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Rodent Models of Obesity and Diabetes

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Abstract

Genetically modified animals are a widely used tool in biomedical research, since it allows modeling diseases, studying their pathological conditions and identifying and validating new drugs. One of the most common diseases studied in recent years is metabolic disorders resulting from abnormalities in enzyme systems involved in the intermediary metabolism of living organisms with a heavy impact on society. To understand the physiological mechanisms underlying these disorders, animal models, currently the transgenic type, have been employed. It is important to emphasize that there are various metabolic disorders that are not only *congenital* but can be *acquired* or a coexistence of both types. The aim of this chapter, therefore, is to describe the most commonly used rodent models focusing mainly on global emerging pathologies, obesity, diabetes and metabolic syndrome.

Keywords: diabetes, obesity, metabolic syndrome, mice model, rat model

1. Introduction

The use of experimental animals involved in metabolic pathologies goes back a few hundred years. Various mammals such as dogs, rabbits, pigs, primates and rats were frequently used by researchers to understand the physiological mechanism of diseases from the pancreatectomy to isolation and purification of insulin in the 1920s to the use of toxic compounds to cause disease and the current use of genetically modified animals [1]. The advantages of using rodents for experimentation are several since it can be improved on besides the reproducibility and reliability of the study results. As expected, animal models for metabolic diseases are as complex and heterogeneous as the diseases themselves, since each one of them has specific modifications incomparable with others. Moreover, inbred lines continue, while new endogenous lines are used in many fields of research [2].

METABOLIC DISORDERS	
CONGENITAL	ACQUIRED AND CONGENITAL
Fabry disease	Diabetes
Phenylketonuria	Obesity
Prader-Willi syndrome	Dyslipidemia
Galactosemia	Hipolipidemia
Tay-Sachs's disease	Hyperthyroidism
Porphyria	Hypoparathyroidism
Pompe disease	Hypothyroidism
Niemann-Pick disease	Cushing's syndrome
Morquio's syndrome	Hyperuricemia
Maroteaux-lamy syndrome	Hemochromatosis
Hunter Syndrome	Hyperparathyroidism
Lesh-Nyhan syndrome	
Hurler syndrome	
Homocystinuria	
Hartnup	
Gaucher disease	

Figure 1. Congenital and metabolic disorders.

Most metabolic diseases in humans are a consequence of the rupture of cellular processes. However, the relationships between genetic defects, underlying molecular interaction networks and phenotypic expression, are little known [3]. Congenital metabolic diseases are disorders produced by a variation in the coding sequence of the DNA resulting in deficiencies or absence of a protein, generally an enzyme, producing metabolic blockages, whereas acquired metabolic diseases are due to diseases of endocrine organs or failure of metabolically active organs [4] (**Figure 1**). In this regard, the chapter focused mainly on both genotypic and phenotypic characteristics of animal models employed in the investigation of emerging metabolic diseases.

2. Mouse models

Current research has seen the increased use of animal models in exploring mechanisms and pathophysiological processes involved in metabolic diseases (**Table 1**) both in congenital and in acquired disease conditions, more importantly in the design and development of therapeutics and drugs for treatment.

