Research Article

Peculiarities of Metabolism of Rats with Fructose-induced Insulin Resistance Against the Background of Congenital and Acquired Iodine Deficiency

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Abstract

Animals following a high-fructose diet during eight weeks, have experienced changes in metabolism and the signs of insulin resistance have developed. Under such conditions, moderate hyperglycemia, hyperinsulinemia, hyperuricemia, an increase of the level of glycosylated hemoglobin in whole blood were observed. The significant role of the HOMA-IR index, as an early marker of carbohydrate metabolism disorders at the stage of pre-diabetes, has been confirmed. In experimental animals against the background of the high-fructose diet, the changes in the lipid spectrum of the blood were revealed: an increase of the total cholesterol level, low-density lipoproteins, triglycerides against the background of a high-density lipoproteins decrease. These disorders and a significant increase of the atherogenicity reflect the development of secondary dyslipidemia. In this case, the disorders of carbohydrate metabolism were combined with the degree of dyslipidemia. Males were found to have at increased risk of development the insulin resistance and comorbid pathology. Iodine deficiency, especially of congenital nature, is an aggravating factor of metabolic disorders. The obtained data can serve as a basis for extend of preventive measures and identification of the priority treatment schemes for type 2 diabetes mellitus in residents of endemic regions.

Keywords

insulin resistance; iodine deficiency; sexual dimorphism; blood lipid spectrum; carbohydrate metabolism

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Problem statement and analysis of the latest research

The development of insulin resistance and diabetes mellitus is associated with alimentary factors, among which the consumption of dietary fructose and sucrose is very important [1, 2, 7]. Fructose is known to cause the development of metabolic syndrome associated with the increase of body weight (development of abdominal obesity) and increased glucose tolerance [3, 9]. Considering the high risk of secondary dyslipidemia on the background of

iodine deficiency and the possibility of impaired lipid metabolism under the conditions of insulin resistance, the study of peculiarities of the combined effect of these factors on the body is of great interest.

Taking into account the similar effects of fructose on metabolic processes in rats and humans, the **objective of the study** was to investigate the effects of insulin resistance caused by fructose loading on carbohydrate, lipid, and protein metabolism in the context of congenital and acquired iodine deficiency taking into consideration sexual dimorphism.

1. Materials and Methods

The studies were performed using non-pedigree mature rats weighing 150-230 g, which were divided into the following groups: group I – control (intact animals, 12 males and 12 females), groups II and III – comparison groups: group II – animals with congenital iodine deficiency (20 males and 20 females), group III – animals with acquired iodine deficiency (20 males and 20 females), group IV – animals that were under the conditions of high fructose feeding with adequate iodine supply (20 males and 20 females), group V – animals with fructose-induced insulin resistance and congenital iodine deficiency (20 males and 20 females), group VI – animals with fructose-induced insulin resistance and acquired iodine deficiency (20 males and 20 females). Animals of the experimental groups IV-VI followed the high-fructose diet (20% fructose solution) during 8 weeks [7, 8]. Animals of the experimental groups II, III, V and VI followed the iodine-deficient diet, in particular; animals of the groups II and V – followed such a diet in the second generation; animals of the groups III and VI – followed it for 45 days of the experiment [4]. Control rats followed a standard vivarium diet. Care, feeding and euthanasia have been compliant with current international animal welfare requirements.

In order to assess the thyroid status of animals, the contents of free triiodothyronine (fT₃) and thyroxine (fT₄), thyrotropic hormone (TSH) in blood serum was determined using the method of enzyme-linked immunosorbent assay, followed by determination of the indices fT₃/fT₄ and TSH/fT₄ [4]. The condition of the iodine supply of rats was evaluated by the concentration of iodine in the daily portions of urine collected by the exchange cell method. Carbohydrate metabolism in animals was characterized by the level of glycosylated hemoglobin (HbA1c) in whole blood, glucose contents, immunoreactive insulin (IRI) and uric acid in fasting blood serum, and HOMA-IR (Homeostasis Model Assessment Insulin Resistane) indices were estimated [5, 8]. Lipid metabolism was calculated by determination of total cholesterol (TC), low density cholesterol (TC LDL) and high density cholesterol (TC HDL), triglyc-

