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Investigation Of the Protective and Therapeutic Effects of Diphenhydramine in An In Vitro Parkinson's Model

Difenhidramin'in İn Vitro Parkinson Modelinde Nöroprotektif ve Terapötik Etkilerinin Belirlenmesi

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Abstract

Objective: Parkinson's disease (PD) is a neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons. Neuroprotective treatments are becoming more and more necessary due to the growing prevalence of Parkinson's disease (PD), and these are being investigated as a means to slow the disease's progression. Diphenhydramine (DPH), acting as a histamine 1 receptor antagonist, crosses the blood-brain barrier and exerts effects on the central nervous system. The aim of the present study is to evaluate the neuroprotective and therapeutic effects of DPH in an in vitro PD model induced by 6-hydroxydopamine (6-OHDA).

Materials and Methods: An in vitro PD model was established in Glioblastoma (U-118 MG) cells using 6-OHDA. DPH was applied at three different concentrations before and after 6-OHDA application. The protective effect of DPH was evaluated by assessing cell viability using the XTT cell proliferation assay. The results were analyzed using statistical analysis methods.

Results: The present study demonstrated that dose-controlled administration of DPH has both neuroprotective and therapeutic effects on an in vitro Parkinson's model established with 6-OHDA in the U-118MG cell line. According to our findings, DPH at concentrations of 1, 10, and 100 µM significantly increased cell viability compared to the 6-OHDA control group. DPH at 1 and 10 µM concentrations showed important potential for therapeutic and neuroprotective use.

Conclusion: The in vitro study indicates that DPH has neuroprotective and therapeutic effects on PD-modeled U-118MG neuronal cells by increasing cell viability. Nevertheless, in vivo studies are needed to evaluate the effects of DPH on animal models of PD.

Keywords: Parkinson's Disease, Glioblastoma U-118MG, Diphenhydramine, 6-hydroxydopamine, Neuroprotective and Therapeutic Effect.

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Öz

Amaç: Parkinson hastalığı (PH), nörodejeneratif hastalıklardan biri olup dopaminerjik nöronların ilerleyici kaybı ile karakterize edilmektedir. PH'nın yaygınlığının artması nedeniyle nöroprotektif tedavilere olan ihtiyaç artmakta ve bu tedaviler hastalığın ilerlemesini yavaşlatmak amacıyla araştırılmaktadır. Difenhidramin (DFH), histamin 1 reseptör antagonisti olarak etki göstermekte ve kan-beyin bariyerini geçerek merkezi sinir sistemi üzerinde etkili olmaktadır. Çalışmamızda, 6-hidroksidopamin (6-OHDA) ile oluşturulan in vitro PH modelinde, DFH'nin nöroprotektif ve tedavi edici etkilerini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Glioblastoma (U-118MG) hücrelerinde 6-OHDA ile in vitro PH modeli oluşturuldu. 6-OHDA uygulamasından önce ve sonra 3 farklı konsantrasyonda DFH uygulandı. DFH'nin koruyucu etkisi için hücre canlılığı, XTT hücre proliferasyon testi kullanılarak incelendi. Sonuçlar, istatiksel analiz yöntemleri ile değerlendirildi.

Bulgular: Çalışmamızda, DFH'nin doz kontrollü uygulamasının, U-118MG hücre hattında 6-OHDA ile oluşturulan in vitro Parkinson modeli üzerinde hem nöroprotektif hem de terapötik etkileri olduğunu göstermiştir. Çalışmamız sonucunda elde ettiğimiz bulgulara göre; DFH'nin 1, 10 ve 100 µM konsantrasyonlarda, 6-OHDA kontrol grubuna kıyasla, hücre canlılığını önemli ölçüde artırdığı bulunmuştur. DFH'nin 1 ve 10 µM konsantrasyonları, terapötik ve nöroprotektif kullanım için önemli bir etki göstermektedir.

Sonuç: Yapılan in vitro çalışma DFH'nin, PH modellenmiş U-118MG nöronal hücrelerin canlılığını arttırarak hücreler üzerinde nöroprotektif ve tedavi edici etkilere sahip olduğunu göstermektedir. Bunun yanında, DFH'nin PH hayvan modelleri üzerindeki etkilerini değerlendirmek için in vivo çalışmalar gereklidir.