Disease	Model	Features	References
<i>Congenital</i>			
Fabry disease	GLAko mouse	Mouse with a complete lack of α -galactosidase A activity. Appear clinically normal, with normal blood and urine analyses and a normal adult lifespan	[5]
Phenylketonuria	PKU mouse	A significantly decrease in level of Phe in the plasma	[6]
Prader-Willi syndrome	Snrpn ^{tm2Cbr} mouse	The mouse exhibits postnatal lethality	[7]
Galactosemia	GalT KO mouse	Accumulated some galactose and its metabolites upon galactose challenge but was seemingly fertile and symptom free	[8]
Tay-Sachs's disease	Tay-Sachs (Hexa ^{-/-}) mouse	In females there are severe progressive hind-limb weaknesses with impaired motor coordination, balance and mild ataxia	[9]
Porphyria	Uros(mut248) mouse	Production of red urine and shows erythrodontia. Bones are abnormally fragile	[10]
Pompe disease	GAA ^{-/-} mouse	A progressive accumulation of lysosomal glycogen in heart and skeletal muscle and diaphragm	[11]
Niemann-Pick disease	ASM (^{-/-}) mouse	A severe, neurodegenerative course and death that occurs by 8 months of age	[12]
Maroteaux-lamy syndrome	MPS VI mouse	A skeletal and chondral dysplasia	[13]
Hunter syndrome	IDS-deficient mouse	A progressive accumulation of glycosaminoglycans (GAG) in many organs and excessive excretion of these compounds in their urine. Neuropathological defects	[14]
Lesh-Nyhan syndrome	HPRT-deficient mouse	Changes in brain dopamine function	[15]
Hurler syndrome	MPS I-H KO mouse	Mice showed no detectable α -L-iduronidase activity	[16]
Homocystinuria	"human only" (HO) mouse	Severe elevations in both plasma and tissue levels of Hcy, methionine, S-adenosylmethionine and S-adenosylhomocysteine and a concomitant decrease in plasma and hepatic levels of cysteine	[17]
Hartnup	HPH2 mouse	A deficient amino acid transport	[18]
<i>Acquired</i>			
Dyslipidemia	LDLR ^{-/-} mouse	A severe hyperlipidemia and extensive atherosclerosis	[19]
	apoE ^{-/-} mouse	A more severe hyperlipidemia characterized by elevations in VLDL and reductions in HDL, which lead to spontaneous atherosclerosis	[20]
Hyperuricemia	Induced by hypoxanthine	An increase in urinary uric acid	[21]

Table 1. Summary of model rodents of some congenital or acquired metabolic diseases.

2.1. Type 2 diabetes models

Type 2 diabetes (T2D) is a metabolic disorder that is caused by insufficient insulin secretion and/or insulin resistance in peripheral tissues and liver [22]. To help develop new diabetic therapies, it is important to highlight the complex mechanisms of diabetes mellitus. Animal models of T2D are as complex and heterogeneous as the syndrome itself as experienced in humans.

2.1.1. *db/db* mice

These diabetic mutant mice are modifications of the C57BL strain [23, 24]. The mutation in the leptin OB-R receptor was identified in 1996, and this model has been widely used in the evaluation of antiobesity and antidiabetic compounds and therapies due to its manifestation of hyperphagia and morbid obesity, reproductive failure and severe insulin resistance [25].

2.1.2. *BKS db* mice

The C57BLKS/J (BKS) consanguine mouse strain is a widely used animal model of T2D. A recessive mutation that occurs spontaneously in the BKS strain produces early-onset diabetes and obesity with moderate initial hyperinsulinemia followed by insulinopenia since pancreatic islets undergo atropia due to degeneration of β cells [25]. Moreover, they show polyphagia and obesity and a marked increase in weight and blood glucose after 3–4 weeks of their birth [26, 27].

2.1.3. *KKAy* mice

The KKAy mouse, due to its genetic mutation, is the spontaneous animal model of hyperglycemia and hyperlipidemia and its symptoms are similar to T2D [28]. The mutation Ay often becomes obese and infertile within months after birth, and the observed increase in the adipose tissue is due to hypertrophy of fat cells; however, obesity results from a reduction in hypothalamic norepinephrine and dopamine [29]. In this strain of mice, diabetic characteristics such as obesity, hyperinsulinemia and hyperglycemia are observed in early ages, between the 6th and 8th week, and then return to normal at approximately 40 weeks of age. Degranulation, glycogen deposition and hypertrophy of β cells are observed in these animals at 5–10 weeks of age, suggesting that insulin synthesis and release are increased with hyperinsulinemia. Renal lesions such as diffuse glomerulosclerosis, nodular changes and thickening of the peripheral glomerular basement membrane are also observed [29].

