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Progress in Creating Diet-Induced Models of Metabolic Syndrome in Animals and the Possibility of Extrapolating New Models to Pathological Processes in Humans

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Abstract Metabolic syndrome (MS) is characterized by multifactorial pathological changes, such as obesity, hyperglycemia, hypertension and dyslipidemia. The main factors in the development of the syndrome are considered to be abdominal obesity and insulin resistance. In medical practice, it is recommended to establish MS in a patient with a combination of abdominal obesity and two of four factors: an increase in the level of triglycerides (TG) in the blood (more than 1.7 mmol/l), 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), increases in blood pressure more than 130 and 85 mm Hg. Art., increased fasting plasma glucose levels more than 5.6 mmol/l [1]. Diet-induced models are considered the most adequate in terms of the etiology and mechanisms of development of metabolic disorders in humans. Diet influences whole body metabolism and regulation through hormonal, carbohydrate and lipid metabolism. Currently, models on rabbits, mini-pigs, etc. are increasingly used. Each experimental model has its own characteristics that affect the final result of the study, so none of them can be completely extrapolated to humans. Thus, the choice of model depends on the objectives of the experiment.

Keywords Metabolic syndrome, Diet-induced diet, Experimental model

1. Introduction

There has been significant progress in creating diet-induced models of metabolic syndrome in animals, particularly rodents. These models involve feeding animals a high-fat, high-sugar diet to induce obesity, insulin resistance, dyslipidemia, and other features of metabolic syndrome. These models have provided valuable insights into the underlying mechanisms of metabolic syndrome and have been instrumental in testing potential therapeutics.

However, there are limitations to extrapolating findings from animal models to pathological processes in humans. While these models can mimic certain aspects of human metabolic syndrome, they do not fully capture the complexity and heterogeneity of the human condition. Additionally, differences in metabolism and physiology between species can limit the direct applicability of findings from animal studies to humans.

Despite these challenges, researchers continue to refine and develop new animal models that more closely recapitulate human metabolic syndrome. By incorporating genetic modifications, microbiome manipulations, and other advanced techniques, scientists hope to create more accurate representations of human disease processes. Additionally, efforts are underway to integrate data from animal studies with clinical observations to better understand the relevance of animal models for human health.

Overall, while diet-induced animal models have provided valuable insights into metabolic syndrome, careful consideration is needed when extrapolating findings to humans. Continued efforts to improve the relevance of these models to human pathology will be crucial for advancing our understanding and treatment of metabolic syndrome. Metabolic syndrome is characterized by multifactorial pathological changes, such as obesity, hyperglycemia, hypertension and dyslipidemia. The main factors in the development of the syndrome are considered to be abdominal obesity and insulin resistance. In medical practice, it is recommended to establish MS in a patient with a combination of abdominal obesity and two of four factors: an increase in the level of triglycerides (TG) in the blood (more than 1.7 mmol/l), 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), increases in blood pressure more than 130 and 85 mm Hg. Art., increased fasting plasma glucose levels more than 5.6 mmol/l [1].

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Diet-induced models are considered the most adequate in terms of the etiology and mechanisms of development of metabolic disorders in humans. Diet influences whole body metabolism and regulation through hormonal, carbohydrate and lipid metabolism. Currently, non-rodent models are increasingly being used - rabbits, mini-pigs, etc. Each experimental model has its own characteristics that affect the final result of the study, so none of them can be completely extrapolated to humans. Thus, the choice of model depends on the objectives of the experiment.

2. Purpose of the Research

This article reviews the progress made in creating experimental MS models over the past 10 years.

3. Materials and Methods

Currently, combined experimental models of MS with a high content of both fat and carbohydrates, including the so-called "cafeteria diet", are becoming increasingly widespread in scientific research [2]. It is believed that it is these combined models that are closest to modern human nutrition and are adequate in terms of the mechanisms of MS development. It has been shown that a high-fat diet plus sucrose causes metabolic syndrome faster than a high-fat diet alone [3].

4. Results and Discussion

Previously, diet-induced models of MS were developed in rodents: with an increased amount of fat 30–60% of the caloric intake, cholesterol 0.1–1.25% of the caloric intake, table salt 8%, sucrose and fructose 60–70% of the caloric intake diet both in genetically modified animals (rats of the ZDF, DahlSS lines, mice AKR, A/J) and wild breeds of animals (rats of the Wistar and Sprague Dawley (SD) lines, mice of the C57BL/6 line, golden hamsters, guinea pigs) [4].