Anahtar Kelimeler: Parkinson Hastalığı, Glioblastoma U-118 MG, Difenhidramin, 6-hidroksidopamin, Nöroprotektif ve Terapötik Etki.

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Introduction

Neurodegenerative diseases are those characterized by increased oxidative stress, synapse loss, and cell death and which have a major impact on quality of life (1). Diseases of the degenerative neurological system have a significant impact on global populations' health and well-being. Three of the most prevalent neurodegenerative diseases include Parkinson's disease (PD), Alzheimer's disease, and amyotrophic lateral sclerosis. PD is the second most common neurodegenerative disease, with approximately 6 million patients globally (2).

PD is more common as people age, especially a significant rise appearing around age 65 (3). PD is defined by the loss of dopaminergic neurons in the substantia nigra, the part of the brain region responsible for producing of the neurotransmitter dopamine, resulting in decrease of dopamine within the synaptic cleft (4). The most noticeable symptoms of the condition as it progresses are those that are associated with movement and motion, such as rigidity, tremor, postural instability, slowness of movement, gait, and walking difficulties (5). However, wide range of many other neurotransmitter systems are also affected in PD also there is some evidence for the involvement of the histaminergic system (6-8). Many approaches have been studied for the treatment of PD. Until a dramatic decrease in dopamine levels was demonstrated in the brains of patients dying of PD, treatment of this disease was an empirical one, based on incidental observations of medications prescribed for other purposes and, to a lesser extent, just for symptoms (9,10). Levodopa is used in practice; however, motor fluctuations and dyskinesias make the long-term use of levodopa challenging. Furthermore, thanks to their antiparkinsonian effects, the antihistamine benadryl, the antiviral drug amantadine, amphetamine and apomorphine are also used; however, their usage has been limited due to side effects and low efficacy (11-14). Therefore, targeting non-dopaminergic systems may be a helpful alternative method to improve efficacy and motor issues in PD (15).

Histamine is a vital neurotransmitter in the central nervous system that plays a key role in learning, memory, motor, neuroendocrine, and inflammation responses. It is primarily present in mast cells and basophils and is an essential inflammatory intermediary in peripheral tissue allergies and inflammatory reactions (16,17). Histamine is found in the bodies of many species and regulates a variety of physiological activities including smooth muscles, the gastrointestinal, cardiovascular, and immunological systems, as well as central and peripheral neurons (18). Four metabotropic receptor types—histamine H1, H2, H3, and H4—have been identified as a result of recent advancements in drugs that target histamine receptors for a variety of illnesses (19). The histamine H1 receptor, which is highly concentrated in several brain regions, impacts attention, sleep-wake rhythm, wakefulness, and cognition in the hypothalamus, amygdala, thalamus, and cortex (20). Diphenydramine (DPH) primarily acts by antagonizing the histamine 1 receptor, although it also has additional mechanisms of action (21). Chemical structure of DPH is presented in Figure 1. DPH, a first-generation antihistamine drug, can cross the blood-brain barrier and because of it has effects on the central nervous system (20-22). DPH protects the brain following traumatic brain injury by reducing oxidative stress, cerebral edema, and neuronal degeneration (23). After DPH reaches the brain, central H1-receptors are triggered, causing dizziness, drowsiness, convulsions and sedation (24-26). DPH, combined with L-dopa, amantadine or selegiline, was previously used in anesthesia to minimizing tremor symptoms in Parkinson's patients undergoing ophthalmic surgery, as well as an emergency treatment for extrapyramidal side effects created by street drugs and antipsychotics (27-31).

Although there is research on the neuroprotective effects of histamine receptor antagonists in PD, the scope and diversity of these studies are limited. There have been no studies on the neuroprotective effects of DPH on PD. Therefore, in this study, we investigated the neuroprotective and therapeutic effects of DPH, a powerful histamine 1 receptor antagonist that can cross the blood-brain barrier, in an in vitro PD model.

