Dual Dopaminergic Actions Contribute to Discriminative Stimulus Functions of Orally Administered Modafinil in Rats

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Introduction

- Modafinil (Provigil®) is a mild CNS stimulant currently marketed as a wake-promoting agent for the treatment of excessive daytime sleepiness associated with narcolepsy and other sleep disorders.
- It has also been investigated to treat psychostimulant dependence (Dackis et al., 2005; Anderson et al., 2009; Reichel & See, 2010) and fatigue in Parkinson's disease (Hoal et al., 2002), amyotrophic lateral sclerosis (Carter et al., 2005), and dementia (Howcroft et al., 2002).
- Research investigating modafinil's mechanism of action has resulted in evidence to support a variety of neurotransmitter systems including the catecholamines, serotonin, glutamate, GABA, orexin, and histamine (Minzenberg & Carter, 2008). In particular, the dopamine transporter system (DAT) has been implicated in studies utilizing a variety of assays (Wisor et al., 2001; Dopheide et al., 2007; Zolkowska et al., 2009).
- Drug discrimination is a behavioral assay commonly employed to characterize the pharmacological mechanisms of drug action. Modafinil has been shown to produce full substitution in rats trained to discriminate 10 mg/kg cocaine (Paterson et al., 2010) and significant partial substitution in rats trained to discriminate low doses of d-amphetamine or cocaine (Dopheide et al., 2007; Quisenberry et al., unpublished findings).
- Dopheide et al. (2007) also reported that modafinil enhanced the discrimination of low d-amphetamine and cocaine doses, implicating the potential for additive effects between modafinil and psychomotor stimulants.
- Considering the possible effectiveness of modafinil as an agonist replacement therapy for psychostimulant abuse (Shearer et al., 2009) and the prevalence of polysubstance abuse, evaluation of modafinil's effects in combination with other psychostimulants is warranted.
- To date, there are no published reports utilizing modafinil as a training stimulus to investigate its mechanism of action. Therefore, the current study employed drug discrimination procedures to evaluate the combined effects of modafinil and d-amphetamine and to determine the pharmacological actions contributing to modafinil's discriminative stimulus effects.

Methods

Subjects**:** Eight male Sprague-Dawley rats (300-500 g) were singly housed with free access to water and maintained at 85% of free-feeding body weights.

Apparatus: Training and test sessions were conducted in eight standard operant conditioning chambers equipped with retractable levers and housed within sound-attenuating compartments (Med Associates, St. Albans VT).

Procedures: Rats were trained to discriminate oral administration of 256 mg/kg modafinil from vehicle (5% arabic gum) under a FR 20 schedule of food reinforcement. Criteria for discrimination acquisition were a minimum of 80% correct lever responding prior to completion of the first FR and for the total session for at least eight of 10 consecutive training sessions. When these criteria were met, stimulus generalization and antagonist tests were conducted with the compounds listed below.

Generalization tests:

- modafinil (16-384 mg/kg, i.g.)
- d-amphetamine hemisulfate (0.03-3.0 mg/kg, i.p.)
- 1.0 mg/kg AMPH (i.p.) + modafinil (16-384 mg/kg, i.g.)
- PNU-91356A (0.03-0.3 mg/kg, i.p.)
- GBR-12909 (5-20 mg/kg, i.p.)
- (-)-nicotine hydrogen tartrate (0.1- 0.8 mg/kg, i.p.)

Antagonist Tests:

- Sch 39166 (0.03-0.3 mg/kg, i.p.) + 256 mg/kg modafinil
- haloperidol (0.125-0.5 mg/kg, i.p.) + 256 mg/kg modafinil

