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The Unique Psychostimulant Profile of (\pm)-Modafinil: Investigation of Behavioral and Neurochemical Effects in Mice

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Abstract

Blockade of dopamine (DA) reuptake via the dopamine transporter (DAT) is a primary mechanism identified as underlying the therapeutic actions of (\pm)-modafinil (modafinil) and its R-enantiomer, armodafinil. Herein, we explored the neurochemical and behavioral actions of modafinil to better characterize its psychostimulant profile. Swiss-Webster mice were implanted with microdialysis probes in the nucleus accumbens shell (NAS) or core (NAC) to evaluate changes in DA levels related to acute reinforcing actions of drugs of abuse. Additionally, subjective effects were studied in mice trained to discriminate 10 mg/kg cocaine (i.p.) from saline. Modafinil (17–300 mg/kg, i.p.) significantly increased NAS and NAC DA levels that at the highest doses reached ~300% at 1 hour, and lasted >6 hours in duration. These elevated DA levels did not show statistically significant regional differences between the NAS and NAC. Modafinil produced cocaine-like subjective effects at 56–100 mg/kg when administered at 5 and 60 minutes before the start of the session, and enhanced cocaine effects when the two were administered in combination. Despite sharing subjective effects with cocaine, modafinil's psychostimulant profile was unique compared to that of cocaine and like compounds. Modafinil had lower potency and efficacy than cocaine in stimulating NAS DA. Additionally, the cocaine-like subjective effects of modafinil were obtained at lower doses and earlier onset times than expected based on its dopaminergic effects. These studies suggest that although inhibition of DA reuptake may be a primary mechanism underlying

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modafinil's therapeutic actions, non DA-dependent actions may be playing a role in its psychostimulant profile.

Keywords

cocaine abuse and addiction; dopamine microdialysis; nucleus accumbens shell; ADHD; Modafinil; Methylphenidate

Introduction

Several recent studies suggest (\pm)-modafinil (modafinil) (Provigil®; (2-[(diphenylmethyl)sulfinyl] acetamide) as a potential treatment for dependence on stimulants, such as cocaine and methamphetamine, in certain populations of subjects (Dackis *et al.*, 2003; Dackis *et al.*, 2005; Hart *et al.*, 2008; Kalechstein *et al.*, 2010; Kampman *et al.*, 2015). Modafinil was approved by the US Food and Drug Administration as a wakefulness-promoting agent, and is listed as a Schedule IV compound in the Controlled Substances Act (Food and Drug Administration, 2007). However, preclinical and clinical studies suggest that modafinil lacks the abuse potential of amphetamine and methylphenidate (Martinez-Raga *et al.*, 2008) and case reports of modafinil abuse are rare (Ozturk & Deveci, 2014; Krishnan & Chary, 2015).

Preclinical assessments of the abuse potential of modafinil are noteworthy for inconsistent results. For example, Gold and Balster (1996) reported intravenous self-administration of modafinil when substituted for cocaine in rhesus monkeys. However, a subsequent report (Deroche-Gamonet *et al.*, 2002) indicated that modafinil did not produce reinforcing effects in rats. In a study with human subjects (Stoops *et al.*, 2005) break points on progressive-ratio schedules increased with increasing dose, but only if the subjects were required to complete simple arithmetic problems after taking the drug. Further, studies of modafinil place conditioning have yielded similarly inconsistent results with some showing positive (Wuo-Silva *et al.*, 2011; Shuman *et al.*, 2012) and some negative (Deroche-Gamonet *et al.*, 2002; Quisenberry *et al.*, 2013b) outcomes. Finally, studies of drug discrimination have found partial (Gold & Balster, 1996; Dopheide *et al.*, 2007; Quisenberry *et al.*, 2013a) or full substitution (Paterson *et al.*, 2010; Loland *et al.*, 2012) for cocaine or *d*-amphetamine. In subjects trained to discriminate modafinil from saline injections cocaine methylphenidate and GBR 12909 fully substituted whereas *d*-amphetamine did not (Quisenberry & Baker, 2015).

Consistent with abuse liability is evidence that modafinil increases in vivo levels of DA by blocking the DAT, as do standard psychostimulants such as methylphenidate or cocaine (Volkow *et al.*, 2009; Zolkowska *et al.*, 2009; Loland *et al.*, 2012). However, standard psychostimulants have higher affinity for the DAT when it is in a conformation open to the extracellular compared to the intracellular space (Ferrer & Javitch, 1998; Loland *et al.*, 2008). In contrast, the affinity of modafinil for the DAT in an outward conformation is similar to its affinity for an inward facing DAT (Loland *et al.*, 2012), which is reminiscent of binding profiles for other compounds that have been considered atypical DAT inhibitors (Loland *et al.*, 2008; Newman & Katz, 2009; Tanda *et al.*, 2009b; Schmitt & Reith, 2011;

Schmitt *et al.*, 2013). Thus the lack of pronounced selectivity of binding to DAT conformations may contribute to the unique in vivo pharmacological profile of modafinil. For example, although modafinil and its R- and S-enantiomers stimulate extracellular levels of DA in the NAS, in mice (Loland *et al.*, 2012), a brain region related to the reinforcing effects of psychostimulants (Pontieri *et al.*, 1995; Tanda *et al.*, 1997), the stimulation showed relatively long time courses and significantly lower maxima compared to that for cocaine (Loland *et al.*, 2012).

