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Modafinil improves methamphetamine-induced object recognition deficits and restores prefrontal cortex ERK signaling in mice

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ABSTRACT

Chronic use of methamphetamine (METH) leads to long-lasting cognitive dysfunction in humans and in animal models. Modafinil is a wake-promoting compound approved for the treatment of sleeping disorders. It is also prescribed off label to treat METH dependence. In the present study, we investigated whether modafinil could improve cognitive deficits induced by sub-chronic METH treatment in mice by measuring visual retention in a Novel Object Recognition (NOR) task. After sub-chronic METH treatment (1 mg/kg, once a day for 7 days), mice performed the NOR task, which consisted of habituation to the object recognition arena (5 min a day, 3 consecutive days), training session (2 equal objects, 10 min, day 4), and a retention session (1 novel object, 5 min, day 5). One hour before the training session, mice were given a single dose of modafinil (30 or 90 mg/kg). METH-treated mice showed impairments in visual memory retention, evidenced by equal preference of familiar and novel objects during the retention session. The lower dose of modafinil (30 mg/kg) had no effect on visual retention scores in METH-treated mice, while the higher dose (90 mg/kg) rescued visual memory retention to control values. We also measured extracellular signal-regulated kinase (ERK) phosphorylation in medial prefrontal cortex (mPFC), hippocampus, and nucleus accumbens (NAc) of METH- and vehicle-treated mice that received modafinil 1 h before exposure to novel objects in the training session, compared to mice placed in the arena without objects. Elevated ERK phosphorylation was found in the mPFC of vehicle-treated mice, but not in METH-treated mice, exposed to objects. The lower dose of modafinil had no effect on ERK phosphorylation in METH-treated mice, while 90 mg/kg modafinil treatment restored the ERK phosphorylation induced by novelty in METH-treated mice to values comparable to controls. We found neither a novelty nor treatment effect on ERK phosphorylation in hippocampus or NAc of vehicle- and METH-treated mice receiving acute 90 mg/kg modafinil treatment. Our results showed a palliative role of modafinil against METH-induced visual cognitive impairments, possibly by normalizing ERK signaling pathways in mPFC. Modafinil may be a valuable pharmacological tool for the treatment of cognitive deficits observed in human METH abusers as well as in other neuropsychiatric conditions.

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1. Introduction

Methamphetamine (METH) is a psychostimulant with a high potential for abuse and addiction. Repeated exposure to METH causes abnormal changes in neurotransmitter activity involved in learning, reward, and executive function (Bamford et al., 2008; Feltenstein and See, 2008). METH also alters neuronal plasticity in brain regions that

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mediate cognition and motivation (Kauer and Malenka, 2007; Robinson and Kolb, 2004). METH addiction generally begins with recreational use and progresses over time into a compulsive and chronically relapsing disorder, accompanied by psychiatric symptoms including hallucinations and delusions, as well as long-term cognitive deficits (Scott et al., 2007). METH-dependent individuals exhibit high rates of cognitive dysfunction in several neuropsychological domains that include sustained attention, episodic memory, information processing, and impulse control (Monterosso et al., 2005; Nordahl et al., 2003; Simon et al., 2010; Morgan et al., 2012). These cognitive deficits might undermine efforts by METH addicts to stop or reduce METH use and negatively affect the outcome of treatment (Vocci and Appel, 2007). Given the potential links between cognition and treatment outcome in METH dependence, therapeutic approaches that improve cognitive function may be quite promising in the management of METH addiction.

Modafinil (Provigil) is a psychostimulant and cognitive enhancer drug, approved by the U.S. Food and Drug Administration for treating narcolepsy and other sleep disorders. Different studies showed that modafinil cognitive-enhancing properties improved outcome in the treatment of pathologic gamblers (Zack and Poulos, 2009), alcoholics (Schmaal et al., 2013), and patients suffering from other neuropsychiatric conditions (Scoriels et al., 2013). The use of modafinil as a treatment for cocaine and METH dependence remains inconclusive, with studies showing positive outcomes (Dackis et al., 2005; McGaugh et al., 2009) and studies showing promising but yet non-significant results in reducing drug use (Dackis et al., 2012; Shearer et al., 2009; Heinzerling et al., 2010). For both cocaine and METH users, modafinil was efficacious in improving several domains of cognitive and executive functions (Kalechstein et al., 2013; Ghahremani et al., 2011; Kalechstein et al., 2010; Hester et al., 2010; Finke et al., 2010).

Modafinil's mechanism of action, although somewhat poorly understood, appears to involve multiple neurotransmitter systems. For example, modafinil can act as a weak DA transporter (DAT) inhibitor that increases extracellular dopamine (DA) levels (Mereu et al., 2013). Modafinil influences GABAergic, glutamatergic, noradrenergic, serotoninergic, histaminergic, and orexinergic systems (for a review see Minzenberg and Carter, 2008; Scoriels et al., 2013). In addition, modafinil enhances electrotonic coupling by increasing the effectiveness of gap junctions between neurons (Urbano et al., 2007; Garcia-Rill et al., 2007). We also demonstrated that modafinil can protect against METH toxicity (Raineri et al., 2011, 2012). Specifically, modafinil was able to prevent METH-induced toxic effects that included DA depletion and reductions in tyrosine hydroxylase (TH) and DAT levels in the striatum (Raineri et al., 2011). Furthermore, modafinil also attenuated METH-induced hyperthermia, glial activation, and increased expression of pro-apoptotic proteins (Raineri et al., 2012).