Results

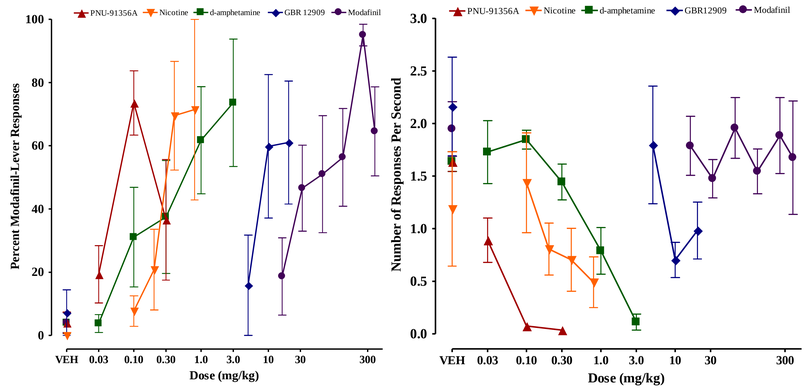

Figure 1. Results of substitution tests with PNU-91356A (n=8), nicotine (n=3-5), d-amphetamine (n=8), GBR 12909 (n=5-6), and modafinil (n=8). Percent drug-lever selection is shown on the left and response rate is shown on the right. All test compounds produced dose-dependent increases in modafinil lever selection and reduced response rate to a greater extent than modafinil. PNU-91356A and d-amphetamine produced nearly complete substitution at doses that severely reduced responding. Nicotine and GBR 12909 produced partial substitution at the highest dose tested. Additional tests with higher doses are in progress.

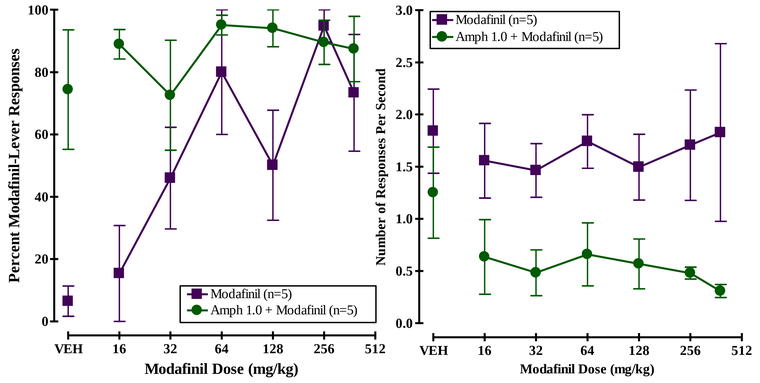

Figure 2. Results of 1.0 mg/kg d-amphetamine combined with each dose of modafinil (16-384 mg/kg) compared to modafinil alone (n=5). The AMPH + MOD combination significantly increased modafinil lever-selection (left) and decreased response rate (right) to a greater extent than modafinil alone.

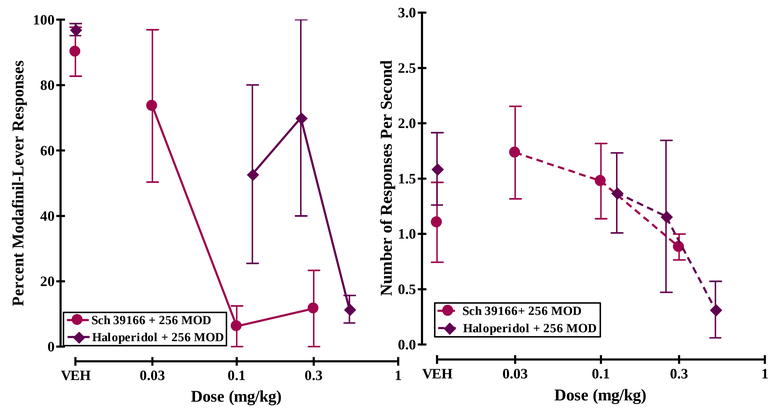

Figure 3. Preliminary results with Sch 39166 (n= 4-5) and haloperidol (n= 3-4) administered in combination with 256 mg/kg modafinil indicate that modafinil discrimination is attenuated by both D_1 and D_2 dopamine receptor blockade.

Summary and Conclusions

- Modafinil established stimulus control in all eight animals within an average of 36 (± 2.4) discrimination training sessions (range: 23-43).
- d-Amphetamine produced nearly complete substitution for modafinil at a dose that markedly suppressed responding. These findings are consistent with a previous report (Dopheide et al., 2007) and unpublished findings from our laboratory that modafinil substitutes partially in rats trained to discriminate d-amphetamine.
- A dose of d-amphetamine that initially produced only partial substitution for modafinil produced complete substitution when combined with a range of modafinil doses. The rate suppressant effects of the AMPH+MOD combination was also greater than the effects of either drug alone.
- Preliminary results showing partial substitution with the D_2 agonist, PNU-91356A and the DAT inhibitor, GBR 12909 and complete blockade with the D_1 antagonist, Sch 39166 and the D_2 antagonist, haloperidol suggest dual dopaminergic mechanisms contribute to the discriminative stimulus functions of modafinil.
- The unexpected finding that nicotine produced partial substitution for modafinil is of particular interest. The extent to which dopaminergic actions contribute to similar discriminative stimulus functions of nicotine and modafinil warrant further investigation.

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