Materials and Methods

Cell Culture

Glioblastoma (U-118MG) cell line was obtained from the American Type Tissue Culture Collection (ATCC, ATCC, Manassas, VA, USA) and cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) (Gibco/BRL, Gaithersburg, MD, USA) supplemented with 1% Penicillin-Streptomycin (Gibco/BRL,

Gaithersburg, MD, USA) 1% L-glutamine (Hyclone) and %10 Fetal Bovine Serum (FBS) (Gibco/BRL, Gaithersburg, MD, USA) at 37°C and 5% CO2. An inverted microscope was used to observe the growth of the cells every day. The cells were passaged by diluation whenever they reached a confluence of about 75-80%.

Determination of suitable 6-OHDA and DPH concentration in medium

When choosing the appropriate concentrations of 6-OHDA (50 μM) and DPH (1 μM, 10 μM, 100 μM) for the study, we looked at concentrations that had been tried out in other investigations and whose efficacy we had independently verified (32-34). To precisely determine the therapeutic and protective concentrations of DPH, at least three repetitions were carried out. Based on the analysis, care was taken to make sure that the results of the three repetitions are consistent with one another.

Cell Viability Assay

The XTT (2,3-bis [2-methoxy-4-nitro–5-sulfophenyl]-2H-tetrazolium-5-carboxyanilide salt) method was employed to assess the proliferation and vitality of cells (35). U-118MG cells were seeded into 96-well plates and were cultivated overnight. The medium in the plates was removed after 24 hours. An in vitro model of PD was established by adding 50 μM of 6-OHDA to each well in DMEM without phenol red. Three different concentrations (1, 10 and 100 μM) of DPH were administered. To assess the protective effects of DPH, it was administered 4 hours before 6-OHDA and to evaluate its therapeutic effects, it was administered 4 hours after 6-OHDA. 20 hours were spent incubating. After the culture time was over, XTT solution (Cell Proliferation Kit II, Sartorius, Israel) was added to the wells and left for 4 hours. A microplate reader (Thermo Scientific MultiskanTM FC, Finland) was used to determine the absorbance values at 450 nm wavelength at the end of the experiment.

Statistical analysis

For the stand-alone DPH application, a one-way ANOVA test was performed, followed by multiple comparisons using Dunnett's post hoc test. Results were evaluated at a significance level of $p<0.05$. For comparisons before and after 6-OHDA application, a one-way ANOVA test was conducted, with pairwise comparisons performed using Tukey's post hoc test. The significance level was again set at $p<0.05$. All statistical analyses were conducted using GraphPad Prism version 10.4.0.621 (GraphPad Software, San Diego, CA, USA). Results were reported in APA format, with statistical significance levels indicated as follows: $p<0.05$; 0.05 (*), 0.01 (**), 0.001 (***).

Results

According to our findings, when applied alone, high doses of DPH reduced cell viability by 4.8% (Figure 2.), but when DPH is used together with 6-OHDA, it increases cell viability compared to 6-OHDA alone. In this case, DPH administered pre-treatment to 6-OHDA demonstrated protective effects of 11.7%, 10.2%, and 2.6% at 1 μM, 10 μM, and 100 μM concentrations, respectively (Figure 3.A.). Similarly, when DPH was administered post-treatment 6-OHDA, an increase in cell viability was also observed (Figure 3.B.). At 1 μM and 10 μM concentrations, therapeutic effects with cell viability increases of 10.2% and 6.9%, respectively, were observed; however, at 100 μM, cell viability decreased by 5.3%. Based on these results, the 1 μM and 10 μM concentrations are identified as the most suitable levels.

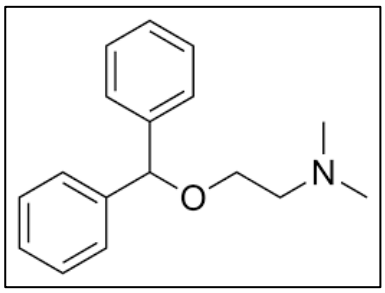

Figure 1. Chemical structure of Diphenhydramine (DPH).

