides separated by a removable wall. The two sides were unbiased and differed in smell, floor texture, and visual stimuli, but did not differ in dimension or overall lighting. One side was lined with unscented cat litter and contained only white walls. The other side was scented with cleaner (3% Quatricide) on a smooth plastic floor with visual stimuli (stickers) on the walls. Each side was randomly designated the Saline or Drug side (counterbalanced by group). During training and all tests of sensitization, the dividing wall allowed access to only one side. During CPP testing, the solid wall was replaced with an identical wall with a small hole allowing passage between the sides. Chambers were placed on the floor and recorded from an overhead camera. Limelight software (Actimetrics, Evanston, IL) tracked each animal at 8 frames per second and used a reference measurement to convert pixels into distance traveled. For CPP testing, it recorded locomotion and time spent in each side. Light was provided from two 150-watt bulbs distant from the chambers and background noise (65-dB) was provided by HEPA air cleaners.

2.2.3. Behavioral training

Mice were randomly assigned to one of four groups indicating which drug they would receive on each training day (Fig. 1A). Modafinil mice ($n = 12$) received 75 mg/kg modafinil, Cocaine mice ($n = 12$) received 15 mg/kg cocaine HCl (salt weight), Modafinil + Cocaine mice ($n = 12$) received the same doses of modafinil and cocaine, and Saline control mice ($n = 12$) received saline during drug pairing. 75 mg/kg was chosen as the modafinil dose because it has been widely used in rodents and was the highest dose we could give this mouse strain without significant mortality (unpublished data). 15 mg/kg of cocaine was chosen as a moderately high dose relevant to addiction that produces place preference and sensitization. Training lasted for 7 consecutive days, during which the dividing wall was solid and allowed access to only one side of the chamber at a time. On each day, mice received an injection of saline and were immediately placed into the Saline side of the chamber. After 15 min, they were removed from the chamber, given a group-appropriate drug injection, and placed into the Drug side. After an additional 15 min, they were returned to their home cage.

2.2.4. Conditioned place preference (CPP) testing

CPP testing occurred 3 days after the final day of training. The solid wall separating the two sides of the chamber was replaced with an identical insert with a small hole allowing passage between

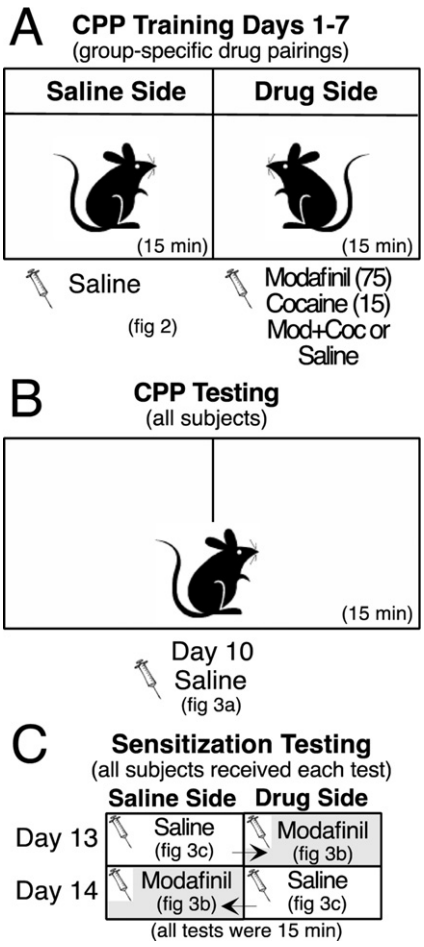

Fig. 1. Schematic of procedure for Experiment 1. (A) On Days 1–7, mice first received an injection of saline and were placed into the Saline Side of the chamber for 15 min. Immediately after, mice receive a group-specific drug injection (modafinil, cocaine, modafinil + cocaine, or saline) and were placed in the Drug Side of the chamber for 15 min. This data is depicted in Fig. 2. (B) During conditioned place preference testing a small hole between the two sides of the chamber allowed free access to either side of the chamber. On Day 10, all mice received an injection of saline and were placed into the chamber for 15 min. This data is depicted in Fig. 3A. (C) In order to test the context and drug specificity of sensitization, all mice received modafinil and saline on each of the Saline and Drug Sides. On Day 13, mice first received an injection of saline and were placed into the Saline Side for 15 min. Immediately after, mice received an injection of modafinil (0.75 mg/kg) and were placed into the Drug Side. Conversely, on Day 14, mice first received an injection of saline and were placed into the Drug Side for 15 min. Immediately after, mice received an injection of modafinil (0.75 mg/kg) and were placed into the Saline Side. This data is depicted in Fig. 3B and C. For Experiment 2, animals were then trained identically to part A above with either low dose modafinil (LoMod) or saline.

the two sides. All groups received the same drug treatments during testing. The testing paradigm is shown in Fig. 1B. On Day 10, mice were given a standard place preference test: following an injection of saline, they were placed into the small hole between the two sides of the chamber and allowed to explore both sides for 15 min. Time spent in each side was measured by computer.

