

Animal models in metabolic syndrome.

Modelos animais na síndrome metabólica.

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ABSTRACT

Knowledge about animal models for metabolic study is the basis of research in this area. This work aims to review the main animal models used in the study of obesity and metabolic syndrome. For this, we performed a search in the Pubmed database using the terms “animal models”, “obesity”, “metabolic syndrome” and “bariatric surgery”. Several species of animals can be used for the study of metabolic disorders. However, rodents are the most commonly used, both as monogenic models and as diet-induced obesity (DIO) ones. Monogenic animals are the best choice if only one aspect is being evaluated. DIO animals tend to better demonstrate the interaction between disease, environment and genetics. However, they are still not fully effective in providing understanding of all disease mechanisms.

Keywords: Models, Animal. Obesity. Metabolic Syndrome. Bariatric Surgery.

INTRODUCTION

Obesity and metabolic syndrome are among the main causes of worldwide mortality and their pathogenic mechanisms are not fully understood¹. Therefore, developing new methods of researching diseases to promote prophylaxis, control or cure of these diseases becomes a priority. The use of animals in experimentation was and continues to be of great importance in medical research, including for the study of metabolism. However, the results obtained in preclinical studies are not necessarily similar to those found in humans². Translating the findings in animals to humans can be a challenge, both for the

difference in the physiology between species and for the failure of adoption of the research model itself³. Therefore, the choice of a valid model for the study of any disease, aiming at the maximum similarity with what occurs in human patient, is fundamental².

This work aims to review the main animal models used in the study of obesity metabolic syndrome.

METHODS

We searched articles in the Pubmed database, in the last ten years, selected through the terms “animal models”, “obesity”, “metabolic syndrome” and “bariatric surgery”.

RESULTS

Rodent models

The main rodent models used for the study of obesity and metabolic syndrome are genetically modified models, the most common being monogenic animals (mutation linked to only one gene), and diet-induced obesity (DIO) models^{2,4}.

Monogenic models have the advantage of developing more severe conditions with a very different phenotype, which facilitates mainly studies of drugs, since the effects are better observed. In addition, they tend to produce shorter experiments because they do not require long feeding programs to induce obesity⁵. As the genetic basis is homogeneous and the environmental factors are controlled, the variability of the results is minimal, allowing the use of smaller samples⁶. Observations derived from these pure lineages, however, may not be similar to those found in the human population, since obesity is known to be a multifactorial disease. In this case, DIO models seem to be the ones closest to the mechanisms that promote obesity and metabolic syndrome in humans².

Another disadvantage of monogenic animals is the high mortality due to ketosis in certain strains, as in the case of the db/db mouse, in addition to the need for sophisticated care of the animals, which makes the research more expensive⁶. In general, the cost of a monogenic animal is US\$ 100 to US\$ 400, varying with the lineage chosen, which may even increase depending on gender, weight and age chosen for the research. On their turn, the Wistar and the Sprague Dawley (SD) rats, the most used DIO models, can be purchased on average for twenty dollars each^{7,8}.

Genetically Modified Animals

Monogenic animals

One of the monogenic animals most used in the study of obesity and metabolic syndrome, mainly type 2 diabetes (DM2), is the ob/ob mouse⁹. The spontaneous mutation leading to obesity has been known since the 1950s, but a greater emphasis on the ob gene product, leptin, arose only after 1994⁴. The ob/ob mouse does not produce leptin, the hormone responsible for satiety, but is still sensitive to it⁹. The pronounced obesity that occurs in these animals also has other causes, such as the defect in thermogenesis of brown adipose tissue, which leads to a greater deposition of energy ingested as fat¹⁰, and increased hepatic lipogenesis¹¹.

This animal presents an early pronounced obese phenotype as a first feature, characterized by hyperphagia^{2,4}, followed by hyperinsulinemia, moderate hyperglycemia and insulin resistance, as well as hypothyroidism⁴. The animal has hepatic steatosis, but the progression to hepatitis does not occur. For this, it is necessary the exposure of the mouse to a toxic agent, unlike humans, in which progression is a natural consequence of the disease¹².