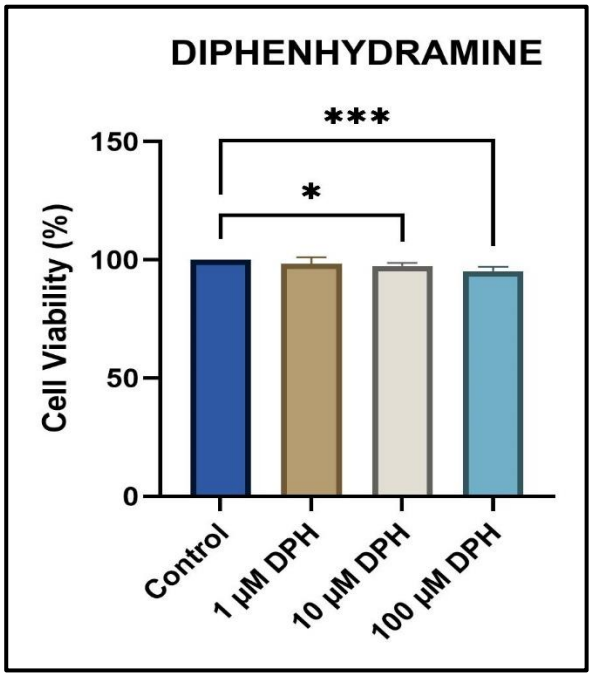

Figure 2. Effect of Diphenhydramine (DPH) alone on cell viability. The data are expressed as means of percentages ± SD (n=8). *: P < 0.05, ***: P< 0.001.

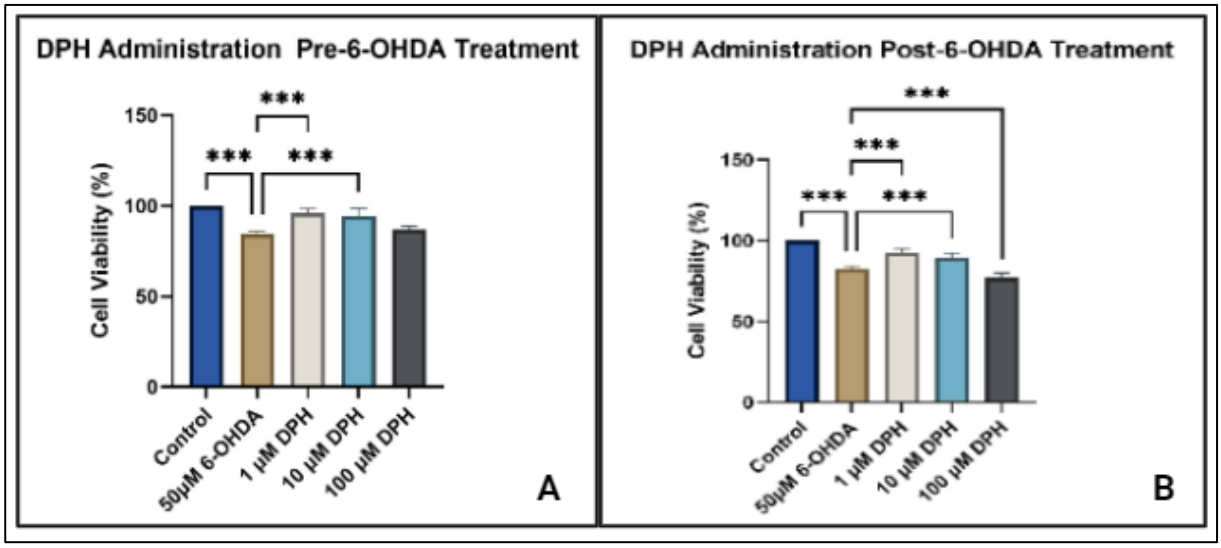

Figure 3. Comparative analysis of Diphenhydramine (DPH) effects on cell viability pre administration of 6-OHDA treatment (A) and post administration of 6-OHDA treatment (B).

Discussion

In the present study, the objective of our investigation was to assess the neuroprotective and therapeutic properties of DPH against 6-OHDA-induced PD in U-118MG cells. In the present study, we found that DPH at concentrations of 1 and 10 µM has neuroprotective and therapeutic effects; in contrast, a high concentration of DPH (100 µM) decreases cell viability.

