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ORIGINAL ARTICLE

Increased Serum Kynurenine/Tryptophan Ratio in Rats Fed Added Sugar

İlave Şekerlerle Beslenen Ratlarda Artmış Serum Kinürenin/Triptofan Oranı

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ABSTRACT

Aim: The consumption of added sugars containing fructose has increased dramatically. Various studies have revealed that added sugar consumption may be involved in the pathogenesis of cardiovascular, metabolic, and neurocognitive disorders by triggering subclinical inflammation. The imbalance in the kynurenine pathway metabolites may be associated with inflammation and oxidative stress. This study aims to investigate the effect of high-fructose corn syrup-55 (HFCS-55), invert sugar and sucrose intervention on the kynurenine pathway metabolite levels (tryptophan, kynurenine, 3-hydroxykynurenine, 3-hydroxyanthranilic acid, quinolinic acid, and kynurenic acid) in Wistar rats.
Material and Methods: Twenty-four Wistar male rats (8-12 weeks old, weighing 300-350 g) were included in the study. After one week of conditioning, the animals were randomly divided into four groups: chow diet and tap water (control, n = 6), chow diet and tap water including 10% HFCS-55 (55% sucrose, 45% glucose), chow diet and tap water including 10% sucrose, chow diet and tap water including 10% invert sugar (33% sucrose, 66% glucose and fructose). At the end of the 3-month experimental period, serum kynurenine metabolites levels were measured by tandem mass spectrometry.
Results: Serum kynurenine levels and kynurenine/tryptophan ratio were significantly higher ($p<0.05$) and serum kynurenic acid levels were significantly lower ($p<0.05$) in rats fed with HFCS, sucrose and invert sugar compared to the control group.
Conclusion: Our findings suggest that consumption of added sugar may lead to an imbalance in the kynurenine pathway metabolites. The altered kynurenine metabolism may trigger inflammation and oxidative damage, and may predispose to chronic diseases.

Keywords: Tryptophan; kynurenine; HFCS; sucrose; inflammation.

ÖZ

Amaç: Fruktoz içeren ilave şekerlerin tüketimi önemli ölçüde artmıştır. Çeşitli çalışmalar, ilave şeker tüketiminin subklinik inflamasyonu tetikleyerek kardiyovasküler, metabolik ve nörobilişsel bozuklukların patogenezinde rol oynayabileceğini ortaya koymuştur. Kinürenin yolağı metabolitlerindeki dengesizlik, inflamasyon ve oksidatif stres ile ilişkili olabilir. Bu çalışmanın amacı, Wistar ratlarda yüksek fruktozlu mısır şurubu-55 (YFMŞ-55), invert şeker ve sukroz müdahalesinin kinurenin yolağı metabolit seviyeleri (triptofan, kinürenin, 3-hidroksikinürenin, 3-hidroksiantranilik asit, quinolinik asit ve kinürenik asit) üzerindeki etkisini araştırmaktır.
Gereç ve Yöntem: Yirmi dört Wistar erkek rat (8-12 haftalık, 300-350 g ağırlığında) çalışmaya dahil edildi. Bir haftalık koşullandırmadan sonra, hayvanlar rastgele dört gruba ayrıldı: normal besin ve musluk suyu (kontrol, n = 6), normal besin ve %10 HFCS-55 (%55 sakaroz, %45 glikoz) içeren musluk suyu, normal besin ve %10 sakaroz içeren musluk suyu, normal besin ve %10 invert şeker içeren musluk suyu (%33 sakaroz, %66 glikoz ve fruktoz). 3 aylık deney süresinin sonunda, tandem kütle spektrometrisi ile serum kinurenin seviyeleri ölçüldü.
Bulgular: Kontrol grubuna göre HFCS, sakkaroz ve invert şeker ile beslenen ratlarda serum kinurenin düzeyleri ve kinurenin/triptofan oranı anlamlı olarak daha yüksek ($p<0.05$) ve serum kinurenik asit düzeyleri anlamlı olarak daha düşük ($p<0.05$) bulundu.
Sonuç: Bulgularımız, ilave şeker tüketiminin kinurenin yolu metabolitlerinde bir dengesizliğe yol açabileceğini düşündürmektedir. Değişen kinurenin metabolizması, inflamasyonu ve oksidatif hasarı tetikleyebilir ve kronik hastalıklara zemin hazırlayabilir.

