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Türk Hijyen ve Deneysel Biyoloji Dergisi

Modulation of the immunological response to acute stress in rats is aided by serotonin

Sıçanlarda akut strese karşı immünolojik yanıtın modülasyonu serotonin tarafından desteklenmektedir

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ABSTRACT

Objective: Since stress has become an inseparable aspect of human existence, the interplay between stress and the immune system is a primary focus of research. Despite serotonin being a crucial regulator of the immune and stress systems, its potential involvement in the stress-induced immunological response remains unexamined. This study employed two serotonin receptor antagonists to assess the modulatory influence of serotonin on the immunological response to acute stress.

Methods: Fifty-four Wistar albino rats (n=9/group) were allocated into six groups: control (C), acute stress (AS), ondansetron (O), methiothepin (M), acute stress + ondansetron (ASO), and acute stress + methiothepin (ASM). Rats were administered intraperitoneal injections of ondansetron or methiothepin at doses of 2 mg/kg and 0.2 mg/kg, respectively, prior to the introduction of acute stress. Acute stress was induced by a cold-immobilization procedure. Immediately following the stress procedure, the animals were euthanized using exsanguination. A complete blood count was taken,

ÖZET

Amaç: Stres insan yaşamının ayrılmaz bir parçası haline geldiğinden, stres ve bağışıklık sistemi arasındaki etkileşim öncelikli araştırma konuları arasında yer almaktadır. Serotonin hem bağışıklık hem de stres sistemlerinin önemli bir modülatörü olmasına rağmen, stresin neden olduğu bağışıklık yanıtındaki olası rolü günümüze kadar araştırılmamıştır. Bu çalışmada, serotoninin akut strese karşı bağışıklık yanıtı üzerindeki modülatör rolünü değerlendirmek için iki serotonin reseptör antagonisti kullanılmıştır.

Yöntem: Elli dört adet Wistar albino sıçan (n=9/grup) altı gruba ayrıldı: kontrol (C), akut stres (AS), ondansetron (O), metiyotepin (M), akut stres + ondansetron (ASO) ve akut stres + metiyotepin (ASM). Sıçanlara, akut stres indüksiyonundan önce intraperitoneal ondansetron veya metiyotepin enjeksiyonları (sırasıyla 2 mg/kg ve 0.2 mg/kg) uygulandı. Akut stres, soğuk immobilizasyon prosedürüyle oluşturuldu. Stres prosedürünün tamamlanmasından hemen sonra hayvanlar intrakardiyak kan alınarak feda edildi. Tam kan sayımı yapıldı ve ELISA kullanılarak

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and plasma levels of serotonin, IL-6, and IL-17 were quantified by ELISA.

Results: Acute stress significantly decreased leukocyte counts and IL-17 levels relative to the control group (p = 0.003 and 0.002, respectively). Methiothepin had comparable effects on both parameters. On the other hand, neither acute stress nor serotonin receptor antagonists significantly altered IL-6 levels. Nonetheless, when rats were administered a serotonin receptor antagonist and subjected to acute stress (the ASO and ASM groups), the differences in IL6 levels reached statistical significance (p<0.0001). Despite both serotonin antagonists exhibiting comparable effects on immunological response under acute stress, we were unable to observe any alterations in plasma serotonin levels across all groups.

Conclusion: These results suggest that the serotonergic system may play a modulatory role in the acute stress-induced immune response and that this modulation is more likely occurring at the receptor level. This phenomenon might be related to desensitization or downregulation of serotonin receptors.

Key Words: Stress, acute stress, immune system, IL17, IL6

plazma serotonin, IL-6 ve IL-17 seviyeleri belirlendi.

Bulgular: Akut stres, kontrol grubuyla karşılaştırıldığında lökosit sayısını ve IL-17 düzeylerini önemli ölçüde azalttı (sırasıyla p = 0.003 ve 0.002). Metiyotepin her iki parametre üzerinde de benzer etkiler gösterdi. Öte yandan ne akut stres ne de serotonin reseptör antagonistleri IL-6 düzeylerini önemli ölçüde değiştirmedi. Bununla birlikte, sıçanlar hem serotonin reseptör antagonisti aldığında hem de akut strese maruz kaldığında (ASO ve ASM grupları), IL-6 seviyelerindeki farklılıklar anlamlı hale geldi (p<0.0001). Her iki serotonin antagonisti de akut streste immün yanıt üzerinde benzer etkiler gösterse de hiçbir grupta plazma serotonin düzeylerinde bir değişiklik tespit edemedik.