Compared to classical psychostimulants such as cocaine or amphetamine, the sites of action and behavioral effects of modafinil appear to be different (Mereu et al., 2013). Modafinil showed lower liability to abuse and lower risk of adverse effects on organ systems including the cardiovascular system (Minzenberg and Carter, 2008). Clinically relevant modafinil doses can robustly activate fronto-cortical areas involved in higher cognitive functions and a network of pro-arousing areas, which provide a plausible substrate for the wake-promoting and pro-cognitive effects of the drug (Gozzi et al., 2012). Of relevance to the present study, METH-dependent subjects showed a greater effect of modafinil on brain activation in bilateral insula/ventrolateral prefrontal cortex and anterior cingulate cortices than control participants, suggesting that modafinil improves learning in METH-dependent participants by enhancing neural function in those regions (Ghahremani et al., 2011).

The intracellular signaling pathways that mediate modafinil actions in fronto-cortical areas remain unknown. A potential candidate is the mitogen-activated protein kinase extracellular signal-regulated kinase (MAPK-ERK) cascade. The ERK1/2 pathway plays a critical role in memory function under physiological and pathological conditions (Mizoguchi et al., 2004; Kamei et al., 2006; Nagai et al., 2007; Cammarota et al., 2008). ERK1/2 signaling pathway linked to dopamine D1 receptors (Valjent et al., 2000; Zanassi et al., 2001) is involved in METH-associated contextual memory in rats (Mizoguchi et al., 2004). Additionally, it has been demonstrated that repeated METH treatment in mice induced cognitive impairment in a novel object recognition test, which was associated with deficits of the ERK1/2 pathway in the prefrontal cortex (PFC) (Kamei et al., 2006).

As it was mentioned above, there is only limited information on the mechanisms by which modafinil improves cognition in patients with addictive behaviors in terms of underlying neural substrates. Therefore, in the present study, we designed experiments aimed at testing modafinil's ability to improve cognitive deficits induced by sub-chronic METH treatment in mice. We used a novel object recognition (NOR) task, which is similar to visual recognition tests widely used in subhuman primates (Ennaceur, 2010), and is sensitive to METH-induced cognitive impairments (Bisagno et al., 2002; Kamei et al., 2006; Reichel et al., 2011). The NOR task evaluates the rodents' ability to recognize a novel object in the environment, and discrimination and memory performance is obtained upon identification of familiarity and novelty (Antunes and Biala, 2012). So, we also examined how modafinil and METH differentially modulated fronto-cortical phosphorylation of the MAPK isoforms ERK1/ERK2 following exposure to novelty.

2. Materials and methods

2.1. Animals

C57BL/6 male mice (2–3 month-old) from the School of Exact and Natural Sciences of the University de Buenos Aires (UBA) were housed in a light and temperature-controlled room (12-h light/dark cycle, 22 °C), and were given free access to laboratory chow and tap water. Principles of animal care were followed in accordance with "Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research" (National Research Council, 2003) and approved by Universidad de Buenos Aires authorities (Protocol Number: A5801-01) using OLAW and ARENA directives (NIH, Bethesda, USA).

2.2. Pharmacological reagents

Drugs were purchased from either Sigma (St. Louis, MO) or Tocris (Ellisville, MO). Modafinil (racemic mixture of R- and S-enantiomers) was generously donated by Laboratorios Beta S.A. (Argentina).

2.3. Drug treatments

(+)-Methamphetamine hydrochloride (Sigma, St Louis, MO) was administered subcutaneously (sc) once a day for 7 days (1 mg/kg, calculated as free base, dissolved in sterile saline solution). The METH regimen used in this study was performed according to studies by Kamei et al. (2006). Four days after the last METH injection, modafinil (30 or 90 mg/kg, dissolved in DMSO-Arabic gum 5% in sterile saline solution) was injected and 1 h later mice were subjected to behavioral analysis (Novel Object Recognition task or Novelty exposure, Fig. 1A and B). Vehicle groups received the same volume of sterile saline and DMSO/Arabic gum/saline. Drugs were injected at a volume of 10 ml/kg of body weight.

2.4. Novel Object Recognition (NOR) task

The NOR task was adapted according to previously reported methods (Kamei et al., 2006). The NOR task evaluates the rodents' ability to recognize a novel object in the environment. Basically, in the NOR task there are no positive or negative reinforcers, and this methodology assesses the natural preference for novel objects displayed by rodents (Ennaceur, 2010). The task procedure consists of three phases: habituation, training, and a test phase. In the habituation phase, each animal is allowed to freely explore the arena in the absence of objects. The animal is then removed from the arena and placed in its cage. During the training phase, a single animal is placed in the arena containing two identical sample objects (A + A) for 5 min. The experimental context is not drastically different during the training and the test phase. After a retention interval begins the test phase, and the animal is