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High-fructose intake-induced dyslipidemia and oxidative stress accompanied by hippocampal dysfunctions in hypertensive but not hypertriacylglycerolemic rats

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Abstract. A high-fructose intake is metabolically analogous to a high-fat diet. The impact of high-fructose intake was investigated in spontaneously hypertensive (SHR) and hypertriacylglycerolemic (HTG) rats to find out the impact of which risk factor of metabolic syndrome – hypertension or hypertriacylglycerolemia – will cause more complications. Rats were fed a standard or a fructose diet (F60) with 60% of added fructose for 5 weeks. The F60 diet increased the total serum cholesterol content of both HTG-F60 and SHR-F60 rats. Further, in SHR-F60 it increased serum triacylglycerols, TBARS in the liver, a specific activity of NAGA in the kidney, aggravated glucose tolerance, deteriorated synaptic plasticity, and reduced somatic and dendritic responses in the hippocampus. SHR rats were more sensitive to the F60 diet, suggesting that hypertension along with a high-fructose intake result in a more pronounced disorder compared to hypertriacylglycerolemia. This work wants to draw attention to fructose-induced health risks associated with hypertension.

Key words: Fructose — Oxidative stress — Lipid profile — Hypertension — Synaptic plasticity

Introduction

Increased sugar consumption is seen as contributing to global obesity and diabetes mellitus type 2 epidemics, and is associated with cardiovascular and neurodegenerative risks. Due to the unique fructose metabolic properties, the fructose component of sucrose can be particularly harmful. Already in past, it has been found that high intakes of refined carbohydrates, particularly fructose, may increase the risk of insulin resistance (Tornheim and Lowenstein 1976). In developed countries, there has been a shift in the amount and source of sweeteners used over the several last decades. Before, fructose intake was between 16–20 g/day, mainly due to the consumption of fresh fruit. However, fructose consumption has increased to 60–150 g/day and comes mostly from sucrose (Park and Yetley 1993). The introduction of high-fructose corn syrup in the 1970s led to its accelerated consumption. Fructose is preferred because it is at least 1.5-times sweeter than sucrose and its production is inexpensive. As a result, it is widely used in the food industry (Bray et al. 2004).

Fructose metabolism occurs primarily in the gut, liver, and kidney, where specific fructolytic enzymes are expressed (Tappy 2021). In the gut, fructose is taken up and released by enterocytes mostly as fructose but it is also converted and released as glucose, lactate, and fatty acids (Pepin et al. 2019). In the liver, fructose is phosphorylated to fructose 1-phosphate (F1-P) by the enzyme fructokinase. Most of the F1-P is metabolized and converted by hepatocytes to glucose, which can be stored as glycogen or released into the bloodstream. Hepatocytes can also convert F1-P to lactate and fatty acids. Fatty acids accumulate in the liver, which in turn promotes the production and secretion of very low-density lipoproteins,

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leading to increased circulating triacylglycerol levels and dyslipidemia (Pepin et al. 2019). As fructose is metabolized in the liver to lipids and causes a large increase in plasma triacylglycerol concentrations, in many metabolic ways a high-fructose diet is analogous to a high-fat diet.

High-fructose diet rapidly induces the expression of all main features of the metabolic syndrome (Hannou et al. 2018). Metabolic syndrome was defined by a constellation of physiological, biochemical, clinical, and metabolic factors like insulin resistance, visceral adiposity, dyslipidemia, endothelial dysfunction, hypertension, genetic predisposition, and chronic stress, which directly increase the risk, especially of cardiovascular diseases (Cornier et al. 2008). Chronic inflammation is known to be associated with visceral obesity and insulin resistance which is characterized by the production of adipocytokines such as tumor necrosis factor-α, interleukin-1, interleukin-6, leptin, etc. They contribute to the development of pro-inflammatory status and chronic subclinical vascular inflammation, which modulates and leads to atherosclerotic processes. In patients with metabolic syndrome, hypertension was the most common component of the syndrome and was present in more than 80% (Grassi et al. 2007). On the contrary, a significant proportion of hypertensive patients currently meet the criteria for the diagnosis of metabolic syndrome, and these patients were shown to have more cardiovascular events than patients without metabolic syndrome (Verdecchia et al. 2021).

In this work, we aimed to the impact of a high-fructose intake on biochemical parameters (serum and tissue oxidative stress; serum dyslipidemia; inflammation), and functional parameters (neurotransmission and synaptic plasticity in the hippocampus; glucose tolerance; blood pressure and heart rate) in two rat strains: spontaneously hypertensive rats and hereditary hypertriacylglycerolemic rats, both considered suitable animal models for the study of metabolic syndrome-like conditions yet without obesity (Zicha et al. 2006; Kaprinay et al. 2016; Kwitek 2019). While spontaneously hypertensive rats have the blood pressure values about 180–200 mmHg and triacylglycerol levels about 0.4–0.5 mmol/l, hypertriacylglycerolemic rats have the blood pressure values about 130–140 mmHg and triacylglycerol levels about 2.5–3 mmol/l (our previous measurements). We wanted to find out which the main typical feature of these two rat strains (hypertension or hypertriacylglycerolemia) along with a high-fructose intake will be more harmful and riskier for health.