In wild-type mice of the C57BL/6J line, the addition of 45–60% fat to the diet contributes to the fairly rapid development of obesity and hyperglycemia within 8 weeks [5].

The most common laboratory strains of mice and rats for most biomedical research are the outbred Wistar rat strain and the inbred C57Black/6 and BALB/C mouse strains. It has been shown that rodent models of metabolic syndrome generally reproduce the main components of this pathology. However, in biochemical terms, significant differences in systems associated with lipid metabolism have been found between rodents and humans, which makes rodents resistant to the development of atherosclerosis and coronary heart disease. In particular, mice and rats lack cholesteryl ester transfer protein (CETP), which provides reverse cholesterol transport [6]. Large-scale genomic studies in humans have found a more significant correlation between CETP gene polymorphisms and HDL-C concentrations than among other loci, which to a certain extent influences the effectiveness of lipid-lowering drug therapy [7]. It has been revealed that with a lack of protein - the carrier of cholesterol esters, the development of age-related atherosclerotic changes significantly slows down and life expectancy increases [8].

There are other differences in the metabolism of rodents and humans. Thus, 70% of cholesterol in humans is synthesized in the body and 30% comes from food, while in rodents most of the cholesterol comes from food [9]. HDL predominates in the blood plasma of mice and rats, while LDL predominates in humans and rabbits. It has long been established that in rabbits on a regular diet, approximately 40% of blood plasma cholesterol is contained in HDL, and in rabbits on a cholesterol (atherogenic) diet, more than 90% of cholesterol is contained in VLDL and LDL [10,11].

The ability of mice and rats to form bile acid from cholesterol and, accordingly, help reduce cholesterol, is significantly higher than that of humans and rabbits [7].

It has been established that the reaction to nutritional imbalances in mice and rats is different. In rats, compared to mice, there was a significantly more pronounced reaction of the lipoprotein spectrum to nutritional imbalances, especially to cholesterol levels, which is manifested in an increase in LDL content, a decrease in HDL and an increase in the atherogenic index. The development of steatosis was noted in the liver of rats fed diets with cholesterol. In Wistar rats and C57Bl/6 mice, the liver is most sensitive to fructose. Changes in the levels of hormones that regulate carbohydrate metabolism (GLP, glucagon), as well as ghrelin, due to the consumption of fructose supplements were significantly greater in mice compared to rats. The effect of a combination of cholesterol and fructose on leptin levels in mice and rats was in the opposite direction [12].

The work [13] carried out a comparative study of the main indicators of carbohydrate and lipid metabolism during a fructose-enriched diet and a high-fat diet under experimental conditions in white outbred rats. The authors observed an increase in glucose, insulin, and lipid metabolism in the experimental groups. Moreover, the content of glucose and insulin in a fructose-enriched diet increased by 18.7% ($p = 0.009$), 22.2% ($p = 0.076$), 21.5% ($p = 0.009$), 50% ($p = 0.009$), 62.5% ($p=0.009$), 106.3% ($p=0.009$) according to the days of the experiment, respectively. The increase in lipid metabolism indicators was more pronounced in the experimental group, which had a high fat content in their diet, already in the first time period of the experiment: cholesterol - by 80.8% ($p = 0.009$), low-density lipoproteins - by 100% ($p = 0.009$), triglycerides - by 120% ($p=0.009$), high-density lipoproteins - by 60.9% ($p=0.009$).

In work [14], against the background of the use of high-calorie diets containing 45 and 60% fat, outbred 8-week-old male mice develop moderate hyperglycemia, glucose tolerance, glycogen accumulation decreases and the formation of coarse and fine steatosis in the liver, as well as a tendency to increase DPP-4 dipeptidyl peptidase activity after 17 weeks with a 45% fat content and 13 weeks with a 60% fat content. The use of a more high-calorie diet with a lipid content of

60% leads to metabolic disorders not only of lipid, but also of carbohydrate metabolism.

Unlike rats, mice are less commonly used as a model for sucrose- or fructose-induced insulin resistance and hypertriglyceridemia. Their metabolic response to a diet rich in fructose and sucrose is highly variable and depends on the strain of mice. For example, the C57BL/6 mouse line, used to model MS with a fat-rich diet, does not develop insulin resistance, or its formation occurs very slowly after feeding with fructose [15].

