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Review

A REVIEW ON THE MODELS OF OBESITY AND METABOLIC SYNDROME IN RATS

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ABSTRACT

Purpose: The metabolic syndrome represents a cluster of abnormalities, including obesity, insulin resistance, dyslipidaemia and Type 2 diabetes, which increase the risk of developing cardiovascular diseases. The purpose of this study was to discuss advantages and disadvantages of different models of obesity and metabolic syndrome in rats.

Methods: In this review we analyze the data about models of obesity and metabolic syndrome (MetS) in rats.

Results: According to the data there are dietary, genetic and pharmacological models. The main diet-induced models in rats are: high-fat diet (HFD), high-carbohydrate diet (HCD), combined high-fat and high-carbohydrate diet (HFCD), and dietary regimens simulating dietary habits in people. Zucker rats, the obese spontaneously hypertensive rats (Spontaneously Hypertensive Rats – SHR), and selected rats of low aerobic capacity (Low-Capacity Runners – LCR), are used as genetic models to investigate MetS. Parenteral use of Streptozotocin in sub-diabetes doses also finds application in the experimental studies of MetS.

Conclusion: Based on the analysis of these three groups of models we conclude that when required to monitor changes in metabolism at different stages of inducement of obesity and the MetS in rats, it is appropriate to use a combined high-fat and high-fructose diet.

Key words: Obesity, metabolic syndrome, rats, dietary models

A REVIEW ON THE MODELS OF OBESITY AND METABOLIC SYNDROME IN RATS

The Metabolic Syndrome (MetS) is a socially important issue which has drawn the attention of many physicians and researchers. It is caused by a number of risk factors and leads to substantially increased morbidity of cardiovascular diseases and diabetes mellitus type 2 (1). Leading factors for the development of the symptom complex include obesity, reduced physical activity and improper diet (2). Lifestyle variations often make it difficult to apply effective treatment strategies.

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Etiology of MetS is multi-factor and like in most diseases includes genotype and lifestyle. In recent decades the increased occurrence of the condition is attributed to changed dietary habits and reduced physical activity. When studying the pathogenesis of MetS and related therapeutic approaches it is appropriate to use diet-induced animal models for methods not applicable to humans.

One advantage of the animal models is the opportunity of precise control of diet and motor activity. Another important advantage is the opportunity to carry out histological studies of MetS, which are difficult to perform in humans.

Rats are the most common laboratory animals used in experimental models for the study of metabolic turnover of substances in the body.

They are convenient for investigating the adaptive changes to different functional, morphological and biochemical factors. In order to induce the metabolic syndrome various dietary, genetic and pharmacological models have been developed.

DIETARY MODELS OF THE METABOLIC SYNDROME

The basic diet-induced models in rats are the following: high-fat diet, high-carbohydrate diet, combined high-fat and high-carbohydrate diet, diet with a high content of NaCl and fructose, dietary regimens simulating dietary habits in people, as well as prenatal and perinatal dietary manipulations.

1. High-Fat Diet

Depending on the quantity of ingested fats the diets are divided into low-fat ones where fats represent 10 en % (Low-Fat Diets (LFD), high-fat ones where fats make up 30-50 en % (High-Fat Diets (HFD), very high-fat diets where the intake of fats exceeds 50 en %. (Very High-Fat Diets (VHFD).

With HFD and VHFD the effect of diet on the body mass depends on the total amount of fats ingested (3). Test animals, in wich obesity has been induced through high-lipid diet, often develop the other elements of the MetS as well (4).

The type of ingested fats also has an affect on the body mass and metabolism. In an experiment with Wistar rats fed with 40 en % HFD, containing different fats (cod-liver, palm, and soya oil), the biggest body mass was achieved in the group receiving soya oil (3). Other studies show that the experimental animals fed with cod-liver oil did not increase substantially their body mass and also had higher insulin sensitivity (5, 6).

R. Buettner *et al.* studied the metabolic and molecular effects of olive oil, cocoa oil, lard and cod-liver oil using HFD, and found that the highest level of obesity, insulin resistance and hepatic steatosis as well as activation of SREBP1c (sterol response element-binding protein 1c) – the main transcriptional regulation of hepatic synthesis of fatty acids, resulted from the ingestion of lard (6).