Sonuç: Bu sonuçlar, serotonerjik sistemin, akut strese bağlı bağışıklık yanıtında modülatör bir rol oynayabileceğini ve bu modülasyonun reseptör seviyesinde meydana gelme olasılığının daha yüksek olduğunu göstermektedir. Bu etki, serotonin reseptörlerinin duyarsızlaştırılması veya aşağı regülasyonu ile ilişkili olabilir.

Anahtar Kelimeler: Stres, akut stres, bağışıklık sistemi, IL17, IL6

INTRODUCTION

People use the word "stress" to refer to any condition that creates anxiety without considering its effects on the body. In fact, stress may be more appropriately defined as the body's response to any environmental changes that disturb the maintenance of homeostasis. Stressors can be classified into five groups: acute time-limited, brief naturalistic, event sequence, chronic, and distant (1). Stress triggers a wide variety of changes, including immune responses. Previously, it was believed that the stress response would always have a suppressive effect on the immune system. This belief is supported by the insufficiency of T cell maturation, the suppression of the synthesis of pro-inflammatory cytokines, and the rise in the release of anti-inflammatory compounds (2-4). It is now accepted, however, that its effects on the immune system are variable and depend mainly on the duration and type of stressor (5). Xiang et al. showed that acute mental stress increases the T helper cell type I (Th1) response, whereas Assaf et al. showed that chronic stress may reduce the Th1 response while increasing the T helper cell type II (Th2) response

(6,7). A number of studies have been conducted in an effort to provide an explanation for the interactions that occur within the stress system, specifically the interactions that occur between the hypothalamic-pituitary-adrenal (HPA) axis and the immune system. Although many immune system changes seen under stressful conditions could be due to elevated glucocorticoid levels, stress can even cause changes in the immune system in adrenalectomized animals, suggesting that other mediators are involved (8).

Serotonin (5- hydroxytryptamine; 5HT) is mainly known for its role in the limbic system, but it is also essential in various central mechanisms, including in the regulation of appetite, sleep, and body temperature (9). Central serotonergic responses can be stimulated by corticotropin-releasing hormone (CRH), secreted by the hypothalamus under stress (8). Furthermore, serotonin is of vital importance in platelet aggregation and hemostasis. Platelets are the main reservoir for peripheral serotonin. The peripheral roles of serotonin are not limited to hemostatic mechanisms, as serotonin is also crucial for gastrointestinal motility and blood pressure regulation (9). Moreover, serotonin also plays an essential role in the modulation of the immune system. Studies have shown that serotonin impacts both innate and acquired immune system cells. The significant effects of serotonin on the immune system include T-cell differentiation, modulation of cytokine release, and inflammation (10,11). Nearly all immune system cells contain at least one serotonin response component. T cells express serotonin receptors 1A, 1B, 2A, 2B, 3A, and 7 (12). The widespread effects of serotonin result in complex clinical conditions. A prominent example is the susceptibility to inflammation in patients with major depression and low serotonin levels (13,14). Serotonin is also thought to be important in the pathogenesis of autoimmune diseases, such as Sjögren's syndrome and systemic sclerosis (15–17).

Interleukin-17 (IL-17) secreting T helper cells (Th17) have physiological roles and defend against bacterial and fungal infections. If the Th17 response is not properly limited, however, IL-17 can become a driving force in the pathogenesis of autoimmune diseases (18), which are generally aggravated under stressful conditions. Several studies have also suggested that serotonin levels can modulate IL-17 production (19–21).

Indubitably, serotonin is closely related to both the central stress and the immune systems and is highly likely to mediate a link between these two systems. Despite this evidence, the possible role of serotonin on stress-induced immune responses has yet to be investigated. In this study, we aim to investigate serotonin's modulatory role on the immune system's response to stress. As mentioned previously, stress can cause various changes in the immune system. Given the impracticality of examining all such changes in one study, we limited the scope of our research to the Th17 cell type.

MATERIAL and METHOD

Fifty four Wistar albino rats weighing between 200-300 g were acquired from and kept at the Experimental Animals Breeding and Experimental Research Center of Gazi University in Ankara. All procedures were conducted at the same facility. The rats were acclimatized for two weeks before the studies and were maintained in controlled ambient settings at 21 ± 2°C and 30–70% relative humidity. They were exposed to a 12-hour dark/12-hour light cycle, had unlimited access to tap water, and were fed standard pellet chow daily.