erides (TG), and atherogenic factor coefficient (CA) in blood serum [8]. CA was calculated according to the formula: $CA = (TC - TC\ HDL) : TC\ HDL$. Protein metabolism was reflected by total blood serum protein contents. Statistical analysis of the results was performed using Microsoft Excel and Statistica 5.5 computer programs.

2. Results and Discussion

As a result of the study it was determined that high-fructose diet caused a 61.6 and 35.2% increase in blood serum glucose in males and females, respectively ($p_{1-4} < 0.05$), IRI – at 46.1 and 30.3%, respectively ($p_{1-4} < 0.05$) and HbA1c in the blood – at 59.4% and at 28.1% ($p_{1-4} < 0.05$) as for the control (Fig. 1). The effects of fructose are known to be linked to sex hormones [8]. Therefore, males are at increased risk of development of insulin resistance, and females have a strong reserve of protection for its development. Such a probability is confirmed by the increase of the HOMA-IR index in males more than twice ($p_{1-4} < 0.01$), while in females – at 65.5% ($p_{1-4} < 0.01$) relative to basic values.

Fructose metabolism is characterized by the ability to increase the uric acid (purine metabolite) level in blood serum, which is associated with insulin resistance. In addition, fructose can reduce renal excretion of uric acid due to increased lactate production. The latter one is a competitive inhibitor of uric acid reabsorption in the renal tubules [7]. As a result of the experiment, animals of this group were determined an increase of uric acid contents in males and females at 50.6% and 36.4%, respectively ($p_{1-4} < 0.05$) as for the control, which may be due to hyperinsulinemia, which stimulates uric acid reabsorption in the tubules of the kidneys. Hyperuricemia is known to precede the development of obesity and hypertension, and may be a marker of impaired carbohydrate metabolism.

Lipid metabolism was observed in animals following a high-fructose diet with adequate iodine supply. Thus, an increase of the contents of TC (at 31.2%, $p_{1-4} < 0.05$), LDL cholesterol (at 39.3, $p_{1-4} < 0.01$), TG (at 29.1%, $p_{1-4} < 0.05$) against the background of lowering of HDL cholesterol con-

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Figure 1. Indices of carbohydrate metabolism in intact rats and rats with fructose-induced insulin resistance against the background of congenital and acquired iodine deficiency.

Notes:

- * – significant difference in data in intact animals with regard to sexual dimorphism ($p < 0.05$);
- Δ – significant difference in data in insulin-resistant animals with regard to sexual dimorphism ($p < 0.05$);
- # – significant difference in data in males within the study group.]

tents (at 21.8%, $p_{1-4} < 0.05$) regarding control (Fig. 2), was determined in males of this group. Females had significant changes in LDL cholesterol contents (35.1% increase, $p_{1-4} < 0.01$), HDL cholesterol (16.1% decrease, $p_{1-4} < 0.05$) relative to the values in the control group of animals. Such disorders led to an increase in CA in males – six-

fold ($p_{1-4} < 0.05$), in females – four-fold ($p_{1-4} < 0.05$) according to data in intact animals. Such dynamics of changes in the lipid spectrum of the blood characterize the development of secondary dyslipidemia, mainly in males and the increased risk of development – in females.

Figure 2. Indices of blood lipid spectrum in intact rats and rats with fructose-induced insulin resistance against the background of congenital and acquired iodine deficiency.

Notes:

- * – significant difference in data in intact animals with regard to sexual dimorphism ($p < 0.05$);
- Δ – significant difference in data in insulin-resistant animals with regard to sexual dimorphism ($p < 0.05$);
- # – significant difference in the data in males within the study group.]

