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Improvement of learning processes following chronic systemic administration of modafinil in mice

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Abstract

This study was aimed at determining the effects of a chronic modafinil intraperitoneal administration on the rate of learning in a series of five serial spatial discrimination reversals (SSDR) in a T-maze. Results showed that a daily modafinil administration at 64 mg/kg but not at 32 mg/kg induced a faster learning rate as compared to controls. This learning improvement in experimental mice was due to the faster emergence of a win-stay rule over days of testing. In contrast, a second experiment showed that the same modafinil treatment had no significant effect on contingently reinforced alternation rates over five successive days of testing, as compared to controls. Thus, the results show that modafinil spared the ability to shift responses over trials and consequently, that the use of the win-stay rule to solve the SSDR task observed in modafinil-treated animals is due to an improvement of learning processes.

Keywords: Alternation; Cognitive learning set; Modafinil; Learning processes

1. Introduction

Modafinil (diphenyl-methyl)sulphinil-2-acetamide) is a wake-promoting drug, which is effective in the treatment of narcolepsy and idiopathic hypersomnia (Bastuji and Jouvet, 1988). Several studies have shown that modafinil has an agonistic action on the alpha 1-adrenergic postsynaptic receptors (Lin et al., 1992), and an antagonistic action on the glutamatergic receptors (Lagarde et al., 1996). Modafinil also reduced the release of extracellular GABA, which decreases GABA-ergic transmission (Piérard et al., 1997). Modafinil therefore modifies glutamatergic and GABA-ergic activities and their interaction (Piérard et al., 1995; Ferraro et al., 1997; Perez de la Mora et al., 1999).

The effects of modafinil on memory processes have not yet been extensively studied, either in humans or animals. To date, only three studies have observed an improvement of short-term memory functions in humans following modafinil intake, but in subjects suffering from severe sleep apnea syndrome (Arnulf et al., 1997) or chronic alcoholism (Saletu et al., 1993). In animals, one study showed that modafinil increases performance in operant conditioning tasks but this improvement was due to a facilitation of sensorimotor processes (Bizot, 1998). 2-DG autoradiography (Engberg et al., 1998), EEG power spectral analysis (Seban et al., 1999), and functional magnetic resonance imaging (Ellis et al., 1999) studies have shown that modafinil substantially modifies the activity of brain areas such as the hippocampus and the prefrontal cortex. Because of the involvement of these two brain areas in learning processes and memory functions (Thomas, 1984; Winocur, 1992), we studied in previous experiments the effects of an acute modafinil administration on an "episodic working" memory task involving spatial information, and showed that modafinil slowed down the forgetting rates as compared to controls in mice, without modifying exploratory activity or anxiogenic reactivity in an hole-board apparatus (Béracochéa et al., 2000).

The aims of the present experiments were to investigate learning processes in normal (not sleep deprived) mice

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following modafinil administration. For that purpose, we analyze the effects of modafinil in a serial spatial discrimination reversal (SSDR) task realized in a T-maze. Indeed, we already showed that normal mice exhibited in this task a substantial improvement of performance over days of testing and that this phenomenon would be the result of an incremental learning process, based on the detection of invariances throughout successive discriminations (Krazem et al., 1995; Borde and Béracochéa, 1999). In the present study, two experiments were designed: in the first one, the effects of chronic modafinil administration on the speed of learning the SSDR task were investigated; in the second experiment, we investigated the effects of the same modafinil treatment on a series of contingently reinforced alternation run in the same T-maze as the one used in the SSDR task. Reinforced alternation has been widely used to study spatial working memory in rodents (Thomas, 1984) and involves the ability to shift responses over successive trials. Thus, this second experiment allowed us to ensure that the ability to shift response functions normally in modafinil-treated mice, in so far as the SSDR task also requires the subjects to shift from session to session the choice of the arm rewarded the day before.

2. Methods

2.1. Animals

The study was conducted using male mice of the Black 6 Jico C57 strain obtained at 6 weeks of age from Iffa-Credo, Lyon, France. On arrival, mice were housed collectively in colony cages (40 cm long×25 cm high×20 cm wide), matched for weight, and placed in an animal room (ambient temperature: 22 °C; automatic light cycle: 08:00 and 20:00 h) with free access to food and water. They remained in collective cages for at least 16 weeks. In all cases, at least 2 weeks before behavioral testing began, mice were housed in individual cages, with free access to food and water.