2.2.5. Sensitization testing

Locomotor sensitization is specific to the context in which the drug is received [34]. Thus, sensitization can be measured as the difference between a challenge in the drug side and a challenge in the saline side [38]. Following CPP tests, the specificity of sensitization was tested by administering a challenge dose of modafinil (0.75 mg/kg) and saline in both the drug- and saline-paired contexts (Fig. 1C). This low dose of modafinil was chosen as a clinically relevant dose and because we have found it acts as a cognitive enhancer (selectively enhancing hippocampus-dependent contextual fear conditioning) without producing locomotor activity [4]. During these tests the dividing wall was solid allowing access to only one side of the chamber at a time. On Day 13, all mice from all groups received saline in the side previously paired with saline, followed 3 h later by modafinil in the side previously paired with drug. On Day 14, mice received saline in the drug-paired side, followed 3 h later by modafinil in the saline-paired side. Each test lasted 15 min, and locomotor activity was scored.

2.3. Experiment 2: examining the rewarding effects of low dose modafinil

2.3.1. Drugs

All drugs were administered intraperitoneally (i.p.) in a volume of 10 ml/kg. Low dose modafinil (Sigma–Aldrich, St. Louis, MO) was suspended in 0.9% saline with 10% Tween 80 [4]. Saline control animals received vehicle of 0.9% saline with 10% Tween 80.

2.3.2. Conditioning context apparatus

Eight mice were tested concurrently, in individual chambers housed in a windowless room. Chambers (44-cm wide, 44-cm high, 31-cm deep, Med Associates, St. Albans, VT) consisted of two distinct sides separated by a wall with a removable hole. The two sides differed in smell, texture, and visual stimuli. Each side was randomly designated the Saline or Drug side (counterbalanced by group). During training, the hole in the dividing wall was closed which allowed access to only one side at a time. Animals were tracked using infrared beams and Activity Monitor software (Med Associates) and locomotor distance traveled was scored. Light was provided from two 150-Watt bulbs distant from the chambers and background noise (65-dBA) was provided by HEPA air cleaners and an iPod speaker playing white noise.

2.3.3. Behavioral training

Training was as in Experiment 1, but a low dose of modafinil (LoMod, 0.75 mg/kg) was substituted for the high dose. This low dose is closer to the dose given to humans (without respect to species differences) and enhances Pavlovian fear conditioning in mice [4]. Two groups were examined: mice were randomly assigned to receive either modafinil (0.75 mg/kg, $n = 12$) or vehicle ($n = 12$) on each day of training. Training lasted for 7 consecutive days, during which the hole in the dividing wall was closed and allowed access to only one side of the chamber at a time. On each day, mice received an injection of saline and were immediately placed into the Saline side of the chamber. After 15 min, they were removed from the chamber, given a group-appropriate drug injection, and placed into the Drug side. After an additional 15 min, they were returned to their home cage.

2.3.4. Conditioned place preference (CPP) testing

As with Experiment 1, CPP testing occurred 3 days after the final day of training. Mice were given a standard place preference test: following an injection of saline, they were placed into the small hole between the two sides of the chamber and allowed to explore both sides for 15 min.

2.3.5. Sensitization testing

As with Experiment 1, the specificity of sensitization was tested by administering a challenge dose of modafinil (0.75 mg/kg) and saline in both the drug- and saline-paired contexts (Fig. 1C). During these tests the dividing wall was solid allowing access to only one side of the chamber at a time.

