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Original research article

Antidepressant-like effect of modafinil in mice: Evidence for the involvement of the dopaminergic neurotransmission

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ABSTRACT

Background: Modafinil is a wake-promoting agent that provides wide ranges of neurological effects. There is evidence that it can produce antidepressant effects. This study investigated the antidepressant effect of modafinil in the tail suspension (TST) in mice.
Methods: Different doses of modafinil was intraperitoneally (*ip*) administrated and then animals were subjected to TST and/or open field test (OFT). Moreover, the implication of the dopaminergic neurotransmission in modafinil's antidepressant effect was studied. For this purpose, animals were pretreated with haloperidol (non-selective dopamine receptor antagonist), or SCH23390 and sulpiride (the dopamine D_1 and D_2 receptor antagonist, respectively), then were assessed by TST. The possible effect of sub-effective dose of modafinil in combination with sub-therapeutic doses of standard antidepressants was also evaluated in separate groups.
Results: Modafinil (75 mg/kg, *ip*) produced antidepressant effect in TST, as compared to a control group, without any alterations in ambulation in OFT. Pretreatment of mice with haloperidol (0.2 mg/kg, *ip*) and sulpride (50 mg/kg, *ip*) blocked the anti-immobility effect of modafinil (75 mg/kg, *ip*). We also found that the administration of SCH23390 (0.05 mg/kg, *sc*) couldn't antagonize the antidepressant effects of modafinil. In addition, a sub-effective dose of modafinil (50 mg/kg, *ip*) potentiated the sub-effective doses of standard antidepressants including of bupropion (1 mg/kg, *ip*), fluoxetine (1 mg/kg, *ip*) and imipramine (0.1 mg/kg, *ip*) and reduced immobility time in TST.
Conclusion: Results show that modafinil induced an antidepressant property in TST and this effect apparently was mediated through interaction with the dopaminergic (D_2 receptors) system.

Introduction

Depression is a psychiatric mood dysfunction, and its 17% prevalence in the population means that it can occur in any given person's lifetime [1,2]. Therefore, it must be considered a major healthcare problem in need of new solutions [1]. Depression impairs mood and cognition abilities, and frequently causes thoughts of death and suicide [3]. Due to these abnormal psychiatric conditions, it poses a significant social burden [4] and reduces the quality of life in depressed individuals [3]. For decades, it was believed that depression accompanies dysfunction of brain noradrenergic and serotonergic systems [5]. The focus on these systems in order to treat depression comes from the development of antidepressants that improve the neurotransmission of these systems [6].

The implication of dopaminergic neurotransmission in the pathophysiology of depression and its role has been emphasized. Pharmacologic silencing of the dopaminergic system through a chemical blockade of its receptors and/or depletion of dopamine content of dopaminergic neurons can mimic depressive-like behavior in animal models [5,6]. Some animal models of depression (e.g. learned helplessness test) are associated with the brain's dopamine deficits, and so dopaminergic agonists increase dopamine neurotransmission and improve depression-like behavior in the affected animals [6,7].

On the other hand, findings from postmortem studies in depressed patients exhibit a decline in cerebrospinal homovanillic acid level as a final metabolite of dopamine, which also correlates with some depression symptoms [7]. Given this, reduced dopamine neurotransmission correlates with the appearance of

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depression [6]. Depression is also associated with impairment of motivation, psychomotor speed [7] and the appearance of anhedonia [5]. All of these symptoms stem from abnormalities within the dopaminergic mesolimbic and mesocortical systems [8]. Most administrated antidepressants currently improve the disease signs in 70–80% of the depressed individuals [3]. On the other hand, use of antidepressant medication is associated with some adverse side effects [1] and it can take over 1–2 months for clinical effects to appear [3]. Therefore, the development of alternative and efficacious medications to treat depressive disorders is a high priority.

Modafinil (2-[(Diphenylmethyl) sulfinyl] acetamide) is a novel wake promoting medication, first approved by the US Food and Drug Administration (FDA) for its application in treating narcolepsy [9,10] and other sleep disorders [9,11]. Due to its wide range of pharmacological effects, there are studies for its use in treating some neurological conditions, such as cognition and memory impairments [12], nicotine and cocaine addictions, attention deficit disorder, schizophrenia [13] and Parkinson's disease [9]. Modafinil's pharmacological effects are mediated in part through the dopaminergic system [11,13]. Given this and other evidence that shows its ability to activate the D_1 and D_2 dopamine receptors [12,14], it seems that it may have a beneficial role in treating depression conditions. Based on this premise, we designed the present study to evaluate modafinil's probable antidepressive effect in a mouse model of depression and the implication of D_1 and D_2 dopaminergic receptors in this effect.

