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Main Features of Genetic Models of Metabolic Syndrome

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Abstract: Metabolic syndrome (MS) is a complex of metabolic, hormonal and clinical pathologies. It is a strong risk factor for the development of cardiovascular diseases, the basis of which is insulin resistance (IR) and compensatory hyperinsulinemia. According to some researchers, today's MS is also interpreted as a syndrome of "affluent". WHO experts assess the current situation regarding the spread of MS as follows: "We are facing a new pandemic that will cover the industrialized countries of the 21st century." The prevalence of MS is twice as high as the prevalence of diabetes mellitus and is expected to increase by 25% over the next 50 years. [1].

Keywords: *metabolic syndrome, modeling, experiment, genetic models.*

Introduction

Metabolic diseases, having various syndromes with specific clinical manifestations, have long attracted the attention of doctors around the world. In the 4th century BC, the Great Hippocrates described the classification of syndromes, and in 1922 F. Lang observed a patient with arterial hypertension. During the observation, he emphasized the association of the disease with obesity in patients with arterial hypertension and explained that obesity is associated with impaired carbohydrate metabolism and increased blood glucose levels. In 1923, Douglas and E. Kaelin reported a syndrome combining hypertension and hypertension. This syndrome was a combination

of hypertension, hyperglycemia, and hyperuricemia.[3] The various combinations of clinical syndromes of central (abdominal) obesity caused by metabolic syndrome have different names: For example, in 1940, J. Vague introduced the concept of central obesity [5]. Metabolic syndrome was called "Metabolic trisyndrome" by J. Camus in 1966, "Polymetabolic syndrome" by P. Avus, "Metabolic syndrome" by P. Avago in 1967, "Wealth syndrome" by N. Mehnert and N. Kuhlmann in 1968, "Hormonal metabolic syndrome" (R. Bjorntorp, 1972) [4]. In 1981, M. Hanefeld and W. Leonard first proposed the term "Metabolic syndrome". In 1988, G. Reaven described "Syndrome X" (hyperinsulinemia, impaired glucose tolerance, hypertriglyceridemia, arterial hypertension (AG), decreased high-density lipoprotein cholesterol). In 1989, N. Kaplan showed that most patients with MS have central obesity and proposed the term "fatal four" (fatal, quartet). The metabolic syndrome was defined by the World Health Organization (WHO) in 1998 as a cluster of risk factors including high blood pressure, low high-density lipoprotein cholesterol, high triglycerides, impaired glucose tolerance or diabetes mellitus, insulin resistance (IR), increased waist-to-hip ratio, and microalbuminuria. Holt S. in 2005 explained the concept of "syndromes X, Y, and Z" according to which certain features of MS, polycystic ovary syndrome, fatty liver disease (syndrome Y), and cancer (syndrome Z) are associated with an increased risk of cardiovascular disease (syndrome X) [5]. Epidemiology. Depending on the gender, age, ethnicity, and diagnostic criteria, MS appears to be a cluster of risk factors for cardiovascular disease (CVD) and diabetes mellitus (SDM2). The prevalence of MS varies widely and varies depending on gender, age, ethnicity, and diagnostic criteria (ranging from 8% in men in India to 25% in the United States, and from 7% in women in France to 46% in Iran). According to the INTERHEART study, MS occurs in an average of 26% of the world population. In South Asian countries, the prevalence of MS is 2.5 times higher than in Europe. MS is more common among obese individuals: 49% of them have MS [2]. Genetic models of metabolic syndrome These methods of modeling MS are actively used to study the specific molecular mechanisms of the development of the syndrome. Basically, these models are monogenic. In this case, the development of pathological changes is caused by a violation of the function of a single protein, while MS in humans occurs as a result of the sum of many factors and developmental mechanisms. There are also polygenic models, among which, for example, are Goto-Kakizaki rats.

