Original Article

Immunoregulatory Effects of Paroxetine in Healthy Volunteers: An *In Vitro* Investigation

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Abstract

Background: Paroxetine has been a commonly prescribed antidepressant for treatment of major depression and various anxiety disorders for almost 30 years due to its fewer side effects and toxicity compared with its counterparts. Despite several investigations performed, the paroxetine immunoregulatory effect in healthy subjects is still controversial. In this study, the paroxetine effect on the cell proliferation along with IL-4 and interferon-gamma (IFN-γ) secretion in peripheral blood mononuclear cells (PBMCs) of physically and mentally healthy subjects is investigated. **Materials and Methods:** Blood was drawn from 20 healthy subjects and PBMCs were isolated. Cells were treated with paroxetine and/or phytohemagglutinin (PHA) for 72 h. IL-4 and IFN-γ concentrations were assessed in the supernatant using an enzyme-linked immunosorbent assay. The BrdU cell proliferation assay was also performed to evaluate the paroxetine effect on PBMCs in the absence or presence of PHA. **Results:** Paroxetine (25 μM) significantly inhibited the production of IL-4 and IFN-γ in PHA-stimulated human PBMC cultures. Surprisingly, paroxetine suppressed cell proliferation in the unstimulated culture in a dose-independent manner. Paroxetine also attenuated cell proliferation in the PHA-stimulated culture, especially at 25 μM concentration. **Conclusion:** The obtained results suggest that paroxetine can be a potent therapeutic option in inflammatory diseases by balancing immune responses.

Keywords: *Cell proliferation, IFN-γ, IL-4, paroxetine, PBMC*

Introduction

The potential clinical applications of paroxetine, a selective serotonin reuptake inhibitor (SSRI), in the treatment of various inflammatory diseases have been reported extensively in the recent literature.[1-4] Cytokine profile alterations under treatment with paroxetine are well studied in patients with mental disorders and murine models.[5-8] In this regard, many molecular pathways in intrinsic and adaptive immunity have been examined to explain the rationale. However, few data are addressing its effect on cytokine production in healthy subjects.

IL-4 is a pleiotropic cytokine and is produced by a wide spectrum of immune cells including $CD4^+$ T cells, NK T cells, and macrophages. Following receptor binding, IL-4 exerts distinct immuno-modulation depending on the cell type.[9] IL-4 regulatory effect in the context of lymphoid cells is well discussed. In this line, IL-4 contribution to lymphocyte differentiation, stimulation, and survival is reported by primary studies.[10] However, IL-4 is mostly known due to its role in promoting Th0 cell differentiation to Th2 and inhibiting Th1 and Th17 cells.[11] Th2-derived IL-4 mediates immune response against parasitic infections.[12] The uncontrolled action of any molecular signaling in the cellular scale can cause abnormalities in the systemic scale. Cytokine-related signaling pathways are no exception. In the case of IL-4, its excess production is associated with abnormalities including allergy, autoimmunity, and cancer.

IFN-γ is a type II interferon and is produced by a variety of immune cells including natural killer cells (NK), CD^{4+} and CD^{8+} T cells, and macrophages. IFN-γ takes part in immune responses directed against the viral, some bacterial, and protozoal invaders. IFN-γ stimulates NK cell activity, increases antigen presentation by antigen-presenting cells (APCs), boosts macrophages activity, activates nitric oxide synthase, and induces activated plasma B cells to produce IgG2a and IgG3. Dysregulated IFN-γ production is correlated with autoimmune diseases.[13]

IL-4 and IFN-γ reciprocal role in modulating immune responses is well established which

How to cite this article: Karimollah A, Hemmatpur A, Asadi M, Hadinedoushan MH. Immunoregulatory effects of paroxetine in healthy volunteers: An *in vitro* investigation. J Rep Pharm Sci 2021;10:118-23.

