Experimental models of metabolic syndrome

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Abstract

Metabolic syndrome (MS) is one of the most significant problems of modern society. Rapidly growing prevalence of MS results in high morbidity and mortality due to its vascular complications. Experimental studies can help us to understand the underlying mechanisms of MS development and progression, as well as to develop potential therapeutic interventions. MS represents a multifactorial complex of pathological changes and the selection of an appropriate experimental model is crucial in investigation of this condition. In this review, we will discuss the most common genetic animal models of MS, along with the models in which MS is caused by exogenous factors.

Key words: metabolic syndrome, model, experimental study, genetic animal model.

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Экспериментальные модели метаболического синдрома

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Резюме

Распространенность метаболического синдрома (МС) в современном обществе прогрессивно увеличивается в течение последних лет, что становится причиной повышенной заболеваемости и смертности. Использование экспериментальных моделей позволяет понять причины развития и прогрессирования МС, исследовать потенциальные методы его профилактики и лечения. МС представляет собой многофакторный комплекс патологических изменений, и выбор адекватной экспериментальной модели является основополагающим в изучении данного состояния. В этом обзоре обсуждаются наиболее распространенные генетические модели, используемые для изучения МС, а также методики моделирования данного синдрома путем внешних воздействий.

Ключевые слова: метаболический синдром, моделирование, эксперимент, генетические модели.

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Introduction

Metabolic syndrome (MS) represents a multifactorial complex of pathological changes, which based on insulin resistance. Back in 1988, Reaven G. M. wrote about a combination of insulin resistance, arterial hypertension, hyperlipidemia and obesity [1]. A choice of diagnostic criteria was one of the difficult problems in the history of study this syndrome. The recommendations of the International Diabetes Federation (IDF) of 2005 are the most common and frequently used. According to the IDF consensus of MS, the main development factors of the syndrome are abdominal obesity and insulin resistance. In obedience to these recommendations, the MS occurs at a combination of abdominal obesity and two of four following factors: 1) increase of the triglycerides (TG) level (over 1.7 mmol/l), 2) reduction high-density lipoprotein (HDL) level (less than 1.3 mmol/l for men and less than 1.29 mmol/l for women), 3) arterial hypertension more than 130 and 85 mmHg, 4) increase the level of fasting plasma glucose more than 5.6 mmol/l [2].

MS often precedes development of Type 2 diabetes mellitus (T2DM), and thus constitutes one of the major risk factors of cardiovascular diseases in modern society [3, 4]. In addition, it is associated with development of hepatic steatosis, renal dysfunction and increased risk of oncological diseases [5–7]. High prevalence of MS and its unconditional effect on the long-term prognosis causes a keen interest in this subject for a long time. To study the pathophysiological basis of the development and methods of MS prevention and treatment the design of acceptable experimental models requires. In this review we will discuss the main available models of MS in rodents at the moment.

Most frequently animals with any genetic defects that leads to the development of various pathologic changes which are characteristic of MS in humans using as experimental model. There are also developments by the induction of these changes by external factors — chemicals and/or diet.

Genetic models of metabolic syndrome

These MS modeling methods are widely used to study specific molecular mechanisms of the syndrome. In general, these models are monogenic. The development of pathological changes in this case, caused by dysfunction of a single protein, while the MS in humans caused by summation of many factors and mechanisms of development. There are also polygenic models, which include, for example, Goto-Kakizaki rats.

Most of the models obtained by selection are associated with spontaneous mutations, enshrined in a series of generations. With the development of new techniques in molecular genetics the producing of knockout animals with induced function loss of a specific gene has become possible. These models more frequently are used for study specific pathophysiological phenomena, rather than complex phenomenon such the MS. The difficulty of creating such models is the fact that homozygous mutations on any gene sometimes are lethal and cause embryo death at the stage of prenatal development [8]. Thus, in this review models with spontaneous mutations obtained by selection will be mainly highlighted.

