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Modafinil effects on reinstatement of methamphetamine-seeking in a rat model of relapse

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Abstract

Rationale—Modafinil (Provigil) is a wake-promoting drug characterized by cognitive enhancing abilities. Recent clinical data have supported the use of modafinil for treatment of chronic psychostimulant addiction and relapse prevention.

Materials and Methods—We used an intravenous methamphetamine (meth) self-administration procedure to assess the dose-dependent effects of modafinil on reinstatement following abstinence and after extinction on conditioned-cue and meth-primed reinstatement of meth-seeking.

Results—Modafinil attenuated active lever responding in multiple reinstatement conditions – context-induced, conditioned cue, and meth-prime. The most pronounced and consistent effect was on meth-primed reinstatement, and modafinil did not reinstate meth-seeking when tested alone.

Discussion—These findings support clinical findings in humans that modafinil may be an effective therapeutic agent for the prevention of relapse in abstinent meth users.

Keywords

methamphetamine; modafinil; reinstatement; relapse; self-administration; abstinence

Introduction

Methamphetamine (meth) is widely abused around the world. In the United States, 18 million people over age 12 have experimented with meth in their lifetime (Substance Abuse and Mental Services Administration, 2007). Initial use produces a general state of well being accompanied by increased wakefulness, talkativeness, and physical activity (NIDA, 2006). Continued use often leads to compulsive drug use, addiction, and long-term health consequences. Negative consequences of meth use include psychosis, attention and memory deficits, poor decision making and impulsivity, increased aggression and violence, dysregulated affect, weight loss, and severe tooth damage (Bray 1993; Hoffman et al. 2006; Klasser and Epstein 2005; Looby and Earleywine 2007); (Mcketin et al. 2006; Paulus et al. 2003); (Salo et al. 2007; Sekine et al. 2006). As with any abused substance, meth addiction is a chronic relapsing disorder meriting the need for effective pharmacotherapies to aid the prevention of relapse.

Early clinical findings suggest that modafinil (Provigil®) may have some efficacy for the treatment of psychostimulant addiction, including meth. Modafinil is approved in the U.S.

for the treatment of narcolepsy and chronic, excessive sleepiness during waking hours. Further, modafinil has cognitive enhancing abilities and may potentially alleviate withdrawal symptoms associated with meth dependence such as impaired cognition, poor impulse control, and altered mood (Ling et al. 2006) (Minzenberg and Carter 2008) (Vocci and Appel 2007). A few clinical studies have demonstrated promising results for modafinil as a treatment for psychostimulant (i.e., cocaine and meth) addiction. Modafinil treatment (200 and 400 mg) with and without concurrent cocaine or meth use did not result in medical risks, craving, or euphoria (Dackis et al. 2003) (De La Garza et al. 2009); (McGaugh et al. 2009). In cocaine-dependent participants, modafinil (400 mg) produced more negative urine samples and increased the potential for participants to reach a protracted abstinence period (Dackis et al. 2003). Furthermore, modafinil reduced cocaine self-administration (Hart et al. 2008), increased the maximum number of non-use days, and reduced craving in cocaine addicts (Anderson et al. 2009). In meth-dependent participants, modafinil produced a trend toward more negative urine samples and decreased measures of anxiety and depression (McGaugh et al. 2009) (Shearer et al. 2009).

The exact mechanisms of modafinil remain unknown, as the drug has widespread central nervous system effects. Many of the therapeutic effects for narcolepsy have been attributed to orexin receptors in hypothalamic areas (Ballon and Feifel 2006) (Scammell et al. 2000). However, the drug has diverse mechanisms, including interactions with the dopamine, norepinephrine, glutamate, GABA, and serotonin systems (reviewed in (Minzenberg and Carter 2008). Modafinil binds with low affinity to monoamine transporters (Madras et al. 2006) (Mignot et al. 1994), and although binding and uptake assays indicate preferential actions at dopamine transporters relative to norepinephrine and serotonin, modafinil binds with reduced affinity compared to cocaine, GBR12909, methylphenidate, and benztropine (Madras et al. 2006); (Zolkowska et al. 2009). Modafinil has also been found to enhance glutamate and inhibit GABA release in various brain regions (Ferraro et al. 1997; Ferraro et al. 1998). The structurally distinct nature of modafinil relative to many classic stimulant drugs may contribute to its unique behavioral profile (reviewed in (Minzenberg and Carter 2008). Although the drug can stimulate locomotor activity at relatively high doses (Duteil et al. 1990) (Edgar and Seidel 1997); (Simon et al. 1996) (Zolkowska et al. 2009), modafinil does not lead to conditioned place preference or maintain self-administration in rats (Deroche-Gamonet et al. 2002).

