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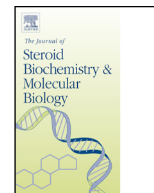

Modifications of Western-type diet regarding protein, fat and sucrose levels as modulators of steroid metabolism and activity in liver

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ABSTRACT

The aim of the study was to evaluate whether the modification of the Western-type diet (high-fat, high-sucrose diet rich in saturated fatty acids) considering macronutrients content would influence hepatic metabolism and activity of steroids. For 3 weeks Wistar rat were fed the Western-type diet (21% fat, 35% sucrose, 19% protein, lard) and its modifications regarding dietary protein (10 and 19%), fat (5 and 21%) and sucrose (0 and 35%) levels. The steroid 5α-reductase type 1 (*Srd5a1*) and androgen receptor (*Ar*) gene expression as well as testosterone (T) conversion towards 5α-reduced derivatives in liver were positively correlated with body weight gain. The Western-type diets with decreased protein content regardless of the sucrose level exerted the most negative effect on the antioxidant system decreasing catalase (*Cat*), sodium dismutase (*Sod1*) and glutathione peroxidase (*Gpx1*) gene expression as well as Cat and Gpx activity and total antioxidant status, simultaneously intensifying lipid peroxidation. The impaired antioxidant system was accompanied by decreased level of hepatic T metabolism towards estrogens: 17β-estradiol (E2) and estriol, and increased estrogen receptor type 1 (*Esr1*) gene expression. Liver *Esr1* mRNA level was differently correlated with T (positively) and E2 (negatively) plasma levels. Whereas the fat reduction in Western-type diet restored the plasma proportion between T and E2. In conclusion it could be stated that Western-type diet modification relating to protein, sucrose and fat content can influence hepatic steroid metabolism and activity; however the estrogens and androgens metabolism in liver would be connected with impairment of liver function or catabolic activity, respectively.

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1. Introduction

Liver is one of the main organs prone to diet-dependent diseases such as nonalcoholic fatty liver disease (NAFLD). It is estimated that about 20% of the population of the United States suffers from NAFLD [1]. The improperly balanced macronutrients in the diet are the reason of the excessive accumulation of triglycerides in the liver which is a first step in so called 'two-hit' hypothesis of liver pathology proposed by Day [2]. On the other hand, the liver is the site of metabolism of most of the compounds in the body. It is an essential element in the metabolism and excretion of steroids. However in case of testosterone (T), the conversion can proceed in two directions: towards biologically inactive sulphates and glucuronides, but also towards the active compounds from the group of estrogens and androgens [3] which in hepatocytes act though estrogen receptor type 1 (Esr1) or androgen receptor (Ar), respectively. The conversion towards androgens is dependent on steroid 5α-reductase type 1 (Srd5a1) activity, which reduces double bond in the steroid A-ring at the position C4-C5 in the compounds of both C19- and C21- steroids. So the testosterone is be converted into more potent androgen such as dihydrotestosterone (DHT) but also into 3α-androstenediol. Srd5a1 is mostly localized in liver, brain or prostate, as opposed to Srd5a2 which plays an important role in the male reproductive system [4]. The T (or androstenedione) conversion towards 17β-estradiol (E2) (or estrone, E1) is mediated by aromatase (Aro), a protein from CYP450 family which participates in creation of estrogen-specific phenolic A-ring [5].

Several research works presented a positive impact of both androgens [6] and the estrogen [7] on the regeneration of the liver after this organ removal. While androgens action mechanism has

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not been known yet, the estrogens antioxidant function could play an important role in this matter. The estrogens exhibit antioxidant properties because of the presence of hydroxyl group in the C3 position in the A-ring [8], or by affecting the gene expression of antioxidant enzymes by activation of the Esr1 which simultaneously performs the function of the transcription factor [9,10].

It is known that diets significantly affect the degree of conversion of T to both forms of active compounds, but such studies are mainly connected with prostate and breast cancer, wherein the increased synthesis of DHT and estrogens promotes the formation of malignancies [11]. It is puzzling, therefore, whether also in liver macronutrients modifications in the Western-type diet (high-fat, high-sucrose, normo-protein diet rich in saturated fatty acids, which is known to impair liver function) will also exert impact on the conversion of T and whether observed changes would be connected with liver antioxidant status and its function.

2. Materials and methods

2.1. Animals, diets and experiment design

The experiment was conducted on 40 male adult Wistar rats with an initial body weight of 260 ± 20 g (Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland). Animals were kept individually in polypropylene cages in stable environmental conditions (temperature 22 °C; humidity 50%; 12:12 light:dark cycle). They were given free access to food and water.

During the first week of adaptation, animals were fed a standard rodents' feed Labofeed H containing: crude protein −220 g, crude fat −42 g, crude fiber −60 g, starch −270 g, ash −55 g (full diet composition available on producer's page; Andrzej Morawski Feed Production Plant, Kcynia, Poland). Subsequently animals were divided into eight dietary groups which nomenclature and composition is shown in Table 1. The basic diet was so called Western-type diet (F21P19S35) based on Merat et al. [12]. Diet modifications related to levels of dietary protein (10 and 19%, low- and normo-protein diets, respectively), fat (5 and 21%, normo- and high-fat diets, respectively) and sucrose (0 and 35%, diet without and with high sucrose content, respectively) levels were examined. The lard, which is a rich source of saturated fatty acids (mainly palmitic acid and stearic acid) and cholesterol, was used as a dietary fat source in all examined groups. The percentage of energy supplied from fat was about 11% and 40% for normo- and high-fat diets, respectively. The experiment lasted for 3 weeks.