Materials and methods

Animals

Male albino mice weighing 25–30 g were used in the present study. Animals were obtained from the animal unit of Tabriz University of Medical Sciences and were kept in standard polypropylene cages (eight per cage), at temperature (22–25 °C), under a 12:12 h light/dark cycle with free access to water and food. All experiments were carried out between 09:00 and 14:00 by an observer who was unaware of the nature of treatments. The animals were used only once for each assessment.

This investigation was done in accordance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health) and confirmed by the Ethical Committee for Animal Experimentation of Tabriz University of Medical Sciences.

Drugs and treatments

The following drugs were used in this study: modafinil, haloperidol (non-selective dopamine receptor blocker), SCH23390 (dopamine D_1 receptor antagonist), sulpiride (dopamine D_2 receptor antagonist), bupropion (selective dopamine reuptake inhibitor with subtle activity on noradrenaline reuptake), fluoxetine (selective serotonin reuptake inhibitor) and imipramine (noradrenaline and serotonin reuptake inhibitor). All drugs were obtained from Sigma Chemical Co., USA.

Drugs were prepared in physiological saline, except for the modafinil, which was suspended in saline with 0.4% sodium carboxy methylcellulose. Haloperidol and sulpiride were dissolved in 5% dimethyl sulfoxide and were made up to the final volume by adding a saline solution. Chemicals were prepared freshly before administration and injected intraperitoneally (*ip*), except SCH23390, which was injected through a subcutaneous (*sc*) route. All drugs were administered at a constant volume of 10 ml/kg body weight.

The present study was conducted in three distinct phases. The first phase was done to evaluate modafinil's ability to decrease immobility time in mice and determine the effective antidepressant dose of modafinil. In this phase, mice were treated with different doses of modafinil (50, 75 and 100 mg/kg) or its vehicle, and 30 min later were subjected to a tail suspension test (TST) and open field test (OFT). Moreover, bupropion, fluoxetine and imipramine (as positive controls) or their vehicles were administrated at doses of 10 mg/kg, *ip*, in separate groups of mice. The doses of antagonists and conventional antidepressants were adopted from previous studies [1,8,15,16].

The second phase was done to evaluate the possible contribution of dopaminergic system on the antidepressant-like effect of modafinil in the TST. In this phase, separate groups of mice were pretreated with haloperidol (0.2 mg/kg, *ip*), SCH23390 (0.05 mg/kg, *sc*), sulpiride (50 mg/kg, *ip*) or their vehicles, and after 30 min, they received modafinil (75 mg/kg) or the vehicle before being tested (the TST) again 30 min later.

In the third phase, modafinil's ability to potentiate the subeffective doses of conventional antidepressants (bupropion, fluoxetine and imipramine) was evaluated. To this end, mice received *ip* injections of the vehicle, bupropion, fluoxetine (both at doses of 1 mg/kg) or imipramine (0.1 mg/kg), and then immediately received modafinil (50 mg/kg) or its vehicle by *ip* route. Thirty minutes later, the animals were subjected to a TST. The locomotor activity of the mice was assessed in separate groups receiving the same treatments.

Tail suspension test (TST)

Depression-like behavior was induced in the test subjects by suspending mice by the tail for 6 min. As described previously, mice that had been both acoustically and visually isolated were hung upside-down 50 cm above a tabletop by adhesive tape placed nearly 1 cm from the tip of the tail. Duration of immobility periods, in seconds, in this imposed posture was recorded as immobility time [1,3,17].

Open field test (OFT)

To rule out any possible effects of the effective dose of modafinil (75 and 100 mg/kg) on locomotor activity, 30 min after *ip* administration of each dose, mice were subjected to the OFT for 6 min. As described previously [1,3], mice were individually placed in the center of wooden open field arena (40 cm × 60 cm × 50 cm) with the floor of box divided into 12 equal rectangles. For each animal, the number of crossed rectangles with all paws crossing was counted and considered as a marker for locomotor activity. After each trial, the arena was cleaned with a 10% ethanol solution to eliminate the presence of any olfactory cues.