When evaluating the abuse potential of modafinil in human subjects, it is important to consider that it is practically insoluble in water and highly unstable when heated at high temperatures. Insolubility and the vehicle used in preclinical studies may contribute to the inconsistent outcomes obtained and make the compound impractical for intravenous injection, a primary route of administration for abuse of cocaine or methamphetamine. Nonetheless, the use of modafinil in non-medical settings has increased in recent years. Indeed, orally taken modafinil use as a “smart drug,” in student populations, but also by professionals to improve cognitive performance, has been the subject of several commentaries (Greely *et al.*, 2008; Cakic, 2009; Partridge *et al.*, 2011). Thus, a better understanding of the behavioral actions and related neurochemistry of modafinil is necessary to monitor its potential for abuse alone and in combination with illicit psychostimulants. To that end, the present study compared the effects of modafinil with those of cocaine in order to assess its relative potential to increase brain DA levels, as assessed by in vivo microdialysis, and to assess subjective effects, assessed in mice trained to discriminate cocaine. Additionally a novel vehicle was used that increased bioavailability of modafinil as evidenced by a leftward shift in the dose-effect curve for increasing extracellular DA levels.

Materials and Methods

Subjects

Male, Swiss-Webster mice (Taconic), weighing 30–40 g and experimentally naïve at the start of the study, were group housed (four mice per cage) in temperature- and humidity controlled rooms on a 12-h light/dark cycle (lights on from 0700–1900h). Mice had free access to food and water at all times except during microdialysis test sessions performed between 09:00 and 18:00 hours. Mice used for drug discrimination procedures had free access to food and water until training started, when they were individually housed with free access to water and with food access designed to maintain them at ~85% of their unrestricted-feeding weights for the duration of the study. All testing was performed between 9:00 AM and 1:00 PM 5 days/week. Subjects were fed 15 g of Purina chow 30 min after sessions. Care of the subjects was in accordance with the guidelines of the National Institutes of Health and the National Institute on Drug Abuse Intramural Research Program, Animal Care and use Program, which is fully accredited by AAALAC International.

Compounds

(±)-Modafinil was synthesized in the Department of Medicinal Chemistry, University of Kansas and in the Medicinal Chemistry Section, NIDA-IRP according to published procedures (Prisinzano *et al.*, 2004; Cao *et al.*, 2011), and dissolved in a vehicle containing

DMSO 10%, Tween-80 15%, and sterile saline 75% (V/V/V). (-)-Cocaine hydrochloride (Sigma-Aldrich, St.Louis, MO or NIDA Drug Supply Program) or methylphenidate hydrochloride (racemic) (NIDA Drug Supply Program), were dissolved in sterile saline. In some experiments, detailed below, methylphenidate was prepared for injection using the vehicle used for injection of modafinil. Pretreatment times and doses of drugs used in the present study are described below and were chosen based on preliminary data obtained in this laboratory.

Microdialysis studies

Mice were anesthetized with a mixture of ketamine and xylazine (60 and 12 mg/kg, respectively), and then placed in a stereotaxic frame (Kopf Instruments, CA, USA); the skull was surgically exposed and a hole was drilled to expose the dura. Concentric dialysis probes were implanted randomly in the right or the left NAS or NAC (Uncorrected coordinates from Paxinos and Franklin (2001) expressed in mm from bregma were: Anterior = +1.5, Lateral = ± 0.6 , Vertical = -5.2 for the NAS; Anterior = +1.3, Lateral = ± 1.3 , Vertical = -4.9 for the NAC) as described previously (Mereu *et al.*, 2015). See Figure 1 for placements. After surgery, subjects were given a subcutaneous injection of saline to replenish body fluids and were allowed to recover overnight in square Plexiglas cages (Med Associates). Cages were equipped with overhead quartz-lined fluid swivels (Instech Laboratories Inc., Plymouth Meeting, PA) for connections to the dialysis probes. All subsequent studies were conducted in these cages (Mereu *et al.*, 2015).

Concentric dialysis probes were prepared using AN69 dialyzing membranes (Hospal Dasco, Bologna, Italy) as described previously (Tanda *et al.*, 2009a; Mereu *et al.*, 2015). The exposed dialyzing surface of the membrane, i.e. that not covered by glue, was limited to the lowest 1.0 mm portion of the probes that were less than 18 mm in total length. Experiments were performed in freely moving animals in the same cages in which they recovered from surgery. Microdialysis test sessions started at 9.00 a.m., approximately 42–47 hours after the surgical procedures. Probes were connected to fluid with swivels (375/D/22QM; Instech Laboratories, Plymouth Meeting, PA, USA) and perfused with Ringer's solution (147.0 mM NaCl, 2.2 mM CaCl₂, and 4.0 mM KCl) delivered by a 1.0 ml syringe, operated by a BAS Bee Syringe Pump Controller (BAS West Lafayette, IN, USA), through the dialysis probes at a constant flow rate of 1 μ l/min. Collection of dialysate samples (10 μ l) started after about 30 min, and samples collected every 10 min were immediately analyzed for DA content.

After establishment of a DA baseline, 2–4 samples differing no more than 15% (approximately after 1 hour), different groups of naïve mice were injected with one dose of modafinil (17, 30, 100, 300, 560 mg/kg i.p.), or vehicle (10 ml/kg i.p. containing, DMSO 10%, Tween-80 15%, and sterile saline 75% by volume). Doses of modafinil were based on effects described previously (Ferraro *et al.*, 1997; Cao *et al.*, 2011; Loland *et al.*, 2012). Sample collection continued every 10 min typically during the first 3 hours after treatment, and every 20 min thereafter (but only 10 of the 20 μ l collected were analyzed).

Dialysate samples (10 μ l) were injected without purification into a high-performance liquid chromatography apparatus equipped with a MD 150 \times 3.2 mm column, particle size 3.0 μ m (ESA, Chelmsford, MA) and a coulometric detector (5200a Coulochem II, or Coulochem

III, ESA) to quantify DA. Potentials for the oxidation and reduction electrodes of the analytical cell (5014B; ESA) were set at +125 mV and -125 mV, respectively. The mobile phase, containing 100 mM NaH₂PO₄, 0.1 mM Na₂EDTA, 0.5 mM n-octyl sulfate, and 18% (v/v) methanol (pH adjusted to 5.5 with Na₂HPO₄), was pumped by an ESA 582 solvent delivery module at 0.50 ml/min. Assay sensitivity for DA was 2 fmoles per sample.