The development of various MS components can be expressed in varying degrees, and for successful animals using in research is extremely important to choose an acceptable model for each specific situation. One of the most common MS models are rodents with impaired realization of the biological leptin action. The well-known model of obesity and MS is Zucker rats with obesity and type 2 diabetes. They are characterized by a mutation in the leptin receptor gene. Spontaneously hypertensive rats SHR with obesity (SHROB), miceob/ob and db/db also are also widely used. Conditionally it is possible to allocate models with intact biological effects of leptin: Otsuka Long-Evans Tokushima Fatty (OLETF), Goto-Kakizaki (GK), Wistar Ottawa Karlsburg W (WOKW).

We should pay special attention for these models. Their main characteristics are given in Table 1.

Zucker rats with obesity and type 2 diabetes

In 1961 L. Zucker and co-authors described spontaneous mutations, leading to obesity development in rats [9]. This mutation was called «fatty», or fa. It is an autosomal recessive and influences the functioning of the extracellular part of the leptin receptor. In cell culture experiments it has been proven that by this

Table 1

THE MAIN CHARACTERISTICS OF GENETIC MODELS OF METABOLIC SYNDROME

	Obesity	Hyperglycemia, impaired glucose tolerance	Arterial hypertension	Dyslipidemia	Reference
Zucker rats with obesity and type 2 diabetes	+	+	+	+	13, 14, 16, 17, 19, 20, 22, 23
Spontaneously hypertensive ratswith obesity (SHROB)	+	+	+	+	25, 26, 28, 29
Micedb/db (C57BL/KsJ-db/db) andob/ob (C57BL/6J-ob/ob)	+	+	–	+	31, 32, 33
Otsuka Long-EvansTokushima Fatty rats (OLETF)	+	+	+	+	34, 35, 36
Goto-Kakizaki rats (GK)	–	+	–	+	38, 39, 45
Wistar Ottawa Karlsburg W rats (WOKW)	+	+	+	+	46, 47

mutation the receptor has a reduced affinity to leptin, and also a signal transmission through the receptor is disrupted [10]. In rats with homozygous mutation fa/fa (ZDF) significantly greater concentration of leptin is required for realization of the biological effect compared with animals with the normal genotype [11]. ZDF are characterized by polyphagia and the development of obesity at 4–5 weeks of life. A nutrition limiting of such animals resulted in a weight reduction, but the fat content in their body had increased as compared with lean animals [12].

Polyphagia and obesity in ZDF are associated with pronounced insulin resistance and hyperinsulinemia [13, 14]. In this case, with time there is a decrease of insulin production due to atrophy of the pancreatic insular apparatus [14, 15]. Thus, this model is characterized by changes similar to the course of MS and T2DM in humans.

Conflicting data about the development of hyperglycemia have been obtained in these animals: according to some studies hyperglycemia to 500 mg/dL (28 mmol/l) has developed by 10–15 weeks of age [16, 17], in other works hyperglycemia was registered only in 6 months of age and glucose level rise was not as significant [18]. Perhaps these differences are related to a genetic heterogeneity of colonies. At the same time the glucose tolerance disturbance according to the results of oral glucose tolerance test is confirmed by all researchers.

Dyslipidemia is one of the distinctive features of this MS model. Increasing total cholesterol level (TC) is registered already at the 10th week of life, and only grows with time [19]. To special features of lipid profile ZDF applies significant increase of very low-density lipoproteins (VLDL) and HDL level, while the low-density lipoprotein (LDL) level is comparable to intact animals [20]. So, using this model as an atherosclerosis model has some difficulty. It is noteworthy that endothelial dysfunction which develops by ZDF is similar to diabetic microangiopathy in humans [21]. Furthermore, these animals have arterial hypertension, but it develops during time, not earlier than the 17th week of life [22, 23].