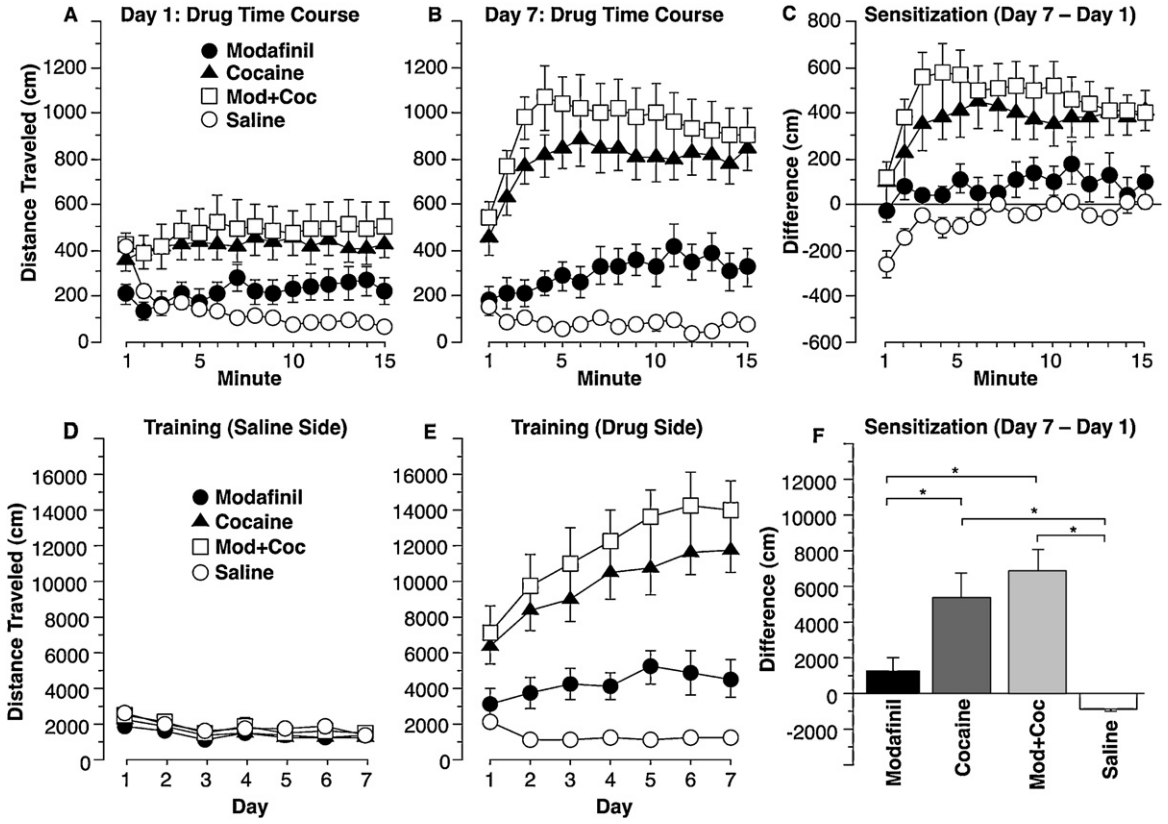

Fig. 2. Induction of sensitization. (A) Time course of drug action on Day 1 of training. Cocaine and Mod + Coc groups showed increased locomotor activity over controls. Modafinil alone failed to induce substantial locomotion. (B) Time course of drug action on Day 7 of training. All three drug groups showed an increased response over the saline control group. (C) Time course of locomotor sensitization. The difference in response from Day 1 to 7 is shown. Cocaine and Mod + Coc mice showed a significant increase in locomotor activity from Day 1 to Day 7. Modafinil mice did not differ from control mice. (D) Locomotor activity after saline treatment, by day. No group differences were observed. (E) Average locomotor activity after drug treatment, by day. Cocaine and Mod + Coc groups were enhanced over control mice. (F) Difference in locomotor activity of drug training trials between Day 1 and Day 7. Cocaine and Mod + Coc mice were enhanced over control mice. Modafinil mice did not differ from control mice. Each point represents the mean ± S.E.M. (*$p < 0.05$).

2.4. Data analysis

Data were entered into a multivariate analysis of variance (MANOVA). Between-group comparisons were done with Fisher's protected least significant difference (PLSD). The level of significance was set at $p \leq 0.05$ and the statement "did not differ" below reflects $p > 0.05$.