At the end of the experiment, mice were euthanized by pentobarbital overdose, brains were removed and left to fix in 4% formaldehyde in saline solution (Tanda *et al.*, 2009a). Brains were sliced, using a vibratome (Vibratome Plus, The Vibratome Company, St. Louis, MO), in serial coronal slices oriented according to the atlas cited above, in order to identify the location of the probes. Data were only used from subjects for which probe tracks were within the correct NAS or NAC boundaries.

Microdialysis data are shown as increases above basal DA values, calculated as the mean of 2–4 consecutive samples immediately preceding the first drug or vehicle injection. All results are presented as group means (\pm SEM). Statistical analysis was carried out with Statistica Software (Tulsa, Oklahoma) using a three-way ANOVA for repeated measures over time, with drug dose, brain area and time as factors. Results from treatments showing overall changes were subjected to post-hoc Tukey's test. Changes were considered to be significant when $p < 0.05$.

Drug Discrimination

Experimental sessions were conducted daily (Monday-Friday) with mice were placed in 29.2 \times 24.2 \times 21 cm operant-conditioning chambers (modified ENV-001; MED Associates, St. Albans, VT) containing two response levers (requiring a downward force of 0.4 N) with pairs of green and yellow light-emitting diodes above each. Food pellets (20 mg, BioServ, Frenchtown, NJ) were dispensed to a tray located between the response levers. Overall illumination was provided by a light mounted near the chamber ceiling. The chambers were enclosed in ventilated enclosures that provided sound attenuation, and were provided with white noise to further mask extraneous noise.

Subjects were initially trained with food reinforcement to press both levers. They were then trained to press one lever after cocaine (10 mg/kg, i.p.) and the other after saline (i.p.) injection. All responses produced audible clicks of a relay mounted behind the front wall of the chamber. The ratio of responses to food pellets (fixed ratio or FR) was gradually increased until, under the final conditions, the completion of 10 consecutive responses on the cocaine- or saline-appropriate lever produced food. Incorrect responses reset the FR response requirement. The right- versus left-assignment of cocaine and saline levers was counterbalanced among subjects. Subjects were injected and placed in chambers, and sessions started after a 5-min time-out period during which lights were off and responses had no consequences, other than the audible click. After the time-out the house light was turned on until the completion of the 10-response requirement and the presentation of food. Sessions ended after 20 food presentations or 15 min, whichever occurred first, with cocaine or saline sessions scheduled in a double alternation sequence (e.g. ...CSSCSS...).

Testing with different doses of cocaine, modafinil, or their combination was initiated after subjects met the training criteria of at least 85% cocaine- or saline-appropriate responding on four consecutive sessions (two sessions of each) over the entire session, and the first FR of the session. Test sessions were conducted at most every third daily session only if subjects met the training criterion for one saline and one cocaine session conducted on days immediately before the test session. Tests were conducted with the pre-session injections of different doses of cocaine, modafinil or their combination 5 min before the test. The test sessions were identical to training sessions with the exception that 10-consecutive responses on either lever were reinforced. The percentage of responses emitted on the cocaine-appropriate lever was assessed as an indicator of the similarity of the subjective effects of the test drug/dose compared to the training dose. The rate of responding in time was also assessed as an indicator of a potential generalized behavioral disruptive effect of the drug. Test doses of modafinil were based on previous reports (Cao *et al.*, 2011; Loland *et al.*, 2012). Tests with different doses of methylphenidate were performed as a control for modafinil effects.

Results

In-vivo brain microdialysis

Basal values of DA in NAS and NAC are reported in the figure captions for each experimental group. No significant differences were found between shell and core DA values in mice treated with different doses of modafinil (ANOVA: $F_{7,46} = 1.42$, $p = 0.218$).

As shown in figure 2A and B, the acute administration of modafinil significantly increased extracellular levels of DA in the NAS and NAC. Moreover, the vehicle had no significant effects on DA levels in the NAC shell (Figure 2A, filled symbols). The lowest dose tested (17 mg/kg) did not significantly modify DA levels, while the 30 mg/kg dose produced a modest increase (approximately 65 to 70 % above basal levels after 40 min). Higher doses induced larger and longer lasting (> 4 hours) increases in DA levels in both NAS and NAC, with maxima reaching about 270 % of basal values in both brain areas. Maximal increases were obtained more rapidly in the NAS (~60 min) compared to the NAC (~180 min). The increases in DA levels produced by modafinil were significantly related to dose in both NAS and NAC, but there were no statistically significant differences between the two brain areas at any dose tested. A 3-way ANOVA showed significant main effect of dose ($F_{2,30} = 5.13$, $p = 0.012$) and time ($F_{24,720} = 9.74$, $p < 0.001$), with a non-significant main effect of brain area ($F_{1,30} = 1.533$, $p = 0.225$). There also were significant interactions of dose by time ($F_{48,720} = 1.78$, $p = 0.0011$), and time by brain area ($F_{24,720} = 1.62$, $p = 0.031$), and non-significant interactions of brain area by dose, or time by dose by brain area.

The DMSO/Tween-80 vehicle substantially improved the activity of modafinil as compared to the Arabic gum vehicle often used in studies in the literature, likely by increasing its CNS bioavailability (Olsen *et al.*, 1973; Mantilla-Plata & Harbison, 1975). As shown in Figure 2C, and Supplemental Figure 1, modafinil was about 3-fold more potent in its effects on DA levels in the NAC shell when dissolved in the DMSO/Tween-80 vehicle compared to when suspended in Arabic Gum.