Most models obtained by selection are associated with spontaneous mutations established in a number of generations. With the development of new technologies in molecular genetics, it became possible to obtain knockout animals with the loss of function of a particular gene. Such models are used more often to study specific pathophysiological phenomena, and not such a complex phenomenon as MS. The difficulty in creating such models is also associated with the fact that homozygous mutations in a gene are sometimes lethal and cause the death of the embryo during intrauterine development [8]. Thus, this review mainly covers models with spontaneous mutations obtained by selection.

The development of certain components of MS can be expressed to different degrees, and for the successful use of an animal line in research, it is important to correctly select the optimal model for each specific situation. One of the most common models of MS is rodents with impaired biological effects of leptin. A well-known model of obesity and MS is the Zucker rat line with obesity and QD 2. This line is characterized by a mutation in the leptin receptor gene. Also widely used are ob / ob and db / db mice, as well as spontaneously hypertensive obese SHR rats (SHROB). Conventionally, we can distinguish models with preserved biological effects of leptin: these are Otsuka Long-Evans Tokushima Fatty (OLETF), Goto-Kakizaki (GK) rats and Wistar Ottawa Carlsburg W (WOKW) rats. The development of polyphagia and obesity in ZDF is associated with severe insulin resistance and hyperinsulinemia. At the same time, over time, a decrease in insulin production is observed due to atrophy of the pancreatic islet apparatus. Thus, this model is characterized by changes similar to MS and QD 2 courses in humans.

In the process of studying this model, conflicting data were obtained on the development of hyperglycemia in these animals: according to some studies, hyperglycemia up to 500 mg / dl (28 mmol / l) developed at 10-15 weeks of life., in other studies hyperglycemia was noted only at 6 months of age, and the increase in glucose levels was not very significant. These differences are probably due to some genetic heterogeneity of the colonies. In addition, impaired glucose tolerance, as determined by the oral glucose tolerance test, was confirmed by all investigators.

Dyslipidemia is a characteristic feature of this model of MS. An increase in total cholesterol (TC) is observed already at 10 weeks of life and only increases with time. The lipid spectrum of ZDF includes a significant increase in very low-density lipoproteins (VLDL) and HDL, while the level of low-density lipoproteins (LDL) is comparable to that of intact animals. Thus, the use of this model as a model of atherosclerosis poses some difficulties. It is worth noting that ZDF develops endothelial dysfunction similar to diabetic microangiopathy in humans. In addition, these animals develop arterial hypertension, but not before 17 weeks of life.

Thus, ZDF rats are one of the most suitable models for studying pathological changes in the body and methods for their correction in MS. It should be noted that the development of MS in humans is associated with many factors, and not only changes in the metabolic effects of leptin, and, as in many other models, it is not appropriate to assess the pathogenesis of MS in this model. .

Spontaneously hypertensive obese rats (SHROV)

SHR rats are a well-known model of arterial hypertension. SHR obese rats (SHROB), like ZDF rats, have a mutation in the leptin receptor gene fac, which leads to impaired signal transmission through the receptor. SHROB are also known as Koletsky rats, since this strain was described in 1973 by a group led by S. Koletsky. Animals are characterized by increased food intake and by the 5th week, males are already overweight, and by 7-12 months of age, the weight of males reaches 750-1000 g.

This model is characterized by the development of dyslipidemia with a significant increase in TG levels and a moderate increase in total cholesterol. At about 3 months of age, animals develop arterial hypertension, systolic blood pressure exceeds 150 mm Hg. Art. with a further increase throughout life. Over time, atherosclerotic damage to the arteries and impaired renal function are also characteristic, as a result of which life expectancy does not exceed 1 year.

Hyperinsulinemia and insulin resistance are present in all animals and are associated with a normal or moderate increase in fasting glucose levels. In addition, impaired glucose tolerance has been identified in many studies. There is also a subtype of Koletsky rats, the SHR/N-cp, which develops severe hyperglycemia. Thus, this model is very useful for studying lipid metabolism disorders in MS and arterial hypertension.