3. Results

3.1. Experiment 1: examining the rewarding effects of high dose modafinil and its interaction with cocaine

3.1.1. Locomotor sensitization during training

Locomotor sensitization was assessed over the 7 days of training. Locomotor activity for all groups is depicted across training as time-course data and averages (Fig. 2). On the first day of training there were significant group differences [$F(3, 44) = 6.51$, $p < 0.05$; Fig. 2A and E]. Cocaine and Modafinil + Cocaine mice, which did not differ from each other, exhibited increased locomotor activity on the first drug pairing compared to Saline controls ($p < 0.05$), while high dose Modafinil mice did not. Group differences continued on Day 7 [$F(3, 44) = 27.31$, $p < 0.05$; Fig. 2B and E]. In order to establish the presence of sensitization, two criteria were required: (1) the Day 7 (chronic) response had to be higher than the Day 1 (acute) response, and (2) the Day 7 response had to be higher than the Day 7 response in Saline controls. These requirements avoid the confound of habituation occurring only in the control group leading to a lack of habituation being mistaken for sensitization [24]. Cocaine, and Modafinil + Cocaine mice, which did not differ, showed higher levels of locomotor activity than Saline animals (p-values < 0.0001). High dose modafinil mice exhibited less locomotor activity than Modafinil + Cocaine or Cocaine mice, and more than Saline controls (p-values < 0.05). In order to further examine sensitization, we subtracted locomotor activity on Day 1 from Day 7, shown as a time course in Fig. 2C, and as an average in Fig. 2F. There were significant group differences in this measure [$F(3, 44) = 12.3$, $p < 0.05$]. Cocaine and Modafinil + Cocaine mice, while not differing from each other (Fig. 2C and F) exhibited a large increase in activity from Day 1 to Day 7 when compared to Saline controls (p-values < 0.0001). Thus, only the Cocaine and Modafinil + Cocaine groups showed significant and substantial sensitization. Visual inspection of Fig. 2C and F suggests that the Modafinil group separated from Saline group, but it is unclear if this was due to increased responding to the drug to a lack of habituation in the Modafinil group, compared to the Saline controls. In order to explore this further, we examined the difference from zero for the Day 7 minus Day 1 subtraction on a minute-by-minute basis. Saline animals were the only ones to show a significant decrease for any minute (one sample two-tailed t-test for each minute, hypothesized mean of 0; min 1, 2, 5, 6, 8, 12, 13, $t(11)$-values < −2.22, $p < 0.06$; other mins, n.s.). Cocaine mice exhibited sensitization across most minutes (min 1–2, n.s.; min 3–15, $t(11)$-values > 3.14, $p < 0.01$). Modafinil mice exhibited no significant differences from Day 1 to Day 7 even on a minute-by-minute basis [$t(11)$-values < 2.18, $p > 0.05$]. Finally, Modafinil + Cocaine mice exhibited significant sensitization across

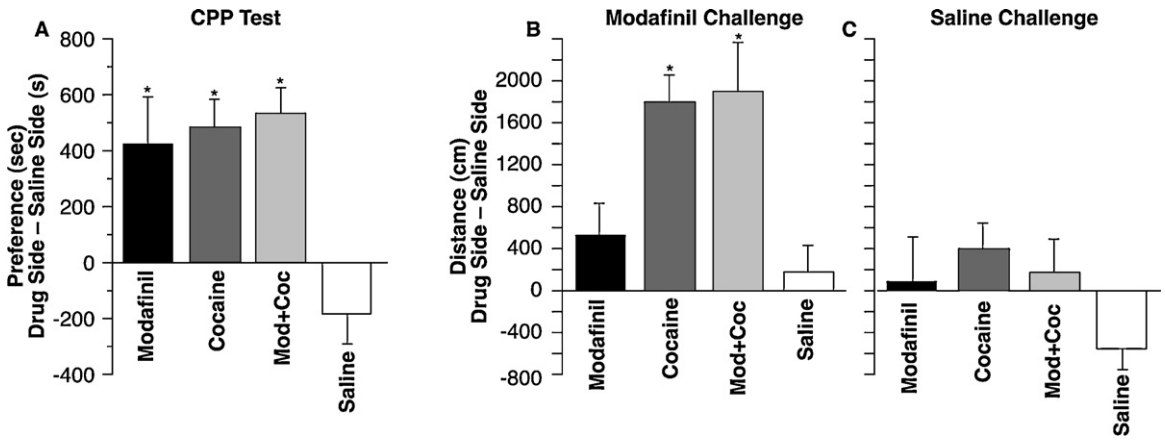

Fig. 3. Place preference and cross-sensitization testing. (A) After a saline injection, all three drug groups spent significantly more time in the drug-paired side of the chamber. The difference in time spent in drug-paired side and saline-paired side is shown. (B) Locomotor activity in the drug-paired side minus the saline paired side after an injection of a challenge dose of modafinil (0.75 mg/kg). Both cocaine- and modafinil + cocaine-trained mice showed higher locomotor activity in the Drug Side of the chamber, when compared to Saline controls. Thus, the sensitization observed in these groups cross-sensitized to modafinil administration. (C) Locomotor activity in the drug-paired side minus the saline paired side after an injection of saline. No significant group effects were found. Each point represents the mean ± S.E.M. (* versus saline side, $p < 0.01$).

most minutes [min 1, n.s.; min 2–15, $f(11) > 4.35$, p-values < 0.01]. Even when considered on a minute-by-minute basis there was no evidence for sensitization in the Modafinil group, only evidence for habituation in the Saline control group. Fig. 2D depicts locomotor activity on the unpaired (saline) side during training. No group differences were found in the drug unpaired side ($F(3, 44) = 0.81$, n.s.).

