Original Article https://doi.org/10.47748/tjvr.1358395

TJVR 2023; 7 (2): 115-122

Turkish Journal of Veterinary Research

https://dergipark.org.tr/tr/pub/tjvr

e-ISSN: 2602-3695

The effect of evening primrose oil on some biochemical parameters in brain tissue in a model of metabolic syndrome induced with fructose in rats

Nizamettin Günbatar [1] Handan Mert [2] Salih Çibuk [3] Leyla Mis [4] Nihat Mert [2]

[1] *Department of Nursing, Faculty of Health Sciences, Van Yuzuncu Yil University, Van, Türkiye*
[2] *Department of Biochemistry, Faculty of Veterinary Medicine, Van Yuzuncu Yil University, Van, Türkiye*
[3] *Department of Health Technician, Vocational School of Health Services, Van Yuzuncu Yil University, Van, Türkiye*
[4] *Department of Physiology, Faculty of Veterinary Medicine, Van Yuzuncu Yil University, Van, Türkiye*

Correspondence: *Nizamettin Günbatar (nizam_gun2011@hotmail.com)*

Received: 11.09.2023 Accepted: 29.09.2023

ABSTRACT

Objective: Metabolic syndrome is a disease characterized by hypertension, dyslipidemia and insulin resistance, and constitutes an important risk factor for cardiovascular disorders. The effect of evening primrose oil (EPO) on insulin, adiponectin and resistin levels in brain tissue was investigated in a fructose-related metabolic syndrome model.

Materials and Methods: The rats were divided into 4 groups as control, evening primrose oil (orally at a dose of 0.1 mLrat/day), fructose (20% fructose added), fructose+evening primrose oil for 57 days. At the end of the experiment, brain samples were taken and homogenized. Then, insulin, adiponectin and resistin in brain tissue levels were determined by ELISA.

Results: Plasma insulin and resistin levels of the fructose group increased ($p \leq 0.05$) compared to the controls, on the contrary, adiponectin levels were significantly decreased ($p \leq 0.05$) in the fructose group. When EPO was given to rats given fructose, increased insulin and resistin levels decreased (2.54 ± 0.28^{a}, 2.12 ± 0.68^{a}), (2.21 ± 0.26^{b}, 2.04 ± 0.21^{a}) while decreased adiponectin levels were increased (0.64 ± 0.42^{c}, 1.02 ± 0.35^{b}).

Conclusion: It was observed that the impaired metabolic changes caused by fructose in the brain tissue were partially improved in the EPO-treated group as a result of the decrease in insulin, resistin and increase in adiponectin. Accordingly, since metabolic changes in the brains of rats fed with high fructose content may also occur in humans with fructose intake from various foods, the use of EPO in the medical setting may be recommended by clinicians to reduce the harmful effects on the brain.

Keywords: *Brain, Fructose, Rats*

INTRODUCTION

Since human metabolism is regulated by glucose, fructose is not a sugar suitable for humans. In addition, fructose and its technological products contribute to obesity, diabetes and the formation of some cancer types, fructose causes lipogenesis, dyslipidemia and hepatosteatosis. It is reported to be caused by imbalance (Levine et al., 2003). Consumption of multiple fructose-sweetened beverages and foods has also been documented to cause hepatosteatosis, visceral obesity, and decreased sensitivity to insulin. As a result of increased consumption of foods, fructose intake has reached 60-150 gr daily. It is estimated that this amount meets 10.2% of the daily energy need. Soft drinks sweetened with high fructose corn syrup constitute the majority of dietary fructose (Malik et al., 2010).

Today, hypertension, dyslipidemia and insulin resistance occur as a result of the metabolic syndrome caused by many exogenous and endogenous factors, and cardiovascular diseases and type 2 diabetes develop. In addition to these findings, it is observed that fructose causes lipid peroxidation in various tissues and oxidant enzyme activities are increased by polymorphnuclear leukocytes infiltrating the tissues (Rayssiguier et al., 2006; Crescenzo et al., 2013; Bircan, 2014).