Animals (males and females, respectively) of this experimental group showed a decrease in total protein contents at 20.3 and 18.1% ($p_{1-4} < 0.05$) relative to basic data.

Attention is drawn to the reduction of fT_3 contents in the blood serum of males and females at 36.1 ($p_{1-4} < 0.05$) and at 30.5 ($p_{1-4} < 0.05$), respectively, relative to control data.

In the group of insulin-resistant animals following iodine-deficient diet in the second-generation (experimental group V), co-directional changes of carbohydrate, lipid and protein metabolism were detected (Figs. 1, 2). In particular, the animals of this group showed an increase of glucose contents (at 46.3 and 27.7% in males and females, respectively, $p_{1-5} < 0.05$) and IRI (at 35.5 and 27.7%, $p_{1-5} < 0.05$), the HOMA-IR index (almost twice in males and at 59.9% in females, $p < 0.05$) relative to control values. Under these conditions, the level of HbA1c in the blood exceeded basic values at 64.3% and at 39.5% ($p_{1-4} < 0.05$) relative to control taking into account the sexual dimorphism. Males and females of this group respectively showed an increase of the contents of TC (more than thrice and twice, $p_{1-5} < 0.01$), LDL cholesterol (3.5- and 2.7-fold, $p_{1-5} < 0.01$), TG (3.1-fold and at 55.7% $p_{1-5} < 0.01$) against the background of the decrease of HDL cholesterol contents (at 78.1 and 55.2%, $p_{1-5} < 0.05$) regarding control (Fig. 2). Under these conditions, the CA exceeded the data in intact animals: in males – almost ten-fold ($p_{1-5} < 0.05$), in females – four-fold ($p_{1-5} < 0.05$).

Animals were found a decrease of the total protein contents at 33.3 and 27.3% ($p_{1-5} < 0.05$) relative to basic data.

It should be emphasized that, in this group of animals, the combined endocrine pathology significantly potentiates changes in metabolism, and the difference in the indices taking into account sexual dimorphism was less pronounced.

Changes in the studied parameters in animals of the experimental group VI (insulin resistance against the background of acquired iodine deficiency; Fig. 1, 2) had the same tendency as in the animals of the group V. However, there is a higher risk of the development of insulin resistance and dyslipidemia

in males than in females, as indicated by significantly higher HOMA-IR (almost twice, $p_{1-6} < 0.05$) and CA (2.2-fold, $p_{1-6} < 0.05$) indices in males relative to females within this experimental group. Such data characterize rather high cardio-vascular risks in animals under the studied conditions.

The dynamics of such potent metabolic changes under conditions of combined pathology may be the consequence of disorders not only of carbohydrate but also of thyroid homeostasis. Thus, the significant changes of indices of the hypothalamic-pituitary-thyroid axis were revealed in animals with combined endocrine pathology (experimental groups V and VI). In particular, in the blood serum of animals of the experimental group V the contents of fT_3 and fT_4 was lower at 73.1 and 82.5% ($p_{1-5} < 0.05$) and at 66.1 and 66.6% ($p_{1-5} < 0.05$) in males and females according to basic data. The functional ability of the thyroid gland of animals in the experimental group VI had concurrent but less pronounced changes.

3. Conclusions

Animals having followed a high-fructose diet, develop insulin resistance and undergo carbohydrate and lipid homeostasis. Increase in HOMA-IR index, hyperuricemia, is a marker of impaired carbohydrate metabolism. Changes in carbohydrate metabolism are co-directed with the degree of dyslipidemia. Higher risk of development of insulin resistance and comorbid pathology is in males. Iodine deficiency, especially of congenital nature, is an aggravating factor of metabolic disorders. The obtained data can serve as a basis for extend of preventive measures and identification of priority treatment schemes for type 2 diabetes mellitus in residents of endemic regions.

4. Prospects of Further Researches

To study the effectiveness of the correction of metabolic disorders in case of excessive fructose income against the background of hypothyroid dysfunction.

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