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Experimental Models of Metabolic Syndrome

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Abstract: In recent years, the prevalence of metabolic syndrome (MS) in modern society has been increasing, which leads to an increase in morbidity and mortality. The use of experimental models allows us to understand the causes of the development and progression of MS and to study potential methods of its prevention and treatment. MS is a multifactorial complex of pathological changes, and the choice of an adequate experimental model is fundamental in studying this condition. This review discusses the most common genetic models used to study MS, as well as methods for modeling this syndrome through external influences.

Key words: *syndrome, modeling, experiment, genetic models.*

Metabolic syndrome (MS) is a multifactorial complex of pathological changes based on insulin resistance. In 1988, Reaven G.M. wrote about the combination of insulin resistance, arterial hypertension, hyperlipidemia and obesity [1]. One of the difficult tasks in the history of studying this syndrome was the selection of diagnostic criteria. The most widely used and frequently used are the 2005 guidelines of the International Diabetes Federation (IDF). According to the IDF consensus on MS, the main factors in the development of the syndrome are abdominal obesity and insulin resistance. According to these recommendations, a patient has MS when there is a combination of abdominal obesity and two of four factors: 1) an increase in the level of triglycerides (TG) in the blood (more than 1.7 mmol / l), 2) a decrease in the level of high-density lipoproteins (HDL) (less than 1.3 mmol / l in men and less than 1.29 mmol / l in women), 3) an increase in blood pressure above 130 and 85 mm Hg. Art., 4) an increase in the level of glucose in fasting plasma above 5.6 mmol / l [2]. MS often precedes the development of type 2 diabetes (T2D) and is therefore one of the main risk factors for cardiovascular disease in modern society [3, 4]. In addition, it is associated with the development of hepatic steatosis, impaired renal function and an increased risk of developing cancer [5-7].

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 is the 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 over a number of generations. With the development of new technologies in molecular genetics, it has become possible to obtain knockout animals with the loss of function of a specific gene. Such models are more likely to be used to study specific pathophysiological events rather than a complex phenomenon such as MS. The difficulty in creating such models is also related to the fact that homozygous mutations in a gene are sometimes lethal and cause embryonic death during intrauterine development [8]. Thus, this review mainly covers models with spontaneous mutations acquired 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 very 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.

Methodology

This study utilizes various animal models to investigate metabolic syndrome (MS). These models are categorized into genetic and external influence-based models.

1. Genetic Models

- **Zucker Diabetic Fatty (ZDF) Rats**: These rats have a mutation in the leptin receptor gene, leading to obesity, insulin resistance, and hyperglycemia, representing MS's key components.
- **Spontaneously Hypertensive Obese (SHROB) Rats**: These rats exhibit hypertension, dyslipidemia, and insulin resistance, making them useful for studying lipid metabolism and MS.
- **Db/Db and Ob/Ob Mice**: These mice are deficient in leptin or its receptor, resulting in obesity, insulin resistance, and dyslipidemia, making them suitable for MS research.
- **OLETF Rats**: A model for studying the effects of high-calorie diets and sex hormones on obesity and metabolic dysfunction.
- **GK Rats**: A model for studying Type 2 diabetes and insulin resistance, focusing on hyperglycemia and MS components.
- **WOKW Rats**: A polygenic MS model that encompasses obesity, hyperglycemia, hypertension, insulin resistance, and dyslipidemia.

2. External Influence Models

- **Alloxan and Streptozotocin**: These chemicals induce Type 2 diabetes and MS symptoms when combined with high-calorie diets, providing a model for examining induced metabolic changes.

Result

It is worth considering these models in more detail. Their main characteristics are presented in Table 1.

Table 1

MAIN FEATURES OF GENETIC MODELS OF METABOLIC SYNDROME.