Despite the previous clinical findings, modafinil has never been tested in preclinical models of reinstatement to meth-seeking (see (Yahyavi-Firouz-Abadi and See 2009) for a review). Animal models of drug self-administration and reinstatement incorporate various trigger factors (e.g., cues, stress, or drug priming) for the testing of potential pharmacotherapies for blocking reinstatement (Panlilio and Goldberg 2007); (Sanchis-Segura and Spanagel 2006); (Stewart 2000). In order to assess the translational relevance of modafinil in preventing relapse, we tested whether modafinil blocks meth-seeking after prolonged abstinence, and using extinction followed by reinstatement via conditioned cues or a meth priming injection. Further, we established whether modafinil by itself affects meth-seeking after self-administration. These assessments of modafinil in a reinstatement model provide the first preclinical determination of the drug's potential as a treatment for relapse prevention in meth addiction.

Methods and Procedures

Subjects

Forty-six male Long-Evans rats (Charles-River) weighing 250-300 g at the time of delivery were housed on a reversed 12:12 light-dark cycle in a temperature- and humidity-controlled vivarium. Rats were individually housed. Rats received *ad libitum* water throughout the

study and 25 g of standard rat chow (Harlan, Indianapolis, IN, USA) daily until self-administration stabilized, at which time animals were maintained *ad libitum*. Procedures were conducted in accordance with the “Guide for the Care and Use of Laboratory Rats” (Institute of Laboratory Animal Resources on Life Sciences, National Research Council) and approved by the IACUC of the Medical University of South Carolina.

Apparatus

Sixteen standard self-administration chambers (30×20×20 cm, Med Associates) were housed inside sound-attenuating cubicles fitted with a fan for airflow and masking noise. Each chamber contained two retractable levers, two stimulus lights, a speaker for tone delivery, and a house light to provide general illumination. Additionally, each chamber was equipped with a balanced metal arm and spring leash attached to a swivel (Instech). Tygon® tubing extended through the leash and was connected to a 10 ml syringe mounted on an infusion pump located outside the sound-attenuating cubicle.

Drugs

Methamphetamine hydrochloride was purchased from Sigma (St. Louis, MO, USA). Meth (dissolved in sterile saline) was administered intravenously at a volume of 20 µg/50 µl infusion. Modafinil was purchased from Toronto Research Chemicals (Toronto, ON, Canada), suspended in 0.25% methylcellulose (Sigma, St. Louis, MO, USA), and injected IP at a volume of 2 ml/kg (Edgar and Seidel 1997; Scammell et al. 2000). Drugs used for anesthesia were ketamine (Vedco Inc, St Joseph, MO, USA), xylazine (Lloyd Laboratories, Shenandoah, IA, USA), equithesin (sodium pentobarbital 4 mg/kg, chloral hydrate 17 mg/kg, and 21.3 mg/kg magnesium sulfate heptahydrate dissolved in 44% propylene glycol, 10 % ethanol solution), and ketorolac (Sigma, St. Louis, MO, USA). During self-administration catheters were flushed with heparin (Elkins-Sinn, Cherry Hill, NJ, USA) and cephazolin (Schein Pharmaceuticals, Florham Park, NJ, USA). Catheter patency was verified with methohexital sodium (Eli Lilly, Indianapolis, IN, USA).

Surgery

Anesthesia consisted of IP injections of ketamine (66 mg/kg), xylazine (1.3 mg/kg), and equithesin (0.5 ml/kg). Ketorolac (2.0 mg/kg, IP) was given just prior to surgery as an analgesic. One end of a silastic catheter was inserted 33 mm into the external right jugular and secured with 4.0 silk sutures. The other end ran subcutaneously and exited from a small incision just below the scapula. This end attached to an infusion harness (Instech Solomon, Plymouth Meeting, PA, USA) that provided access to an external port for IV drug delivery. An antibiotic solution of cefazolin (10 mg/0.1 ml) was given post surgery and during recovery along with 0.1 ml 70 U/ml heparinized saline. During self-administration rats received an IV infusion (0.1 ml) of 10 U/ml heparinized saline before each session. After each session, catheters were flushed with cefazolin and 0.1 ml 70 U/ml heparinized saline. Catheter patency was periodically verified with methohexital sodium (10 mg/ml dissolved in 0.9% physiological saline), a short-acting barbiturate that produces a rapid loss of muscle tone when administered intravenously.