Received: 25 May 2020
Accepted: 15 Mar 2021
Published: 31 May 2021

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Access this article online

Website: www.jrpsjournal.com

DOI: 10.4103/jrptps.JRPTPS_66_20

Quick Response Code:

are reflected in Th2 and Th1 differentiation and macrophage polarization to M_2 and M_1 phenotypes by these cytokines, respectively.[14,15] Therefore, the IL-4/IFN-γ ratio is associated with the Th2/Th1 ratio and immune response balance. Disturbed balance between Thl and Th2 cytokine profiles can result in the development of diseases like allergy (Th2), multiple sclerosis, and rheumatoid arthritis (Th1).[16] IL-4 and IFN-γ are not typically the cytokines noted to be altered in patients with depression or anxiety. However, considering their vital role in balancing the immune responses alongside the abnormalities caused by their dysregulation, pharmaceuticals regulating IL-4 and IFN-γ production are of great importance. In spite of the confirmed anti-inflammatory properties, the net effect of paroxetine on IL-4 and IFN-γ profile is not well established yet. Therefore, we investigated IL-4 and IFN-γ production in PHA-stimulated PBMCs of healthy subjects under paroxetine treatment.

Previous *in vitro* studies revealed that antidepressants can modulate cell proliferation and apoptosis. Studies on paroxetine have provided different results in neural and cancerous cells. Accordingly, paroxetine is proposed to promote neuronal proliferation,[17] while it is stated to inhibit cell proliferation in neoplastic cells.[18,19] To our knowledge, there are few data regarding paroxetine effect on proliferation of the peripheral cells derived from healthy subjects. Therefore, we examined PBMCs' proliferation under the paroxetine treatment in healthy subjects.

Materials and Methods

Ethical statement

It is important to note that the volunteers gave consent to take part in the study. Tests with the use of human samples have been approved by the University Ethical Committee with ethical code: IR.SSU.MEDICINE.REC.1395.232.

PBMC isolation, culture, and treatment

Peripheral blood was obtained from 20 healthy volunteers. PBMCs were isolated performing Ficoll (Baharafshan, Iran) gradient centrifugation. Isolated PBMCs were washed two times with RPMI-1640 medium. Cells were then suspended in RPMI-1640 medium (BioIdea, Iran) with 10% fetal bovine serum (FBS, Biochrom, Berlin, Germany). The percentage of viable cells was assessed by Trypan blue (Innoclon, Iran), and cells with a viability of more than 95% were selected for culture. Cells were transferred in duplicate into the wells of a 96-well microplate at densities of 100,000 cells/well. The plate was incubated at 37ºC under 5% CO_2 with 90% humidity. Phytohemagglutinin (PHA) can stimulate the secretion of proinflammatory cytokines by cultured PBMCs.[20] Thus PHA (10 µg/mL) (PHA, Sigma-Aldrich, USA) was added to the wells to stimulate cells to proliferate in the presence or absence of paroxetine (Sigma-Aldrich, USA).

IFN-γ and IL-4 protein assay

Target cytokine protein levels were measured using an enzyme-linked immunosorbent assay (ELISA). According to the previous results of our group, paroxetine exerts most immunosuppressive effect at 25 µM.[21] Therefore, we assessed IFN-γ and IL-4 levels after treatment with paroxetine at 25 µM. After 72 h co-treatment of cells with PHA+ paroxetine, the plate was centrifuged for 10 min and the supernatant was removed. Levels of IFN-γ and IL-4 in the culture were determined according to the provided protocol (E. Bioscience, San Diego, CA, USA). In brief, supernatants were added to the precoated wells with monoclonal antibodies for target cytokine and incubated for 3 h at room temperature. Plates were washed three times to remove unbound substances, an enzyme-linked polyclonal antibody specific for the cytokine then was added and plates were incubated for 1 h at room temperature. Following a wash to remove any unbound antibody-enzyme reagent, the substrate solution was pipetted into the wells and incubated for 30 min at room temperature. At this step, color develops in proportion to the amount of cytokine bound in the initial step. To stop further staining, the stop solution was added to each well. Optical density measurements were taken at 450 nm.

BrdU cell proliferation assay

To determine the paroxetine effect on cell proliferation, we used BrdU cell proliferation ELISA kit (Roche Diagnostics, Indiana, IN, USA). For this purpose, cells were seeded at a density of 10^5 cells/well in 10% FBS/RPMI-1640 medium in a 96-well plate and incubated for 48 h at 37ºC under 5% CO_2 with 90% humidity. Then, the various concentrations of paroxetine (1, 5, 10, 25, and 50 µM) were added to the wells. After 72 h incubation, 10 µL/well of labeling solution was added to the wells and incubated under the previously mentioned condition. The microculture plate was centrifuged for 10 min, and the supernatant was removed afterwards. Following the procedure performed according to manufacturer's instruction. The optical densities were determined with an ELISA reader (Stat Fax, 3200 Microplate Reader, Awareness Technology, Inc., USA) at a test wavelength of 450 nm.

