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ORIGINAL INVESTIGATION

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Study of the addictive potential of modafinil in naive and cocaine-experienced rats

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Abstract *Rationale:* Modafinil is a drug that promotes wakefulness and, as such, is used to treat hypersomnia and narcolepsy. Preclinical and clinical studies suggest that modafinil could possess weak reinforcing effects in drug-experienced subjects. However, its abuse potential in drug-naive healthy individuals is still totally uninvestigated, despite the fact that availability of modafinil has recently increased. *Objectives:* The purpose of our study was to investigate the potential addictive properties of modafinil by testing its reinforcing effects in naive rats. The interactions of modafinil with the reinforcing effects of cocaine were also tested. *Methods:* First, using i.v. self-administration and place conditioning tests, we studied the reinforcing and rewarding effects of a large range of doses of modafinil in naive rats. Second, we tested the influence of modafinil on reinforcing and incentive effects of cocaine in rats trained for cocaine self-administration. The effects of modafinil were compared with those of amphetamine and haloperidol. *Results:* Modafinil did not produce reinforcing or rewarding effects and did not modify the effects of cocaine. *Conclusions:* Our results suggest that modafinil does not possess an addictive potential in naive individuals. Furthermore, it would be behaviorally distinct from classical central nervous system stimulants which are known to alter cocaine-induced effects. However, as shown previously in nonhuman primates and in humans, modafinil could possibly have reinforcing effects in cocaine-experienced individuals.

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Introduction

Modafinil [(±)2-(benzydryl-sulfinyl) acetamide] is a drug that promotes wakefulness. It is used to treat hypersomnia and narcolepsy (Bastuji and Jouvet 1988). Although the profile of modafinil is unique and very different from that of classical psychostimulants, such as amphetamine and cocaine, it nevertheless shares some common properties with these drugs. Thus, in addition to its awaking effects, modafinil acts as a psychomotor stimulant in animals (Duteil et al. 1990). Furthermore, a recent study suggests that its wake-promoting effects could involve the mesolimbic dopaminergic system (Wisor et al. 2001). These behavioral and neurochemical features of modafinil raise the question as to its potential addictive properties.

Recent changes in modafinil availability render the question of its addictive potential particularly important. Although available in France since 1992, it has only been delivered under restricted conditions for the treatment of hypersomnia and narcolepsy. Furthermore, people suffering from narcolepsy and hypersomnia are maintained under a daily chronic treatment with modafinil which, because of these pathologies, is usually not interrupted. Under such circumstances, it is certainly very difficult to identify the development of dependence to modafinil. Over the past 3 years, it has become available in numerous countries including the USA, Canada, Japan, Italy, Ireland, and Switzerland. Furthermore, modafinil is now being tested for the treatment of a larger range of pathologies including multiple sclerosis fatigue and attention deficit/hyperactivity disorder (ADHD). Lastly, the efficacy of modafinil has also been tested in a simulated shift work study.

On the basis of these observations, we tried to better characterize the addictive potential of modafinil. Avail-

able data do not allow a clear answer to this question. Preclinical and clinical studies suggest that it could possess weak reinforcing effects in drug-experienced individuals. Gold and Balster (1996) showed that modafinil could act as a substitute for the reinforcing effects of cocaine in monkeys and could generalize to the discriminative effects of cocaine in rats. Jasinski (2000) recently showed that modafinil could produce methylphenidate-like subjective pleasurable effects in drug-experienced humans, although it produced behavioral and physiological effects that differed significantly from those of methylphenidate and amphetamine. Although no sign of dependence has been reported in drug-naive subjects during treatment with modafinil (Bastuji and Jouvet 1988), its abuse potential in drug-naive healthy individuals remains largely uninvestigated.

A classical approach to assess the addictive potential of a new drug consists of investigating whether it shares common pharmacological and behavioral properties with established drugs of abuse in animals. This includes determination of the drug's reinforcing value and its interactions with the reinforcing effects of established drugs of abuse. Two major behavioral tests are used in rodents to predict the reinforcing value of new compounds. First, drug-induced place preference; most of the drugs producing addiction in humans also produce subjective effects in animals that can be conditioned to a particular environment (Bardo et al. 1995; Bardo and Bevins 2000). Second, i.v. self-administration; drugs of abuse can also maintain operant responding reinforced by their i.v. delivery (Yokel 1987). The relative reinforcing value of a new compound can be determined by increasing the response requirement as stipulated by progressive ratio schedules (Richardson and Roberts 1996; Stafford et al. 1998; Rowlett 2000; Piazza et al. 2000). Certain drugs are reinforcing but their i.v. self-administration is maintained only at low ratio requirements suggesting a low addictive potential (Marinelli et al. 1998).

Addictive drugs share common neurochemical substrates. Consequently, an addictive drug is able to modify behavioral responding to another addictive drug. This statement is particularly true for drugs from the same class. The nature of these drug interactions, initially interpreted as modifications of the reinforcing effects (Yokel and Wise 1975; Koob and Bloom 1988), is still not clarified (Arnold and Roberts 1997; Sizemore and Martin 2000). Nevertheless, noncontingent administration of a psychostimulant drug will consistently modify the self-administration behavior of another psychostimulant, i.e., an increase or a decrease in responding according to the self-administration protocol used (Arnold and Roberts 1997; Sizemore and Martin 2000).