The oil obtained from the seed of primrose (*Oenothera biennis* L), a wild medicinal flower, contains different vegetable oils but is rich in gamma linolenic acid. It is used in traditional medicine in many different parts of the world to treat many internal and external diseases. Commercially, evening primrose oil and different vegetable oils containing γ-linolenic acid (GLA) are sold in encapsulated form as food supplements. Evening primrose oil is known to favorably modify a deteriorating lipid profile (Singer et al., 1986; Villalobos et al., 1998; Abo-Gresha et al., 2014).

The brain is a metabolically very active organ. Significant energy is used for events such as regulating ion concentration in synaptic transmission, generation of electrical potentials, active uptake of excitatory neurotransmitters and synthesis processes in the brain. The brain uses glucose, an important metabolic substrate, as its main energy source (Herculano-Houzel, 2011). Glucose metabolism in the brain is oxidative, with most of the glucose being oxidized to carbon dioxide and water. Complete oxidation of glucose to carbon dioxide and water may not always occur. This is called the glycogen pathway, and it is important for astrocytic glycogen stores (Reagan et al., 2002; Shah et al., 2012).

Adiponectin is thought to play an important role in the modulation of glucose and lipid metabolism in insulin-sensitive tissues in both humans and animals. Decreased circulating adiponectin levels have been demonstrated in genetic and diet-induced mouse obesity models of obesity (Yamauchi et al., 2001).

Resistin is known to be produced in adipose tissue in mice. It has been hypothesized that resistin level may be a triggering factor of diabetes and obesity-related metabolic disorders in mice (Urbanovych et al., 2015). Resistin is an in vitro insulin antagonist in human preadipocytes. Overexpression of resistin, which has been shown to be proinflammatory cytokines in recent studies, by liver cells impairs glucose uptake and glycogenesis. Positive correlations with proinflammatory factors have been demonstrated in adults with pathophysiological conditions such as atherosclerosis, kidney disease, respiratory tract inflammation, and type 2 diabetes mellitus (DM2) (Jinhua, 2012).

In this study, the effect of evening primrose oil on insulin, adiponectin and resistin levels in brain tissue was investigated in a fructose-induced metabolic syndrome model.

MATERIALS and METHODS

The animal material of this study was obtained from Van Yüzüncü Yıl University Experimental Animals Unit. Forty male Wistar albino rats, 12-16 weeks old, weighing 250-300 g, were used. During the experiment, the rats were housed in rooms with 12 hours of dark/lighting and a temperature of 22±2°C, in cages with constant feed and fresh water in front of them. Standard rat food, drinking water or tap water with 20% fructose was given ad libitum. The study was carried out in accordance with the code of ethics, and with the approval of the local ethics committee of the animal experiments of Van Yuzuncu Yil University (Decision number: 31.08.2023, 2023/10-06).

Experimental applications

Animals were randomly divided into 4 groups. Trial period is 57 days. Control group (10 rats): Standard rat food and tap water were given.

Evening primrose oil group (EPO) (10 rats): Standard rat feed and tap water were given. In addition, evening primrose oil (Biotama, Turkey) was administered orally by gavage at a dose of 0.1 mL/rat/day (Kaya, 2010) for 57 days.

Fructose group (10 rats): Standard rat food and tap water with 20% fructose added (Bircan, 2014) were given for 57 days.

Fructose+Evening Primrose Oil Group (Fructose+EPO) (10 rats): Evening primrose oil was administered orally at a dose of 0.1 mL/rat/day, with standard rat food and tap water with 20% fructose added, for 57 days.

Taking the samples

After the experimental application, only water was given and the animals were fasted overnight. The rats were given 90 mg/kg of ketamine i.p., after the animals were sacrificed, the brain was immediately removed and weighed. It was kept in a deep freezer at -80 degrees.

Frozen brain tissue samples were weighed after thawing and homogenized in cold 0.1 M phosphate buffer (pH=7.4) solution in a homogenizer (Heidolph Slient Crusher M, Bear, Delaware United States) (He Supernants were obtained by centrifugation at 4500 rpm for 20 minutes at 4°C (Mohamed et al., 2015).

