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Original paper

In vitro Cytotoxic Effects of Sertraline on Normal Cells

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Abstract

Background and aim: Studies have shown the cytotoxic effects of sertraline on various cells; however, the results are significantly contradictory. Accordingly, the present study investigated the cytotoxic effects of sertraline on normal human embryonic kidney (Hek293) cells.

Materials and methods: In this experimental-laboratory study, Hek293 cells were divided into control group (no sertraline treatment) and sertraline treatment groups (1.56, 3.12, 6.25, 12.5, 25, 50 and 100 µg / ml). Cell viability was assessed by MTT 24 and 48 hours after sertraline treatment. Data were analyzed using one-way analysis of variance.

Results: Treatment with 1.56 and 3.12 µg / ml of sertraline for 24 hours had no significant effect on the Hek-293 cells viability, however, the concentrations ≥6.25 µg / ml of sertraline significantly reduced the cell viability. Treatment of cells for 48 hours significantly reduced cell viability at concentrations ≥3.12 µg / ml of sertraline.

Conclusion: The results of this study showed that sertraline can have a cytotoxic effect on non-cancerous cells and this effect depends on the dose and duration of treatment. This finding is important from sertraline side effects points of view on normal cells of the body considering its dose and period of consumption.

Keywords: *Sertraline, Hek293, Viability*

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Introduction

The normal cells of our body are affected daily by many substances, compounds and drugs. These drugs can disrupt the function of normal cells and seriously damage them. On the other hand, some drugs do not have an adverse effect on the natural cells of our body and can even improve their function. Hek293 cell line, which is also known as renal embryonic cells, is one of the normal cells used in biological research to investigate the effects of chemical and pharmaceutical compounds on normal cells. This cell line has epithelial morphology and was isolated from human fetal kidney. This cell line can be used in industrial biotechnology and toxicology research. It is also used in the effectiveness test and virus killing test [1].

It seems that use of antidepressants can have effects on the normal cells of our body. Sertraline is one of the antidepressants that is increasingly used. Sertraline is a selective serotonin reuptake inhibitor that is prescribed in most psychiatric disorders, including major depression, panic, social and generalized anxiety disorders, and obsessive-compulsive disorder. The structure of sertraline has a secondary amine with two chiral centers, which has fewer side effects compared to tricyclic antidepressants [2]. In addition to being effective in the treatment of depression, sertraline is also used in other cases. Among recent studies, sertraline has been investigated as an anti-tumor agent and positive and useful result have been obtained [3]. For the anti-tumor effect of sertraline, we can mention the cytotoxic effect of sertraline on ovarian cancer [4]. Research shows that the use of antidepressants, including sertraline, by cancer patients due to the depression they get after being diagnosed with cancer has helped the effectiveness of chemotherapy, and it reduces the progress of cancer [5]. Also, antidepressants such as sertraline play a role in the treatment of Parkinsons disease [6]. From other studies, we can mention the antifungal effect of sertraline against *C. auris* involved in candidiasis infection [7]. The result show that during dialysis, blood pressure drop occurs in dialysis patients, that sertraline reduces the number of symptoms and interventions of blood pressure [8], which if combined with L-carnitine, has better effects in improving blood pressure drop in dialysis patients [9]. In other studies, the effect of sertraline on language development of young children with Fragile X Syndrome (FXS) can be mentioned [10]. Also, studies related to antidepressants show that various types of chronic pain do not respond to conventional pain relievers such as opioids, but can be treated with antidepressants such as serotonin and noradrenaline reuptake inhibitors [11]. Other studies related to chronic pain relief include the use of tricyclic antidepressants, along with anticonvulsant for chronic pain relief [12]. Antidepressant drugs have side effects, which can be mentioned as side effects of sertraline, reversible liver damage and Steven Johnson syndrome. Also, sertraline is prescribed for pregnancy stress, which in this situation not only disturbs the mother's health, but in connection with stress, it can endanger the physical development, reflex and neurobehavioral. Other common side effects of antidepressants include sexual dysfunction, digestive problems, sleep disorders, apathy and fatigue [2], [13]. These findings show that sertraline affects a wide range of cells. The present study examines the cytotoxic effects of sertraline on embryonic kidney cells (Hek293).

