ORIGINAL RESEARCH

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Metamizole modulates the concentrations of cytokines and hematopoietic growth factors in an experimental model of depression

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Abstract

Objective: In recent years, evidence of antidepressant-like activity of non-steroidal anti-inflammatory drugs has been presented. Furthermore, associations between cytokines, which are important components of the immune system, as well as hematopoietic growth factors and depression have also been demonstrated. In this study, it was aimed to analyze the effect of metamizole on the expression of cytokines and hematopoietic growth factors in mice exposed to unpredictable stress models.

Method: In order to develop chronic depression behaviors, an unpredictable chronic mild stress model was applied to mice. The depression group was not given any drug and other groups were given 100 and 200 mg/kg metamizole. Forced swimming test was performed to evaluate the effect of metamizole against depression. Relative concentrations of interleukin-1 alpha (IL-1α), IL-1 beta (IL-1-ß), IL-2, IL-4, IL-6, IL-10, IL-12, IL-17, Interferon gamma (IFN-γ)-, tumor necrosis factor-alpha (TNF-α), Granulocyte-colony-stimulating factor (G-CSF), and Granulocyte-macrophage colony-stimulating factor (GM-CSF) were analyzed in serum samples of animals with semi-quantitative ELISA.

Results: In the forced swimming test, the immobility time of the depression group significantly increased compared to the control group. The immobility time of groups treated with metamizole significantly decreased compared to the depression group and approached the control. Significant decreases were observed in the relative concentration levels of cytokines and hematopoietic growth factors in the groups treated with 100 and/or 200 mg/kg metamizole compared to the depression group except for IL-1α, IL-4, and IL-10.

Conclusion: Evidence showing the contribution of COX enzymes to the pathophysiology of depression is increasing. In this context, the results indicate that metamizole, which can inhibit both isoforms of COX, may cause changes in cytokine levels and hematopoietic growth factors in a depression model. However, more controlled clinical studies are needed.

Keywords: Metamizole, depression, non-steroidal anti-inflammatory drugs, cytokines, hematopoietic growth factors

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) block arachidonic acid metabolism by inhibiting the cyclooxygenase (COX) enzyme. They inhibit COX-1 and COX-2 at different levels depending on their chemical structures. This inhibition prevents the production of prostanoids, which contributes to inflammation and also mediates their analgesic and antipyretic effects (1). Metamizole is a widely used NSAID with potent analgesic and antipyretic properties. It blocks prostaglandin biosynthesis in the spinal cord by inhibiting both cyclooxygenase isoforms (COX-1 and COX-2) and shows analgesic effects. Due to adverse effects such as agranulocytosis, its clinical use has been restricted in certain countries (2,3). There is evidence suggesting that frequently

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used NSAIDs exert effects beyond their classical roles in pain and inflammation. For instance, NSAIDs have been shown to modulate the tumor microenvironment and cellular proliferation by enhancing chemosensitivity and apoptosis and reducing cell migration (4). In addition, several studies have reported that NSAIDs may alter the expression of neuronal factors and hormones in various cell types (5). More recently, NSAIDs have been associated with antidepressant-like effects in experimental models of depression (6–9). Furthermore, systematic reviews suggest that NSAIDs may exert such effects in patients diagnosed with major depressive disorder (MDD) and are considered reasonably safe in this context (10,11).