In the resulting supernatant, Rat Insulin ELISA Kit YL Biont (Item No.: YLA0037RA), Rat adiponectin, ELISA Kit YL Biont (Item No.: YLA0076RA), Rat Resistin ELISA Kit YL Biont (Item No. YLA0203RA), ELISA kits, a Examined using a Statfax 2600 automatic washer and a Statfax 2100 reader.

Statistical analysis

"SPSS Statistic 20" package program was used in the analysis of the data. Kruskal Wallis test was used for statistical analysis of all parameters. Results with less than $p<0.05$ are considered to be statistically significant between groups.

RESULTS

Effects of evening primrose oil on some parameters in brain tissue in rat with fructose-induced metabolic syndrome were shown in Table 1.

Insulin levels of brain tissue in the fructose group were found to be higher than those in the control and EPO groups. This surplus decreased when EPO was added to the fructose given group. However, there was no statistically significant difference between the insulin level changes of both the control and fructose groups. However, it is seen that EPO reduces the insulin-raising effect of fructose.

Adiponectin level in the brain tissue was found to be significantly lower in the fructose group than in the control and EPO groups. This decline increased when EPO was added to the fructose given group. A statistical significance was found between the changes in fructose and adiponectin levels of the other groups.

The level of resistin in the brain tissue followed a similar path to other parameters. Again, it was found to be significantly higher in the fructose group than in the control and EPO groups. This increase decreased when EPO was added to the fructose group. Statistically significant changes were found between the resisitin level changes of fructose and other groups (Table 1).

Table 1. Brain tissue levels of insulin, adiponectin and resistin in metabolic syndrome in rats induced with fructose.

Parameters	Control X±SD	EPO X±SD	Fructose X±SD	Fructose+EPO X±SD	*P*
Insulin (µg/g tissue)	1.98±0.23^{a}	1.64±0.91^{a}	2.54± 0.28^{a}	2.12±0.68^{a}	0.098524 NS
Adiponectin (µg/g tissue)	1.29±0.98^{a}	1.133±0.52^{a}	0.64±0.42^{c}	1.02±0.35^{b}	0.000129 *
Resistin (pg/g tissue)	1.91±0.22^{a}	1.65±0.35^{c}	2.21±0.26^{b}	2.04±0.21^{a}	0.002526*

a,b,c: The differences between values containing different letters in the same line were found to be statistically significant at the $p\leq0.05$ level. Evening primrose oil (EPO).

DISCUSSION

In laboratory animals fed a high fructose diet, some disorders paralleling metabolic syndrome markers have been identified. Similarly, in humans, it has been observed that first of all, hypertension and insulin resistance are formed, followed by impaired glucose metabolism and uptake pathways, followed by an increase in triglyceride synthesis and lipogenesis (Bircan, 2014; Arslan and Şanlıer, 2016). For this reason, giving high fructose diets to experimental animals is critical for establishing metabolic syndrome and observing changes, identifying disease-causing mechanisms and developing new strategies for disease prevention/treatment (de Moura et al., 2008).

Bircan (2014) added 20% fructose to the drinking water of rats for 8 weeks. At the end of this period, when the fructose administered group was compared with the control group, it was determined that it caused a statistically significant increase in systolic blood pressure, serum insulin and triglyceride levels, insulin resistance developed and metabolic rate was increased. Created the syndrome model in rats (Bircan, 2014).

Liver in metabolic syndrome induced by fructose diet; It is the organ that is most affected by the metabolic changes and is the earliest damaged due to both being the main organ responsible for fructose metabolism and its function in carbohydrate and lipid metabolisms (Grattagliano et al., 2008; Bagul et al., 2012).

The extracellular glucose concentration in the blood is important in the transport of glucose to the brain tissue. Short-term hyperglycemia, which occurs when the amount of glucose in the blood plasma increases compared to normal values as a result of different foods and disorders in the organism, or long-term hyperglycemia, as in diabetes (Horani and Mooradian, 2003). Some of these metabolic pathways constitute the indirect pathway of passive responses independent of neuronal activity. In addition, it has been shown that the active responses of hyperglycemia in gene expression in neurons in the central nervous system have a very important place in neuronal damage (Klein and Waxman, 2003).