Using these procedures, we analyzed the addictive properties of modafinil in rats. First, we compared the ability of modafinil (32, 64, 128, 256 mg/kg i.p.) and amphetamine (2 mg/kg i.p.) to produce place conditioning. Second, we compared the ability of modafinil (vehicle, 0.28, 0.55, 1.1, or 1.7 mg/kg per injection) and cocaine (0.8 mg/kg per injection) to induce i.v. self-administration. The strength of modafinil and cocaine reinforcing effects were tested using a between-session progressive ratio schedule; i.e., ratio requirement was progressively increased every two to three sessions (Piazza et al. 2000). Furthermore, we tested the interactions of modafinil with the reinforcing and incentive effects of cocaine. For this purpose, additional (3rd, 4th, and 5th) experiments were conducted. In the third experiment, the effect of modafinil (vehicle, 32, 64, 128 mg/kg i.p.) on the dose–response curve for cocaine i.v. self-administration was compared with the effects of the D1/D2 dopamine antagonist haloperidol and the indirect dopamine agonist amphetamine. Both dopamine agonists and antagonists have been shown to modify cocaine self-administration (for review Pulvirenti and Koob 1994; Rothman and Glowa 1995). In the fourth experiment, the effect of modafinil was tested on rats trained for cocaine self-administration in a between-session progressive ratio schedule. Finally, in the fifth experiment, we tested the ability of modafinil (64 mg/kg i.p.) to modulate cocaine-induced reinstatement (0.2, 0.4, 0.8 and 1.6 mg/kg i.v.).

Materials and methods

Subjects

Male Sprague-Dawley rats (Iffa Credo, Lyon, France) weighing 280–300 g at the beginning of the experiments were used. For the place conditioning study animals were group housed (three per cage); for all other experiments, animals were individually housed. Animals had free access to food and water. A 12-h/12-h dark/light cycle (on 2400 hours, off 1200 hours for self-administration experiments; on at 0800 hours, off at 2000 hours for the place conditioning experiment) was used in the animal house. Temperature (22±1°C) and humidity (60±5%) were also controlled. Self-administration experiments were conducted during the dark period, while the place conditioning experiment was conducted during the light period.

Drugs

Modafinil (Laboratoire L. LAFON, Maisons-Alfort, France) was suspended in 0.9% NaCl containing 5% Arabic gum for i.p. injections and dissolved in a cyclodextrine solution for i.v. injections. Cocaine (Coopération Pharmaceutique Française, Bordeaux, France), amphetamine, and haloperidol (Sigma-Aldrich Chimie, Saint Quentin Fallavier, France) were dissolved in 0.9% NaCl.

Constitution of the experimental groups

It has previously been shown that locomotor activity in a novel environment is positively correlated with sensitivity to the psychomotor and reinforcing effects of psychomotor stimulants (Piazza et al. 1989; Hooks et al. 1991a, 1991b). Therefore, we ensured a homogeneous distribution of this factor throughout the different experimental groups. After a 7-day period of habituation to the housing conditions, and before any other manipulation, animals were exposed to a novel environment and were then evenly distributed in the different experimental groups according to their activity score over the 2 h of testing (from 0600 to 0800 hours). The novel environment was a circular corridor (10-cm wide and 70-cm in diameter). Four photoelectric cells placed at the perpendicular axis of the apparatus automatically recorded locomotion.

Surgery

A silastic catheter (internal diameter 0.28 mm; external diameter 0.61 mm; dead volume 12 µl) was implanted, under ether anesthesia, in the jugular vein. The proximal end was placed in the right atrium while the distal end was passed under the skin and fixed in the mid-scapular region. Rats were allowed to recover for 5–7 days after surgery. During the first 4 days following surgery, rats received an antibiotic treatment [gentamicine (gentalline), 1 mg/kg i.v.]. After surgery, catheters were flushed daily with a saline solution containing unfractionated heparin (100 IU/ml).

Behavioral tests

Intravenous self-administration apparatus

The i.v. self-administration set-up (Imetronic, Pessac, France) was similar to that previously described by Deroche et al. (1997). Briefly, animals were placed daily in a self-administration chamber where their chronically implanted intra-cardiac catheter was connected to a pump-driven syringe. Two holes, located in opposite sides of the self-administration box, were used as devices to record responding. A cue light was placed on one of the short sides of the cage, 5 cm above the floor. Introduction of the animal's nose into one hole (active device) turned on the cue light and then, 1 s later, switched on the infusion pump (infusion speed 20 µl over 1 s). The cue light remained on for a total of 4 s. Nosepokes in the other hole (inactive device) had no scheduled consequences. Each injection was followed by a 20-s time-out period. The unit dose of drug available was determined by the unit volume per reinforcer, which was programmed by changing the activation time of the infusion pump. Experimental contingencies were controlled and data collected by a PC Windows-compatible software (Imetronic, Pessac, France). Self-administration behavior was considered stable when the number of injections remained constant over three consecutive sessions (±10%).

