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Action of modafinil – increased motivation via the dopamine transporter inhibition and D1 receptors?

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Abstract

Background—Modafinil is prescribed for the treatment of narcolepsy. It has been postulated that modafinil may treat cognitive disruption in neuropsychiatric disorders. The mechanisms underlying such modafinil-induced improvements in performance have yet to be delineated however. Recent evidence suggests that modafinil may block the dopamine transporter (DAT) and that the dopamine D1 receptor (D1R) may contribute to modafinil effects.

Methods—Dopamine D1R wildtype (WT), heterozygous (HT), and knockout (KO) mice received vehicle, modafinil, or the selective DAT blocker GBR12909 in a progressive ratio breakpoint study.

Results—Both modafinil and GBR12909 increased motivation in the task as measured by an increase in breakpoint in WT and HT mice. These drug-induced increases in motivation were reduced in dopamine D1R HT mice relative to their WT littermates. D1R KO mice did not respond in the task.

Conclusions—These data support the hypothesis that modafinil increases motivation. Moreover, given the similarity of effects with GBR12909, the data corroborate evidence that the behavioral effects of modafinil may be due to DAT inhibition. Furthermore, the dopamine D1R may play a downstream role in mediating modafinil-induced increases in motivation. Thus studies reporting cognition-enhancing effects of modafinil may have been influenced by its ability to increase motivation.

Keywords

Modafinil; dopamine transporter; D1 receptor; motivation; knockout; mice

Introduction

Modafinil (2-[Diphenylmethyl)sulfinyl]acetamide; Provigil©) is an anti-narcoleptic prescribed for narcolepsy-associated somnolence, shift-work sleep disorder, and obstructive/sleep apnea syndrome. It is being investigated for treating cognitive dysfunction in several patient populations (1). While modafinil is considered safe, side-effects have been observed, including one case of psychosis (2). Understanding the mechanism(s) of modafinil action may help identify similar compounds having fewer side-effects.

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Several possible mechanisms for the action of modafinil exist, including inhibiting dopamine transporters (DAT) and/or norepinephrine transporters (NET), or increasing dopamine, serotonin, glutamate, and histamine release (1). While it was suggested that effective doses of modafinil are insufficient to inhibit DAT and hence do not act via this mechanism (3), PET studies in monkeys and man indicate 50% binding of modafinil to DAT at lower plasma concentrations than seen at therapeutic doses (4,5). Moreover, mice lacking DAT do not exhibit modafinil-induced wakefulness, although these results are confounded by elevated dopamine D1 and D2 receptor (D1R and D2R) levels in these mice (6). D1R and D2Rs may mediate modafinil-induced wakefulness (7), but evidence remains unclear. Similar behavioral effects of modafinil and selective DAT inhibitors, such as GBR12909 (8), support DAT inhibition as a mechanism for modafinil-induced hyperactivity and stereotypy.

The putative pro-cognitive effect of modafinil for treating neuropsychiatric disorders are of interest (1). Turner et al (9) described modafinil-induced improvement in schizophrenia patients performing the intradimensional/extradimensional shift test of executive function. Given the link between motivation and executive functioning in schizophrenia (10), we investigated whether modafinil may increase motivational levels. Moreover, we assessed whether modafinil would increase motivation in D1R wildtype, (WT), heterozygous (HT), or knockout (KO) mice in a progressive ratio breakpoint study (PRBS) to also assess D1R contribution. We examined whether the effects of modafinil were consistent with those of the selective DAT inhibitor GBR12909. We hypothesized that modafinil and GBR12909 would increase motivation in a gene dose-dependent manner – attenuated in HT mice and ineffective in KO mice.

Materials and Methods

Animals

Dopamine D1R mice, from Jackson Laboratory (Bar Harbor, ME), were backcrossed for 12 generations onto a C57BL/6J background. Male and female mice WT (n=8), HT (n=8), and KO (n=5) were derived from heterozygous breeding pairs and genotyped. Procedures were approved by the UCSD Institutional Animal Care and Use Committee.

