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Short Communication

Effects of post-training modafinil administration in a discriminative avoidance task in mice

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†In memoriam.

Keywords: anxiety; locomotion; memory consolidation; mice; modafinil

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Objective: Although the cognitive-enhancing abilities after modafinil have been demonstrated, its effects on memory consolidation remain overlooked. We investigated the effects of repeated modafinil administration on consolidation of a discriminative avoidance task.
Methods: Mice were trained in the plus-maze discriminative avoidance task. After training, mice received intraperitonial modafinil (doses of 32, 64 or 128 mg/kg). Animals were treated for more 9 consecutive days; 30 min after the last injection, testing was performed. In addition, the effects of 32 mg/kg modafinil on consolidation at different time points were examined.
Results: The smaller dose of modafinil (32 mg/kg) impaired memory consolidation, without modifying anxiety or locomotion. Still, modafinil post-training administration at 1 or 2 h impaired memory persistence.
Conclusions: Modafinil impaired memory consolidation in a dose- and time-dependent fashion.

Significant outcomes

- Repeated administration of 32 mg/kg (but not 64 or 128 mg/kg) modafinil impaired consolidation of a discriminative avoidance task in mice.
- Modafinil, at the dose of 32 mg/kg, impaired memory persistence when given 1 or 2 h after training.
- The memory impairment was not accompanied by anxiety alterations.

Limitations

- The effects of pre-test administration of modafinil may have influenced performance during testing; later post-training time points intervals were not evaluated.

Introduction

Modafinil is a psychostimulant that acts as a wake-promoting drug and has been approved unanimously for the treatment of excessive daytime sleepiness in narcolepsy and, in some European countries and in the United States of America, for obstructive sleep apnea, and shift work syndrome. Clinical studies have pointed modafinil positive effects when used to treat Parkinson's disease (1), multiple sclerosis (2),

schizophrenia (3) and attention deficit hyperactivity disorder (4). In addition, modafinil seems to be widely prescribed off-label to enhance alertness, attention, memory for dementia and depression (5). Of note, an illicit market exists for academic doping as well (6).

It has been demonstrated that modafinil alters the activity of brain areas involved with memory, such as the hippocampus and prefrontal cortex (7). Within this context, studies indicate that modafinil has cognitive-enhancing abilities in rodents performing a variety of learning/memory exercises in the T-maze based on spontaneous alternation behavior (8), and also enhanced learning (7).

Concerning its repeated administration, modafinil was reported to improve learning (9). Although many studies have reported cognitive-enhancing abilities of this wake-promoting drug (10), the possible facilitative effects of modafinil on memory have been overlooked when memory consolidation was specifically investigated. In this way, a study conducted by Shuman et al. (10) reported that the administration of modafinil immediately after training had no effects on either cued or contextual fear paradigms. In contrast, we have recently demonstrated that the post-training acute administration of modafinil impaired memory consolidation in mice subjected to the plus-maze discriminative avoidance task (11).

Aims of the study

The investigation of the effects of the post-training administration of modafinil on the plus-maze discriminative avoidance task can be interesting because this animal model can concurrently evaluate learning and memory, anxiety and locomotion (12–17). The present findings provide evidence of potential amnestic proprieties of modafinil when repeatedly administered or administrated in distinct time points after training.

Material and methods

Subjects

Three month-old Swiss EPM-M1 male mice (outbred, raised and maintained in the Center for Development of Experimental Models in Medicine and Biology of the Universidade Federal de São Paulo) were used. Animals weighing 30–35 g were housed under controlled temperature (22–23°C) and lighting (12 h light, 12 h dark; lights on at 06:45 a.m.) conditions. Food and water were available *ad libitum* throughout the experiments. Animals used in this study were maintained in accordance with the National Institute of Health Guide for the care and use of laboratory animals (NIH Publications N° 8023), revised 2011. The Institutional Ethical Committee of UNIFESP approved the experimental procedures under protocol #1162/08.

Drug

Modafinil (Cephalon®) was dissolved in 0.5% Arabic gum and intraperitoneally (i.p.) administered in a volume of 10 ml/kg body weight at doses of 32, 64 or 128 mg/kg. Modafinil vehicle was used as the control solution and administered i.p. This dose range was selected based on previous work of our group (11,18).