Place conditioning

An apparatus based on topographical cues was used (Deroche et al. 1999; Cabib et al. 2000). Each box contained two black Plexiglas chambers (30 cm long × 30 cm large × 40 cm high) connected by a central alley (30 cm long × 10 cm large × 40 cm high). Each box had two openings (8 cm large × 40 cm high), one per chamber, which could be closed by sliding doors. In each chamber, two triangular Plexiglas parallelepipeds (10/10/14.5 cm sides × 40 cm high) were used to make different chamber shapes and volumetric patterns (always covering the same surface of the chamber). The shape of the chamber was then used as conditioned stimuli. A series of photoelectric beams allowed recording of the time spent in each chamber as well as the locomotor activity. After every trial, the walls and the floor of the boxes were wiped with fresh tap water.

Procedures

Study of the appetitive and reinforcing effects of modafinil

Experiment 1: comparison of modafinil- and amphetamine-induced place conditioning. Modafinil (vehicle, 32, 64, 128, 256 mg/kg) and amphetamine (vehicle, 2 mg/kg) were tested in seven independent experimental groups (n=8 per group). The entire procedure lasted ten consecutive days. First, a pre-conditioning session (20 min) was conducted during which the rats were allowed to visit the apparatus (all doors opened) in a drug-free state. The following day, using an unbiased procedure, the conditioning began. Rats were confined daily for 30 min alternatively in one of the two chambers. Four drug pairings alternated with four vehicle pairings. The pairing procedure was accomplished over 8 days, i.e., one pairing per day. Rats were injected (i.p.) immediately before being confined in the assigned chamber. Within each experimental group, all conditions (drug associated with one compartment or the other, conditioning starting with drug or vehicle) were counterbalanced. The test for conditioning was performed the day after the last conditioning session. Rats were placed in the central alley, the sliding doors immediately opened and the time spent in each of the two compartments was monitored in a drug-free state for a period of 20 min.

Experiment 2: comparison of modafinil- and cocaine-induced i.v. self-administration. Four doses of modafinil (0.28, 0.55, 1.1, 1.7 mg/kg per injection) plus vehicle, and one dose of cocaine (0.8 mg/kg per injection) were tested in six independent experimental groups (n=7, 6, 8, 8, 5, 9, respectively). The daily sessions lasted 1 h. The volume of each self-injection was 20 µl, except for the highest dose of modafinil for which a volume of 30 µl was used. The entire procedure lasted 19 consecutive days. From day 1 to day 11, animals were tested using a fixed ratio 1 (FR1) schedule. From day 11 to day 19, the FR was progressively increased according to the following procedure: 2 days at FR3, 3 days at FR6, and 3 days at FR10.

Effects of modafinil on the reinforcing and incentive effects of cocaine

Experiment 3: effects of modafinil on cocaine i.v. self-administration using a dose–response procedure. Animals (n=7) were trained to self-administer cocaine using a within-session dose–response schedule. In this schedule, each daily self-administration session lasted 130 min and was divided into five parts. Three doses of cocaine (0.25, 0.5, 1 mg/kg per injection) were successively tested over 30-min periods in descending order. Each self-administration period was separated from the other by a 20-min interval, during which cocaine was not available and the house light was turned on. After stabilization, the effects on the dose–response curve of amphetamine (1.5 mg/kg i.p., just before the session), haloperidol (0.1 mg/kg i.p., 1 h before the session), and modafinil (vehicle, 32, 64, 128 mg/kg i.p., 20 min before the session) were tested. Drugs were tested in distinct sessions separated by one or more baseline days and according to a Latin square design.

Experiment 4: effects of modafinil on cocaine i.v. self-administration using a progressive ratio schedule. Animals (n=23) were trained to self-administer cocaine (1 mg/kg per injection) at FR1 during 1-h daily sessions. After stabilization of the behavior, the FR was progressively increased to FR5. Once the behavior had stabilized at FR5, animals were separated into four experimental groups and assigned one dose of modafinil (vehicle, 32, 64, or 128 mg/kg, i.p.). Modafinil was administered 20 min before each self-administration session for six consecutive sessions at FR5 and during the between-session progressive ratio schedule that followed. During this period, the ratio requirement was progressively increased according to the following schedule: FR10 (one session), FR20 (two sessions), FR30 (one session), FR45 (three sessions), FR60 (one session), FR85 (one session), and FR 110 (one session).

Experiment 5: effects of modafinil on the reinstatement of cocaine i.v. self-administration. Animals (n=10) were trained for cocaine self-administration using a within-session dose–response schedule. Three doses of cocaine were tested daily: 0.2, 0.4, 0.8 mg/kg per injection in descending order. After stabilization of responding, the reinstatement procedure (Deroche et al. 1999) was conducted over 4 days. During these sessions, the drug was never available, i.e., an extinction procedure was applied. Over the first 2 days, and according to a Latin square design, animals received an injection of modafinil (64 mg/kg i.p.) or vehicle administered 90 min after the start of the extinction session. Thirty minutes later, one saline injection was automatically administered every 30 min (in this order: 20 µl, 40 µl, 80 µl, and 160 µl i.v.). Over the

third and fourth days, the same protocol was applied but, instead of saline, animals received cocaine (in this order: 0.2, 0.4, 0.8, and 1.6 mg/kg i.v.).

