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Oral Modafinil Facilitates Intracranial Self-Stimulation in Rats: Comparison to Methylphenidate

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Abstract

Modafinil is a low-potency inhibitor of dopamine transporters (DAT) approved clinically to promote wakefulness. In most procedures used for abuse-liability assessment, modafinil produces effects similar to those of abused DAT inhibitors like cocaine and methylphenidate, although modafinil often displays lower effectiveness. However, modafinil has failed to maintain drug self-administration or produce conditioned place preferences in rats. The low potency and poor solubility of modafinil complicate its delivery by parenteral routes of administration commonly used in rats, and this may contribute to negative results. This study evaluated effects of orally administered modafinil in rats using an assay of intracranial self-stimulation (ICSS) that has been used to examine effects of other DAT inhibitors. Adult male Sprague-Dawley rats equipped with electrodes in the medial forebrain bundle responded for pulses of brain stimulation that varied across a range of frequencies (158–56 Hz) during daily behavioral sessions. Modafinil (20–600 mg/kg, p.o.) and methylphenidate (1.0 – 10 mg/kg, i.p.; 3.2 – 32 mg/kg, p.o.) produced dose- and time-dependent facilitation of ICSS, an effect produced by abused DAT inhibitors and other classes of abused drugs. These results agree with other evidence for stimulant-like abuse liability of modafinil and demonstrate sensitivity of ICSS to orally administered drug.

Keywords

intracranial self-stimulation; rat; modafinil

Introduction

Modafinil is a wake-promoting drug that inhibits dopamine transporters (DAT) with low potency (Madras et al., 2006; Zolkowska et al., 2009). Modafinil usually produces effects similar to those of abused DAT inhibitors (e.g. cocaine and methylphenidate) in studies of abuse-liability assessment in humans (Jasinski and Kovacevic-Ristanovic, 2000; Rush et al., 2002; Stoops et al., 2005; Makris et al., 2007), monkeys (Gold and Balster, 1996; Newman et al., 2010), and rats (Gold and Balster, 1996; Zolkowska et al., 2009; Paterson et al., 2010; Rowley et al., 2014), although potency and maximal effectiveness of modafinil are often

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relatively low. In contrast to this general profile, modafinil failed to maintain drug self-administration after i.v. delivery or to produce conditioned place preference after i.p. delivery in rats (Deroche-Gamonet et al., 2002; Heal et al., 2013; Quisenberry et al., 2013b; Uguen et al., 2013).

The low potency and poor solubility of modafinil complicate accurate dose delivery via parenteral routes of administration in preclinical studies and may contribute to negative results in tests of abuse liability in rats. Oral (p.o.) drug administration in rats permits delivery of relatively large volumes by oral gavage through large-bore (e.g. 18 gauge) ball needles, and this facilitates investigation of effects produced by drug suspensions like those required for modafinil. In this study, abuse-related effects of p.o. modafinil were evaluated in rats using an intracranial self-stimulation (ICSS) procedure used previously to evaluate other DAT inhibitors (Rosenberg et al., 2013; Bonano et al., 2014a, b). In this procedure, abused DAT inhibitors and other drugs of abuse increase (or “facilitate”) ICSS rates (Carlezon and Chartoff, 2007; Negus and Miller, 2014). We hypothesized that p.o. modafinil would also facilitate ICSS. Effects of oral modafinil were compared to effects of i.p. and p.o. methylphenidate.

Methods

Subjects

Five adult male Sprague-Dawley rats (ENVIGO, Frederick, MD) with free access to food and water were housed individually on a 12 hour light-dark cycle (06.00-18.00, lights on) in an AAALAC-accredited facility.

Assay of Intracranial Self-Stimulation (ICSS)

Overview—Procedures were similar to those used previously to study other monoamine uptake inhibitors (Rosenberg et al., 2013; Bonano et al., 2014a, b; Negus and Miller, 2014). Each rat underwent stereotaxic surgery under isoflurane anesthesia for implantation of a stainless steel electrode (Plastics One, Roanoke, VA) into the left medial forebrain bundle (2.8 mm posterior to bregma, 1.7 mm lateral to midsagittal suture, 8.8 mm ventral to skull). Subsequently, training began in chambers equipped with a response lever, stimulus lights over the lever, and an ICSS stimulator (Med Associates, St. Albans, VT). During experimental sessions, the electrode and stimulator were connected via bipolar cables routed through a swivel connector (Model SL2C; Plastics One). A microcomputer and associated software (Med Associates) were used to control experimental events and collect data.