A sizable section of the population is still afflicted by neurodegenerative illnesses today. PD is one of the most prevalent of them. The oxidative damage brought on by the production of free radicals is the origin of the calcium channel anomalies, glial cell excitation, mitochondrial malfunction and alpha-synuclein deposits observed in PD (36). Numerous processes are being used to treat the disease's symptoms, even though its causes are still not entirely understood. Hence, experimental PD models, both in vivo and in vitro, that can replicate important aspects of the dopaminergic system and recapitulate the disease phenotype are therefore crucial for studying early events of disease genesis and progression (37). In vitro models containing 6-OHDA,

1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP), 1-methyl-4-phenylpyridinium (MPP+), Rotenone and Paraquat are some of the examples used in the treatment of PD (38). A helpful method for researching the molecular processes linked to neuronal death in PD is neuronal exposure to 6-OHDA. 6-OHDA promotes neuronal damage and death by raising oxidant levels and disrupting the mitochondrial respiratory chain. González et al. showed that human neuroblastoma cells exposed to 6-OHDA in vitro had a loss of membrane integrity, an increase in cellular ROS levels, and a decrease in mitochondrial metabolic activity. In this study, we used 6-OHDA as a model. The effects of 6-OHDA on cell viability showed similar results to those of González and colleagues (39).

Furthermore, there is some proof that PD is associated with the histaminergic system and the study findings have demonstrated a large increase in histamine levels in the substantia nigra, putamen, and globus pallidus of PD patients (40). Presence of histamine may be induced in the globus pallidus, putamen, and substantia nigra by a variety of factors, including increased histaminergic fiber density (41, 42). To stop the onset of neuronal degeneration in the case of PD, it can be crucial to shield neuronal cells from excessive histamine levels. Drugs designed to have an antihistaminic effect have been shown to have anti-Parkinsonian effects primarily because they have the pharmacological characteristic of blocking muscarinic neurotransmission (43). Studies indicate that DPH, an antihistamine with anticholinergic properties, can be used in the treatment of PD (44). Histamine type 1 and 2 receptor (H1/2r) antagonists, particularly DPH and cimetidine, have been shown by Lin et al. to improve skin permeability barrier homeostasis when applied topically (45). Pan et al., evaluated the protective effect of DPH against traumatic brain injury (TBI) in light of its antioxidant and anti-inflammatory effects in their animal study. Accordingly, DPH demonstrated a neuroprotective role against TBI by showing improvement in neuronal survival at the tested dose and by attenuating oxidative stress, inflammation and mitochondrial apoptosis pathways (23). Upon reviewing the current literature, we found that in vivo studies on the cytotoxicity of DPH in cancer research show similarities to our in vitro studies (46). However, it has not been directly included in in vitro cell viability studies with DPH. Therefore, in our study, we determined the DPH concentrations based on a previous study we conducted and relevant reference articles (32-34). While looking for neuroprotective effects, we also look for therapeutic effects of the DPH on the Parkinson's cell model for enriching and expanding our research on DPH. And in our research, with dose-controlled therapeutic effects for PD at 1 and 10 μM DPH we find significant effect for therapeutic use.

Conclusion

These results show that DPH has both protective as well as therapeutic aspects against damage effected by cells as result of exposure to 6-OHDA. The implications emphasize the prospective use of DPH as a neuroprotective agent. For the treatment of at least some PD symptoms, targeting H1 receptor that influence effects of histamine may be helpful. This finding may help in the development of new therapies for PD and gives clues to the pathophysiology and possibly also etiology in PD. Also, further studies are required to evaluate the effects of DPH in animal models of PD. Moreover, the cytotoxicity that has been observed implies that DPH might dose-dependently control the survival of glioblastoma cells. More studies should be carried out to ascertain how exactly DPH affects glioblastoma cells and its efficacy as an adjuvant therapy in conjunction with glioblastoma treatment protocols.

Ethics Committee Approval: Ethics Committee Approval was not required for this article because it solely involved the use of commercially available cell lines and did not include any human, animal, or materials derived from them.

Informed Consent: Human volunteers were not used in the study.

Conflict of Interest: Authors declared no conflicts of interest.

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