Methamphetamine self-administration

Following at least 5 days of recovery, rats were given daily 2 hr sessions to self-administer meth on a fixed ratio 1 schedule of reinforcement. The house light always signaled the beginning of a session and remained on throughout the session. During the sessions, a response on the active lever resulted in activation of the pump for a 2-s infusion (20 µg/50 µl bolus infusion) and presentation of a stimulus complex consisting of a 5-s tone (78 dB, 4.5 kHz) and a white stimulus light over the active lever, followed by a 20 s time out. Responses

occurring during the time out and on the inactive lever were recorded, but had no scheduled consequences. All sessions took place during the dark cycle in two cohorts between 9 am and 1 pm. Sessions were conducted 6 days/week until the rat reached a criterion of more than 10 infusions during a session for 14 cumulative days. All ensuing experiments featured the same self-administration procedures; a schematic representation of abstinence, extinction, and reinstatement testing for each experiment is depicted in Figure 1.

Abstinence, extinction, and reinstatement

Following meth self-administration, rats were placed into abstinence and/or extinction before reinstatement testing. During 14 days of abstinence, rats were transported from the colony room, handled, weighed, and fed but not placed in the self-administration chamber. During extinction, rats were placed in the self-administration chamber for daily 2-hr sessions for 14-15 days; responding on either lever had no scheduled consequences. To have met extinction criterion, responses on the active (i.e., drug-seeking) lever needed to be ≤ 25 presses for 2 consecutive days. When this criterion was met, rats were tested for meth-primed or cue-induced reinstatement. During the meth-prime test, responding on either lever had no scheduled consequences. For cue reinstatement, active lever presses resulted in presentation of the conditioned light+tone in the same manner as during self-administration. Further daily extinction sessions occurred between reinstatement tests until the criterion of ≤ 25 presses for 2 consecutive days was met.

Experiment 1: Modafinil dose response curves for meth-primed and cue-induced reinstatement

In this experiment, self-administration and extinction occurred as described above. When extinction criterion was met, rats were assigned to receive either meth-primed ($n=6$) or cue-induced ($n=11$) reinstatement tests. Each rat underwent four reinstatement tests in which they received modafinil injections (0, 30, 100, or 300 mg/kg IP) 90 min prior to being placed in the test chamber. Our laboratory has repeatedly demonstrated that responding maintains stability over multiple reinstatement tests (Berglund et al. 2006; Feltenstein et al. 2007; Kippin et al. 2005; Ledford et al. 2003). Test order was counter-balanced as much as sample size allowed and resulted in a unique test order for each rat. For meth-primed reinstatement, rats were injected with 1 mg/kg (IP) meth immediately before placement into the chamber. This dose has been found to produce robust reinstatement of meth-seeking in previous studies (Rogers et al. 2008; Schwendt et al. 2009).

Experiment 2: Modafinil effects on reinstatement following abstinence and extinction

After meth self-administration, rats entered a 14-day abstinence period. On day 15 of abstinence, rats were returned to the drug-taking environment for a 2-hr test. Note that this test is termed “context-induced” to differentiate from “conditioned cue” or “meth prime” reinstatement tests that occurred after daily extinction. On this test, rats ($n=11$ /per group) were divided into groups based on their prior meth intake. The subjects received either modafinil (100 mg/kg) or vehicle 90 min before placement into the chamber. During testing, lever presses on both levers were recorded without any programmed consequences.

Following this test, rats underwent daily extinction, followed by cue-induced and meth-primed reinstatement as described above. To negate the impact of non-contingent meth exposure (i.e., a drug prime) on cued reinstatement, the cue test was conducted first. Drug assignment depended on the previous test and was counter balanced as much as sample size allowed.

