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ORIGINAL INVESTIGATION

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Evaluation of the cocaine-like discriminative stimulus effects and reinforcing effects of modafinil

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Abstract Modafinil [(diphenyl-methyl)sulphinyl-2-acetamide] is a novel psychostimulant drug which is effective in the treatment of narcolepsy and idiopathic hypersomnia. It also has neuroprotective effects in animal models of striatal neuropathology. Although the cellular mechanisms of action of modafinil are poorly understood, it has been shown to have a profile of pharmacological effects that differs considerably from that of amphetamine-like stimulants. There is some evidence that modafinil has central α_1-adrenergic agonist effects. In the present study modafinil was evaluated for cocaine-like discriminative stimulus effects in rats and for reinforcing effects in rhesus monkeys maintained on intravenous cocaine self-administration. Modafinil, *l*-ephedrine and *d*-amphetamine all produced dose dependent increases in cocaine-lever responding, with maximal levels of 67%, 82% and 100%, respectively. Modafinil produced full substitution in four out of the six rats tested while the highest levels of substitution were associated with substantial response rate decreasing effects. Little evidence was obtained that the discriminative stimulus effects of modafinil were produced by α_1-adrenergic activation, based upon results of tests performed in combination with prazosin. In the self-administration procedure, modafinil and *l*-ephedrine functioned as reinforcers in rhesus monkeys. The reinforcing and discriminative stimulus effects of modafinil required very high doses: modafinil was over 200 times less potent than *d*-amphetamine and was also less potent than *l*-ephedrine. These results show that modafinil has some cocaine-like discriminative stimulus effects and, like other abused stimulants, can serve as a reinforcer at high doses.

Key words Modafinil · Ephedrine · Cocaine · Amphetamine · Self-administration · Drug discrimination · Rhesus monkey · Rat

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Introduction

Modafinil has shown promise for the treatment of narcolepsy, idiopathic hypersomnia and performance deficits resulting from sleep loss (Bastuji and Jouvet 1988; Boivin et al. 1993; Pigeau et al. 1995). This drug produces locomotor stimulation in rats and mice and increases nocturnal awakening in monkeys (Duteil et al. 1990; Hermant et al. 1991). Repeated administration of modafinil in rodents has neuroprotective effects in the striatum after ischemic, chemical and transection injury to dopaminergic pathways (Fuxe et al. 1992; Ueki et al. 1993a,b). Despite these psychomotor stimulant-like actions, modafinil exerts effects different from amphetamines on spontaneous firing of dopamine and noradrenergic neurons (Akaoka et al. 1991) and on electroencephalographic recording of sleep in rats (Touret et al. 1995), monkeys (Lagarde and Milhaud 1990) and cats (Lin et al. 1992). Furthermore, modafinil does not produce stereotypies like those produced by amphetamine, nor does it potentiate amphetamine-induced stereotypies (Duteil et al. 1990). Interestingly, many of the behaviors produced by modafinil are reversed by the α_1-adrenergic antagonist, prazosin, but not by antagonists acting at α_2-adrenergic or dopamine receptor subtypes, leading to speculation that some of modafinil's actions arise from central α_1-adrenergic activation (Duteil et al. 1990; Hermant et al. 1991; Simon et al. 1994). The purpose of this study was to evaluate further the similarities and

differences between modafinil and abused central stimulants such as cocaine and amphetamine.

The discriminative stimulus properties of drugs in animals are often used as a model of subjective drug effects in humans (Balster 1991). Drug discrimination procedures can be used to compare the effects of various stimulant drugs to those of cocaine. Prior research has shown that amphetamine and cocaine have comparable stimulus properties in rats and monkeys (Woolverton 1991). This is consistent with the common psychomotor stimulant-like intoxication and abuse potential of these drugs in humans (Fischman et al. 1976), and forms the rationale for the use of this test in abuse potential prediction (Holtzman 1990; Balster 1991). One aim of the present investigation was to evaluate the discriminative stimulus properties of modafinil in cocaine-trained rats. Substitution tests with *d*-amphetamine and *l*-ephedrine were performed as positive controls. The role of noradrenergic systems in the stimulus effects of modafinil were examined by pretreating the rats with prazosin, an α_1-adrenergic antagonist, prior to measuring cocaine-occasioned responding.