Z.H. Yang et al. investigated the short-term effect of a combined high-calorie diet consisting of milk fat (21% by weight) and sucrose (34% by weight) on the induction of the development of MetS in 8-week-old C57BL/6 mice. The authors noted massive deposition of lipids in many organs (muscles, liver, skeletal muscles, adipose tissue), which is associated with increased expression of genes involved in the synthesis of lipogenesis enzymes in the liver, the result of which is the production of fatty acids and triglycerides. There was also increased activity of genes encoding lipoprotein lipase, responsible for the hydrolysis of chylomicrons and VLDL and the assimilation of lipids by tissues for the purpose of their deposition. The expression of genes encoding proteins that are involved in insulin signal transmission decreased, which reduced tissue resistance to insulin against the background of its increased concentration in the blood [16].

Thus, due to biochemical differences, MS models in rodents do not always allow adequate extrapolation of the results obtained to humans. Also, one should take into account the difficulty of conducting a long-term dynamic experiment in small animals, different metabolic rates, as well as the impossibility of taking electrophysiological indicators in mice and anatomical and physiological inconsistencies in the cardiovascular and other systems of rodents and humans. However, rodent models of MS generally reproduce the main manifestations of the metabolic syndrome, and therefore they can be used for screening purposes, as well as for studying the effect of biologically active substances on metabolic pathways that are similar in rodents and humans.

The emergence of genetically modified rodent models creates new opportunities to study the molecular mechanisms of MS development and study pharmacological agents. The most famous genetically modified model of MS is fa/fa Zucker fatty rats (ZFR) and Zucker diabetic fatty rat (ZDF) rats. The ZFR animal line has a mutation in the leptin receptor gene on chromosome 5. This defect leads to a decrease in the binding of leptin to the surface of receptor-expressing cells, while the affinity for leptin does not change. Excessive expression of TNF-α in ZFR leads to the development of endothelial dysfunction against the background of induction of NADPH oxidase with subsequent formation of superoxide anions. This animal line can be used as an independent model of MS; pathological changes in animals develop when kept on a standard diet [17]. ZDF rats are selectively inbred to hyperglycemia and are a substrain of the ZFR strain. ZDF carry an autosomal recessive defect in pancreatic β-cell transcription, the inheritance of which occurs independently of mutation of the leptin receptor gene (Lepr). It should be noted that the gene responsible for the defect has not yet been identified. It has been established that this defect is not enough to cause diabetes, and only in combination with a mutation of the Lepr gene can hyperglycemia develop [18]. ZDF rats are less obese but more insulin resistant than ZFR rats [17].

To date, several dozen genetically modified lines of rodents have been obtained in various laboratories around the world, which can be used to study various aspects of the pathogenesis of MS and identify the mechanisms of action of drugs [19,20].

Experimental diet-induced models of MS in rabbits are more adequate to human MS than diet-induced models in rodents, since the metabolism of rabbits is close to that of humans. In one of the latest works on this problem, Arias-Mutis et al. [21] developed a rabbit model of metabolic syndrome using a combined high-fat and high-carbohydrate diet (10% hydrogenated cocoa butter, 5% lard, 15% sucrose solution) for 28 weeks.

In [22], a multifactorial study of MS was carried out in rabbits on a combination diet with the addition of crystalline cholesterol to the daily diet at a dose of 250 mg/kg body weight mixed with grated carrots (approximately 100 g) against a background of physical inactivity. A freshly prepared 5% sucrose solution was poured into the animals' drinking bowl every day. Every 2 days, insulin was injected subcutaneously into the animals at a dose of 0.1 units from the back. / 100 g body weight. The experiment was carried out for 60 days. The study showed that in animals of the experimental group with the MS model, the studied physiological and biochemical parameters (blood pressure, absolute weight gain, levels of C-peptide, sugar, cortisol, phosphorus, calcium, triglycerides, cholesterol, LDL and HDL in the blood) increased. upward trend.

Renner et al. [23] present a model of MS in minipigs that is close to human MS. To create the model, ovariectomized females were used and maintained on a high-fat/high-energy diet for 70 weeks. Animals under these conditions developed severe subcutaneous and visceral obesity (body fat >50% body weight versus 22% in L-GM), elevated plasma cholesterol, triglycerides, and free fatty acids, and insulin resistance (HOMA-IR). 5 versus 2 in L-GM), impaired glucose tolerance and increased resting and active heart rate. However, fasting glucose concentrations remained within normal limits throughout the study. This model can be used to evaluate new treatments for obesity and comorbidities, to identify triggers and mechanisms of adipose tissue inflammation, as well as mechanisms that prevent complete metabolic decompensation despite morbid obesity.