Treatment with leptin in these animals usually decreases food intake and increases the uptake of glucose in various tissues. In addition, chronic decrease in dietary intake reduces body weight and improves insulin sensitivity. The administration of recombinant leptin in obese humans due to the deficiency of this hormone demonstrated the same effects observed in mice. However, most obese individuals do not present obesity due to deficiency in leptin production. In contrast, this hormone is usually elevated due to a resistance to leptin, demonstrating that the animal's physiology does not fully reflect human's².

The db/db mouse is phenotypically similar to ob/ob, developing obesity rapidly after weaning, but presents a more severe hyperglycemia due to deficiency in the leptin receptor⁴. The glycemic level in animals at seven weeks is on average 700mg/dl, and sustained throughout their life, unlike what occurs in ob/ob animals, in which levels decrease and normalize after 12 weeks of age¹³. Leptin levels are high, since there is no defect in its production¹⁴. The permanence of hyperglycemia throughout the life of the animal is advantageous in certain experiments in which age influences results. A study aimed at assessing neurological changes induced by hyperinsulinemia and diabetes used db/db mice in different life stages (four, 14 and 26 weeks of age) to verify and correlate the progression of insulin resistance until the onset of diabetes and its evolution. This animal

model allowed the researchers to verify the progression of cerebral atrophy due to age, associated with the metabolic alteration¹⁵.

Although db/db mice are widely used for the study of DM2 and its complications, like retinopathy and neuropathy, these animals do not develop all the alterations found in humans, such as amyloid deposition in the pancreas, for example⁴.

The KK mouse presents resistance to insulin and moderate obesity of polygenic origin. However, the introduction of the agouti (Ay) mutation, considered a monogenic defect, produces the KK-Ay model, which develops DM2 earlier^{2,16}. The agouti protein functions as a melanocortin-4 receptor antagonist, which affects the body's energy regulation, predisposing to obesity^{2,17}. The KK-Ay mouse presents hyperleptinemia and resistance to leptin, without any defect in the ob gene, as well as a decrease in adiponectin levels, similar to that occurring in humans¹⁸.

Overweight in these animals ensues as early as two months of age, stabilizing at six months around 50 to 60g, with 33% of body weight being composed of fat. The animal tends to present hyperinsulinemia, glucose intolerance and hyperglycemia, but it normalizes after one year of age. Glomerular lesion and glycosuria were also observed in this model. As obesity in this animal occurs due to an increase in dietary intake, dietary restriction tends to revert excess weight¹⁷. As both obesity and DM2 appear early in these animals, the experiment time turns out to be shorter. A study using five-week-old, obese and diabetic KK-Ay females evaluated the administration of a compound obtained from royal jelly with therapeutic potential for DM2 for four weeks. Even in the short term, the researchers identified improvement in glycemic levels and insulin resistance¹⁶.

The Zucker rat, like the db/db mouse, develops obesity because of a defect in the leptin receptor, caused by a mutation in the *fa* gene¹⁹. This animal produces leptin, but there is no action of the hormone in its receptor, leading to a state of hyperphagia, with high levels of plasma leptin. Besides leptin, other orexigenic hormones are also high in this model²⁰. Adult Zucker rats present 40% of their weight in the form of fat, as well as insulin resistance, but glycemia is normal, without evident DM2 development¹⁸. These data are similar to a part of the human population that presents obesity and insulin resistance, but it is not diabetic². The pancreatic lesion in these animals, however, does not occur in the same way as in humans²¹. This animal model is mainly used for pharmacological studies of antiobesity drugs and insulin sensitizers, as well as incretin analogues²².

Crossbreeding of Zucker rats eventually developed a less obese, but diabetic subtype, called the Zucker Diabetic Fatty (ZDF) rat. Male ZDF rats are more prone to the

development of DM2, being used for its study, as well as obesity, leptin signaling or the interaction between these three alterations⁵.