3.1.2. Conditioned place preference

All animals received a place preference test after receiving a saline injection (Fig. 1B). Data is depicted as the difference in time spent in the drug- and saline-paired sides of the chamber. Group differences were found ($F(3, 44) = 7.88$, $p < 0.001$). Cocaine, Modafinil + Cocaine, and Modafinil groups, which did not differ from each other, showed a significant preference for the drug-paired side compared to the Saline control group (p-values < 0.001; Fig. 3A). Overall, these data show that cocaine and high dose modafinil induce a strong and significant place preference; no additional place preference is seen if cocaine and high dose modafinil are combined (i.e., Modafinil + Cocaine) during training.

3.1.3. Specificity of sensitization

To examine context-specific sensitization we conducted modafinil and saline tests with the animals restricted to one side of the chamber (Fig. 1C). We administered modafinil in both the drug-paired and unpaired sides of the chamber. Group means (±standard deviation) were as follows: Modafinil on the Drug Side, MOD = 2124(±1450), COC = 2915(±1031), MOD + COC = 3110(±1672), SAL = 1974(±1380); Modafinil on the Saline Side, MOD = 1617(±1355), COC = 1119(±613), MOD + COC = 1230(±842), SAL = 1795(±928); Saline on the Drug Side, MOD = 1867(±1107), COC = 2290(±729), MOD + COC = 2379(±1245), SAL = 1999(±1242); Saline on the Saline Side, MOD = 1659(±1306), COC = 1731(±983), MOD + COC = 2180(±1252), SAL = 2508(±1306). We subtracted the unpaired side from the drug side to obtain a measure of context specific sensitization to modafinil [38]. Group differences were found (Fig. 3B, $F(3, 44) = 6.92$, $p < 0.001$), as both the Cocaine ($p < 0.01$) and Modafinil + Cocaine ($p < 0.001$) groups exhibited increased locomotor activity for the drug-side compared to Saline controls. Thus, administration of modafinil induced cross-sensitization in mice that previously received Cocaine or Modafinil + Cocaine. Animals that had received only modafinil during training, on the other hand, did not exhibit sensitization in the drug-paired context. These effects were not due to conditioned hyperactivity as no group differences were found when saline was administered on both sides (Fig. 3C, $F(3, 40) = 1.88$, $p > 0.05$). This is consistent with prior work showing that a conditioned locomotor response is not readily observed within the CPP paradigm [38].

3.2. Experiment 2: examining the rewarding effects of low dose modafinil

3.2.1. Locomotor sensitization during training

Locomotor sensitization of low dose modafinil (LoMod) was assessed over the 7 days of training (Fig. 4). This data is depicted minute-by-minute (Fig. 4A) and in summary (Fig. 4B). Low dose modafinil did not induce increased locomotor activity over vehicle control on either Day 1 or Day 7 [$F(1, 22)$ values < 2.1, p-values > 0.1; Fig. 4B]. There were also no group differences on the drug unpaired side [$F(1, 22)$ values < 1.1, p-values > 0.3; Fig. 4B]. Indeed, both groups exhibited a significant decline from Day 7 to Day 1, reflecting normal habituation [drug paired side, Day 1 vs Day 7, paired two-tailed t-tests, $t(11)$ values > 6.3, p-values < 0.0001]. When difference scores were computed to estimate this reduction (Fig. 4C), it is evident that mice receiving low-dose modafinil and those receiving saline showed a similar decline [$F(1, 22) = 2.75$, $p > 0.1$].

3.2.2. Conditioned place preference

All animals received a place preference test after receiving a saline injection (Fig. 1B). Neither group exhibited a significant place preference [Fig. 4D, left; one sample t-tests vs hypothesized mean of 0, $t(11)$ values < 0.6, p-values > 0.5], nor did they differ from each other [$F(1, 22) = 0.3$, $p > 0.5$].