Cytokines are protein molecules produced by immune system cells that enable communication between cells and regulate immune responses. However, excessive or unregulated production of cytokines can lead to the development of immune system diseases such as autoimmune diseases. In particular, interleukins [(interleukin (IL)-1, IL-3, IL-4, IL-6, IL-10, IL-12)], interferons [(interferon-alpha (IFN-α), interferon-gamma (IFN-γ)], and tumor necrosis factor-alpha (TNF-α) play an important role in this process. These molecules contribute to disease pathogenesis by triggering mechanisms such as excessive inflammation, loss of autoimmune tolerance, changes in T cell differentiation, and attraction of inflammatory cells to the tissue (12). The relationship between cytokines and behavior has long been of interest as well. It has been demonstrated that TNF-α and IL-1 can cause the alteration of sexual behavior (13), and that IFN-α may induce depressive-like behaviors, which can be mitigated by NSAID treatment (14). Similarly, administration of IL-1 has been found to trigger behavioral changes through both COX-1 and COX-2 pathways (15). Depression itself may alter immunological parameters, and the therapeutic effects of selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) have been partially attributed to their limited anti-inflammatory actions (16). Notably, inflammatory mediators such as C-reactive protein, TNF, IL-1, IL-6, and PGE-2 have been implicated in the pathophysiology of depression and in the mechanisms of antidepressant therapies (17). However, data on the role of metamizole, which affects both COX isoforms within the context of depression-related inflammation, remain scarce. Moreover, proinflammatory cytokines have been mostly investigated in these studies. Depression is a heterogeneous psychopathological condition characterized by impaired mood regulation, slowed cognitive functions, and dysfunction in autonomic and neuroendocrine systems, resulting from the interaction of genetic predisposition, environmental stressors, neuroinflammation, and neurotransmitter imbalances (18). Many stress factors can trigger the development of depression. In the Unpredictable Chronic Mild Stress Model, depression development is induced in rodents by exposure to multifaceted stress factors (19, 20). However, even a single factor in daily life, such as hearing loss, can be a stress factor in the development of depression (21). Designing multifaceted studies on depression will contribute more to the understanding of the disease.

Hematopoietic growth factors are polypeptide signaling molecules that regulate the proliferation, differentiation, survival, and functional maturation of hematopoietic stem and progenitor cells in the bone marrow. These factors ensure homeostasis of hematopoiesis and its adaptation to stress conditions. Among the hematopoietic growth factors, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and erythropoietin (EPO) are the most important. These molecules bind to their specific receptors on target cells, activate intracellular signaling pathways, and thus regulate the life cycle of hematopoietic cells (22).

In this study, it was aimed to semi-quantitatively investigate the effects of metamizole on both proinflammatory and anti-inflammatory cytokine concentrations in a depression model induced by unpredictable stress. Additionally, we examined the impact of metamizole on hematopoietic growth factors.

METHOD

Animals and experimental groups

The experiments were conducted using male Swiss Albino mice (n = 9 per group, weighing 20–25 g), obtained from the Çukurova University Health Sciences Experimental Application and Research Center. For environmental adaptation, the animals were maintained for one week under a 12-hour light/dark cycle at a constant temperature of 24 ± 1°C, with ad libitum access to food and water. The study protocol was approved by the local ethics committee for animal experiments of Çukurova University. Control animals were housed in a separate room in groups of three per cage and were not exposed to any stress factors throughout the experiment. In the depression group, mice were housed individually and subjected to a regimen of unpredictable stressors. Two additional groups were formed to assess the effects of metamizole at doses of 100 mg/kg and 200 mg/kg in stressed animals. The drug was administered to the depression + metamizole groups in the second week. These mice received daily intraperitoneal (i.p.) injections of metamizole (Sigma, Germany), dissolved in 0.9% saline, at a fixed time each day for five consecutive weeks, with doses adjusted according to body weight. At the end of the experiments, blood samples were collected from all animals for further analysis.

Unpredictable chronic mild stress model

Mice subjected to the unpredictable chronic mild stress (UCMS) paradigm exhibit neurobehavioral alterations that resemble the symptoms of chronic depression observed in humans. The UCMS model employed in this study was adapted from the protocols designed for rodents. This model consists of repeated exposure to mild physical and psychological stressors (19,20). According to the protocol, animals were exposed to various stressors over a six-week period. These included, multiple times per day: exposure to unfamiliar objects (e.g., stones), placement in damp bedding, frequent changes of bedding, temporary housing in cages without bedding, brief confinement in cages with a shallow layer of water, cage switching, tilting of cages at a 45° angle (3 to 12 h), exposure to predator sounds for 15 minutes, reversal of the light/dark cycle, and brief illumination during the dark phase.