Plus-maze discriminative avoidance task

The apparatus employed was a modified elevated plus-maze, made of wood, containing two enclosed arms with sidewalls and no top (28.5 × 7 × 14 cm, 03 lx at the floor level), opposite to two open arms (28.5 × 7 cm, 9 lx at the floor level). A 100-W lamp was placed exactly over the middle of one of the enclosed arms (aversive enclosed arm, 660 lx at the floor level). In the training, each mouse was placed in the centre of the apparatus and, over a period of 10 min, every time the animal entered the enclosed arm containing the lamp, an aversive situation was produced until the animal left the arm. The aversive stimuli were the 100-W light and a cold air blow produced by a hair dryer placed over the aversive enclosed arm. In the testing (performed in the same room with the observer in the same position), the mice were again placed in the centre of the apparatus and observed for 3 min without receiving the aversive stimulation. In all experiments, the animals were observed in a random order and in a blind manner, and the apparatus was cleaned with a 5% alcohol solution after each behavioural session.

The total number of entries into any of the arms (an entry was defined as the entry of all four paws into one arm), percent time spent in the aversive enclosed arm (time spent in aversive enclosed arm/time spent in both enclosed arms) and percent time spent in the open arms (time spent in open arms/time spent in both open and enclosed arms) were calculated. Learning and memory were evaluated by the percent time spent in the aversive enclosed arm during the training and testing sessions, respectively. Anxiety-like behavior was evaluated by the percent time spent in the open arms of the apparatus. Total number of entries into any of the arms was used to evaluate motor activity.

Experimental design

Experiment I Effects of repeated modafinil administration on consolidation in mice submitted to the plus-maze discriminative avoidance task.

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A total of 48 animals were randomly assigned to one of the following groups: vehicle (VEH, $n = 12$), 32 mg/kg modafinil (MOD32, $n = 12$), 64 mg/kg modafinil (MOD64, $n = 12$) or 128 mg/kg modafinil (MOD128, $n = 12$). Mice were trained in the plus-maze discriminative avoidance task. Immediately after, they received an acute i.p. injection of vehicle or modafinil at the different doses. Mice also received nine subsequent daily injections of vehicle or different modafinil doses; 30 min after the last injection (10th day after training), animals were submitted to testing.

Experiment II Effects of 32 mg/Kg modafinil administered in specific intervals after training in mice submitted to the plus-maze discriminative avoidance task.

A total of 50 mice were trained in the plus-maze discriminative avoidance task. After being trained, they were allocated into five groups ($n = 10$), which received 32 mg/kg MOD at different time points (1, 2, 3 or 6 h after training). Vehicle group (VEH) received i.p. vehicle injections at all the time points; MOD groups received MOD 1, 2, 3 or 6 h after training and vehicle injections at all the remaining time points; 10 days after training the testing was performed.

Statistical analysis

Total number of entries in any of the arms, percent time spent in the aversive enclosed arm (time spent in aversive enclosed arm/time spent in both enclosed arms), and percent time spent in open arms (time spent in open arms/time spent in both open and enclosed arms) were calculated and compared by the analysis of variance (ANOVA) and Tukey's test. Significance was accepted at p values below 0.05.

Results

Experiment I Effects of repeated modafinil administration on consolidation in mice submitted to the plus-maze discriminative avoidance task.