Statistical analysis

Statistical analysis was performed via GraphPad Prism 6.07 Software. Data were expressed as mean ± standard error (SEM). Student's *t*-test was applied to analyze protein levels. One sample *t*-test was also performed to analyze proliferation assay results. An analysis of variance test (one-way) was carried out, followed by Bonferroni's *post hoc* test to determine the difference between means of different concentrations of paroxetine in the proliferation assay. A *P*-value less than 0.05 was considered statistically significant.

Results

Paroxetine suppressed PBMCs proliferation

To explore the paroxetine effect on cell proliferation in the absence of mitogen, we treated unstimulated cells with paroxetine. Interestingly, paroxetine suppressed PBMCs proliferation, independent of the concentration [Figure 1A].

As indicated in Figure 1B, paroxetine treatment also resulted in significant inhibition of mitogen-stimulated cells proliferation at 10, 25, and 50 μM.

Paroxetine suppressed IL-4 and IFN-γ concentration

ELISA results revealed that paroxetine (25 μM) significantly decreased IL-4 and IFN-γ secretion by cultured PBMCs [Figure 2A and B]. The IL-4/IFN-γ ratio was also calculated to investigate the influence of paroxetine on the Th2/Th1 ratio. Paroxetine did not exert any significant effect on this ratio [Figure 2C]. A schematic description of the experimental procedure and the results are depicted in Figure 3.

Discussion

Paroxetine, a selective serotonin reuptake inhibitor (SSRI), is a well-known and commonly prescribed antidepressant. However, its second pharmacological nature has gained attention and been the subject of numerous studies in recent years. Here we studied differential cytokine secretion by PBMCs after mitogenic stimulation when treated with paroxetine. The immunoassay results revealed that paroxetine (25 μM) diminished IL-4 and IFN-γ secretion at the presence of mitogen stimulant (PHA).

IFN-γ is reported to be decreased under treatment with an SSRI class of antidepressants such as citalopram, fluoxetine, and sertraline.[22] However, data addressing alterations in IFN-γ secretion in response to paroxetine are approximately rare. Studies by Hernández *et al.*[23,24] proposed that IFN-γ plasma concentrations vary in patients with major depression (MDD) at different time points of treatment with paroxetine. They stated that after 52 weeks of paroxetine treatment, IFN-γ levels were comparable to those of healthy controls. However, Chen *et al.*[6] reported a positive effect of paroxetine on plasma levels of the IFN-γ in MDD patients. The study by Myint *et al.*[25] also reported increased IFN-γ levels in male rats in response to paroxetine. It can be concluded from the residing data that paroxetine immunomodulatory effects through the IFN-γ differ between healthy and mentally ill subjects. IFN-γ contribution to the autoimmune diseases including systemic lupus erythematosus, inflammatory bowel disease, and multiple sclerosis has been established.[26] Moreover, IFN-γ pathogenic role in liver cirrhosis and diabetes mellitus is stated by numerous investigations.[27] Consequently, IFN-γ is a potent therapeutic target in many immune-based diseases. Given that paroxetine diminished IFN-γ in healthy subjects-derived PBMCs, it might be applicable clinically, but further exclusive investigations are acquired to confirm this hypothesis.