J. Y. Kim et *al*. assumed that application of HFD in rats led to a state equivalent to MetS in humans. He maintained the hypothesis that increased content of triglycerides in muscles was responsible for the insulin resistance of rodents fed with HFD, as well as in people with reduced insulin sensitivity (7).

S. Woods *et al*. found that in rats a ten-week diet rich in of synthetic, semi-refined lipids led to a significant increase of body mass and body fats, development of hyperleptinemy and insulin resistance. The authors recommend HFD as suitable for research of the mechanisms by which food intake affects the regulation of energy balance (8).

Dietary regimens with lower fat content also find application in research studies. N. Chen *et al.* found that rats receiving food with 15 en % fats also developed changes specific for MetS. They investigated the protective effect of epigallocatechin, green tea, and black tea in improper dietary regimens. The study results indicated improvement of glucose tolerance and suppression of adipocyte differentiation with green and black tea. Increased thermogenesis was found with epillagocatechin thereby explaining the role of these components in the prevention of obesity (9).

In the case of normal food intake, rats maintain low levels of total cholesterol and LDL-chol, and high levels of HDL-chol, which made it difficult to induce hypercholesterolemia and atherosclerosis. Successful methods to achieve these changes included high intake of saturated fatty acids and of cholesterol – values above 0.2% of body weight. To facilitate the process bile acids were also added, which improved the adsorption in the intestines. S. Sasaki *et al.* applied high-cholesterol diet in rats for 6 weeks and recorded increased plasma values of cholesterol and triglycerides. In the same study were found atherosclerotic changes and enhanced variability in the arterial pressure values (10).

Applying HFD and high energy diets in Sprague-Dawley rats, B. Levin *et al.* found that only half of the experimental animals developed obesity, while the other half did not increase essentially their body mass (11, 12).

High variability of glucose tolerance, insulin sensitivity and triglyceride levels in the plasma were reported as deficiency of HFD (11, 13). Moreover, it takes more than 15 weeks to achieve MetS by that method. Application of HFD for the purpose of inducing MetS has a number of advantages. With them development of obesity is guaranteed. HFD enable the monitory of the connection between body mass, quantity of consumed fats and the effect from the use of different types of fats; HFD are also easy to introduce.

2. High-Carbohydrate Diets

The increased prevalence of obesity and MetS, and related complications correlate with the growing carbohydrate consumption in recent years (14, 15). Thus, our attention has been focused on high-carbohydrate diets as models for studying these conditions.

Use of refined carbohydrates, such as HFCS (high fructose corn syrup) and sucrose, are associated with increase of body mass, rise of the level of circulating triglycerides, and development of insulin resistance in humans and animals (15, 16).

Basic dietary models applied in experimental conditions include sucrose, fructose and glucose ones taking into account variations depending on the type of carbohydrate included. The increased fructose intake, for example, is considered one of the main factors in the development of obesity and the metabolic syndrome.

R. Kanarek *et al.* published a study on the various effects of sucrose, fructose and glucose in rats. It was found that the groups receiving sucrose and fructose solutions increased substantially their body mass and had reduced glucose tolerance. The animals receiving granulated sugar had the biggest growth per consumed kilocalories and significantly increased retroperitoneal fatty tissue (17).

Wistar and Sprague-Dawley rats are the breeds most often used as a models for sucrose-induced insulin resistance and hypertriglyceridemia and both conditions may be induced for two weeks (18, 19). It has been also found that this can be achieved even in one week (20).

Applications of high-fructose and high-sucrose diets allows for studies on muscle and liver changes in a state of insulin resistance (21, 22, and 23). B. Huang *et al* used high-sucrose diet and achieved development of hepatic steatosis and dyslipidemia. Subsequently, by the means of leptin infusion, the authors adjusted partially the hepatic changes but did not achieve any changes in the plasma glucose and insulin levels (24).

R. Panchamoorthy and R. Anuradha studied in detail the effects of L-carnitine in rats on fructose diet for 30 days, and found that L-carnitine supplementation helped in the prevention of disruptions of the glucose metabolism (25).

One advantage of the mono- and di-saccharide models applied was the rapidly achieved insulin resistance and hypertriglyceridemia. However, there developed significant increase of body mass and obesity following a prolonged diet.