Forced swimming test

The forced swimming test was originally developed by Porsolt and colleagues to evaluate the efficacy of compounds against depression (23). According to the protocol, animals were individually placed in a tank filled with water maintained at 23 ± 2 °C for a duration of six minutes. A decrease in immobility time is considered indicative of an antidepressant-like effect. During the 6-minute testing period, agitation and immobility durations were recorded. Data from the first 2 minutes were excluded from the analysis to avoid bias due to initial escape-oriented behavior. Mobility was assessed during the final 4 minutes, and immobility time was calculated by subtracting the mobile time from 240 seconds.

ELISA analysis of cytokines and hematopoietic growth factors

Serum samples were obtained by centrifuging the blood collected from the animals and stored at –40°C until the day of analysis. The samples were analyzed using a Multi-Analyte ELISA assay kit (Qiagen, Germany) according to the manufacturer's instructions. Each sample and the standards in the kit were studied in duplicate. In order to minimize manipulation errors, the experiment was repeated for samples that gave incompatible results. Following the incubation steps, absorbance values were measured using a multimode microplate reader (BioTek Synergy H1, USA). The absorbance data were normalized based on the values obtained from the positive and negative controls. The values from the control group were set to 1, and all other sample values were calculated relative to this baseline. The results were expressed as relative concentration coefficients.

Statistical analysis

In the forced swimming test, the data (time) obtained from the groups were directly compared. The absorbance values obtained by semi-quantitative ELISA were transformed to 1 for the control group. Using this data, the relative concentration values as fold change corresponding to the absorbance values of the other groups were obtained. The results obtained by statistical analysis were analyzed with the GraphPad Prism version 9.0.0 program and shown as mean ± SD. Data distributions were tested for normality using the Shapiro-Wilk test. Kruskal-Wallis and then Dunn's multiple comparison post-hoc test were used in the analysis of the obtained data. p-value less than 0.05 was accepted as significant.

RESULTS

Forced swimming test

In the forced swimming test, performed to evaluate depressive and antidepressant-like effects, the immobility time in the depression group (196.9±10.13 sec) was significantly increased compared to the control group (124.0±6.29 sec; $p < 0.0001$). This increase observed in the depression group was significantly reduced in the groups treated with metamizole at doses of 100 mg/kg (145.2±10.20 sec; $p = 0.0391$) and 200 mg/kg (144.2±8.87 sec; $p=0.0297$). No significant differences were observed between the treatment groups and the control group (Figure 1).

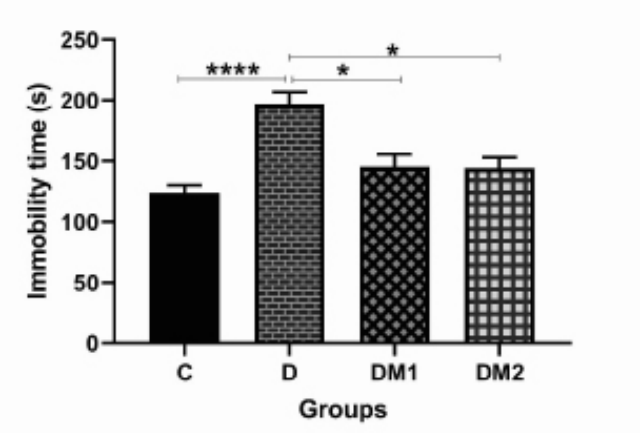

Figure 1. Immobility time in control, depression and metamizole-treated depression groups during UCMS on forced swimming test. Data are shown as mean ± SD. Kruskal Wallis and Dunn's multiple comparison. *p<0.05, ****p<0.0001, C: Control, D: Depression, DM1: Depression Metamizol 100 mg/kg, DM2: Depression Metamizol 200 mg/kg

