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Nigella Sativa Oil Improves Oxidative Stress, Inflammation and Changes in Neurotransmitter Structures in Fructose-Induced Metabolic Syndrome

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ABSTRACT

Metabolic syndrome (MetS) causes inflammation in adipose tissue along with oxidative stress and cellular damage. We aimed to investigate the protective effects and biochemical mechanisms of nigella sativa oil on MetS caused by excessive fructose intake in rats. 21 male Sprague-Dawley rats were used in the study. Rats; were divided into groups as control group, metabolic syndrome group and nigella sativa oil group. While the rats in the control group were fed only tap water and pellet food, the rats in the experimental group were fed with tap water with 10% fructose and pelleted diet for 10 weeks ad libitum. Nigella sativa group was given 0.1 ml of nigella sativa oil daily by oral tube for 4 weeks. After the study was completed, the rats were decapitated and serum biochemistry parameters, BDNF, neurotransmitters, cytokine and antioxidant levels were measured. Serum glucose, insulin, insulin resistance (HOMA-IR) and lipid profile levels increased with metabolic syndrome were significantly reduced with nigella sativa oil. Nigella sativa oil (NSO) regulated brain-derived neurotrophic factor (BDNF), 5-hydroxyindole acetic acid (5-HIAA), 5-hydroxytryptamine (5-HT), nor-adrenaline (NA), adrenaline (AD), dopamine (DA), tumor necrosis factor-α (Tnf-α), interleukin-6 (IL-6), total antioxidant status (TAS) and total oxidant status (TOS) parameters in the fructose-induced metabolic syndrome rat model. NSO was found to be a promising application option in preventing the development of oxidative stress and inflammatory damage caused by metabolic syndrome and in elucidating the complex mechanisms of neurotransmitters.

Keywords: BDNF, Cytokines, Metabolic syndrome, Nigella sativa oil, Neurotransmitter, Oxidative stress

INTRODUCTION

It is a group of diseases whose incidence is increasing day by day all over the world and which is also referred to as MetS, fatal quadruple, insulin resistance syndrome, which has fatal consequences. Although it is known that lack of physical activity, fast food-based diet and genetic factors are effective in the formation of MetS, its mechanism has not been clarified yet. The prevalence of MetS in adults is considered to be 22% on average, and this rate increases with age. It has been reported that this rate is 6.7% in young individuals (between the ages of 20-29) and 43.5% in the elderly (between 60-69 years of age) (Akbıyık et al. 2022). MetS is a pathological condition characterized by glucose intolerance, hyperinsulinemia, dyslipidemia, abdominal obesity, hypertension, kidney diseases, and increased insulin resistance. It is known that obesity and insulin

resistance contribute to the development of MetS. Hormones secreted from adipose tissue are thought to play a role in the pathogenesis of MetS. The most common and accepted diagnostic criteria table for the diagnosis of MetS is the table made by NCEP-ATP III. The presence of three of the five criteria in this table is sufficient to diagnose metabolic syndrome (Doğan 2019). In experimental and clinical studies, insulin resistance, increase in plasma free fatty acids and inflammatory cytokines are said to be responsible for the etiopathogenesis of MetS (Charrière et al. 2003; Lorenzo et al. 2008).

High fructose, which is widely used to create an experimental metabolic syndrome model in rats, is also used as a sweetener in various fruits and industrial products (Er 2017). Fructose diet is known to be an important source of oxidative stress in rodents. Auto-oxidation of glucose accumulating in the cell, disorders in arachidonic acid metabolism and increased fatty acid oxidation are other important factors affecting fructose-induced oxidative stress (Reddy et al. 2009).

Microbiota, which is now referred to as an organ due to its function in recent years, constitutes all of the microorganisms known as triggers of many diseases such as obesity, type 2 diabetes, metabolic syndrome and cardiovascular diseases, depending on the changes in the beneficial / harmful bacteria ratio. Production of bioactive metabolites and having a healthier microbiota are possible with an active lifestyle. There are mechanisms that create an anti-inflammatory response depending on the intestinal bacterial composition, physical activity, severity and duration of the activity (Chen et al. 2018).