Another property shared by abused stimulants is their reinforcing effects in the drug self-administration procedure (Johanson and Balster 1978; Woolverton and Nader 1990). In this procedure, new drugs are tested to determine whether or not they will maintain the responding of rhesus monkeys trained to lever press for intravenous delivery of a known drug reinforcer like cocaine. The results with the test compound are compared to those obtained with saline or vehicle, the negative controls. A second aim of the present investigation was to study the self-administration of modafinil in a cocaine substitution procedure in rhesus monkeys. Again, *d*-amphetamine and *l*-ephedrine were tested as positive controls.

The purpose of these experiments was to examine the ability of modafinil to maintain responding in a monkey self-administration procedure and to generalize to cocaine in a rat drug discrimination procedure. Other stimulant drugs were included in the evaluation to help compare the efficacy and potency of modafinil with drugs known to possess or lack abuse liability. Given that initial reports had characterized modafinil as having α_1 adrenergic agonist properties, it was not expected that modafinil would support self-administration or generalize to cocaine in the drug discrimination procedure.

Materials and methods

Subjects

For drug discrimination studies, six adult male Sprague Dawley rats (COBS CD; Charles River, Wilmington, Mass.) were housed individually in a temperature-controlled environment under a regular 12-h light/dark cycle. Rats had free access to water but were maintained at approximately 350–400 g body weight by controlled feeding provided following drug discrimination sessions.

For self-administration studies, three adult male rhesus monkeys (*Macaca mulatta*), with previous experience in drug self-administration experiments, and one experimentally naive, adult female (M1099) rhesus monkey weighing between 5.7 and 11 kg were used as subjects. The monkeys were housed in fiberglass cubicles (1.0 × 1.0 × 1.0 m) which also served as the experimental chambers. The cubicles were equipped with fans to provide filtered air and a transparent front door which allowed visual contact among monkeys. Water was continuously available through drinking spouts located at the rear of the cubicles. The monkeys were fed Purina Monkey Chow and a chewable multiple vitamin each day following the self-administration session. The monkeys were surgically prepared with silicone intravenous catheters (0.08 cm i.d.; Ronsil Rubber Products, Belle Meade, N.J.) under phencyclidine (1.0 mg/kg, IM)-pentobarbital (10–30 mg/kg, IV) anesthesia. The internal and external jugular veins and the femoral veins could be catheterized. Catheters were routed subcutaneously from the catheterized vein and exited through the skin in the midscapular area. All studies were conducted in an AAALAC accredited facility under the guidelines published in the "Principles of laboratory animal care" (NIH Publication No. 85-23, revised 1985).

Apparatus

Rat drug discrimination training and testing was carried out in standard operant conditioning chambers (BRS/LVE, Laurel, Md.) equipped with a houselight and two response levers located 18 cm apart on one wall. An automatic pellet dispenser delivered 45-mg food pellets into a food trough located between the levers. The operant conditioning chambers were housed within sound attenuating outer chambers equipped with a ventilation fan. Recording of lever pressing behavior and control of the schedule contingencies was accomplished with an IBM-compatible microcomputer utilizing MED-PC software (Med Associates, East Fairfield, Vt.).

Monkey self-administration was carried out in cubicles equipped with two response levers mounted on the door of each experimental cubicle 30 cm above the floor. A food receptacle was located between the response levers and three jeweled stimulus lights (white-red-white) were located above the levers. Peristaltic infusion pumps (Cole-Parmer Co., Chicago, Ill.) delivered 10-s, 1.0-ml infusions through the catheters which passed from the pumps through the back of the cubicles and into protective spring arms. The spring arms, which were fastened to a stainless steel restraint harness fitted to each monkey (Deneau et al. 1969) and attached to the rear of the cubicle, allowed the monkeys nearly complete mobility within the cubicles. The experimental contingencies and data recording were controlled by a PDP11 computer located in an adjacent room.