Following adaptation to the environment and handling, animals were randomly allocated to one of six groups: control (C), acute stress (AS), ondansetron (selective 5-HT3 receptor antagonist) (O), methiothepin (M) (nonselective 5-HT1/2 receptor antagonist), acute stress + ondansetron (ASO) and acute stress + methiothepin (ASM) (n=9/group). Drug groups accordingly received 2 mg/kg ondansetron or 0.2 mg/kg methiothepin. All drugs were dissolved in 1 ml physiologic serum and were administered

intraperitoneally (ip). The C and AS groups received 1 ml solvent. The stress protocol was initiated 30 minutes after the injections for the acute stress groups.

Rats were restrained and kept in a 4°C environment for 2 h to induce cold-immobilization stress. The other groups were kept in their usual environment for 2 h. This is a well-established and widely used method to induce acute stress (22-25). At the end of this period, all animals were anesthetized with ketamine (90 mg/kg) and xylazine (10 mg/kg) and exsanguinated by taking blood from the heart into citrate-containing vacuum tubes. Complete blood counts were taken using fresh blood samples. The remaining blood was centrifuged to separate the plasma. It was then frozen and stored at −80°C until the levels of serotonin, interleukin-17 (IL-17), and interleukin-6 (IL-6) were determined with an enzyme-linked immunosorbent assay (ELISA). We used eBioscience Platinum ELISA kits to assess the levels of IL-6 and IL-17 and an Elabscienes ELISA kit to determine the level of serotonin. Ondansetron (Zofran®) was from Glaxo Wellcome GmbH, Germany. Methiothepin mesylate salt (M149-100MG) was from Sigma-Aldrich, USA. Ketamine (Ketalar) from Pfizer (production in Kırklareli, Turkey), Xylazine (Basilazin %2) from baVet, İstanbul, Turkey. Statistical Analysis: In each group and for all parameters, we had 9 data points (there was no missing data). The findings are reported as the mean value with an associated standard error of deviation from the mean. Distinction was deemed statistically significant at the 0.05 level. Statistical analyses were performed using the STAT/Statistics program (Statdirect, Wirral, UK). We used the Kruskal-Wallis test as the initial statistical test, and when the p value was <0.05, we utilized the Conover-Iman test for pairwise comparisons.

The study was approved by the Gazi University, Institutional Experimental Animal Care and Use Ethics Committee (Date: 06.11.2015 and Number: 36069). We followed the Guiding Principles for the Care and Use of Laboratory Animals and the relevant Turkish by-laws meticulously while carrying out the procedures detailed in this publication.

RESULTS

Leukocyte count was significantly reduced by acute stress in our experimental setting. While ondansetron tended to reduce leukocyte count, no significant difference existed between the control and ondansetron groups. On the other hand, methiothepin reduced leukocyte count in the same manner as acute stress. The ASM group animals also had significantly lower leukocyte counts than the control animals, and these results were not different from those of the M or AS groups (Figure 1). These results suggest that lower serotonin levels might be responsible for the downregulation of leukocytes in the event of acute stress. However, the serotonin levels did not differ between any of the groups (Figure 2). Other than leukocyte count, acute stress did not affect any other complete blood count parameter.

Acute stress also did not significantly alter IL-6 levels, as the mean IL-6 level was lower in the AS group (122.6 ± 10.6 pg/ml) than in the C group (143.2 ± 5.6 pg/ml). Similarly, neither methiothepin nor ondansetron led to significant changes in IL-6 levels. Interestingly, when acute stress was combined with the serotonin antagonists, the difference in IL-6 levels became significant (Figure 3). IL-6 levels in the ASO group were considerably lower than the C, O, and AS groups. Likewise, the ASM group exhibited noticeably reduced IL-6 levels in comparison to the C, M, and AS groups.

It is known that IL-6 is necessary for Th17 maturation. Therefore, we expected to see alterations in IL-17 levels similar to those seen in IL-6. As hypothesized, acute stress led to a reduction in IL-17 levels, but this time, the difference was statistically significant. Furthermore, IL-17 levels were significantly reduced by both ondansetron and methiothepin. The ASO group also had significantly lower IL-17 levels than the C group. In contrast, the IL-17 level of the ASM group was not different from the C group (Figure 4).