Along with these recommendations, some therapeutic plants used in phytotherapy and traditional medicine have been frequently investigated in recent years. Nigella sativa is widely used as a traditional medicine in folk medicine in the Middle and Far East. It is also known that black cumin has an antioxidant role in protecting against liver cirrhosis and fibrosis (Kanter 2008). It is said that NSO regulates and normalizes the immune system in the body, destroys tumor cells and can be used to protect from viruses that damage cells (Kanter 2008). Nigella sativa (nigella sativa) is an annual 20-40 cm tall, herbaceous plant known as black seed, black cumin or cornflower seed, a member of the Ranunculaceae family, with light blue flowers (Figure 1).

Figure 1. Molecular structure of Nigella sativa and thymoquinone

It has been reported that NSO regulates the immune system in the body, destroys tumor cells, is a hepatoprotective and powerful antioxidant against liver damage, its oil and thymoquinone prevent lipid peroxidation and eicosanoid formation (Ali and Blunden 2003; Daba and Abdel-Rahman 1998). In this study, we aimed to elucidate the effects of NSO in a rat model with fructose-related metabolic syndrome; the complex relationship of antioxidant defense system, inflammation, neurotransmitter system and BDNF.

MATERIALS AND METHODS

Regulation of Experimental Animals and Experimental Study

This study was carried out in accordance with standard experimental animal studies after obtaining the approval of Fırat University Animal Experiments Ethics Committee (26.03.2014 and 2014/8 80). In this study, 21-week-old male Sprague-Dawley rats weighing an average of 200-240 grams were used. Experimental procedures were applied after the rats were fed ad libitum with standard pellet feed and drinking water and adapted to the environment. Rats were 7 rats in each group; They were divided into groups as (group 1) control group, (group 2) MetS group and (group 3) MetS +NSO group. While the rats in the control group were fed only drinking water and pellet food, 10% fructose + standard pellet food diet was added to the drinking water for 10 weeks to form MetS in the rats in the experimental group (Sánchez-Lozada et al. 2007). In group 3, MetS was created by adding 10% fructose to drinking water for ten weeks, and then 0.1 ml of NSO was given daily by oral catheter for four weeks (Perveen and Hainder 2013). Groups 1 and 2 were decapitated 10 weeks after the start of the experiment, and Group 3 after 14 weeks.

Laboratory Analysis

Blood samples taken were taken into gel biochemistry tubes, and their serum was obtained by centrifugation at 4000 rpm for 5-10 minutes. There was no pinkish red or red serum with signs of hemolysis. Glucose, total cholesterol, triglyceride, HDL, LDL, VLDL, TAS and TOS levels were measured using appropriate commercial kits using Siemens Advia 2400 autoanalyzer device with appropriate commercial kits. HOMA-IR= [fasting insulin (mIU/L) X fasting blood sugar (mmol/L)] / 22.5 calculated as. The threshold for insulin resistance; Accepted as HOMA-IR> 2.5 (Mattehews et al. 1985). BDNF, IL-6, TNF-α and Insulin levels were studied by ELISA method using appropriate commercial rat kits. Nörotransmiter analizleri için Eureka marka ticari rat kitleri (5-HIAA, 5-HT, NA, AD, DA) kullanılarak HPLC cihazı ile kullanım kılavuzuna uygun olarak çalışıldı.

Statistical Evaluation

The sample size of the study was determined to be 21 rats (n = 7; 3 groups) using the G*Power package program (Version 3.1.9.2) with alpha error 0.05 and 85% power with effect size 0.79 (Faul et al. 2007). The IBM Statistical Package for the Social Sciences statistical package (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: Amerika) was used to analyze the data. In this study, conformity to the assumption of normality from the prerequisites of the parametric tests was assessed using the Shapiro-Wilk test. The Kruskal Wallis test was used to evaluate the data in the groups, and the Mann Whitney-U test was used for binary comparisons between the groups. Data obtained in the groups after the study were given as Mean ± Standard deviation. $p<0.05$ value was accepted as the lowest statistical significance level.

RESULTS

Basal and Weekly Weight Measurements

The first and last weights of the rats taken in the experiment. Significant statistical differences observed between the weights. The rat weights relationship given in Table 1. All parameters except HDL increased statistically significantly after MetS. In the biochemistry panel, the HDL level decreased and these values showed a statistically significant improvement again after NSO application.

Table 1. Difference of Rat Weights of Groups.