ELISA analysis of cytokines and hematopoietic growth factors

The results of the semi-quantitative ELISA analysis, expressed as relative interleukin concentrations (mean±SD), are presented in Table 1. According to the findings, no significant difference was detected in IL-1α concentrations among the groups. However, IL-1ß levels were elevated in the depression group compared to the control group. Notably, metamizole treatment, particularly at the 200 mg/kg dose, led to a significant reduction in IL-1ß levels. IL-2, a cytokine associated with

Table 1. The relative fold change data of interleukins concentrations in control, depression (stressed) and metamizole treated groups

Relative concentrations of inteleukines (Fold change)					
Interleukins	Groups				
	Control	Depression	Depression Metamizol 100 mg/kg	Depression Metamizol 200 mg/kg	p-values
Interleukin-1α	1±0.18	0.98±0.16	0.95±0.17	0.98±0.21	ns
Interleukin-1ß	1±0.09	1.38±0.1	1.23±0.15	0.95±0.13	***p=0.0009, D vs. C ***p=0.0001, DM2 vs. D *p=0.0259 DM2 vs. DM1
Interleukin-2	1±0.07	0.95±0.07	0.96±0.08	0.78±0.09	***p=0.0004 DM2 vs. C *p=0.017 DM2 vs. D **p=0.009 DM2 vs. DM1
Interleukin-4	1±0.09	0.92±0.08	0.92 ± 0.09	0.81 ± 0.12	**p=0.0056 DM2 vs. C
Interleukin-6	1±0.09	1.44±0.11	0.64±0.14	0.58 ± 0.12	*p=0.013 DM2 vs. C ***p=0.0003 DM1 vs. D ****p<0.0001 DM2 vs. D
Interleukin-10	1±0.09	0.97±0.12	0.95±0.11	0.79±0.18	ns
Interleukin-12	1±0.11	1.16±0.16	1.15±0.12	0.74±0.14	***p=0.0004 DM2 vs. D ***p=0.0008 DM2 vs. DM1
Interleukin-17	1±0.13	1.14±0.21	1.14±0.14	0.78±0.17	**p=0.0073 DM2 vs. D **p=0.0034 DM2 vs. DM1

Kruskal Wallis and Dunn's multiple comparison. Data are shown as mean±SD. C: Control; D: Depression; DM1: Depression Metamizol 100 mg/kg; DM2: Depression Metamizol 200 mg/kg

T cell activation, remained unchanged in the control, depression, and 100 mg/kg treatment groups, but showed a marked decrease in the 200 mg/kg metamizole group compared to all other groups. For the anti-inflammatory cytokine IL-4, a significant reduction was observed only in the 200 mg/kg metamizole group compared to the control group. IL-6, which may produce different immunological responses, was decreased in both 100 mg/kg and 200 mg/kg groups compared to the depression group. Moreover, IL-6 levels were also significantly reduced in the 200 mg/kg group compared to the control.

Although IL-10 concentrations, another anti-inflammatory cytokine, remained unchanged across groups, IL-12 levels were significantly reduced in the 200 mg/kg group compared to both the depression and 100 mg/kg groups. A similar result was obtained for IL-17.

Table 2 presents the cytokine results from the ELISA analyses as mean±SD. In this study, although IFN-γ concentrations were elevated in the depression group, no statistically significant increase was observed for TNF-α. However, for both cytokines, the concentrations were reduced in the 200 mg/kg metamizole group compared to the depression group and the 100 mg/kg metamizole group.