Experiment 3: Modafinil effects alone on reinstatement of meth-seeking

In this experiment, self-administration and extinction occurred as described in Experiment 1. Following extinction, rats ($n=7$) were injected IP with 0, 100, or 300 mg/kg modafinil 90 min before placement in the chamber. Additionally, each rat received a meth prime reinstatement test to verify reinstatement by meth alone. The test order was counterbalanced resulting in a unique sequence for each rat.

Data analysis

The number of active and inactive lever presses served as the main dependent measures. One-way analysis of variance (ANOVA, Experiments 1 and 3) and planned t-tests (Experiment 2) were used to determine the effects of modafinil on context-induced, meth-primed, and cue-induced reinstatement where appropriate. To determine whether specific treatments induced reinstatement, planned comparisons were conducted between extinction responding and the particular treatment. The effects of modafinil on extinction responding used a mixed ANOVA with drug as the between-subjects factor and session as the within-subjects factor. Tukey tests were used for post hoc comparisons. Data points two standard deviations from the mean were excluded (Hill and Lewicki 2007). Significance was set at $p<0.05$ for all tests and all data are presented as the mean $\pm$ SEM.

Results

Experiment 1: Modafinil dose dependently attenuates reinstatement

Self-administration of meth was readily acquired and maintained as indicated by preferential responding on the active lever relative to the inactive lever ($t_{17}=6.26$, $p<0.0001$) (Figure 2a). Mean meth intake on the last 3 days of self-administration was 1.78 ± 0.14 mg/kg per session and the total number of days to reach criterion for meth self-administration ranged from 14 to 18. Lever responding decreased across extinction trials (Figure 2b) as evidenced by a significant repeated-measures ANOVA of session for the active ($F_{13,208}=8.07$, $p<0.001$) and inactive ($F_{13,208}=3.61$, $p<0.001$) levers.

Modafinil blocked reinstatement to a meth-priming injection (Figure 3) in a dose dependent manner for active lever presses (within-subjects ANOVA, $F_{3,15}=7.26$, $p<0.005$). Specifically, 100 and 300 mg/kg modafinil decreased responding relative to vehicle (Tukey test $p<0.05$). Moreover, planned comparisons showed that vehicle-treatment reinstated meth-seeking (active lever responses) relative to extinction ($t_5=4.18$, $p<0.01$); however, responding after 30, 100 and 300 mg/kg modafinil resulted in no significant differences from extinction levels. Modafinil did not affect inactive lever presses during meth-primed reinstatement testing.

Modafinil also tended to decrease cue-induced reinstatement (Figure 4); however, this effect did not achieve significance for the within-subjects ANOVA ($F_{6,30}=2.40$, $p=0.09$). Planned comparisons confirmed that relative to extinction responding, meth-seeking was increased in the 0, 30, and 100 mg/kg modafinil conditions ($t_s \geq 2.62$, $p_s < 0.05$), but not after 300 mg/kg pretreatment. Modafinil failed to alter inactive lever presses during cue-induced reinstatement tests.

Experiment 2: 100 mg/kg modafinil effects on reinstatement following abstinence and extinction

Data from rats that underwent 14 days of abstinence and subsequent extinction and reinstatement testing are shown in Figure 5. For the context-induced reinstatement test following abstinence, the groups (vehicle and modafinil) were matched according to daily meth intake on the last 3 days of self-administration (1.80 ± 0.13 mg/kg). Further, the

vehicle and modafinil groups did not differ in active or inactive lever presses (Figure 5a) and total days of self-administration ranged from 14 to 18. On the context-induced reinstatement test, modafinil (100 mg/kg) showed a trend to attenuate lever responding ($t_{20}=1.98$, $p=0.06$). For the vehicle group, active lever responses were higher on the context-induced reinstatement test than the last 3 days of self-administration ($t_{33}=2.14$, $p<0.05$), an effect not apparent in the modafinil-treated rats. Both groups also showed a modest increase in inactive lever responding relative to self-administration ($ts>2.36$, $p<0.05$).

Following this relapse test, lever responding was extinguished for 14 days. Both groups displayed a decrease in active lever responding throughout the extinction period (Figure 5b). A mixed ANOVA for active lever responding across sessions for rats treated with vehicle or modafinil showed a significant group by session interaction ($F_{13,260}=2.76$, $p<0.001$). Rats that received modafinil on the first day of extinction (i.e., context test) responded less on the active lever on extinction days 1 and 2 (Tukey, $p<0.05$). A significant group by session interaction on the inactive lever revealed an increase in vehicle responding on the second day of extinction ($F_{13,260}=2.01$, $p<0.05$, and Tukey, $p<0.05$).