Table 1. Composition of a standard diet and a high-fructose diet with 60% of fructose

Component (g/kg of pellets)	Standard diet	High-fructose diet
Wheat	500	0
Barley	100	0
Oats	100	100
Wheat bran	40	40
Soy	60	60
Meat and bone meal	110	110
Vegetable oil	10	10
Supplementary mineral food	15	15
Natrium chloride	2	2
Methionine	1.25	1.25
Lysine	0.90	0.90
Lantern dryers	60	60
Fructose	0	600

Material and Methods

Animals and diet

The experiments conformed to the Guide for the Care and Use of Laboratory Animals and were approved by the State Veterinary and Food Administration of the Slovak Republic (decision number: 3853/18-221/3) and the Ethical Committee of the Centre of Experimental Medicine. Hypertriacylglycerolemic male rats (HTG, n = 28), and spontaneously hypertensive male rats (SHR, n = 28) (Breeding Station Dobra Voda, Slovak Republic, reg. no. SK CH 24016) were used at age of 14 weeks in the onset of the experiment. The rats of both strains were divided into two groups of 14 animals: a control group that received a standard diet, a complete rat and mouse feeding mixture (KKZ-P/M), and a second group that received a modified feeding mixture with added fructose of 60% (F60) with proportionally reduced cereal content of wheat and barley (Table 1) to receive a high-fructose diet of 14.57 kJ/g and a standard diet of 13.26 kJ/g nutritional values. Food and drinking water was *ad libitum* and their consumption was calculated by weighing and measuring the amount of total food (in grams) and total water (ml) given to the rats and subtracting the remaining food (in grams) and water (ml) in the cage every day. The animals had a light/dark light mode of 12 h/12 h. The experiment with a standard or a 60% fructose diet lasted 5 weeks according to Oron-Herman et al. (2003) who reported that complete metabolic syndrome was induced by such a protocol in rats, including hyperinsulinemia, hypertriglyceridemia, and hypertension. Rats were terminated at the 20th week of age, i.e. about 5 months.

Biochemical determination of interleukin-1 alpha (IL-1α)

Pro-inflammatory marker IL-1α was determined in the blood serum by a diagnostic method using an ELISA biochemical assay instrument (Invitrogen, Thermo Fisher Scientific). IL-1α was assessed from rat blood serum obtained from centrifuged blood samples collected at the end of the

experiment after the decapitation of the animals. The plate was washed two times with a wash buffer. Biotin conjugate was added to the sample, standard or blank according to the schedule. The microplates were incubated for 120 min at 18–25°C, stirring constantly. Fluids were removed, washed three times and streptavidin-horseradish peroxidase was added. After second incubation and washing three times, the tetramethylbenzidine substrate solution was added. The last incubation was without access to light and a stop solution was added. The absorbance of the resulting stained compound was measured immediately spectrophotometrically on the microplates (Labsystem Multiscan RC) at 450 nm.

Biochemical determination of thiobarbituric acid reactive substances (TBARS)

The thiobarbituric acid (TBA) test was used as an index for lipid peroxidation based on the reactivity of the final lipid peroxidation product malondialdehyde with TBA to form a red adduct (Garcia et al. 2005). The double heating method, according to Draper and Hadley (1990) was used to determine TBARS. The trichloroacetic acid solution was added to the blood serum or the cortical, kidney, or liver tissue homogenated into centrifuge tubes and then placed in a hot water bath. After 15 min, the mixture was cooled with water and centrifuged for 10 min at 3000 × *g* and 4°C. The supernatant was added to the TBA solution and placed in a hot water bath of 95°C for 15 min. Subsequently, the solution was cooled in water and its absorbance was measured on microplates using a spectrophotometer (Labsystem Multiscan RC, Canada) at 550 nm.

Biochemical determination of the specific activity of N-acetyl-β-D-glucosaminidase (NAGA)

Liver, kidney, brain cortex, and blood serum were frozen after their preparation at minus 80°C. On the day of the specific activity of NAGA determination, the samples were thawed and placed in an ice-cold phosphate buffer (PBS) having a pH of 7.4, containing Triton X-100 (0.1%), and subsequently homogenized with a homogenizer. The homogenate was centrifuged at 15,000 × *g* for 20 min at 4°C. The specific activity of NAGA was tested according to a standard method using 4-nitrophenol (Barrett and Heath 1977). The samples were measured on microplate spectrophotometrically at 420 nm (Labsystem Multiscan RC, Canada).

Glucose tolerance test (GTT)

All animals fasted for 14 hours before the scheduled GTT. The GTT was performed on seven experimental animals from each experimental group. The animals were administered 50% glucose solution intraperitoneally (i.p.) in a volume of 0.4 ml/100 g rat body weight. The rats were then placed in a stabilization chamber and bled from the tail vessel from which glucose levels were measured. Glucose was measured with a glucometer (Contour plus, Bayer, Germany) and the measuring papers before glucose administration (i.p.) and further in time 30, 60, 90, and 120 min after glucose solution administration.

Blood pressure measurement

Blood pressure was measured by non-invasive tail-cuff plethysmography (PowerLab 4/30, AD Instrument, USA) slightly modified (Lipták et al. 2017) on awake rats. Blood pressure was determined at the onset of an experiment before the diet started and after 5 week-lasting fructose or standard diet. Before the pressure measurement itself, the animals were warmed for 8–10 min using the infrared lamp to increase the body temperature and dilate the arteries. Systolic blood pressure and heart rate were determined as the average of five consecutive measurements.