Table 2. The relative fold change data of cytokines concentrations in control, depression (stressed), and metamizole treated groups

Relative concentrations of cytokines (Fold change)					
Cytokines	Groups				
	Control	Depression	Depression Metamizol 100 mg/kg	Depression Metamizol 200 mg/kg	p-values
IFN-γ	1±0.1	1.41±0.28	1.37±0.22	0.88±0.31	*p=0.0343, D vs. C **p=0.0053, DM2 vs. D **p=0.0086, DM2 vs. DM1
TNF-α	1±0.12	1.06±0.19	1.04±0.1	0.73±0.2	*p=0.0267, DM2 vs. D *p=0.018, DM2 vs. DM1

Kruskal Wallis and Dunn's multiple comparison. Data are shown as Mean±SD; IFN-γ-: Interferon gamma; TNF-α: Tumor necrosis factor alpha; C: Control; D: Depression; DM1: Depression Metamizol 100 mg/kg; DM2: Depression Metamizol 200 mg/kg

Table 3. The relative fold change data of hematopoietic growth factors concentrations in control, depression (stressed), and metamizole treated groups

Relative concentrations of hematopoietic growth factors (Fold change)					
Hematopoietic growth factors	Groups				
	Control	Depression	Depression Metamizol 100 mg/kg	Depression Metamizol 200 mg/kg	p-values
Granulocyte-Colony Stimulating Factor	1±0.22	1.42±0.23	0.88 ± 0.15	0.85±0.15	*p=0.0342 D vs. C **p=0.0023 DM1 vs. D **p=0.0015 DM2 vs. D
Granulocyte Macrophage-Colony Stimulating Factor	1±0.09	1.23±0.24	1.10±0.20	0.84±0.09	***p=0.001 DM2 vs. D *p=0.0392 DM2 vs. DM1

Kruskal Wallis and Dunn's multiple comparison. Data are shown as mean ± SD. C: Control, D: Depression, DM1: Depression Metamizol 100 mg/kg, DM2: Depression Metamizol 200 mg/kg

The data for hematopoietic growth factors are presented in Table 3. In mice exposed to depression, G-CSF concentra-

tions were elevated, whereas the increase in GM-CSF levels did not reach statistical significance. However, G-CSF levels were significantly reduced in the 100 mg/kg and 200 mg/kg metamizole treatment groups compared to the depression group. For GM-CSF, a significant reduction was observed in the 200 mg/kg group compared to both the 100 mg/kg and depression groups. Findings of this study suggest that depression may alter the concentrations of cytokines and hematopoietic growth factors, and that metamizole treatment may attenuate these changes.

DISCUSSION

Immune activation and cytokines may contribute to the development of depressive disorders by inducing structural and functional changes within the central nervous system (24,25). There is evidence that IFN-γ and IL-2, which are used in the treatment of cancer and viral diseases, can induce depressive symptoms. The prevalence of MDD associated with IFN-γ has been reported to range from 10% to 40%. IL-1ß and TNF-α are known to increase Ca^{2+} influx through NMDA and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, contributing to neuronal death. Interestingly, decreased plasma levels of TNF-α and IL-6 have been associated with poor response to antidepressant treatment (24). Psychological stress and various disease states can activate the immune system, leading to elevated levels of IL-1α, IL-1ß, IL-6, TNF-α, IL-17, and other cytokines, which may contribute to inflammation-associated depression. Non-immunological peripheral stimuli can also trigger cytokine release within the brain. In the CNS, cytokines are produced by neurons, microglia, and astrocytes. Additionally, peripheral cytokines can cause triggering and can cross the blood-brain barrier via monocyte migration, leakage, or active transport mechanisms, despite their large molecular size (25). Studies indicate that inflammatory cytokines may activate the hypothalamic–pituitary–adrenal (HPA) axis via excessive cortisol release, playing a significant role in the pathophysiology of depression (26,27). Furthermore, proinflammatory cytokines may induce the enzyme indoleamine 2,3-dioxygenase, which converts the source of serotonin, tryptophan, into kynurenine. Quinolinic acid, the bioactive metabolite from the kynurenine pathway, is an NMDA receptor agonist that contributes to depression and is potentially neurotoxic (27). These findings support that depression may be related to the cytokine-inflammation or cause the inflammation. The inflammation suggests the contribution of COX enzymes to the pathophysiology of depression and how their inhibitors affect stress-induced cytokine changes.