The effects of modafinil on stimulation of extracellular levels of DA were also assessed with a 1 μ M concentration of TTX in the perfusion Ringer's solution. Drugs that increase DA levels by blocking uptake are dependent on, and those that release DA independent of neuronal firing. As TTX blocks firing of neurons in the area immediately surrounding the microdialysis probe (Carboni *et al.*, 1989; Solinas *et al.*, 2006), it was used to determine if the increases in DA produced by modafinil were through a blockade of uptake or release of DA (Di Chiara *et al.*, 1996). As shown in Figure 3, within 30 min of TTX perfusion DA levels decreased from 100 to about 5 percent or less in the NAC shell. When modafinil was administered 90 min after TTX perfusion, it had no effect on DA levels (Fig. 3).

Cocaine discrimination

Cocaine injected (i.p.) 5 min before the session dose-dependently increased the percentage of drug-appropriate responding in mice trained to discriminate cocaine (10 mg/kg, i.p.) from saline injections (Fig. 4, upper panel, filled symbols). Methylphenidate (Fig. 4, open circles) fully substituted for cocaine with a potency equal to that of cocaine. Modafinil substitution for cocaine (Fig. 4, triangles) approached 80% at doses of 56 and 100 mg/kg when administered 5 min before the session. When administered 60 min before the session (Fig. 4, squares), complete substitution was more reliably obtained without a change in potency. Modafinil was about 10-fold less potent than cocaine. Only the highest dose of methylphenidate produced substantive decreases in response rates (Fig. 4, lower panel) suggesting a lack of complete cross tolerance between methylphenidate and the alternately administered cocaine.

Modafinil treatment produced significant leftward shifts in the dose-effect curve for the discriminative-stimulus effects of cocaine (Fig. 5, upper panel). The changes in cocaine effects produced by modafinil were dose related, with higher doses shifting the cocaine curve progressively further to the left. The potency of cocaine in combination with 30 mg/kg of modafinil was more than 10-fold greater than that for cocaine alone (Fig. 5, upper panel). The ED₅₀ value of 3.61 mg/kg for cocaine when administered alone decreased progressively to 1.46, 1.10, and 0.257 mg/kg, with increasing doses of modafinil. The latter two values were significantly different from those obtained with cocaine alone (95% confidence intervals did not overlap). Additionally, modafinil pretreatments decreased the slope of the cocaine dose-effect curve due to increases in the percentage of cocaine-appropriate responses at the lowest doses from the additional modafinil effects. None of the dose combinations produced substantive decreases in response rates (Fig. 5, lower panel).

Discussion

Three main findings on the psychostimulant actions of modafinil are described in the present report. First, under the present experimental conditions, modafinil dose-dependently affected DA extracellular levels in the NAS and NAC, but its effects were not statistically different between the two accumbens sub-regions. In behavioral studies, intraperitoneal injections of modafinil almost fully substituted for the subjective effects of cocaine when injected 5 minutes before the session, and fully generalized with the cocaine cue when injected 60

minutes before the session. Finally, modafinil pretreatment potentiated the effects of cocaine in drug-discrimination studies, with significant leftward shifts of the dose-response function.

Thus, our results confirm and extend our knowledge about the unique psychostimulant profile of modafinil. As shown in microdialysis studies, modafinil effects on stimulation of extracellular DA levels overlap with those of typical psychostimulants that are known to increase DA levels in striatal areas (Tanda *et al.*, 2009a; Mereu *et al.*, 2015). These effects of modafinil on DA levels were blocked by addition of TTX to the perfusion ringer solution. In these conditions there is no coupling between firing of DA neurons and exocytotic release of DA (Carboni *et al.*, 1989; Di Chiara *et al.*, 1996; Solinas *et al.*, 2006). Only DA releasers like amphetamines would be able to stimulate DA levels under these conditions (Westerink *et al.*, 1987). Lack of stimulation suggests that the effects of modafinil on DA levels are due to blockade of the DA reuptake after a firing-dependent, exocytotic vesicular and physiological release of DA. Also, behavioral effects of modafinil, like the ability to produce cocaine-like subjective effects, or to potentiate cocaine discriminative-stimulus effects, are typical of several abused psychostimulants (Witkin *et al.*, 1991; Li *et al.*, 2006). However, important instances in which modafinil effects do not overlap with those of known psychostimulants (Simon *et al.*, 1995; Zolkowska *et al.*, 2009) have also been described. For example, though modafinil significantly increased DA levels in the NAS, in contrast with abused psychostimulants and other drugs abused by humans, the effect was not significantly different from that obtained in the NAC (Pontieri *et al.*, 1995; Pontieri *et al.*, 1996).

The nucleus accumbens is known to play an important role in brain mechanisms mediating drug-reinforcement including the transition from abuse to addiction (Di Chiara *et al.*, 1999; Koob, 1999). In rodents, it has been repeatedly shown that acute administration of drugs abused by humans, elicits an increase in DA levels in the NAS, an effect that appears selective or preferential as compared to NAC DA stimulation (Pontieri *et al.*, 1995; Pontieri *et al.*, 1996; Tanda *et al.*, 1997; Cadoni *et al.*, 2000; Mereu *et al.*, 2015) suggesting that the reinforcing effects of these drugs are more related to a dopaminergic response in the NAS than in the NAC after acute administration (Di Chiara *et al.*, 1999). The inconsistency in producing significant differences in DA stimulation in NAS compared to NAC may play a role in the low abuse liability of modafinil. Indeed, modafinil does not have reinforcing effects in tests of its self-administration (Deroche-Gamonet *et al.*, 2002) even though it binds to the DAT at clinically used doses (Volkow *et al.* 2009). Also, because of its particular chemical structure, modafinil is only administered orally in human subjects. Indeed, it is not soluble in water (cannot be injected), and it is thermosensitive (cannot be smoked). Thus its reinforcing actions (if any) in humans might be even lower than those found in experimental animals, for which special vehicles are used for systemic i.p. and i.v. administration.