It has been observed that magnocellular neurosecretory cells in the hypothalamic supraoptic and paraventricular nuclei increase vasopressin release against the increased hyperosmolarity as a result of chronic glucose increases (Dheen et al., 1994). These cells contain mechanosensitive voltage-gated sodium channels that detect changes in extracellular osmolarity. The continuation of the hyperosmolar state causes "up-regulation" of sodium channels and a decrease in the threshold value for the generation of the action potential with the increase in the number of sodium channels. Encephalopathy, which manifests itself with cognitive and behavioral disorders, may occur as one of the late complications of diabetes. The incidence of progressive dementia due to chronic hyperglycemia in people with diabetes is also high (Grober et al.,2011). Increased free radical production, vasogenic edema, decrease in cerebral blood flow as a result of short-term or long-term hyperglycemia, as well as changes in gene expression in central nervous system cells cause neuronal and endothelial damage. In fact, hyperglycemic states that reach behavioral disorders in animals were also observed when fructose was given, and in the brain tissue analyzes performed, insulin, adiponectin and resistin levels were found to be high in hiperglycemic group (de Moura et al., 2008). According to our results, metabolic syndrome occurred in rat given fructose for about 2 months significant biochemical changes were observed in high fructose group.

During fructose metabolism, pyruvate production is faster because the phosphofructokinase step, which is one of the rate-limiting enzymes in glucose metabolism, is skipped. The pyruvate formed is converted into triglycerides in the liver rather than energy production by the Kreps cycle. Therefore, increased fatty acid synthesis can increase circulating fatty acids and stored fat. This may lead to lipotoxicity, which reduces the insulin sensitivity of cells due to the production of fatty acids in tissues other than adipose tissue (Neilson, 2007). In this study, while insulin levels in the brain tissue were 1.98 μg/g tissue in the control group, it was measured as 2.54 μg/g tissue in fructose rats. In the group given fructose+EPO, this value decreased to 2.12 μg/g tissue, showing the positive effect of EPO.

The presence of increased levels of glucose in the brain due to high fructose nutrition or different reasons has been reported in humans and different experimental animals (Dorn et al., 1983). Insulin can cross the ENT, CSF levels of mice increased slightly after peripheral infusions of this hormone, suggesting that insulin probably crosses the ENT via a saturable transport system. The system of transport of insulin from the blood to the brain is affected by certain factors such as glucocorticoids or in various pathophysiological conditions such as hunger and obesity, during aging as well as hibernation. It can be regulated in individuals with diabetes mellitus (Blázquez et al., 2014). As a result of post-mortem biochemical brain analyzes, the presence of C-peptide and immunoreactive insulin was detected in cadaver brain tissue (Young, 1986). These substances were detected in the highest amount in the hypothalamus, while their brain levels were much higher than in the blood. Based on these findings, it can be argued that the insulin detected here is a component of the brain itself. Because, as a result of studies at the molecular level, the presence of insulin mRNA was found in the CA1 and CA3 regions of the hippocampus, the dentate gyrus, and the granule cell layer of the olfactory organ (Devaskar et al., 1994). Hyperglycemia and subsequently increased insulin level were detected in the brain tissue. It is worth repeating that, with the effect of lowering blood glucose and insulin levels (Mert et al., 2022), EPO has a positive effect on glycemia and a lowering effect on brain insulin level was observed (Table 1). The reversal of the increase in blood glucose, that is, proving the hypoglycemic effect of EPO, by administering evening primrose oil to streptozotocin-induced diabetic rats in previous years, was also shown in this study when high fructose was administered and EPO supplementation was made, the results are consistent with those of the studies known in the literature (Söğütlü et al., 2019). In the presented study the levels of insulin were increased in

fructose group, addition of EPO slightly decreased the insulin amount but statistical importance were not observed between the research groups.