Some studies have investigated COX expression in depressive states. In rodents exposed to UCMS, cortical COX-2 overexpression has been associated with depressive behavior, accompanied by enhanced activation of the PGE2–EP2/EP3 pathway and reduced cAMP/PKA/CREB/BDNF signaling (28). In another study, depressive-like behavior induced by lipopolysaccharide (LPS) and mediated by prostaglandins was reversed by nimesulide and indomethacin. Although some findings suggest a predominant role for COX-2, the efficacy of indomethacin, which has a higher affinity to COX-1, points to the involvement of both COX isoforms (29). Metamizole, which was used in this study, can inhibit both COX-1 and COX-2, and it has not been previously used to detect the levels of cytokines and hematopoietic growth factors in a depression model. While most prior studies have focused on COX–2–selective inhibitors, reports show that a single dose of celecoxib or indomethacin ameliorated depressive-like behavior in mice treated with IFN-α. Ibuprofen exerted antidepressant-like effects only when co-administered with IFN-α, indicating that there may be differences in the effect-to-administration for NSAIDs (30). In the model applied in this study, metamizole was administered daily for five weeks, beginning one week after the onset of stress exposure, thereby simulating chronic treatment.

Beyond stress models, NSAIDs have also been studied in cancer-related depression. Ibuprofen improved the depressive-like behavior assessed by the forced swimming test in mice with adenocarcinoma, reduced cancer-related inflammation, and lowered plasma IL-6 concentrations. In addition, IL-1ß and IL-6 mRNA expressions in hippocampal tissue was reduced compared to tumor groups (31). In psoriasis, a chronic inflammatory disease, monitoring and potentially preventing anxiety and depression may be possible with the measurement of proinflammatory cytokine levels. Keenan et al. (32) detected the serum levels of TNF-α, IL-1ß, IL-6, IL-12, IL-17A, and IL-23 in patients with psoriasis and noted that increases in TNF-α, IL-17A, and IL-23 were associated with depressive symptoms. In this study, both pro- and anti-inflammatory cytokines (10 in total), as well as hematopoietic growth factors, were quantified as relative concentration coefficients. Compared to the non-stressed control group, the depression group showed significant increases only in IL-1ß and IFN-γ concentrations. Conversely, in mice treated with metamizole, IL-1ß, IL-2, IL-6, IL-12, IL-17, IFN-γ, and TNF-α levels were all reduced compared to the depression group. These results suggest that the development of depression may be modulated by the cytokine-inflammation axis and that the observed changes are more strongly associated with proinflammatory rather than anti-inflammatory cytokines.

Based on the existing data, recent systematic reviews and meta-analyses have begun to explore the therapeutic potential of anti-inflammatory treatments in MDD. Although

NSAIDs may offer clinical benefits, current evidence is not yet sufficient to support their widespread use in depression treatment, and further research is warranted. These reviews also suggest that cytokine inhibitors may be beneficial, although concerns remain regarding infection risk and overall safety (33–35).

Hematopoietic growth factors are widely used to mobilize stem cells into peripheral blood during bone marrow transplantation. G-CSF and GM-CSF are also employed in the treatment of metamizole-induced agranulocytosis (36,37). In hematopoietic progenitor cell cultures, G-CSF has been shown to markedly enhance PGE2 production via ß-adrenergic receptor signaling (38). PGE2 is considered one of the mediators involved in the development of depression (17,28). In a murine model of casein-induced peritonitis, PGE2 was found to stimulate G-CSF production via the prostanoid EP2 receptor, and this effect was reversed by indomethacin (39). Additionally, adolescents with MDD have been reported to have elevated concentrations of G-CSF and GM-CSF compared to healthy controls. In the same study, levels of VEGF, FGF, IL-7, IL-9, and IL-17A were also elevated, while a 4-week fluoxetine treatment reduced cytokine as well as G-CSF and GM-CSF concentrations (40).