Models of MS have also been obtained in dogs. Overweight in dogs can be induced within 4–12 weeks by providing excess food in various forms: a standard diet of meat and kibble; a diet of meat with added fat or commercial diets high in fat or fructose, or both. The increase in energy intake is most noticeable during the first 1-2 weeks on these supplemented diets, but hyperphagia persists throughout the

time the animals have ad libitum access to the diets. Elevated fasting glucose and insulin concentrations are not observed in these models, but metabolic defects are clearly visible in all of them, despite modest increases in body weight [24].

The most commonly used species in metabolic disease research include rhesus macaques (Macaca mulatta), cynomolgus macaques (Macaca fascicularis), baboons (Papio spp.), African green monkeys (Chlorocebus spp.), and common marmosets (Callithrix jacchus), which may have diet-induced models of MS have been obtained [25].

5. Conclusions

To date, the metabolic consequences of excess fat accumulation are well understood, but the actual triggers and underlying mechanisms of adipose tissue inflammation are unclear [23]. A better understanding of the triggers and mechanisms of inflammation may reveal new therapeutic targets for the treatment of obesity and related comorbidities. In this regard, animal models that exhibit critical aspects of human obesity and comorbidities are important for expanding our knowledge of pathological processes and evaluating drug candidates for translation to humans. Rodent models of diet-induced obesity are most often the first-line option for pharmacological screening, but have little predictive value for drug efficacy and safety in humans. Given the close similarities in human anatomy and physiology to pigs and non-human apes, they may serve as models to bridge the mouse-human gap.

REFERENCES

[1] Alberti K.G., Zimmet P., Shaw J., IDF Epidemiology Task Force Consensus Group. The metabolic syndrome - a new worldwide definition // Lancet. - 2005. - Vol. 366, № 9491. - P. 1059–1062.

[2] Kovaleva M.A., Makarova M.N., Selezneva A.I., Makarov V.G. Primenenie zhivotnyh so spontannoj gipertenziej dlja modelirovanija metabolicheskogo sindroma. Obzory po klinicheskoj farmakologii i lekarstvennoj terapii, 2012; 4: 91–94.

[3] Neuhofer A., Wernly B., Leitner L., Sarabi A., Sommer N.G., Staffler G., Zeyda M., Stulnig T.M. An accelerated mouse model for atherosclerosis and adipose tissue inflammation. Cardiovasc Diabetol. 2014 Jan 17; 13: 23. DOI: 10.1186/1475-2840-13-23.

[4] Aydin S., Aksoy A., Aydin S., Kalayci M., Yilmaz M., Kuloglu T., Citil C., Catak Z. Today's and yesterday's of pathophysiology: Biochemistry of metabolic syndrome and animal models / Suleyman Aydin [et al.]. Nutrition. 2014. Jan; 30 (1): 1–9.

[5] Chu D.T., Malinowska E., Jura M., Kozak L.P. C57BL/6J mice as a polygenic developmental model of diet-induced obesity. Physiol Rep. 2017 Apr; 5 (7).

[6] Wong SK, Chin KY, Suhaimi FH, Fairus A, Ima-Nirwana S. Animal models of metabolic syndrome: a review. Nutrition & metabolism. 2016; 13: 65.

[7] Звягина М.В., Маль Г.С., Бушуева О.Ю., Быканова М.А., Летова И.М., Грибовская И.А., Солодилова М.А., Полоников А.В. Влияние генотипов белка-переносчика эфиров холестерина на эффективность гиполипидемической терапии розувастатином у больных ишемической болезнью сердца с атерогенными гиперлипидемиями // Фундаментальные исследования. – 2015. – № 1-3. – С. 517-521.

[8] Nomura A., Won H.H., Khera A.V. et al. (2017) Protein-Truncating Variants at the Cholesteryl Ester Transfer Protein Gene and Risk for Coronary Heart Disease. Circ. Res., 121(1): 81–88.

[9] Shiomi M., Koike T., Ito T. Contribution of the WHHL rabbit, an animal model of familial hypercholesterolemia, to elucidation of the anti-atherosclerotic effects of statins. Atherosclerosis. 2013, vol. 231. no. 1. P.39-47.

[10] Roberts D.C.K., West C.E., Redgrave T.G., Smith J.B. Plasma cholesterol concentration in normal and cholesterol-fed rabbits. Atherosclerosis. 1974. vol. 19. no. 3. P. 369-380.