Statistical analysis

Statistical analysis of each data set was done by SPSS 21 software. The data were presented as the mean ± SEM and were analyzed by two and/or one-way ANOVA and *post hoc* Tukey's test. Statistical significance for this study was defined at $p < 0.05$.

Results

Effects of modafinil on the TST and OFT

One way ANOVA, revealed a significant effect of modafinil [$F(3, 32) = 28.15$ $p < 0.01$] on the immobility time. *Post hoc* analysis showed that modafinil at the doses of 75 and 100 mg/kg decreased the immobility time in TST (Fig. 1), which indicates that modafinil in these doses produces an antidepressant-like effect. Also, the injection of the modafinil vehicle did not produce any effect in TST.

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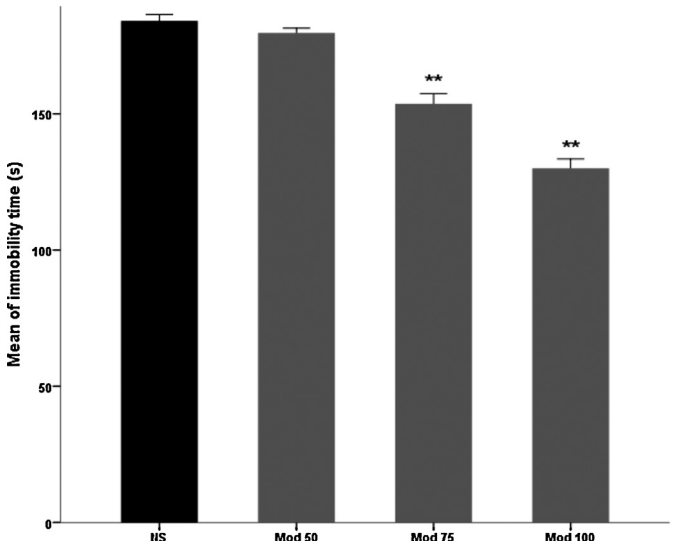

Fig. 1. Effect of administration of different doses of modafinil (50, 75 and 100 mg/kg, *ip*) on the immobility time in the TST. Each bar represents the mean ± SEM. $^{**}p < 0.01$ compared with the normal saline treated group. (NS, normal saline; Mod, modafinil).

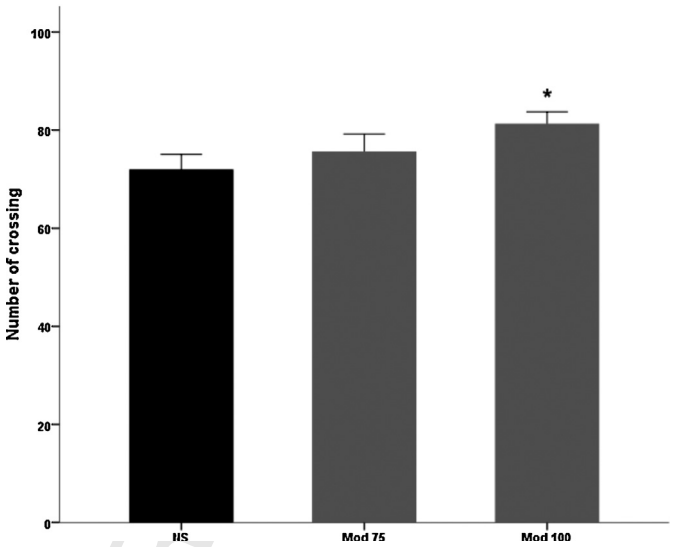

Fig. 2. Effect of administration of different doses of modafinil (75 and 100 mg/kg, *ip*) on the number of crossings in the OFT. Each bar represents the mean ± SEM. $^{*}p < 0.05$ compared with the normal saline treated group. (NS, normal saline; Mod, modafinil).

One way ANOVA, revealed a significant effect of modafinil [$F(2, 24) = 5.36$ $p < 0.05$] on the number of crossing. *Post hoc* analysis showed that modafinil at the dose of 100 mg/kg increases locomotor activity in the OFT as compared to the control group ($p < 0.05$), (Fig. 2).

Hence, reduction in the immobility time in the TST at this dose was due to its psycho-stimulant effect. In contrast, modafinil at the dose of 75 mg/kg was not able to alter the locomotor function; therefore this dose was applied as an effective antidepressant dose and the dose of 100 mg/kg was excluded from future evaluations.