Adiponectin, an endocrine substance synthesized and released from adipose tissue (Yamauchi et al., 2001), has an important role in the regulation of carbohydrate and fat metabolism in insulin-sensitive tissues. While it reduces glycogenesis in the liver, it increases the oxidation of fatty acids and glucose uptake in muscle tissue (Fruebis et al.,2001). Adiponectin is anti-diabetic, antiatherogenic and anti-inflammatory. Since they have a role in (Al-Rashed et al., 2016; Kamari et al., 2007) deficiency, some metabolic disorders and subsequent diseases develop. In addition, these theoretically mentioned issues have been proven clinically in different studies (Arita et al., 1999) Experimentally, biochemical analyzes performed on the metabolic syndrome created at the end of high fructose nutrition yielded similar results to our study. In the aforementioned studies, it was reported that adiponectin level decreased (Kamari et al., 2007; Shokouh et al., 2017), insulin level and insulin resistance increased (Tran et al., 2009; Zhou et al., 2013). Hyperinsulinemia was shown to decrease circulating adiponectin levels (Yu et al., 2002). In this study, adiponectin levels were found to be significantly decreased in rats fed high fructose compared to controls. It is observed that the level of adiponectin increases significantly with the application of EPO, and the level of insulin decreases with the application of EPO (Table 1). Our findings is consistent with the findings Zhou et al. (2013).

Adiponectin is a hormonal regulator that facilitates the transition of free fatty acids from circulation to fat cells. In cases where the storage capacity of the adipose tissue decreases, such as obesity, and/or, in cases where the existing energy resources, such as increased energy requirement in the periphery, such as acute inflammation, are desired to be transferred to the peripheral tissue instead of being stored in the adipose tissue, the serum level is down-regulated and decreases (Fu and Luo, 2005)

Coronary artery disease (CAD) is an important complication frequently encountered in diabetic patients. While plasma adiponectin levels were found to be lower in individuals with CAD than in diabetic patients without CAD, these results show that adiponectin may have antiatherogenic properties. In addition, low adiponectin levels have been associated with atherogenic lipid profile in clinical studies. It is reported that adiponectin has a role in increasing the tyrosine phosphorylation of the insulin receptor, which is known to contribute to the increase of insulin sensitivity. Thus, a series of biochemical processes follow each other that will contribute positively to the regulation of the lipid profile in the liver. These are metabolic phenomena such as decreased free fatty acid mobilization and increased fatty acid oxidation, decreased hepatic glucose output and very low density lipoproten (VLDL) triglyceride synthesis (Chandran and Phillips, 2003)

Adiponectin is a plasma protein of 30 kDa with a molecular weight of 247 amino acids synthesized from adipose tissue. This cytokine is a collagen-like protein within the soluble collagen superfamily (Scherer et al., 1995; Kishore and Reid, 2000) As previously explained, adiponectin has prominent anti-inflammatory and antiatherogenic effects, especially in macrophages and endothelial cells. Again, it can be said by looking at the data that this substance plays a protective role in the pathological events that occur at the beginning of the disorder in the formation of atherosclerosis and vascular damage models, and the disorders are shaped in decreasing amounts.

Fu and Luo (2005) reported that low plasma adiponectin levels are associated with the development of obesity, insulin resistance, and cardiovascular disease. They suggested the existence of a peroxisome proliferator–activated receptor γ (PPAR-γ)-mediated mechanism on the observed changes. Other researchers have reported that some seed oils in the diet have the ability to activate PPAR-ɣ, resulting in adiposity, decrease in leptin, and increase in adiponectin (McFarlin, 2009).

Abo-Gresha et al. (2014) administered evening primrose oil to rats suffering from hypercholesterolemic myocardial infarction for 6 weeks in order to examine the antithrombotic, anti-inflammatory and cholesterol-lowering effects of EPO. Based on the findings, they found that EPO had a direct hypocholesterolemic effect and caused cardiac recovery through its indirect effect on the synthesis of eicosanoids.