Data analyses

For all the experiments, analysis of variance (ANOVA) for repeated measures was used. Depending on the experiments, the group (2 levels for amphetamine, 5 levels for modafinil in experiment 1; 5 and 4 levels for modafinil in experiments 2 and 4, respectively) was used as a between-subjects factor and the compartment (2 levels in experiment 1), the treatment (amphetamine, haloperidol, 2 levels; modafinil, 4 levels in experiment 3), the dose of drug (3 to 4 levels in experiment 3 and 5 for cocaine or saline; 4 levels for modafinil in experiment 3), the hole (active vs inactive, 2 levels), and sessions (11 levels in experiment 2) were used as within-subjects factors.

Post-hoc analyses (Newmann-Keuls) were used to determine the locus of significant main effects and interactions. A significant level of $P<0.05$ was used for all statistical analyses.

Results

Study of the appetitive and reinforcing effects of modafinil

Experiment 1: comparison of modafinil- and amphetamine-induced place conditioning

The experimental groups did not differ with regard to the time spent in each compartment during the pre-test. The conditioning procedure induced a significant preference for the environment paired with amphetamine that appeared over the last 15 min of the test ($F_{1,7}=9.34$, $P<0.05$). Results were cumulated over this period for all treatments. Pairing with modafinil did not induce place preference. Whatever the dose tested, modafinil treated animals did not show a preference for one or the other compartment (Fig. 1).

During conditioning, both modafinil and amphetamine had significant behavioral effects (data not shown). Indeed, a dose-dependent increase in locomotor activity was observed after modafinil and amphetamine. When compared with vehicle-treated animals, the highest effect for modafinil was found for the 128-mg/kg dose ($F_{1,14}=13.56$, $P=0.002$). In addition, the effect of 2 mg/kg amphetamine was highly significant ($F_{1,14}=26.92$, $P=0.0001$). The comparison of the highest locomotor response observed after modafinil (128 mg/kg) with that observed after amphetamine (2 mg/kg) indicated that the locomotor activity induced by the two drugs did not differ significantly.

Experiment 2: comparison of modafinil- and cocaine-induced i.v. self-administration

Modafinil did not induce i.v. self-administration (Fig. 2a). Over the 11 days of the acquisition period, no significant differences in the number of injections across doses of modafinil were observed (treatment × day interaction, $F_{15,95}=0.52$, $P=0.92$), and the number of injections significantly decreased over days (day effect $F_{10,220}=4.98$, $P<0.0001$), which suggests that exploration and habituation were mainly driving the behavior of modafinil groups. The opposite pattern was observed in animals self-administering cocaine. In this case, the number of injections significantly increased over days ($F_{10,80}=2.47$, $P<0.015$), reaching a stable level around the 5th day of testing. The between-session progressive increase in ratio requirement produced a different effect in modafinil and in cocaine-trained animals (Fig. 2b). In the cocaine group, increase in ratio was paralleled by a progressive increase in the number of responses in the active hole (ratio effect $F_{10,190}=10.67$, $P<0.0001$), resulting in a higher number of nose-pokes in the active hole than in the inactive one (hole effect $F_{1,8}=8.31$, $P<0.022$), and this difference increased as the ratio increased (hole × ratio interaction $F_{9,72}=5.06$, $P<0.0001$; data not shown). As a consequence of this adjustment in behavior, cocaine

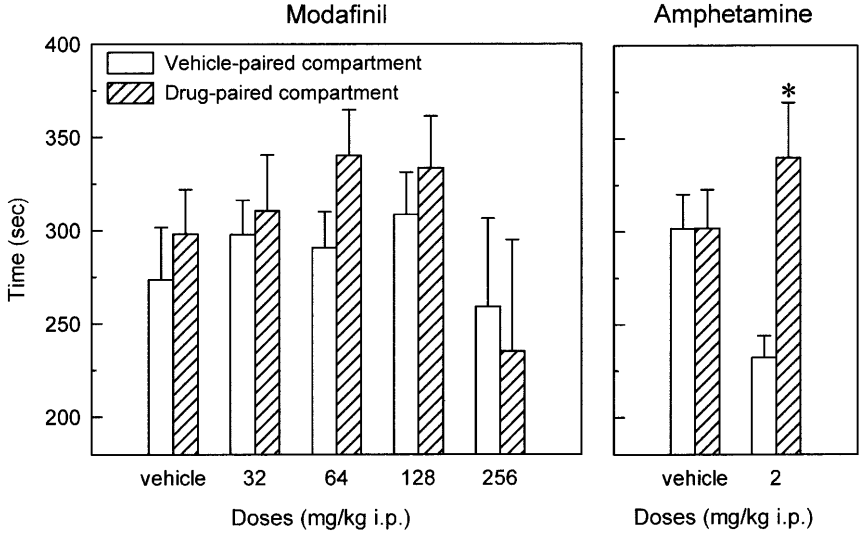

Fig. 1 Time spent in drug- and vehicle-paired compartments during the test phase of the place conditioning paradigm for modafinil (*left panel*) and amphetamine (*right panel*). Data are expressed as the mean cumulated time over the last 15 min of the test (±SEM). The time spent in the vehicle- and modafinil-paired compartments did not differ, showing that none of the doses tested induced place conditioning, while a significant preference was seen for the amphetamine-paired compartment