Material and Methods

Drug Preparation

During this experimental laboratory research, which has been approved by the Committee of Ethics in Research of the International Association of Scientists (IAS) No. IASSP.21.2CL, Hek293 embryonic kidney cell line was purchased from the Pasteur Institute, Tehran, Iran. The cells were kept frozen in a nitrogen tank at a temperature of -196 ^{0}C. Sertraline was prepared in the form of pure powder from Pharmachemie Company and the concentrations of 1.56, 3.12, 6.25, 12.5, 25,

50 and 100 μg/ml were prepared. To prepare different concentrations of the drug, 10 mg of sertraline was dissolved in 200 μL of DMSO. Then, by adding cell culture medium, the volume was increased to 10 mL. The concentration of the drug in this solution was 1 mg/ml. After filtering, the required concentrations were prepared.

Cell Culture

The medium was removed from a confluent cell culture. 10 mL of PBS was added and then substituted with 4 mL of 0.25% Trypsin-EDTA 1x solution and incubated for 5 min. 8 mL of DMEM medium was supplemented with 1% (w/v) streptomycin, 1% (w/v) penicillin and 10% (w/v) FBS and aspirate multiple times to resuspend all the trypsinized cells. 10 uL of the culture was mixed with 10 μL of Trypan Blue 0.4% dye and 10 uL of the mixture was added into a cell-counter slide. 10^6 of living cells were transferred from the old culture into a 50 mL cell culture flask. DMEM medium was supplemented with 1% (w/v) streptomycin, 1% (w/v) penicillin and 10% (w/v) FBS, up to a final volume of 25 mL and was incubated until the cells become confluent.

MTT Assay

The cytotoxic effect of sertraline on Hek293 cells was investigated by colorimetric method and using tetrazolium dye (MTT). During this method, the activity of succinate dehydrogenase enzyme is measured in the mitochondria of living cells. In this reaction, under the influence of succinate dehydrogenase, the yellow solution of MTT turned into insoluble purple formazan crystals and the absorption of these crystals was read after dissolving in DMSO solution.

To evaluate the cytotoxic effects of sertraline on Hek293 cells, 180 microliters of cell suspension (2×10^4 cells per milliliter) were cultured in 96-well microplates and incubated for 24 hours. After incubation, 20 μL of sertraline was added to each well containing Hek293 cells. And incubated for 24 and 48 hours. 20 μL of MTT solution (5 mg/ml) was added to each well and incubated for another 3 hours. 150 μL of DMSO was replaced with the supernatant to dissolve the formazan crystals. Optical absorbance was measured at 570 nm with ELISA reader. The concentrations of drug which exhibited 50% cell viability for Hek293 cells (IC50 values) were calculated from curves constructed by plotting cell survival (%) versus drug concentration (μM). The reading values were converted to the percentage of the control (percentage cell survival). All experiments were performed triplicate.

Statistical Analysis

SPSS20 software was used for statistical analysis. Kolmogorov-Smirnov test was performed to ensure the normal distribution of data, which was followed by one-way analysis of variance (ANOVA) and Tukey post hoc test. P values less than 0.05 were considered statistically significant.

Results

The results of MTT showed that treatment of Hek293 cells with 1.56 and 3.12 μg/ml of sertraline for 24 hours had no significant effect on cell viability, however, sertraline with concentration of 6.25 μg/ml and more caused a significant decrease in cell viability compared to control group. The viability of Hek-293 cells was increased (Figure 1).

