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Research report

Individual differences are critical in determining modafinil-induced behavioral sensitization and cross-sensitization with methamphetamine in mice

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HIGHLIGHTS

- Behavioral sensitization to modafinil and methamphetamine was assessed in mice.
- There are important individual differences in sensitization to both drugs.
- Modafinil sensitization was clearly expressed only in a subgroup of mice.
- Expression of modafinil, but not methamphetamine, sensitization was context-dependent.
- Modafinil–methamphetamine cross-sensitization only occurred in a subgroup of mice.

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ABSTRACT

Modafinil is a non-amphetaminic psychostimulant used therapeutically for sleep and psychiatric disorders. However, some studies indicate that modafinil can have addictive properties. The present study examined whether modafinil can produce behavioral sensitization in mice, an experience and drug-dependent behavioral adaptation, and if individual differences play a role in this process. We further tested context-related factors and cross-sensitization between modafinil and methamphetamine. Important individual differences in the behavioral sensitization of Swiss Albino mice were observed after repeated administration of 50 mg/kg modafinil (Experiment 1), or 1 mg/kg methamphetamine (Experiment 2). Only mice classified as sensitized subgroup developed clear behavioral sensitization to the drugs. After a withdrawal period, mice received challenges of modafinil (Experiment 1), or methamphetamine (Experiment 2) and locomotor activity was evaluated in the activity cages (previous context) and in the open field arena (new context) in order to evaluate the context dependency of behavioral sensitization. The expression of sensitization to modafinil, but not to methamphetamine, was affected by contextual testing conditions, since modafinil-sensitized mice only expressed sensitization in the activity cage, but not in the open field. Subsequently, locomotor cross-sensitization between methamphetamine and modafinil was assessed by challenging modafinil-pretreated mice with 1 mg/kg methamphetamine (Experiment 1), and methamphetamine-pretreated mice with 50 mg/kg modafinil (Experiment 2). We observed a symmetrical cross-sensitization between the drugs only in those mice that were classified as sensitized subgroup. Our findings indicate that repeated exposure to modafinil induces behavioral sensitization only in some animals by similar neurobiological, but not contextual, mechanisms to those of methamphetamine.

1. Introduction

Modafinil (diphenyl-methyl sulphinil-2-acetamide) is a wake-promoting psychostimulant that was found to be effective for treatment of excessive daytime sleepiness associated with narcolepsy, obstructive sleep apnea syndrome, and shift work sleep disorder [1]. Some studies have suggested that modafinil can induce neurochemical and behavioral changes that are somewhat similar to the effects of drugs of abuse [2–7]. It was shown that an acute administration of modafinil increases extracellular dopamine levels in the nucleus accumbens or striatum of rodents [4–6,8–10], nonhuman primates [11,12] and human subjects [13]. Concerning the addictive-like behavior effects, there are some conflicting data in the literature. Deroche-Gamonet et al. [14] found that modafinil

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did not induce self administration or conditioned place preference (CPP) in rats, however recent studies observed CPP to modafinil in mice [4,7]. The latter studies suggest that modafinil induces significant rewarding effects.

Repeated administration of psychostimulants promotes neuroadaptations in the dopaminergic mesocorticolimbic system [15,16]. These alterations are also associated with a phenomenon called behavioral sensitization that can be visualized as a progressive increase in psychomotor response to repeated drug exposure (induction) or as an increased response to a drug challenge after a period of abstinence (expression) [15–17] Similarly to other psychostimulants repeated administration of modafinil also promotes sensitization of its locomotor stimulation [2,3,7].

Recently, there has been interest in investigating individual differences in the response to repeated exposure to drugs of abuse, particularly whether animals will develop or show resilience to behavioral sensitization. The strategy of classifying subgroups with extreme behavioral response profile can be used as a tool to understand how individual variability to drug effects is associated with specific neuroadaptations. Accordingly, individual behavioral differences have been found in the locomotor responses to repeated administration of drugs of abuse such as ethanol [18–22], cocaine [23–25], methamphetamine [22], amphetamine [26] and morphine [27]. These authors have ascribed individual differences to genetics and environmental factors (reaction to novelty, contextual learning, stress condition), and also to specific neuroadaptive changes in dopaminergic and glutamatergic transmission.

Concerning non-pharmacological environmental factors supposed to influence behavioral sensitization [e.g. [28]], Quadros et al. [19] observed that mice that show a different profile of response in ethanol sensitization also show differences in conditioned fear response in a contextual fear conditioning paradigm. Their results suggest that the individual differences in behavioral sensitization to ethanol would be associated with differences in learning and memory processes [19]. Individual differences observed in the development of behavioral sensitization to one drug can, consequently, affect the response to other drugs observed in cross-sensitization tests. Abrahao et al. [22] found that individual differences in the behavioral response to chronic treatment with ethanol or morphine may predict the locomotor responses to other drugs, suggesting possible common neurobiological effects between the drugs.

The aim of present study was to investigate some factors (pharmacologic and non-pharmacologic) related with individual differences in development of behavioral sensitization to modafinil. Specifically, we tested if individual differences in behavioral sensitization to modafinil would be associated with a different profile of response in fear conditioning. We also investigated whether modafinil sensitization could be expressed in a different testing context, and whether modafinil-sensitized mice would show a cross-sensitized response to a methamphetamine challenge. A separate group of mice was similarly tested in regards to methamphetamine-induced sensitization, for comparison purposes.