Also used for the study of DM2, the Goto-Kakizaki (GK) rat is a non-obese and spontaneously diabetic animal, obtained by the selection of Wistar rats with high glycemic levels²⁴. GK animals present fasting hyperglycemia, hyperinsulinemia, glucose intolerance at two weeks of age and early onset of diabetic complications²⁵, being considered one of the best models for the study of this disease⁶.

Polygenic animals

One of the polygenic models used in metabolic research is the New Zealand obese (NZO) mouse, an animal that develops hyperphagia and juvenile obesity, even eating low-fat diets. In addition, they may also develop DM2²⁶. Because of the variation in the occurrence of diabetes, this model was crossed with another animal intolerant to glucose, aiming at the development of the disease as it occurs in humans. Although some strains develop the condition, some animals, however, not always present the condition²⁷. This demonstrates how the development of obesity and metabolic syndrome is a complex process, both in animals and humans, making it difficult to fully understand its pathogenesis.

The rodent strain JCR:LA is the most used, as it develops cardiac ischemia and insulin resistance, besides atherosclerosis²⁷. This lineage presents a much more extreme obesity than that observed in the Zucker rat, as well as severe hyperlipidemia⁶. Despite this, this model has significant differences in the morphology of atherosclerotic lesions and cannot yet demonstrate the same pathogenesis of humans²⁸.

Obese animals induced by diet

The most common feature of genetically modified animals, with the exception of GK, is the early onset of obesity. In humans, however, weight gain can occur at any age, being more common with its advancement. In addition, the degree of obesity in patients with DM2 is variable, being less severe in young people, unlike what occurs in these rodents, which can affect many aspects of research⁵.

DIO animal models are the closest to the mechanisms promoting obesity and metabolic syndrome in humans. These animals are usually used to study the role of diet, pathophysiology and etiology of the disease, as well as pharmacological tests. However, the results of the studies are discrepant, mainly in relation to the diets composition and the type of model used^{2,29}. The modern diet in humans is usually composed of high level of

fats and carbohydrates. Rodent studies are based on these diets, but there is variation in the amount of components used, as well as in their source, which may alter the animal's phenotype² and end up developing a model of obesity and/or DM2 with non-standardized characteristics. In general, diets with high levels of fructose mimic the human diet and, when associated with high fat content, promote weight gain, abdominal fat, hyperglycemia and hyperinsulinemia in mice³⁰. Fructose appears to be important in the development of metabolic syndrome, as well as obesity itself, since this sugar leads not only to insulin resistance, but also to leptin resistance, resulting in weight gain³¹⁻³³.

Usually the diets used are commercially standardized. However, there are options such as the cafeteria diet, in which the animals choose the foods offered. The advantage of this diet is its high palatability, in addition to the great similarity with the human diet. Nonetheless, because it is not standardized, the nutritional content becomes difficult to evaluate and the animals may present deficiency of proteins and hypovitaminosis. Although it causes important weight gain, this diet tends to be less used than commercial ones³.

Certain mice strains such as S5B/PI or A/J are considered resistant to diet-induced obesity, whereas SD and Wistar rats develop this condition more easily, which shows that the genetic basis is important in body weight gain². The DIO strain most commonly used is SD rats, animals that are prone to dietary weight gain since tender ages, as well as C57BL6/J mice, obese and potentially hyperglycemic and hyperinsulinemic animals, which develop obesity over the period of life even when fed standard diet, similar to what occurs in humans^{29,34,35}. A study evaluating the efficacy of Roux-en-Y gastric bypass in C57BL6/J animals with non-alcoholic steato-hepatitis confirmed not only that this animal could be used as a model of hepatic alteration but also that surgery could confer modulation of hepatic mitochondrial function, contributing to a favorable effect on the disease³⁶.

Recently another polygenic animal strain, the Wistar rat, has been used for studies of diet-induced obesity and has demonstrated an increase in body weight^{37,38}. On the other hand, results on changes in insulinemia are conflicting. Some animals develop hyperinsulinemia³⁹, while others do not⁴⁰. Evaluation of glucose intolerance is also poorly reported³⁷. The female Wistar rat model has also been used as a DIO model during pregnancy, both for the development of a gestational obesity model and for the evaluation of offspring from an obese mother. The use of hypercaloric diet during the gestational period and lactation of Wistar rats seems to alter the obesity phenotype in the offspring of obese mothers, demonstrating the importance of maternal nutrition³⁸.