	Start weight	End weight	Weight differences	p
Control (n=7)	243.43±9.86	361.71±42.14	118.14±38.31	p <0.05
MetS (n=7)	230.57±18.69	382±34.43	151.43±30.88	p <0.05
NSO (n=7)	240.14±5.01	370.71±33.98	130.57±30.36	p <0.05
p	p >0.05	p >0.05	p <0.05	

The data are presented as means and standard deviation (Kruskal Wallis, Mann-Whitney U).

p <0.05 is considered significant.

Biochemical Measurements

When the groups were compared; Serum glucose, lipid parameters, insulin and HOMA-IR levels were significantly impaired by MetS. Parameters that deteriorated with the NSO application were regulated to levels close to control. Levels of LDL, total cholesterol and triglycerides increased by MetS returned to control levels with NSO. HDL levels decreased with MetS and returned to control levels with NSO (Table 2). There was no statistically significant difference in serum IL-6 levels (P>0.05) (Table 3). NA and AD levels, which increased statistically significantly compared to the control, returned to levels that were not different from the control with NSO. TNF-α levels showed a statistically significant increase with MetS (p<0.01) (Table 3). 5-HT levels showed a statistically significant decrease with MetS (p<0.01) (Table 3). All these changes were regulated to close to control levels with NSO (Table 3).

Table 2. Serum glucose, lipid parameters, insulin and HOMA-IR levels.

Parameters	Group 1 (n=7)	Group 2 (n=7)	Group 3 (n=7)	P
Glucose (mg/dl)	102±4.62	140.14±4.67	110.57±7.35	Group 1-2, P <0.01 Group 1-3, P <0.05 Group 2-3, P <0.01
T. Cholesterol (mg/dl)	68±5.13	84.43±7.63	71.71±6.31	Group 1-2, P <0.01 Group 2-3, P <0.01
Triglycerides (mg/dl)	63.71±5.82	97.86±7.17	60.71±6.42	Group 1-2, P <0.01 Group 2-3, P <0.01
HDL(mg/dl)	16.86±2.86	11.63±1.86	14.37±1.88	Group 1-2, P <0.01 Group 2-3, P <0.05
LDL(mg/dl)	38.4±5.34	53.23±10.01	45.2±7.06	Group 1-2, P <0.05
Insulin (mIU/L)	8.19±2.23	10.98±5.13	9.01±1.71	Group 1-2, P <0.01 Group 1-3, P <0.01 Group 2-3, P <0.01
HOMA-IR	2.06±0.09	3.8±0.25	2.46±0.17	Group 1-2, P <0.01 Group 1-3, P <0.01 Group 2-3, P <0.01

The data are presented as means and standard deviation (Mann-Whitney U testi).
Group1: Control, Group 2: MetS, Group 3: MetS +NSO,
p <0.05 is considered significant, NS: No significant

Table 3. Cytokines, oxidative stress, neurotransmitter and BDNF levels.

Parameters	Group 1 (n=7)	Group 2 (n=7)	Group 3 (n=7)	p
IL-6 (ng/L)	542,27±53,93	603,43±36,49	584,04±25,34	NS, p>0,05
TNF-α (ng/L)	392,67±25,34	540,61±9,58	530,33±60,55	Grup 1-2, p<0,01 Grup 1-3, p<0,01
TAS (mmol.T.E/L)	1,77±0,07	1,56±0,07	1,7±0,26	Grup 1-2, p<0,01 Grup 1-3, p<0,05
TOS (μmol.H_2O_2.E/L)	19,17±1,59	24,55±1,72	23,21±4,2	Grup 1-2, p<0,01 Grup 1-3, p<0,05
5-HIAA (μg/L)	0,21±0,01	0,2±0,01	0,2±0,01	NS, p>0,05
5-HT (μg/L)	25,41±2,47	6,21±0,91	17,01±1,19	Grup 1-2, p<0,01 Grup 1-3, p<0,05 Grup 2-3, p<0,01
NA (ng/L)	191,43±11,44	729,57±14,18	211,86±1,61	Grup 1-2, p<0,01 Grup 2-3, p<0,01
AD (ng/L)	53,36±3,98	62,83±2,54	45,43±2,16	Grup 2-3, p<0,01
DA (ng/L)	17,9±2,37	38,61±2,69	22,56±2,74	Grup 1-2, p<0,01 Grup 2-3, p<0,01
BDNF (pg/ml)	166,54±13,97	150,98±17,46	176,01±7,58	Grup 2-3, p<0,05

The data are presented as means and standard deviation (Mann-Whitney U testi).