3.2.3. Specificity of sensitization

As with Experiment 1, we administered modafinil in both the drug-paired and unpaired sides of the chamber (Fig. 1C). Group means (±standard deviation) were as follows: Modafinil on the Drug Side, LoMOD = 852(±383), SAL = 728(±397); Modafinil on the Saline Side, LoMOD = 714(±429), SAL = 608(±379); Saline on the Drug Side, LoMOD = 713(±312), SAL = 649(±302); Saline on the Saline Side, LoMOD = 718(±364), SAL = 646(±313). We again subtracted the unpaired side from the drug side to obtain a measure of context specific sensitization to modafinil [38]. Low dose modafinil did not produce context specific sensitization in the drug side when compared to vehicle controls [$F(1, 22) = 0.03$, $p > 0.8$; Fig. 4D, middle]. In addition, when given a saline challenge, the low dose modafinil group did not produce conditioned hyperactivity in

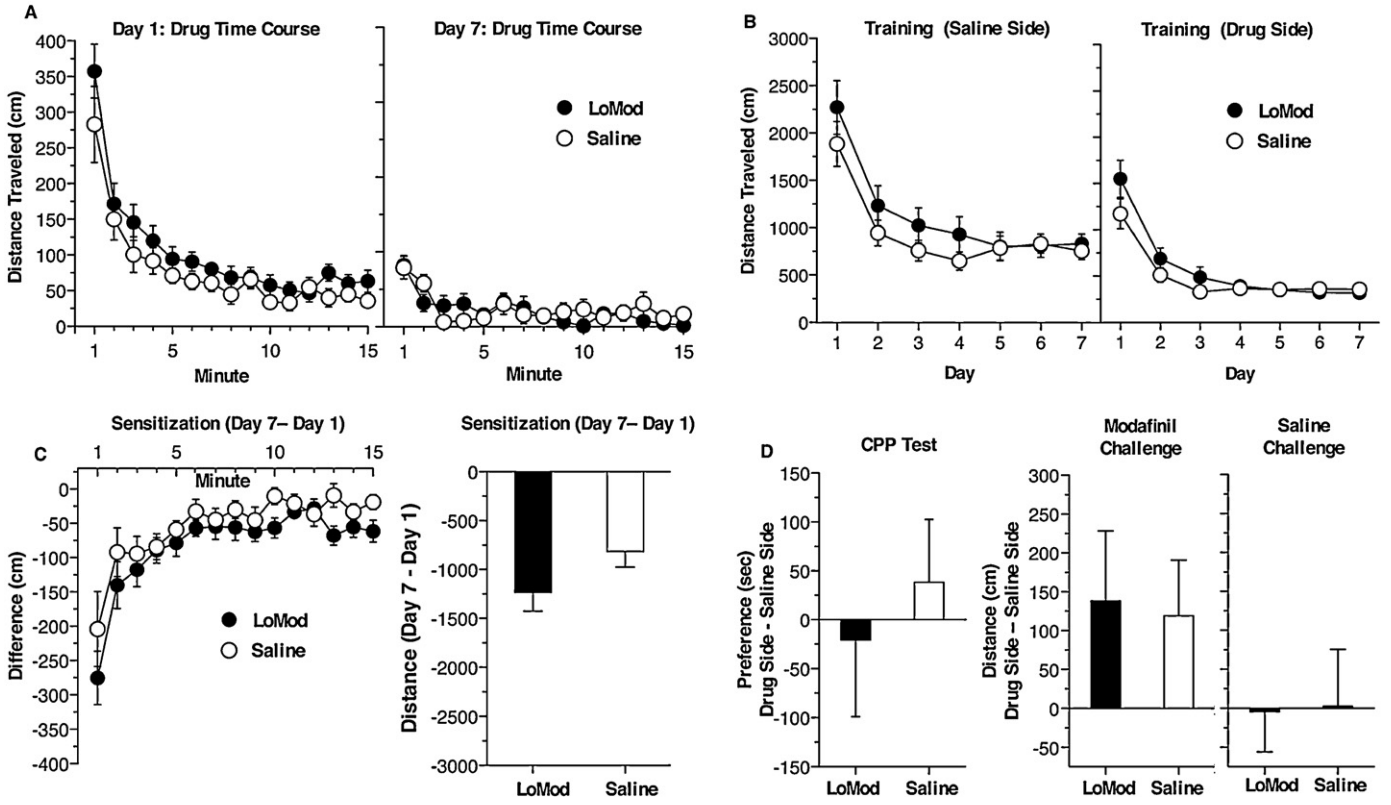

Fig. 4. Low dose modafinil does not induce sensitization or place preference. (A) Time course of drug action on Day 1 (*left*) and Day 7 (*right*) of training. Low-dose Modafinil (LoMod) and Saline groups did not differ. (B) Average locomotor activity after saline treatment (*left*) and drug treatment (*right*), by day. No group differences were found. (C) Difference in locomotor activity of drug training trials between Day 1 and Day 7 shown as minute-by-minute (*left*) or averages (*right*). Both groups showed equivalent decreases from Day 1 to Day 7. (D) *Left*, conditioned place preference test displayed as the difference in time spent in the Drug and Saline sides. Both groups of mice spent a roughly equal amount of time in each side of the chamber. *Middle*, locomotor activity in the drug-paired side minus the saline paired side after an injection of a challenge dose of modafinil (0.75 mg/kg). Neither the LoMod or Saline group showed higher locomotor activity in the drug paired side. *Right*, locomotor activity in the drug-paired side minus the saline paired side after an injection of saline. Neither the LoMod or Saline group showed higher locomotor activity in the drug paired side. Each point represents the mean ± S.E.M.

the drug side when compared to vehicle controls [$F(1, 22) = 0.01$, $p > 0.09$; Fig. 4D, right].

4. Discussion

We examined the interactions between modafinil and cocaine in the induction of locomotor sensitization and conditioned place preference. We found a number of interesting results: (1) high dose modafinil (75 mg/kg) induced a robust place preference equal to cocaine, but did not alter the place preference induced by cocaine when the two were co-administered during training; (2) high dose modafinil produced very little to no locomotor sensitization and did not alter sensitization when co-administered with cocaine; (3) mice previously sensitized to cocaine showed a hypersensitive response to low dose modafinil. (4) Low dose modafinil did not produce a place preference or locomotor sensitization. These findings are discussed in turn below.

4.1. Modafinil induces conditioned place preference