One way ANOVA, indicated a significant effect of treatments [$F(4, 40) = 31.52$ $p < 0.01$] on the immobility time. *Post hoc* analysis showed that modafinil (75 mg/kg), bupropion, fluoxetine and imipramine (10 mg/kg) decreased the immobility time in TST in comparison with normal saline treated group ($p < 0.01$), (Fig. 3). As seen, all of the antidepressants produced an antidepressant effect in this model. However, administration of vehicles didn't impact the immobility time, and therefore its results haven't shown in this figure.

Involvement of dopaminergic system on the antidepressant-like effect of modafinil

Modafinil (75 mg/kg, *ip*) produced an antidepressant effect ($p < 0.01$) and the possible implications of the dopaminergic system on modafinil's effect were investigated in separate groups of mice.

A two-way ANOVA revealed significant differences of modafinil treatment [$F(1, 32) = 40.52$ $p < 0.001$], haloperidol pretreatment [$F(1, 32) = 37.15$ $p < 0.001$] and modafinil treatment × haloperidol pretreatment interaction [$F(1, 32) = 18.75$ $p < 0.01$]. The results presented in Fig. 4A, shows that pretreatment of mice with haloperidol (0.2 mg/kg, *ip*) prevented anti-immobility effect of modafinil in the TST.

A two-way ANOVA revealed significant differences of modafinil treatment [$F(1, 32) = 15.53$ $p < 0.05$] and SCH23390 pretreatment [$F(1, 32) = 6.25$ $p < 0.05$] but not modafinil treatment × SCH23390 pretreatment interaction [$F(1, 32) = 2.21$ $p > 0.05$].

As shown in Fig. 4B, pretreatment of mice with SCH23390 (0.05 mg/kg, *sc*) did not alter anti-immobility effect of modafinil in the TST.

A two-way ANOVA showed significant differences of modafinil treatment [$F(1, 32) = 13.18$ $p < 0.05$], sulpiride pretreatment [$F(1, 32) = 33.1$ $p < 0.001$] and modafinil treatment × sulpiride pretreatment interaction [$F(1, 32) = 11.9$ $p < 0.01$].

The results presented in Fig. 4C, shows that pretreatment of mice with sulpiride (50 mg/kg, *ip*) inhibited anti-immobility effect of modafinil in the TST.

Interaction of modafinil with antidepressants in TST

Separate groups of mice received concomitant injections of sub-effective doses of bupropion (1 mg/kg, *ip*) and fluoxetine (1 mg/kg, *ip*) or imipramine (0.1 mg/kg, *ip*) with modafinil. These treatments did not have any effect on the animals locomotor activity in the OFT, hence the related data were not appeared in results.

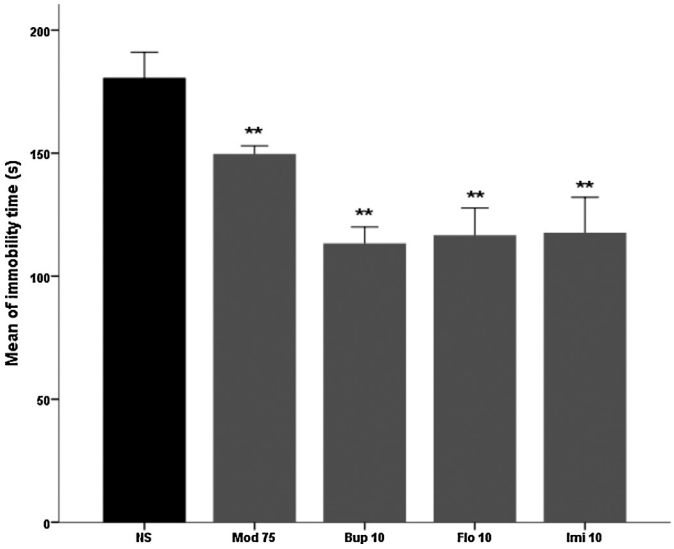

Fig. 3. Effect of administration of modafinil (75 mg/kg, *ip*), bupropion, fluoxetine and imipramine (10 mg/kg, *ip*) on the immobility time in the TST. Each bar represents the mean ± SEM. $^{**}p < 0.01$ compared with the normal saline treated group. (NS, normal saline; Mod, modafinil; Bup, bupropion; Flo, fluoxetine).