Rat drug discrimination training and testing procedures

Rats were trained to discriminate cocaine (10 mg/kg, IP) from saline using a standard drug discrimination procedure (Balster et al. 1991). Briefly, rats were trained in a two-lever operant procedure under a fixed-ratio (FR) 32 schedule of reinforcement during daily 30-min sessions. During training, responding on the injection-appropriate lever was reinforced while responding on the incorrect lever reset the FR response requirement. Injection-appropriate lever responding was determined by injection of either cocaine or saline 10 min prior to the session. Cocaine and saline were administered according to a double alternation sequence (saline, saline, cocaine, cocaine, saline, etc.). Drug discrimination training continued until rats consistently completed the first FR on the injection-appropriate lever. Prior to being used in the present study, the rats had been tested with cocaethylene and other dopaminergic agonists, alone and in

combination with cocaine (Woodward et al. 1991; Mansbach and Balster 1993).

Control tests with each of the training conditions were conducted prior to each dose-effect determination for comparison with test drugs. During test sessions, completed FRs (FR-32) for consecutive responses on either lever were reinforced, while responses on one lever reset the FR requirement on the other lever. Tests were conducted on Tuesdays and Fridays only in subjects that achieved greater than 85% of total responses on the injection-appropriate lever, as well as emitted the first consecutive 32 responses on the injection-appropriate lever on the previous training day.

Substitution tests were conducted in an identical manner to control tests. For substitution test sessions, various doses of modafinil (3–250 mg/kg), *d*-amphetamine (0.1–3.0 mg/kg) or *l*-ephedrine (3–30 mg/kg) were administered prior to testing. Modafinil was administered 30 min presession, whereas *d*-amphetamine and *l*-ephedrine were administered 10 min presession. Following the substitution tests, antagonism tests with prazosin (0.3 mg/kg) were conducted by injecting prazosin alone or 10 min prior to modafinil (250 mg/kg). Rats were tested 30 min after the modafinil injection, and 40 min after the prazosin injection.

Monkey self-administration training and testing procedures

The monkeys were tested during daily 1-h self-administration sessions. The white stimulus lights above the left lever were lit at the beginning of each session. During the 10-s infusions, the white lights were turned off and the red stimulus light was illuminated. Monkeys obtained infusions by presses of the left lever under a FR-30 schedule of reinforcement. Responses during infusions were recorded but did not count toward completion of the fixed-ratio requirement.

During baseline conditions, cocaine hydrochloride 0.02 mg/kg per infusion (M1102) or 0.05 mg/kg per infusion (M1099, M1106, M1145) was the available solution. Vehicle, saline or various doses of modafinil were substituted for the baseline drug when three consecutive sessions were obtained in which the number of cocaine infusions did not vary more than 20% among sessions. The subjects were returned to the baseline conditions for at least three sessions between substitution tests.

For substitution tests, vehicle, saline and modafinil were substituted for four consecutive days and were followed and preceded by cocaine baseline conditions. Doses of modafinil (0.03, 0.1 and 0.3 mg/kg per infusion) were substituted in an irregular order. Higher doses could not be tested because of difficulties preparing a homogeneous suspension. In addition, *d*-amphetamine (0.01 or 0.03 mg/kg per infusion) and *l*-ephedrine (0.1 mg/kg per infusion) were tested as positive controls in three of the monkeys. *d*-Amphetamine substitution tests were carried out using the same emulphor: ethanol vehicle (see below) used to suspend the middle dose of modafinil, to control for the possible interaction of the vehicle with the reinforcing effects of modafinil.

Data analysis

For rat drug discrimination studies, the degree of substitution for the training drug was assessed by measuring the percentage of cocaine-lever responding during test sessions. For individual subjects, full substitution was defined as ≥ 85% cocaine-lever responding. Response rates were recorded as responses per second. The means (± SEM) for these measures were averaged across subjects. Behavioral disruption was indicated when response rates fell below 0.05 responses per second, and data for that test session were not included in the group average for cocaine-lever selection.

For monkey self-administration studies, the number of infusions over the last three sessions of substitution conditions were used in data analyses. Average number of cocaine infusions (± SD) were obtained from the last three sessions collapsed across all the cocaine baseline conditions. A test dose of modafinil was considered to be a reinforcer if the mean number of infusions exceeded the mean number of vehicle infusions and their ranges did not overlap.