2.2. Apparatus

All tests were carried out in a T-maze constructed of gray Plexiglas. Stem and arms were 35 cm long, 10 cm wide, and 25 cm high. The start box (10×12 cm) was separated from the stem by a horizontal sliding door. Horizontal sliding doors were also placed at the entrance of each arm. A low-intensity diffuse illumination (10 lx) was provided above the apparatus.

2.3. Procedure

Both in the SSDR and in the alternation tasks, mice were handled for 10 min/day over three consecutive days before testing began. They were then submitted to a food deprivation schedule initiated over four consecutive days so that, at the time of training, the mice weighed 86–90% of their initial free-feeding weights. Food ration was adjusted individually in order to maintain the same level of deprivation throughout the ensuing experimental period.

2.4. Habituation

Habituation was carried out over the fourth day of deprivation. All animals were allowed 10 min of free exploration of the apparatus in order to familiarize them with the experimental conditions. Food reward was available or given during this free-exploration session (BIO-SERV pellets, 20 mg) to ensure that each animal learned to go to the end of the maze arms in order to obtain it.

2.5. SSDR task

As described in Fig. 1 (upper part), the formal testing was composed of a learning phase including different phases: an acquisition phase (Day 1) followed by a series of four reversal sessions (Days 2–5).

The acquisition session (Day 1) consisted of a succession of trials On each trial, the mouse was placed in the start box, and 20 s later, the door of the box was opened. When the animal entered one of the two arms, the door of that arm was closed. After a 20-s confinement in the chosen arm, the mouse was removed and placed again in the start box for the next trial. For each trial, the chosen arm and the time that elapsed between the opening of the door of the start box and the closing of the door of the chosen arm (running time) were recorded. For each mouse, the baited arm selected on Day 1 was its ‘‘nonpreferred’’ arm during the habituation (i.e., the opposite arm to the one that the animal had chosen first). The acquisition session was continued until the subject reached the criterion of four correct responses out of four consecutive trials.

Following acquisition, daily reversal sessions took place over four consecutive days during which the baited arm was reversed from day to day. Each reversal session was pursued until the animal achieved the same criterion of four consecutive errorless trials.

Two additional ‘‘retention’’ trials were given at the end of each session (see Fig. 1, lower part): one trial 5 min and one trial 24 h after the criterion was met. In this case, the 24-h retention trial of each learning session, in fact, constituted the first trial of the following session. In this case, the reward was immediately placed into the goal arm opposite to the one baited the day before; the animal was not aware of this change, so that it continued to respond at the first trial according to the last discrimination acquired.

This behavioral paradigm enabled us to measure: (i) the rate of acquisition of the initial spatial discrimination (Day 1), (ii) the performance on the first reversal session (Day 2), (iii) the performance savings over successive daily sessions (from Days 1 to 5), and (iv) the rate of forgetting of each