3. Combined High-Fat and High-Carbohydrate Diet (HFCD-High-Fat-Carbohydrate Diet)

MetS inducing high-fat and high-carbohydrate models have various advantages. Increased levels of triglycerides are observed mainly in high fructose-fed rats whereas obesity is mainly achieved through a high-fat diet (4, 26).

At present there exist successfully applied HFCD. J.Y. Deng *et al.* showed inducement of MetS by means of a high-cholesterol/high-fructose diet. They studied the decrease of insulin resistance of the heart and deterioration of myocardial contractility in rats (27). Another study traced changes in metabolism and cardiac activity during prolonged HFCD. The results showed significant lipid accumulation in the myocardium, left ventricular hypertrophy and morphological liver damage. Test animals did not present with elevated arterial pressure and no changes in the cardiac activity values at rest were recorded (28). In rats the combination of high-cholesterol and high-fructose diet is connected with an increase of cholesterol plasma levels, decrease of HDL-cholesterol and doubling the weight of the liver (29).

In our study we investigated changes in time run to exhaustion during four-month HFCD for inducing MetS in male Wistar rats. Time to

exhaustion at 8th week, 12th week and at the end of the experiment was significantly reduced in comparison with controls (30).

One advantage of the use of HFCD was that the cardiac tissue was damaged relatively rapidly, which allows for a detailed study of morphological, biochemical and functional features of the pathogenesis of cardiovascular changes, in addition of the metabolic ones.

4. Diet with High Content of NaCl and Fructose

These diets are used for provoking of hypertension in rats, but they can also lead to the development of MetS. T. Ogihara *et al* studied the effect of increased salt intake using a diet with high content of NaCl (8% NaCl) for two weeks. No substantial change in body mass was achieved, but the values of systolic arterial pressure, plasma glucose levels, and liver gluconeogenesis increased (31). With high-fructose diets (60 en %), increased arterial pressure and signs of renal damage were observed even in the case of slightly increased intake of NaCl (32, 33). Such dietary manipulations are mainly applied in the research of anti-hypertensive medications.

5. Diets Imitating Human Dietary Habits

Most people have improper dietary regimens characterized by high intake of fats, refined sugar and NaCl. The high energy density of foods, affordable prices and good flavour characteristics in addition to reduced physical activity lead to wide spread obesity and related diseases.

In rats, the so-called "Western diet" which is characterized by increased intake of saturated fatty acids, cholesterol, sugar and NaCl, affects glucose homeostasis, fat profile and adipocyte hormones (34). The use of tasty food in unselected Wistar rats causes hyperphagia, increased energy intake, as well as brown adipose tissue growth, elevated body temperature and plasma leptin levels (35). S. Brante *et al.* found that the so-called cafeteria diets (containing crushed biscuits, waffles, snacks, etc.) represent an effective model of a metabolic syndrome causing obesity, deteriorated glucose tolerance, and inflammatory status (36).

These dietary manipulations offer great opportunities for studying the biochemical, genetic and physiologic mechanisms of obesity and the diseases related thereto. On the other hand, diets imitating dietary habits in people are diverse and it is not always possible to determine exactly which factor has had the highest effect.

6. Prenatal Dietary Manipulations

Prenatal dietary restriction leads to fetal retardation of the endocrine and metabolic status (37).

Reduced intake of proteins during pregnancy causes reduction of the beta-cellular proliferation and reduced size of the islets of Langerhans in the early ontogenesis (38). S. Langley-Evans investigated dietary protocols for inducement of hypertonia and found additional changes in the beta-cells and insulin sensitive tissues in cases of reduced protein intake by the mother (39).

In rats HFD during pregnancy causes fetal insulin resistance, abnormal cholesterol metabolism and high arterial pressure (40, 41).

Prenatal dietary experiments are difficult to perform, could raise ethical questions with regard to the humane attitude towards animals, and should be considered for research projects only when use of other models is not possible.