First, in line with recent reports [22,23], the current study found that modafinil (75 mg/kg) induced a strong place preference. It was surprising, however, that modafinil and cocaine induced a similar level of place preference, since cocaine is considered to be much more reinforcing. Nonetheless, our results should not be used to conclude that modafinil is equally as rewarding as cocaine because there are likely ceiling effects involved in the CPP paradigm. Moreover, CPP can indicate whether a drug is rewarding, but is not a sensitive measure of the degree of reward given that even natural reinforcers, such as sucrose, can induce CPP [39]. In addition, we used a high dose of modafinil (75 mg/kg) that is unlikely to be comparable to doses approved for use in humans, which are around 1–5 mg/kg [4].

4.2. Modafinil and behavioral sensitization

Second, high dose modafinil induced little or no behavioral sensitization. Two previous studies have found modafinil induces some locomotor sensitization [23,24]. It is unclear why sensitization occurred in the other studies, but not in the current study. One difference between the studies is the time window examined. The current study examined only the first 15 min after i.p. modafinil administration. Paterson et al. [24] examined behavior for the first 30 min after oral administration, while Wuo-Silva et al. [23] examined a delayed 10 min period beginning 30 min after i.p. administration. It is possible that the time window examined was not sufficient to see locomotor sensitization. This appears unlikely, however, because modafinil was sufficient to observe sensitization in cocaine-trained animals within the 15-min test. Furthermore, previous rodent studies have shown that peak locomotor activity occurs between 20 and 40 min after administration [33,40] however these studies only examined 20 min bins and thus it is unclear where the true peak activity occurs. Examining the minute-by-minute data in Fig. 2 indicates that the locomotor activity of the Modafinil mice is not increasing at the end of the 15-min trial and thus it is unlikely to increase further. Furthermore, the

pharmacokinetics of modafinil are not well understood and differences in the solvent used could produce differences in metabolism and bioavailability. Using the current procedure, we have shown that modafinil is active, even at very low doses, 15 min after administration [4].

Regardless, the current study cannot rule out that some locomotor sensitization may occur. However, even if modafinil does produce sensitization, it is far less than other addictive stimulants [37,41]. Behavioral sensitization may be a critical factor in the transition from casual drug use to addiction [36,37]. Thus, even if modafinil is rewarding, it may never reach the level at which it can drive compulsive behavior. This conception could explain the seemingly paradoxical findings that modafinil is rewarding yet there have been no reported cases of addiction. We hypothesize that although modafinil engages many of the same mechanisms as cocaine [20], it fails to produce addicts because it does not sufficiently engage the circuitry required for sensitization. In addition, the lack of significant sensitization observed in this study may be accounted for by the lack of acute locomotor activity produced by modafinil. We have previously reported no locomotor activating effects of acute modafinil (0.075–75 mg/kg, [4]) and this motor stimulant property may be required for behavioral sensitization. Indeed, we could find few references where i.p. modafinil produced hyperactivity in a novel environment, as opposed to dishabituation of activity in a familiar environment [33,42,40,43]. This is in sharp contrast to cocaine, which readily elicits locomotor activity even at very low doses in a novel environment [44].