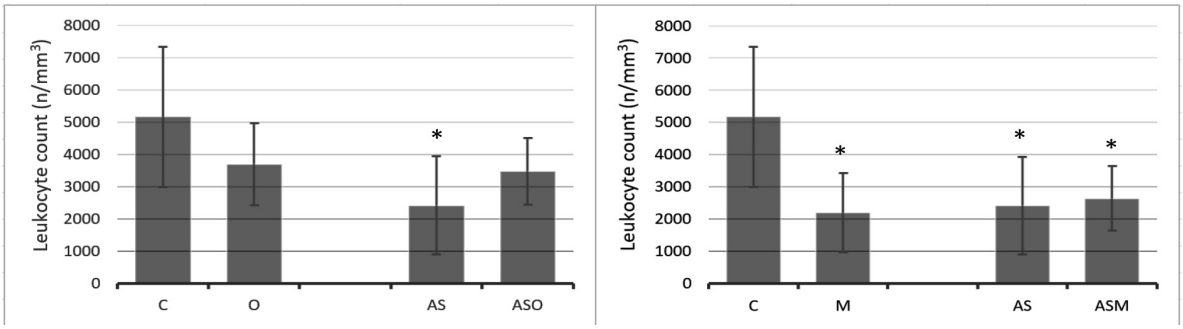

Figure 1. Acute stress reduced leukocyte counts (C: 5175 ± 770 vs. AS: 2425 ± 536; *p*=0.003). Methiothepin also reduced leukocyte counts (C vs. M: 2179 ± 409; *p*= 0.0003). When AS and M were combined, no further reduction in leukocyte counts was observed (*p*>0,05 for M vs. ASM and AS vs. ASM). AS (acute stress), ASM (acute stress + methiothepin), ASO (acute stress + ondansetron), C (control), M (methiothepin), O (ondansetron).

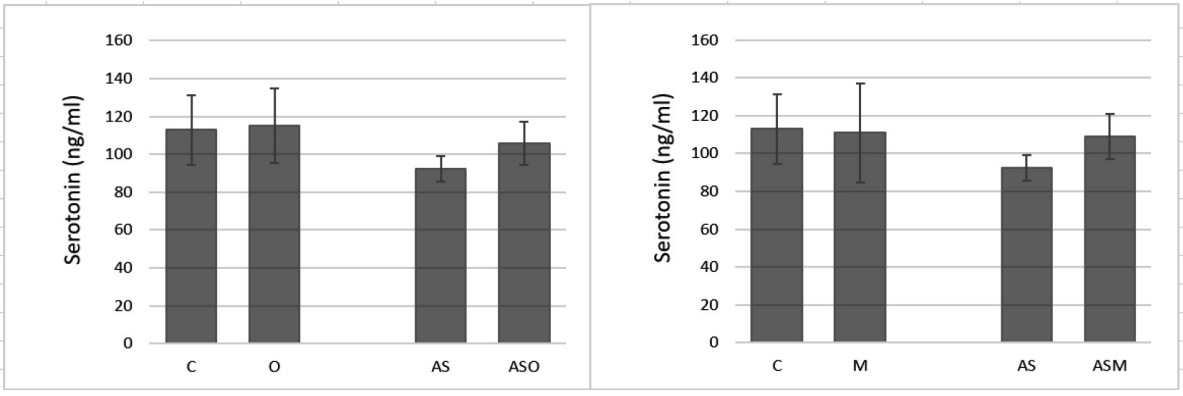

Figure 2. Plasma serotonin levels were not significantly altered by acute stress or serotonin receptor antagonists. AS (acute stress), ASM (acute stress + methiothepin), ASO (acute stress + ondansetron), C (control), M (methiothepin), O (ondansetron).