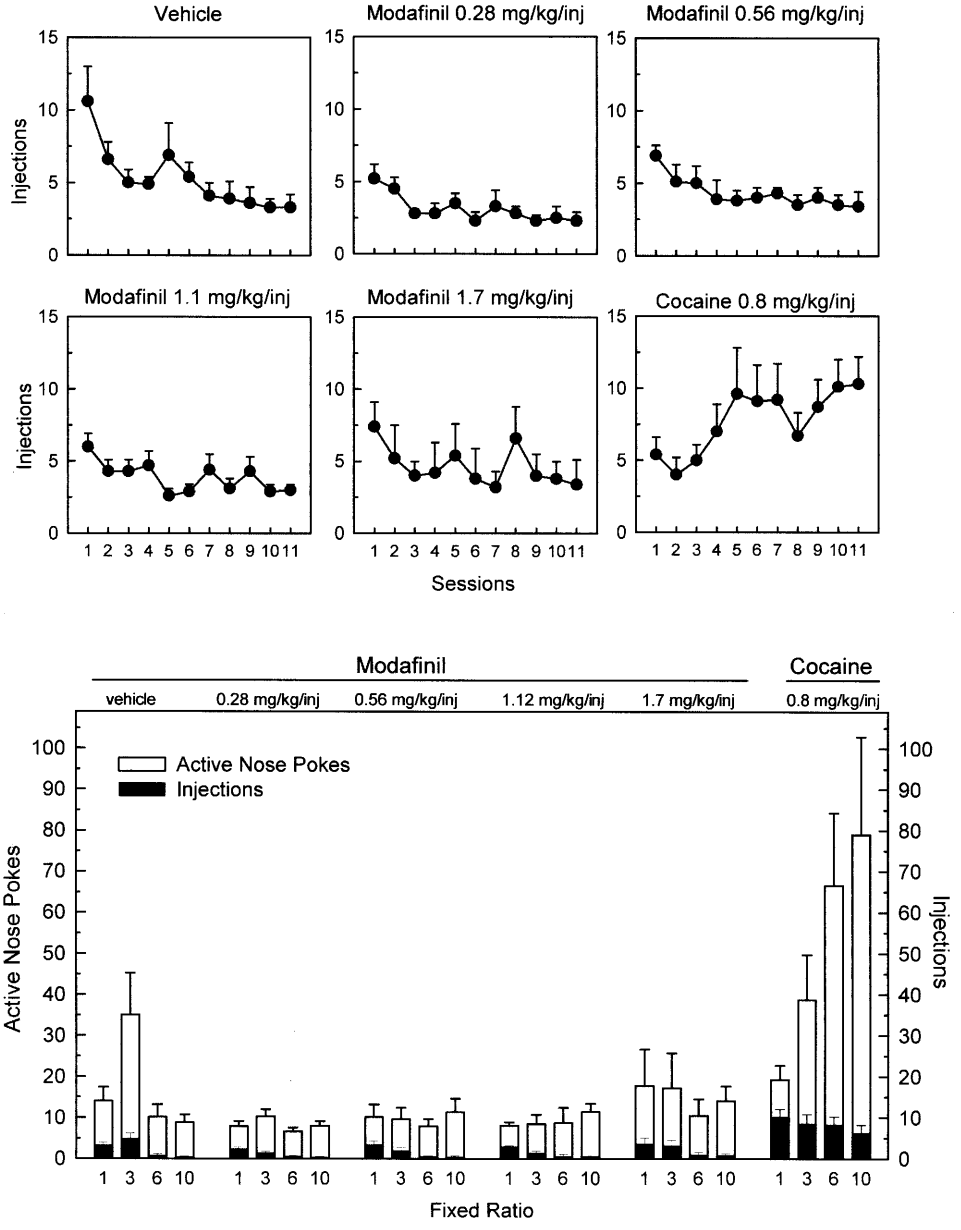

Fig. 2 *Top panel*: self-administration of modafinil (vehicle, 0.28, 0.55, 1.1, 1.7 mg/kg per injection) and cocaine (0.8 mg/kg per injection) during acquisition phase [11 days at fixed ratio (FR)1]. Data are expressed as the mean daily number of self-injections (±SEM). During acquisition, the number of cocaine self-injections progressively increased and stabilized. On the contrary, all modafinil groups showed a decreasing number of self-injections that did not differ from that of the vehicle group. *Bottom panel*: self-administration of modafinil (vehicle, 0.28, 0.55, 1.1, 1.7 mg/kg per injection) and cocaine (0.8 mg/kg per injection) as a function of ratio (FR1, FR3, FR6, FR10). Data are expressed as the mean number (±SEM) of active nose-pokes (*white box*) and self-injections (*black box*) over the last two sessions for each fixed ratio. As the ratio increased, rats responding for cocaine maintained a stable drug intake. On the contrary, rats responding for modafinil showed a progressive decrease in self-injections reaching almost zero for the highest ratio similarly to the vehicle group

was self-administered at a similar amount over all ratios (Fig. 2b). During this procedure, modafinil groups did not differ for the number of injections. Whatever the dose of modafinil tested, the number of injections per session significantly decreased over ratios (day effect $F_{9,252}$=22.52, P<0.0001).