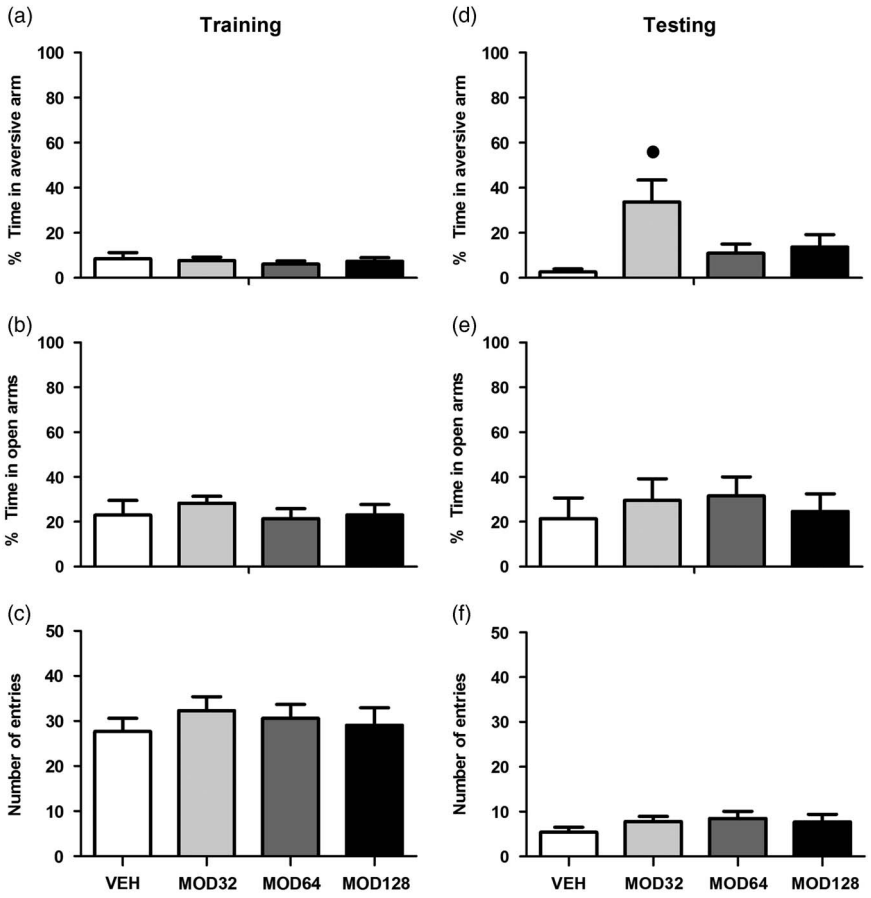

Fig. 1. Effects of repeated post-training modafinil administration on memory of mice subjected to the plus-maze discriminative avoidance task. Mice were trained in the plus-maze discriminative avoidance task without receiving any experimental manipulation. Immediately after training, mice were intraperitoneally treated with vehicle (VEH, $n = 12$) or modafinil at the doses of 32 (MOD32, $n = 12$), 64 (MOD64, $n = 12$) or 128 mg/kg (MOD128) for 10 consecutive days. Results are presented as the mean ± SE of percent time spent in the aversive enclosed arm in the training (a) and testing (d), percent time spent in the open arms in the training (b) and testing (e) and number of entries in the training (c) and testing (f). ● $p < 0.05$ compared with the other groups (analysis of variance and Tukey's test).

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During the training, the ANOVA for time spent in the aversive enclosed arm did not reveal any statically significant differences among the groups [$F(3,44) = 0.35$; $p > 0.05$] (Fig. 1a), demonstrating similar basal learning of the task. In addition, ANOVA did not reveal significant differences among the groups regarding the percent time spent in the open arms [$F(3,44) = 0.42$; $p > 0.05$] (Fig. 1b) or the number of entries [$F(3,44) = 0.53$; $p > 0.05$] (Fig. 1c), as expected.

During testing, the ANOVA followed by Tukey's test showed that mice repeatedly treated with 32 mg/kg modafinil (the MOD32 group) displayed an increased percent time in the aversive enclosed arm compared with mice treated with vehicle or with the higher doses of modafinil (the VEH, MOD64 and MOD128 groups) [$F(3,44) = 3.61$; $p < 0.05$] (Fig. 1d). Finally, ANOVA did not reveal any significant differences in the percent time spent in the open arms [$F(3,44) = 0.29$; $p > 0.05$] (Fig. 1e) or in the total number of entries [$F(3,44) = 0.80$; $p < 0.05$] (Fig. 1f).

Experiment II Effects of 32 mg/Kg modafinil administered in specific intervals after training in mice submitted to the plus-maze discriminative avoidance task.

Data from the training demonstrated that there were no significant differences in the basal performance of the different groups. Indeed, ANOVA did not reveal significant effects for the percent time spent in the aversive enclosed arm, time spent in the open arms and total number of entries in the training session (Figs 2a, b and c).

In the testing, ANOVA for percent time spent in the aversive enclosed arm revealed significant effects