As previously shown for modafinil and its R- and S-enantiomers (Loland *et al.*, 2012), the presence of a “ceiling effect” for stimulation of DA levels in the accumbens shell may be related to the disconnect between DA reuptake blockade and their lack of reinforcing effects. We have now confirmed this plateau to the increases in DA levels in the NAC as well as the NAS. We also suggest that this ceiling effect on DA stimulation might be one of the factors playing a role in the lack of preferential DA response in the NAS. Indeed, the dose response effect of modafinil shows a smaller and less robust increase in DA levels as compared to

cocaine. The rapid increase in NAS DA levels obtained at the highest doses tested might suggest a preferential increase in this area compared to the NAC, which has not been confirmed by the statistical analysis. However, the limit of NAS and NAC DA stimulation under the described ceiling conditions would reduce the amplitude of the increase in DA, thus blunting the potential differences between these brain areas.

It is noteworthy that in our hands, DA levels could be significantly increased by lower doses of modafinil than previously found (Ferraro *et al.*, 1997). Ferraro *et al.*, (1997) reported that modafinil stimulates DA levels to values lower than those produced by GBR12909, nomifensine and amphetamine. However, in their study only a single dose of modafinil was used to treat anesthetized rats and they did not evaluate the relationship between DA release and behavioral effects. The lower effects previously found might be explained by differences in modafinil bioavailability from the vehicle used in the experiments. In fact, because of the low solubility of modafinil, we tested different vehicles and found that modafinil administered in the vehicle used in several previous studies (Tanganelli *et al.*, 1994; Ferraro *et al.*, 1996; Ferraro *et al.*, 1997; Ferraro *et al.*, 1999; de Saint Hilaire *et al.*, 2001) (Arabic gum suspension in saline) produced similar but less potent effects than modafinil dissolved in our present vehicle (DMSO/Tween-80/Saline), suggesting a lower bioavailability with the former.

In agreement with previous studies (Dopheide *et al.*, 2007; Loland *et al.*, 2012) in mice trained to discriminate the subjective effects of cocaine, 10 mg/kg i.p., from those of saline, modafinil produced near full generalization (75%) to the cocaine discriminative stimulus when injected 5 minutes before the session. The mesolimbic DA system has been implicated in mediating cocaine's subjective effects (Callahan *et al.*, 1997). We have also found that the amount of stimulation of DA levels in the NAS elicited by cocaine could be strictly related to its subjective effects determined in discrimination procedures (Kohut *et al.*, 2014). In that study doses of cocaine-like drugs that increased DA to levels equal to/greater than ~200% to 225% of basal values produced consistent cocaine-like subjective effects (Kohut *et al.*, 2014). It should be noted that in the present experiments, modafinil approached or produced full generalization with the cocaine cue at a dose of 56 mg/kg i.p. administered 5 or 60 minute before the start of the session. Based on the data available from the present microdialysis experiments in mice, 30 and 100 mg/kg, we can infer that the dose of 56 mg/kg of modafinil would not produce an increase in DA during the first 20 minutes after injection that compares with the average increase in DA levels produced by a 10 mg/kg dose of cocaine. If translated into human dosage, 56 mg/kg of modafinil administered in mice would correspond to about 4.6 mg/kg (FDA, 2005). This dosage is actually not far from the daily prescribed dosage of 200 or 400 mg, equivalent to 3.33 and 6.66 mg/kg for a 60 kg person, respectively. However, one limitation of our study is that only the acute effects of modafinil have been reported. Thus it is hard to provide a complete meaningful equivalent of doses in our present study compared to human doses that are chronically administered. Thus modafinil demonstrates higher behavioral efficacy than expected at low doses (generalization with discriminative cues), and lower neurochemical efficacy at higher doses (ceiling in DA stimulation). Moreover, pretreatments with varying doses of modafinil, which did not elicit significant increases in DA, enhanced the dose-response effects of cocaine in mice trained to discriminate cocaine from saline. These results suggest that together with

blockade of the DAT, possibly changes in glutamate and orexin brain levels, for example, may be at play and involved in the behavioral actions of modafinil (see review by Mereu *et al.*, 2013).

Recent clinical trials have shown promising results for modafinil as a treatment for stimulant use disorders (Dackis *et al.*, 2005; Hart *et al.*, 2008; Anderson *et al.*, 2009; Heinzerling *et al.*, 2010; Kampman *et al.*, 2015). Such clinical results support further elucidation of modafinil's mechanism(s) of action, especially as these may inspire the development of novel medications for the treatment of psychostimulant abuse and other neuropsychiatric disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Animal experimentation described in this manuscript was approved by the local ACUC of the NIDA/IRP, Baltimore, MD. The animals in the present study were maintained in an AAALAC International accredited facility in accordance with NIH Policy Manual 3040-2, Animal Care and Use in the Intramural Program (released 1 November 1999). Care of the subjects was in accordance with the guidelines of the National Institutes of Health and the National Institute on Drug Abuse Intramural Research Program Animal Care and Use Program, which is fully accredited by AAALAC International. This work was funded by the NIDA Intramural Research Program.

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List of nonstandard abbreviations

ANOVA	analysis of variance
CSF	cerebrospinal fluid
DA	dopamine
DAT	dopamine transporter
EXT	extinction
FR	fixed ratio
i.p.	intraperitoneally
i.v.	intravenously
LEDs	light-emitting diodes
NS	non-significant
NAS	nucleus accumbens shell
NAC	nucleus accumbens core
S.E.M.	standard error of the mean

