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Sex differences in dopamine binding and modafinil conditioned place preference in mice

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ABSTRACT

Background: Studies in humans and rodents have demonstrated under certain conditions some reinforcing properties of modafinil, a drug being examined clinically for its potential to treat psychostimulant abuse. However, the majority of rodent studies examining the abuse potential of modafinil have used high doses that may not be clinically relevant. In fact, recent work has indicated that doses similar to those administered to humans are not reinforcing in mice.
Methods: The current study examined sex differences in the ability of low-dose modafinil (0.75 mg/kg, IP) to induce a conditioned place preference in mice, and assessed sex-dependent alterations in dopamine D1, D2 and DAT binding sites in reward-related regions in naïve and modafinil-treated mice.
Results: Low-dose modafinil failed to induce a conditioned place preference in male mice, while female mice demonstrated a significant modafinil place preference. Several dopamine binding differences were also detected in naïve and modafinil-treated mice, including sex differences in D1 and D2 availability in reward-related regions, and are discussed in relation to sex-dependent differences in the reinforcing effects of modafinil and psychostimulants in general.
Conclusions: These findings implicate sex differences in the reinforcing properties of modafinil in mice, and indicate that clinical evaluation of the sex dependence of the reinforcing properties of modafinil in humans is warranted.

1. Introduction

Modafinil is a psychostimulant that promotes wakefulness and thus is used to treat excessive daytime sleepiness associated with narcolepsy, shift-work sleep disorder, and obstructive sleep apnea in humans, and in recent years has been used for its ability to enhance cognition (Repantis et al., 2010; Wood et al., 2014). Because modafinil exerts its effects on arousal through its interactions with monoamine transporters, especially the dopamine transporter (DAT; Madras et al., 2006), but with lower affinity (Mignot et al., 1994) and/or a different conformational binding mechanism (Schmitt and Reith, 2011) than cocaine, it has been examined as a potential agonist treatment for psychostimulant abuse (Martinez-Raga et al., 2008). Several studies in humans have demonstrated that modafinil may be an effective treatment for cocaine-dependent individuals due to its purported lack of reinforcing effects. For example, modafinil failed to serve as a reinforcer (Vosburg et al., 2010), or substitute for cocaine-like discriminative stimulus effects or produce subjective ratings of 'high,' in cocaine abusers (Rush et al., 2002a, 2002b). Furthermore, modafinil decreased craving (Anderson et al., 2009) and increased abstinence duration (Dackis et al., 2005) in cocaine-dependent individuals relative to placebo. In contrast, modafinil has been demonstrated to produce some subjective "positive" drug effects (Rush et al., 2002b; Stoops et al., 2005), and in a recent study failed to affect cocaine abstinence, craving, or withdrawal (Dackis et al., 2012).

Preclinically, the potential reinforcing properties of modafinil have been extensively examined in rodents, but these studies have yielded contrasting results. Modafinil failed to produce a conditioned place preference (CPP; Deroche-Gamonet et al., 2002; Quisenberry et al., 2013) or induce self-administration (Deroche-Gamonet et al., 2002), and failed to reinstate responding following extinction of cocaine or methamphetamine self-administration or alter cocaine-induced reinstatement (Deroche-Gamonet et al., 2002; Holtz et al., 2012; Reichel and See, 2010) in rats, suggesting a lack of reinforcement by modafinil. In contrast, modafinil has been demonstrated to robustly reinstate an extinguished cocaine CPP in rats (Bernardi et al., 2009), and induce locomotor sensitization and CPP in mice (Nguyen et al., 2011; Shuman et al., 2012;

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Wuo-Silva et al., 2011), consistent with psychostimulant reinforcement. Modafinil has also been shown to attenuate cocaine prime-induced reinstatement following self-administration (Mahler et al., 2014) and drug-primed and cue- and context-induced reinstatement following methamphetamine self-administration (Mahler et al., 2014; Reichel and See, 2010, 2012), supporting its use as a potential agonist treatment for psychostimulant abuse.

Modafinil binds to the DAT in both humans (Kim et al., 2014; Volkow et al., 2009) and animals (Madras et al., 2006; Zolkowska et al., 2009). Thus its effects are likely primarily mediated by increased extracellular DA levels in dopamine terminal regions, such as striatal regions mediating reinforcement (Ferraro et al., 1996; Volkow et al., 2009; Zolkowska et al., 2009). Consistent with these findings, repeated exposure to modafinil in rodents results in neuroadaptations in dopamine substrates. For example, a modafinil CPP dosing regimen (3×125 mg/kg) produced changes in DAT, dopamine receptor 1 (D1), and dopamine receptor 2 (D2) availability in a number of mesolimbic regions in male mice as measured following CPP testing. DAT and D2 binding were increased and decreased, respectively, in the caudate putamen (CPu) and nucleus accumbens (NAc), and D1 was increased in the CPu, NAc, and substantia nigra, relative to vehicle-treated mice (Nguyen et al., 2011). Decreases in D2 availability have in general been consistently demonstrated to be associated with psychostimulant reinforcement (Anderson and Pierce, 2005), while psychostimulant-induced changes in D1 and DAT have shown greater variability, likely based on different doses, dosing regimens, etc. (Anderson and Pierce, 2005; Bailey et al., 2008).

