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Effects of Escitalopram and Bupropion On Oxidative Stress Parameters and Blood Count Findings in Female Rats

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ABSTRACT

In this study, the effects of two antidepressants with different mechanisms on rat blood oxidative stress parameters and blood count findings were studied. Escitalopram is a selective serotonin reuptake blocker (SSRI) derivative and bupropion has a mechanism of action on noradrenaline and dopamine and increases their synaptic amount by inhibiting their uptake.
Adult, female, Wistar-albino rats were divided into 3 different groups with a total of 24 animals. Rats in escitalopram group were administered with 20 mg/kg/day escitalopram and rats in the bupropion group were administered with 20 mg/kg/day bupropion for 28 days via gastric gauge. The rats in the control group were given tap water via gastric gauge.
Hematocrit and hemoglobin parameters were significantly higher in Escitalopram and Bupropion than control group. No significant difference was observed in weight gain at the end of 28 days. In this experimental model, 28 days of 20 mg/kg escitalopram or bupropion use did not cause a significant increase in total oxidant status or a significant decrease in total antioxidant status.
Oxidative stress index which combines these two findings imply a possible oxidative stress in female rat blood due to Escitalopram treatment.

Keywords: Depression, antidepressant, SSRI, escitalopram, bupropion, noradrenaline

Introduction

Depression is an important health problem which causes mental as well as cardiovascular problems worldwide (1). Alongside with psychotherapy, medication with chemical drugs forms the basis of modern pharmacotherapy of depression. The classical antidepressant effect is to block one or more of the serotonin, norepinephrine and/or dopamine transporters, thereby augmenting monoamine levels in relevant brain parts. This pharmacological action mechanism is consistent with the monoamine hypothesis in depression. In its simplest form, this means a reduction of the monoamine in depression and the improvement of depression by increasing the amount of antidepressants. However, depression may also include complex interaction between such monoamines as well as glutamate and histamine in the brain (2). A number of antidepressants, called selective serotonin reuptake inhibitors (SSRIs) are theoretically acting by blocking serotonin reuptake in the synaptic cleft. Within this group, escitalopram (ESC) may be considered as a model SSRI with the effect of pure serotonergic reuptake inhibition. Similarly, selective norepinephrine reuptake inhibitors (SNRI) are acting on norepinephrine reuptake transporters. SNRI's are also favored in treatment of depression (3). Bupropion (BUP) which is a member of SNRI group, transport of both dopamine and norepinephrine is accepted as the responsible mechanism for its shown antidepressant activity. Although these aforementioned molecules are more widely used for treatment due to their lower side effects compared to previously used antidepressants such as monoamine oxidase inhibitors or tricyclic antidepressants (4) they are still blamed for various untoward outcomes such as neurological, cardiovascular and sexual side effects (5). The use of antidepressants is increasing all over the world and more data is required for their impacts on different health perspectives.

The preservation of the integrity of erythrocytes and the optimal blood flow are important for a healthy microcirculation and cardiovascular health (6, 7).

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Adverse conditions, such as various chemicals and oxidative stress, can cause oxidation of membrane lipids or the protein skeleton in the membrane, resulting in damage to the erythrocyte membrane and, ultimately, its integrity (8). Oxidative stress is classified within the etiology of certain diseases such as Alzheimer, Parkinson, epilepsy and metabolic diseases such as diabetes mellitus (9, 10, 11). Some studies present results stating alleviation of oxidative stress with antidepressants during experimental stress models on animals (12). Most of those models establish a depression model on the experimental animals than testing the effect of antidepressants in different parameters. On the other hand, there are research results stating that antidepressants itself may pose an oxidative stress on different tissues or organs (13). The aim of the study is to investigate the effects of two antidepressants with different action mechanisms, commonly used in the treatment of many psychiatric disorders, on erythrocytes and to investigate the effect of oxidative stress parameters. Since many of the research was tested on male animals this study is conducted to assess the effects of those antidepressants on female animals.