TO timeout
modafinil (±)modafinil

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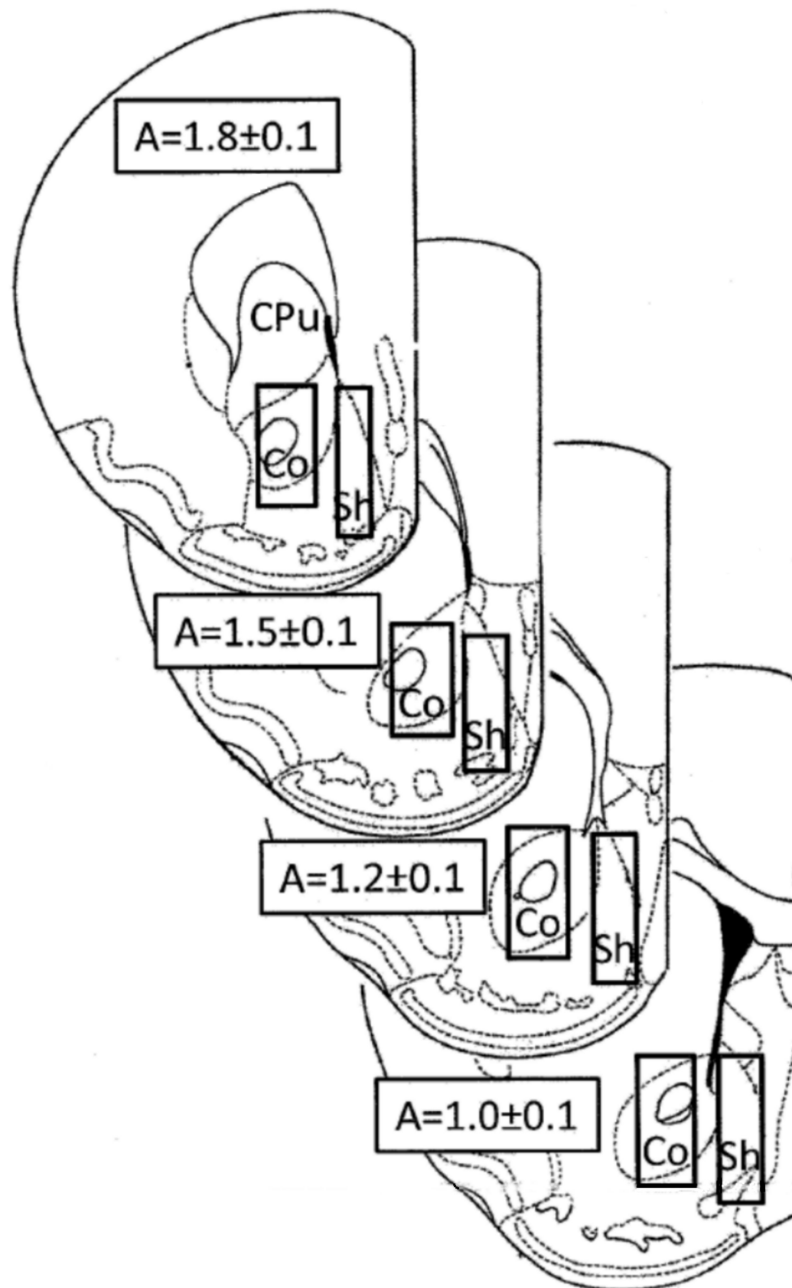


Figure 1. Forebrain sections, redrawn from Paxinos and Watson (1987), show the limits of the positions of the dialyzing portions of the microdialysis probes (superimposed rectangles). The anterior coordinate (measured from bregma) is indicated on each section. CPU, caudate putamen; Co, nucleus accumbens core; Sh, nucleus accumbens shell.

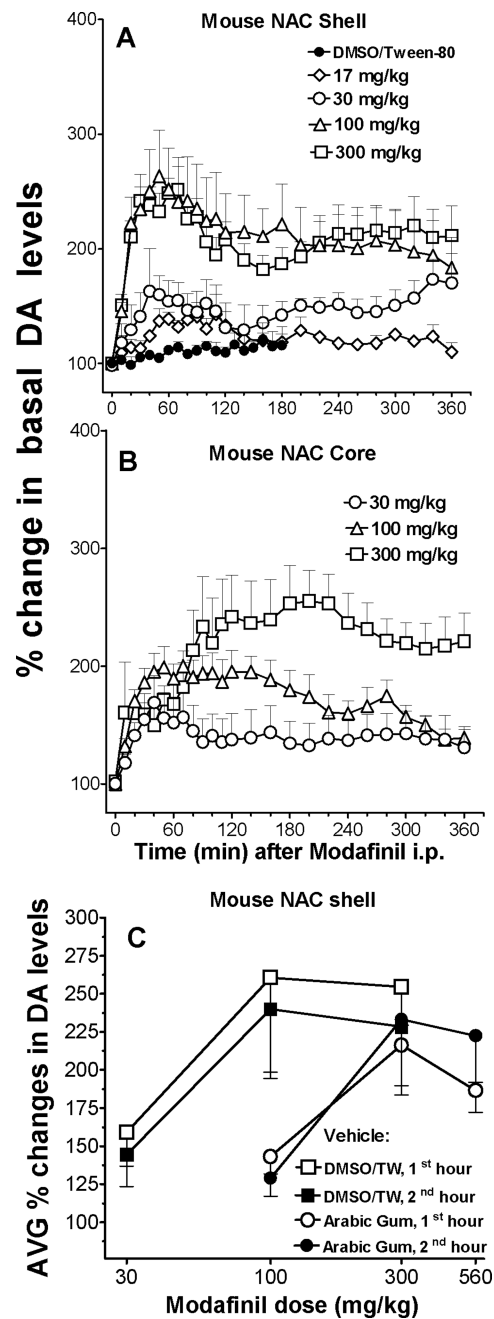


Figure 2.

Time courses for the effects of modafinil (17, 30, 100, or 300 mg/kg i.p.) administered at time 0 on extracellular levels of DA in dialysates from the NAS (A), or NAC (B). Each point represents means (with vertical bars representing S.E.M.) of the amount of DA in 10-min dialysate samples, expressed as percentage of basal values, uncorrected for probe recovery. Basal values (fmol/sample \pm SEM) and number of mice per group were as follows: 46.4 ± 12.5 , $n=4$; 44.0 ± 9.2 , $n=5$; 53.0 ± 5.7 , $n=8$; 60.8 ± 5.2 , $n=9$, for NAS placements in modafinil 17, 32, 100, and 300 mg/kg treated animals respectively; and 55.2 ± 14.6 , $n=6$; 78.2 ± 15.8 , $n=5$; 64.2 ± 13.6 , for NAC placements in modafinil 32, 100, and 300 mg/kg

treated animals respectively. Percentage values for DA are represented on the figure at the point corresponding to the end of the sampling period.