Training—Rats were initially trained to lever press for brain stimulation consisting of a 0.5-sec train of square-wave cathodal pulses (0.1 msec pulse duration, 158 Hz, amplitude adjusted individually for each rat). Ultimately, daily behavioral sessions consisted of three 10-min components, each consisting of 10 1-min trials. Responding had no scheduled consequences for the first 10 s of each trial, and five non-contingent stimulations were delivered at the available frequency. During the remaining 50 s of each trial, responding under a fixed-ratio 1 (FR 1) schedule produced brain stimulation and illumination of the stimulus lights. Within each component, the available brain-stimulation frequency

descended across trials in 0.05 log unit steps from 158 to 56 Hz. Training was complete when two-way ANOVA indicated no Day $\times$ Frequency interaction across three consecutive sessions.

Testing—Test sessions consisted of three baseline components, followed first by drug administration, and then by pairs of test components that began after 10, 30, 100 and (for some treatments) 180 min. Drugs, doses, and routes of administration were: methylphenidate (1.0 – 10 mg/kg, i.p.; 3.2 – 32 mg/kg, p.o.) and modafinil (20-600 mg/kg p.o.). Treatments were delivered i.p. in volumes of 1.0 ml/kg with 27-gauge needles. Treatments were delivered p.o. in 10 ml/kg by oral gavage using 18-gauge curved 2.25 mm ball needles. Test sessions were generally conducted on Tuesdays and Fridays, and three-component training were conducted on other weekdays.

Data Analysis

The primary dependent variable was reinforcement rate during each frequency trial. These data were normalized to percent maximum control rate (% MCR), with MCR defined as the mean of the maximal rates for any trial of the second and third baseline components for that session: %MCR = (reinforcement rate during a frequency trial/MCR) $\times$ 100. Data from each test-component pair were averaged across rats to yield mean frequency-rate curves for each manipulation. Results were compared by repeated-measures two-way ANOVA with brain-stimulation frequency and dose as the two factors. A significant ANOVA was followed by a Holm-Sidak post-hoc test. The criterion for significance was $p < 0.05$.

An additional summary measure of ICSS across all brain-stimulation frequencies was calculated as % Baseline Stimulations = [(mean stimulations per component during each pair of test components)/(mean stimulations per baseline component)] $\times$ 100. These data were averaged across rats and analyzed by repeated-measures two-way ANOVA with dose and time as the two factors. A significant ANOVA was followed by Dunnet's post-hoc test. The criterion for significance was $p < 0.05$. Oral administration of vehicle produced small decreases in ICSS relative to baseline. Accordingly, to compare drug potencies at time of peak effect (10 min), drug effects were normalized to vehicle effects using the equation % Vehicle Stimulations = [(mean stimulations per component after drug)/(mean stimulations per component after vehicle)] $\times$ 100. Linear regression was used to determine an ED150 value, defined as the dose that increased ICSS to 150% of vehicle levels. ED150 values were considered statistically different if 95% confidence limits did not overlap.

Drugs

($\pm$)-Methylphenidate (NIMH; Bethesda, MD) was dissolved in 0.9% bacteriostatic saline. ($\pm$)-Modafinil (NIDA, Bethesda, MD) was suspended in 18:1:1 water:ethanol:Kolliphor® EL (Sigma-Aldrich, St. Louis, MO).

Results

The overall mean $\pm$ SEM MCR was 60 ± 3 stimulations per trial, and the mean $\pm$ SEM number of baseline stimulations per component was 271 ± 1 . Figure 1 shows full frequency-rate

curves obtained 10 min after administration of vehicle or selected doses of methylphenidate and modafinil. Methylphenidate (i.p. and p.o.) and modafinil (p.o.) produced ICSS facilitation expressed as increases in ICSS rates across a range of low to intermediate brain-stimulation frequencies. Figure 1 also shows summary data for ICSS collapsed across all brain-stimulation frequencies for each time point after each treatment. Methylphenidate (i.p. and p.o.) and modafinil (p.o.) produced dose- and time-dependent increases in ICSS that peaked after 10-30 min and lasted up to 180 min after high modafinil doses. Figure 2 shows dose-effect curves for each drug obtained after 10 min. ED150 (95% CL) values in mg/kg were 2.28 (1.00-3.87), 8.67 (5.82-12.33) and 66.07 (29.51-162.93) for i.p. methylphenidate, p.o. methylphenidate, and p.o. modafinil, respectively. ED150 values were significantly different, and relative potencies were i.p. methylphenidate > p.o. methylphenidate > p.o. modafinil.