Drugs

Cocaine hydrochloride and *d*-amphetamine sulfate were provided by the National Institute on Drug Abuse (Rockville, Md.). Modafinil was supplied by Sanofi Recherche, Montpellier, France. *l*-Ephedrine hydrochloride was purchased from Sigma (St Louis, Mo.). For rat drug discrimination studies, cocaine was dissolved in 0.9% saline and all other drugs were suspended in 0.5% tragacanth gum. Prazosin hydrochloride was purchased from Sigma (St Louis, Mo.) and suspended in sterile water with a few drops of Tween-80. For rats, all injections were administered IP in 1 ml/kg volumes, except for doses of modafinil above 30 mg/kg which were delivered in 2,3 or 5 times this volume.

For monkey self-administration studies, the cocaine and *l*-ephedrine were dissolved in 0.9% saline for injection, with concentrations adjusted so that infusions were administered in a volume of 1.0 ml. The modafinil was suspended in an emulphor: ethanol (1:1) vehicle at a concentration of 25 mg/ml. This stock solution was then diluted with 0.9% saline to give an infusion volume of 1.0 ml. This vehicle has been shown previously to be effective for studying the self-administration of water-insoluble compounds (Carney et al. 1977). *d*-Amphetamine was prepared in the emulphor:ethanol:saline concentrations that corresponded to the 0.1 mg/kg per infusion dose of modafinil. Vehicle tests were performed using the emulphor:ethanol:saline concentrations that corresponded to the 0.3 mg/kg per infusion dose of modafinil. This vehicle preparation resulted in 4.7 mg/kg per infusion of ethanol in a 10 kg monkey.

Results

Rat drug discrimination studies

Modafinil produced dose-dependent increases in cocaine-lever selection, reaching a maximum of 67% for the group. Doses of 3–100 mg/kg modafinil produced exclusively saline lever responding in all subjects, with little effect on response rates (Fig. 1). Modafinil was found to substitute for cocaine in one of the six rats starting with 150 mg/kg and in three additional rats with the highest dose tested (250 mg/kg). Cocaine-lever selection with the highest dose of modafinil was associated with a 59% reduction in response rates when compared with response rates during the saline control test conducted at the start of the modafinil dose-effect curve determination.

Both *d*-amphetamine and *l*-ephedrine also produced dose-dependent increases in cocaine-lever responding (Fig. 1), with a maximum mean of 100% and 82%, respectively. *d*-Amphetamine showed a somewhat greater selectivity than either modafinil or *l*-ephedrine for production of cocaine-like discriminative stimulus effects versus effects on rates of responding. As was the case with modafinil, *l*-ephedrine only produced greater than 50% cocaine-lever responding associated with substantial decreases in rates of responding. Cocaine and *d*-amphetamine produced over 50% cocaine-lever

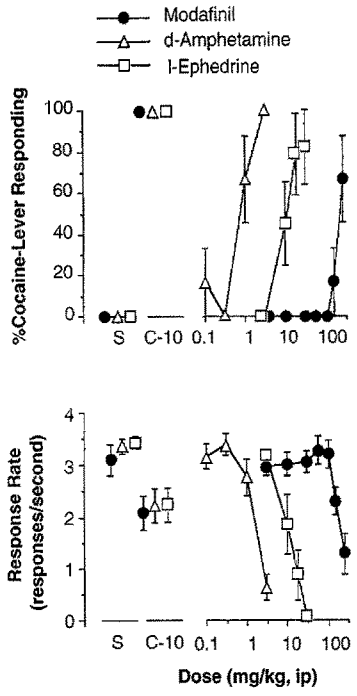

Fig. 1 Mean (± SEM) percentage of cocaine-lever responding (*upper panel*) and response rates (*lower panel*) following various doses of modafinil, *d*-amphetamine or *l*-ephedrine in rats trained to discriminate 10 mg/kg cocaine from saline. Points above *S* and *C-10* represent corresponding saline vehicle and cocaine (10 mg/kg) control tests conducted before each dose-effect curve determination

responding at a dose that produced less than 50% decreases in response rates. Although modafinil was effective in producing cocaine-like effects in four of the six rats tested, it was approximately 250 times less potent than *d*-amphetamine and about 15-fold less potent than *l*-ephedrine.

A role for α_1-adrenergic activation in the discriminative stimulus properties of modafinil was examined using the antagonist, prazosin. Prazosin (0.3 mg/kg) completely failed to antagonize either the cocaine-like discriminative stimulus effects or the response rate effects of modafinil 250 mg/kg (data not shown). In fact, the combined effects of modafinil and prazosin were to nearly eliminate responding in all but a few rats. Prazosin alone failed to produce any cocaine-like discriminative stimulus effects.