	Obesity	Hyperglycemia	Arterial hypertension	Dyslipidemia	Source
Zucker rats with obesity and QD 2 (ZDF)	+	+	+	+	13, 14, 16,

					17, 19, 20, 22, 23
Spontaneously hypertensive obese rats (SHROV)	+	+	+	+	25, 26, 28, 29
Mice JB/JB (C57BL/KsJ-db/db) and ob/ob (C57BL/6J-ob/ob)	+	+	–	+	31, 32, 33
Otsuka Long-Evans Tokushima Fatty (OLETF) rats	+	+	+	+	34, 35, 36
Goto-Kakizaki (GK) rats	–	+	–	+	38, 39, 45
Wistar Ottawa Carlsburg W (WOKW) rats	+	+	+	+	46, 47

receptors [10]. In homozygous fa/fa mutant rats - ZDF - significantly higher concentrations of leptin are required to exert a biological effect than in animals with a normal genotype [11]. ZDF is characterized by polyphagia and the development of obesity by 4-5 weeks of life. Dietary restriction of such animals led to a decrease in body weight, but their body fat content remained higher than that of lean counterparts [12].

The development of polyphagia and obesity in ZDF is associated with severe insulin resistance and hyperinsulinemia [13, 14]. At the same time, over time, insulin production is reduced due to atrophy of the pancreatic islet apparatus [14, 15]. 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 regarding the development of hyperglycemia in these animals: Some studies have reported hyperglycemia of up to 500 mg/dl (28 mmol/l) at 10–15 weeks of life [16, 17], while others have reported hyperglycemia only at 6 months of age and the increase in glucose levels was not significant [18]. These differences are likely due to some genetic heterogeneity within 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. Elevated total cholesterol (TC) levels are observed as early as 10 weeks of life and only increase with time [19]. The lipid profile of ZDF mice includes a significant increase in very low-density lipoprotein (VLDL) and HDL levels, while low-density lipoprotein (LDL) levels are comparable to those in intact animals [20]. Thus, the use of this model as a model of atherosclerosis poses some challenges. It is worth noting that ZDF develops endothelial dysfunction similar to diabetic microangiopathy in humans [21]. In addition, these animals develop arterial hypertension, but not before 17 weeks of life [22, 23].

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 [24]. 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 [25].

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 [26].

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 [27].

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 [28, 29]. There is also a subtype of Koletsky rats, the SHR/N-cp, which develops severe hyperglycemia [30]. Thus, this model is very useful in studying lipid metabolism disorders in MS and arterial hypertension.

JB/JB (C57BL/KsJ-db/db) and ob/ob (C57BL/6J-ob/ob) mice 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 [31]. Both models are characterized by hyperphagia and relatively high body weight at 15 weeks of age. In db/db animals, glycemic levels at 5 weeks of life do not differ significantly from wild-type mice, but then gradually increase and reach significant differences by 7 weeks of life [32]. However, in ob/ob mice, glycemic levels remain at a much lower level for a long time and reach a significant increase at 15 weeks. The reason for the more pronounced SD in db mice is unclear. Both animals exhibit dyslipidemia with elevated TG and total cholesterol levels [33]. Both animal lines are good models of obesity and MS with QD 2, but without arterial hypertension.

Otsuka Long-Evans Tokushima Fatty (OLETF) rats

The pathological changes in these rats are associated with impaired function of the cholecystokinin receptor, which controls food intake. OLETF rats exhibit hyperphagia and become obese over time [34]. At 18 weeks of age, the animals develop hyperglycemia and by 8 weeks, elevated TG levels are noted with normal values of total cholesterol [35]. Blood pressure in OLETF rats is slightly higher than in control animals after 14 weeks [36]. What is remarkable in this model is that the development of pathological changes is more clearly related to the sex of the animals than to others. Castration of males significantly reduces the risk of developing QD 2, and testosterone therapy reverses disease manifestations [37].

Goto-Kakizaki (GK) rats

GK rats were derived from Wistar rats by long-term selection for hyperglycemia. These animals are characterized by hyperglycemia, insulin resistance, dyslipidemia, but not by weight gain. At birth, these animals have a reduced beta cell mass, and this defect only increases with age.

This model is often used in research to study DM2 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.

Discussion. 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. 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 fully stable and require careful monitoring of metabolic parameters over time.

