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Effects of modafinil and R-modafinil on brain stimulation reward thresholds: implications for their use in the treatment of psychostimulant dependence

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Abstract

Background—Modafinil and its enantiomer R-modafinil are approved for the treatment of various sleep disorders, and may also be efficacious in the treatment of psychostimulant abuse. However, the ability of modafinil and R-modafinil to alter brain reward function has not yet been assessed.

Purpose—This study assessed the effects of modafinil and R-modafinil on brain reward function using the intracranial self-stimulation (ICSS) paradigm.

Study design—Male Sprague-Dawley rats were trained to respond for ICSS using current-intensity threshold determination procedures. Changes in ICSS thresholds were then assessed following administration of modafinil and R-modafinil (50, 100, and 150 mg/kg), or cocaine (2.5 – 20 mg/kg) as a positive control.

Results—ICSS thresholds were reduced by modafinil at the 150 mg/kg dose, as well as by cocaine at the 10 and 20 mg/kg doses. R-modafinil only produced non-significant trends towards reducing ICSS thresholds.

Conclusion—Modafinil and R-modafinil have limited effects on brain reward function in otherwise drug-naïve subjects. Additional assessments of these effects in the context of psychostimulant dependence are needed.

Keywords

psychostimulant; modafinil; R-modafinil; cocaine; abuse liability; intracranial self-stimulation

1. Introduction

Modafinil (2-[(diphenylmethyl)sulfinyl]acetamide, MOD) and its *R*-isomer armodafinil ((-)-2-[(*R*)-(diphenylmethyl)sulfinyl]acetamide; R-MOD; see Fig. 1) are wake-promoting and cognitive-enhancing drugs currently approved by the U.S. Food and Drug

Administration (FDA) for the treatment of excessive daytime sleepiness associated with narcolepsy, shift work sleep disorder, and obstructive sleep apnea [22]. In addition, preclinical and clinical studies have demonstrated potential efficacy for these drugs in the treatment of cognitive dysfunction and/or fatigue associated with attention deficit hyperactivity disorder, schizophrenia, Parkinson's disease, multiple sclerosis, post-polio syndrome, major depressive disorder, bipolar depression, dysthymia, chronic fatigue syndrome, fibromyalgia, and post-anesthetic recovery [8, 16, 28]. In recent years, various studies have also indicated some potential efficacy of MOD for the treatment of cocaine or amphetamine-type stimulant use disorders [2, 4, 13, 23, 27, 31, 33].

Although MOD and R-MOD possess psychostimulant properties, evidence suggests that they have both neurochemical and behavioral effects distinct from those of traditional cocaine- and amphetamine-like stimulants [22]. While their precise therapeutic mechanisms of action are not fully understood, several lines of research indicate that at therapeutically relevant doses, MOD and R-MOD inhibit the reuptake of dopamine via presynaptic dopamine transporters (DAT), and exhibit DAT occupancy similar to that of methylphenidate [17, 18, 21, 37]. While post-FDA approval surveillance studies have not revealed significant patterns of MOD or R-MOD abuse, a small collection of both preclinical and clinical studies suggest that these drugs, particularly at high doses, may possess a degree of abuse liability that is higher than previously thought [3, 12, 14, 15, 32, 36].

However, not all studies have demonstrated rewarding or reinforcing effects of MOD or R-MOD [7, 9, 11, 26]. Given the lack of consensus regarding their abuse liability, especially at higher doses, the present study sought to assess the effects of MOD and R-MOD on brain reward function as measured by their ability to affect current intensity thresholds for intracranial self-stimulation (ICSS). Furthermore, since most clinical trials with MOD and R-MOD have shown increased potential efficacy in subjects dependent on cocaine vs. amphetamine-type stimulants [1, 5, 10, 20, 25], and modafinil is believed to inhibit presynaptic dopamine transporter function [18, 21, 22, 33], we assessed the effects of cocaine on ICSS thresholds as a positive control.

2. Methods

2.1. Subjects

All experimental procedures were conducted with the approval of the Institutional Animal Care and Use Committee at Arizona State University and according to the Guide for Care and Use of Laboratory Animals as adopted by the National Institutes of Health. Upon arrival from Harlan Laboratories (Livermore, CA), male Sprague-Dawley rats (n=17, approximately 250 g), were individually housed on a 12-hour light dark cycle (lights off at 7:00 am) and provided ad libitum access to food and water.