Rats' body weight was monitored once each week and the food intake was counted by daily measurement of unconsumed diet through the whole experiment.

After the 3-week feeding period, rats were anesthetized by inhalation with AErrane (Isoflurane, Baxter International Inc., Deerfield, IL, USA) and bled by cardiac puncture. Blood with EDTA as anticoagulant was centrifuged (20 min, $500 \times g$, 4 °C) and the collected plasma was stored at −20 °C until further analysis. The liver was removed, intensively washed in PBS buffer, drained on filter paper and instantly frozen in liquid nitrogen. The small fragments of livers were preserved in RNALater (Sigma-Aldrich, St. Louis, MO, USA) for further gene expression analysis.

The study was approved by the Third Local Animal Care and Use Committee in Warsaw (Poland).

2.2. Plasma activity of alanine and aspartate aminotransferase

Alanine (ALT) and aspartate (AST) aminotransferases activity in plasma was determined with ready assay kits (PTH Hydrex, Warsaw, Poland) based on kinetic methods according to International Society for Clinical Chemistry.

2.3. Liver activity of antioxidant enzymes, total antioxidant status and lipid peroxidation

The liver fragments were homogenized in 50 mM phosphate buffer (pH 7) with EDTA (1 mM) in proportion tissue to buffer 1:10. Then homogenates were centrifuged ($9000 \times g$, 20 min, 4 °C) and the obtained supernatant was used for further analysis.

The activity of sodium dismutase (Sod), glutathione peroxidase (Gpx) and glutathione reductase (Gsr) in liver homogenates was determined with use of ready colorimetric assay kits from Randox Laboratories (cat. No. SD125, RS504 and GR2386, respectively; Crumlin, UK). The catalase (Cat) activity was measured according to Johansson and Borg [13] with Wheeler's modification [14]. The total antioxidant status of liver (TAS) was determined with use of kit from Randox Laboratories (cat. No. NX2332; Crumlin, UK). The lipid peroxidation level was based on colorimetric reaction of malondialdehyde (MDA, the end-products of lipid peroxidation) with thiobarbituric acid (TBA). The obtained results were expressed in relation to protein content in liver homogenates measured with Bradford colorimetric method (Bioquant®, Merck KGaA, Darmstadt, Germany).

Table 1
Diets nomenclature and composition.

Components[a,b], g/100 g of diet	Dietary Group							
	F5P10S0	F5P10S35	F5P19S0	F5P19S35	F21P10S0	F21P10S35	F21P19S0	F21P19S35 (Western-type diet)
Wheat starch	74.7	39.7	65.7	30.7	58.7	23.7	58.7	14.7
Sucrose (S)	0	35	0	35	0	35	0	35
Casein (P)	10	10	19	19	10	10	19	19
Fat (lard) (F)	5	5	5	5	21	21	21	21

[a]The diets components were purchased from: wheat starch—Hortimex (Konin, Poland), sucrose—Chempur (Piekary Śląskie, Poland), casein—PHZ SM Lacpol (Murowana Goślina, Poland), fat – lard—Sokołów S.A. (Sokołów Podlaski, Poland), potato starch—BAFRA (Łańcuta, Poland), mineral mix components—Sigma-Aldrich (St. Louis, MO, USA) and PoCH (Gliwice, Poland), vitamin mix—MP Biomedicals (Santa Ana, CA, USA), DL-methionine and choline—Sigma-Aldrich (St. Louis, MO, USA).
[b]Components added to all diets in equal amounts: g/100 g of diet: potato starch—3.7, mineral mixture[c]—5, vitamin mixture[d]—1, DL-Methionine—0.3 and choline—0.3.
[c]Mineral mix composition (in 100 g of mix) according to Reeves (1997): $CaCO_3$—35.7 g, K_2HPO_4—25 g, NaCl—7.4 g, K_2SO_4—4.66 g, $C_6H_5K_3O_7{}^*H_2O$—2.8 g, MgO—2.4 g, $C_6H_5FeO_7$—606 mg, $ZnCO_3$—165 mg, $Na_2SiO_3{}^*9H_2O$—145 mg, $MnCO_3$—63 mg, $CuCO_3$—30 mg, $CrK(SO_4)_2{}^*12H_2O$—27.5 mg, H_3BO_3—8.15 mg, NaF—6.35 mg, $NiCO_3$—3.18 mg, Li_2CO_3—1.74 mg, Na_2SeO_4—1.025 mg, KIO_3—1 mg, $(NH_4)_6Mo_7O_{24}{}^*4H_2O$—0.795 mg, NH_4VO_3—0.66 mg, made up to 100 g with sucrose.
[d]Vitamin mix composition (AIN-93-VX Vitamin Mix, according to the producer certificate (MP Biomedicals, Santa Ana, CA, USA))(%): niacin—3.00, calcium pantothenate—1.60, pyridoxine-HCl—0.70, thiamin-HCl —0,60, riboflavin— 0.60, folic acid—0.20, D-biotin—0.02, vitamin B_{12} (0.1% solution in mannitol) —2.50, α-tocopherol (powder, 250 U/g)—30.00, vitamin A—retinol palmitate (250 000 U/g)—1.60, vitamin D_3 (400 000 U/g)—0.25, vitamin K (phylloquinone)—0.075, made up to 100 g with sucrose.

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