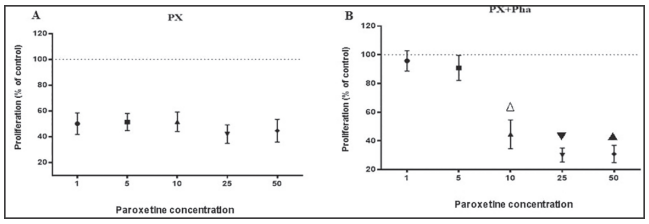

Figure 1: Paroxetine effect on PBMCs proliferation (A) in the absence of PHA and (B) in the presence of PHA Δ; *P* = 0.003, ▼; *P* =0.0, ▲; *P* = 0.0). The results are means ± SEM

The effect of members of SSRIs on IL-4 production has been previously elucidated,[28,29] but similar to IFN-γ there are few investigations respecting the paroxetine effect on IL-4 alterations. In this line, Chen *et al.* indicated that paroxetine can significantly decrease the IL-4 levels in MDD patients. Though, Horikawa *et al.*[30] did not observe significant altered IL-4 secretion from IFN-γ-activated murine microglia under paroxetine treatment. In consistence with their findings, Hernández *et al.*[24] reported no significant change in the levels of IL-4 in MDD patients after treatment with paroxetine. This discordance could be partly due to the probable paroxetine different modes of action between mentally ill and healthy subjects. The mentioned inconsistencies might also be due to the fact that IL-4 has two spliced isoforms with different actions. Therefore, more exclusive studies are needed to explore the subject. Anti-IL-4 drugs are reported to be effective in the treatment of eosinophilic asthma.[31] Thus in case of confirming the IL-4 suppressive effect in future studies, paroxetine would be a promising medicine in the treatment of asthma due to its few side effects.

The IL-4/IFN-γ ratio has been long introduced as an indicator of Th2/Th1 responses. Therefore, we calculated the ratio to examine the paroxetine influence on the Th2/Th1 balance. Despite a moderate reduction, paroxetine did not exert a significant effect on the ratio. It has been stated recently that paroxetine shifts cytokine production toward Th1, which is partly due to the serotonin effect on the Th2/Th1 balancing system.[6,32] This can explain the moderate downward trend in the IL-4/IFN-γ ratio observed in our study. Kim *et al.*[33] reported that 6 weeks of treatment with antidepressants including paroxetine did not alter IL-4, IFN-γ, and IL-4/IFN-γ ratio in MDD patients. However, a similar study by

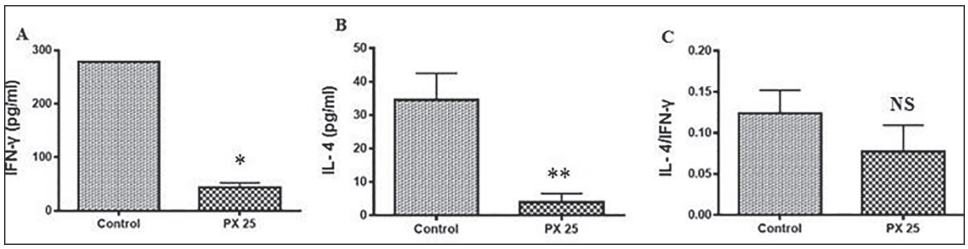

Figure 2: Paroxetine significantly suppressed (A) IFN-γ; **P* < 0.0001 and (B) IL-4 ***P* = 0.0335. (C) The IL-4/IFN-γ ratio did not alter significantly under paroxetine treatment. The results are means ± SEM