Electrophysiological extracellular measurement of electrically evoked somatic and dendritic responses and synaptic plasticity at the CA3-CA1 synapse in rat hippocampal slices

At the end of the 5-week experiment, the animals were decapitated and their brains were dissected immediately and placed in the ice-cold artificial cerebrospinal solution saturated with 95% O_2 and 5% CO_2 at pH 7.4. Hippocampus was prepared and cut by the tissue slicer (McIllwain Tissue Chopper, Stoelting, USA) into 400-μm transverse sections. They were incubated for at least 90 min in the incubation chamber and measured later separately at the measuring chamber. The flow rate of the artificial cerebrospinal fluid (ACSF) into the measuring and incubation chambers was approximately 0.6 ml/min and the temperature of ACSF was maintained at 31–33°C. Electrophysiological measurement has been described previously (Gasparova et al. 2018). In brief, a bipolar stainless steel stimulating electrode was placed on the Schäffer collaterals at the CA3 area, and a glass registration electrode filled with ACSF was placed in the CA1 area of the pyramidal cells, on the *stratum pyramidale* to measure somatic response or on the *stratum radiatum* to measure dendritic response at the CA3-CA1 synapse. The synaptic plasticity was measured according to protocol with a high-frequency stimulation of a single train of 100 Hz with 1 s duration. Mean response during the 10-min stabilization period was normalized as 1. The electrically evoked responses were recorded and digitized using an AD/DA converter (DigiData 1322A, Molecular Devices, USA) with a sampling frequency of 10 kHz. Recorded data were stored and analyzed offline (AxoScope 10.2 and pClamp 10.2 software). The induction of long-term potentiation (LTP) as well as its maintenance was measured and compared in respective experimental groups.

Statistical analyses

Values are expressed as mean ± S.E.M. The statistical significance in values between experimental groups was analyzed using a one-way analysis of variance (ANOVA) and the Tukey-Kramer test was used as a *post-hoc* test. The values of $p < 0.05$ were considered to be significantly different.

Results

Impact of high-fructose intake on biometrical and basal parameters

Body weight of rats fed the F60 diet did not differ from body weight of relevant rat strain fed a standard diet (Fig. 1A). SHR-F60 group consumed less food at 1st and 5th week of the F60 diet compared to SHR rats fed a standard diet (Fig. 1B), and HTG-F60 rats from 1st to 4th week of the F60 diet drank significantly less water (Fig. 1C). There was no difference in the liver weight due to the F60 diet. However, kidney weight was reduced at SHR-F60 groups comparing relevant group fed a standard diet (Table 2).

Effect of fructose on serum lipid profile, inflammation, and serum and tissue oxidative stress

Biochemical and functional parameters tested are given at Table 2. Total cholesterol levels significantly increased in both HTG-F60 and SHR-F60 groups compared to their values before the onset of the diet. TAG levels increased significantly in SHR-F60 rats compared to their values before the diet. There was no significant change in the serum level of inflammatory marker IL-1α due to the F60 diet in

