Pharmacology, Biochemistry and Behavior 110 (2013) 208–215

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Combined effects of modafinil and d-amphetamine in male Sprague–Dawley rats trained to discriminate d-amphetamine

Amanda J. Quisenberry [a], Thomas Prisinzano [b], Lisa E. Baker [a,*]

[a] Department of Psychology, Western Michigan University, United States
[b] Department of Medicinal Chemistry, University of Kansas, United States

ARTICLE INFO

Article history:
Received 28 September 2012
Received in revised form 9 July 2013
Accepted 13 July 2013
Available online 21 July 2013

Keywords:
Modafinil
d-Amphetamine
Drug discrimination
Training dose
Drug combinations

ABSTRACT

Modafinil is a novel wake-promoting drug with FDA approval for the treatment of sleep-related disorders that has recently been investigated as a potential agonist replacement therapy for psychostimulant dependence. Previous research in animals and humans indicates modafinil has a lower abuse liability than traditional psychostimulants, although few studies have carefully assessed modafinil's stimulus properties in combination with other psychostimulants. The current study trained male Sprague–Dawley rats to discriminate subcutaneous injections of 0.3 mg/kg (n = 8) or 1.0 mg/kg d-amphetamine (n = 8) from saline under an FR 20 schedule of food reinforcement and substitution tests were administered with d-amphetamine (0.03–1.0 mg/kg, s.c.), modafinil (32–256 mg/kg, i.g.), and a low modafinil dose (32 mg/kg, i.g.) in combination with d-amphetamine (0.03–1.0 mg/kg, s.c.) to determine if these drugs have additive effects. The selective D_2 dopamine agonist, PNU-91356A, was also tested as a positive control and ethanol and morphine were tested as negative controls. Results indicate that modafinil produced dose-dependent and statistically significant d-amphetamine-lever responding in both groups and nearly complete substitution in animals trained to discriminate 1.0 mg/kg d-amphetamine. Modafinil pretreatment slightly increased the discrimination of low d-amphetamine doses in animals trained to discriminate 0.3 mg/kg d-amphetamine. These results support previous findings that modafinil and d-amphetamine may have additive effects. In consideration of recent interests in modafinil as an agonist treatment for psychostimulant dependence, additional preclinical investigations utilizing other methodologies to examine modafinil in combination with other stimulants, such as behavioral sensitization paradigms or drug self-administration, may be of interest.

Published by Elsevier Inc.

1. Introduction

Modafinil is a wake-promoting drug with behavioral effects similar to those of traditional psychostimulants (Hermant et al., 1991; Turner et al., 2003; Webb et al., 2006). Although it is currently FDA approved only for the treatment of narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shift work sleep disorder (Rosenberg et al., 2003), modafinil has been reported to demonstrate clinical efficacy in treating chronic fatigue syndrome (Turkington et al., 2004) and adult attention deficit hyperactivity disorder (ADHD) (Mann and Bitsios, 2009). Furthermore, several recent studies have evaluated modafinil as a potential treatment for psychostimulant dependence (Dackis et al., 2005; McGregor et al., 2008; Shearer et al., 2009; Schmitz et al., 2012) or the cognitive deficits associated with a history of methamphetamine abuse (Dean et al., 2011; Ghahremani et al., 2011). Of particular importance, modafinil appears to have a lower risk of side effects commonly associated with traditional psychostimulants, such as potential for abuse, sleep rebound, or increases in locomotor activity (Deroche-Gamonet et al., 2002; Lin et al., 1992).

Investigations of modafinil's subjective effects in human psychostimulant users are indicative of a low abuse liability. In a recent study implementing a choice self-administration procedure with 12 cocaine abusers not seeking treatment, modafinil was not selected more frequently than placebo (Vosberg et al., 2010). Other human laboratory studies of modafinil's psychoactive effects indicate that oral modafinil administration at clinically effective doses does not appear to have strong reinforcing properties and produces subject-rated effects that are distinguishable from those of cocaine or amphetamine (Malcolm et al., 2006; Rush et al., 2002; Warot et al., 1993).