Materials and Methods

Animals and Experimental Procedure: 24 female adult Wistar-albino rats were divided randomly into 3 different groups (n=8 in each group). Control group; were given tap water with oral gauge. Escitalopram group (ESC); administered 20 mg/kg escitalopram in 10 ml/kg volume for 28 days with oral gauge. Bupropion group (BUP); administered 20 mg/kg bupropion in 10 ml/kg volume for 28 days with oral gauge. Escitalopram and Bupropion in commercial forms were given to animals. Dosage was set according to a study by Ortiz and Artigas (14). Food and tap water were given *ad libitum* throughout the experimental period. Animals obtained from Van Yuzuncu Yil University Experimental Animal Research Center was also kept in the same center in a room with controlled temperature (~22C) and light (12 hours light/12 hours dark). Weight gain of the animals was monitored in this whole period.

An ethical permission was obtained from Van Yuzuncu Yil University Experimental Animals Local Ethical Committee (Date: 26.10.2017, number: 10). At the end of this experimental procedure animals were sacrificed under ketamine/xylazine anesthesia. Venous blood was withdrawn into EDTA containing tubes for hemogram analysis and also plasma was obtained for biochemical analysis.

Complete Blood Count: Red blood cell number, hematocrit and hemoglobin values were recorded following venous blood sampling at the end of the experimental procedures. Complete blood count was performed with a coulter counter.

Plasma TAS and TOS Measurements: Total antioxidant status (TAS), total oxidant status (TOS) and oxidative stress index (OSI) were investigated as oxidative stress parameters in the plasma. A spectrophotometric kit was used for TAS and TOS measures (RelAssay) and OSI was calculated with a formula basically considering a ratio between measured amount of TOS versus measured amount of TAS.

Statistical Analysis: Data were presented as Mean ± SEM. Kruskal-Wallis test was used to investigate significance among groups and Mann Whitney U tests were performed to evaluate comparisons between two groups by using SPSS 20.0 for Windows. $p<0.05$ was accepted as statistically significant.

Results

Rats were weighed at the beginning and at the end of the protocol. No deaths or complications were observed in rats during the experiment and the rats gained weight at the end of this period. Although final weight of ESC group (229) is lower than Control (234) and BUP (237) groups, no significant difference was found between groups.

Oxidative Stress Parameters: At the end of the experimental protocol, antidepressant drugs applied to animals were evaluated for their impact on oxidative stress parameters.

When the total oxidant status of the groups was examined, an increase was observed in the antidepressant groups ESC (6.918±2.252) and BUP (7.517±1.11) compared to the control (4.931±2.598) group but no significant difference was observed (Table 1).

Total antioxidant status was decreased in both of the antidepressant groups ESC (0.545±0.318) and BUP (0.783±0.25) compared to the control (0.976±0.313) group but no significant difference was found (Table 1).

The OSI index calculated from TOS and TAS parameters showed that the highest oxidative stress index occurred in the ESC (0.189±0.134) and followed by the BUP (0.104±0.031) group. The difference between the ESC group and the control (0.059±0.039) group was significant ($p<0.05$, Table 1).

Blood Count Findings: Certain differences were observed in terms of erythrocyte count, hematocrit and hemoglobin values due to antidepressant use.