Monkey self-administration studies

Under baseline conditions, the number of infusions of cocaine (0.02, 0.05 mg/kg per infusion) per 1 h session averaged between 33 and 62 (Fig. 2). Although the average number of cocaine infusions differed among animals, it was generally quite stable from session to session for each subject. When saline was substituted for cocaine, the number of infusions decreased substantially in each subject (Fig. 2). The results of substitution tests with the emulphor:ethanol vehicle did not differ from the results of saline substitution (Fig. 2), providing evidence that the low dose of ethanol contained in the vehicle did not serve as a reinforcer.

According to the previously stated criteria, modafinil did function as a reinforcer when substituted for cocaine. All monkeys self-administered a greater number of infusions for at least one dose of modafinil when compared with the number of vehicle infusions self-administered (Fig. 2). The number of infusions of modafinil was greater than those of vehicle in two monkeys (M1102 and M1145) at 0.1 mg/kg modafinil, while 0.3 mg/kg modafinil maintained a greater number of infusions than vehicle in all four subjects. The number of infusions at these doses of modafinil were comparable to, or greater than, the number of cocaine infusions.

As dose per infusion increased, the total intake of modafinil increased. The mean intake of modafinil for all monkeys ranged from 0.4 mg/kg at the 0.03 mg/kg per infusion dose to 34.7 mg/kg at the 0.3 mg/kg per infusion dose. One monkey took as much as 36 mg/kg during a single 1-h session, while two others took above 17 mg/kg. There were no observable side effects of modafinil self-administration and subjects resumed their baseline level of cocaine self-administration on the day following modafinil substitutions.

In general, *d*-amphetamine and *l*-ephedrine availability resulted in greater numbers of infusions than saline availability (Fig. 2). Only three monkeys were included in these studies because monkey 1102 did not have a patent catheter at the time of these tests. The 0.03 mg/kg per infusion dose of *d*-amphetamine tested in monkey 1145 was associated with prolonged stimulant associated stereotypies (biting of jacket) and hypervigilant behaviors. The dose was then lowered to 0.01 mg/kg per infusion for the other two subjects. In all three monkeys, the mean number of *d*-amphetamine infusions exceeded the mean number of saline infusions and was comparable to the cocaine baseline. In two of the monkeys (M1145 and M1106) the range of amphetamine infusions did overlap that obtained with saline, due to the extreme day-to-day variability in intake. The number of infusions of *l*-ephedrine (0.1 mg/kg per infusion) per session was greater than that of saline and comparable to the cocaine baseline in all three monkeys.

Discussion

These results indicate that modafinil can serve as a reinforcer for drug self-administration in cocaine-trained rhesus monkeys and can produce substantial levels of cocaine-like discriminative stimulus effects in rats. When modafinil was substituted in monkeys trained to self-administer cocaine during daily sessions, responding for modafinil resembled responding when