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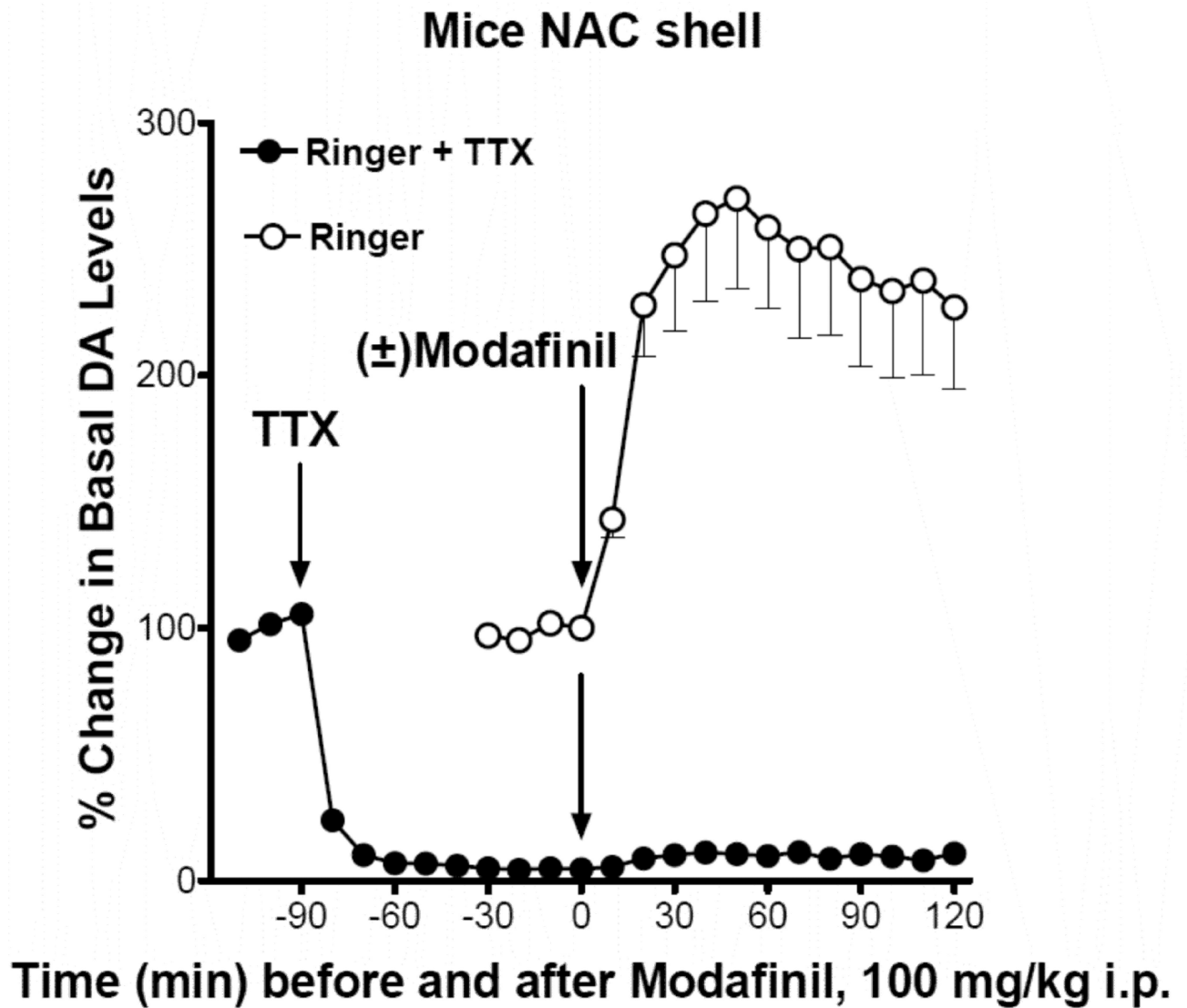


Figure 3.

Time course of effects of modafinil (100 mg/kg i.p.) on stimulation of NAS DA levels with and without the addition of TTX 1 μ M in the perfusion Ringer solution. Basal values (fmol/sample \pm SEM) and number of mice in the TTX treated group were: 46.9 \pm 11.6, n=5. See Fig. 2 for more information about DA data-points.