Animal models of substance abuse, including drug self-administration, conditioned place preference (CPP), and behavioral sensitization have provided somewhat mixed findings regarding modafinil's abuse liability. In rats, modafinil failed to establish CPP or self-administration (Deroche-Gamonet et al., 2002), although at least one study reported self-administration of high modafinil doses by rhesus monkeys (Gold

* Corresponding author at: Department of Psychology, 3754 Wood Hall, Western Michigan University, Kalamazoo, MI 49008, United States. Tel.: +1 269 387 4484; fax: +1 269 387 4550.
E-mail address: lisa.baker@wmich.edu (L.E. Baker).

0091-3057/$ – see front matter. Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.pbb.2013.07.011

and Balster, 1996). Recent studies utilizing mice as experimental subjects have reported modafinil to establish CPP (Nguyen et al., 2011) and one study reported that modafinil-induced CPP was equivalent to that of cocaine (Shuman et al., 2012). Bernardi et al. (2009) reported that modafinil reinstated an extinguished place preference to cocaine in rats. Furthermore, behavioral sensitization has been demonstrated following repeated modafinil treatment (Paterson et al., 2010) and a combination of cocaine and modafinil treatment (Shuman et al., 2012). The expression of cross sensitization to modafinil in cocaine-pretreated mice (Shuman et al., 2012) and methamphetamine-pretreated mice (Da Costa Soeiro et al., 2012) suggests a similar mechanism of action between modafinil and the psychomotor stimulants.

The dopamine transporter (DAT) has been implicated in modafinil's neurochemical mechanism of action (Minzenberg and Carter, 2008; Wisor et al., 2001). Besides assessing abuse liability, preclinical behavioral assays can also provide valuable evidence regarding pharmacological actions of drugs. In particular, drug discrimination is a widely accepted behavioral assay that is predictive of pharmacological mechanisms of drug action. To date, modafinil has been investigated in only four published drug discrimination studies with nonhumans. In the first of these studies, modafinil was assessed in six rats trained to discriminate 10 mg/kg cocaine (Gold and Balster, 1996). Modafinil produced dose-dependent increases in cocaine-lever selection, but group data yielded only partial substitution (67%) at doses that significantly suppressed responding. However, it is noteworthy that four of the six rats exhibited complete stimulus generalization to cocaine following administration with 250 mg/kg modafinil in that study. More recent studies have reported full substitution with 300 mg/kg modafinil in rats (Paterson et al., 2010) and with 100 mg/kg modafinil as well as both of its enantiomers in mice trained to discriminate 10 mg/kg cocaine (Loland et al., 2012).

Dopheide et al. (2007) was the first study to assess the combined effects of modafinil and other stimulants in a drug discrimination procedure. They tested modafinil (32, 64, 128 mg/kg) administered by oral gavage at various post-injection times (10 to 240 min) in three groups of male Sprague–Dawley rats trained to discriminate one of two low doses of cocaine (1.6, 5 mg/kg) administered intraperitoneally (i.p.) or a low d-amphetamine dose (0.3 mg/kg) administered subcutaneously (s.c.). They also tested 32 mg/kg modafinil in combination with a range of cocaine and d-amphetamine doses in all three groups of rats. Although modafinil alone failed to fully substitute for d-amphetamine or cocaine in that study, 32 mg/kg modafinil enhanced the discrimination of d-amphetamine and a low cocaine dose and shifted the dose–effect curves to the left. These findings suggest that modafinil may have additive effects with other stimulants.

The current study assessed the effects of modafinil alone and in combination with d-amphetamine in rats trained to discriminate either a low dose (0.3 mg/kg) or moderately high dose (1.0 mg/kg) of d-amphetamine. Based on the results of Dopheide et al. (2007) it was hypothesized that modafinil alone would produce only partial substitution for d-amphetamine and that modafinil would potentiate the discriminative stimulus effects of low d-amphetamine doses.