Other rodent models

The development of DM2 can be performed with the use of streptozotocin, as in the case of the high-fat diet-fed streptozotocin-treated (HFD/STZ) model. In this case, a hyperinsulinemic and insulin resistant DIO animal receives the toxin that has the function of destroying β -cells and promoting DM2. Together, the two factors mimic the pathogenesis of DM2 as in humans⁴¹. Discussions have occurred with this model, since streptozotocin is an agent used to induce type 1 diabetes, in which insulin production fails. In humans, after the occurrence of both type 1 and type 2 diabetes, residual β -cells continue to exist, but there is a difference in the number of these cells among types of diabetes, with type 1 having a lower number. Induction with toxin usually affects β -cells in a severe manner, which could promote early diabetes in the obese model and contrast with natural pathogenesis⁴¹.

Rodents models in bariatric surgery

Rodents are also used to study the metabolic aspects of surgery, the most commonly used animals being the SD, ZFD, Zucker and GK strains⁴², and more recently the Wistar rat, mainly for the sleeve gastrectomy technique⁴³. The gastrointestinal tract of rodents is similar to that of the human, but care must be taken since the small size of the animal requires greater surgical accuracy, as well as microsurgery instruments. In addition, when working with rodent surgical models, it is generally recommended to use two sham operation control groups, with one receiving the same amount of food as the experiment study group⁴².

Other animal models

In addition to rodents, other species may be used in metabolic studies, including non-human primates. These animals are particularly useful for the study of obesity and metabolic syndrome, since obesity in monkeys tends to occur late due mainly to overeating. In addition, overweight is commonly associated with metabolic changes similar to those occurring in the metabolic syndrome in humans, such as abdominal obesity, hyperinsulinemia, glucose intolerance, and increased levels of triglycerides and cholesterol^{1,4}.

Domestic animals, such as dogs and cats, can also be used, mainly because they share the same environmental risk factors as humans, such as physical inactivity, as well as inadequate food. Obese domestic cats tend to develop resistance to insulin and DM2, similar to humans. These animals also present prolonged pre-diabetes, characterized by

insulin resistance, and develop neuropathy and retinopathy, as well as pancreatic amyloidosis, hypertension and dyslipidemia. It is very likely that DM2 in this species is also a polygenic disease, similar to humans, but the investigation of genetic factors in felines is still beginning⁴⁴.

Although canine models are relatively well used in the area of metabolic diseases⁴⁵, the pathogenesis of obesity-associated comorbidities differs from the human and is less understood in this species. Some races are more predisposed to the development of diabetes, especially type 1, while others are less, and this disease is usually associated with conditions such as pancreatitis¹, unlike humans. These animals compensate for hyperglycemia better than other species, not losing β -cells and not developing pancreatic amyloidosis^{1,44}. Insulin resistance may occur, but the entire DM2 presentation is very rare. Dogs also have hypertriglyceridemia and hypercholesterolemia, but are extremely resistant to atherosclerosis. These findings lead us to believe that these animals have protection mechanisms that do not exist in humans or that humans have pathophysiological elements for metabolic syndrome that do not exist in dogs⁴⁶.

Pigs are considered to be good models for obesity and metabolic syndrome because of their diet, propensity to overweight, cardiovascular anatomy and lipoprotein metabolism comparable to humans⁴⁷. Unlike dogs that do not develop vascular disease, pigs present atherosclerotic lesions with anatomical and histopathological characteristics similar to those occurring in humans, being widely used for this type of study. The major disadvantage of using these animals, however, is the size of the species, as well as high maintenance costs. In addition, these animals need a period of at least two years for the formation of atherosclerotic plaques to occur, prolonging the time of the experiment and making it more costly¹.