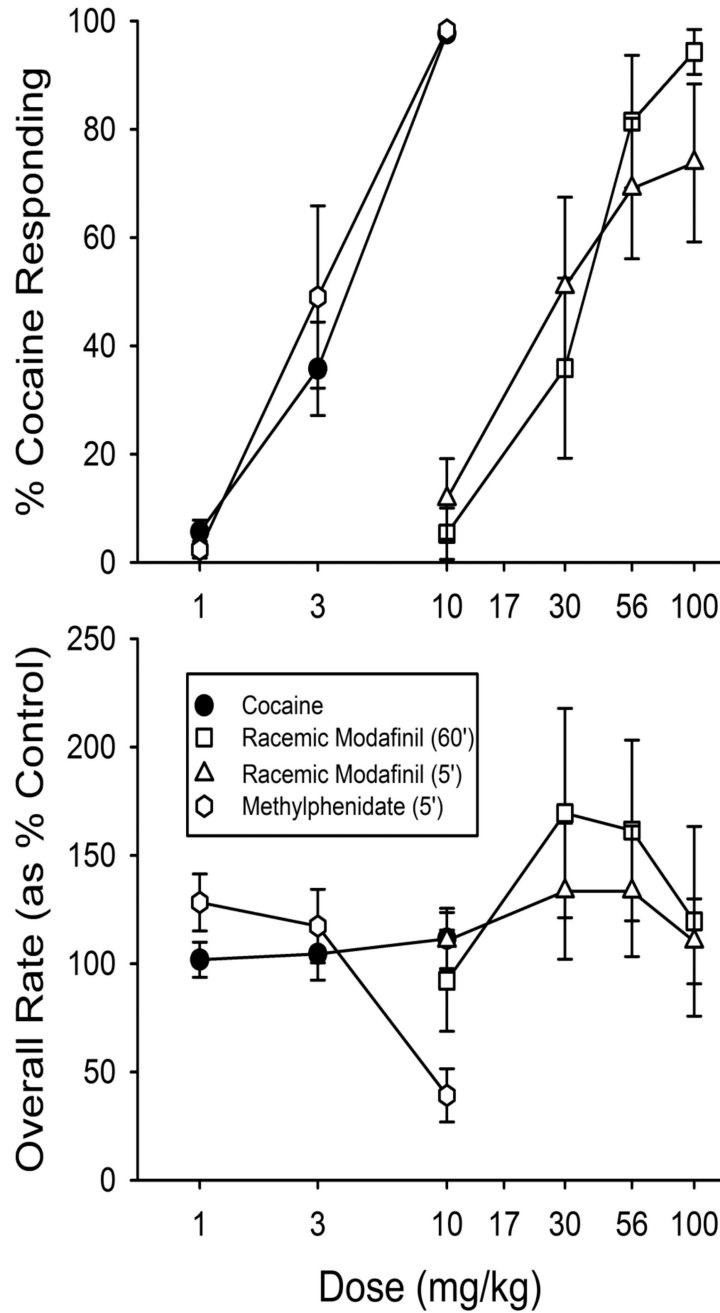


Figure 4. Dose-dependent effects of cocaine, modafinil, and methylphenidate in mice trained to discriminate cocaine from saline. Each point represents the mean of six subjects with SEM represented by the error bars. Abscissae: Dose of cocaine, modafinil, or methylphenidate in mg/kg. Top panel ordinates: Percentage of responses on the cocaine-appropriate lever. Bottom panel ordinates: Rates of responding as a percentage of vehicle control rates. Note that modafinil (10–100 mg/kg i.p.) almost fully (~75 % cocaine lever responding) substituted for cocaine when injected 5 minutes before the session, and completely (>90 % cocaine lever responding) substituted for cocaine when injected 60 minutes before the

sessions (top panel). The effects of methylphenidate (1–10 mg/kg i.p.) administration 5 minutes before the session are also shown. Overall rate of responding was not significantly modified by modafinil or cocaine at any dose tested though the highest dose of methylphenidate decreased response rates (bottom panel).

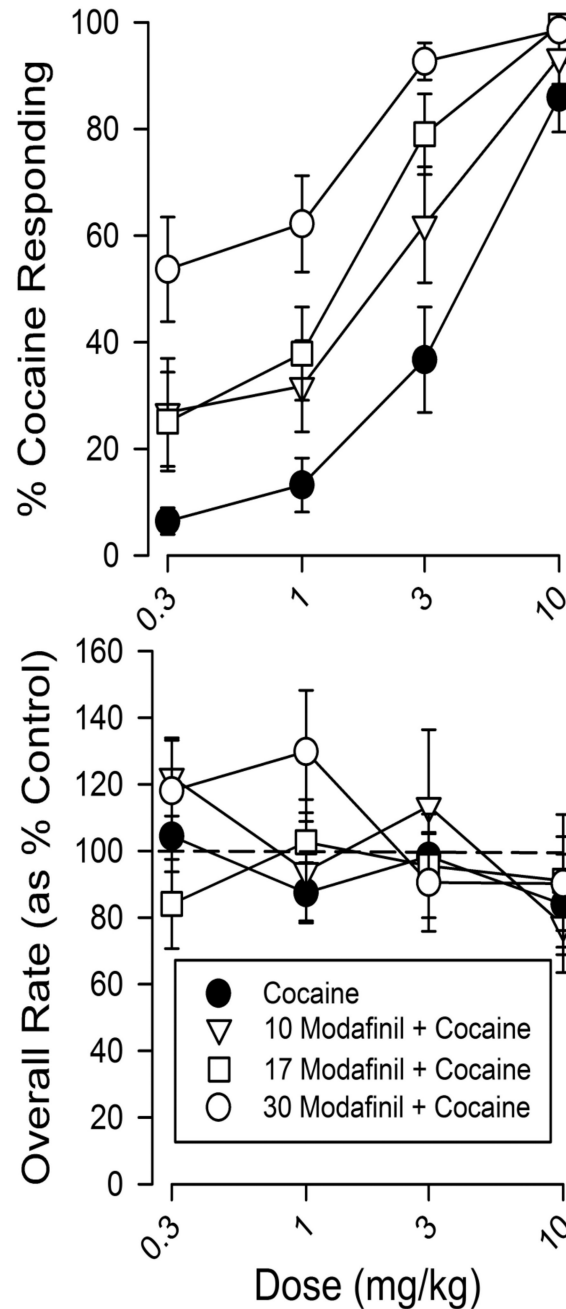


Figure 5.

Dose-dependent effects of cocaine in mice trained to discriminate cocaine from saline when cocaine was administered alone or in combination with several doses of modafinil. Each point represents the mean of six subjects with SEM represented by the error bars. Abscissae: Dose of cocaine in mg/kg. Top panel ordinates: Percentage of responses on the cocaine-appropriate lever. Bottom panel ordinates: Rates of responding as a percentage of vehicle control rates. Note that modafinil significantly shifted the discriminative-stimulus effects of

cocaine to the left (top panel). Modafinil did not modify the overall rate of responding even at doses in which it enhanced the subjective effects of cocaine (bottom panel).

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