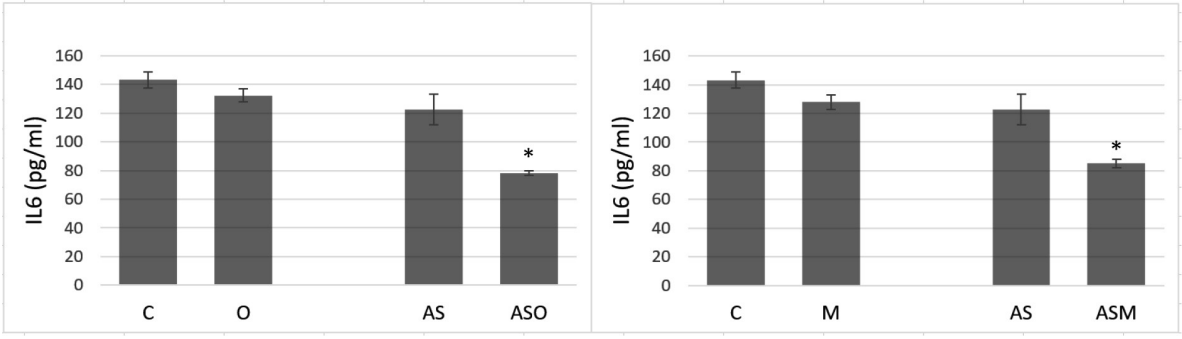

Figure 3. Acute stress reduced IL-6 levels, but the difference was not statistically significant (C: 143.2 ± 5.6 vs. AS: 122.6 ± 10.6 pg/ml, *p*>0.05). Similarly, neither methiothepin nor ondansetron significantly altered IL-6 levels. IL-6 levels in the ASO and ASM groups, however, were significantly lower than all other groups but did not differ from each other (*p* values of all pairwise comparisons between the ASO group and the C, O, and AS groups were <0.0001, *p* values of all pairwise comparisons between the ASM group and the C, M, and AS groups were <0.0001, The *p* value of the comparison between the ASO and ASM groups was 0.21). AS (acute stress), ASM (acute stress + methiothepin), ASO (acute stress + ondansetron), C (control), M (methiothepin), O (ondansetron)

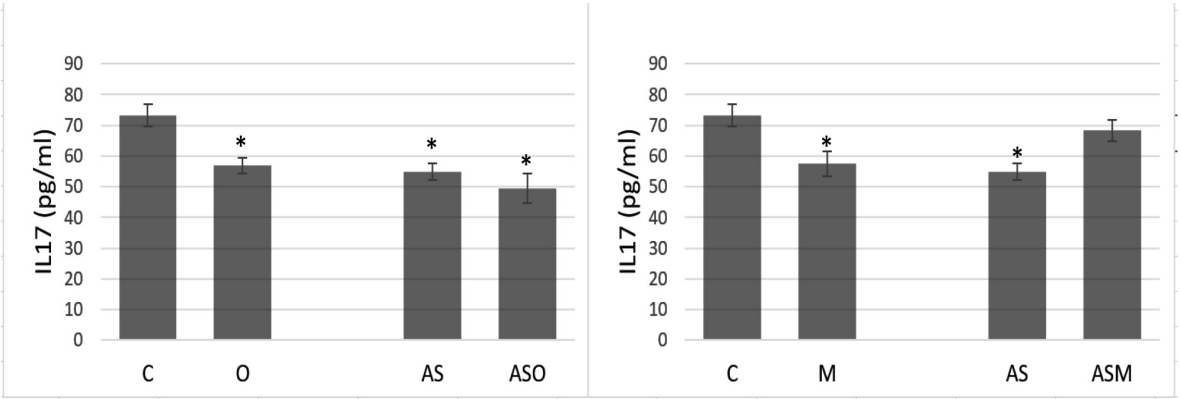

Figure 4. IL-17 levels were reduced by AS, O, and M (compared with the C group, P values were 0.002, 0.008, and 0.01, respectively). IL-17 levels of the ASO group were also significantly lower than that of the C group ($p<0.0001$), but they were not different from the AS or O groups. Conversely, the IL-17 levels of the ASM group were not different from those of the C group. AS (acute stress), ASM (acute stress + methiothepin), ASO (acute stress + ondansetron), C (control), M (methiothepin), O (ondansetron).

DISCUSSION

The effects of stress on the immune system have been under investigation for a long time. Despite the breadth of this research, there are still very few points that the scientific community agrees on. One such example is whether stress alters immune function. The use of various types of stress (social, academic, pain or cold-induced, etc.), durations (acute time-limited, short natural, sequence of events, chronic, distant, etc.), and immune responses in different studies cause difficulties in drawing conclusions (22-25). According to a meta-analysis on this subject published in 2004, acute time-limited psychological stress increases IL-6 levels (1). On the other hand, Assaf et al. reported that IL-6 levels were not altered by acute academic stress. Their results, in fact, show a minor reduction in IL-6 levels, but this difference was not significant (6). These results align with the results of our current study. Research published by Cheng et al., in which the effects of single stress induction at different time points were evaluated, may link our results and the meta-analysis. According to this study, acute stress initially reduces IL-6 levels, but after 6 hours, IL-6 levels increase above control levels (26). Since we collected the blood samples right after the induction of the acute stress like Assaf et al. did in their study our results resemble the initial changes observed by Cheng et al. On the other hand, aforementioned meta-analysis included studies that evaluated IL6 levels in the later period which might conceptually overlap with the later time points used by Cheng et al. To our knowledge, this is also the only study that evaluated the effects of acute stress on IL-17. The study showed that IL-17 began to increase only 6 hours after stress induction. An early reduction in IL-17 levels, as they have observed in IL-6 levels, was absent. These results contradict the results of our study, as we found that acute stress significantly reduced IL-17 levels. Despite our diligent efforts to search literature for studies linking "acute stress" and IL17 and/or Th17 we could not reach any other trough PubMed, Scopus or DergiPark. Conversely; IL17 related with "chronic stress"(27), depression like behavior, and even with depression by several publications as stated by recent review (28).