Anahtar Kelimeler: Triptofan; kinürenin; HFCS; sakkaroz; iltihap

Introduction

Intake of added sugars such as sucrose, invert sugar, and high-fructose corn syrup (HFCS) has increased dramatically in the last century. A growing body of evidence suggests that consumption of added sugars might have adverse health effects (1). Fructose is the main component of added sugars. Fructose metabolism is distinct from other sugars in that it causes a decrease in intracellular ATP levels, nucleotide turnover, and stimulation in uric acid production (2). This biochemical pathway is associated with mitochondrial oxidative stress leading to the blockade of fatty acid oxidation and stimulation in lipogenesis and gluconeogenesis (3).

The main added sugars in the human diet are HFCS and sucrose. HFCS forms are classified according to their fructose content as HFCS-55 (55% fructose and 45% glucose), HFCS-42 (42% fructose and 58% glucose) and HFCS-90 (90% fructose and 10% glucose) (4, 5). Invert sugar is another of the most used sweeteners by the industries in sugary foods and beverages. It is obtained by acid or enzymatic hydrolysis of sucrose and glucose, fructose and sucrose content varies depending on the degree of hydrolysis (6). Intake of added sugar is related to many diseases such as diabetes, obesity, cardiovascular diseases, liver diseases, cancer, cognitive disorders, and rodent models have characterized

various aspects of the resulting disease phenotypes (7). Chronic, low-grade inflammation is a key factor in the pathogenesis of these chronic diseases (8-10). Therefore, identifying modifiable risk factors that can reduce chronic inflammation is essential to prevent chronic diseases. According to observational studies, added sugar consumption may stimulate subclinical inflammation. At the center of the potential related mechanisms is that added sugar consumption increases de novo free fatty acid synthesis in the liver and these fatty acids trigger the production of reactive oxygen species, oxidative stress, and inflammatory processes (11). However, there is controversy and confusion regarding the metabolism and health effects of fructose, sucrose, and HFCS, and further studies are needed (12).

Recently, an increasing number of studies have demonstrated the relationship of the kynurenine pathway with inflammation, immune system activation, and neurodegeneration. It is the primary metabolic route of tryptophan and is responsible for approximately 99% of tryptophan catabolism, which is not used for protein synthesis (13). The metabolism of tryptophan via the kynurenine pathway is initiated by the enzymes tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO1 and IDO2) (14). IDO1 plays a minor role in tryptophan catabolism under physiological conditions, while the IDO1-dependent metabolism is strongly stimulated by interferons and other cytokines in inflammatory conditions (15). Kynurenine pathway has two main branches. Under physiological conditions, kynurenine is preferably converted into 3-hydroxykynurenine, 3-hydroxyanthranilic acid, quinolinic acid, and NAD+, these reactions are catalyzed by the enzymes kynurenine 3-monooxygenase (KMO), kynureninase (KYNU), 3-hydroxyanthranilic acid dioxygenase (3HAO) and quinolinate phosphoribosyl transferase (QPRT), respectively. The remaining kynurenine is converted to kynurenic acid by the kynurenine amino transferases (KATs) (16). Inflammation leads to alterations in the balance of the kynurenine pathway metabolites (15). It has been shown that imbalances in the kynurenine pathway may be involved in the pathogenesis of many diseases or disorders such as Alzheimer's, multiple sclerosis, amyotrophic lateral sclerosis, schizophrenia, bipolar disorder, depression, cancer, diabetes, cardiovascular diseases, rheumatoid arthritis (17-19).

In summary, although the consumption of added sugar is thought to be a risk factor for various chronic diseases through oxidative stress and inflammation-mediated mechanisms, there are conflicting findings on this subject, and more studies are needed. Therefore, in our study, we aimed to contribute to the elucidation of the effects of added sugar consumption on health by measuring the metabolites of the kynurenine pathway (tryptophan, kynurenine, 3-hydroxykynurenine, 3-hydroxyanthranilic acid, quinolinic acid, and kynurenic acid), which are markers associated with inflammation and oxidative stress, in Wistar rats administered added sugar.

Material and methods

Animals

Wistar Albino male rats, 8-12 weeks old (n = 24), weighting 300-350 g, were housed in their cages at constant temperature (24 ± 2 ° C), humidity (60%), 12-hour light / dark cycle and with free access to food and water. During the study, rats were housed in polycarbonate thermoregulated cages with 6 rats per cage in the Animal House of Selcuk University Experimental Medicine Research and Application Center (SUDAM), Konya, Turkey. After one week of conditioning, the animals were randomly divided into four groups: chow diet (Bil Yem, Turkey) and tap water (control, n = 6), chow diet (Bil Yem, Turkey) and tap water including 10% HFCS-55 (Cargill, U.S.A., 55% sucrose, 45% glucose), chow diet (Bil Yem, Turkey) and tap water including 10% sucrose (Konya Seker, Turkey, 50% sucrose, 50% glucose), chow diet (Bil Yem, Turkey) and tap water including 10% invert sugar (Torku, Turkey, 33% sucrose, 66% glucose and fructose). Ethical approval was obtained from Selcuk University Local Ethics Committee. The solid and liquid diet compositions are detailed in Table 1.