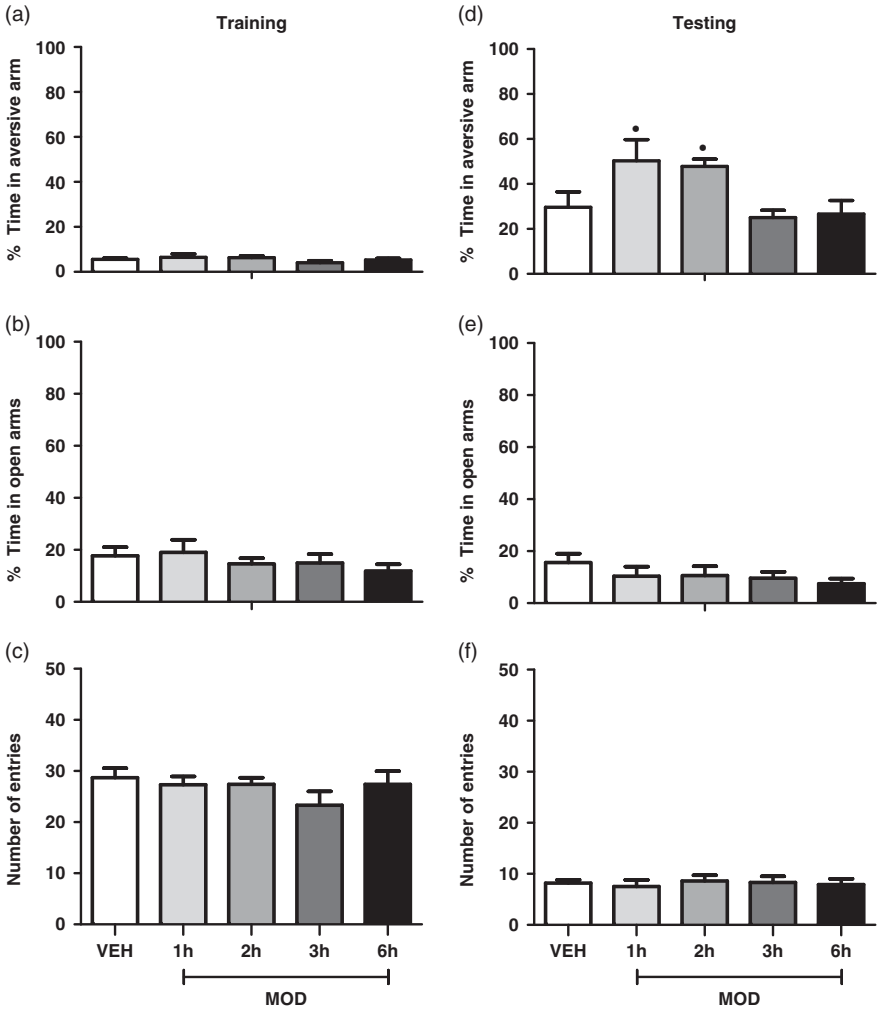

Fig. 2. Effects of 32 mg/kg modafinil administration on memory consolidation at different time points of mice subjected to the plus-maze discriminative avoidance task. Mice were trained in the plus-maze discriminative avoidance task without receiving any experimental manipulation. After training, mice were intraperitoneally treated with vehicle (VEH, $n = 10$) or modafinil at 1- ($n = 10$), 2- ($n = 10$), 3- ($n = 10$) or 6-h interval ($n = 10$). Results are presented as the mean ± SE of percent time spent in the aversive enclosed arm in the training (a) and testing (d), percent time spent in the open arms in the training (b) and testing (e) and number of entries in the training (c) and testing (f). ● $p < 0.05$ compared with the other groups (analysis of variance and Tukey's test). MOD, modafinil.

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of treatment [$F(4,45) = 3.83$; $p = 0.009$]. Tukey's *post-hoc* demonstrated that mice treated with 32 mg/Kg MOD, 1 or 2 h after training, presented an enhancement on this parameter compared with the other groups (Fig. 2d).

When the percent time spent in the open arms and the number of entries of the testing were analysed, ANOVA did not reveal significant effect of treatment on both parameters (Figs 2e and f, respectively).

Discussion

Here, we verified that when repeatedly administered, 32 mg/kg (but not 64 or 128 mg/kg) modafinil induced amnesia in a discriminative avoidance task in mice. Such impairment was not followed by modification in anxiety or motor activity. In addition, we demonstrated that this dose of modafinil promoted consolidation deficits when administered 1 or 2 h after training (but not 3 or 6 h).

Several behavioural changes can influence the processes of acquisition, processing, storage and retrieval of various memory systems. In this scenario, the plus-maze discriminative avoidance task is a behavioural model able to evaluate the interactions among these mnemonic processes, anxiety and locomotor activity in rodents in an integrative and concomitant manner. In this paradigm, learning can be assessed by the magnitude of the discrimination of both enclosed arms (12). The storage of the task (and, consequently, the processes of consolidation and recall) is detected in the testing by the percent time in the aversive enclosed arm. In this context, the avoidance of the aversive enclosed arm upon testing has been validated as a measurement of retention, because amnestic manipulations decrease this effect (12–15). In contrast, memory-improving treatments increase this effect (16,17). Furthermore, this behavioural model allows simultaneous and independent assessment of anxiety levels (through the avoidance of the open arms of the apparatus) and locomotor activity (through the number of entries in all arms of the apparatus). Thus, the model's effectiveness in detecting the effects of factors known anxiolytics (12) and anxiogenic (13) has been repeatedly demonstrated. In parallel, manipulations known to increase or decrease the locomotor activity were able to increase (12) or decrease (14,15) the total number of entries into the arms of the apparatus, respectively.