Modafinil (100 mg/kg) attenuated both cue and meth-primed reinstatement (Figure 5c). On the cue-induced reinstatement test, modafinil decreased responding on the active lever relative to rats that received vehicle ($t_{20}=2.23$, $p<0.005$), without impacting the inactive lever. Responding on the inactive lever was not elevated beyond extinction for either group; however, active lever presses were increased for both groups on the cue test relative to extinction responding ($ts>4.55$, $p<0.0001$). On the meth-primed reinstatement test, rats given 100 mg/kg modafinil responded less on the active lever in comparison to controls ($t_{20}=2.23$, $p<0.05$), but not the inactive lever. Both groups responded more on the active lever in comparison to extinction (vehicle, $t_{32}=5.08$, $p<0.0001$; modafinil, $t_{32}=2.69$, $p<0.01$); however, only the vehicle group responded more on the inactive lever ($t_{32}=4.60$, $p<0.0001$).

Experiment 3: Modafinil alone fails to reinstate meth-seeking

Modafinil at the same doses that reduced meth-primed or cued reinstatement failed to affect meth-seeking when given alone (Figure 6). For this experiment, average meth intake for the last 3 days of self-administration was 1.73 ± 0.25 mg/kg and the number of days to reach self-administration criterion ranged from 14 to 16. Animals showed similar patterns of lever responding during self-administration (Figure 6a) and extinction (Figure 6b) as the previous groups. While the meth prime injection engendered robust reinstatement of meth-seeking, modafinil had no effects at any dose (within-subjects ANOVA, $F_{3,18}=23.98$, $p<0.001$). Active lever responses for the meth-primed reinstatement test were substantially higher than responding in the 0, 100, and 300 mg/kg modafinil conditions (Tukey, $p<0.05$), with responding after modafinil showing absolutely no differences from baseline extinction rates.

Discussion

The findings that modafinil attenuated both meth-primed and conditioned cue reinstatement in an animal model of reinstatement corroborates recent clinical research that showed modafinil does not increase drug desire (Dackis et al. 2003; De La Garza et al. 2009; Shearer et al. 2009), but actually decreases craving for cocaine (Anderson et al. 2009). The fact that modafinil alone completely lacked the ability to stimulate meth-seeking further strengthens the potential usefulness of modafinil as a possible therapeutic agent for psychostimulant addiction.

Importantly, the reduction in meth-seeking is unlikely to be caused by modafinil-induced changes in general activity. Modafinil failed to affect inactive lever presses, suggesting a lack of generalized locomotor effects. Additionally, in the current study, reinstatement tests

occurred 90 min after modafinil administration, at a time point when modafinil-induced locomotor activation is generally decreased. Low doses of modafinil (20-80 mg/kg, IP) increased motor activity in Long Evans rats up to 50 min after treatment (Simon et al. 1996). Higher doses (100 and 300 mg/kg, IP) stimulated motor activity in a dose related manner, but the effect subsided after approximately 90 min for rats administered 100 mg/kg modafinil (Edgar and Seidel 1997). While some motor activating effects have been reported with IV modafinil (20 and 60 mg/kg) (Zolkowska et al. 2009), these effects peaked approximately 40 min after modafinil exposure and subsided by 100 min. In our laboratory, we have confirmed that modafinil (100 mg/kg, IP) had no impact on activity (horizontal or vertical) of rats tested in a novel environment (data not shown) at the time point used for reinstatement testing in these experiments. These data, combined with the lack of generalized activity on the inactive lever, suggest that nonspecific activity did not impact reinstatement testing.