Effects of modafinil on the reinforcing and incentive effects of cocaine

Experiment 3: effects of modafinil on cocaine i.v. self-administration using a dose–response procedure

Rats acquired cocaine self-administration. A discrimination between active and inactive holes was observed (ANOVA, hole effect $F_{1,6}$=26.27, P<0.005; data not shown). Furthermore, the number of active nose-pokes and self-injections was dose-dependent (dose effect, active hole $F_{2,12}$=19.79, P<0.0002, self-injections, $F_{2,12}$= 22.41, P<0.0001; Fig. 3). On the contrary, inactive nose-poking was independent of the dose (data not shown). Pretreatment with amphetamine and haloperidol had opposite effects on the dose–response curve for cocaine self-administration. Amphetamine induced a leftward shift of the curve ($F_{1,6}$=6.69, P<0.05), while haloperidol induced a rightward shift ($F_{1,6}$=39.73, P<0.005). In contrast, whatever the dose tested, modafinil did not modify either the number of active nose-pokes or the number of cocaine self-injections.

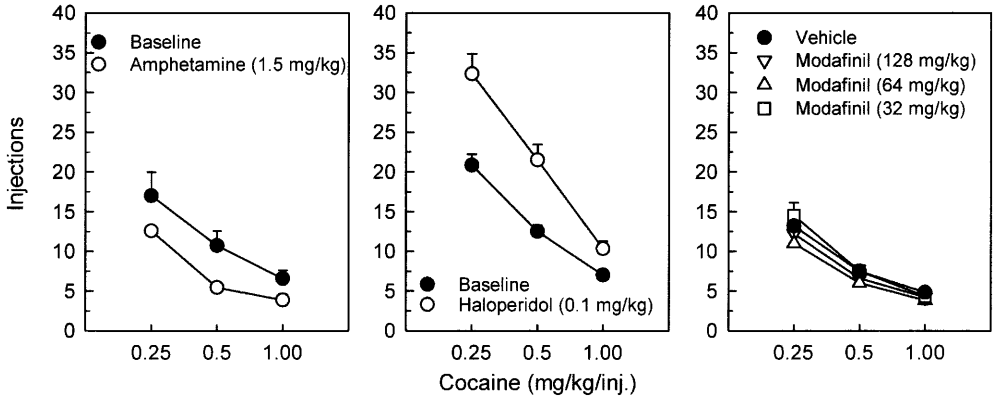

Fig. 3 Influence of amphetamine (1.5 mg/kg; *left panel*), haloperidol (0.1 mg/kg; *middle panel*), and modafinil (vehicle, 32, 64, 128 mg/kg; *right panel*) on the dose–response curve for cocaine self-administration. Data are expressed as the mean number of self-injections (±SEM) for each dose of cocaine. Amphetamine induced a leftward- and haloperidol induced a rightward-shift of the dose–response curve, interpreted respectively as an increase and a decrease of the reinforcing properties of cocaine. No influence of modafinil was seen on the dose–response curve for cocaine self-administration