2.2. Surgical procedures

Following two days of acclimation, rats were deeply anesthetized with isoflurane (2% v/v) vaporized in oxygen at a flow rate of 2 l/min and secured in a stereotaxic frame. Each rat was implanted unilaterally with a stainless steel bipolar electrode (PlasticsOne, Roanoke,

VA, USA; 2 mm diameter, insulated except at the ventral tip) into the medial forebrain bundle (anterior-posterior -0.05 mm; medial-lateral ± 1.7 mm, dorsal-ventral -8.3 mm from bregma and dura). Electrodes were secured to the head with skull screws and dental cement. Half of the rats received electrodes in the left hemisphere and the other half in the right hemisphere. Rats were treated daily with 2.5 mg/kg meloxicam for 3 days to minimize post-surgical discomfort each day during a total of 7 days of post-surgical recovery.

2.3. Drug preparation

Modafinil and R-modafinil were both obtained from the NIMH Chemical Synthesis and Drug Supply Program (Research Triangle Park, NC, USA), and were suspended in 10% v/v Tween 80 in sterile saline and administered in a volume of 3 ml/kg and administered via the intraperitoneal (i.p.) route. Doses of 50, 100, and 150 mg/kg were chosen based on previously published studies in rodents [7, 9, 11, 26, 36]. Cocaine hydrochloride (Sigma-Aldrich, St. Louis, MO) was dissolved in sterile saline and administered i.p. in a volume of 1 ml/kg. A range of doses (2.5, 5, 10, and 20 mg/kg) was chosen based on prior characterization of cocaine effects in current-intensity threshold procedures in rodents [19].

2.4. Experimental design

Operant conditioning chambers (ENV-007CT; MED Associates, St. Albans, VT) equipped for ICSS procedures were housed individually in sound-attenuating cubicles equipped with an exhaust fan to provide ventilation and mask external noise. Located on one wall of the chamber were a house light and two nose-poke response apertures each containing a light-emitting diode (LED). Located outside the cubicle was a dual programmable electrical stimulator (PHM-150B/2; Med Associates) interfaced to a computer to deliver electrical current to the electrode via a cable connected to an electrical commutator mounted atop the testing chamber. Chambers were interfaced to a PC, and Med-PC IV software was used to control all stimulation parameters, test functions, and data collection. Following post-surgical recovery, rats underwent a minimum of 10 days of baseline threshold assessment and were required to meet stable baseline criteria, defined as when the average ICSS thresholds varied less than 10% [34, 35]. Additional baseline testing without drug treatments continued throughout the experiment to monitor threshold stability. On test days, drugs were administered 20 min prior to commencement of threshold determination procedures. Saline injections were given on Tuesdays and drug injections were given on Wednesdays and Fridays in a randomized block design, with each rat receiving each dose once. Current intensity thresholds for ICSS were determined in discrete trial procedures described in our previous studies [34, 35] and elsewhere [19]. All rats in the MOD ($n=6$) and R-MOD ($n=6$) groups received 3–5 threshold determinations at each dose, while rats in the cocaine group ($n=5$) received 2–3 determinations at each dose.

2.5. Statistical Analyses

All statistical analyses were conducted using SigmaPlot (Systat Software, Inc., San Jose, CA, USA). For each rat, raw ICSS current intensity thresholds (in μ A) for all vehicle and drug sessions were converted to percent change from the mean of thresholds obtained after vehicle administration. Due to the greater number of thresholds obtained for vehicle versus the individual doses for each subject, percent change scores were analyzed by Kruskal-

Wallis one way analysis of variance on ranks, with Dunn's post-hoc multiple comparisons versus saline control. All data points represent mean $\pm$ SEM. A significance criterion of $p < 0.05$ was used for all analyses.

3. Results

3.1. Modafinil and R-modafinil

The effects of MOD and R-MOD on current intensity thresholds for ICSS are shown in Fig. 2. For MOD, a significant effect of dose was observed ($H(4)=10.244$, $p=0.037$), and post-hoc comparisons revealed significant differences in the percent change in ICSS thresholds between vehicle and the 150 mg/kg dose. For R-MOD, a trend towards reductions in ICSS thresholds was observed, but these analyses did not reach statistical significance ($H(4)=7.954$, $p=0.093$).

3.2. Cocaine

The effects of cocaine on current intensity thresholds for ICSS are shown in Fig. 3. A significant effect of dose on ICSS thresholds was observed ($H(5)=38.16$, $p<0.001$), and post-hoc comparisons revealed significant differences in percent change in ICSS thresholds between saline vehicle and the 10 and 20 mg/kg doses. No other comparisons were statistically significant.

