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The protective effect of venlafaxine on hydrogen peroxide-induced cytotoxicity in C6 glioma cells

Venlafaksi'nin C6 Glioma Hücrelerinde Hidrojen Peroksit Kaynaklı Sitotoksisitede Koruyucu Etkisi

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ABSTRACT

Aim: Neurodegeneration is the progressive loss and structural deterioration of neuronal cells. Hydrogen peroxide (H_2O_2) is formed by dismutation and causes oxidative stress in neuronal cells. Venlafaxine is a drug that increases both serotonin and noradrenaline in the synaptic gap.In this study, the effect of venlafaxine on H2O2-induced cytotoxicity in C6 cells was investigated.
Methods: First of all, different doses of venlafaxine (25, 50, and 100 µM) were tried to find the appropriate dose in C6 glioma cells. Then, the effect of venlafaxine on H_2O_2-induced cytotoxicity in the cells was investigated. For this purpose, cell viability rate, proinflammatory markers IL-1β and TNF-α, and NO and iNOS levels were examined by ELISA kits.
Results: H_2O_2-treated caused cytotoxicity in the C6 glioma cells; when venlafaxine 25, 50, and 100 µM doses were evaluated in terms of cell viability, it was observed that the 100 µM venlafaxine applied group significantly increased cell viability compared to the other groups. When we look at the levels of IL-1β and TNF-α, it is observed that there is an increase in the H_2O_2 applied group and a significant decrease in the venlafaxine (100 µM) applied group. It was observed that NO and iNOS levels increased in the H_2O_2 applied group compared to the other groups. It was observed that Venlafaxine treatment reduced the increased NO and iNOS levels caused by H_2O_2.
Conclusion: The study results showed that venlafaxine may have a protective effect on H_2O_2-induced cytotoxicity in C6 glioma cells.

Key Words: Cytotoxicity, C6 cells, Venlafaxine, Hydrogen Peroxide

ÖZ

Amaç: Nörodejenerasyon, nöron hücrelerinin ilerleyici kaybı ve yapısal bozulmasıdır. Hidrojen peroksit (H_2O_2) dismutasyonla oluşur ve nöron hücrelerinde oksidatif strese neden olur. Venlafaksin, sinaptik boşlukta hem serotonini hem de noradrenalini artıran bir ilaçtır.Bu çalışmada venlafaksi'nin C6 hücrelerinde H_2O_2 kaynaklı sitotoksisite üzerindeki etkisini araştırıldı.
Yöntem: Öncelikle C6 glioma hücrelerinde uygun dozu bulmak için farklı dozlarda venlafaksin (25, 50 ve 100 µM) denendi. Daha sonra venlafaksi'nin hücrelerde H_2O_2 kaynaklı sitotoksisite üzerine etkisi araştırıldı. Bu amaçla hücre canlılık oranı, IL-1β, TNF-α, NO ve iNOS düzeyleri ELISA kitleri ile incelendi.
Bulgular: H_2O_2 ile inkübasyon C6 glioma hücrelerinde sitotoksisiteye neden oldu. Venlafaksin 25, 50 ve 100 µM dozları hücre canlılığı açısından değerlendirildiğinde, 100 µM venlafaksin uygulanan grubun diğer gruplara göre hücre canlılığını anlamlı düzeyde arttırdığı görüldü. IL-1β ve TNF-α düzeylerine bakıldığında H_2O_2 uygulanan grupta artış, venlafaksin (100 µM) uygulanan grupta ise IL-1β ve TNF-α düzeylerinde anlamlı oranda azalma olduğu görüldü. H_2O_2 uygulanan grupta NO ve iNOS düzeylerinin diğer gruplara göre arttığı gözlendi. Venlafaksin tedavisinin H_2O_2'nin neden olduğu artan NO ve iNOS düzeylerini azalttığı görüldü.
Sonuç: Çalışma sonuçları venlafaksinin C6 glioma hücrelerinde H_2O_2 kaynaklı sitotoksisite üzerinde koruyucu etkiye sahip olabileceğini gösterdi.

