A microdialysis and behavioural investigation of modafinil in freely-moving rats

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INTRODUCTION

Modafinil (Provigil®) is an unusual stimulant that is widely used to treat narcolepsy in the USA and Europe. It has an enigmatic mechanism of action (see reviews by Minzenberg & Carter, 2008; Heal et al, 2012). Modafinil has stimulant-like effects in humans and animals, but its pharmacology is different from the catecholaminergic stimulants d-amphetamine and methylphenidate. Although modafinil has low micromolar affinity for DAT (Zolkowska et al, 2006; Madras et al, 2008) and no affinity for NET or SERT (Madras et al, 2006; Minzenberg & Carter, 2008), positron emission tomography (PET) experiments have paradoxically revealed that therapeutic doses of modafinil occupy a substantial proportion of striatal DAT sites in the brains of humans (Volkow et al, 2009). Modafinil also decreased [123I]Catecholamine binding (Volkow et al, 2009), indicating occupancy of DAT sites resulted in increased synaptic concentrations of dopamine.

RESULTS

• In the PFC, modafinil (300 and 600 mg/kg po) significantly increased the extracellular concentrations of noradrenaline (Figure 1A) and dopamine (Figure 1B). These effects were most pronounced in the first 2 hr after administration and supported by AUC analysis (Figure 1C). This stimulant was without effect at the lowest dose of 100 mg/kg. Modafinil (100 - 600 mg/kg po) did not alter 5-HT efflux in the PFC (Figure 1C).

• In the striatum, modafinil (300 and 600 mg/kg po) increased dopamine efflux (Figure 2A,B). The increases were rapid in onset and lasted for approximately 1 hr and were approximately equal in magnitude at both doses (Figure 2A,B). Modafinil was without effect at the lowest dose of 100 mg/kg (Figures 2A, B).

• Modafinil (100 - 600 mg/kg po) did not alter striatal 5-HT efflux (Figure 2B).

• Modafinil (100 - 600 mg/kg po) produced moderate dose-dependent increases in the locomotor activity of the rats (Figure 3). However, the locomotor activity evoked by modafinil was not significantly correlated with the increase in extracellular dopamine in the striatum (r² = 0.024 at 300 mg/kg; r² = 0.002 at 600 mg/kg).

CONCLUSIONS

The results revealed that the lowest dose of 100 mg/kg po of modafinil was at the threshold of pharmacological effect. Higher doses of modafinil increased the extracellular concentrations of noradrenaline and dopamine in PFC and dopamine in the striatum. Although the magnitude of modafinil’s effect on extraneuronal catecholamine concentrations in the PFC is similar to that observed with lisdexamfetamine or methylphenidate (Rowley et al, 2012), the increase in striatal dopamine efflux was much smaller.

Measurement of locomotor activity was considered a simple and reliable measure of locomotor activity. The lack of correlation between striatal dopamine efflux and motor activity suggests other neurotransmitter(s) have a role in mediating its behavioural effects.

The current findings that modafinil has a much greater ability to enhance catecholaminergic function in the PFC than dopaminergic neurotransmission in the striatum, and in addition, that another as yet unknown neurochemical mediator may be the primary driver of modafinil’s stimulant actions help to explain why modafinil has an unusual pharmacological profile.