High dose modafinil did not alter the acute response to cocaine or the formation of locomotor sensitization and conditioned place preference when the two drugs were co-administered. The acute (Day 1) and chronic (Day 7) locomotor response were slightly enhanced, although not significantly. While both drugs have actions on dopaminergic, adrenergic, and serotonergic neurotransmission, the relative potency or pharmacodynamic differences between their actions may account for the differences in the locomotor and rewarding properties of the drugs. This is consistent with the current finding that modafinil does not blunt the acute locomotor effect of cocaine, and in fact, appears to slightly augment this response (Figs. 2 and 3A). This finding, however, could be a result of the high dose used and may not generalize to lower doses. Indeed, future studies should focus on interactions at a range of cocaine and modafinil doses to explore possible dose-related effects.

4.3. Modafinil cross-sensitization with cocaine

Thirdly, we found that a low dose of modafinil cross-sensitized in cocaine-trained mice. Modafinil was able to elicit a sensitized response in animals that were trained with either cocaine or a combination of cocaine and modafinil. Thus, in order for modafinil to elicit the expression of sensitization, cocaine is required during training and modafinil alone is insufficient to produce the underlying changes that lead to sensitization. The ability of modafinil to cross-sensitize with cocaine is consistent with work indicating that modafinil can cause reinstatement of cocaine self-administration [16] and conditioned place preference [45]. Those experiments, however, were done at high doses (64–128 mg/kg), and the current results expand these findings to our low challenge dose of 0.75 mg/kg. Modafinil, therefore, activates the pathway that is sensitized in animals with previous experience with cocaine. This is also consistent with what is known about the mechanism of modafinil. Cocaine sensitization can reduce autoreceptor activity and increase D1 receptor sensitivity [46–48]. Modafinil may activate this circuitry by increasing dopamine in the accumbens [17–20].

4.4. Low dose modafinil

Finally, we found that a low dose of modafinil (0.75 mg/kg) does not produce a place preference or locomotor sensitization. This low dose is far lower than the doses that are generally tested in mice, but is sufficient to express locomotor sensitization (Fig. 4B) and enhance learning [4]. It is unclear how a rodent dose of modafinil translates to human use, but we have argued that the equivalent dose is unlikely to be 100 times larger than what is given in humans (100–200 mg or 1–3 mg/kg; [4]). This low dose may be a better model of human modafinil administration that the very high doses seen in previous studies. Furthermore, this difference in dose could account for the lack of addiction in human subjects. It is possible, then, that modafinil could be very rewarding if given at high doses or through an alternate route of administration. Regardless of which dose is a better model of human use, future rodent studies should focus on a wide range of doses. Significantly, the cost of modafinil is presently very high (up to $20 per 100 mg tablet) indicating that high dose administration in humans is very unlikely.

4.5. Modafinil and reward

Together, the current data reinforce the notion that modafinil can be rewarding in mice, but only when given at a high dose or in cocaine-experienced subjects. Acute reward, however, is not necessarily the sole component of addiction. We found that modafinil produced very little, if any, behavioral sensitization like other addictive stimulants [37,41]. In addition, there appear to be no withdrawal symptoms or a negative motivational state associated with drug termination that could drive negative reinforcement [2]. Perhaps modafinil has relatively weak potency and slow absorption, especially orally as it is taken, compared to the stimulants of abuse. Thus, despite having a modest reward profile, modafinil is unlikely to drive addictive behavior.

Modafinil is suggested as a pharmacotherapy for cocaine addiction. Agonist therapy has emerged as a promising candidate for treating addiction [14] and relies on weak activation to reduce craving and withdrawal. Modafinil meets this profile, as it appears to be a weak dopaminergic agonist. Weak or slow agonist therapy has generally been effective for Heroin (with buprenorphine) and nicotine (with varenicline) addiction, but has not been established as effective for psychostimulant addiction [49,50]. Animal studies indicate that modafinil may not be a useful long-term therapeutic, as it can enhance reinstatement of cocaine self-administration [16], induce place preference (Fig. 4), and cross-sensitize with cocaine (Fig. 4), however, these effects have not been seen in human cocaine addicts [51]. Thus, while modafinil holds some promise as a therapeutic to reduce cocaine craving, more studies are needed to identify ways to minimize the potential for triggering relapse.

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