Anahtar Kelimeler: Sitotoksisite, C6 hücreleri, Venlafaksin, Hidrojen peroksit

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Introduction

The development of neurodegenerative illnesses is significantly influenced by oxidative stress (OS). Compared to other organs, the brain is especially susceptible to OS [1]. Despite only accounting for 2% of the body's weight, the brain utilizes approximately 20% of the oxygen provided by our metabolism. This high oxygen consumption makes the brain more susceptible to oxidative stress than other organs. Neuron and glial cells, owing to their high metabolic activity, are particularly vulnerable to OS and mitochondrial dysfunction [2].

Venlafaxine is an antidepressant drug that increases both serotonin and noradrenaline in the synaptic cleft [3]. Venlafaxine is a medication that is used to treat various diseases such as attention deficit disorder, diabetic neuropathy, migraine prophylaxis, obsessive-compulsive disorder, fibromyalgia, post-traumatic stress disorder, and premenstrual dysphoric disorder [4]. It can be used alone or in combination with other drugs for these diseases. Although venlafaxine is as effective as tricyclic antidepressant group drugs, it has better tolerability and fewer side effects than this group of drugs [5].

One of the most commonly used chemicals in creating oxidative stress models in in vitro studies is hydrogen peroxide (H_2O_2) [6]. H_2O_2 is a molecule that acts as a signal inside and outside cells. It can influence the fate of cells. At low levels, it helps with cell growth, immunity, and metabolism. However, when cells are exposed to high levels of H_2O_2, which are not natural, it can cause oxidative stress. If stress is not relieved, the cell may go into apoptosis [7]. It is routine practice to study astrocyte function, including oxidative stress measures, using C6 glioma cells. Furthermore, these cells react fast to outside stimuli like H_2O_2, which might result in OS [8]. Sugammadex (SUG) was found to have an adverse effect on C6 glial cells' viability following H_2O_2-induced oxidative stress and apoptosis, according to a study by Sahin et al. This study also showed that SUG increased H_2O_2-induced damage and reduced C6 cell viability after H_2O_2-induced oxidative stress [9]. Although there are some studies about venlafaxine in the literature, the exact protective effect and basic mechanisms of Venlafaxine against oxidative damage in C6 glial cells are unclear. Therefore, we investigated in this work how well venlafaxine protected C6 glial cells from H_2O_2-induced oxidative damage and how this effect related to the levels of iNOS, TNF-α, IL-1β, nitric oxide (NO), and cell survival rate.

Materials and Methods

Cell line and chemicals

C6 cells were obtained from ATCC, and Venlafaxine and H_2O_2 (Sigma-Aldrich Co., St Louis, MO, USA) were dissolved in DMEM. Stock solutions were prepared before treatment.

Cell Viability Assays

The cells were grown in DMEM supplemented with 10% fetal bovine serum, 1% L-glutamine, and 1% penicillin/streptomycin (Sigma-Aldrich Co., St Louis, MO, USA). Cells were kept in a humidified environment with 5% CO_2 at 37 °C. The cells in a well-growing state were seeded on 96-well plates at a density of 1×10^4 cells per well, and venlafaxine and H_2O_2 were added according to the experimental group. The control group was not administered any medication. Cells in the H_2O_2 group were treated with 0.5 mM H_2O_2 for 24 hours [10]. Cells in the Venlafaxine group were treated with venlafaxine at different concentrations (25, 50, and 100 µM) for 24 h [11]. Cells in the Venlafaxine + H_2O_2 group were pretreated with venlafaxine for 1 h with different concentrations (25, 50, and 100 µM) and then exposed to 0.5 mM H_2O_2 for 24 h. The experiment measured cell viability between groups using the Cell Counting Kit-8 (CCK-8) assay. The BioTek ELx808™ instrument was used to measure cell viability at OD450 nm by following the instructions provided in the commercial kits. The data were presented as a percentage compared to the control group (% of control). After examining the cell viability rates, it was determined that a dose of 100 µM was appropriate for venlafaxine. The cells were multiplied again, and four groups were created: control, H_2O_2, venlafaxine+H_2O_2, and venlafaxine.