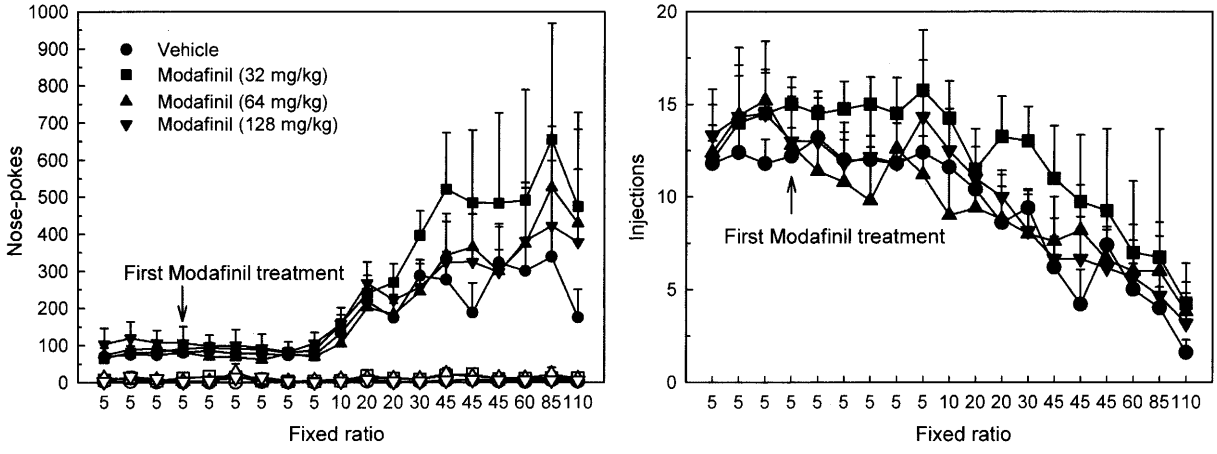

Fig. 4 Influence of modafinil (vehicle, 32, 64, 128 mg/kg) on cocaine self-administration in a progressive ratio schedule [fixed ratio (FR)5, 10, 20, 30, 45, 60, 85, 110]. *Left panel*: mean number of responses (±SEM) in the active (*black symbols*) and inactive (*white symbols*) holes. *Right panel*: mean number of self-injections (±SEM). The responses increased and reached a plateau, while the number of injections first remained constant and then decreased at the highest ratios. Modafinil had no significant influence on responding, showing that it did not modify the motivation for cocaine self-administration

Experiment 4: effects of modafinil on cocaine i.v. self-administration using a progressive ratio procedure

Modafinil did not modify cocaine self-administration at FR5. The four experimental groups did not differ either regarding the number of injections or the number of nose-pokes. Similarly, modafinil did not modify cocaine self-administration as the ratio increased. The four experimental groups did not differ either regarding the number of injections or the number of nose-pokes (Fig. 4).

Experiment 5: effects of modafinil on the reinstatement of cocaine i.v. self-administration

In animals pretreated with modafinil vehicle, noncontingent saline injections did not significantly modify responding in the active and inactive holes (Fig. 5, left panel). On the contrary, cocaine injections induced a specific and dose-dependent increase of responding in the hole previously associated with cocaine (dose effect $F_{3,27}$=8.72, P<0.0005; Fig. 5, right panel). In animals pretreated with modafinil, noncontingent saline injections induced a specific and volume-dependent increase of responding in the hole previously associated with cocaine (treatment × dose interaction $F_{3,27}$=2.96, P<0.05). The two lower volumes of saline were responsible for this effect. Modafinil did not significantly modify the dose–response curve for cocaine-induced reinstatement (treatment effect $F_{1,9}$=0.78, P=0.39; treatment × dose interaction $F_{3,27}$=1.4, P=0.26).

Discussion

In naive rats, modafinil failed to induce place preference and i.v. self-administration at either low or increasing ra-

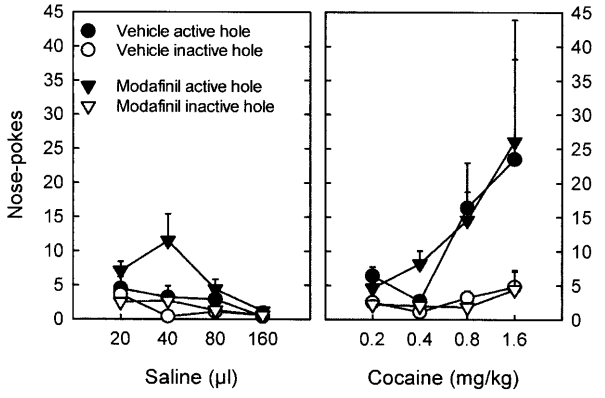

Fig. 5 Influence of modafinil (vehicle, 64 mg/kg) on reinstatement of cocaine self-administration. *Left panel*: influence of modafinil on the effect of noncontingent injections of different volumes of saline (20, 40, 80, 160 µl). *Right panel*: influence of modafinil on the effects of noncontingent injections of cocaine (0.2, 0.4, 0.8, 1.6 mg/kg). Cocaine injections induced similar reinstatement levels in modafinil- and vehicle-treated groups. The different volumes of saline produced the same effects in vehicle-pretreated animals, i.e., they did not reinstate self-administration behavior. However, the two lower volumes of saline produced reinstatement in modafinil-pretreated animals. Data are expressed as the mean number of nose-pokes (±SEM) in both active (*black symbols*) and inactive (*white symbols*) holes

tio requirements. These observations suggest that modafinil has no addictive potential in drug-naive healthy individuals. The results reported here indicate that modafinil has a behavioral profile clearly distinct from that of classical psychostimulant drugs and are in agreement with neurochemical (Duteil et al. 1990; Akaoka et al. 1991; De Sereville et al. 1994; Mignot et al. 1994; Ferraro et al. 1997) and clinical studies (Jasinski 2000) suggesting that modafinil is not an amphetamine-like agent.

Conversely to classical psychostimulant drugs, modafinil did not interact with the reinforcing and incentive properties of cocaine. This observation is in apparent disagreement with the study of Gold and Balster (1996) showing that modafinil can act as a substitute for self-administered cocaine in monkeys and generalizes to cocaine discriminative effects in rats. It can be proposed that modafinil would not be able to modify the effects of cocaine but would be able to act as an incentive in the absence of the drug. Gold and Balster (1996) tested the effects of modafinil in drug-free animals, while we tested them in the presence of cocaine. This explanation is supported by Jasinski (2000) who showed that modafinil produces pleasurable effects, but has a very low addictive potential in drug-experienced humans. It is also supported by our own observation that modafinil (64 mg/kg) may itself produce a weak reinstatement of self-administration behavior.