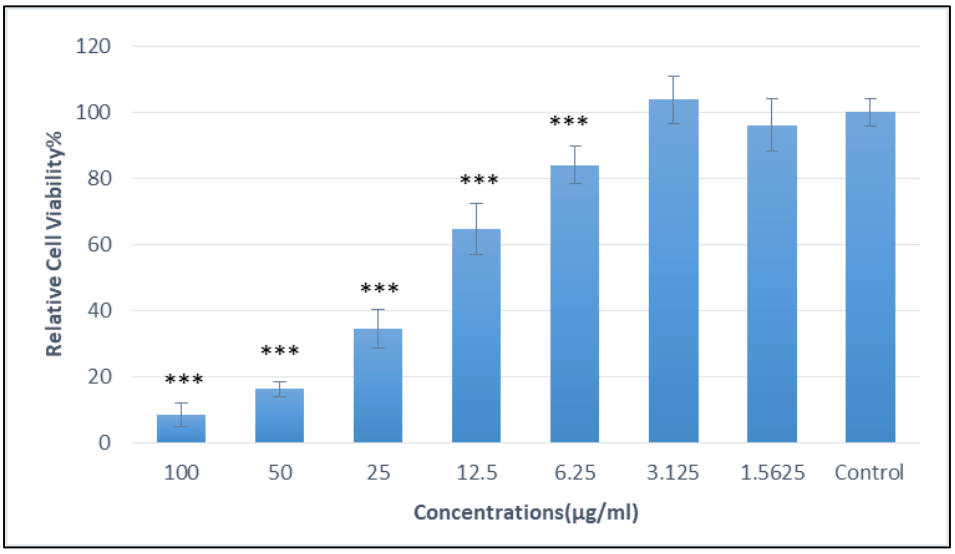

Figure 1. Viability of Hek293 cells treated with different concentrations of sertraline (µg/ml). * indicates significant difference compared with control group (***:p<0.001).

The IC50 value for 24 hours of treatment with drug was 18.8 µg/ml (Figure 2).

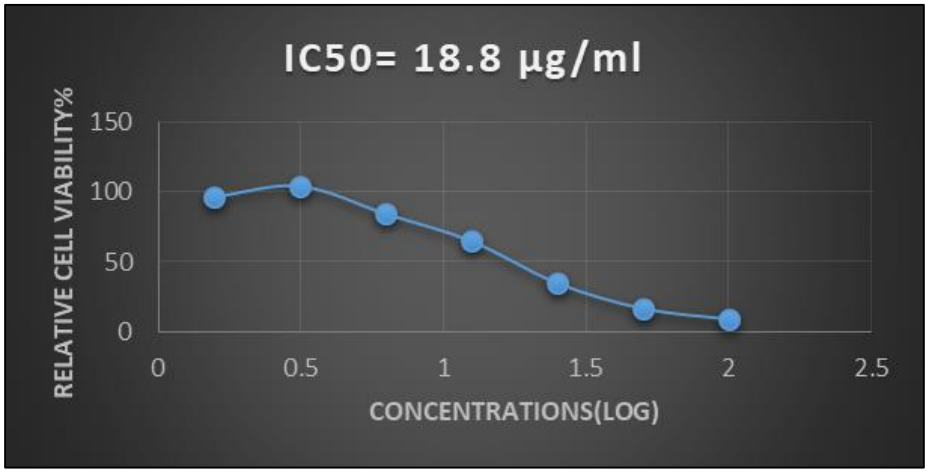

Figure 2. IC50 value for 24 hours of treatment with sertraline.

The MTT results obtained from the treatment of cells for 48 hours showed that treatment with 1.56 µg/ml of sertraline did not significantly change the viability of Hek293 cells, however, higher concentrations of sertraline caused a significant decrease in the viability of Hek293 cells (Figure 3).