Measurement of Biochemical Parameters

The cells were lifted using 0.25% Trypsin-EDTA and placed into sterile falcon tubes when they

achieved 80% confluency. After that, the tubes were centrifuged for 20 minutes at 1000 rpm, following the directions on the commercial kits. To make a cell suspension, the cell pellets were suspended in PBS (pH 7.4) after the supernatants were removed. Repeated rounds of freezing and thawing were used to lyse the cells and release their internal components. Following a 10-minute centrifugation at 4000 rpm and 4°C, the mixture was collected, and the supernatants were collected for biochemical analysis. The total protein levels in the samples were ascertained using the Bradford protein assay kit (Merck Millipore, Darmstadt, Germany). IL-1β, TNF-α, NO, and iNOS levels were measured at OD450 nm using commercial ELISA kits and the BioTek ELx808TM device following the instructions provided in the kit procedure (YL Biont, Shanghai, China).

Statistical Analysis

The data was analyzed using SPSS software (Version 23.0) with one-way ANOVA. For any significant differences observed in the data, the post-hoc Tukey test was used. The level of statistical significance was set to $p < 0.05$. All data are expressed as mean ± standard deviation.

Results

Effect of venlafaxine on the cell viability exposed to H_2O_2

The cell viability for venlafaxine was determined in both control and glutamate-treated C6 cells at various doses (25, 50, and 100 µM/mL). The cells were pretreated with increasing doses of Venlafaxine for 1 h and then incubated with or without 0.5 mM H_2O_2 for the next 24 h. As seen in Figure 1, it was observed that the doses used only for Venlafaxine did not affect cell viability compared to the control group. It was determined that applying a dose of 100 µM/mL Venlafaxine to groups with H_2O_2 toxicity significantly increased the cell viability rate ($p < 0.05$). It was observed that cell viability decreased as the Venlafaxine dose decreased in the Venlafaxine+ H_2O_2 groups ($p < 0.05$).

Effect of venlafaxine on TNF-α and IL-1β levels in H_2O_2-induced cytotoxicity

As seen in Figure 2A, after the appropriate dose of Venlafaxine (100 µM/mL) was selected for treatment, TNF-α levels were measured after the specified incubations in the groups. Compared to the control group, the TNF-α level of the H_2O_2 group was significantly higher ($p < 0.05$). While the TNF-α level in the Venlafaxine+ H_2O_2 group was higher than in the control group, it was lower than in the H_2O_2 group ($p < 0.05$). There was no significant difference in TNF-α level in the Venlafaxine group compared to the control group, but it was lower compared to the Venlafaxine+ H_2O_2 and H_2O_2 groups ($p < 0.05$).

When the effect of venlafaxine against H_2O_2 cytotoxicity was measured with the IL-1β level Elisa kit in C6 cells, it was seen that the IL-1β level of the H_2O_2 group was at the highest level compared to all other groups ($p < 0.05$). It was determined that the IL-1β level in the Venlafaxine + H_2O_2 group was higher than the control group but lower than the H_2O_2 group ($p < 0.05$). There was no significant difference in IL-1β level in the Venlafaxine group compared to the control group ($p > 0.05$), but it was lower than the Venlafaxine+ H_2O_2 and H_2O_2 groups ($p < 0.05$) (Figure 2B).

Effect of venlafaxine on NO and iNOS level in H_2O_2 induced cytotoxicity

The H_2O_2 group had the highest NO and iNOS levels compared to all other groups ($p < 0.05$). There was no statistically significant difference between the control, venlafaxine, and venlafaxine+ H_2O_2 groups ($p > 0.05$). When the venlafaxine+ H_2O_2 group and the H_2O_2 group were compared between the groups, it was determined that NO and iNOS levels were significantly lower in the venlafaxine+H_2O_2 group ($p < 0.05$) (Figure 3A and B).