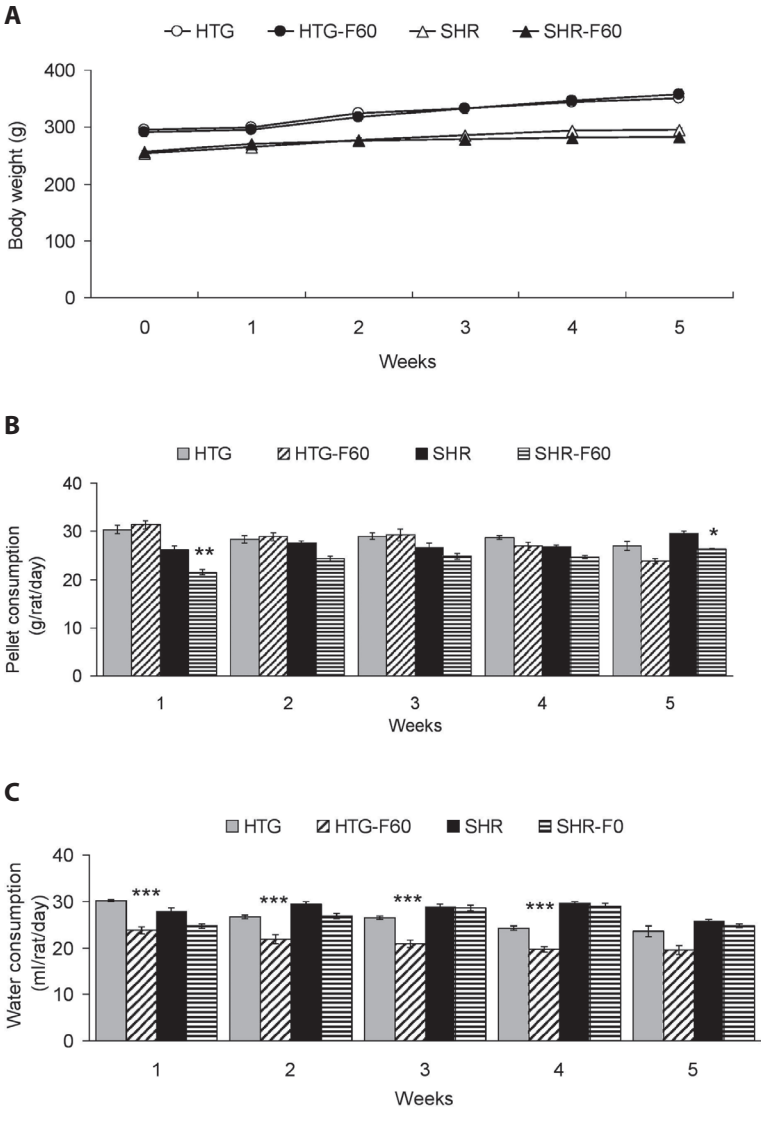

Figure 1. Body weight of rats (**A**), pellet consumption (**B**) and amount of drunk water (**C**). Rats were weighed once a week, pellet consumption and drunk water was measured every day. Values are means ± SEM, $n = 14$ rats/group. There was no difference in the body weight of rats fed a F60 diet comparing a relevant group of rats fed a standard diet. SHR-F60 group had reduced pellet consumption in a 1st (** $p < 0.01$) and 5th (* $p < 0.05$) week *versus* SHR rats. Amount of drunk water was reduced at HTG-F60 group from 1st to 4th week (*** $p < 0.001$) *versus* HTG rats. HTG, hypertriacylglycerolemic rats fed a standard diet; HTG-F60, hypertriacylglycerolemic rats fed a fructose diet with the 60% fructose content (F60); SHR, spontaneously hypertensive rats fed a standard diet; SHR-F60, spontaneously hypertensive rats fed a fructose diet with the 60% fructose content.

Table 2. Effect of a high-fructose diet on biochemical and function parameters, and biometric data

	HTG		HTG-F60		SHR		SHR-F60	
	Basal	End	Basal	End	Basal	End	Basal	End
Serum lipid profile								
Serum total cholesterol (mmol/l)	1.37 ± 0.05	1.38 ± 0.04	1.28 ± 0.04	1.52 ± 0.06*	0.94 ± 0.02	1.08 ± 0.02	1.01 ± 0.04	1.28 ± 0.02*
Serum TAG (mmol/l)	2.98 ± 0.15	2.44 ± 0.17	2.87 ± 0.14	3.41 ± 0.19	0.52 ± 0.03	0.40 ± 0.02	0.50 ± 0.03	0.67 ± 0.04*
Serum inflammation								
Serum interleukin-1α (pg/ml)	–	158.9 ± 15.6	–	215.7 ± 30.0	–	173.7 ± 11.6	–	197.8 ± 45.4
Serum oxidative stress								
Serum TBARS (nmol/mg prot.)	2.44 ± 0.05	2.78 ± 0.07	2.47 ± 0.07	2.80 ± 0.09	2.84 ± 0.05	2.98 ± 0.06	2.94 ± 0.05	2.84 ± 0.12
Serum NAGA (μg/mg prot.)	0.13 ± 0.003	0.13 ± 0.004	0.14 ± 0.005	0.12 ± 0.003	0.13 ± 0.004	0.15 ± 0.003	0.13 ± 0.005	0.14 ± 0.004
Tissue oxidative stress								
Liver TBARS (nmol/mg prot.)	–	2.83 ± 0.10	–	3.09 ± 0.19	–	2.65 ± 0.10	–	3.42 ± 0.18#
Kidney TBARS (nmol/mg prot.)	–	5.50 ± 0.20	–	6.30 ± 0.28	–	5.07 ± 0.13	–	4.77 ± 0.36
Cortex TBARS (nmol/mg prot.)	–	5.99 ± 0.34	–	6.00 ± 0.36	–	5.58 ± 0.22	–	5.90 ± 0.38
Liver NAGA (μg/mg prot.)	–	13.72 ± 0.29	–	14.22 ± 0.26	–	12.42 ± 0.37	–	11.36 ± 0.38
Kidney NAGA (μg/mg prot.)	–	45.21 ± 0.80	–	43.73 ± 1.12	–	37.18 ± 0.81	–	45.30 ± 1.51#
Cortex NAGA (μg/mg prot.)	–	11.46 ± 0.17	–	10.83 ± 0.22	–	10.31 ± 0.22	–	10.15 ± 0.16
Glycemia								
Blood glucose (mmol/l)	8.08 ± 0.55	7.99 ± 0.48	7.64 ± 0.44	7.86 ± 0.25	7.64 ± 0.22	7.24 ± 0.19	7.18 ± 0.13	6.74 ± 0.17
Cardiovascular functions								
Systolic blood pressure (mm Hg)	138.8 ± 1.3	140.8 ± 1.6	141.5 ± 1.8	143.2 ± 1.5	201.3 ± 2.0	222.0 ± 2.1*	201.9 ± 1.9	221.1 ± 2.7*
Heart rate (bpm)	321.9 ± 3.2	331.5 ± 4.4	317.1 ± 3.0	325.9 ± 5.4	447.6 ± 5.6	407.8 ± 4.6	427.3 ± 4.7	396.9 ± 4.4
Organ weights								
Liver (g)	–	11.1 ± 0.3	–	10.8 ± 0.4	–	10.5 ± 0.2	–	9.11 ± 0.2
Kidney (g)	–	1.91 ± 0.04	–	1.71 ± 0.03	–	2.18 ± 0.03	–	1.97 ± 0.03#

Values are means ± SEM, $n = 14$ rats/group. Statistical difference * $p < 0.05$ *vs.* basal value in the same group; statistical diference # $p < 0.05$ *vs.* value of relevant rat strain fed a standard diet. HTG, hypertriacylglycerolemic rats fed a standard diet; HTG-F60, hypertriacylglycerolemic rats fed a fructose diet with the 60% fructose content (F60); SHR, spontaneously hypertensive rats fed a standard diet; SHR-F60, spontaneously hypertensive rats fed a fructose diet with the 60% fructose content.