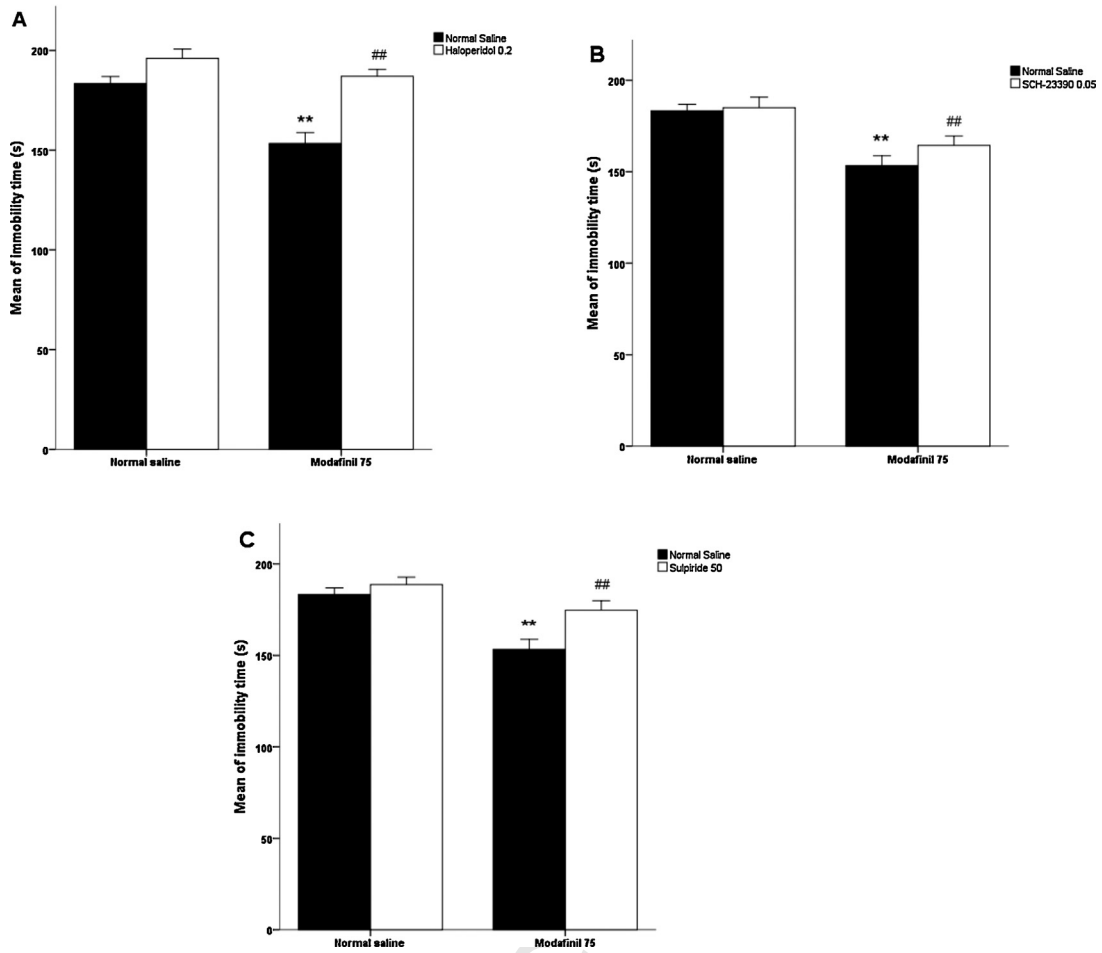

Fig. 4. Effect of pretreatment of mice with haloperidol (0.2 mg/kg, *ip*) (A), SCH23390 (0.05 mg/kg, *sc*) (B) and/or with sulpiride (50 mg/kg, *ip*) (C) on the modafinil-induced reduction in immobility time in the TST. Each bar represents the mean ± SEM. $^{**}p < 0.01$ and $^{\#\#}p < 0.01$ compared with the normal saline and the modafinil (75 mg/kg, *ip*) received groups, respectively.

As depicted in Fig. 5A, co-administration of sub-effective dose of modafinil (50 mg/kg, *ip*) was able to potentiate the action of a sub-effective dose of imipramine (0.1 mg/kg, *ip*).