Discussion

ICSS facilitation by methylphenidate is consistent with effects of other DAT inhibitors in this procedure (Negus and Miller, 2014). The relative potency of methylphenidate across routes of administration agrees with prior evidence for approximately 4-fold greater potency by i.p. than p.o. methylphenidate to produce stimulant-like effects in rats (Gerasimov et al., 2000; Heal et al., 2013). These studies confirmed sensitivity of this ICSS procedure to effects produced by p.o. administration of an abused DAT inhibitor.

Modafinil, delivered p.o. also produced a dose- and time-dependent facilitation of ICSS. Insofar as ICSS facilitation is often interpreted as an abuse-related drug effect (Negus and Miller, 2014), these results agree with other data to suggest stimulant-like abuse potential for modafinil. For example, modafinil maintained self-administration in humans and rhesus monkeys (Gold and Balster, 1996; Stoops et al., 2005), and produced stimulant-like subjective or discriminative-stimulus effects in humans (Jasinski and Kovacevic-Ristanovic, 2000; Rush et al., 2002; Makris et al., 2007), rhesus monkeys (Newman et al., 2010), and rats (Gold and Balster, 1996; Paterson et al., 2010; Heal et al., 2013; Quisenberry et al., 2013a). The 8-fold lower potency of p.o. modafinil vs. p.o. methylphenidate observed here is similar to their potency difference to substitute for discriminative stimulus effects of amphetamine in rats (Heal et al., 2013).

Facilitation of ICSS by p.o. modafinil contrasts with the failure of i.v. modafinil to maintain self-administration or of i.p. modafinil to produce conditioned place preference in rats (Deroche-Gamonet et al., 2002; Heal et al., 2013; Quisenberry et al., 2013b; Uguen et al., 2013). The reasons for this discrepancy are currently unknown; however, the low potency and poor solubility of modafinil complicate accurate drug-dose delivery by common parenteral routes. In support of this possibility, i.p. modafinil was recently shown to facilitate ICSS in rats; however, effects were weak and significant only at 150 mg/kg (Burrows et al., 2015). The higher potency of modafinil administered p.o. (present study) vs. i.p. (Burrows et al., 2015) contrasts with the lower potency of p.o. vs. i.p. methylphenidate and suggests that p.o. administration produced more efficient modafinil delivery. More generally, these two studies agree that modafinil produces stimulant-like abuse-related effects in ICSS procedures in rats.

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Figure 1.

Facilitation of ICSS following administration of methylphenidate (i.p. and p.o.) and modafinil (p.o.). Panels a-c show full frequency rate curves 10 minutes after administration of vehicle (Veh) or the dose of drug that produced maximum ICSS facilitation. Horizontal axes: Frequency of electrical brain stimulation in Hz (log scale). Vertical axes: Percent maximum control reinforcement rate (% MCR). Filled symbols show significant differences from vehicle as determined by repeated-measures two-way ANOVA followed by the Holm-Sidak post-hoc test, $p < 0.05$. Panels d-f show a summary measure of the total number of stimulations per component. Horizontal axes: Time post-injection in minutes. Vertical axes: percent baseline stimulations per component (% Baseline Stimulations). Filled symbols show significant differences from vehicle as determined by a repeated-measures two-way ANOVA followed by a Dunnett's post-hoc test, $p < 0.05$. Statistical results are as follows: (a) significant main effects of dose ($F_{1,4}=111.2$, $p < 0.001$) and frequency ($F_{9,36}=40.39$, $p < 0.001$) and a significant interaction ($F_{9,36}=55.06$, $p < 0.001$), (d) significant main effects of dose ($F_{2,8}=24.53$, $p < 0.001$) and time ($F_{2,8}=27.63$, $p < 0.001$) and a significant interaction ($F_{4,16}=3.94$, $p < 0.05$), (b), significant main effects of dose ($F_{1,4}=33.28$, $p < 0.01$) and frequency ($F_{9,36}=29.11$, $p < 0.001$) and a significant interaction ($F_{9,36}=2.54$, $p < 0.05$), (e), significant main effect of dose ($F_{3,12}=44.26$, $p < 0.001$) and a significant Dose $\times$ Time

interaction ($F_{6, 24}=3.49$, $p<0.05$), (c), significant main effects of dose ($F_{1,4}=20.69$, $p<0.05$) and frequency ($F_{9,36}=36.85$, $p<0.001$) and a significant interaction ($F_{9,36}=3.56$, $p<0.05$), (f), significant main effects of dose ($F_{4, 16}=13.47$, $p<0.001$) and time ($F_{3, 12}=7.55$, $p<0.01$).

Figure 2.

Potency of methylphenidate (i.p. and p.o.) and modafinil (p.o.). Horizontal axis: Dose of drug in mg/kg (log scale). Vertical axis: number of stimulations per component expressed as percent of vehicle values. ED150 values are reported in text.