Table 1: Oxidative Stress Parameters of Groups

		Median	Mean	Std. Dev.	Min.	Max.	p
TOS	Control	4.535	4.931	2.598	1.514	8.539	0.198
	Escitalopram	7.082	6.918	2.252	3.386	9.764	
	Bupropion	7.496	7.517	1.11	6.351	9.265	
TAS	Control	1.07	0.976	0.313	0.4	1.252	0.108
	Escitalopram	0.542	0.545	0.318	0.166	1.012	
	Bupropion	0.736	0.783	0.25	0.506	1.135	
OSI	Control	0.047 [b]	0.059	0.039	0.013	0.137	0.042
	Escitalopram	0.132 [a]	0.189	0.134	0.046	0.384	
	Bupropion	0.095 [ab]	0.104	0.031	0.075	0.161	

TOS: Total Oxidant Status. TAS: Total Antioxidant Status. OSI: Oxidative Stress Index. $p<0.05$. Different letters in the same column indicate statistically significant difference between groups

Table 2: Blood Count Findings of Groups

	RBC	HCT	HGB
Control	8.08±0.2	44.43±0.5 [b]	15.63±0.2 [b]
Escitalopram	8.58±0.1	47.54±0.8 [a]	16.54±0.2 [a]
Bupropion	8.48±0.2	46.06±0.9 [a]	16.38±0.3 [a]

Values are given as mean±S.E.M. RBC: Red blood cell count ($x10^6/mm^3$). HCT: Hematocrit (%). HGB: Hemoglobin count (g/dL). Statistical significance (*) was set as $p<0.05$ compared to control. Different letters in the same column (a, b) indicate statistically significant difference between groups

The RBC (Red Blood Cell) value, which represents the number of red blood cells, was higher in ESC and BUP groups compared to the control. However, no statistically significant difference was observed in the aforementioned values. The values observed in the hematocrit (HCT) parameter were found to be significantly higher in the ESC and BUP groups compared to the control group ($p<0.05$). The values of hemoglobin were highest in the ESC and BUP groups and the values in this group were found to be statistically significant compared to the control group ($p<0.05$). Results of blood count findings are given in Table 2.

Discussion

Depression, which is an important health problem, is one of the most common psychiatric disorder in almost all societies. Although psychotherapy, exercise, diet and lifestyle change are the approaches, the current treatment of depression is still largely performed with medication of antidepressant drugs. Antidepressants have different mechanisms of action and are known to alter the levels of serotonin, dopamine and noradrenaline in the brain. However, there is also information about the side effects of antidepressants. The aim of this study was to investigate the effect of two antidepressant drugs with different mechanisms of action on the blood oxidative stress parameters in female rats in the same experimental procedure.

Women suffer more from depression than man in aspects of frequency, severity, duration and comorbidities (15). In addition, antidepressant therapy is not giving similar results in two genders. Several studies are performed to elucidate reasons in brain wiring or sex steroids but still more studies are needed to clarify this disparity. Thus, we have selected female animals for experimental procedures of our study. In the present study, it was observed that antidepressant use was associated with increased hemoglobin (HGB), red blood cell count (RBC) and hematocrit (HCT) values measured by complete blood count. Hemoglobin and hematocrit usually increase or decrease together because they both depend on the number of RBCs. In a study conducted in support of our findings, significant increases in RBC count, HCT, and red cell distribution width (RDW) were observed after 12 weeks of SSRI treatment in adolescents with major depressive disorder (MDD) who had not previously used medication. An increasing trend in HGB levels was also identified by Puangsri *et al* (16). Oxidative stress can influence hematological parameters through both direct and indirect mechanisms. The most commonly observed

effects include erythrocyte damage, and alterations in hemoglobin, platelet, and leukocyte levels (17).

No significant difference was observed in animal weight analysis. The present situation can be evaluated in terms of the fact that these 2 different antidepressant molecules did not cause a significant difference in food consumption and weight gain in female rats.