4. Discussion

To our knowledge, the present study represents the first examination of the ability of MOD and R-MOD to affect brain reward function as assessed by changes in ICSS thresholds. Our findings show that when given acutely, only high doses of MOD (150 mg/kg) significantly lower ICSS thresholds, indicating a facilitation of brain reward function. In contrast, while R-MOD produced a trend towards reductions in ICSS threshold at a similar high dose, these effects were not statistically significant relative to vehicle control. In either case, the reductions in ICSS thresholds produced by the higher dose of MOD was less robust (~10%) than those produced by the higher doses of cocaine (~10–20%). Taken together, these findings indicate that only supraphysiological doses of MOD facilitate brain reward function, which is consistent with recent reports of abuse and dependence in humans produced by high doses of the drug [3, 12, 14, 15, 32]. In addition, the lack of robust effects of MOD on ICSS thresholds is also consistent with animal studies that have failed to demonstrate rewarding or reinforcing effects of this drug in place preference and self-administration paradigms [7, 11, 26].

However, it is worth mentioning that several other groups of investigators have indeed demonstrated rewarding or reinforcing effects of MOD under some experimental conditions. For example, some investigators have shown that MOD produces a conditioned place preference in mice at doses of 50–75 mg/kg [29, 36], and also produces additive and cross-sensitizing effects on locomotor activity induced by other psychostimulants [30]. In addition, drug discrimination studies in rodents have revealed that modafinil can substitute for cocaine with an ED_{50} dose of 96 mg/kg [24]. Furthermore, Gold and Balster [9] demonstrated that intravenous modafinil produced reinforcing effects in non-human primates, albeit at high

doses only. In light of the current findings, it is apparent that under certain experimental conditions and doses, MOD can produce some rewarding or reinforcing effects.

As mentioned previously, several lines of clinical evidence suggest that modafinil may have some clinical benefit for subpopulations of patients with psychostimulant dependence [2, 4, 13, 23, 27, 31, 33]. Thus, one limitation of the current study is that effects of MOD and R-MOD on brain reward function were assessed in otherwise drug-naïve animals. Along these lines, Deroche-Gamonet [7] demonstrated that MOD exerts some incentive effects in cocaine-experienced rats as opposed to cocaine-naïve animals. Thus, future studies are clearly warranted examining the effects of MOD and R-MOD on ICSS thresholds in subjects with a history of repeated exposure to cocaine or amphetamine-type stimulants.

An unexpected finding of the present study was the observation of significant effects of MOD on brain reward function, but no effects of its R-enantiomer R-MOD. It has been reported that both MOD and R-MOD are weak DAT inhibitors [18, 21, 22, 33], with the R-enantiomer having a three-fold higher affinity for DAT as compared to the S-enantiomer [17]. Both MOD and R-MOD also have similar elimination half-lives [6]; however, there appear to be circadian differences in plasma concentrations of the two drugs, with R-MOD producing higher plasma concentrations of the drug later in the day than MOD [6]. Thus, the differing chronopharmacological profiles of R-MOD and MOD may contribute to the differential effects on brain reward function. In the present study, ICSS thresholds were determined during the subjects' dark (active) phase, and it is therefore possible that different effects of MOD or R-MOD might be observed at other time points in the circadian cycle.

In summary, we demonstrate that acute administration of MOD but not R-MOD dose-dependently decreases ICSS thresholds in rats, but only at high doses. The degree to which MOD decreases ICSS threshold is less robust than that produced by cocaine. These findings generally support post-marketing surveillance data that MOD and R-MOD possess a limited degree of abuse liability, and at physiologically relevant doses are likely safe medications for the treatment of psychostimulant dependence.

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Modafinil

R-modafinil

Figure. 1.
Chemical structures of modafinil and R-modafinil.

Figure 2. Effects of acute administration of MOD (50, 100, or 150 mg/kg), R-MOD (50, 100, or 150 mg/kg), or vehicle on ICSS current intensity thresholds. Data are expressed as percent change from vehicle (mean $\pm$ SEM). * $p < 0.05$ vs. vehicle. $n = 6$ animals per group.

Figure. 3.

Effects on acute administration of cocaine (2.5, 5, 10, or 20 mg/kg) or saline vehicle on ICSS current intensity thresholds. Data are expressed as percent change from vehicle (mean $\pm$ SEM). * $p < 0.05$ vs. vehicle. $n = 5$ animals.