Mice JB/JB (C57BL/KsJ-db/db) and ob/ob (C57BL/6J-ob/ob)

The db/db strain of mice is characterized by a defect in the leptin receptor and rapidly increasing insulin resistance over time. Ob-mutated mice have impaired leptin production, and treatment of such animals with leptin reduces the severity of insulin resistance, reduces food intake, and prevents the development of QD 2. Both models are characterized by hyperphagia and relatively high body weights at 15 weeks of age. In db/db animals, glycemic levels at 5 weeks of life are not significantly different from those in wild-type mice, but then gradually increase and reach significant differences at 7 weeks of life. In ob/ob mice, however, glycemic levels remain at a much lower level for a longer period of time and reach a significant increase at 15 weeks. The reason for the more pronounced SD in db mice is not clear. Both animals show dyslipidemia with elevated TG and total cholesterol levels [33]. Both animal lines are good models of MS with obesity and QD 2, but without arterial hypertension. Otsuka Long-Evans Tokushima Fatty (OLETF) Rats

The pathological changes in these rats are associated with a disruption of the cholecystokinin receptor, which controls food intake. OLETF rats exhibit hyperphagia and become obese over time. At 18 weeks of age, the animals develop hyperglycemia, and by 8 weeks, elevated TG levels are noted with normal values of total cholesterol. Blood pressure in OLETF rats is slightly higher than in control animals after 14 weeks. A remarkable feature of this model is that the development of pathological changes is more clearly dependent on the sex of the animals than in others. Castration of males significantly reduces the risk of developing QD 2, and testosterone therapy restores the manifestation of the disease.

This model is often used in research to study QD 2 and its complications. GK rats are characterized by the development of hyperglycemia-associated renal dysfunction, peripheral polyneuropathy, and fundus changes. In addition, the appearance of endothelial dysfunction over time has been noted. At the same time, blood pressure remains within normal limits.

Thus, this model is more suitable for studying type 2 diabetes and its complications, but does not fully understand the changes characteristic of MS.

Wistar Ottawa Carlsburg W (WOKW) rats

This line of rats with MS was obtained relatively recently, in 1995, and represents a polygenic model, which brings it closer to the features of MS in humans. These animals are characterized by hyperphagia and obesity. With age, these animals develop hyperinsulinemia, carbohydrate tolerance, dyslipidemia, predominance of TG levels, and moderate arterial hypertension. Symptoms of MS in these animals appear at the age of 8-10 weeks. Modeling the metabolic syndrome using external influences

Of the chemical agents used to model carbohydrate metabolism disorders, the most common are alloxan and streptozocin. It is known that they are used to model diabetes mellitus with absolute insulin deficiency, similar to DM. Type 1 diabetes in humans (QD 1). In neonatal rats, low doses of streptozocin can cause moderate hyperglycemia, insulin resistance, and decreased HDL levels, but without obesity. Therefore, this model cannot be considered an adequate model of MS and QD 2 M is more often used to study.

However, combining low doses of streptozocin with dietary modification gives a more favorable result. Some investigators use experimental protocols in which animals are given a high-calorie (high-fat, high-fructose) diet in combination with low doses of streptozocin .

Methods for modeling MS using isolated dietary modification are also well known. Many animals on a high-calorie diet develop all the features of MS, which is very close to the development of MS in humans. A standard rodent diet contains approximately 10% fat, while a high-fat diet can contain 30% or more. High-fat diets have been used for decades and have proven their effectiveness. The addition of animal fats is significantly more effective in inducing metabolic disorders than vegetable fats. However, recent data suggest that vegetable oil (olive oil) can also induce significant obesity and insulin resistance in rodents. In addition, methods have been developed to model MS by adding carbohydrates to animal feed. The main ones in this case are diets enriched with fructose and sucrose (the main source of fructose). Against the background of a diet enriched with fructose, rodents develop insulin resistance, glucose intolerance, dyslipidemia, and increased blood pressure.