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

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

References:

1. Бирулина Ю.Г., Иванов В.В., Буйко Е.Е., Быков В.В., Дзюман А.Н. Носарев А.В., Григорьева А.В., Гусакова С.В. Морфологические изменения в сердце и аорте крыс при диет-индуцированном метаболическом синдроме // Бюллетен Сибирский государственный медицинский университет (СибГМУ) Россия, 2022 634050, г. Томск, Московский тракт, birulina20@yandex.ru https://doi.org/10.20538/1682-0363-2022-3-13-21
2. Michos E.D., Khan S.S. Further understanding of ideal car- diovascular health score metrics and cardiovascular disease. Expert. Rev. Cardiovasc. Ther. 2021;19(7):607–617. DOI: 10.1080/14779072.2021.1937127.
3. Rodríguez-Correa E., González-Pérez I., Clavel-Pérez P.I., Contreras-Vargas Y., Carvajal K. Biochemical and nutritional overview of diet-induced metabolic syndrome models in rats: what is the best choice? Nutr. Diabetes. 2020;10(1):24. DOI: 10.1038/s41387-020-0127-4.
4. Saklayen M.G. The global epidemic of the metabolic syn- drome. Curr. Hypertens. Rep. 2018;20(2):12. DOI: 10.1007/ s11906-018-0812-z.
5. Jiménez-González S., Marín-Royo G., Jurado-López R., Bar- tolomé M.V., Romero-Miranda A., Luaces M. et al. The cross- talk between cardiac lipotoxicity and mitochondrial oxidative stress in the cardiac alterations in diet-induced obesity in rats. Cells. 2020;9(2):451. DOI: 10.3390/cells9020451.

6. Saraf R., Huang T., Mahmood F., Owais K., Bardia A., Khab- baz K.R. et al. Early cellular changes in the ascending aorta and myocardium in a swine model of metabolic syndrome. PLoS One. 2016;11(1):e0146481. DOI: 10.1371/journal. pone.0146481.
7. Leonardi B.F., Gosmann G., Zimmer A.R. Modeling diet-in- duced metabolic syndrome in rodents. Mol. Nutr. Food Res. 2020;64(22):2000249. DOI: 10.1002/mnfr.202000249.
8. Wong S.K., Chin K.Y., Suhaimi F.H., Ahmad F., Ima-Nirwana S. The effects of a modified highcarbohydrate 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.
9. Okatan E.N., Kizil S., Gokturk H., Can B., Turan B. High-car- bohydrate diet-induced myocardial remodelling in rats. Curr. Res. Cardiol. 2015;2(1):5–10. DOI: 10.4172/2368- 0512.1000020.
10. Tran V., De Silva T.M., Sobey C.G., Lim K., Drummond G.R., Vinh A. et al. The vascular consequences of metabolic syn- drome: rodent models, endothelial dysfunction, and current therapies. Front. Pharmacol. 2020; 11:148. DOI: 10.3389/ fphar.2020.00148.
11. Ruan X.H., Ma T., Fan Y. Ablation of TMEM126B protects against heart injury via improving mitochondrial function in high fat diet (HFD)-induced mice. Biochem. Biophys. Res. Commun. 2019;515(4):636–643. DOI: 10.1016/j. bbrc.2019.05.084.
12. Sahraoui A., Dewachter C., Vegh G., Mc Entee K., Naeije R., Bouguerra S.A. et al. High fat diet altered cardiac metabolic gene profile in Psammomys obesus gerbils. Lipids Health Dis. 2020;19(1):123. DOI: 10.1186/s12944-020-01301-y.
13. Feriani A., Bizzarri M., Tir M., Aldawood N., Alobaid H., Allagui M.S. et al. High-fat diet-induced aggravation of cardiovascular impairment in permethrin-treated Wistar rats. Ecotoxicol. Environ. Saf. 2021; 222:112461. DOI: 10.1016/j. ecoenv.
14. Lepczyński A., Ożgo M., Michałek K., Dratwa-Chałupnik A., Grabowska M., Herosimczyk A. et al. Effects of three-month feeding high fat diets with different fatty acid composition on myocardial proteome in mice. Nutrients. 2021;13(2):330. DOI: 10.3390/nu13020330.
15. Logvinov S.V., Naryzhnaya N.V., Kurbatov B.K., Gorbu- nov A.S., Birulina Y.G., Maslov L.L. et al. High carbohydrate high fat diet causes arterial hypertension and histological changes in the aortic wall in aged rats: The involvement of connective tissue growth factors and fibronectin. Exp. Geron- tol. 2021; 154:111543. DOI: 10.1016/j.exger.2021.111543.
16. Таримов К.О., Субботкин М.В., Куланова А.А., Петренко В.И., Кубышкин А.В., Фомочкина И.И. и др. Сравнительный анализ коррекции морфофункциональных нарушений в сердечно-сосудистой системе при моделированном метаболическом синдроме. Ожирение и метаболизм. 2020;17(2):208–219. DOI: 10.14341/omet12296.
17. Martinez-Quinones P., McCarthy C.G., Watts S.W., Klee N.S., Komic A., Calmasini F.B. et al. Hypertension induced mor- phological and physiological changes in cells of the arteri- al wall. Am. J. Hypertens. 2018;31(10):1067–1078. DOI: 10.1093/ajh/hpy083.
18. Saklayen MG (2018) The Global Epidemic of the Metabolic Syndrome. Curr Hypertens Rep 20 (2): 12. https://doi.org/ doi:10.1007/s11906-018-0812-z
19. Reaven, G. M. (1988). Role of insulin resistance in human disease. *Diabetes*, 37(12), 1595–1607.
20. International Diabetes Federation (IDF). (2005). The IDF consensus worldwide definition of the metabolic syndrome. Brussels, Belgium: IDF.
21. Alberti, K. G. M. M., Zimmet, P., & Shaw, J. (2006). Metabolic syndrome—a new worldwide definition. *The Lancet*, 366(9491), 1059–1062.
22. Eckel, R. H., Grundy, S. M., & Zimmet, P. Z. (2005). The metabolic syndrome. *The Lancet*, 365(9468), 1415–1428.
23. Lonardo, A., Nascimbeni, F., Mantovani, A., & Targher, G. (2018). Hypertension, diabetes, atherosclerosis and NASH: Cause or consequence? *Journal of Hepatology*, 68(2), 335–352.
24. Kassi, E., Pervanidou, P., Kaltsas, G., & Chrousos, G. (2011). Metabolic syndrome: Definitions and controversies. *BMC Medicine*, 9, 48.
25. Vague, J. (1956). The degree of masculine differentiation of obesities: A factor determining predisposition to diabetes, atherosclerosis, gout, and uric calculous disease. *The American Journal of Clinical Nutrition*, 4(1), 20–34.