Group1: Control, Group 2: MetS, Group 3: MetS +NSO,

p <0.05 is considered significant, NS: No significant

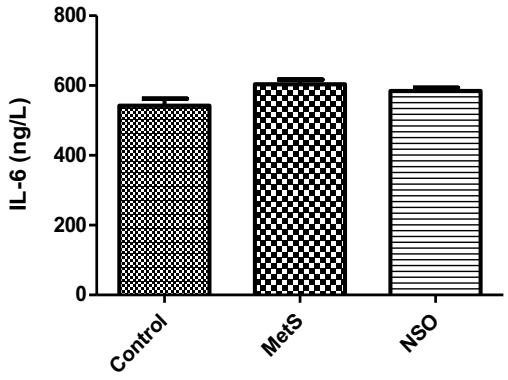

Figure 2. Serum IL-6 levels obtained in the groups. Control: Group 1, MetS: Group 2, NSO: Group 3

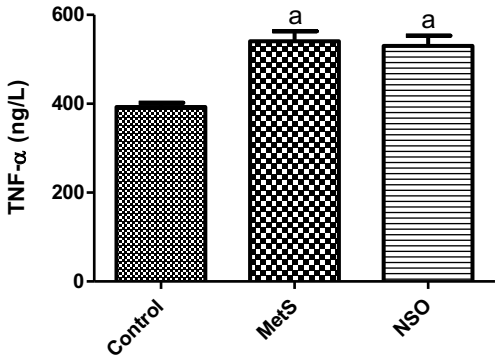

Figure 3. Serum TNF-α levels obtained in the groups. Control: Group 1, MetS: Group 2, NSO: Group 3. a: p<0,01 grup 1-2, grup 1-3

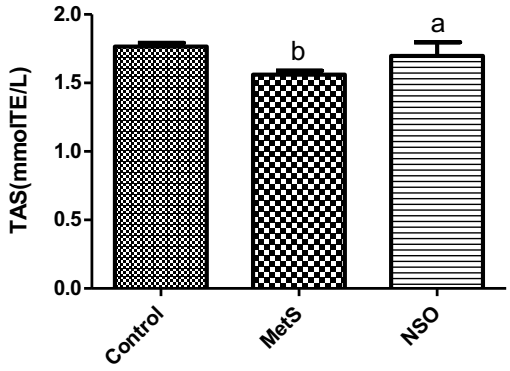

Figure 4. Serum total antioxidant capacity levels obtained in the groups. Control: Group 1, MetS: Group 2, NSO: Group 3
a: p<0,05 grup 1-3, b: p<0,01 grup 1-2

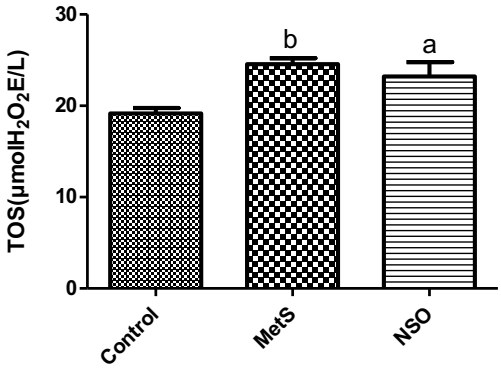

Figure 5. Serum total oxidant capacity levels obtained in the groups. Control: Group 1, MetS: Group 2, NSO: Group 3
a: p<0.05 group 1-3, b: p<0.01 group 1-2

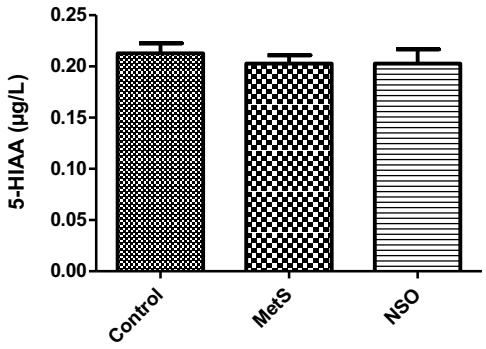

Figure 6. Serum 5-HIAA levels obtained in the groups. Control: Group 1, MS: Group 2, NSO: Group 3