Discussion

OS occurs when there is an imbalance between oxidant substances in the body and antioxidant defence systems; one of the most prominent indicators is the increase of reactive oxygen species within the cell. As a result, reactive oxygen species overproduction causes damage to tissues and disrupts normal physiological functions. Studies have confirmed that oxidative stress is a factor in the onset and progression of neurodegenerative diseases in the central nervous

system [12, 13].

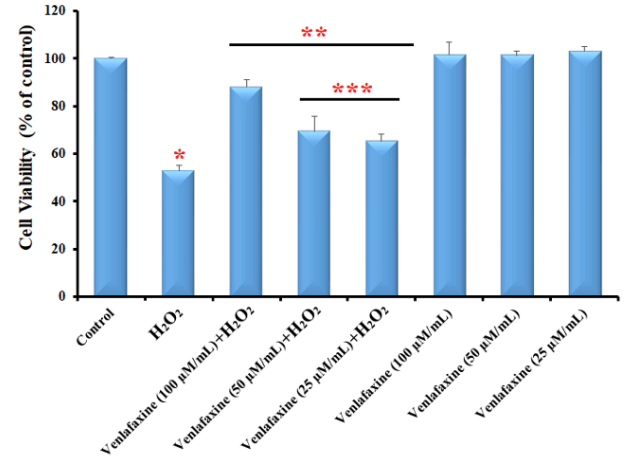

Figure 1. Effect of venlafaxine on cell viability in H_2O_2 induced cytotoxicity in C6 cells. All data are presented as the means ± SD. *p<0.05, compared with the control group; **p<0.05, compared with control and H_2O_2 groups, ***p<0.05, compared with Venlafaxine (100 µM/mL) + H_2O_2 group

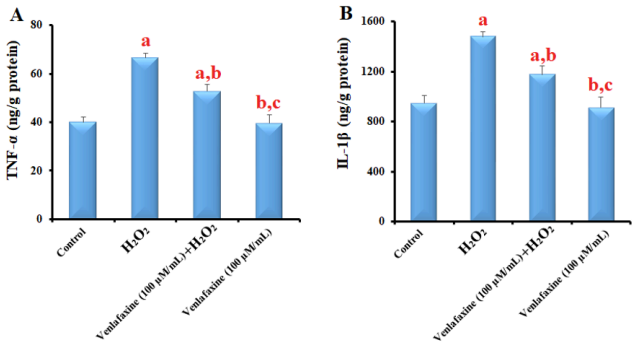

Figure 2. Effect of venlafaxine on TNF-α (A) and IL-1β (B) levels in H_2O_2 induced cytotoxicity in C6 cells. All data are presented as the means ± SD. ap<0.05, compared with the control group; bp<0.05, compared with H_2O_2 group, cp<0.05, compared with Venlafaxine (100 µM/mL) + H2O2 group.

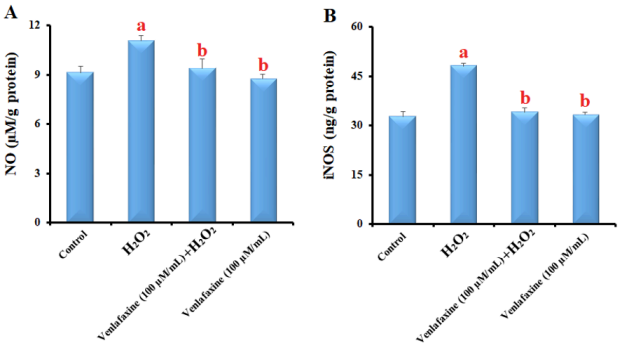

Figure 3. Effect of venlafaxine on NO (A) and iNOS (B) levels in H_2O_2 induced cytotoxicity in C6 cells. All data are presented as the means ± SD. ap<0.05, compared with the control group; bp<0.05, compared with H_2O_2 group.