A recent body of research has focused on the similarities between modafinil and psychostimulant drugs, urging caution about possible reinforcing mechanisms and abuse liability (Bernardi et al. 2009; Volkow et al. 2009; Zolkowska et al. 2009). Specific emphasis has been placed on modafinil binding to dopamine transporters in the nucleus accumbens and the resultant increased extracellular dopamine levels, since dopamine reuptake inhibition is the hallmark action of classic psychostimulant drugs (Ritz et al. 1987; Volkow et al. 2009). Nevertheless, the clinical data do not support the assertion that modafinil has potent reinforcing effects or abuse liability (Malcolm et al. 2002); (Rush et al. 2002; Vosburg et al. 2009). Animal models present a somewhat conflicting profile, as modafinil shares at least some partial discriminative stimulus properties with cocaine and d-amphetamine in rats (Dopheide et al. 2007; Gold and Balster 1996), maintains self-administration in cocaine-experienced primates (Gold and Balster 1996), and reinstates an extinguished preference for a cocaine-paired environment (Bernardi et al. 2009). In contrast, modafinil does not intrinsically act as a reinforcer or have conditioned rewarding effects in rats (Deroche-Gamonet et al. 2002), although this study reported a very modest effect of modafinil (64 mg/kg) to increase reinstatement of nose-poking at a level well below that seen with cocaine-priming. Our results with modafinil showed no ability to reinstate meth-seeking behavior, suggesting little or no abuse liability in meth users. One interpretation of modafinil's low abuse liability is that this drug may be a viable candidate for psychostimulant addiction. Further research in animal models and human addicts is warranted to determine the extent of modafinil's future potential for treatment of psychostimulant addiction and relapse prevention.

Although most emphasis has focused on modafinil as a weak inhibitor of monoamine transport (Madras et al. 2006; Mignot et al. 1994; Volkow et al. 2009; Zolkowska et al. 2009), the drug also elevated glutamate levels in the hippocampus, thalamus, and striatum (Ferraro et al. 1997; Ferraro et al. 1998). It is possible that modafinil-induced increases in glutamate concentrations may restore basal levels of glutamate to attenuate reinstatement in a manner similar to the blockade of cocaine-primed reinstatement of cocaine-seeking following glutamate prodrug administration, such as *N*-acetylcysteine (Baker et al. 2003). Specifically, cocaine withdrawal causes reductions in basal extracellular glutamate concentrations, but potentiated increase in glutamate release during cocaine-primed reinstatement (McFarland et al. 2003). Basal glutamate concentrations are regulated by the glutamate/cystine antiporter (Baker et al. 2002) and are down regulated during cocaine withdrawal (Baker et al. 2003). *N*-acetylcysteine is a cystine prodrug that restores basal glutamate levels and prevents cocaine-primed reinstatement and the associated increase in glutamate levels during reinstatement (Baker et al. 2002). Perhaps modafinil effectively restores imbalances to the glutamate system caused by chronic meth, thus reducing reinstatement or preventing relapse to meth-seeking ((Kalivas 2009).

Extinction results in the learning of a new response contingency, rather than a forgetting of the previous learning (Bouton 2002). The use of extinction training during a period of withdrawal from chronic drug self-administration produces different behavioral profiles (Fuchs et al. 2006; Neisewander et al. 2000; See et al. 2007; Zavala et al. 2007) and neuroadaptations (Schmidt et al. 2001; Self 2004; Sutton et al. 2003) relative to rats that have drug withheld during an abstinence period without extinction training (see Reichel and Bevins 2009 for review). To study both aspects of withdrawal, we incorporated an abstinence period prior to extinction of the operant response. After 14 days of abstinence, modafinil (100 mg/kg IP) blunted meth-seeking. On the context-induced reinstatement test (i.e., first day returned to the chamber following abstinence), one would expect an increase in active lever pressing relative to meth self-administration, reflecting an incubation of craving (Shepard et al. 2004). This incubation was evident in control rats; however, modafinil appeared to block incubation (i.e., active lever responses) of the meth-associated context when compared to active lever responses during self-administration. Moreover, modafinil-induced reductions in lever pressing persisted on ensuing extinction sessions, even in the absence of continued modafinil treatment.

Reductions in response output when the drug is not bioavailable are important from a drug treatment perspective, since persisting drug effects are a desirable feature of anti-relapse medications. Modafinil may have acted as a cognitive enhancer during the context-induced reinstatement test (akin to the first day of extinction), when behavioral output resulted in lack of reinforcement. Modafinil may have strengthened learning of the new contingency, since rats showed reduced responding on subsequent days. Support for modafinil as a cognitive enhancer comes from findings that modafinil improved working memory performance in rats and mice (Béracochéa et al. 2003; Piérard et al. 2006; Ward et al. 2004), accelerated initial learning on a task that requires context-appropriate strategies to make correct responses (Béracochéa et al. 2003), and improved accuracy on a 3-choice reaction time task (Morgan et al. 2007). This cognitive enhancing ability raises the question of whether modafinil is acting on memory processes, rather than addiction processes. Chronic methamphetamine has pronounced effects on memory function in both animal and human models (see Scott et al 2007 for a review) further indicating an overlap in addiction and memory processes. Examination of modafinil's effect on a natural reinforcer will begin to parse apart the distinction between memory and/or addiction processes in this model of reinstatement.