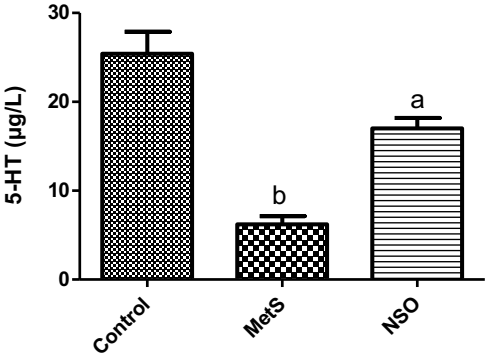

Figure 7. Serum 5-HT levels obtained in the groups. Control: Group 1, MS: Group 2, NSO: Group 3. a: p<0.05 groups 1-3, b: p<0.01 groups, 1-2 groups 2-3

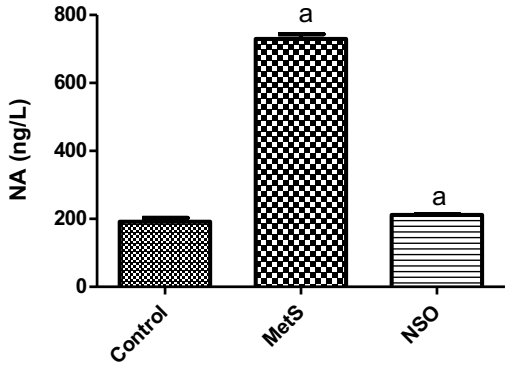

Figure 8. Serum noradrenaline levels obtained in the groups. Control: Group 1, MS: Group 2, NSO: Group 3
a: p<0.01 group 1-2, group 2-3

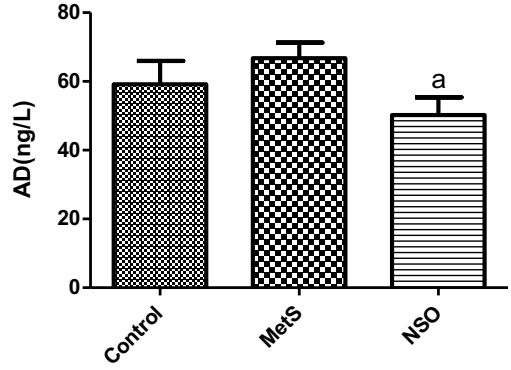

Figure 9. Serum adrenaline levels obtained in the groups. Control: Group 1, MS: Group 2, NSO: Group 3. a: p<0.01 group 2-3

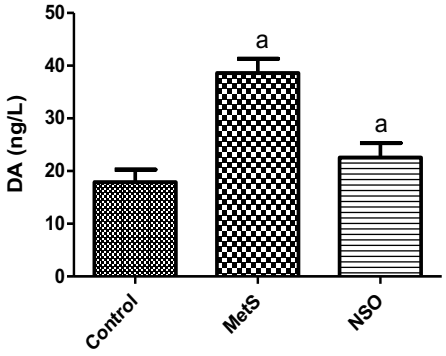

Figure 10. Serum dopamine levels obtained in the groups. Control: Group 1, MetS: Group 2, NSO: Group 3. a: p<0.01 group 1-2, group 2-3

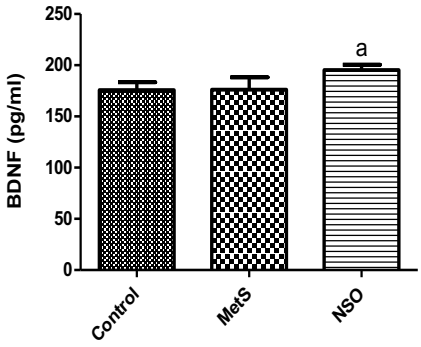

Figure 11. Serum BDNF levels obtained in the groups. Control: Group 1, MS: Group 2, NSO: Group 3. a: p<0.05 group 2-3