Metabolic syndrome, which occurs experimentally or with diseases in animals and humans, is closely related to oxidative stress. Nikotinamid adenin dinükleotit fosfat hidrojen (NADPH) oxidase and possibly adipocyte mitochondria are the main source of reactive oxygene species (ROS) in experimental metabolic syndrome, and it has been proven that oxidative stress stimulates insulin

resistance in adipocytes. It has been determined that the decrease in adiponectin production in adipocytes is caused by oxidative stress, and obesity, which is shaped by malnutrition and some hormonal disorders, has also been shown to trigger oxidative stress. Oxidative stress is not only a consequence of the metabolic syndrome, its role is an important factor and essential link in the pathogenesis of the metabolic syndrome (Tran et al., 2009; Maslov et al., 2018). As a result of the detection of oxidative stress in fructose fed rats, feeding with a high fructose diet was associated with increased oxidative stress and the development of insulin resistance (Bloch-Damti and Bashan, 2005; Delbosc et al., 2005), when these rats were treated with antioxidants, ROS production was found to decrease and insulin resistance was inhibited (Song et al., 2005). Increased reactive oxygen species and increased uric acid levels have been reported to contribute to fructose-induced hypertension (Tran et al., 2009).

A new hormone called resistin (insulin resistance), which has been linked to obesity and type 2 diabetes, was first found in mice and later in humans (Berger, 2001). Following resistin's first identification in 2001, several important discoveries were reported (Stephan et al., 2001). Among these, plasma resistin levels can be stimulated by diet. Presence of induced and genetic forms in obese mouse models; increased insulin sensitivity by administration of anti-resistin antibody in obese or insulin-resistant animals; New findings include treating healthy mice with impaired glucose tolerance and insulin action with recombinant resistin and that resistin administration impairs insulin-induced glucose uptake in adipocytes. From these observations, it was concluded that resistin plays an important role in insulin resistance and obesity in the diabetic mouse model. Determining the usability of the findings in human studies has also been difficult. While resistin is secreted from white adipose tissue in mice, it has been reported that it is synthesized from circulating blood monocytes and to a lesser extent from white adipose tissue in humans (Savage et al., 2001). In many studies conducted in humans to date, it has been reported that there is a positive correlation between elevated serum resistin level and obesity, insulin resistance and obesity. First, resistin has been reported to be expressed in human hepatocytes and induce insulin resistance (Sheng et al., 2008). Furthermore, human resistin mRNA levels were found to be higher in peripheral blood mononuclear cells compared with female patients with type 2 diabetes (DM2) and healthy women, suggesting a role for resistin in the pathogenesis of human DM2. In some rodent models, resistin mRNA expression in adipose tissue of obese animals has been shown to be uncorrelated with serum resistin levels that do not correlate with serum insulin or glucose.It has been reported that both increases and does not change (Lee et al., 2003). In this study, resistin levels elevated in the fructose group decreased slightly when EPO was given to rats in the fructose group. Statistical significance was observed between the fructose group compared to the others.

CONCLUSION

Metabolic syndrome is characterized by hypertension, dyslipidemia and insulin resistance, an important risk factor for cardiovascular disorders and type 2 diabetes, has been established experimentally. The examined parameters were selected from substances that undergo significant changes in metabolic disorders. It has been suggested that the administration of fructose begins to increase in a way that leads to the formation of insulin resistance by increasing the level of insulin, that the decrease in the level of adiponectin is an important parameter in the development of obesity and insulin resistance, and that the resistin level may also be a triggering factor for diabetes and obesity-related metabolic disorders. In support of this information, insulin and resistin levels were found to increase in brain tissue in this study, and levels decreased with EPO administration. On the contrary, the level of adiponectin decreased in fructose-treated rats, while the administration of EPO increased the level of adiponectin in brain tissue. Fructose-induced impaired metabolic changes in brain tissue were partially ameliorated when EPO was administered. Accordingly, the use of EPO in the medical setting may be recommended by clinicians to reduce the harmful effects on the brain, since metabolic changes in the brains of mice fed with high fructose content can also occur with the intake of fructose from various foods in humans.

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ACKNOWLEDGMENTS

Author contributions: NG, HM and NM designed the study. SÇ and LM performed analysis. HM, NG, NM, SÇ participated in drafting and revising the manuscript

Financial Disclosure: The authors declared that this study has received no financial support.

Conflict of Interests: The authors declared that there is no conflict of interests.

Additional information: All authors have read and agreed to the published version of the manuscript Correspondence and requests for materials should be addressed to NG.

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