

An analytical review on probable anti-parkinsonian effect of modafinil

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Review Article

Abstract

Restoring of dopamine levels in Parkinson's disease (PD) has been considered as the main symptomatic therapy. In this strategy, long-term administration of L-DOPA (3, 4-dihydroxyphenylalanine) results in motor impairments. This necessitates novel approaches in which PD is tackled with lower deleterious side effects. Modafinil is an awake-promoting agent clinically used for treatment of excessive daytime sleeping. This medication increases dopamine levels and decreases oxidative stress, and can thus exert anti-parkinsonian effect. Therefore, this review will give an account of the probable anti-parkinsonian mechanisms of modafinil.

KEYWORDS: Parkinson's Disease, Modafinil, Dopamine, Oxidative Stress

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Introduction

Parkinson's disease (PD) is an age-related debilitating locomotor disorder, affecting nearly 2% of people older than 60 years. In this disease irreversible destruction of dopaminergic neurons is seen.¹ This leads to a decline of approximately 60-70% in striatal dopamine levels.² As a result, cardinal clinical symptoms of disease, such as tremor at rest, bradykinesia, akinesia, and muscle rigidity, appear in PD.^{3,4}

L-DOPA (3,4-dihydroxyphenylalanine) remains as a standard pharmacotherapy for alleviation of PD motor symptoms; its long-term administration, however, gives rise to motor impairments in patients with PD. These un-wanted motor problems are known as L-DOPA induced dyskinesia (LID) and on-off phenomena.⁵ There is a pressing need to develop novel strategies in order to obviate these impairments.

Modafinil 2-[(Diphenylmethyl) sulfinyl]acetamide (Figure 1) is a novel psychoactive agent which was first approved by the Food and Drug Administration (FDA) for its wake promoting effect in 1980.⁶ Nowadays, it is classified as a schedule IV drug by the FDA.⁷ In addition, it is used for treatment of shift work disorders and sleep apnea.⁸

Modafinil has been postulated to exert wide ranges of pharmacologic effects upon multiple neurotransmitter systems.⁹ For instance, modafinil is able to alternate GABAergic, dopaminergic, catecholamine, norepinephrine, and serotonergic systems. Furthermore, following administration of modafinil, increased locomotion was observed in rats, mice, and cats.¹⁰

Contrary to other psychostimulants, modafinil shows lower abuse potential and toxic effects to the vital organs.¹¹ This property has increased interest for investigation of the

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influence of modafinil on fatigue syndromes, drug-resistant depression, and attention deficit/hyperactivity disorder (ADHD). Taking into account the pivotal role of dopaminergic system in PD and modafinil ability to regulate this system, it might be postulated that modafinil has anti-parkinsonian effects. This study reviews current literature on anti-parkinsonian effects and related mechanisms of modafinil.

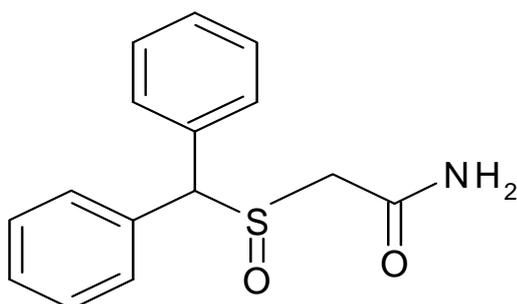


Figure 1: Chemical structure of Modafinil

Methods

For reviewing of available data about anti-parkinsonian effects of modafinil, those relevant papers which have been published during 2001-2012 have been searched in the validated scientific databases, such as Pubmed and Scopus, and repetitious and invalid articles have been eliminated from this study. Raw data was extracted from the established papers and two investigators classified these data.

Modafinil neuroprotective effects:

According to results obtained from pre-clinical data, modafinil is able to protect some types of neurons from toxins and prevent neurodegeneration.^{12,13}

Jenner et al. evaluated the neuroprotective and anti-parkinsonian effects of modafinil on monkeys. They found that modafinil stimulates locomotor effects on PD animals, and has a protective effect on damaged neurons.¹⁴ Other studies indicated that modafinil reduced striatal GABA, raised the reduced levels of glutathione in damaged neurons, and declined lipid peroxidation

levels. These results propose that modafinil has a neuroprotective effect via its ability to attenuate or prevent oxidative stress.¹⁵ Furthermore, modafinil could directly act on brain enzymes to directly reduce free-radical levels.¹⁶