A key concern of many of these behavioral and molecular findings in rodents is that the doses of modafinil peripherally administered to rodents (30–300 mg/kg) may be much higher than those that are effective in humans, and thus represent doses that are not clinically relevant. In fact, a recent study by Shuman et al. (2012) examined the reinforcing properties of modafinil at a dose (0.75 mg/kg) demonstrated to produce cognitive enhancement in mice (Shuman et al., 2009), the standard of clinical effectiveness in non-sleep deprived humans (Neale et al., 2013; Repantis et al., 2010). The authors demonstrated that repeated administration of modafinil at this low dose did not induce locomotor sensitization and failed to produce a CPP in mice (Shuman et al., 2012). Thus, the authors concluded that modafinil administered to rodents in clinically relevant doses is not reinforcing.

Previous studies have indicated sex differences in both drug addiction in humans and measures of reinforcement regarding drugs of abuse in rodents (reviewed in Becker and Hu, 2008; Bobzean et al., 2014). For example, in terms of cocaine, female rats have been demonstrated to acquire cocaine self-administration more rapidly and administer more cocaine (Lynch and Carroll, 1999) and show increased cocaine-primed reinstatement (Lynch and Carroll, 2000) than their male counterparts. Similar results have been demonstrated using CPP, with, for example, female rats demonstrating cocaine CPP at lower doses (Zakharova et al., 2009) and higher cocaine-induced reinstatement of CPP following extinction (Bobzean et al., 2010) relative to male rats (but see Hilderbrand and Lasek, 2014; Schindler et al., 2002). Sex-dependent differences in circuitry mediating reinforcement have been shown to contribute to these differences in the response to cocaine (Becker and Hu, 2008; Bobzean et al., 2014). Furthermore, the efficacy of modafinil as a treatment for cocaine dependence in humans may be sex-dependent (Dackis et al., 2012). Thus, the current study examined sex differences in locomotor sensitization and CPP in male and female mice using a low, clinically relevant dose of modafinil (0.75 mg/kg modafinil) (Shuman et al., 2012; Shuman et al., 2009). Furthermore, we measured DAT, D1, and D2 receptor availability in mesolimbic areas, including the ventral tegmental area (VTA), NAc core (AcbC) and shell (AcbSh), and CPu, as a function of sex and modafinil treatment.

2. Materials and methods

2.1. Subjects

Male and female C57Bl/6 mice (Charles River, Germany) aged 10–14 weeks old at the start of experiments served as subjects. Mice were single-housed in a temperature-controlled (21 °C) environment maintained on a 12-h light–dark cycle (lights on at 6 a.m.). Food and water was available ad libitum. All experiments were performed in accordance with EU guidelines on the care and use of laboratory animals. All behavioral testing was conducted during the light phase between 0800 h and 1700 h.

2.2. Drugs

Modafinil (Tocris, Germany) was suspended in a 10% Tween 80 (in 0.9% NaCl) vehicle solution for intraperitoneal (IP) injection of 0.75 mg/kg (10 ml/kg), based on previous studies (Bernardi and Spanagel, 2014b; Shuman et al., 2012, 2009). [3*H*]-SCH23390 [specific activity 80.5 Ci/mmol, KD = 0.7 nM, Bmax = 347 fmol/mg (Schulz et al., 1985)], [3*H*]-Raclopride [specific activity 74.4 Ci/mmol, KD = 2.08 nM, Bmax = 20.0 fmol/mg (Hall et al., 1990)] and [3*H*]-Mazindol [specific activity 20.7 Ci/mmol, KD = 18.2 nM, Bmax = 0.0073 fmol/mg (Javitch et al., 1984)] were obtained from PerkinElmer (Massachusetts, USA). Bacitracin, bovine serum albumin, ascorbic acid and nomifensine were obtained from Sigma-Aldrich (St. Louis, MO, USA). Desipramine hydrochloride, SKF and sulpiride were obtained from Tocris Biosciences (Bristol, UK).

2.3. Apparatus and behavioral procedures

Modafinil CPP was assessed in two Panlab place preference boxes (Panlab, Spain). Each box consists of two chambers ($20 \times 18 \times 25$ cm) with distinct visual and tactile cues separated by a clear acrylic rectangular corridor. Sessions are monitored via a video-tracking system (Ethovision 2.0, Noldus, the Netherlands) that determines spatial placement within sessions and distance traveled (cm).

CPP was assessed using a biased design, as previously described (Bernardi and Spanagel, 2013, 2014a). Briefly, animals were conditioned to modafinil in their non-preferred environment, in three phases: pre-test, conditioning, and post-test. During the pretest, mice were injected with vehicle (IP, 10 ml/kg) and placed into the apparatus for a 15-min test of initial preference to the distinct environments. During conditioning, which entailed one trial per day on eight consecutive days (four modafinil, four vehicle), mice received modafinil (0.75 mg/kg IP) immediately prior to 15-min conditioning trials in their non-preferred compartment or vehicle (10 ml/kg IP) immediately prior to 15-min trials in their preferred compartment. On the day following the last conditioning trial, mice were injected with vehicle (10 ml/kg IP) and given a 15-min drug-free test of preference, during which mice had access to both compartments. Preference was determined by the difference between time spent in the non-preferred side during the pretest and posttest.

2.4. DAT and DA receptor autoradiography

Separate groups of male and female mice were administered vehicle ($n = 5$–6/sex; 10 ml/kg IP) or modafinil ($n = 5$–6/sex; 0.75 mg/kg, IP) in an injection procedure similar to that used for CPP (every other day for a total of 4 injections), but were never