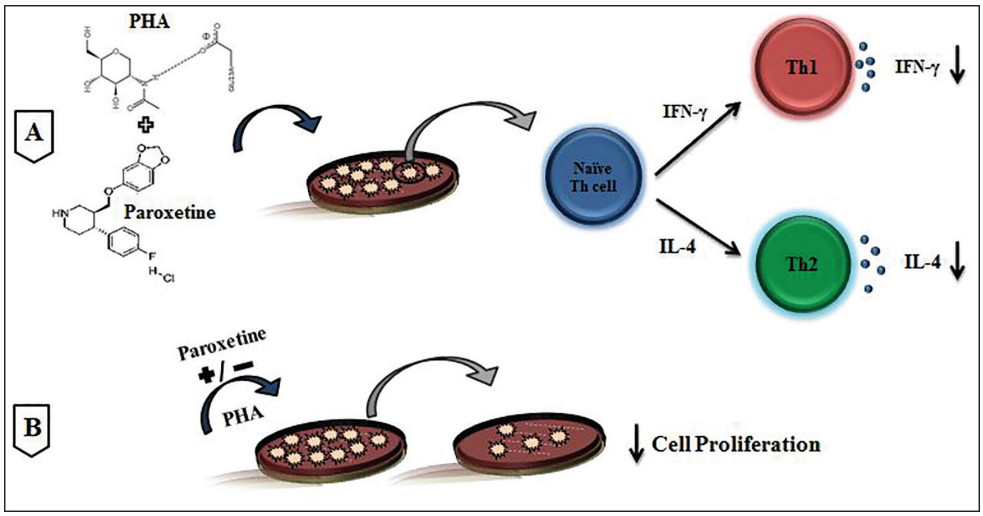

Figure 3: A schematic illustration of study procedure and results. (A) Treatment of PHA-LPS-stimulated PBMCs with paroxetine suppressed IL-4 and IFN-γ. (B) It also significantly suppressed cell proliferation in the stimulated and unstimulated cultures

Myint *et al.*[34] indicated that 8 weeks of treatment with antidepressants (including paroxetine) significantly increased the IL-4/IFN-γ ratio. Moreover, a study by our group showed that paroxetine treatment increases IL-10 production.[21] Prior investigations established that most antidepressants decrease the IFN-γ/IL-10 ratio via inhibiting IFN-γ and increasing IL-10.[35] Therefore, we hypothesized that paroxetine differently affects inflammatory responses at the level of T helper immunoregulation, depending on one's central nervous system inflammatory status. This aspect of paroxetine action can be exploited and directed favorably due to the patients' need and clinical condition.

We further explored whether paroxetine could suppress PHA-induced cell proliferation. Paroxetine considerably decreased BrdU incorporation into the PHA mitogenic stimulated cell's DNA, measured by ELISA. There is a large volume of data addressing the inhibition of cell proliferation under treatment with antidepressants.[18,36] Nevertheless, evidence explaining paroxetine-mediated cell proliferation is controversial. For instance, Roman *et al.*[37] and Ronchetti *et al.*[38] failed to find any significant effect on T-cell proliferation by paroxetine. While Lau *et al.*[39] proposed that paroxetine could promote subventricular zone cell proliferation. Likewise, Jahromi *et al.*[17] reported that paroxetine promoted proliferation of human adipose-derived stem cells during neurogenic differentiation. The reports concerning the inhibitory effect of paroxetine on cell growth are largely limited to the neoplastic cells.[19,40] Meanwhile, in consistence with our results, Lin *et al.*[41] indicated that paroxetine can inhibit the proliferation of vascular smooth muscle cells. A similar study by Rzezniczek *et al.*[42] also reported paroxetine-induced growth inhibition in PBMCs of healthy subjects. The mentioned evidence suggests that paroxetine could differently influence cell proliferation depending on the cell type and cellular circumstance as Rzezniczek *et al.* showed attenuated paroxetine-induced inhibition of peripheral blood mononuclear cell growth in depressed patients when compared with the healthy controls. It is important to note that paroxetine significantly inhibited cell proliferation independent of concentration in the absence of PHA. Concerning the similar methodology of BrdU cell proliferation and apoptosis ELISA kits, it could be inferred from this finding that decreased cell proliferation in the absence of the mitogen might be at least partly due to the paroxetine-induced apoptosis. In confirmation of this hypothesis, apoptotic characteristic of paroxetine has been reported numerously by *in vitro* studies and in various human and murine cell types.[43-45] Moreover, plenty of studies indicated the anti-tumor effect of paroxetine via apoptosis induction.[46] Additionally, there are several lines of evidence proposing proliferative and anti-apoptotic characteristics of IL-4.[10,47,48] Therefore, our findings concerning proliferative responses to paroxetine might be because of the suppressed IL-4 levels by paroxetine at least in immune cells. However, there are data attributing the cell growth inhibitory characteristic of paroxetine to serotonin transporters (SERT).[42] Thus more detailed studies should be performed to unveil the exact underlying mechanisms.

Conclusion

Regarding various immunomodulatory effects of paroxetine and because paroxetine is among FDA-approved drugs, it can be promising in the treatment of many inflammatory diseases resulting from imbalanced cytokine production. The present findings also suggest that immunomodulatory effects of paroxetine might be different between healthy and depressed patients.

Acknowledgements

We thank all the people in Shahid Sadoughi University of Medical Sciences who kindly helped us to perform this investigation.

Financial support and sponsorship

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interests

There are no conflicts of interest.

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