If modafinil can enhance extinction learning, this effect may have impacted the conditioned cued reinstatement test. In Experiment 1b, modafinil exerted a nonsignificant reduction on the conditioned-cue reinstatement test when multiple test sessions were used. Unlike the meth-primed reinstatement tests, during cued reinstatement, an active lever response results in presentation of the stimulus complex (light+tone) without meth, resulting in extinction of the light+tone. With modafinil treatment, extinction of the stimulus complex may be enhanced and thus impact subsequent reinstatement tests. In this regard, it is notable that when only one cued reinstatement test was given (i.e., Experiment 2), modafinil produced significant attenuation of cued reinstatement. Future studies will address cognitive enhancing effects of repeated modafinil during extinction and relapse.

Although the full behavioral features and precise mechanisms of action are yet to be determined, modafinil shows clear and growing promise as a pharmacotherapy for meth addiction (McGaugh et al. 2009; Shearer et al. 2009). Our results support the further assessment of modafinil in both animal models and clinical trials for the treatment of psychostimulant addiction. Modafinil's unique behavioral profile relative to psychostimulant drugs and cognitive enhancing abilities merit further exploration for modafinil as a treatment option. Specifically, testing the ability of modafinil to reverse both meth-induced cognitive

deficits and meth-seeking (Rogers et al. 2008) after acute and chronic treatment will determine the potential long term benefits of modafinil treatment in addiction.

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Figure 1. Reinstatement testing procedure. Experiment 1a and 1b tested reinstatement to a meth prime and conditioned cue, respectively, following a range of modafinil (IP) injections. Experiment 2 tested modafinil's effect on reinstatement following abstinence and reinstatement to a conditioned cue and meth-prime following extinction. Experiment 3 tested whether a range of modafinil doses would reinstate meth-seeking relative to a meth prime.

Figure 2.

Lever responding (mean $\pm$ SEM) during chronic meth self-administration and extinction. (a) Lever responses exhibited by rats ($n=17$) during the last 3 days of meth self-administration. (b) Lever responses during daily extinction sessions. Responses during extinction resulted in no programmed consequences. Significant differences from active lever are indicated ($*p<0.05$).

Figure 3.

Modafinil blockade of meth-primed reinstatement of meth-seeking. Rats ($n=6$) received vehicle or modafinil (30, 100, or 300 mg/kg) before reinstatement testing and active lever responses resulted in no programmed consequences. Data represent active and inactive lever responses (mean $\pm$ SEM). Significant differences from vehicle ($*p<0.05$) and extinction ($†p<0.05$) responding are indicated.

Figure 4. Modafinil attenuation of conditioned-cued reinstatement of meth-seeking. Rats ($n=11$) active lever presses resulted in a presentation of the previously meth paired light + tone stimulus complex. Responses (mean $\pm$ SEM) are shown for the active and inactive levers. Significant differences from extinction responding are indicated ($^{\dagger}p < 0.05$)

Figure 5.

Lever responding (mean $\pm$ SEM) during chronic meth self-administration, context-induced reinstatement, extinction, and reinstatement testing. (a) Lever responses exhibited by rats ($n=11$) during the last 3 days of meth self-administration and after 14 days of abstinence from meth. (b) Lever responses during daily extinction sessions. Responses during extinction resulted in no programmed consequences. (c) Lever responses during reinstatement testing. Significant differences between modafinil and vehicle are indicated (* $p < 0.05$).

Figure 6.

Lever responding (mean $\pm$ SEM) during chronic meth self-administration, extinction, and reinstatement testing. (a) Lever responses exhibited by rats ($n=7$) during the last 3 days of meth self-administration. (b) Lever responses during daily extinction sessions. Responses during extinction resulted in no programmed consequences. (c) Lever responses during reinstatement testing. Significant differences are indicated for meth-prime reinstatement (* $p<0.05$).