[11] Tall A.R. Plasma cholesteryl ester transfer protein. J. Lipid Res. 1993. vol. 34. no. 8. P. 1255-1274.

[12] Апрятин С.А., Мжельская К.В., Трусов Н.В., Балакина А.С., Кулакова С.Н., Сото С.Х., Макаренко М.А., Ригер Н.А., Тутельян В.А. Сравнительная характеристика in vivo моделей гиперлипидемии у крыс линии Вистар и мышей линии С57Bl/6. Вопр. питания. 2016. № 6. С. 14-23.

[13] Гилева О.Г., Бутолин Е.Г., Терещенко М.В., Иванов В.Г. Оценка показателей углеводного и липидного обмена у крыс в зависимости от вида высококалорийного питания // Ожирение и метаболизм. - 2022. - Т. 19. - № 1. - С. 47-52.

[14] Ковалева М.А., Гущин Я.А., Макарова М.Н., Макаров В.Г. Сравнительное исследование использования высоко калорийных диет, обогащенных разным количеством липидов, для моделирования метаболического синдрома. Лабораторные животные для научных исследований. 2019; 1.

[15] Ricci M.R., Ulman E.A. DietInduced Metabolic Syndrome in Rodent Models animal // LABNEWS. – 2007. – March.

[16] Yang Z.H., Miyahara H., Takeo J., Katayama M. Diet high in fat and sucrose induces rapid onset of obesity-related metabolic syndrome partly through rapid response of genes involved in lipogenesis, insulin signaling and infl ammation in mice // Diabetology & Metabolic Syndrom. – 2012. – V. 4, № 32. doi:10.1186/1758-5996-4-32.

[17] Ковалева М.А., Макарова М.Н., Макаров В.Г. Генетически модифицированные линии лабораторных животных, используемые в качестве модели метаболического синдрома и сахарного диабета. Лабораторные животные для научных исследований. 2018; 1.

[18] Wang B., Chandrasekera C., Pippin J.J. Leptin- and Leptin Receptor-Deficient Rodent Models: Relevance for Human Type 2 Diabetes. Current Diabetes Reviews. 2014. Vol. 10: 131–45.

[19] Р.А. Клёсов, О.И. Степанова. Генетические биомодели метаболического синдрома. Биомедицина, №1, 2017, с. 50-58.

[20] Е.Н. Кравчук, М.М. Галагудза. Экспериментальные модели

метаболического синдрома. Артериальная гипертензия, Том 20, № 5, 2014, с.377-383.

[21] Arias-Mutis OJ, Marrachelli VG, RuizSaurı´A, Alberola A, Morales JM, Such-Miquel L, et al. (2017) Development and characterization of an experimental model of diet-induced metabolic syndrome in rabbit. PLoS ONE 12(5): e0178315.

[22] Ж.О. Мирсултанов, А.А. Мавлонов, О.О. Бабаханов, Ш.У. Солиев. Усовершенствование экспериментального моделирования метаболического синдрома у кроликов. Фармация и фармакология, №1, 2022, с.56-59.

[23] Renner S, Blutke A, Dobenecker B, Dhom G, Müller TD, Finan B, Clemmensen C, Bernau M, Novak I, Rathkolb B, Senf S, Zöls S, Roth M, Götz A, Hofmann SM, Hrabě de Angelis M, Wanke R, Kienzle E, Scholz AM, DiMarchi R, Ritzmann M, Tschöp MH, Wolf E. Metabolic syndrome and extensive adipose tissue inflammation in morbidly obese Göttingen minipigs. Mol Metab. 2018 Oct; 16: 180-190.

[24] Kleinert M, Clemmensen C, Hofmann SM, Moore MC, Renner S, Woods SC, Huypens P, Beckers J, de Angelis MH, Schürmann A, Bakhti M, Klingenspor M, Heiman M, Cherrington AD, Ristow M, Lickert H, Wolf E, Havel PJ, Müller TD, Tschöp MH. Animal models of obesity and diabetes mellitus. Nat Rev Endocrinol. 2018 Mar; 14(3): 140-162. doi: 10.1038/nrendo.2017.161.

[25] Pound, L. D., Kievit, P. & Grove, K. L. The nonhuman primate as a model for type 2 diabetes. Curr. Opin. Endocrinol., Diabetes Obes. 21, 89–94 (2014).