Venlafaxine is primarily known for its antidepressant effects. However, recent studies have begun to unveil its potential neuroprotective properties. For instance, venlafaxine has been shown to protect against glutamate-induced cytotoxicity in PC12 cells, suggesting a broader neuroprotective role that could be attributed to its antioxidative properties [14]. Similarly, research by Eren et al. demonstrated that venlafaxine could mitigate depression-induced oxidative stress in the rat brain, further supporting the notion that venlafaxine possesses antioxidative and neuroprotective effects [15]. Cytotoxicity induced by H_2O_2 and the resulting increase in OS is considered one of the mechanisms underlying many pathological conditions, such as cell death, DNA damage, and inflammation. H_2O_2 increases oxidative stress by affecting intracellular signalling pathways, which can lead to dysfunction in various cell types [16]. This result is consistent with the study conducted by Abdel-Wahab et al. in 2011, suggesting the potential antioxidant properties of venlafaxine and its capacity to reduce oxidative damage [17]. In the current study, we observed that venlafaxine treatment significantly improved the viability of cells exposed to H_2O_2 (Figure 1).

TNF-α and IL-1β are cytokines that play a vital role in inflammation [18]. These cytokines act on various cellular functions such as cell death, cell proliferation, differentiation, and modulation of immune responses. The increase in TNF-α and IL-1β levels occurs due to multiple stimuli such as cellular stress, tissue damage, or pathogenic invasion. For example, cytotoxicity induced by ROS such as H_2O_2 can trigger the production of TNF-α and IL-1β by increasing intracellular oxidative stress and bypassing cellular defence mechanisms. Excessive production of these cytokines plays a central role in the pathophysiology of inflammation and may contribute to the progression of cellular damage and tissue dysfunction [19-21]. This study showed that the TNF-α level in the H_2O_2 group was significantly higher than the control group. TNF-α level in the venlafaxine+ H_2O_2 group is higher than the control group but lower than the H_2O_2 group. In the Venlafaxine group, the TNF-α level is similar to the control group and lower than the Venlafaxine+ H_2O_2 and H_2O_2 groups. Regarding IL-1β level, the H_2O_2 group has the highest value

compared to all other groups. The venlafaxine + H_2O_2 group had a higher IL-1β level than the control group but lower than the H_2O_2 group. The IL-1β level of the Venlafaxine group did not show a significant difference with the control group but was lower than the Venlafaxine+ H_2O_2 and H_2O_2 groups (Figure 2A and B).

Studies have shown that NO and iNOS are critical mediators in intracellular signalling pathways and inflammatory processes. In particular, high NO levels produced by iNOS are a source of nitrosative stress that can cause cell damage and death [22, 23]. The findings of this study, consistent with this literature, show that H_2O_2-induced oxidative stress is associated with an increase in NO and iNOS levels. The increase in NO and iNOS levels after H_2O_2 exposure may increase cellular damage through the synergistic effects of oxidative and nitrosative stress [24]. This may be important in understanding pathological processes such as neurodegenerative diseases and inflammation. For example, neurodegenerative conditions such as Alzheimer's disease and Parkinson's disease have been associated with increased oxidative and nitrosative stress [25]. The current study showed that the H_2O_2 group had the highest NO and iNOS levels compared to all other groups. There was no statistically significant difference between the control, venlafaxine, and venlafaxine+ H_2O_2 groups. When the venlafaxine+ H_2O_2 and H_2O_2 groups were compared, it was determined that NO and iNOS levels were significantly lower in the venlafaxine+ H_2O_2 group (Figure 3A and B). These results suggest that venlafaxine may be a potential therapeutic agent in modulating cellular stress responses of NO and iNOS.

Conclusion

In this study, the effect of venlafaxine on viability, TNF-α, IL-1β, NO, and iNOS levels in C6 cells exposed to H_2O_2-induced cytotoxicity was investigated. The results indicate that venlafaxine can increase the viability of C6 cells under oxidative stress and modulate the inflammatory response.

Conflict of Interest: The authors declare that they have no conflicts of interest.

Ethics Declarations: The current study has no study with human and human participants. The study is not subject to ethics committee approval.

ORCID and Author contribution: A.A. (0000-0002-5109-2000), K.Y. (0000-0002-6585-4010), A.Ş.T. (0000-0002-5810-8415). All the authors designed the study, performed the experiments, and analyzed the data. AA performed biochemical parameters. KY drafted the manuscript. All authors read and approved the final manuscript.

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