DISCUSSION

MetS is defined as a complex condition in which clinical, biochemical and metabolic factors develop together with insulin resistance and adipose tissue dysfunction on the basis of family history, malnutrition and insufficient exercise. It is known that TNF-α production is associated with tissue inflammation at the source of insulin and macrophage activation, and macrophage activation stimulates glucose tolerance and insulin resistance (Venancio and Suchecki 2015). The effect of TNF-α on insulin resistance increases the release of free fatty acids from adipocytes (Lastra et al. 2006). When the organism encounters an inflammatory or infectious stimulus, TNF-α production occurs (Bradley 2008). In addition, in many conditions such as infection, inflammation and autoimmune diseases, C-reactive protein (CRP) is synthesized in the liver under the control of IL-6 and its serum level increases. Phase response and acute phase reactants such as IL-6 and sialic acid, α-1 acid glycoprotein, CRP, serum amyloid A and IL-6 increase in type 2 diabetes (Opal and DePalo 2000). Increased circulating melatonin levels reduce the levels of inflammation markers such as IL-6, TNF-α, and circulating anti-inflammatory cytokines (Barquilla et al. 2014). In addition, mice fed a high-fat diet had increased cytokine, cholesterol, and triglyceride concentrations, but significantly decreased insulin, glucose, triglyceride, cholesterol, TNF-α, IL-6, LDL levels with melatonin administration. HDL showed the opposite effect (Barquilla et al. 2014). In our study, TNF-α increased statistically with MetS (p<0.01), while IL-6 levels increased nonsignificantly with MetS compared to the control group, and this increase was observed to decrease with NSO application (Figure 2, 3) . TNF-α, which is produced by MetS to regulate the deterioration in the number of fat cells, stimulates lipolysis, increases leptin production and causes insulin resistance by reducing the number of insulin receptors, impairs insulin receptor tyrosine kinase activity, thus reducing glucose uptake by cells (Goldstein 2002). In our study, it was observed that the increased levels of inflammation and cytokines, which are known to increase especially in connection with high LDL and lipid profile after MetS, and the increased levels of pro-inflammatory cytokines such as TNF-α and IL-6, which occur in the cell membrane mediated by insulin resistance, decreased with NSO. In our study, TOS levels increased statistically significantly after MetS compared to the control group and decreased compared to the MetS group after NSO administration (Figure 4, 5). TAS levels were statistically significantly decreased compared to the control group after MetS and increased statistically significantly compared to the MetS group after NSO administration. It is seen that the decrease in antioxidant capacity levels is caused by stress-related damage after MetS and NSO supports the increase of total antioxidant capacity enzyme levels. In a study, it is said that TOS levels in rats exposed to irradiation-induced oxidative stress were found to be statistically higher than the control group (p<0.001) and this increase in oxidative

parameters was prevented in the thymoquinone group (Cikman et al. 2015). In another study conducted in vitro, it was reported that NSO is a radical scavenger and its superoxide anion capture capacity is significantly high in the evaluation of antioxidant activity (Bouasla et al. 2014). TAS and TOS levels obtained in our study support the aforementioned studies.

The hypothesis that stress is an important risk factor in patients with depression is constantly accepted. Stress situations that may occur after MetS will lead to neurochemical changes and behavioral changes in experimental animals. Stress-induced behavioral deficits in experimental animals are commonly investigated using an animal model of depression (Haider et al. 2014). According to the classical hypothesis, serotonin deficiency is said to cause depression. Drugs that increase serotonin function are commonly used as medical antidepressants (Haider et al. 2014). A decrease in 5-HIAA, which is shown as a serotonin antagonist characterized by decreased serotonin capacity, is observed. In addition, reductions in 5-HT and its metabolite 5-HIAA in rat brains induce monoamine oxidase inhibitors. It has been reported that decreased 5-HT levels and increased capacity in rat brains as a result of repeated administration of Nigella sativa oil (Haider et al. 2014). Long-term application of Nigella sativa oil is said to potentiate the functions of monoamines by inhibiting the neurochemical profile of the brain and the activity of negatively-acting enzymes and converting them into signals for movement (Perveen et al. 2014).

In addition to altered behavioral changes after MetS, glucose metabolism and cognitive changes have negative effects on the functions of neurotransmitters (Francis et al. 2010, Lesemann et al. 2012). In particular, there is a positive correlation between glucose metabolism and DA, and it is known to decrease in cognitive functions. It is known that serotonin synthesis in the brain is possible with tryptophan, the precursor of serotonergic neurons, and increased brain tryptophan levels also contribute to the development of brain 5-HT metabolism (Perveen et al. 2014). In a study in which Nigella sativa oil was given at repeated doses, it was reported that brain tryptophan and 5-HT levels increased (Perveen et al. 2014). Tryptophan hydroxylase is a rate-limiting enzyme in 5-HT biosynthesis and affects tryptophan. Therefore, increased brain tryptophan also increases 5-HT synthesis in the brain. It is also stated that physiological and pharmacological brain tryptophan levels under different conditions are a marker of increased plasma tryptophan levels and have an important role (Perveen et al. 2014).