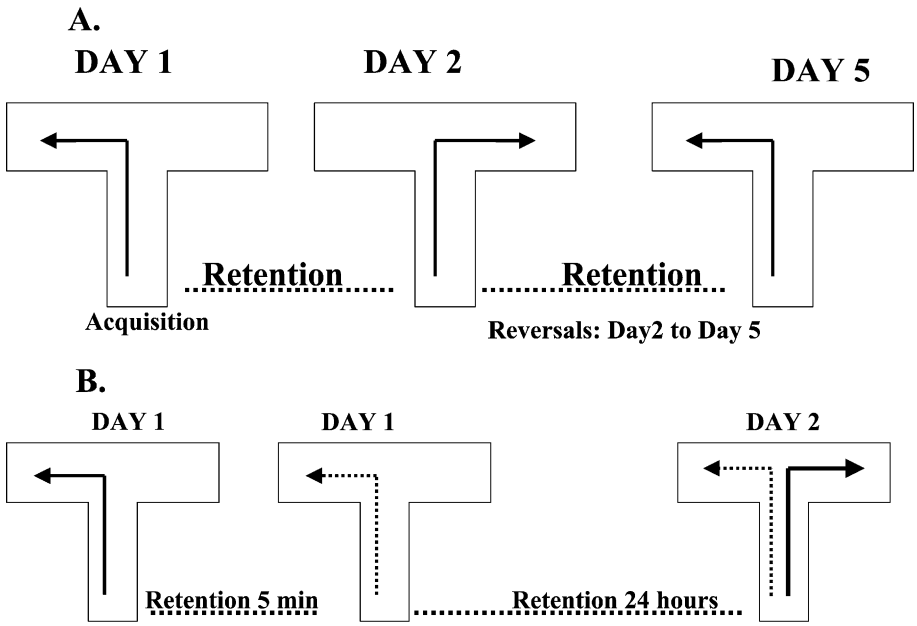

Fig. 1. (A) Learning phase: Learning sessions consisted of an initial acquisition session (Day 1) followed by four reversal sessions (Days 2–5). The four reversal sessions (Days 2–5) were given at 24-h intervals. Solid arrows indicate the correct response for each session. (B) Memory: Two single retention test trials were given at 5 min and 24 h after the end of each learning session (Day 1 in the example). In this way, the 24-h test trial (Day 2 in the example) constituted the first trial of the following learning session. Broken arrows depict the correct response for each retention test trial.

daily discrimination over a 24-h period. This behavioral design is summarized in Fig. 1.

2.6. Alternation task

All subjects were given daily sessions of six successive trials separated by a 5-s intertrial interval. To begin a trial, the subject was placed in the start box for 5 s before the door to the stem was opened. When the subject entered one of the arms, the door to that arm was closed. The chosen arm and the time that elapsed between opening the door and choosing the arm (choice latency) were registered. Following a 30-s confinement period in the chosen arm, the subject was removed and placed in the start box for a new trial. Visible traces of urine and feces were removed from the stem and arms between trials. In the alternation procedure used, the subjects were always rewarded (one food pellet) on the first trial of each session, but thereafter, they were rewarded only for alternation. When an error was made, food remained available in the opposite goal arm, so that the subjects correct themselves on the subsequent trial. The alternation task lasted five successive days.

The SSDR task and the contingently reinforced alternation task were run using independent groups.

2.7. Modafinil administration

The effects of modafinil on performance were studied by giving the subjects a single modafinil injection 30 min before testing began, each day of testing, both in the SSDR and in the alternation tasks. Independent groups of mice were used. In all experiments, subjects were 17–20-week-old mice at the time of testing. In both the SSDR and the alternation tasks, the animals were submitted to two conditions: a vehicle group that received an gum arabic solution (n=10) and two modafinil groups (M32: 32 mg/kg, n=10 and M64: 64 mg/kg, n=10). The choice of these two doses was based on previous studies showing that these doses of modafinil induced delay-dependent improvement of performance in a working memory task (Béracochéa et al., 2000).

In all experiments, modafinil was suspended in a 0.5% gum arabic solution and administered intraperitoneally (0.1 ml/10 g of mouse). Behavioral testing started 30 min after modafinil or vehicle injections.

2.8. Data analysis

In the SSDR task, the results are expressed either as the number of trials necessary to reach criterion (learning) or as the percentage of correct responses (retention). In the alternation task, results are expressed in percentage of correct choices. Two-way analysis of variance (ANOVA) with one repeated measure (either days of testing or retention intervals) were performed to assess the effects of several treatments on the animal's performance. Differences between groups were analyzed by factorial ANOVA.

2.9. Ethical statement

All pharmacological and experimental procedures were in accordance with official French Regulations for the Care and Use of Laboratory Animals.

3. Results

3.1. Experiment 1: Effects of modafinil on the SSDR task

3.1.1. Rate of forgetting

Analysis of performances on trials delivered either 5 min or 24 h after the criterion was met over the five successive sessions showed no significant between-groups differences on both delay intervals ($F<1$); the performance accuracy declines from the 5-min retention trials (92.0%, 88.0%, and 90.0% correct responses rates for M64, M32, and control subjects, respectively) to the 24-h retention trials (86.0%, 78.0%, and 84.0% correct responses rates for M64, M32, and control subjects, respectively, but the rate of forgetting was not significantly different among the groups [Groups×Retention Intervals: $F(2,27)=0.78$].

3.1.2. Acquisition (Day 1)

During Day 1 of testing (first discrimination), the number of trials required to reach the criterion was not significantly different among the groups [groups: $F(2,27)=0.73$].

3.1.3. First reversal (Day 2)

An overall analysis showed a significant between-groups differences on Day 2 of testing [first reversal: groups: $F(2,27)=7.6$, $P<.005$] but no significant interaction was found between groups and days (Days 1 and 2) of testing [Group×Days: $F(2,27)=2.23$, $P=.07$].