A two-way ANOVA revealed significant differences of modafinil treatment [$F(1, 32) = 15.38$ $p < 0.01$], imipramine pretreatment [$F(1, 32) = 24.01$ $p < 0.001$] and modafinil treatment × imipramine pretreatment interaction [$F(1, 32) = 5.53$ $p < 0.05$].

Fig. 5B, shows that concomitant administration of sub-effective dose of modafinil (50 mg/kg, *ip*) with sub-effective dose of fluoxetine (1 mg/kg, *ip*) augments its antidepressant action.

A two-way ANOVA revealed significant differences of modafinil treatment [$F(1, 32) = 15.52$ $p < 0.01$], fluoxetine pretreatment [$F(1, 32) = 18.96$ $p < 0.01$] and modafinil treatment × fluoxetine pretreatment interaction [$F(1, 32) = 5.41$ $p < 0.05$].

As depicted in Fig. 5C, co-administration of sub-effective dose of modafinil (50 mg/kg, *ip*) with sub-effective dose of bupropion (1 mg/kg, *ip*) potentiates the action of bupropion.

A two-way ANOVA revealed significant differences of modafinil treatment [$F(1, 32) = 14.45$ $p < 0.01$], bupropion pretreatment [$F(1, 32) = 25.96$ $p < 0.001$] and modafinil treatment × bupropion pretreatment interaction [$F(1, 32) = 5.54$ $p < 0.05$].

Discussion

Our data indicated that systemic modafinil exerts an anti-depressive-like behavior on mice in the TST, and this ability is dependent on an interaction with dopaminergic neurotransmission. On the other hand, findings showed that modafinil (50 mg/kg, sub-effective dose) in combination with sub-effective doses of conventional antidepressants potentiated their effects and decreased the immobility time in TST.

Moreover, investigation of the spontaneous locomotor activity of modafinil by OFT indicated that the ability of modafinil at the dose that produced an antidepressant-like effect (75 mg/kg, *ip*) is not able to alter normal locomotion function. Given this, it may be suggested that the antidepressant effect of modafinil is not due to its psycho-stimulant effect. The OFT is an effective task to rule out any false results in the investigation of potential antidepressant drugs [1,18].

Generally, depression results from an inability to overcome unpleasant environmental stimulus [16]. The TST as a model of despair produces unavoidable, unpleasant and stressful conditions; hence it is used as a validated model of this unpleasant state in mice [19], and the TST is very sensitive to all classical antidepressant drugs, including tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs) [20]. The pharmacologic profile of modafinil is complex, but it may alter the amount of different neurotransmitter systems [9]. It binds to the dopamine and noradrenaline transports and blocks the re-uptake of these monoamines, thereby elevating their synaptic levels [21]. Moreover, other neurotransmitter systems serotonergic, gabaergic, glutamatergic and histaminergic are also influenced by modafinil action. Furthermore, clinical studies have demonstrated that modafinil is able to enhance alertness, amount of energy and mood condition in human cases [22]. In regards to the pivotal role of the dopaminergic system in