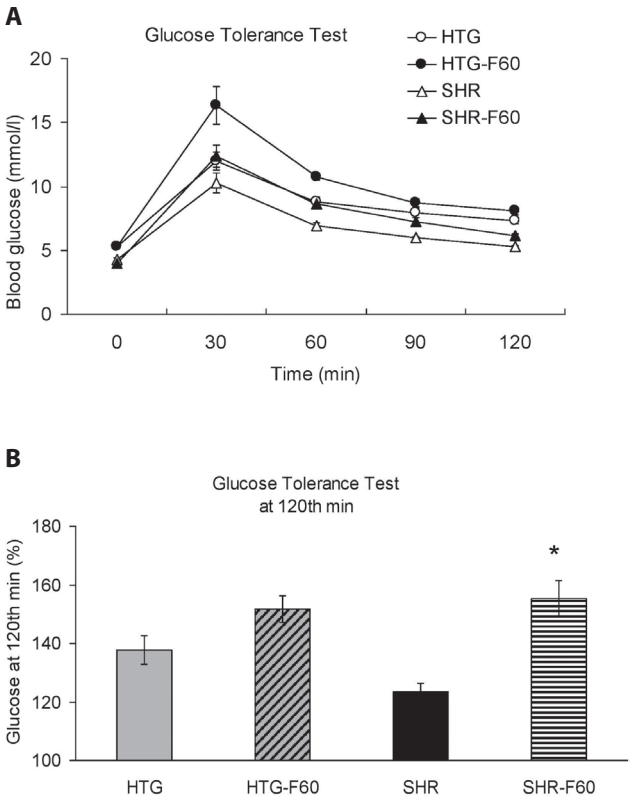

Figure 2. Glucose tolerance test (GTT). Glucose solution was administered to rats i.p.; $n = 7$ rats/group. Both groups fed a fructose diet had a trend to increased blood glucose values compared rats fed a standard diet from 30 to 120 min of GTT (**A**). Blood glucose values of SHR-F60 rats remained significantly increased (* $p < 0.05$) comparing to values of SHR rats at the end of GTT, where glucose level at the onset of GTT is expressed as 100% in each group (**B**). For abbreviations of groups, see Figure 1.

both rat strains. Oxidative stress in tissues (liver TBARS and kidney NAGA values), both at the SHR-F60 group, was significantly increased compared to the values of SHR group on a standard diet. Pre-prandial blood glucose level on the onset of the experiment compared to the end of 5-week-lasting experiment did not differ at any group tested regardless diet. Systolic blood pressure increased at the end of 5-week experiment in both SHR groups regardless the type of diet (Table 2).

Effect of fructose on glucose tolerance

Glucose tolerance test with blood glucose values from zero to 120th min are given in the Figure 2A. At 120th min of GTT, SHR-F60 rats had significantly increased blood glucose levels compared to their relevant group fed a standard diet (Fig. 2B), where 100% value represent glucose level at the onset of GTT in the each group.

Effect of fructose on neurotransmission and synaptic plasticity in the rat hippocampus

A significant effect of a high-fructose diet on the neurotransmission in the hippocampus was found in SHR-F60 rats (Fig. 3). Somatic responses (Fig. 3A–C) recorded at the *stratum pyramidale* and the dendritic responses (Fig. 3D–F) recorded at the *stratum radiatum* of the CA1 area were significantly reduced in the SHR-F60 group compared to SHR fed a standard diet. Further, the induction and maintenance of LTP was monitored (Fig. 4). While LTP induction was unaffected by fructose in both rat strains (Fig. 4A), impaired LTP maintenance was manifested during 40-min recordings in SHR-F60 rats compared to SHR fed a standard diet (Fig. 4B, D).

Discussion

There is a considerable amount of work in the literature dealing with the impact of excessive fructose intake. Data vary, and discrepancies may be due to different experimental conditions, composition, intensity and length of a diet, animal models, their age and different techniques. In our experiment, a 5-week-lasting high-fructose diet did not cause significant differences in the body weight of rats compared to groups with a standard diet. Similarly, it was reported during the first 8 weeks of a high-fructose diet where the body weight of fructose-fed male albino rats did not differ compared to controls (Abd El-Haleim et al. 2016), however, a difference was found at the end of the experiment on the 10–12 weeks. In mice, Tillman et al. (2014) observed a transient increase in the body weight of mice after a 60% fructose diet in the first weeks, and further from week 8 to 14, there was no statistical difference in body weight between control and fructose fed mice. A study on humans reported that a diet containing 1.5 g fructose/kg of body weight administered daily to healthy humans over 4 weeks did not cause any significant changes in body weight (Lê et al. 2006). It would be expected that animals on a high-fructose diet could drink much more water, however, in the present experimental conditions HTG-F60 rats from a week 1 to 4 drank significantly less water compared to their standard diet fed groups. Garcia-Arroyo et al. (2020) found that long-term water restriction and fructose administration had a synergistic devastating effect on renal impairment. Further, it was reported that high fructose intake can increase the risk of non-alcoholic fatty liver disease and increased fat is stored in liver cells (Roeb and Weiskirchen 2021). In our experiment, no change in liver weight due to a 60% fructose diet was found, but histological determination could reveal a possible increase in the liver fat. In this work, we focused on the biochemical and functional consequences due to exces-

sive fructose consumption, and the animals were subjected to several different tests and determinations.