In our study, we observed that 5-HT levels, which were statistically decreased in rats with MetS compared to the control, increased statistically significantly in the group administered with NSO. We think that this increase activates 5-HT metabolism in the brain with the effect of NSO, and also affects the tryptophan hydroxylase rate-limiting enzyme, leading to an increase in tryptophan production and an increase in 5-HT and 5-HIAA levels in the blood. In our study, since the capacity of reduced brain 5-HIAA levels in rats with MetS is a product of the 5-HT mechanism, it resulted in a decrease in the levels of its metabolite 5-HIAA.

In our study, it was observed that DA levels increased as a result of glucose metabolism disorder associated with MetS. Dopamine and noradrenaline levels increased significantly in the MetS group compared to the control, but decreased significantly in the Nigella sativa group compared to the MetS group. Adrenaline, on the other hand, increased in the MetS group, insignificantly compared to the control, and statistically significantly decreased in the NSO-administered group compared to MetS and control. Accordingly, in the light of the literature, it is understood that black seed oil increases the synaptic 5-HT availability by increasing plasma and brain tryptophan concentrations and can be extremely useful in resisting stress with long-term application. It is thought that increased 5-HT synthesis with NSO may increase monoamine functions by increasing the activity of anti-stress enzymes. In one study, serum, IGF-1b, and TNF-α levels were elevated in STZ-treated diabetic mice in a CBL-controlled model of enhanced cognitive memory functions. In rats

whose diabetic status was confirmed by hyperglycemia and high HbA1c, STZ was administered for 4 weeks and DA, NE, NA levels were decreased compared to the control (Georgy et al. 2013).

In a similar study, age-related learning and memory states in rats: oxidative stress, decreased antioxidant enzyme activities, and decreased brain neurotransmitter levels were also found to decrease potential memory function (Haider et al. 2014). Considering the Nigella sativa application method and dose differences in neurotransmitter levels in our study, it is possible to say that it has curative effects after MetS. Another study previously reported that reduced 5-HT levels and anxiolytic effects were regulated by Nigella sativa oil (Perveen et al. 2014). With increased 5-HT in the brain, BDNF plays an important role on hippocampal neurons for cognitive functions (Kim et al 2010). When CBL is administered intermittently in obese diabetic mice (Menon et al. 2012), it reduces the level of HbA1c, a component of which is BDNF (Ono et al. 2000). In particular, reduced HbA1c and lipid peroxidation levels by CBL through its antioxidant power, effects on consciousness and memory in the hippocampus were mentioned (Yan et al. 2011).

In our study, it is possible to say that cytokines, which we think increase in relation to LDL cholesterol and other parameters after MetS, are effective in maintaining the balance of the central nervous system and are in line with BDNF in the protection of nerve cells (Hohlfeld et al. 2000). Expressing these effects in the peripheral and central nervous system, BDNF provides by binding to the tyrosine kinase B receptor with high affinity. Interestingly, BDNF levels are increased by neurons expressing the tyrosine kinase A receptor (Merighi et al. 2008). It is known that cytokines and BDNF, which are produced in response to stimuli in the brain and in the periphery, are important in trauma, stroke, ischemia, neurodegeneration, many ailments, and the preservation of the central nervous system balance (Dantzer 2006).

CONCLUSION

In this study, increased MetS in rats by applying fructose; Statistically significant decreases were observed on glucose, insulin, HOMA-IR and lipid profile levels after NSO administration. The positive effects of Nigella sativa oil were determined against the oxidative stress and subsequent damage caused by MetS. Compared to the MetS group, positive and curative effects were detected in the NSO-administered group on TAS and TOS levels. The changes in neurotransmitter, cytokines and BDNF levels that occurred after the effects of oxidative stress and inflammation in the brain after MetS were regulated by NSO application. In this study, BDNF, neurotransmitters, oxidative stress and anti-inflammatory cytokines were evaluated together in the MetS model. In the light of the data we obtained with this study, it was seen that the use of NSO would be an important and promising application option in the prevention and treatment of the development of MetS and similar diseases.

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