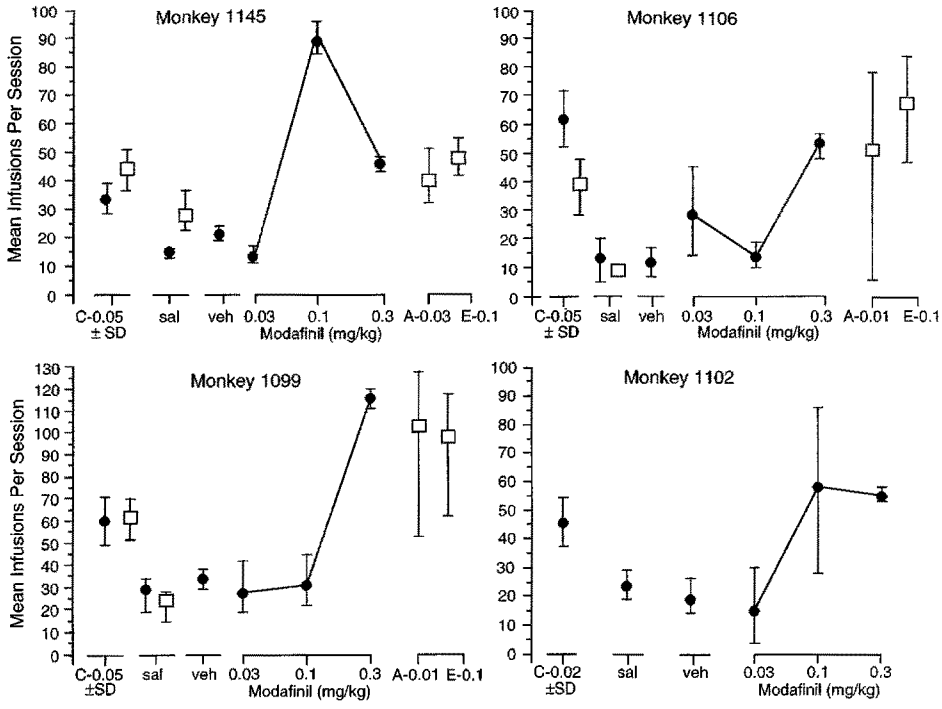

Fig. 2 Substitution tests with saline, vehicle and three doses of modafinil in four individual rhesus monkeys trained to self-administer IV cocaine injections (0.02 or 0.05 mg/kg per infusion). Shown above *C* are the mean (± SD) number of cocaine infusions for the 3 sessions preceding all substitution tests. Other values represent the mean and range of the last 3 days of substitution tests with saline (*sal*), vehicle (*veh*), various doses of modafinil, *d*-amphetamine (*A*; 0.01 or 0.03 mg/kg per infusion) or *l*-ephedrine (*E*; 0.1 mg/kg per infusion). The *solid circles* represent cocaine, saline and vehicle treatments associated with the modafinil dose-effect evaluation, while the *open squares* represent cocaine and saline treatments associated with amphetamine and ephedrine determinations. Note the difference in the ordinate scale for monkey 1099 (*lower left*)

cocaine was available, and was dissimilar to responding when saline or vehicle was available. First, the number of infusions resembled that maintained by cocaine. Secondly, the number of daily infusions usually remained stable or increased during a modafinil substitution. This pattern differs from the decreasing trend in the number of daily infusions obtained from the first to the last day when an ineffective reinforcer, like vehicle or saline, is substituted.

Limited substitution tests with *d*-amphetamine and *l*-ephedrine also provided evidence for reinforcing effects. In the case of *d*-amphetamine, the large variability in number of infusions from day to day resulted in a range that overlapped the number of infusions of saline in two of the subjects; nonetheless, the high infusion rates obtained on many sessions and the results of previous tests with this drug (Balster and Schuster 1973) show it to have reinforcing effects in this model. *l*-Ephedrine also maintained a greater number of infusions than saline at a dose of 0.1 mg/kg per infusion in all three monkeys tested.

Overall intake of modafinil increased as a function of dose per infusion. It is common for total dose to increase as a function of dose per infusion when response rates are independent of dose (Balster and Woolverton 1982). In the present study, examination of the full descending limb of the dose-effect curve was not possible because the weak potency of modafinil in this procedure precluded the testing of higher doses. Intake of up to 36 mg/kg IV was not associated with any observable behavioral toxicity or withdrawal, consistent with other studies involving repeated dosing in monkeys (Hermant et al. 1991).

Although additional information would be gained by examining the reinforcing effects of modafinil in naive monkeys, the self-administration substitution procedure utilized in this study has been used extensively to evaluate the abuse potential of new stimulant drugs (e.g., Beardsley et al. 1986; Mansbach et al. 1990) based on the rationale that known drugs of abuse typically serve as reinforcers when tested under these conditions (Johanson and Balster 1978). The finding that modafinil maintained responding suggests that it should be examined carefully in human studies for possible pleasurable effects and abuse potential. However, the present results with *l*-ephedrine indicate the extreme sensitivity of self-administration substitution procedures for the reinforcing effects of drugs in the stimulant class. Although there are reported instances of ephedrine abuse (e.g. Bruno et al. 1993), laboratory testing in human subjects has shown that it is much less efficacious than amphetamine for abuse-related effects (Martin et al. 1971; Chait 1994). Therefore, modafinil may have no greater abuse potential than *l*-ephedrine.