The glucose tolerance test is used to determine a subject's ability to handle a glucose load. SHR-F60 rats showed a significant increase in glucose levels at 120th min compared to their respective standard diet fed group of which glucose levels remained less elevated after 2 h compared to their pre-glucose values. A study by Olatunja et al. (2013) reported that intake of a fructose diet containing 40% fructose for 6 weeks in female Wistar rats did not adversely affect glucose tolerance test. Discrepancies in the findings could indicate a possible strain and gender difference in glucose metabolism or may be related to slightly different dietary conditions. Studies on humans indicate that high fructose-sweetened beverages for 10 to 12 weeks increased blood glucose and fasting insulin (Stanhope et al. 2009), increased insulin resistance levels (Taskinen et al. 2017), and in a study with 80 g fructose/day for three weeks, fructose increased baseline endogenous glucose production in the liver (Aeberli et al. 2013), and may lead to decreased hepatic insulin sensitivity (Softic et al. 2020). In the present experiment, SHR-F60 nor HTG-F60 rats responded to high-fructose intake by increasing fasting glucose levels.

Excessive fructose intake is one of the presumed causes of the development of metabolic syndrome and obesity, and both conditions are associated with the development of hypertension (Madero et al. 2011). We found a significant increase in blood pressure after 5 weeks of a high-fructose diet in the SHR-F60 group. However, there was an increase in the blood pressure also in SHR rats on a standard diet. This could be a spontaneous increase in blood pressure associated with age of rats at the end of the experiment (5 months of age) as it was reported that aging leads to an increase in vessel stiffness and this stiffening is worse when coupled with chronic hypertension (Lindesay et al. 2016). The specific relationship between fructose and elevated blood pressure is still unclear, as experimental studies lead to different conclusions. A study that tested the hypothesis

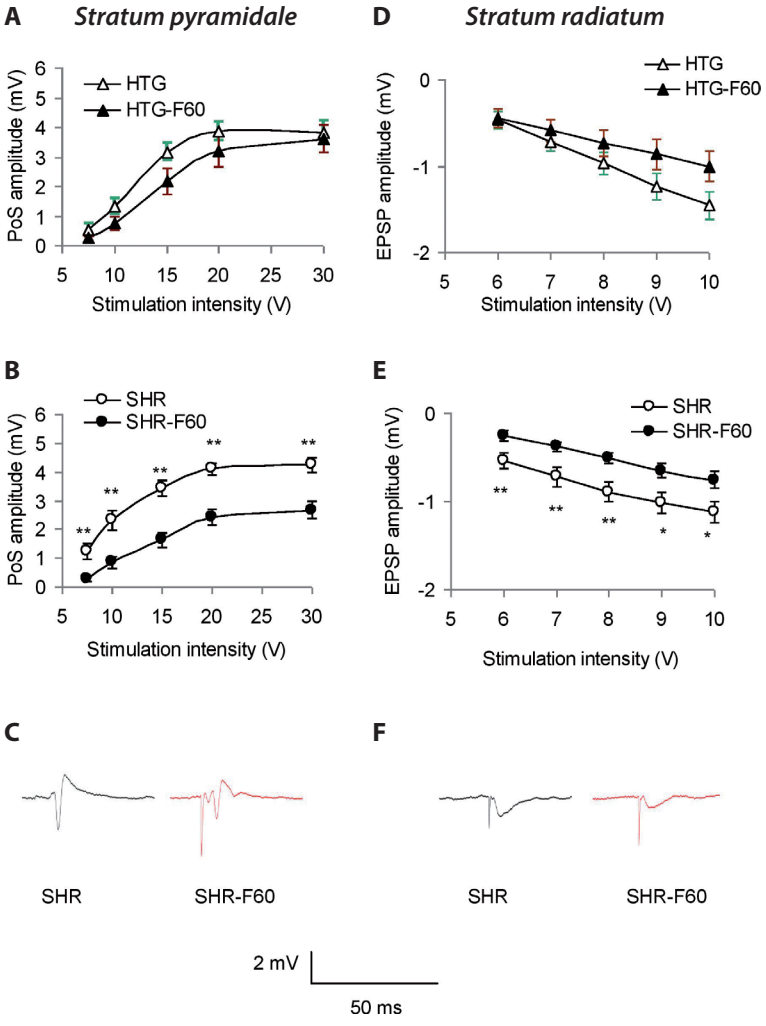

Figure 3. Effect of a high-fructose diet on neurotransmission in the rat hippocampus. Somatic response (population spike amplitude, PoS) recorded in the *stratum pyramidale* **(A)** and dendritic response (excitatory postsynaptic potential amplitude, EPSP) recorded in the *stratum radiatum* **(D)** of the CA1 hippocampal area of HTG-F60 rats did not differ from responses of HTG rats. Somatic response (**B**) as well as dendritic response (**E**) of SHR-F60 rats were significantly reduced comparing to responses of SHR rats. Representative recordings of somatic **(C)** and dendritic **(F)** responses of SHR and SHR-F60 are given. Values are means ± S.E.M., $n = 18$ to 24 hipocampal slices/group from $n = 14$ rats in a group. Significant differences between PoS and EPSP amplitudes of SHR-F60 group *versus* SHR group are marked *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$. For abbreviations of groups, see Figure 1.