3.1.4. Performance saving over days (from Days 1 to 5)

Results are summarized in Fig. 2A. A global analysis showed that the number of trials necessary to reach the criterion decreased significantly over days of testing [days: $F(4,108)=262.8$, $P<.0001$]. The rate of learning over days was significantly different for all groups [Groups×Days: $F(8,108)=9.5$, $P<.0001$] and a between-groups difference was also observed [groups: $F(2,27)=64.5$, $P<.0001$]. This was due to scores exhibited by M64 mice whose learning rates were significantly faster over days of testing as compared to controls [$F(4,72)=4.2$, $P=.003$] whereas the M32 group exhibited a normal learning rate [$F(4,72)<1.0$].

An analysis carried out on the first five reacquisition trials (from the second to the sixth trial) of each reversal session showed that modafinil-treated mice developed more rapidly than controls a tendency to choose more often the arm baited during the ongoing session (win-stay strategy) [$F(8,108)=4.9$, $P=.001$]. Such a win-stay strategy was mainly observed in the M64 group ($P<.001$) but not in the M32 group ($P>.05$) as compared to controls (see Fig. 2B).

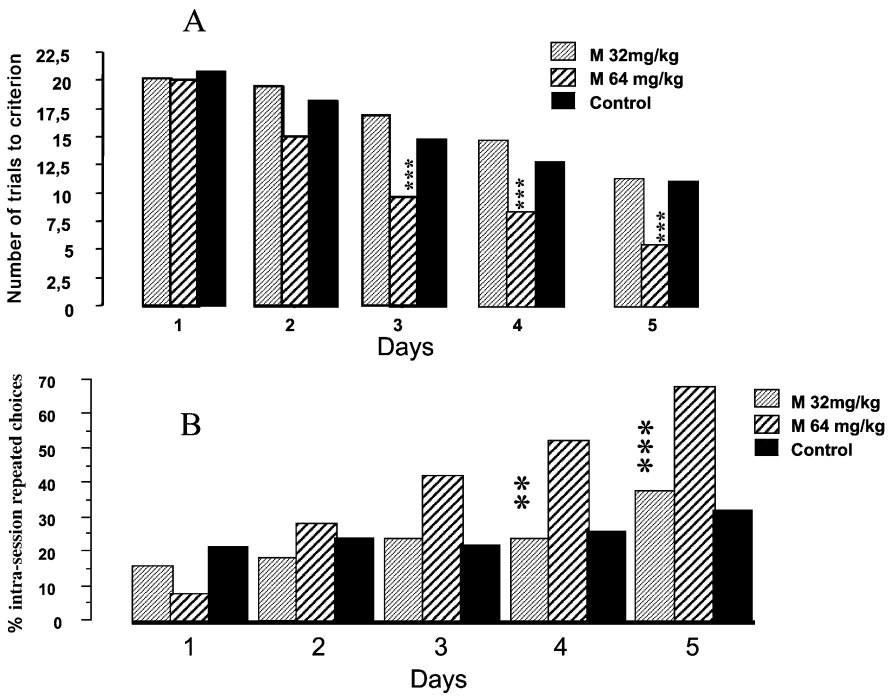

Fig. 2. (A) Mean number of trials required to master the criterion (four successive errorless trials) over the 5 days of testing in modafinil-treated mice and controls, $^{**}P<.02$. (B) Percentage of intra-session repeated choices in modafinil and control subjects over the 5 days of testing. As can be seen, M64-treated mice progressively developed a significant tendency to repeat intra-session choices as compared to the two other groups, $^{**}P<.02$; $^{***}P<.001$ as compared to the two other groups.

3.2. Experiment 2: Effects of modafinil on contingently reinforced alternation

There was a significant increase of alternation rates over days of testing [days: $F(4,108)=16.0$, $P<.0001$]. The mean alternation rates over the 5 days of testing was similar in all groups (88±1.2%, 88±1.6%, and 92±2.8% for controls, M32, and M64, respectively) [groups: $F(2,27)<1.0$] and the evolution of performance across days of testing was also similar in all groups [Groups×Days: $F(8,108)=0.52$].

Modafinil-treated animals exhibited shortest running latencies as compared to controls (12.7, 14.0, and 17.7 s for M64, M32, and controls, respectively), but these differences were not statistically significant [$F(2,27)=1.6$, $P=.21$].

4. General discussion

As compared to controls, chronic modafinil administration at 64 mg/kg but not at 32 mg/kg induced behavioral changes in the SSDR task. More specifically, modafinil-treated subjects required fewer trials than controls to master the criterion over days of testing and the rate of learning was also faster. In contrast, the rate of forgetting over a 24-h retention interval was normal. Modafinil-treated mice also exhibit normal alternation behavior in a contingently reinforced procedure.