Oxidative stress refers to the situation in which the antioxidant molecules and enzymes present at the cellular level in blood or other tissues cannot balance the oxidant molecules produced in metabolic or pathological processes. Although oxidant molecules are effective in some cellular signaling pathways, they may cause damage to DNA and other molecules in the cell. In the measurement of oxidative stress, lipid peroxidation (MDA) products, glutathione (GSH) which is an important protector against oxidative stress, as well as the amount or activity of enzymes such as catalase (CAT) and superoxide dismutase (SOD) can be measured. In addition to measuring all these different parameters another approach in the subject is to measure total antioxidant status (TAS), total oxidant status (TOS) and the ratio of these two (TOS/TAS) as an index of oxidative stress (OSI). Higher OSI values indicate increased oxidative stress. In this study, it has been shown that ESC, which is a selective serotonin reuptake blocker (SSRI) derivative, did not cause a significant increase in total oxidant status or a significant decrease in total antioxidant status, however oxidative stress index which combines these two findings imply a possible oxidative stress in female rat blood. The OSI index calculated from TOS and TAS parameters showed that the highest oxidative stress occurred in the ESC group compared to the control group. The difference between the control group and the ESC group was significant ($p < 0.05$). In our study, the reason for comparing different mechanisms of action in the same parameter (OSI) is to determine which molecule will cause more oxidative stress in the same experimental setup in terms of oxidative stress. Bupropion was not found to alter oxidative stress parameters significantly in our study. There are studies concerning some untoward effects of bupropion such as endoplasmic reticulum stress (18) but no apparent effect on oxidative stress in blood was mentioned in scientific literature. Our results are consistent with such findings.

Studies concerning interrelation between depression and oxidative stress show that anxiety and depression poses patients to attenuated antioxidants, increased oxidants and results such as lipid peroxidation. Such negative impacts of depression are reversed with antidepressant treatment (19, 20, 21). Studies on experimental animals also show that SSRI's are effective in reversing the oxidative stress conditions especially in experimental stress conditions such as restrainer stress. In a study by Novio *et al* (22), mice were immobilized for a period of 6 hour, 5 mg/kg fluoxetine administered prior to (30 min) acute stress alleviated the untoward effects of stress. Similarly, human studies showed that antidepressant treatment increased total antioxidant capacity and lowered total oxidant status as well as oxidative stress index (23). Studies performed on animals and data obtained from studies with human subjects reveal that long term (12 to 24 weeks) antidepressant treatment exert a mitigation in oxidative stress posed by major depression. However, high doses of some antidepressant molecules were reported to exert prooxidant activity revealed by *in vitro* and *in vivo* animal models (24). Our study is shorter compared to such treatments (4 weeks). In such short time period, some other studies on major depression patients (4 to 8 weeks) no significant effects were found in oxidant and antioxidant parameters (24).

On the other hand, there are studies presenting oxidant effect of antidepressants. An enhanced oxidative stress on erythrocytes due to 21 days of 20 mg/kg/day sertraline administration (but not with 5 days of acute administration) was reported by Arihan *et al* (25). In a study by Atli *et al* (13) 20 mg/kg sertraline (SSRI) treatment resulted in a decreased GSH level ($p<0.05$) and increased MDA level ($p<0.05$) compared to control in testicular tissue of rats. Another experimental study performed on male Wistar-albino rats showed that median testicular MDA levels increased in two months of 10 mg/kg sertraline (3.2), 10 mg/kg fluoxetine (2.8 $p=0.092$), 10 mg/kg escitalopram (2.65) and 20 mg/kg paroxetine (2.25) administrations compared to control (2.15). Although none of the administration caused a significant increase, trend in MDA increase when considered with other studies in the subject suggests a possible augmentation in lipid peroxidation (26). In a study by Abdel-Salam *et al* (27), sertraline administered in 10 or 20 mg/kg via the subcutaneous route to mice for 10 days caused a decrease in catalase activity, decrease in PON1 activity in the brain. In the liver MDA was increased and PON1 activity was decreased with sertraline. Dissimilar results concerning antioxidant – oxidant effect of antidepressant drugs may be related with the dose, mode of treatment and duration of exposure to antidepressant molecule.