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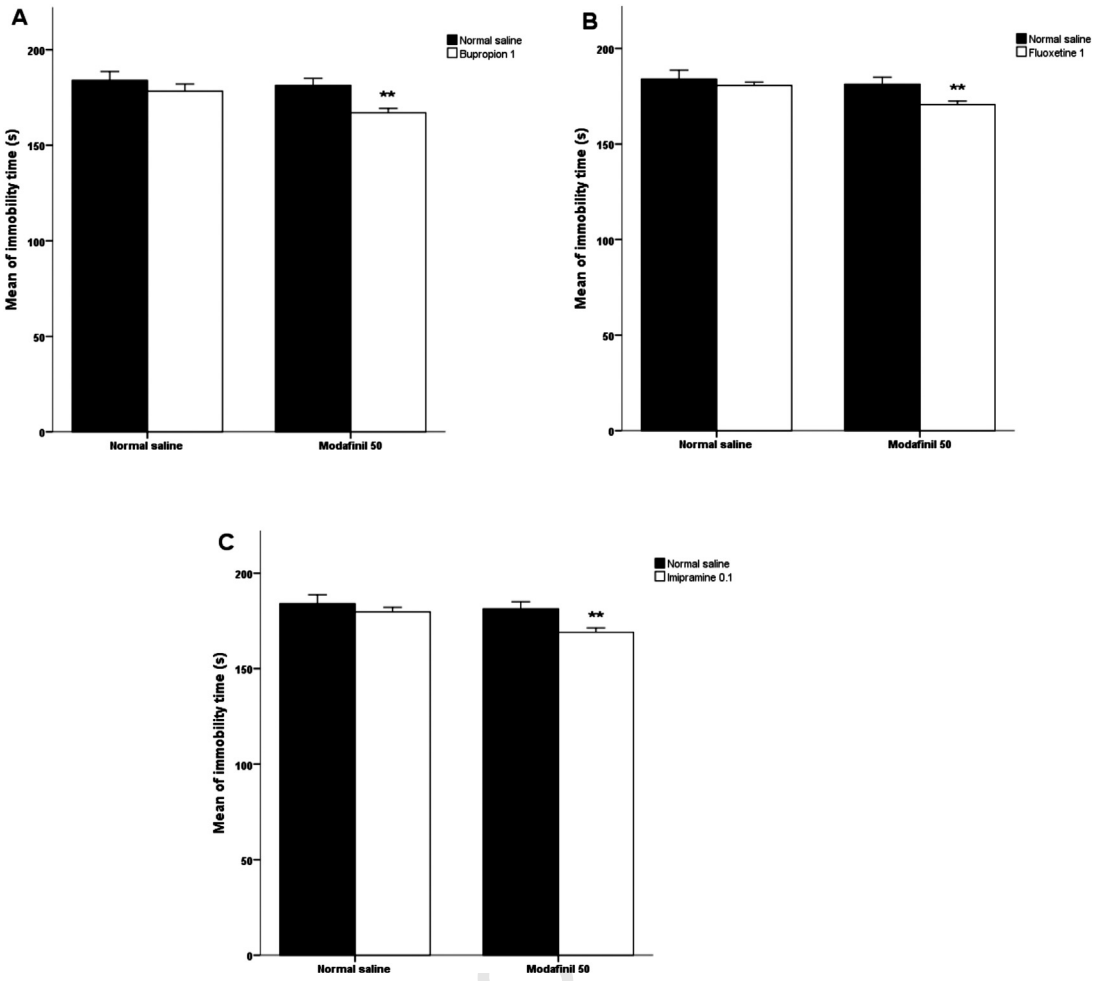

Fig. 5. Effect of co-administration of modafinil (50 mg/kg, *ip*, sub-effective) with sub-effective doses of bupropion (1 mg/kg, *ip*) (A), fluoxetine (1 mg/kg, *ip*) (B) and imipramine (0.1 mg/kg, *ip*) (C) on the immobility time in TST. Each bar represents the mean ± SEM. $^{**}p < 0.01$ compared with the normal saline treated group.

depression [23] and modafinil's ability to then regulate that level, it suggests that modafinil has the potential to produce antidepressant properties.

A majority of depressed individuals suffer from anhedonia (the lack of responsiveness to life's pleasurable activities), loss of motivation and interest, feelings of worthlessness and guilt and diminished concentration ability and suicidal thoughts [24]. Loss of motivation and experience of anhedonia are the core symptoms of depression and other psychiatric conditions [25], resulting from the brain's reward system dysfunction [24]. The function of the brain's reward system [6,26] is mediated through mesolimbic pathways. The nucleus accumbense (NA) receives dopaminergic neurons from the ventral tegmental area (VTA) [25,27]. It is known that response to hedonic experiences increases NA dopamine neurons firing and dopamine release. However, impairment of dopaminergic neurons in this area is accompanied by the appearance of depression [28,29]. Findings from human cases show that stimulation of dopamine release by deep brain stimulation to the NA improves the motivation and anhedonia in patients with major depressive disorder [28]. Hence, the observed effect for modafinil in reduction of TST induced depression-like behavior could be attributed in part to its effect on the dopamine levels. Within the NA, modafinil increases dopamine levels through inhibition of GABA transmission [9].

Microdialysis studies conducted by Murillo-Rodrigues et al., have demonstrated that modafinil provokes dopamine release in the NA region of rats [30]. The ability of modafinil to increase accumbal dopamine levels is also supported by Volkow et al. using positron-emission tomography (PET) [31].