GENETIC MODELS

1. Zucker rats (ZDF)

Obese Zucker rats (ZDF) are widely investigated and are among the best models for the study MetS. ZDF possess a (fa/fa) mutation and leptin receptor deficiency. These animals grow obese at the age of 3-5 weeks. At 14 weeks approximately 40% of their body is already composed of fat (42). Male animals develop diabetes mellitus. Female rats grow obese only, without developing diabetes mellitus, and have a long period of preserved insulin sensitivity. ZDF are characterized by hyperphagia, dyslipidemia, disrupted glucose tolerance, insulin resistance, hyperinsulinemia, increased expression of ghrelin, hypertension, endothelial dysfunction, proinflammatory and oxidative status (43).

The ZDF have proven useful in the demonstration of the efficacy of pharmaceutical agents directed at macrovascular function, nephropathy, myocardial injury, and lipidemia (44, 45, and 46).

A. Wendel and M. Belury published a study on effects of conjugated linoleic acid and Troglitazone on lipid accumulation and composition in lean and ZDF. Their results showed that, like Troglitazone, conjugated linoleic acid normalizes glucose tolerance and plasma lipids and also improves hepatic steatosis and fatty acid composition in ZDF. They suggested that the effects of these two agents on glucose tolerance may be associated with a reduction in stearoyl-CoA desaturase-1 (44).

A. Noto *et al*. investigated the effect of dietary conjugated linoleic acid on hepatic steatosis liver function and lipid metabolism in obese insulin-resistant rats. They found out that conjugated linoleic acid supplementation reduced liver lipid concentration, improved liver function and serum lipid profile compared with control fed *fa/fa* rats (47).

M. Monteiro et al. investigated the changes in orexigenic signals in the ZDF after gastric banding. They concluded that gastric banding prevents the increase in orexigenic signals that occur during caloric deprivation. They supported the hypothesis that sustained weight loss observed after gastric banding does not depend solely on food restriction (48)

Due to the prolonged pre-diabetes condition female ZDF are considered suitable for investigation of insulin resistance. Established ZDF represent a secure model for inducement of deviations of MetS, however they are difficult to procure and expensive price. They are also genetically modified which is not the case with most of the affected people.

2. SHR (Spontaneously Hypertensive Rats)

Another genetic model is represented by the obese spontaneously hypertensive rats. They often have low body mass at birth. SHR milk has an altered electrolyte balance, lower protein content, and fatty acid content different from that of other breeds. Mature rats are characterised by obesity, hypertriglyceridemia and hypertension. SHR are predominantly used for studies of arterial hypertension and the related medication treatment.

3. LCR (Low-capacity runners)

LCR represent a genetic model of rats with low aerobic capacity. They develop hypertension, endothelial dysfunction, insulin resistance, hyperinsulinemia, visceral obesity, hypertriglyceridemia, and elevated plasma levels of nonesterified fatty acids (49).

Genetic models are easy to use although, with them, the factors related to lifestyle are eliminated.

PHARMACOLOGICAL MANIPULATIONS

The most frequently used preparation for beta-cellular damage is Streptozotocin (STZ). Even in the case of a single application, depending on the dose, a condition of insulin dependent diabetes mellitus can be achieved. A. Junod *et al* studied the metabolic effects of different doses of Streptozotocin applied intravenously to Wistar rats. High doses (100 mg/kg) induced diabetes mellitus even 24 hours after the injection whereas a dose of 20 mg/kg did not indicate deviations in the glucose tolerance test (50).

M. Shaalan *et al.* applied HFCD and Streptozotocin (35 mg/kg) to study the impact of Rosiglitazone and Glimepiride on the glucose homeostasis, fat profile and adipocyte hormones in diabetes mellitus type 2 and insulin resistance (51).

Chemically induced diabetic rodents show fatty liver inflammation along with decreased ventricular contractility and function (52, 53).

Medication models are easily available and secure but they do not allow for monitoring the changes at different stages of the metabolic syndrome.

CONCLUSION

The choice of an obesity model and MetS determine to a great extent the experiential results. Sometimes researchers modify or combine established methods in order to achieve the desired changes.

Considering the presented data, we can draw the conclusion that if it is necessary to monitor changes in metabolism, markers of inflammatory and thrombotic status, functional factors, morphologic and molecular alterations at different stages of obesity inducement and metabolic syndrome in rats, it is appropriate to use a combined high-fat and high-fructose diet. Thus, on one side, acceleration of the phenotypic

manifestation of deviations is achieved, and on the other side, conditions are established for modifications and approximation of the controlled diet to the real dietary regime of most of the affected people.

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