Some evidence suggests that the COX-2 inhibitor meloxicam has a regulatory effect on hematopoiesis and survival in mice exposed to radiation. This effect of meloxicam may be indirect and may be due to its interaction with cells that produce hematopoietic growth factors and its promotion of G-CSF production (41). However, some studies show that PGE2 has a stimulatory effect on the contrary (38). In the present study, G-CSF levels were also found to be increased in the untreated depression group. These results probably indicate that NSAIDs may cause different results depending on the clinical condition and type.

In addition to the hematopoietic system, G-CSF, GM-CSF, macrophage colony stimulating factor (also known as colony stimulating factor 1) (CSF-1) and cytokines also have target cells in the nervous system. CSF-1 plays a role in the macrophage differentiation of hematopoietic stem cells. In addition, it has been found to be active in the nervous system. The molecule has regulatory effects on microglia and in particular, the deficiency of its receptor (CSF-1R) has been shown to be associated with neurological diseases. It has been revealed that the receptor expression is reduced in the spleens of patients with MDD but not in the central nervous system, and that CSF-1 mRNA expression is upregulated in the dorsal medial prefrontal cortex. A similar study conducted with mice exposed to chronic unpredictable stress also showed that stress increases CSF-1 expression in the dorsal medial prefrontal cortex and induces activation of the CSF-1R pathway (42). This study also showed that the expression of hematopoietic factors changes under stress conditions. This evidence shows that the development of depression is not only dependent on neurological factors, but also multiple factors such as growth factors and cytokines play an active role.

SSRIs and SNRIs, including fluoxetine, are first-line treatments for depression and may exert part of their therapeutic effect through anti-inflammatory mechanisms (16). In male mice exposed to stress, fluoxetine reduced IFN-γ mRNA expression, which is an important factor in depression (43). Similarly, sertraline has been shown to decrease IL-1ß and TNF-α mRNA levels (44). In this study, stress exposure significantly increased G-CSF concentrations, while GM-CSF elevation did not reach statistical significance. Notably, metamizole administration led to reductions in these elevated growth factor levels. Particularly, the observed changes in proinflammatory cytokines support the involvement of the COX pathway in the pathophysiology of depression.

Limitations of the Study

Ten cytokines and two hematapoietic growth factors were analyzed in the study. In addition, studying cortisol levels, which are a marker of stress, was also among the goals, but it was abandoned due to evaluation in terms of the amount of serum sample obtained. Instead, a forced swimming test was performed in mice to evaluate the antidepressant-like effect of metamizole. Semi-quantitative ELISA was preferred both because of the insufficient amount of serum and because it allowed the study to be performed with a single kit.

CONCLUSION

The results present proinflammatory and anti-inflammatory cytokines together in a single study of the depression model and additionally demonstrate findings showing the relationship of hematopoietic growth factors. The study differs from similar studies because it also evaluated hematopoietic factors. The results indicate that metamizole may reduce the production of cytokines that are more effective in proinflammatory mechanisms. In addition, the levels of hematopoietic factors that increase under the influence of stress factors may also decrease with the use of metamizole. Therefore, it has become clear that the stress-hematopoiesis-cytokine relationship should be investigated within this framework. When considered together with existing data on SSRIs and SNRIs, the results suggest that NSAIDs such as metamizole may have therapeutic potential in the treatment of depression. Further clinical studies are needed to clarify and confirm the role of NSAIDs in this context.

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Authorship Contribution: Concept: EM, OK, FA, Design: EM, OK, FA, Supervising: EM, FA, Financing and equipment: FA, EM, OK, FB, Data collection and entry: EM, OK, FB, DNS, FA, Analysis and interpretation: EM, OK, FB, DNS, FA, Literature search: EM, OK, FB, DNS, FA, Writing: EM, FB, DNS, Critical review: OK, FB.

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