Although modafinil did not induce place preference, the doses of modafinil studied were behaviorally active. Indeed, during the conditioning phase, the 128 mg/kg dose of modafinil induced a locomotor activation but did not induce any preference for the drug-paired compartment. On the contrary, amphetamine induces both place conditioning and locomotor activation. Modafinil is one of the rare psychomotor stimulants that do not possess rewarding and reinforcing effects. This dissociation of effects does not support the "psychomotor stimulant theory of addiction" (Wise and Bozarth 1987), which suggests that a compound possessing psychomotor stimulant properties should be addictive.

During the acquisition phase for modafinil self-administration, and whatever the dose tested, the number of self-injections decreased over days, and rats never discriminated between active and inactive holes. Increases in ratio requirement were not followed by a compensatory increase in responding, with the number of injections reaching almost zero at the highest ratio. As expected for cocaine-induced self-administration, an increase in ratio resulted in a parallel increase in responding.

As previously shown for heroin (Martin et al. 1996) and cocaine (Deroche et al. 1999) self-administration, the within-session dose–response paradigm is particularly useful for testing sensitivity to the reinforcing effects of the drug. Thus, dose–response curves for cocaine self-administration obtained with a within- or a between-session protocol are sensitive to the same pharmacological treatments. Pretreatment with the indirect dopamine agonist amphetamine induced a leftward shift of the dose–response curve for cocaine self-administration. In parallel, haloperidol, an antagonist of the D1/D2 dopamine receptors known to decrease the reinforcing effects of cocaine (Roberts and Vickers 1984), induced a rightward shift. On the contrary, and whatever the direction, modafinil was unable to modify the dose–response curve for cocaine self-administration. Similarly, a subchronic treatment with modafinil was not able to modify cocaine intake (1 mg/kg per injection) maintained at FR5. Modafinil did not modify the motivation to self-administer cocaine either, as shown by the lack of effects of the subchronic treatment on the progressive ratio schedule.

According to the literature (Deroche et al. 1999; Schenk and Partridge 1999), noncontingent injections of cocaine reinstated cocaine self-administration behavior in a dose-dependent manner. The tested dose of modafinil did not modify cocaine-induced reinstatement. However, pretreatment with modafinil did modify responding in response to saline infusion. Whatever the volume tested, noncontingent injections of saline did not induce reinstatement in vehicle-pretreated animals. In modafinil-pretreated animals, the two lower volumes of saline induced reinstatement. It could be proposed that modafinil acts as an incentive in cocaine-experienced rats. However, this effect would be weak since modafinil did not modify responding to the lower doses of cocaine.

Although modafinil shares the awakening and locomotor activating effects of classical psychostimulants, it does not seem to have reinforcing properties on its own or to interact with the reinforcing properties of psychostimulants. Differences in the neurochemical targets of these compounds could explain these behavioral differences. Thus, it has been shown that modafinil and am-

phetamine produce differential patterns of c-Fos brain activation (Engber et al. 1998). It is largely admitted that the classical psychostimulant drugs exert their reinforcing effects by activating the mesolimbic dopamine pathway (for review, see Le Moal and Simon 1991). Although recent studies using pathological models showed that modafinil-induced wakefulness could depend on dopamine activation (Wisor et al. 2001), several observations suggest that, in physiological conditions, modafinil would not interact with this system. In vivo voltammetry and microdialysis studies have shown that, in the range of doses tested in the present study, modafinil does not increase dopamine release in the caudate nucleus in mice (De Sereville et al. 1994) and in the nucleus accumbens in rats (Ferraro et al. 1997). In the same way, modafinil does not modify the electric activity of mesencephalic dopaminergic neurons (Akaoka et al. 1991). Furthermore, the D1/D2 dopamine antagonist haloperidol does not block the arousal effects of modafinil while it consistently decreases the amphetamine-induced increase in arousal (Lin et al. 1992). These observations are in agreement with a study which reported that modafinil showed a low affinity for dopamine re-uptake sites (Mignot et al. 1994). Although the precise neurochemical targets of the arousal effects of modafinil remain unclear, it has been proposed that modafinil effects could implicate the noradrenergic transmission. The arousal (Lin et al. 1992) and locomotor effects (Duteil et al. 1990) produced by modafinil are blocked by α1 adrenergic receptor antagonists. This effect would imply a direct interaction between the drug and adrenergic receptors. Thus, a depletion of the noradrenaline pool by α-methyl-*p*-tyrosine alters the modafinil-induced arousal effects (Lin et al. 1992) and modafinil affects the electrical activity of locus coeruleus noradrenergic neurons (Akaoka et al. 1991).

In conclusion, our results indicate that modafinil is not a typical psychostimulant drug and does not possess reinforcing or addictive properties in cocaine-naive rats.

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