Table 1. Composition of the solid and liquid diets administered during the study to the different groups.

	Basal Diets	Sugar Solutions		
Composition	Chow diet	10% HFCS-55 Solution	10% Sucrose Solution	10% Invert Sugar Solution
Carbohydrate, %	62	10	10	10
of which sugars, %	-	10	10	10
Protein, %	23	-	-	-
Fat, %	4	-	-	-
Fiber, %	7	-	-	-
Minerals, %	5	-	-	-
Moisture, %	12	90	90	90

At the end of the 3-month experimental period, the rats have fasted for 12 hours and then the animals were anesthetized by intraperitoneal injection of ketamine (87 mg/kg) and xylazine (13 mg / kg), and body weights were recorded.

Sample Collection

Approximately 1 mL blood sample was taken into the serum separator gel tubes from the tail vein of Wistar rats between 8.00 and 10.00 AM. The blood samples in serum separator gel tubes were centrifuged at 2000 x g for 10 min and the serum samples were separated, portioned into eppendorf tubes, and stored at -80° C until analysis.

Tandem Mass Spectrometric Analysis

Chemicals

L-Tryptophan (CAS Number: 73-22-3), L-kynurenine (CAS Number 2922-83-0), Kynurenic acid (CAS Number 492-27-3), 3-Hydroxyanthranilic acid (CAS Number 548-93-6), 3-Hydroxy-DL-kynurenine (CAS Number 484-78-6), Quinolinic acid (CAS Number 89-00-9), HPLC grade water (CAS Number: 7732-18-5), acetonitrile (CAS Number 75-05-8), formic acid (CAS Number: 64-18-6) and L-Kynurenine- d4 Trifluoroacetic Acid Salt (Catalog No: K661007) were obtained from Sigma Aldrich and Toronto Research Chemicals (North York, ON, Canada), respectively.

Instrumentation

Chromatographic separation was performed using a Shimadzu HPLC system (Kyoto, Japan) and Phenomenex C18 HPLC column (50 mm x 4.6 mm). API 3200 triple quadrupole mass spectrometer equipped with an electrospray ionization interface was used (Applied Biosystems/MDS Sciex) as the detector. The mobile phase A and B consisted of 0.1% formic acid/water (v/v%) and 0.1% formic acid/acetonitrile (v/v%), respectively. The total run time was 5 minutes. The Q1 to Q3 ion transitions were 205.2/146.2, 209.1/94.1, 190.2/144.0, 154.0/136.0, 225.1/110.0, 168.0/124.0, and 213.1/140.1 for tryptophan, kynurenine, kynurenic acid, 3-hydroxyanthranilic acid, 3-hydroxykynurenine, quinolinic acid, and kynurenine-d4, respectively. Ionspray voltage, source temperature, curtain, ion source (GS1), and ion source (GS2) gas values were adjusted to 5000 V, 350 °C, 20, 50, 50 psi, respectively. Intra and inter-assay CV% values were lower than 7% and recovery values were higher than 96% for all metabolites.

Sample Preparation

Serum tryptophan, kynurenine, kynurenic acid, 3-hydroxyanthranilic acid, 3-hydroxykynurenine, and quinolinic acid concentrations were measured with the modification of the method developed by Tong et al (20). Briefly; 300 µL of serum sample was taken into eppendorf tubes and 100 µL of kynurenine-d4 was added. To precipitate proteins, the mixture was vortexed with 1000 µL acetonitrile containing 1% formic acid (v/v%) for 30 seconds and centrifuged at 15000 rpm for 10 minutes. The supernatants were evaporated under nitrogen gas at 40°C. The residues were dissolved in 200 µL acetonitrile containing 0.1% formic acid: water (25:75, v/v%) mixture. 30 µL was injected into LC-MS/MS system.

Statistical Analysis

Statistical analysis was performed with SPSS statistical software package version 21.0. Shapiro-Wilk test was performed to find out the distribution. One-way ANOVA analysis (post-hoc analysis with LSD or Games-Howell) was performed to compare more than two groups. $p<0.05$ was considered as statistically significant.

