**Subjective and reinforcing effects of modafinil in rats**

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**INTRODUCTION**

Modafinil (Provigil®) is an unusual stimulant that is widely used to treat narcolepsy in USA and Europe. It has an enigmatic pharmacological mechanism of action (see reviews by Minzenberg & Carter, 2008; Heali et al, 2012a). Recent neurochemical experiments performed in vitro and in vivo indicate that although modafinil has relatively low affinity (∼5μM) for the human dopamine reuptake transporter (DAT) (Madras et al, 2000; Zolkowska et al, 2009), clinical doses of modafinil, i.e. 200 and 400 mg, occupy ∼46% of DAT sites in the caudate, ∼53% in the putamen and ∼60% in the nucleus accumbens in human subjects in vivo (Volkow et al, 2009). In humans, modafinil’s subjective effects are somewhat cocaine-like (Rush et al, 2002a) and this stimulant has also been reported to serve as a positive reinforcer in recreational drug users (Jasinski, 2000). Modafinil is a Schedule 4 Controlled Drug (C-IV) in the USA, but it is not a CD in the UK. In view of modafinil’s interesting pharmacology, we conducted a series of experiments to investigate the discriminative properties of this stimulant in rats trained to discriminate between a low dose of d-amphetamine and saline and determined whether it would serve as a positive reinforcer in rats trained to self-administer a low dose of cocaine.

**METHODS**

Groups of 6-9 young adult female PVG rats were trained to discriminate d-amphetamine (0.5 mg/kg, i.p) from saline in a 2-lever operant procedure using a FR-5 schedule of sweetened milk rewards. It was a well established model for determining similarities between the subjective effects of test compounds in comparison to reference drugs with known abuse liability profiles. Generalisation was classified as: Amphetamine (75%) responses on the d-amphetamine lever, Partial generalisation to d-amphetamine (26.74% responses on the d-amphetamine lever) or Saline (<25% responses on the d-amphetamine lever).

The self-administration study was performed using groups of 7-9 male, Sprague-Dawley rats (Charles River). Rats were trained to self-administer a low dose of cocaine (0.32 mg/kg, i.v.), injection, i.e. on a FR-2 schedule of reinforcement (maximum 20 injections/1 h session/day). When consistent self-administration of cocaine had been established, the rats were switched to saline (1 ml/kg, i.p.) to demonstrate extinction. Modafinil (0.166, 0.498 or 1.66 mg/kg, i.p.) was substituted for cocaine in the paradigm (maximum of 10 sessions). After completing modafinil testing, rats were given access to saline followed by cocaine saline (0.32 mg/kg, i.v.) to ensure that the expected responses of the rats had not been altered. Each testing session was initiated by a non-contingent injection of cocaine, saline or modafinil.

Modafinil was injected i.p. as a fine suspension in 1% methylcellulose in 0.9% saline and dissolving in 40% (2-hydroxypropyl)-β-cyclodextrin (w/v) in deionised water for i.v. injection.

**RESULTS**

• Figure 1A shows that d-amphetamine (0.1-0.5 mg/kg, i.p.) dose-dependently generalised to the training cue in rats trained to discriminate between d-amphetamine (0.5 mg/kg, i.p) and saline.

• All of the doses of modafinil, i.e. 50, 100 and 150 mg/kg, i.p., partially generalised to d-amphetamine when tested 30 min after dosing (Figure 1B). When the interval was increased to 60 min, the pharmacological effect of modafinil was reduced (Figure 1B). Modafinil (100 mg/kg, i.p.) produced only 28% generalisation to amphetamine (5/10 Saline, 2/5 Partial generalisation; 2/5 Amphetamine) compared with 45% generalisation to d-amphetamine at 30 min (5/5 Saline; 2/5 Partial generalisation; 1/5 Amphetamine).

• Modafinil (150 mg/kg i.p.) had no effect the operant response rates of rats, but at 200 mg/kg, i.p. operant responding decreased by ≥37% in 11/16 animals (Table 1).

• Modafinil (0.166, 0.498 or 1.66 mg/kg, i.v.) did not maintain self-administration at levels significantly above saline (Figure 2) showing that at these doses it did not serve as a positive reinforcer in rats. When the data were assessed for individual animals, 3/9 (33%) rats self-administered the high dose of modafinil at levels above saline. However, in each case, the rats showed highly variable intakes of modafinil and all rats were tested for the maximum of 10 sessions without achieving consistent responding on the drug.

• Modafinil (0.166, 0.498 and 1.66 mg/kg, i.v.) increased the rate of operant responding across the 3 doses (Table 2) demonstrating that the selected doses of modafinil were pharmacologically active in rats.

**CONCLUSIONS**

• Modafinil partially generalised to d-amphetamine indicating that it produces some d-amphetamine-like discriminative effects. However, substantial inter-animal variability was present at all of the doses revealing that modafinil was clearly recognised as d-amphetamine-like by some rats and different from d-amphetamine by others.

• Our results confirm the findings of Dopheide et al (2007) who also observed that modafinil partially failed to generalise to d-amphetamine. These findings are also consistent with the observation that modafinil partially generalised (~60%) to the cocaine cue in drug-experienced human volunteers trained to discriminate between cocaine and placebo (Rush et al, 2002a).

• Modafinil did not maintain self-administration at levels above saline when tested across a range of pharmacologically active doses indicating that this atypical stimulant probably does not serve as a positive reinforcer in cocaine-trained rats. However, this result is not definitive because modafinil’s limited solubility prevented the exploration of higher doses in the self-administration model.

• Our finding is consistent with the observation that modafinil also failed to serve as a positive reinforcer in drug-naïve rats and did not induce place preference (Deroche-Gamonet et al, 2002). In human subjects, modafinil served as a reinforcer in human volunteers performing a cognitive task, although not when they were relaxing (Stoops et al, 2005). However, the weakness of modafinil’s reinforcing effect relative to cocaine has been shown by its failure to serve as a positive reinforcer in stimulant abusers (Rush et al, 2002b; Vosburg et al, 2010) and by its lack of clinical efficacy in the treatment of cocaine dependence (Anderson et al, 2009).

• In summary, our results complement observations made in human subjects suggesting that modafinil has only weak stimulant and reinforcing properties. The findings are also consistent with our results from the neurochemical and behavioural profiling of modafinil in rats (Rowley et al, this meeting).

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