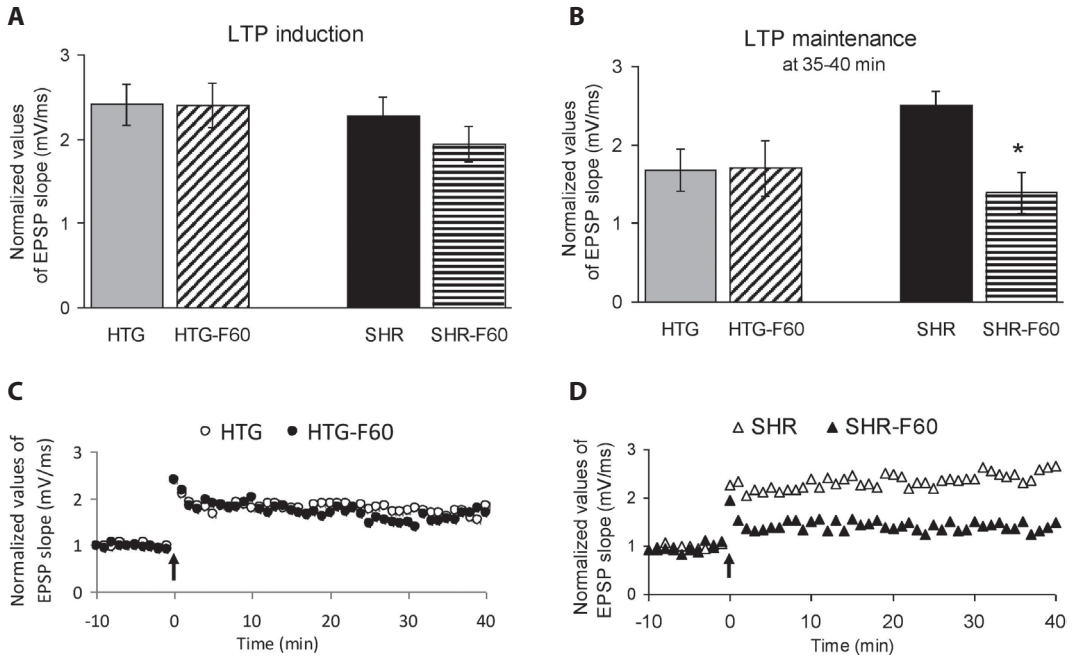

Figure 4. Effect of a high-fructose diet on long term potentiation (LTP). The induction of LTP **(A)** was induced by a high-frequency stimulation (HFS) of 100 Hz with duration of 1 s. LTP was measured extracellularly at the CA3-CA1 synapse at the *stratum radiatum* of the rat hippocampus. The maintenance of LTP **(B)** was recorded during 40 min after HFS. The normalized value of 1 represents calculated average value from the measured values obtained during 10-min of stabilization before HFS stimulation. The time course of the excitatory postsynaptic potential (EPSP) slope during stabilization and after LTP induction (marked with an arrow) is shown for HTG and HTG-F60 rats (**C**) as well for SHR and SHR-F60 rats (**D**). In A and B, values are means ± S.E.M., $n = 10$ to 15 hippocampal slices/group, while in C and D there are only mean values without deviations due to the clarity of the images. A significant difference in the LTP maintenance at 35–40 min of SHR group *versus* SHR-F60 rats, * $p < 0.05$. For group abbreviations, see Figure 1.

that fructose-induced insulin resistance caused hypertension reported that a high-fructose diet given for 8 weeks did not cause any change in baseline mean arterial pressure in Sprague-Dawley rats monitored by telemetry. In contrast, systolic blood pressure measured by tail-cuff plethysmography was significantly higher in fructose-fed rats compared to control-fed animals (D`Angelo et al. 2005). The authors concluded these discrepancies by explaining the possible increased stress during the measurement of blood pressure by the tail-cuff method. On the base of physiological setting of SHR rats, we consider that SHR rats could be more sensitive to the stress involved by the plethysmographic measurement of blood pressure compared to HTG rats, and therefore their blood pressure was increased in both SHR groups at the end of the experiment regardless of diet.

High fructose intake causes hypertriacylglycerolemia characterized by excessive levels of TAG-rich lipoproteins (Ichigo et al. 2019; Kunes et al. 2000). Several animal model studies have shown that fructose compared to glucose strongly induces de novo synthesis of fatty acids and TAG accumulation in the liver (Koo et al. 2008). We confirmed a significant increase in TAG due to the 60% fructose diet in SHR-F60 group. A significant increase in total serum cholesterol was found in both, HTG-F60 and SHR-F60 rats. SHR-F60 was a group that responded to high-fructose intake by increasing both monitored serum lipid profile parameters – total cholesterol and TAG.

Oxidative stress along with chronic inflammation is associated with metabolic diseases. Nutritional stress caused by a high-fat or high-carbohydrate diet also promotes oxidative stress, as evidenced by increased lipid peroxidation, protein carbonylation, decreased antioxidant system, and reduced glutathione levels (Tan et al. 2018). Here, increased levels of TBARS were found in the liver of SHR-F60 rats. A study by Busserolles et al. (2003) showed that rats fed a fructose diet had a high plasma and urinary TBARS levels compared to rats fed a starch diet. Lipid peroxidation was increased in samples obtained from patients with metabolic syndrome (Martins et al. 2021). NAGA is a hydrolytic lysosomal enzyme found in many tissues of the body. Serum NAGA activity is increased in hypertension, diabetes mellitus, and renal diseases (Lee et al. 2018), and this has been observed not only in essential hypertension but also as an effective predictor of future hypertension (Wen and Kellum 2012).