Serotonin functions as a monoaminergic neurotransmitter and a peripheral hormone. Target cells possess a minimum of one serotonin response element, such as serotonin receptors (7 subtypes),

the serotonin transporter (SERT), or the covalent attachment of serotonin to various effector proteins. In this study, we chose to use ondansetron, which is a selective 5HT-3 receptor antagonist, and methiothepin, which is a non-selective antagonist that can interact with the 5HT-1A, 1B, and 7 receptors that are found on leukocytes (12). The serotonergic system is closely intertwined with the HPA axis and sympathetic nervous system. Stress elevates the turnover rates of serotonin in several brain regions, and upregulates some brain serotonin receptors by doing so, adjusts the brain to respond appropriately to environmental cues that indicate danger (29–32). In a similar manner, when naïve T cells are activated, they not only increase their synthesis of tryptophan hydroxylase (TPH1), which is an enzyme that is necessary for the creation of 5-HT from its precursor tryptophan, but they also increase their expression of 5-HT receptors. Robson and colleagues theorized that an increase in 5-HT synthesis and responsiveness leads to an autonomous feedback loop, where 5-HT signaling is necessary for T cell-mediated immunity. The authors drew similarities between these results and the results of Leon-Pointe, et al., as impaired 5-HT synthesis was shown to reduce T cell proliferation (33,34). Likewise, our study confirms these results, as 5-HT receptor antagonists reduced leukocyte count. Moreover, IL-17 levels were significantly reduced by 5-HT receptor antagonists, whereas IL-6 levels were not significantly altered in our study. Despite the clarity of our findings about IL-17, we could not find any supportive results in the literature. Three recent research studies did, however, indirectly evaluate the effect of serotonin on IL-6 and IL-17 levels. Two of them showed that serotonin reduces the levels of IL-6 and IL-17 (20,35). The discrepancy in findings between these studies and ours may be because these studies were conducted in vitro, and our study was conducted in vivo. Third, reported an increase in IL6 level with unaffected serum serotonin concentration under chronic stress conditions (36).

Serotonin is closely related to both the central stress and the immune system. To our knowledge, however, its possible role in stress-induced immune responses has yet to be investigated. When considering the fact, however, that stress is also closely related to affective disorders, the interaction between stress and serotonergic systems has been under investigation for decades. One important conclusion derived from several studies is that corticosterone alters serotonin receptor activity in the central nervous system (37–39). In this study, we showed that, even though acute stress could not significantly alter plasma serotonin levels, its effect on IL-6 and IL-17 levels was similar to that of serotonin receptor antagonists. Moreover, when animals received ondansetron or methiothepin and were subjected to acute stress, the reduction in IL-6 levels reached significance. Our results may be explained from the point of view of central nervous system studies. Given that corticosterone can alter the effectiveness of serotonin receptors in the central nervous system, a similar effect could be expected in the periphery.

In conlusion; the purpose of this study was to evaluate the modulatory effect that serotonin plays in the stress response of the immune system. According to the findings of our study, being exposed to acute stress has a major impact on the immune system. Acute stress not only significantly reduced leucocyte counts but also reduced plasma IL-17 levels compared to control. On the other hand, the serotonin receptor antagonists methiothepin and ondansetron were also able to alter plasma IL-17 levels. Additionally, methiothepin reduced leucocyte count compared to control. Interestingly, we did not see a change in serotonin levels. This suggests that the serotonergic system is involved in the immune system's response to acute stress but that this effect might be related to desensitization or downregulation of serotonin receptors.