Analysis of the results showed that the improvement of the rate of learning in the SSDR task with the highest modafinil dose is due to the rapid emergence of a ''win-stay'' strategy. Indeed, the analysis performed on the six first trials of the reversal sessions showed that modafinil-treated animals emitted less frequently than controls the response learned the day before, in spite of normal long-term (24 h) memory; in contrast, they developed a tendency to enter more frequently the arm baited during the ongoing session, a strategy that requires only to make a simple association between a specific body-turn and the reward location in the maze, regardless the association learned the day before.

One could argue that the development of the win-stay strategy in the M64 group is the consequence of a deleterious effect of the chronic modafinil administration on win-shift abilities. In this perspective, modafinil would induce sensorimotor impairments leading to an enhancement of perseveration response. Two arguments rule out such a hypothesis. Firstly, if it was the case, modafinil-treated subjects should also exhibit an *intersession* perseveration tendency, given the fact that they have normal long-term (24 h) memory, which is not observed. Secondly, as shown in the contingently reinforced alternation task, modafinil did not impair alternation (win-shift) abilities that function normally in experimental mice. Interestingly, previous studies from our group have shown that the development of such a win-stay strategy is also observed in normal mice, but it required additional days of training to appears, the use of such an egocentric strategy reducing the difficulty of the task that can be solved therefore more automatically than by using more complex spatial associations (Krazem et al., 1995).

It has been shown that the SSDR task is importantly sustained by the activity of the cingulate cortex. Indeed, damage of the anterior but not of the posterior cingulate cortex impaired the learning of the SSDR task (Meunier et al., 1991); interestingly, the anterior cingulate cortex receives anatomical inputs from the mediodorsal thalamus (Meunier, 1988), which when damaged also produced similar impairments in the SSDR task (Krazem et al., 1995). These findings are congruent with both clinical studies showing that in humans, frontal lobe pathology dramatically impaired reversal learning (Oscar-Bermann and Zola-Morgan, 1987; Schacter, 1987) and with experimental studies in animals showing impairments in reversal discrimination tasks following mediodorsal thalamic (Slotnick and Kaneto, 1981; Kolb et al., 1982; Staubli et al., 1987) or frontal cortical lesions (Kolb, 1984; Winocur, 1992). The improvement in the SSDR task induced by the modafinil administration may be due to its effects on brain structures involved in the arousal or in the sleep–wakefulness cycle (Lagarde et al., 1995; Lin et al., 1996; Engberg et al., 1998; Lin et al., 2000; Scammell et al., 2000) but also more specifically on brain structures involved in memory processes and cognitive flexibility. Thus, it has been shown that modafinil increases the number of Fos-immunoreactive neurons in the cingulate cortex of treated rats (Scammell et al., 2000), a brain area that, as mentioned above, is critically involved in the SSDR task and reversal learning.

It is of interest to observe that in our experiments modafinil improves the SSDR task but does not modify the alternation one. The lack of effects of modafinil in the alternation task is surprising, in so far as the sequential procedure used in our study also involves behavioral flexibility. In the present study, trials in the alternation procedure were separated only by a short (5 s) intertrial interval. The 5-s intertrial interval induced high levels of alternation rates preventing therefore the possibility to observe any improvement of performance following modafinil administration (ceiling effect). Interestingly, we already showed that the M64 dose produced an improvement of working memory in an alternation task at long (60 and 180 s) but not at short (5 s) intertrial intervals (Béracochéa et al., 2000). These previous findings are congruent with the enhancing effect of modafinil presently observed in the SSDR task. However, these previous data showed that modafinil slowed down the forgetting rates in the alternation task, whereas in the present study modafinil did not influence the rate of forgetting in the SSDR task. The differential effects of modafinil on forgetting rates may be due to the different forms of memory involved in the two tasks. Indeed, the sequential alternation procedure involved an ''episodic working'' memory component, requiring from trials to trials resetting mechanisms on a short-term span. In the SSDR task, each daily discrimination implies a long-term reference memory, which is based on the use of invariant visuospatial

information. It is possible that modafinil does not interact with well learned information as suggested by findings showing that well learned rules are less sensitive to changes in individual neurotransmitter systems than other forms of memory (Sarter, 1990).

In conclusion, the whole set of data of the present study demonstrates that modafinil administration facilitates the emergence of a cognitive skill involving a win-stay response patterning, and that this improvement of learning is not due to an impairment of the ability to shift responses from trials to trials.

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