26. Lusis, A. J., Attie, A. D., & Reue, K. (2008). Metabolic syndrome: From epidemiology to systems biology. *Nature Reviews Genetics*, 9(11), 819–830.
27. Goto, Y., Kakizaki, M., & Masaki, N. (1976). Spontaneous diabetes produced by selective breeding of normal Wistar rats. *Proceedings of the Japan Academy, Series B*, 52(1), 142–147.
28. Friedman, J. M., & Halaas, J. L. (1998). Leptin and the regulation of body weight in mammals. *Nature*, 395(6704), 763–770.
29. Coleman, D. L. (1978). Obese and diabetes: Two mutant genes causing diabetes-obesity syndromes in mice. *Diabetologia*, 14(3), 141–148.
30. Shimomura, I., Hammer, R. E., Ikemoto, S., Brown, M. S., & Goldstein, J. L. (1999). Leptin reverses insulin resistance and diabetes mellitus in mice with congenital lipodystrophy. *Nature*, 401(6748), 73–76.
31. Phillips, M. S., Liu, Q., Hammond, H. A., et al. (1996). Leptin receptor missense mutation in the fatty Zucker rat. *Nature Genetics*, 13(1), 18–19.
32. Kasiske, B. L., O'Donnell, M. P., Keane, W. F. (1985). The Zucker rat model of obesity, insulin resistance, and hyperlipidemia: Effects of dietary modification. *Journal of the American Society of Nephrology*, 2(8), 1231–1238.
33. • Koletsky, S. (1973). Obese spontaneously hypertensive Koletsky rats: Animal model of simultaneous hypertension and obesity. *Experimental Molecular Pathology*, 19(1), 53–70.
34. Hotamisligil, G. S. (2006). Inflammation and metabolic disorders. Nature, 444(7121), 860–867.
35. Samuel, V. T., & Shulman, G. I. (2012). Mechanisms for insulin resistance: Common threads and missing links. Cell, 148(5), 852–871.
36. DeFronzo, R. A., & Ferrannini, E. (1991). Insulin resistance: A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care, 14(3), 173–194.
37. Kahn, B. B., & Flier, J. S. (2000). Obesity and insulin resistance. Journal of Clinical Investigation, 106(4), 473–481.