Due to their size and anatomical similarity to humans, pigs are also employed for surgical procedures. Despite this, some anatomical differences in the gastrointestinal tract exist, among them the presence of developed cecum and long intestinal extension. Unlike rodents, pigs are more used to improve the bariatric technique by laparoscopy and not for the understanding of the pathophysiology of the disease. However, post-surgical follow-up of this species has also demonstrated weight loss and alteration of certain incretins, both in laparoscopic Roux-en-Y gastric bypass and in sleeve gastrectomy⁴².

Minipigs can also be used, with the advantage of being smaller than conventional pigs. Certain strains tend to be used in metabolic research because of the ease of weight gain. These animals need to stay in food restriction to maintain a lean phenotype. When they ingest normal ration *ad libitum*, they present hyperphagic behavior, weighing two to

three times more than animals in restriction. The obesity demonstrated by this lineage is severe and its behavior seems to be similar to the one of insatiable people, craving for food. Despite this, it is a new, not fully known model, and although it develops insulin resistance, so far there has been no development of DM2².

Recently, zebrafish have shown to be an attractive model for studies on metabolic diseases, due to the biology of their adipose tissue, lipid metabolism, pancreatic structure and glucose homeostasis⁴⁸. This vertebrate is traditionally used for biological development studies because it is affordable and easy to handle, as well as allowing genetic changes⁴⁹. The first model of DIO zebrafish was reported in 2010, with induction of hypercaloric diet for a period of eight weeks. Individuals showed an increase in body mass index, hypertriglyceridemia and hepatic steatosis when compared to normal-fed fish. In addition, the comparative analysis of their visceral adipose tissue transcriptome demonstrated that the lipid metabolism of this fish is similar to that of mammals⁴⁸. Obesity may also occur through genetic manipulation⁵¹ or even phenotype-modifying substances, such as green tea extract, which inhibited the accumulation of lipids and altered the expression of lipid catabolism genes⁵².

Similarly, induction of DM2 can be performed in this model by immersing the animal in concentrated glucose solutions⁵³. This method, although convenient, does not mimic the induction of diabetes in humans. Overfeeding of these animals, however, causes insulin resistance, elevated fasting glucose, and glucose intolerance⁵⁴.

FINAL REMARKS

Several animal models can be used to study the pathophysiology and treatment of obesity and metabolic syndrome, but the description of these models is still far from exhaustive, since none of them has been accepted as ideal for the study of these affections as a whole. Monogenic animals are the best choice when evaluating a single aspect. DIO models tend to demonstrate better the interaction of the disease with the environment and the gene, but they are not yet fully effective for the understanding of these disorders. Therefore, not always the results found with the models will lead to valid new treatments in humans. The search for models that present obesity and metabolic syndrome in the same way as humans can help to understand not only the pathophysiology of these conditions, but to allow the development of more effective treatments. Thus, it is likely that new models will be developed to provide this similarity.

The use of animals in research should respect ethical principles and the reduction of their numbers should occur whenever possible. Improving a specific and valid model will

potentially reduce the number of animals as well as the number of studies with them and, therefore, should be encouraged.

RESUMO

O conhecimento sobre modelos animais para estudo metabólico representa a base da pesquisa nessa área. Este trabalho tem por objetivo revisar os principais modelos animais a serem utilizados no estudo da obesidade e da síndrome metabólica. Para isso, pesquisa no banco de dados *Pubmed* foi realizada usando as palavras-chave *animal models, obesity, metabolic syndrome and bariatric surgery*. Várias espécies de animais podem ser usadas para o estudo de distúrbios metabólicos, no entanto, os roedores, tanto modelos monogênicos quanto modelos de obesidade induzida por dieta (DIO), são os animais mais utilizados nessa área. Animais monogênicos são a melhor escolha se apenas um aspecto estiver sendo avaliado. Animais DIO tendem a demonstrar melhor a interação entre doença, ambiente e gene. No entanto, eles ainda não são totalmente eficazes para a compreensão de todos os mecanismos dessa doença.

Descritores: Modelos Animais. Obesidade. Síndrome Metabólica. Cirurgia Bariátrica.

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