Limitation of our study is its being an experimental animal study. Even the depression models for rats are lacking very crucial aspects of depression such as feeling guilty or attempt to suicide (15). In

accordance, investigating effects of antidepressant used in human medication on animals should always considered as a "model" resembling but not fully exhibiting human conditions. In addition, rats are known to have a different serotonergic mechanism. Their thrombocytes are more active compared to human which means that their response to SSRI exposure is different than human. Nevertheless, our data reveals that SSRIs should be considered for their possible impact on oxidative stress. It is argued that SSRI molecules are the most selective with least side effect. In addition, SSRI's are known to exert antioxidant effect on depressed patients and also in animal models inducing depression. However, in animals which are not depressed by external effect, SSRIs may cause such an oxidative stress condition. In further studies, in rats with depression model, these drugs should be tested in a similar way, but tested in different doses and in longer experimental periods because longer periods with antidepressants are shown to exert differential results than acute ones (24). In addition, forced swimming test (in rats) and tail suspension tests (mice) can be tested in conditions with and without depression during escitalopram and bupropion antidepressant treatments in future studies.

In this experimental model, 28 days of 20 mg/kg escitalopram did not cause a significant increase in total oxidant status or a significant decrease in total antioxidant status, however oxidative stress index which combines these two findings imply a possible oxidative stress on female rat blood.

Studies in scientific literature have been conducted mainly on male rats, which causes a bias in both neuroscience and biomedical fields (28) whereas our study is made on female rats. In addition, the use of two antidepressants with different mechanisms together is a contribution of this study to the scientific literature.

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References

1. Smith K. Mental health: a world of depression. Nature 2014; 515: 181.
2. Faquih AE, Memon RI, Hafeez H, Zeshan M, Naveed S. A Review of Novel Antidepressants: A Guide for Clinicians. Cureus 2019; 11: e4185.
3. Berard A, Sheehy O, Zhao JP, Vinet É, Bernatsky S, Abrahamowicz M. SSRI and SNRI use during pregnancy and the risk of persistent pulmonary hypertension of the newborn. Br J Clin Pharmacol 2017; 83: 1126 - 1133.
4. Feighner JP. Mechanism of action of antidepressant medications. J Clin Psych 1999; 60: 4 - 11.
5. Harvey KV, Balon R. Clinical implications of antidepressant drug effects on sexual function. Ann Clin Psych 1995; 7: 189 - 201.
6. Kensey KR. The mechanistic relationship between hemorheological characteristics and cardiovascular disease. Curr Med Res Opin 2003; 19: 587 - 596.
7. Woodward M, Rumley A, Tunstall-Pedoe H, Lowe G. Does sticky blood predict a sticky end? Association of blood viscosity, haematocrit and fibrinogen with mortality in the West of Scotland. Brit J Haematol 2003; 122: 645 - 650.
8. Gray BH, Porvaznik M, Flemming C, Lee LH. tri-n-Butyltin: a membrane toxicant. Toxicology 1987; 47: 35 - 54.
9. Jiang T, Sun Q, Chen S. Oxidative stress: A major pathogenesis and potential therapeutic target of antioxidative agents in Parkinson's disease and Alzheimer's disease. Prog Neurobiol 2016; 147: 1 - 19.
10. Pearson-Smith JN, Patel M. Metabolic Dysfunction and Oxidative Stress in Epilepsy. Int J Mol Sci 2017; 18: E2365.
11. Newsholme P, Cruzat VF, Keane KN, Carlessi R, de Bittencourt PI Jr. Molecular mechanisms of ROS production and oxidative stress in diabetes. Biochem J 2016; 473: 4527 - 4550.
12. Hritcu L, Ionita R, Postu PA, Gupta GK, Turkez H, Lima TC, et al. Antidepressant Flavonoids and Their Relationship with Oxidative Stress. Oxid Med Cell Longev 2017: 5762172.
13. Atli O, Baysal M, Aydogan-Kilic G, Kilic V, Ucarcan S, Karaduman B, Ilgin S. Sertraline-induced reproductive toxicity in male rats: evaluation of possible underlying mechanisms. Asian J Androl 2017; 19: 672 – 679.
14. Ortiz J, Artigas F. Effects of monoamine uptake inhibitors on extracellular and trombosit 5-hydroxytryptamine in rat blood: different effects of clomipramine and fluoxetine. Brit J Pharmacol 1992; 105: 941 - 946.
15. LeGates TA, Kvarta MD, Thompson SM. Sex differences in antidepressant efficacy Neuropsychopharmacol 2019; 44: 140 – 154.
16. Puangsri P, Jinanarong V, Ninla-Aesong P. Impact of antidepressant treatment on complete blood count parameters and inflammatory ratios in adolescents with major depressive disorder. J Psychiatr Res 2023;157: 26-35.
17. Tsamesidis I, Pantaleo A, Pekou A, Gusani A, Iliadis S, Makedou K, Manca A, Carruale a,