In the drug discrimination study, modafinil produced dose-dependent increases in cocaine-lever responding. Nonetheless, complete substitution for cocaine was not obtained in all animals, unlike the results obtained with *d*-amphetamine. One factor which could have attributed to the lack of full substitution is that maximal levels of cocaine-lever responding occurred only at very high doses of modafinil, doses which had substantial response-rate decreasing effects. Even higher doses could not be tested because of this behavioral toxicity. Comparisons of the modafinil dose that produced generalization (250 mg/kg) to a published dose-effect curve for cocaine obtained in these same animals (Woodward et al. 1991) shows modafinil to be over 25 times less potent than the minimally effective cocaine dose (10 mg/kg). This lack of potency for discriminative stimulus effects makes the generalization results more difficult to interpret. Nonetheless, the results complement the findings from the self-administration study in suggesting that high doses of modafinil might have psychomotor stimulant-like effects.

Many other drugs have been tested for cocaine-like discriminative stimulus effects using this procedure. Abused central stimulant drugs such as the amphetamines, methylphenidate and phenmetrazine produce complete generalization from cocaine (Woolverton 1991), as evidenced again here by the results obtained with *d*-amphetamine. Previous studies with less efficacious central stimulants have generally provided evidence for amphetamine-like or cocaine-like discriminative stimulus effects as well (Snoddy and Tessel 1983; Kamien and Woolverton 1989; Lamb and Griffiths 1990; Baker et al. 1993; Terry et al. 1994). In the present study, *l*-ephedrine also was shown to generalize from cocaine, similar to results obtained earlier in *d*-amphetamine- and cocaine-trained rats (Huang and Ho 1974; Gauvin et al. 1989). Cocaine and *d*-amphetamine have also been shown to produce full substitution in rats trained to discriminate *d,l*-ephedrine from saline (Gauvin et al. 1993). In being even less potent than ephedrine for cocaine-like discriminative stimulus effects, modafinil would have to be considered a relatively impotent stimulant.

The cellular mechanisms of action of modafinil are not clearly understood at the present time. Initial studies supported a role for central α_1-adrenergic activation based on the ability of prazosin to block many of the pharmacological effects of modafinil (Duteil et al. 1990; Hermant et al. 1991), while studies of dopamine receptor antagonists provided no evidence of a role for dopaminergic systems in modafinil's behavioral actions (Duteil et al. 1990; Rambert et al. 1990; Lin et al. 1992). The lack of cocaine-like discriminative stimulus effects of modafinil at doses up to 100 mg/kg in the present evaluation are consistent with such results and suggests that modafinil possesses a range of pharmacological effects in rodents at doses of 100 mg/kg and lower that are not mediated through dopaminergic activation. In the present evaluation, a dose of modafinil (250 mg/kg) considerably above those typically studied did produce cocaine-like discriminative stimulus effects in a majority of subjects. In this case, little evidence was obtained that the effects of modafinil were produced by α_1-adrenergic stimulation. Neither cocaine-like discriminative stimulus effects nor the response rate effects of modafinil were blocked by prazosin. Indeed, the combined effects of modafinil and prazosin on rates of responding were greater than the effects of either drug alone.

Because relatively high doses were required to demonstrate the cocaine-like discriminative stimulus effects and reinforcing effects of modafinil, mechanisms other than those involving the noradrenergic system may have been invoked. These results again raise the possibility that modafinil possesses dopaminergic actions in this dose range. Recently, Mignot et al. (1994) have reported weak, but selective, affinity of modafinil for the dopamine uptake carrier in guinea pig striatum. Thus, the possibility that dopamine uptake inhibition may play a role in the *high* dose cocaine-like effects of modafinil cannot be ruled out. It is interesting to note that modafinil is only about 40-fold less potent than cocaine in competition binding for the dopamine uptake carrier (Mignot et al. 1994). If this were true in rats under our test conditions, then the activity of modafinil as a dopamine uptake inhibitor could account for its cocaine-like discriminative stimulus effects, where it was over 25 times less potent than cocaine. Further studies would be necessary to determine if dopaminergic activation serves as the basis for the reinforcing effects of modafinil in monkeys as well.

In summary, high doses of modafinil were found to have reinforcing effects in rhesus monkeys and some cocaine-like discriminative stimulus effects in rats. Thus modafinil shares a profile of a weakly efficacious stimulant with drugs such as ephedrine, and should be evaluated for evidence of clinical abuse potential liability.

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