This study has a few limitations. First, although the method we used to induce acute stress is very well-known and accepted in the scientific community, the measurement of plasma corticosterone levels could

demonstrate the effectiveness of our stress protocol. Moreover, using an additional group of animals that received high doses of serotonin before acute stress induction could have provided insight into whether the effects of acute stress on the immune system were caused by the modulation of serotonin receptors.

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ETHICS COMMITTEE APPROVAL

* The study was approved by the Gazi University, Institutional Experimental Animal Care and Use Ethics Committee (Date: 06.11.2015 and Number: 36069).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Segerstrom SC, Miller GE. Psychological stress and the human immune system: A meta-analytic study of 30 years of inquiry NIH Public Access. Psychol Bull, 2004;130(4):601-30.

2. Franchimont D. Overview of the actions of glucocorticoids on the immune response: A good model to characterize new pathways of immunosuppression for new treatment strategies. Ann N Y Acad Sci, 2004;1024:124-37.

3. Hu X, Li W-P, Meng C, Ivashkiv LB. Inhibition of IFN- signaling by glucocorticoids. J Immunol, 2003;170(9):4833-9.

4. Mozo L, Suárez A, Gutiérrez C. Glucocorticoids up-regulate constitutive interleukin-10 production by human monocytes. Clin Exp Allergy, 2004;34(3):406-12.

5. Vitlic A, Lord JM, Phillips AC. Stress, ageing and their influence on functional, cellular and molecular aspects of the immune system. Age (Omaha), 2014;36(3):1169-85.

6. Assaf AM, Al-Abbassi R, Al-Binni M. Academic stress-induced changes in Th1- and Th2-cytokine response. Saudi Pharm J, 2017;25(8):1237-47.

7. Xiang L, Del Ben KS, Rehm KE, Marshall GD. Effects of acute stress-induced immunomodulation on Th1/Th2 cytokine and catecholamine receptor expression in human peripheral blood cells. Neuropsychobiology, 2011;65(1):12-9.

8. Leonard BE. The HPA and immune axes in stress: the involvement of the serotonergic system. Eur Psychiatry, 2005;20:302-6.

9. Pytliak M, Vargová V, Mechírová V, Felšöci M, Pytliak M. Serotonin receptors-from molecular biology to clinical applications. Physiol Res, 2011;60:15-25.

10. Ahern GP. 5-HT and the immune system. Curr Opin Pharmacol, 2011;11(1):29-33.

11. Cloez-Tayarani I, Changeux J-P. Nicotine and serotonin in immune regulation and inflammatory processes: a perspective. J Leukoc Biol, 2006;81(3):599-606.

12. Herr N, Bode C, Duerschmied D. The effects of serotonin in immune cells. Front Cardiovasc Med, 2017;4:1-11.

13. McNamara RK, Lotrich FE. Elevated immune-inflammatory signaling in mood disorders: A new therapeutic target? Expert Rev Neurother, 2012;12(9):1143-61.

14. Vogelzangs N, Duivis HE, Beekman ATF, Kluft C, Neuteboom J, Hoogendijk W, et al. Association of depressive disorders, depression characteristics and antidepressant medication with inflammation. Transl Psychiatry, 2012;2(2):e79.

15. Brembilla NC, Chizzolini C. T cell abnormalities in systemic sclerosis with a focus on Th17 cells. Eur Cytokine Netw, 2012;23(4):128-39.

16. Chabbi-Achengli Y, Coman T, Collet C, Callebert J, Corcelli M, Lin H, et al. Serotonin is involved in autoimmune arthritis through th17 immunity and bone resorption. Am J Pathol, 2016;186(4):927-37.

17. Habets KLL, Huizinga TWJ, Toes REM. Platelets and autoimmunity. Eur J Clin Invest, 2013;43(7):746-57.

18. Gregor CE, Foeng J, Comerford I, McColl SR. Chemokine-Driven CD4+T Cell Homing: New Concepts and Recent Advances. 1st ed. Vol. 135, Advances in Immunology. Elsevier Inc.; 2017. 119-181 p.

19. Mao L, Ren X, Wang X, Tian F. Associations between autoimmunity and depression: Serum IL-6 and IL-17 have directly impact on the HAMD scores in patients with first-episode depressive disorder. J Immunol Res, 2022;2022:1-6.

20. Sacramento PM, Monteiro C, Dias ASO, Kasahara TM, Ferreira TB, Hygino J, et al. Serotonin decreases the production of Th1/Th17 cytokines and elevates the frequency of regulatory CD4+ T-cell subsets in multiple sclerosis patients. Eur J Immunol, 2018;48(8):1376-88.