Results

The initial weights of the HFCS, sucrose, invert sugar, and control groups were 374.66±20.15, 381.83±19.47, 376.66±17.90, and 381.50±14.81 g, respectively, and there was no statistically significant difference between the groups (p = 0.875). After the 3-month added sugar intervention, weights of the HFCS, sucrose, invert sugar, and control groups were 539.10±54.19, 540.66±50.68, 517.33±66.82 and 490.83±40.93 g, respectively, and there was no statistically significant difference between the groups (p = 0.365).

Serum kynurenine levels and kynurenine/tryptophan ratio were significantly higher ($p<0.05$) and serum kynurenic acid levels were significantly lower ($p<0.05$) in rats fed with HFCS, sucrose, and invert sugar compared to the control group. Serum quinolinic acid ($p<0.001$), 3-hydroxyanthranilic acid (p=0.025), and 3-hydroxykynurenine (p=0.022) levels in rats fed with HFCS were significantly higher than the control group. Moreover, serum 3-hydroxykynurenine (p=0.042), quinolinic acid (p=0.034), and kynurenine/tryptophan ratio (p=0.023) were significantly higher in rats fed with HFCS compared to the invert sugar group (Table 2 and Figure 1).

Table 2. Kynurenine pathway metabolite levels of rats fed added sugars.

	HFCS	Sucrose	Invert sugar	Control	p
					a:0.064
Tryptophan (ng/mL)	15860±932	13160±725	14985±760	15349±854	b:0.128
					c:0.795
					a:0.007
Kynurenine (ng/mL)	372.34±93.52	264.92±22.90	260.42±35.44	161.64±64.95	**b:0.037**
					c:0.047
					a:<0.001
Kynurenine/Tryptophan	0.0233±0.0045**	0.0206±0.0042	0.0174±0.0041	0.0106±0.0035	**b:<0.001**
					c:0.010
					a:0.022
3-hydroxykynurenine (ng/mL)	11.99±4.35**	9.57±6.09	6.38±2.34	5.58±2.32	b:0.138
					c:0.758
					a:0.025
3-hydroxyanthranilic acid (ng/mL)	62.95±19.95	45.39±11.41	55.81±15.10	41.76±12.55	b:0.682
					c:0.123
					a:<0.001
Quinolinic acid (ng/mL)	6.63±0.70**	6.20±1.18	4.17±0.91	2.67±0.81	b:0.288
					c:0.256
					a:0.019
Kynurenic acid (ng/mL)	84.98±8.18	92.86±10.77	96.13±11.46	142.26±30.43	**b:0.034**
					c:0.048

a: HFCS vs control, b: Sucrose vs control, c: Invert vs control, **: statistically significant difference between HFCS and invert sugar groups.

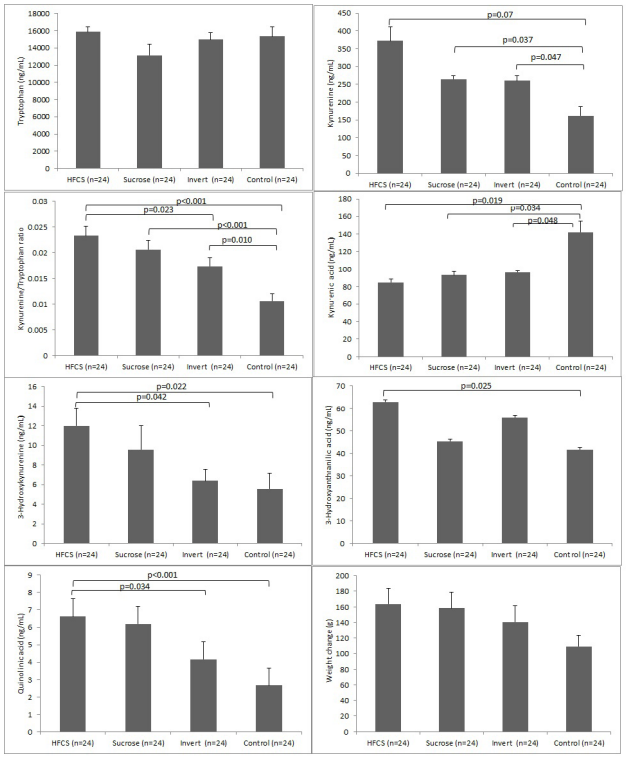

Figure 1. The change of tryptophan-kynurenine pathway metabolite levels and weight in rats fed with added sugars.

Discussion

The health effects of added sugars have become one of the most debated topics in all nutrition. Overconsumption of added sugars has been associated with an increased risk of diabetes, obesity, cardiovascular disease, dyslipidemia, liver disease, cognitive decline, and even cancer (7). However, data to support these claims have been consistently challenged and many contradictory studies have been shown (21-24). Chronic, low-grade inflammation plays a key role in the pathogenesis of all these diseases. According to observational studies, dietary added sugar intake may induce subclinical inflammation (11).