Thus the ZDF rats are one of the most adequate model for the study of pathological changes in the organism at MS and methods for their correction. Nevertheless it is worth noting that the development of MS in humans is caused by many factors, not just the change of the metabolic leptin actions, and it is incompetent to assess MS pathogenesis on this model, as in most others.

Spontaneously hypertensive rats with obesity (SHROB)

SHR rats — is a well-known model of arterial hypertension. The SHR rats with obesity (SHROB), as well as ZDF rats, is characterized by leptin receptor gene mutation fa^{k}, leading to disruption of signal transduction through the receptor. SHROB

are also known as Koletsky rats, because in 1973 this line was described by S. Koletsky and his group [24]. These animals have an increased food intake and to 5 weeks of age they are already overweight, and to 7–12 months of age males have weigh about 750–1000 g [25].

This model is characterized by the development of dyslipidemia with significant TG level increase and a moderate total cholesterol level increase. The arterial hypertension develops at the age about three months, systolic blood pressure becomes over 150 mm Hg. with following increasing of this level throughout life [26]. Over time, atherosclerotic arterial disease and kidney damage also occurs, therefore the life expectancy is not more then 1 year [27].

Hyperinsulinemia and insulin resistance present in all animals and are associated with normal or moderately elevated fasting glucose levels. In this case, the impaired glucose tolerance was found in many studies [28, 29]. There is also a subtype of Koletsky rats — SHR/N-cp, which develop severe hyperglycemia [30]. Thus, this model is very useful in the study of lipid metabolism disorders in MS and hypertension.

Micedb/db (C57BL/KsJ-db/db) andob/ob (C57BL/6J-ob/ob)

Db/dbmice line is characterized by a leptin receptor defect and rapidly increasing insulin resistance. IN mice with ob mutations the leptin production is impaired, and the treatment of these animals by leptin reduces the severity of insulin resistance, decreases food intake and prevents theT2DM development [31]. Both of these models are characterized by hyperphagia and relatively higher weight at the age of 15 weeks.

Glycemia level at 5 weeks of age in the db/db animals is not significantly different from wild type of mice, but later it progressively increases and reaches a significant difference to the 7th week of life [32]. At the same time, glucose level in ob/ob mice is maintained at a low level for longer and achieves significant increase to the 15th week of age. The reason of more pronounced DM in db mice is unclear. In both of these animals dyslipidemia with increased triglycerides and total cholesterol levels is noted [33]. Both of animals lines are a good models of MS with obesity and type 2 diabetes, but without hypertension.

Otsuka Long-Evans Tokushima Fatty rats (OLETF)

Pathological changes in these rats are associated with disruption of cholecystokinin receptor, controlling food intake. In OLETF rats hyperphagia occurs and obesity develops over time [34]. At the age of 18 weeks hyperglycemia develops, and in 8 weeks of age there is an increase of triglyceride level with a normal total cholesterol level [35]. The blood pressure in OLETF rats is slightly higher than in control animals, already after the 14th week [36]. This model is characterized by more pronounced dependence of pathological changes on the animal's sex. Males castration greatly reduces the risk of type 2 diabetes development, at the same time, the therapy by testosterone restores the disease manifestation [37].

Goto-Kakizaki rats (GK)

GK rats were obtained from Wistar rats by a continuous selection based on hyperglycemia. These animals are characterized by hyperglycemia, insulin resistance, dyslipidemia, but have not great weight [38, 39]. At birth these animals have a beta cells mass decrease and with the age this defect grows [40].

In the researchers this model is most often used for study of type 2 diabetes and its complications. For GK rats it is characteristically to develop a renal dysfunction [41], peripheral polyneuropathy [42], changes in the fundus [43], associated with hyperglycemia. In addition, the appearance of endothelial dysfunction was detected with time [44]. At the same time blood pressure is within normal level [45].

Thus, this model is more appropriate for study of type 2 diabetes and its complications, but in full does not implement the changes typical for MS.