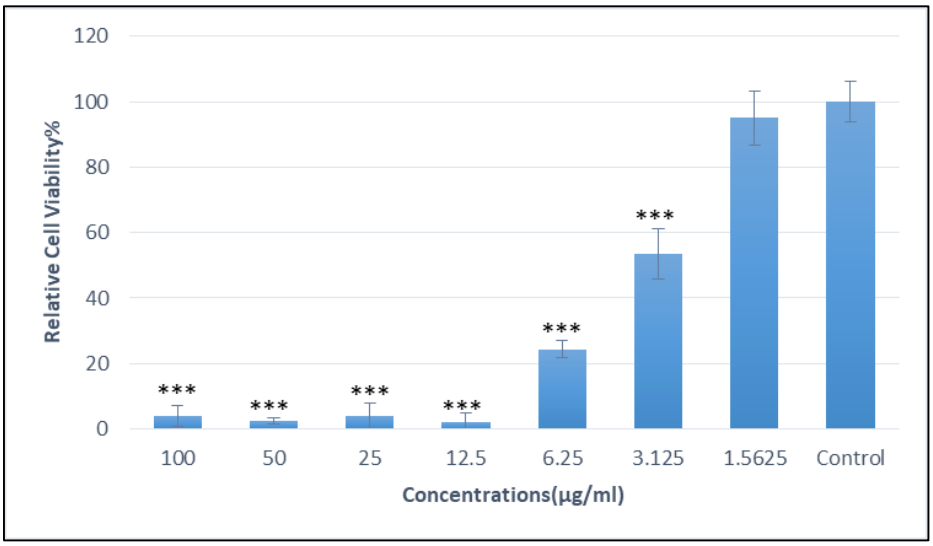

Figure 3. Viability of Hek293 cells treated with different concentrations of sertraline (µg/ml). * indicates significant difference compared with control group (***:p<0.001).

The IC50 value for 24 hours of treatment with drug was 3.4 µg/ml (Figure 4).

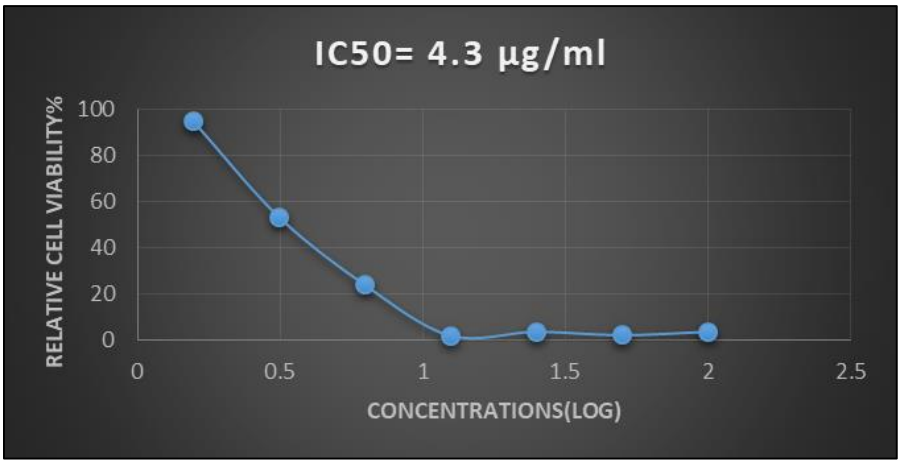

Figure 2. IC50 value for 24 hours of treatment with sertraline.

Discussion

Although many studies have shown that sertraline is used as a drug to treat depression, the cytotoxic effect of sertraline on normal body cells is still a challenging issue. The results of this research showed that the use of sertraline with low doses and in a shorter time does not have significant cytotoxic effects on normal cells. In line with our findings, the result have shown that the use of low doses of sertraline, while not having harmful effects on human neuroblastoma cells in the cell culture environment, can have beneficial effects on the cells [14]. The findings show that sertraline not only does not have a destructive effect on normal immune cells, but can also play a role in reducing inflammation by having a positive effect on immune cells [15]. Examining the effect of sertraline on normal nerve cells also shows that this drug has no harmful effect on these cells and its use has played an effective role in improving the nervous system [16]. However, some findings show that sertraline may have a destructive effect on normal body cells. It has been

shown that children of women who take sertraline during pregnancy are at increased risk and that sertraline can cause DNA damage in cells [17]. Also, sertraline can cause harmful poisoning with a destructive effect on normal body cells [18]. More studies are needed to reveal the exact effects of sertraline on normal body cells *in vitro* and *in vivo*.

Conclusion

Overall, the results of this research show that sertraline in low doses and short time does not have cytotoxic effects on normal cells, although more studies are needed to reveal the exact effects of sertraline on normal cells.

Acknowledgment

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Conflict of interests

The authors have no conflicts of interest to declare.

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