21. Sviridova A, Rogovskii V, Kudrin V, Pashenkov M, Boyko A, Melnikov M. The role of 5-HT2B-receptors in fluoxetine-mediated modulation of Th17- and Th1-cells in multiple sclerosis. J Neuroimmunol, 2021;356:577608.

22. Lyle N, Chakrabarti S, Sur T, Gomes A, Dipankar Bhattacharyya. Nardostachys jatamansi protects against cold restraint stress induced central monoaminergic and oxidative changes in rats. Neurochem Res, 2012;37:2748-57.

23. Saxena B, Singh S. Comparison of three acute stress models for simulating the pathophysiology of stress-related mucosal disease. Drug Discov Ther, 2017;11(2):98-103.

24. Saxena B, Singh S. Investigations on gastroprotective effect of citalopram, an antidepressant drug against stress and pyloric ligation induced ulcers. Pharmacol Reports, 2011;63(6):1413-26.

25. Shen GM, Zhou MQ, Xu GS, Xu Y, Yin G. Role of vasoactive intestinal peptide and nitric oxide in the modulation of electroacupucture on gastric motility in stressed rats. World J Gastroenterol, 2006;12(38):6156-60.

26. Cheng Y, Jope RS, Beurel E. A pre-conditioning stress accelerates increases in mouse plasma inflammatory cytokines induced by stress. BMC Neurosci, 2015;16(1):1-8.

27. Zhang C, Liu B, Pawluski J, Steinbusch HWM, Kirthana Kunikullaya U, Song C. The effect of chronic stress on behaviors, inflammation and lymphocyte subtypes in male and female rats. Behav Brain Res, 2023;439:114220.

28. Mrowietz U, Sümbül M, Gerdes S. Depression, a major comorbidity of psoriatic disease, is caused by metabolic inflammation. J Eur Acad Dermatology Venereol, 2023;37(9):1731-8.

29. Chaouloff F. Physiopharmacological interactions between stress hormones and central serotonergic systems. Brain Res Brain Res Rev,1993;18(1):1-32.

30. Flügge G, Van Kampen M, Mijnster MJ. Perturbations in brain monoamine systems during stress. Cell Tissue Res, 2004;315(1):1-14.

31. Murnane KS. Serotonin 2A receptors are a stress response system: Implications for post-traumatic stress disorder. Behav Pharmacol, 2019;30:151-62.

32. Ponomarev ED. Fresh evidence for platelets as neuronal and innate immune cells: Their role in the activation, differentiation, and deactivation of Th1, Th17, and tregs during tissue inflammation. Front Immunol, 2018;9:1-7.

33. León-Ponte M, Ahern GP, O'Connell PJ. Serotonin provides an accessory signal to enhance T-cell activation by signaling through the 5-HT7 receptor. Blood, 2007;109(8):3139-46.

34. Robson MJ, Quinlan MA, Blakely RD. Immune system activation and depression: Roles of serotonin in the central nervous system and periphery. ACS Chem Neurosci, 2017;8(5):932-42.

35. Yang TH, Hsu PY, Meng M, Su CC. Supplement of 5-hydroxytryptophan before induction suppresses inflammation and collagen-induced arthritis. Arthritis Res Ther, 2015;17(1):1-12.

36. Li H, Wang P, Zhou Y, Zhao F, Gao X, Wu C, et al. Correlation between intestinal microbiotal imbalance and 5-HT metabolism, immune inflammation in chronic unpredictable mild stress male rats. Genes, Brain Behav, 2022;21(6):1-11.

37. Gur E, Dremencov E, Lerer B, Newman ME. Functional effects of corticosterone on 5-HT1A and 5-HT1B receptor activity in rat brain: In vivo microdialysis studies. Eur J Pharmacol, 2001;411(1-2):115-22.

38. Tokarski K, Pitra P, Duszynska B, Hess G. Imipramine counteracts corticosterone-induced alterations in the effects of the activation of 5-HT7 receptors in rat hippocampus. J Physiol Pharmacol, 2009;60(2):83-8.

39. Zahorodna A, Tokarski K, Hess G. Imipramine treatment ameliorates corticosterone-induced alterations in the effects of 5-HT1A and 5-HT4 receptor activation in the CA1 area of rat hippocampus. Eur Neuropsychopharmacol, 2006;16(5):383-90.