In the other portion of study (animals pretreated with haloperidol), the treatment increased immobility time in TST and prevented the antidepressant effects of modafinil (75 mg/kg). Moreover, a pharmacologic blockade of the D_2 receptors using a sulpiride reversed the anti-immobility effect of an effective dose of modafinil. Different lines of evidence show that cerebral dopaminergic transmission may regulate mood function through activation of D_2 receptors [6]. These type of dopaminergic receptors are connected to the G-protein and are located in the NA [32]. They directly regulate the firing of dopaminergic neurons [33]. It is proposed that depression is coupled with reduction of dopamine neurotransmission and leads to compensatory increasing of D_2 receptor density [3]. Hence, in this situation compounds with the agonistic effect on these receptors may mimic the mechanism of antidepressants and improve depressive behavior [6]. The implication of D_2 receptors in depression has been confirmed by experimental studies, which demonstrate that D_2 receptor agonists can reverse depressive behavior in some animal models of depression [6,22,32].

Contrary to D_2 receptors, the blockade of D_1 receptors by SCH23390 could not create an impact on the antidepressant effect of modafinil. The role of these receptors in the pathophysiology of depression is complex and controversial. D_1 blockers such as SCH23390 stimulate dopamine release and increase the firing rate of dopamine neurons [32]. Unlike these findings, several reports

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state that the antidepressant effect of some kinds of regimens with antidepressant potential can be inhibited by the action of SCH23390 in forced swimming test and TST [3,23,34].

Studies show that both D_1 and D_2 receptors are responsive to some of the neurological effects of modafinil. Given this, using D_2 receptors knout mice and pharmacologic silencing of D_1 and D_2 receptors, showed that modafinil through activation of D_1 and D_2 receptors induces its wake-promoting effect [14]. The involvement of these receptors in the cognitive modifying effects of modafinil has been established in previous studies [35].

The cooperative effects of activating of dopamine D_1 and D_2 receptors are not yet fully understood [36]. Although these receptors have opposite mechanisms of action, they are able to provide synergetic [37] and/or opposite effects [38] in complex neuronal procedures. Dias et al. reported that stimulation of D_2 receptors leads to cocaine-seeking behaviors in addicts, but stimulation of D_1 receptors does not exert any effect on such behavior [39]. In the NA, the cooperative effect of these receptors is necessary for the processing of reward-related functions [36], but only a limited population of the dopaminergic neurons contain both of these receptors [36,38]. These functional and anatomical differences may explain why modafinil exerts its antidepressant effect only through the activation of D_2 receptors.

Behavioral and neurochemical evidence point out the more complex mechanisms for modafinil's neuronal effects. For example, immunoblotting and cognitive studies conducted by Sase et al. showed that in a mouse study, modafinil impacts a wide range of brain receptors, including dopaminergic, glutamatergic and nicotinic acetylcholine receptors. Indeed, it may have an impact on the receptor–receptor interactions and modify some of the brain's complex signaling and neurotransmission patterns [12].

Finally, this research showed that modafinil is able to potentiate the sub-effective dose of different types of approved antidepressants, fluoxetine (selective serotonin reuptake inhibitor), imipramine (noradrenaline/serotonin reuptake inhibitor) and bupropion (dopamine reuptake inhibitor). Findings from PET images have revealed that modafinil has an affinity for binding to the brain's amines transporters [35]. Moreover, *in vivo* studies show that it is able to modulate dopamine, noradrenaline and serotonin's extra-cellular levels [40].

Interestingly, Ferraro et al., demonstrated that concomitant administration of modafinil with fluoxetine, paroxetine and imipramine mutually enhances the effects of each in increasing of cerebral serotonin levels [41,42].

Complications such as delayed onset of action and inadequate response to approved antidepressants remain major problems to the remission of depressed patients [43]. Hence, application of treatments to overcome these problems is of importance, and the synergetic effect of modafinil and conventional antidepressants suggest that modafinil may have the potential to improve the effectiveness of currently prescribed medications.

Conclusion

In conclusion, results from this study showed that modafinil is able to induce an antidepressant effect in a mouse model of depressive behavior. Considering the pivotal role of the dopaminergic system and D_2 receptors' involvement in the depression-related behaviors, it may be postulated that modafinil is an effective choice for depressive conditions. On the other hand, our results showed that it potentiates the sub-therapeutic effects of registered antidepressants; hence, it may be used as combination therapy in depressed patients. Due to modafinil's complex neuromodulatory effects, it seems that more preclinical and clinical investigations must be designed to find out its exact neurological effects.

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Conflict of interest

The authors have declared that there is no conflict of interest.

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