Previous study of our group (11) has demonstrated that post-training acute administration of 64 and 128 mg/kg modafinil promoted amnesia, since the animals treated with these doses presented an increased percent time spent in the aversive enclosed arm. Of note, in the present study, when modafinil was repeatedly given (10 consecutive days) such amnestic effect is no longer observed. Conversely, although post-training acute of 32 mg/kg modafinil was ineffective in promoting amnesia, the repeated administration of this dose impaired retention. These results indicate that the consolidation deficits induced by modafinil could be tolerated or sensitised depending on the dose (64 and 32 mg/kg, respectively). From the best of our knowledge, only the study of Shuman et al. (10) investigated the effects of modafinil on memory consolidation. In this way, these authors have reported that the acute modafinil administration was ineffective in modifying the consolidation of context- or cued-conditioned fear tasks in mice. These discrepant findings could lie on the memory tasks employed and the modafinil doses used in both studies (11).

Concerning the effects of repeated administration of modafinil on memory, Burgos et al. (19) showed that the repeated administration of 64 mg/kg modafinil before daily conditioning in rats induced different effects on learning depending on the type of task or the type of memory involved. These authors demonstrated that modafinil did not modify working memory but decreased long-term memory on the Olton 4 × 4 maze, that is, the drug can enhance memory on hippocampus-dependent tasks when chronically administered. On the other hand, the same treatment decreased successful responses in a complex operant conditioning task, suggesting that the repeated administration of the drug impaired a prefrontal cortex-dependent task. In line with that, Béracochéa et al. (9) showed that chronic modafinil administration daily before conditioning (at 64 mg/kg but not at 32 mg/kg) enhanced performance in the spatial discrimination reversals in a T-maze. Together, these studies demonstrated that the repeated treatment with modafinil can negatively or positively modulate memory depending on the task and the dose employed. Notwithstanding, both studies evaluated only the pre-training administration of modafinil.

One possible explanation that could be raised is that the consolidation process has critical time points after training in which the memory trace can become labile again (20–22) and can be modified. We designed experiment II to evaluate the effects of 32 mg/kg modafinil (which induced deficits in experiment I) on consolidation at different time points after the acquisition of the task. When administered 1 or 2 h after training, modafinil resulted in consolidation deficits, which were not detected when the administration occurred 3 or 6 h after training. Collectively, we have demonstrated that this specific modafinil dose did not induce any memory effects when administered immediately after training (11) but did impair memory persistence when administered 1–2 h after it. Indeed, most manipulations of consolidation are effective immediately after learning,

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even if they also have later effects. Within this context, Bekinschtein et al. (20) demonstrated that the protein-synthesis inhibitor, anisomycin, administered 12 h (but not 9 or 24 h) after training in the inhibitory-avoidance or contextual fear-conditioning tasks hindered memory 7 days after acquisition but left it intact at 2 days post-training, showing that there is a novel protein-synthesis-dependent phase in the rat hippocampus that is critical for the memory persistence. From the best of our knowledge this is the first study that demonstrated negative effects of modafinil on memory consolidation and that this deficits are critically influenced by the timing of the drug administration.

Concerning emotionality, we did not observe alterations on anxiety or locomotion. One could argue that modafinil should have increased motor activity in the testing, taking into account that animals received the last injection shortly before the exposure to the plus-maze discriminative avoidance task (PM-DAT). In fact, the acute administration of modafinil was able to promote an increase in the spontaneous activity of mice exposed to an open-field in a dose-dependent manner (18). A speculative explanation for these behavioural differences could be the interaction between the drug and the experimental environment. In other words, the aversive environment could be unfavourable for exploration as opposed to the open-field, a neutral environment. Thus, this environmental component could promote an inhibition of exploration, abolishing the hyperlocomotion effect of the drug.

It has been demonstrated that modafinil inhibits the dopamine transporter with exceptional selectivity (23). In addition, recent evidence indicates that modafinil increases extracellular dopamine in the rat (24), monkey (25) and human brain (26). Still, this drug can interfere with some critical component required for long-term potentiation in the prefrontal cortex, thereby altering neuroplastic capabilities (19). As hippocampal dopamine modulates long-term memory encoding and consolidation (27,28), it could be hypothesised that after modafinil administration, the dopamine-dependent mechanisms in the hippocampus that favour memory encoding early after training might be attenuated, thereby leading to memory deficits in the present emotional discriminative avoidance task.

Collectively, our data suggest that modafinil has potential amnestic effects depending on dose and duration of the treatment. These results points to the need of caution in the prescription of this drug.

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Conflicts of Interest

All authors disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organisations within 3 years of beginning the work that could inappropriately influence (bias) the present work.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guides on the care and use of laboratory animals.

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