Training and testing

Training and testing took place in 5-hole-operant-chambers (25×25×25 cm, Med Associates Inc., St. Albans, VT). Mice were shaped to hole-poke in the central hole for a single food reward (fixed ratio, FR). Once hole-poking reliably, mice were challenged in a 60 min PRBS (11). **Breakpoint** was defined as the last ratio to be completed. Mean response (**MRL**) and reward (**MRewL**) latencies were calculated. During challenges, mice received vehicle, or modafinil (16-, 32-, or 64-mg/kg), in a within-subjects crossover design (experiment 1), on Tuesday and Fridays, with FR1 training and saline injections between testing (Monday, Wednesday, and Thursdays). Two weeks later, this was repeated with saline or GBR12909 (9-, 16-, or 28.5-mg/kg, experiment 2). For more information on drug preparation and statistics, see Supplementary Materials in Supplement 1.

Results

Training

Results are detailed in Supplement 1. WT and HT mice readily trained to a FR1 and did not differ in total responses ($F(1,130)<1$), while KO mice did not respond to a FR1, consistent with previous reports (12), and therefore experimental challenge results were compared only between WT and HT mice. No effects of sex or drug-by-sex interactions were found ($p>0.1$).

Experiment 1: Modafinil effects on motivation and speed of performance

Main effects of drug ($F(3,45)=4.3, p<0.05$) and gene ($F(1,15)=5.2, p<0.05$), and a trend toward a drug-by-gene interaction ($F(3,45)=1.9, p=0.092$; Fig. 1A) were observed for breakpoint. *Post hoc* analyses revealed that 32- and 64-mg/kg modafinil increased breakpoint in WT mice compared to saline, while only 64 mg/kg increased breakpoint in HT mice ($p<0.05$). There was a main effect of drug ($F(3,45)=7.0, p<0.001$; Fig. 1B) observed for MRL, with no gene or drug-by-gene interaction ($p>0.1$). *Post hoc* analyses revealed that modafinil sped MRL in WT and HT mice at every dose ($p<0.05$). Consistent with MRL, a main effect of drug ($F(3,45)=8.0, p<0.0001$; Fig. 1C), but no interactions on MRewL performance was observed ($p>0.1$). *Post hoc* analyses revealed that modafinil lowered MRewL of WT and HT mice at every dose ($p<0.05$). No drug effect was observed in D1R KO mice at any dose in any measure.

Experiment 2: GBR12909 effects on motivation and speed of performance

The main effect of drug ($F(3,45)=3.5, p<0.05$) and the drug-by-gene interaction ($F(3,45)=3.7, p<0.05$; Fig. 2A) were significant for breakpoint. *Post hoc* analyses revealed that GBR12909 increased the breakpoint of WT mice at 16-mg/kg, while 10-mg/kg increased breakpoint in HT mice ($p<0.05$). At 16- and 28-mg/kg GBR12909, WT mice exhibited trends toward increased breakpoint compared to HT mice ($p=0.072$ and 0.059 respectively). Consistent with modafinil, a drug effect was observed on MRL ($F(3,45)=3.0, p<0.05$; Fig. 2B), with no interactions ($p>0.05$). *Post hoc* analyses revealed that the only 10-mg/kg reduced MRL in WT and HT mice ($p<0.05$). For MRewL, a main effect of drug was observed ($F(3,45)=2.9, p<0.05$; Fig 2C), with no interactions ($p>0.05$). *Post hoc* analyses revealed that 10-mg/kg lowered MRewL in WT and HT mice ($p<0.05$). Consistent with experiment 1, no drug effect was observed in D1R KO mice.

Discussion

Modafinil increased motivation and sped the performance of dopamine D1R WT and HT mice in a PRBS. The effects of modafinil were consistent with those of the selective DAT inhibitor GBR12909. The drug-by-gene interactions observed for these two compounds suggest that the drug-induced increases in motivation were more robust in WT compared to HT mice. No effect was observed in D1R KO mice due to their lack of operant responding for reward. The data indicate several important aspects regarding the action of modafinil; 1) it can increase motivation, 2) it may do so as a result of DAT inhibition, and 3) it might also indirectly act on D1Rs to increase motivation.