Wistar Ottawa Karlsburg W rats (WOKW)

This rat line with MS was received relatively recently, in 1995, and it represents a polygenic model. This fact makes it comparable to the characteristics of MS in humans. With age, in these animals hyperinsulinemia, disturbance of tolerance to carbohydrates, dyslipidemia with predominant TG rise and moderate hypertension are developing [46, 47]. The MS symptoms appear in these animals at the age of 8–10 weeks.

The metabolic syndrome modeling by external influences

Among the chemical agents used for simulation of carbohydrate metabolism disorders, the most common are alloxan and streptozotocin. It is well known that they are used for modeling of diabetes with absolute insulin deficiency similar to diabetes type 1 (DM1) in humans [48]. It was established that using of streptozotocin in low doses in neonatal rats may induce moderate hyperglycemia, insulin resistance and reduction of HDL levels, but without obesity [49–51]. Thus, this model can not be considered an adequate model of MS, and more often is used for study of type 2 diabetes.

At the same time, the combination of small streptozotocin doses injection and diet correction leads to more acceptable result. Some researchers use the experimental protocols, in which the animals receive a high-calorie diet (high fat and fructose) in combination with the injection of low doses of streptozotocin [52, 53].

The MS modeling techniques by isolated diet correction are also well known. In many animals receiving high-calorie meals there are developing all the signs of MS, which is very similar to the process of development of MS in humans. A standard rodent chow contains about 10% fat, while the high-fat diet may include 30% fat or more. High-fat diets have been used for several decades and have proven their efficiency [54]. An addition of animal fat is more effective for metabolic disorders inducing compared with vegetable fat [55]. At the same time, according to the data of recent years, vegetable fat (olive oil) also is able to induce significant obesity and insulin resistance in rodents [56].

In addition, there are techniques to develop MS with addition of carbohydrates to animal feed. In this case, the basic diets are enriched with sucrose and fructose (the main source of fructose). Along with diet rich in fructose insulin resistance, impaired glucose tolerance, dyslipidemia, high blood pressure are developed [57].

In last years, combined high-fat diet with a high content of carbohydrates is getting more and more common. Such diet is the most similar to the nutrition of modern human and is considered the most appropriate for MS modeling. As carbohydrates most often is used sucrose or clean fructose, as fats — lard, olive oil or coconut oil. By using such nutrition in all animals the signs of MS are developing [58, 59].

In the case of the MS induction by diet correcting the main difficulty is the choice of the initial animals line. Obesity develops in most of rodents with high-fat diet or adding an excess of carbohydrates, but not all are exposed to further development of MS. The most frequently used rats are the Wistar and Sprague-Dawley. Herewith MS develops in not all Sprague-Dawley animals with high-fat diet (about 32%) [60]. In this case, as well as in others, it becomes very important to monitor metabolic disorders developing in animals over time.

The interesting MS models are the sand rat (Psammomysobesus) and the African grass rat (Arvicanthis niloticus), which naturally eat vegetarian low-calorie diet. In laboratory conditions with high-calorie diet in these animals develops obesity, insulin resistance, and hyperglycemia [61, 62]. By adding fats to the diet hyperlipidemia and atherosclerosis is also developed [63].These models are very similar to MS in humans, considering that initial feebly expressed impairment (insulin resistance) are enhanced by modifying of diet.

Thus, at this moment, a large number of experimental models of MS has been developed, which are able to satisfy the requirement of most studies. At the same time, there are some problems, the main of which — is the fact that almost no one model can not be extrapolated to 100% for human, and each model has its own characteristics that can influence the outcome of the study. All MS models are not completely stable and require a detailed monitoring of metabolic parameters over time.

In conclusion, it should be noted that the choice of appropriate model is one of the founding moment in fulfilling any experimental studies, particularly associated with the study of MS.

Conflict of interest. The authors declare no conflicts of interest

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