The mitochondrion is the biggest producer of reactive oxygen species in cells and modafinil may target this organelle to directly inhibit free-radical production. Moreover, modafinil may enhance cytochrome C's ability to accept and donate electrons by not only allosteric modification, but also a catalytic mechanism.¹⁷ Other cytochrome P450 enzymes, such as CYP2C enzymes, have been found in the brain wherein modafinil may interact. Some studies showed that modafinil suppresses brain CYP2C9 and reduces reactive oxygen species production.¹⁸ In addition, the drug may play an antioxidant role throughout modulation of adenosine levels in the brain.¹⁹

Zeng et al. stated that a dose of modafinil is associated with neuroprotective effects of the drug. These effects are dose dependent and maximal at a dose of 100 mg/kg.²⁰ Hence, this medicine may act as a neuroprotective agent through previously mentioned mechanisms in a dose dependent manner. It may also stop or slow down the degeneration process in PD patients and enhance the patients' condition.

Effect of modafinil on the different neurotransmitter systems

The striatopallidal is the GABAergic inhibitory pathway playing an important role in regulation of normal motor behavior. This system, through releasing GABA, inhibits motor activity. Therefore, inhibition of this system results in facilitation of loco-motion.²¹ Microdialysis assessment of GABA concentration in conscious rat treated with modafinil (30-100 mg/kg) demonstrated that modafinil was able to reduce GABA levels in the striatopallidal pathway.¹⁰

Glutamatergic projection of nucleus accumbens (NA), within the ventral striatum,

also provides a key role of modafinil in regulation of motor activity.²² NA receives dopaminergic afferents from the ventral tegmental area (VTA) and medial substantia nigra.²³ It has been shown that modafinil, through inhibition of accumbens GABA release, increases dopamine level in this area.⁹ Facilitation of glutamate neurotransmission also enhances motor behavior. Accordingly, GABA and glutamate show inverse relationship.²⁴ It was demonstrated that following the treatment with modafinil, glutamate levels within the ventromedial and ventrolateral (motor) thalamus increased.¹⁰ It has been demonstrated that increase in the extracellular levels of glutamate induced by modafinil is abolished by the inactivation of the GABA_A receptor.⁹ This mechanism suggests that modafinil, through interaction with GABAergic system, increases Glutamate levels indirectly and emphasizes the GABAergic projection role in the modafinil ability for enhancement of motor activity.²⁴

Interestingly, serotonergic neurotransmission is manipulated by modafinil. It is believed that serotonin and GABA may inverse the relationship. Modafinil increases serotonin levels in different brain regions, but simultaneously reduces extracellular GABA amounts.²⁴ It has been shown that pharmacologic silencing of the serotonergic system inhibits modafinil's effect on the releasing of GABA.²⁵ It should be mentioned that the serotonergic system plays an important role in the regulation of normal motor behavior. All compartments of basal ganglia receive serotonergic inputs.⁵ It has been found that increasing serotonin levels within the synaptic cleft leads to activation of inhibitory 5HT_{1A} receptors.²⁶ Activation of these receptors induce

dopamine release within the basal ganglia circuitry by inhibition of adenylyl cyclase and opening potassium channels.²⁷ Moreover, selective serotonin reuptake inhibitors (SSRIs), which elevate extracellular levels of serotonin, were shown to be able to have anti-parkinsonian effects on different animal models of PD.^{26,28} In addition to previously mentioned mechanism, striatal dopamine levels are directly affected by modafinil. Since modafinil has affinity to the dopamine transporter, inhibition of this machinery raises dopamine levels within the striatum.¹⁷

Discussion

In vivo studies have shown that modafinil is able to have anti-parkinsonian effects on different animal models.^{14,15} This effect is attributed to modafinil's ability to regulate dopamine levels and reduce oxidative stress. Additionally, in agreement with dopamine level alteration in PD, other neurotransmitter systems, such as the serotonergic system, noradrenergic system, and adrenergic system, are affected.²⁹ Therefore, a wide range of non-motor problems, such as depression, anxiety, sleep disorders, fatigue, and etcetera, are experienced by patients with PD.³⁰ Studies have demonstrated that modafinil is able to attenuate daytime sleepiness in PD.³¹ Moreover, it is established that modafinil improves the antidepressant effects.³²

Regarding different aspects of modafinil pharmacology, it seems that this medicine can have promising effects on PD and related disorders, and may be used as adjuvant therapy in PD. However, further investigations are needed to identify its exact anti-parkinsonian mechanisms.

Conflict of Interests

Authors have no conflict of interest.

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