We hypothesized that both modafinil and methamphetamine would promote individual differences in the development and expression of behavioral sensitization, and also that these drugs would show locomotor cross-sensitization.

2. Material and methods

2.1. Animals

Adult male albino Swiss mice from the CEDEME (Centro de Desenvolvimento de Modelos Experimentais) of UNIFESP (Universidade Federal de São Paulo) colony, 75 days old at the beginning of each experiment were used. The animals were housed in groups in plastic cages (44 cm × 34 cm × 16 cm), and given free access to food and water. Animals were maintained under controlled temperature (22 ± 1 °C), with lights on between 07:00 a.m. and 07:00 p.m. All animal procedures were carried out in accordance with the National Research Council (1996) "Guide for the care and use of laboratory animals" and with an approved animal protocol by the Ethics Research Committee from the UNIFESP (1546/08). All procedures implemented in this study observed ethical criteria for minimizing suffering and the number of animals used.

2.2. Drugs

Modafinil (50 mg/kg, Modiodal® Laboratoire L. Lafon, France) was dissolved in saline (0.9% w/v NaCl) and Tween (vehicle), at concentrations for a target injection volume of 10 ml/kg. This dose was chosen based on a pilot study performed in our laboratory. In the pilot study, locomotor activity was evaluated during 60 min after acute administration of 50, 100, or 150 mg/kg of modafinil or vehicle, 30 min after administration. We observed that modafinil increased locomotor activity at the dose of 100 mg/kg, compared to vehicle. The dose of 50 mg/kg of modafinil did not induce high levels of locomotion and it was in the ascending portion of the inverted *U* curve. To prevent a celling-effect on the acute administration of the drug we chose the dose of 50 mg/kg of modafinil for the chronic treatment. Methamphetamine (1 mg/kg obtained from the Federal Police – São Paulo – Brazil) was dissolved in saline for a target injection volume of 10 ml/kg. The dose of 1 mg/kg was based on a previous study [22]. Drugs were prepared immediately prior to testing. Systemic injections were administered intraperitoneally (i.p.).

2.3. Apparatus

2.3.1. Aversive conditioning apparatus

The conditioning apparatus consisted of an acrylic box measuring 15.28 cm × 16.65 cm × 28.1 cm. The walls were black with a pattern of 20 small white squares (5 squares on each wall). The top was covered with transparent acrylic. The floor was consisted of a metal grid (0.4 cm diameter rods spaced 1.2 cm apart) connected to a shock generator and control module, which delivered footshocks (Insight Ltda., Brazil).

2.3.2. Activity cages

Mice were individually tested in Opto-Varimex activity cages measuring 47.5 cm × 25.7 cm × 20.5 cm (Columbus Instruments, Columbus, Ohio) and equipped with 16 pairs of photoelectric beams distributed in the horizontal axis. Locomotor counts were detected by subsequent interruptions of adjacent photo beams.

2.3.3. Open field arena

Locomotor activity was also evaluated in an open-field arena (AVS; Projetos Especiais, São Paulo, Brazil), which consisted of a circular wooden surface (40 cm in diameter) surrounded by a wall (20 cm high). The surface was painted black and divided into 19 similar parts. Each animal was placed individually in the center of the arena and the amount of ambulation, based on the count of floor units entered, was recorded during a 10 min session. A video camera was placed 1.5 m above the center of the apparatus to record locomotion, which was then appropriately evaluated by hand-operated counters.

2.4. Experimental procedures

2.4.1. Experiment 1: Behavioral sensitization to modafinil: associative learning and cross-sensitization with methamphetamine

The experimental design is detailed in Fig. 1. Briefly, mice were tested on two-day fear conditioning procedure. Fifteen days later, they were repeatedly treated with modafinil or vehicle for the development of behavioral sensitization. After five days from withdrawal, animals were submitted to locomotor challenges, as specified below.

Contextual fear conditioning.

Training. Each mouse was transported to the testing room, individually placed in the aversive conditioning apparatus and allowed to freely explore for 2 min. After this period, each mouse received three footshocks (0.6 mA for 1 s, parameters chosen in pilot experiment) at 30 s intervals. Sixty seconds after the last footshock each mouse was removed from the apparatus and returned to the colony room.

Test for conditioning. The contextual fear conditioning test was performed 24 h after the conditioning session. Each mouse was transported to the testing room and placed in the same aversive conditioning apparatus, but no footshock was delivered. Freezing time, defined as complete immobility of the animal with the absence of vibrissa movements and sniffing [29] was recorded continuously for 5 min.

Development of modafinil behavioral sensitization. Fifteen days after the contextual fear conditioning, the same group of mice was initially placed in the activity cages for 30 min without any drug administration to evaluate their baseline locomotor activity in a novel environment ("novelty test"). The animals were allocated in terms of homogenous baseline locomotor activity scores into 2 groups (vehicle or modafinil). Two days after the novelty test, mice received the administration of vehicle ($n = 12$) or modafinil (50 mg/kg, $n = 37$) for 10 days. On days 1, 5 and 10,