Treatment of diabetic patients with antioxidants caused a significant decrease in malondialdehyde levels, which was accompanied by a decrease in NAGA activity suggesting that serum NAGA activity may be affected by oxidative stress (Skrha and Hilgertova 1999). In the present work, the increased specific activity of NAGA was found in the kidney of SHR-F60 compared to the SHR standard-fed group suggesting putative renal injury, and it correlates with their significantly reduced kidney weight. In the two rat lines studied, oxidative stress was most pronounced in the SHR-F60 group with significantly increased liver TBARS and kidney NAGA levels.

Fructose-induced metabolic syndrome is closely associated with chronic inflammation, elevated levels of systemic inflammation cytokines, and activation of inflammatory signaling in organs including the liver, adipose tissue, kidney, heart, and brain (Miller and Adeli 2008; Porto et al. 2015; Pektas et al. 2016). In our experiment, we did not observed significantly increased levels of blood serum inflammatory cytokine IL-1α due to the fructose diet in both groups on the fructose diet.

Hypertension, dyslipidemia, hyperglycemia, insulin resistance, and non-alcoholic hepatic steatosis are known components of metabolic syndrome and they can lead even to neurological deficits (Farooqui et al. 2012; Moretti et al. 2019; Willmann et al. 2020; Andaloro et al. 2022). The coincidence of metabolic risk factors and cognitive impairment of degenerative or vascular origin starts to be identified as a metabolic cognitive syndrome (Panza et al. 2012). Consumption of a diet rich in saturated fats and added sugars damages the blood-brain barrier, negatively affects cognitive functions, especially mnemonic processes which depend on the integrity of the hippocampus (Stranahan et al. 2008; Hsu and Kanoski 2014; Noble et al. 2017; de Paula et al. 2021). Deterioration in the capacity of the hippocampus to sustain synaptic plasticity in the forms of long-term potentiation and long-term depression was reported in the hippocampus of mice fed 7 weeks with fructose diet (Cisternas et al. 2015). Moreover, mice exposed to fructose showed a reduction in the number of contact zones, the size of postsynaptic densities, and a decrease of neurogenesis in the hippocampus (Cisternas et al. 2015). In the present experiment, a 60% fructose diet resulted in a significantly reduced electrically evoked somatic and dendritic responses recorded on the CA3-CA1 synapse in the SHR-F60 hippocampus. In accordance with the results on mice, in our experiments LTP was significantly deteriorated in the SHR-F60 group, as determined by a reduction of the excitatory postsynaptic potential slope measured at the end of monitored period (35–40 min after high-frequency stimulation) compared to the respective SHR group on a standard diet. In our previous experiments with a different diet, the high-fat-diet induced impairment of synaptic plasticity in HTG rats, when induction of long-term potentiation lasted only about 15–20 min and reversed to baseline values (Gasparova et al. 2018). The decrease in cognitive abilities due to the combined high-fat-fructose diet was confirmed in our previous study on HTG rats in the Morris water maze test (Michalikova et al. 2019). Ross and co-authors reported that a high-fructose diet (60% for 5 months) impaired spatial memory in Sprague-Dawley male rats (Ross et al. 2009). The importance of the negative influence of a high-fructose intake on the development of cognitive decline was reported by Lakhan and Kirchgessner (2013). The high-fructose intake was identified even as a risk factor for developing of dementia (Stephan et al. 2010).

Conclusion

We demonstrate that a high-fructose diet triggers a cascade of biochemical and functional events in spontaneously hypertensive rats. In these rats, a high-fructose diet affected a blood serum lipid profile (increased total cholesterol and TAG levels), increased oxidative stress in the liver (TBARS) and kidney (NAGA), aggravated glucose tolerance, markedly reduced electrically-evoked somatic and dendritic responses in the hippocampus, and deteriorated synaptic plasticity. HTG rats, unlike SHR rats, were more resistant to a high-fructose intake and only one monitored parameter was negatively affected (total cholesterol). The results suggest that we can consider SHR rats as a suitable animal model for the study of negative health consequences due to the excessive fructose consumption, and therefore appropriate also for the testing of pharmacological or non-pharmacological treatment of fructose-elicited disorders. This work wants to draw attention to the risk of excessive fructose consumption in combination with a very common feature of metabolic syndrome – a hypertension.

Authors' contributions. ZG: conception and design of the study, data curation, formal analysis, funding acquisition, investigation, electrophysiological methodology, project administration, software, supervision, validation, visualization, writing – original draft; ER: data curation, formal analysis, investigation, methodology; DS: data curation, formal analysis, investigation, electrophysiological methodology, validation, visualisation; ZB: inflammatory methodology and biochemical analysis, investigation, visualisation; KS: data curation, methodology, blood sampling from the eye vessel, validation; LS: data curation, methodology, blood sampling from the eye vessel, validation; SB: supervision, methodology; RS: conceptualization, data curation, investigation, supervision, validation, writing – review and editing; VK: blood pressure and heart rate measurements.

Conflict of interest. There is no conflict of interest.

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