Lymperaki E, Fozza C. Correlation of oxidative stress biomarkers and hematological parameters in blood cancer patients from Sardinia, Italy. Int J Hematol Oncol Stem Cell Res 2019;13(2): 49-57.

18. Jang EH, Park CS, Kang JH. Bupropion, an atypical antidepressant, induces endoplasmic reticulum stress and caspase-dependent cytotoxicity in SH-SY5Y cells. Toxicology 2011; 285: 1 - 7.
19. Bilici M, Efe H, Koroglu MA, Uydu HA, Bekaroglu M, Deger O. Antioxidative enzyme activities and lipid peroxidation in major depression: alterations by antidepressant treatments. J Affect Disord 2001; 64: 43 - 51.
20. Khanzode SD, Dakhale GN, Khanzode SS, Saoji A, Palasodkar R. Oxidative damage and major depression: the potential antioxidant action of selective serotonin re-uptake inhibitors. Redox Rep 2003; 8: 365 - 370.
21. Kotan VO, Sarandol E, Kirhan E, Ozkaya G, Kirli S. Effects of long-term antidepressant treatment on oxidative status in major depressive disorder: a 24-week follow-up study. Prog Neuropsychopharmacol Biol Psych 2011; 35: 1284 - 1290.
22. Novio S, Nunez MJ, Amigo G, Freire-Garabal M. Effects of fluoxetine on the oxidative status of peripheral blood leucocytes of restraint-stressed mice. Basic Clin Pharmacol Toxicol 2011; 109: 365 - 71.
23. Cumurcu BE, Ozyurt H, Etikan I, Demir S, Karlidag R. Total antioxidant capacity and total oxidant status in patients with major depression: Impact of antidepressant treatment. Psych Clin Neurosci 2009; 63: 639 - 645.
24. Behr GA, Moreira JCF, Frey BN. Preclinical and Clinical Evidence of Antioxidant Effects of Antidepressant Agents: Implications for the Pathophysiology of Major Depressive Disorder. Oxid Med Cell Longev. 2012; 2012: 609421.
25. Arihan O, Yabanoglu SC, Ucar G, Falkmarken ND. Effects of two selected SSRIs on hemorheological parameters in rats. Clin Hemorheol Microcirc 2019; 71: 27 - 38.
26. Erdemir F, Atilgan D, Firat F, Markoc F, Parlaktas BS, Sogut E. The effect of Sertraline, Paroxetine, Fluoxetine and Escitalopram on testicular tissue and oxidative stress parameters in rats. Int Braz J Urol 2014; 40: 100 - 8.
27. Abdel-Salam O, Youness ER, Khadrawy YA, Sleem AA. Brain and liver oxidative stress after sertraline and haloperidol treatment in mice. J Basic Clin Physiol Pharmacol 2013; 24: 115 - 23.
28. Beery, A. K., & Zucker, I. (2011). Sex bias in neuroscience and biomedical research. Neuroscience & Biobehavioral Reviews, 35(3), 565–572.