Aeberli et al. investigated the effects of sugar-sweetened beverages (SSBs) consumed in small to medium amounts for 3 weeks in twenty-nine healthy young men subjects (age: 20–50 years, BMI: 19–25 kg/m2). Six 3-week interventions were designed in random order as follows: 600 mL SSBs containing 1) 40 g fructose / d [medium fructose (MF)], 2) 80 g fructose / d [high fructose (HF)], 3) 40 g glucose / d [medium glucose (MG)], 4) 80 g glucose / d [high glucose (HG)], 5) 80 g sucrose / d [high sucrose (HS)], or 6) dietary advice to consume low fructose. As a result of the study, it was shown that high-sensitivity C-reactive protein (hs-CRP) levels increased significantly after all interventions (60-109%, $p < 0.05$) (25). Jin et al conducted 4-week double-blind, randomized controlled intervention study with 24 overweight Hispanic-American adolescents (hepatic fat> 8%, age 11–18 years, BMI> 85th percentile). Intervention groups were as follows: fructose-sweetened beverage (n = 11) (99 g / day) and glucose-sweetened beverage (n = 13) (99 g / day). As a result of the study, a statistically significant change was observed between the hs-CRP levels among the groups ($p = 0.019$). After the 4-week intervention, subjects receiving glucose drinks showed significant improvement in plasma hs-CRP levels, adipose insulin sensitivity, and LDL oxidation (26).

A randomized, single-blind study involving healthy subjects (n = 14) was conducted by Jameel et al. after an overnight fast, participants were given one of 3 different isocaloric drinks containing 50 g of fructose or glucose or sucrose dissolved water. 30, 6, and 120 minutes after the intervention, blood samples of the participants were collected and their plasma lipid, insulin, and hs-CRP levels were measured. The changes in plasma cholesterol, LDL, and HDL levels (expressed as area under curve, AUC) were found higher in fructose-consuming participants than others. The change in hs-CRP levels was higher in participants consuming fructose than those consuming glucose ($p<0.05$), while no statistically significant difference was found with the sucrose group ($p=0.07$) (27).

However, studies are showing that there is no significant difference in the levels of inflammation markers such as hs-CRP, interleukin-6, and TNF-a in the fructose and glucose intervention groups (28-31).

Increased inflammatory signals induce IDO-1 activity, leading to an imbalance in the kynurenine pathway metabolite levels (32). For example, in a study conducted with rheumatoid arthritis patients, it was reported that serum tryptophan, 3-hydroxykynurenine, and 3-hydroxyanthranilic acid levels decreased while kynurenine, kynurenic acid, and xanthurenic acid concentrations were increased compared to healthy controls (19). Our findings show that serum kynurenine levels and kynurenine/tryptophan ratio were significantly higher in rats fed with HFCS, sucrose, and invert sugar compared to the control group, and the levels of kynurenic acid were significantly lower. Moreover, serum quinolinic acid, 3-hydroxyanthranilic acid, and 3-hydroxykynurenine levels of rats fed with HFCS were significantly higher than the control group. Our findings suggested that the balance between kynurenine pathway metabolite levels was disturbed in rats consuming added sugar and this may be associated with increased inflammation or oxidative stress.

This study indicates that the consumption of added sugar, especially HFCS, may trigger chronic diseases by triggering metabolic events related to inflammatory response and oxidant-antioxidant balance in the organism. Since the consumption of added sugar is a preventable risk factor, studies that reveal the effects of added sugar consumption on health are clinically very important. However, the lack of measurements

of other parameters related to inflammation and oxidant-antioxidant balance, and the limited number of experimental animals are the main limitations of the study.

Conclusions

To our best knowledge, this is the first study to comprehensively investigate the kynurenine pathway metabolite (tryptophan, kynurenine, 3-hydroxykynurenine, 3-hydroxyanthranilic acid, quinolinic acid, and kynurenic acid) levels in rats fed different added sugars (HFCS-55, invert sugar, sucrose). Our findings provide new evidence that the balance between kynurenine pathway metabolite levels is disrupted in rats consuming added sugar and that this may be a risk factor for cardiovascular diseases, neurocognitive disorders, and metabolic diseases through increased inflammation or oxidative stress. Dietary habits are one of the most easily modifiable risk factors. Given the dramatic increase in added sugar intake and potential adverse health effects, it is essential to identify the biochemical and pathological pathways involved in added sugar consumption, and further studies are needed.

Conflict of Interest

The authors declare that they have no conflict of interest relevant to the content of this manuscript.

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