In recent years, a high-fat diet with an increased carbohydrate content has become increasingly popular. This diet is considered to be the closest to the diet of modern humans and the most suitable for modeling MS. Most often, sucrose or pure fructose is used as carbohydrates, and lard, olive or coconut oil are used as fats. When using such a diet, animals develop all the signs of MS. The main difficulty in the case of inducing MS by dietary correction is the selection of the starting line of animals. Most rodents become obese when fed a high-fat diet or given excess carbohydrates, but not all are predisposed to developing MS. The most commonly used rats are Wistar and Sprague-Dawley. However, not all Sprague-Dawley animals develop MS on a high-fat diet (approximately 32%). In this case, as in others, it is very important to observe the metabolic disorders that develop in animals over time. Among the interesting models of MS are the sand rat (Psammomys obesus) and the Nilotic grass rat (Arvicanthis niloticus), which are fed a vegetarian low-calorie diet in the wild. In laboratory conditions, these animals develop obesity, insulin resistance, and hyperglycemia with a high-calorie diet. When these animal fats are added to the diet, they also develop hyperlipidemia and atherosclerosis [63]. These models are very close to MS in humans, since the initial mild impairment (insulin resistance) is aggravated by a change in diet. Thus, to date, many experimental models of MS have been developed that meet the requirements of most studies. However, some difficulties remain, the main one being that almost no model can be 100% extrapolated to humans and each of them has its own specific characteristics that can affect the final outcome of the study. Not all MS models are completely stable and require careful monitoring of metabolic parameters over time.

In conclusion, it should be noted that the selection of an optimal model is one of the key points in conducting any experimental study, especially in the study of MS.

Conflict of interest. The authors declare no potential conflicts of interest.

Reference

1. Belenkov Yu.N., Privalova E.V., Kaplunova V.Yu., Zektser V.Yu., Vinogradova N.N., Ilgisonis I.S., Shakaryants G.A., Kozhevnikova M.V., Lishuta A.S. Metabolic syndrome: historical development, basic diagnostic criteria. Rational Pharmacotherapy and Cardiology 2018;14(5):757-764. DOI: 10.20996/1819-6446-2018-14-5-757-764

2. Butrova SA. Sovremennye vozmojnosti i perspective therapy of metabolic syndrome. Pregnant patient 2007;6–7:31–34

3. Bokarev I. N. Metabolic syndrome // Clinical medicine. - 2014. - T. 92. - no. 8. - S. 71-76.

4. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). J. A. M. A. 2001

5. Uchamprina V. A., Romantsova T. I., Kalashnikova M. F. Metabolic syndrome: argumenty "za" and "protiv" //Ojirenie i metabolizm. – 2012. – no. 2. - S. 17-27

6. Leonteva I. V. Metabolic syndrome as a pediatric problem // Russian vestnik perinatologii i pediatrii. - 2008. - T. 53. – no. 3. - S. 4-16 7. Bozorov A.G., Ikhtiyarova G.A., & Davlatov S.S. (2020). Biochemical markers for prediction of premature labor in urogenital infection) // International Journal of Pharmaceutical Research, 12. P. 4894–4897Wong S.K., Chin K.Y., Suhaimi F.H., Ahmad F., Ima-Nirwana S. The effects of a modified high- carbohydrate high-fat diet on metabolic syndrome parameters in male rats. Exp. Clin. Endocrinol. Diabetes. 2018;126(4):205–212. DOI: 10.1055/s-0043-119352.

7. Okatan E.N., Kizil S., Gokturk H., Can B., Turan B. High-carbohydrate diet-induced myocardial remodeling in rats. Curr. Res. Cardiol. 2015;2(1):5–10. DOI: 10.4172/2368- 0512.1000020.

8. Tran W., De Silva T.M., Sobey C.G., Lim K., Drummond G.R., Vinh A. et al. The vascular consequences of metabolic syndrome: rodent models, endothelial dysfunction, and current therapies. Front. Pharmacol. 2020; 11:148. DOI: 10.3389/fphar.2020.00148.