Previous studies demonstrated an amphetamine-induced increase of breakpoint in mice, suggested to be DAT inhibition-mediated (11). Ambiguity exists however because amphetamine is 4–6-fold more effective on NET than DAT (13). Given that GBR12909 is selective for DAT, the present data indicate that selective DAT inhibition increases motivation in mice. Modafinil similarly increased motivation in mice. These data support recent evidence that the mechanism of action of modafinil on behavior is via DAT inhibition (4,5). While evidence for the behavioral effects of modafinil via DAT inhibition has only been generated in non-humans, modafinil-induced increased motivation in humans (14) supports the likelihood of DAT inhibition-mediation of effects in humans also.

GBR12909- and modafinil-induced increases in motivation interacted with D1R expression. *Post hoc* analyses revealed reduced effect of each drug on mice with only 50% D1R expression (HT mice) compared to WT mice. These data support earlier suggestions that some of the behavioral effects of modafinil are mediated in part by D1R (7). While altered DAT expression in HT mice may also account for these findings, to the authors' knowledge DAT expression in these mice have yet to be studied. Alpha-1 adrenergic receptor activation in D1 mutant mice

may also contribute to the observed drug-by-gene interaction because this receptor may mediate modafinil-induced wakefulness via DAT inhibition-induced increased dopamine (15). Support that the D1R can affect motivation comes from observations that the D1R antagonist SCH23390 reduced motivation in PRBS in both monkeys (16) and rats (17). Moreover, D1R KO mice do not self-administer cocaine (18) or respond as readily as WT to appetitive (12) or aversive stimuli (19). Since the primary effects of GBR12909 and modafinil appear to be DAT inhibition (4,5,8), the interaction with D1R is likely to be an indirect consequence of DAT inhibition-induced increases in synaptic dopamine levels.

Modafinil and GBR12909 sped performance in the task as measured by MRL and MRewL, supporting a common mechanism of action. The U-shaped dose response effect of GBR12909 could be due to NET inhibition at higher doses, which can produce effects similar to amphetamine (20). The lack of U-shaped effect of modafinil is consistent with suggestions that modafinil does not act on NET (15). These data are consistent with observations that modafinil speeds performance (1). The lack of drug-by-gene interactions suggests that D1R are not important for DAT inhibition-mediation of psychomotor speeding.

The evidence that modafinil increases motivational levels should be considered when conducting studies in humans, especially in clinical populations such as schizophrenia where apathy is observed. In fact, the conclusion that modafinil improved set-shifting performance in schizophrenia patients was based on the percentage of patients that continued beyond the extradimensional shift—essentially those that did not give up at that stage (9). Therefore this result may have been confounded by modafinil increasing the motivation of the patients to perform the experiment. A possible link between apathy and executive functioning in schizophrenia patients further complicates the interpretation of the modafinil set-shifting study (10). Although further investigation is required, these studies increase the evidence that modafinil exerts its behavioral effects via DAT inhibition that go beyond wake promotion or hyperactivity. Furthermore, evidence for D1R mediation of modafinil appears likely to reflect downstream effects subsequent to DAT inhibition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Modafinil-induced increase in motivation and speeding of performance

Modafinil increased breakpoint in D1R WT and HT mice, with lower doses being needed for WT mice (A). Due to a lack of response, KO mice were not included in the analyses. Modafinil lowered response (B) and reward latencies (C) irrespective of genotype. Data presented as mean + s.e.m. * denotes $p < 0.05$ compared to vehicle dose.

Figure 2. GBR12909-induced increase in motivation and speeding of performance

GBR 12909 significantly increased breakpoint in D1R WT and HT mice, with greater effects observed in WT mice (A). Due to a lack of response, KO mice were not included in the analyses. GBR 12909 also sped performance at the lowest dose as measured by response (B) and reward latencies (C), irrespective of genotype. Data presented as mean + s.e.m. * denotes $p < 0.05$ compared to vehicle dose, \$ denotes $p < 0.08$ compared to HT mice.