2. Methods

2.1. Subjects

Sixteen male Sprague–Dawley rats (Charles River, Portage, MI) approximately four months old and drug naïve at the beginning of the study were utilized. All animals were housed individually in polycarbonate cages lined with corncob bedding in a colony room with a 12:12 light/dark cycle with lights on from 7:00 a.m. to 7:00 p.m. Water and food were provided ad libitum during the acclimation phase. The animals' weights were maintained at 80% of their free-feeding weights by restricting the amount of food provided each day until the goal weight was reached. All procedures were reviewed and approved by the Western Michigan University Institutional Animal Care and Use Committee and were in accordance with the guidelines of the *Guide for the Care and Use of Laboratory Animals* (National Research Council of the National Academies, 2011) and EU Directive 2010/63/EU.

2.2. Apparatus

Training and testing sessions were conducted in eight standard operant conditioning chambers (ENV-001; MED Associates Inc., Georgia, VT, USA), housed within sound- and light- attenuating shells. Each chamber was equipped with three removable levers located on the front panel, a food pellet dispenser, a 28-V house light, and fan. Forty-five milligram food pellets served as the reinforcers (Bioserv; Frenchtown, NJ). Experimental events were programmed and controlled using Version IV Med-PC software (MED Associates Inc., St. Albans, VT, USA).

2.3. Drugs

d-Amphetamine-hemisulfate (Sigma-Aldrich, St. Louis, MO) was dissolved in a 0.9% NaCl saline solution and administered s.c. Modafinil was synthesized in the laboratory of Dr. Thomas Prisinzano using previously described methods (Prisinzano et al., 2004). Suspensions were prepared fresh each day in a 5% arabic gum solution (Sigma Aldrich, St. Louis, MO) and administered by oral gavage (i.g.) in a volume of 10 ml/kg 30 min prior to test sessions. Morphine (Sigma-Aldrich, St. Louis, MO) and PNU-91356A (Pharmacia & Upjohn, Inc., Kalamazoo MI) were dissolved in 0.9% NaCl and administered s.c. 10 min prior to test sessions. Ethanol (Aaper Alcohol and Chemical Co., Shelbyville, KY) was diluted in sterile water and administered i.g. in a volume of 10 ml/kg 10 min prior to test sessions.

2.4. Experimental procedures

2.4.1. Preliminary training

Initial training consisted of a single one hour session with no levers present and rats were exposed to a fixed-time 60 second schedule of food delivery to acclimate them to the sound and location of food pellet delivery. All subsequent training sessions lasted 20 min and were conducted once per day, five to six days a week between 4:00 and 6:00 p.m. All rats were initially reinforced for responses on the center lever via an autoshaping program under a continuous reinforcement schedule for one ($n = 9$) or two ($n = 7$) 20 min sessions. Only the center lever was present during autoshaping sessions. Once all animals were reliably lever pressing, errorless training commenced with only the left or right lever present.

Drug (D) or vehicle (V) injections were administered subcutaneously 10 min prior to errorless training sessions. Drug injections consisted of 0.3 mg/kg d-amphetamine for one group ($n = 8$) and 1.0 mg/kg d-amphetamine for the other group ($n = 8$) and vehicle injections consisted of 0.9% saline for both groups. For half the animals in each group, errorless training sessions with only the right lever present followed drug injections and errorless training sessions with only the left lever present followed saline injections. Conditions were reversed for the remaining animals in each group. All rats were exposed to twelve errorless training sessions in the following order: V, V, D, D, V, D, D, V, D, V, V, D. Responses were initially reinforced under a fixed-ratio 1 (FR 1) schedule and the FR value was gradually incremented within each training session and across the six errorless training sessions with each stimulus condition. Within each session, the FR was programmed to increment by a designated amount (e.g., 1, 2, or 5) after the delivery of five reinforcers at a particular FR value. Across training sessions, the starting FR value was determined for each individual rat by the last FR value obtained in the previous session. All rats were responding on an FR 20 schedule by the last errorless training session with each stimulus condition.