2.1.4. *BTBR obese* mice

BTBR obese mice have more fat mass than most strains of inbred mice [30]. The BTBR model naturally suffers from hyperinsulinemia when compared to other insulin-resistant mice, but when the ob/ob mutation is placed on a BTBR background, the mice are initially insulin resistant with elevated insulin levels, hypertrophy of pancreatic islets and marked hyperglycemia at 6 weeks of age [31]. An important feature of this model is the degree to which it reproduces the essential structural and functional characteristics of the human diabetic glomerular lesion with glomerular hypertrophy, marked expansion of the mesangial matrix, mesangiolysis and capillary thickening of the basal membrane as well as loss of podocytes [32].

2.1.5. *eNOS*^{-/-} mice

The gene-encoding eNOS or endothelial nitric oxide synthase has been considered a potential candidate gene for diabetic nephropathy because of nephropathic changes observed in mouse models of T1D and T2D, thus mimicking many aspects of human diabetic disease [33]. The eNOS ^{-/-} mice develop a remarkable albuminuria and pathological change characteristics of T2D such as mesangiolytic, microaneurysms and expansion of the increased mesangial matrix. It is useful to study the role of endothelial dysfunction in the development of diabetes and to facilitate the development of new diagnostic and therapeutic interventions [34].

2.1.6. *ALR/LtJ* mice

Resistant mouse (R) Leiter (LT) resistant to alloxan (AL) is closely related to the nonobese diabetic (NOD) strain. This model presents an unusual high quantitative expression of molecules associated with systemic dissipation of cell stress from free radicals. The islets of ALR are remarkably resistant to two different combinations of cytokines (IL-1 β , TNF- α and IFN- γ) that destroy islets of NOD strains susceptible to alloxan [35], and this mechanism induces diabetes mellitus [36]. The strain derived from Swiss mice is widely used to study insulin-dependent diabetes mellitus in mice.

2.1.7. *B6.HRS(BKS)-Cp^{efat}/J*

They are homozygous mice obtained by spontaneous fat mutation (Cp^{efat}) on a genetic background, that is, C57BL/6J. They become remarkably obese at 14–15 weeks of age; male homozygous mutant mice develop obesity at a later age than females [37]. Cp^{efat} mice weigh less than wild-type controls before the weaning age. Later, homozygous mutant mice develop a diabetic phenotype characterized by hyperglycemia and insulin resistance [38].

2.1.8. *LG/J* and *SM/J*

The large-LG/J and small-SM/J strains are inbred mice derived from selection experiments for large and small body size at 60 days [39]; LG/J animals grow faster at 3–10 weeks and have larger tissues at tails, body and liver and higher content of body fat compared with the SM/J strain. SM/J animals grow faster after 10 weeks of age and have higher fasting glucose levels than LG/J animals. SM/J mice are more sensitive to dietary fat gain than LG/J mice for growth after 10 weeks. Moreover, LG/J mice are more susceptible to develop antinuclear antibodies and rheumatoid factor, as well as renal disease characterized by glomerulonephritis, interstitial nephritis and perivasculitis [40].

2.1.9. *NOD/Shi^{LtJ}-Lepr^{db-5J}/LtJ*

Nonobese diabetic (NOD) mouse is an endocrine strain developed during a breeding program to establish a cataract-prone subline of non-consanguineous mice [41]. They are homozygous co-isogenic NOD mice, which develop juvenile diabetes and T2D along with the suppression of post-adolescent age-dependent spontaneous T1D. At 5 weeks of age, these mice are hyperphagic; they eat twice the amount of food from a lean control mouse and develop hyperglycemia that does not require insulin therapy for long-term survival [42].

2.2. Type 1 diabetes

After the discovery of insulin, the availability of animal models for the study of the pathogenesis of T1D was delayed by approximately 50 years.

2.2.1. *Ins2Akita mutants*

A point mutation of the insulin gene 2 in Insta mice (Akita) leads to a pancreatic apoptosis of β cells and hyperglycemia. Thus, these mice are commonly used to investigate T1D complications [43]. Symptoms in heterozygous mutant mice include hyperglycemia, hypoinsulinemia, polydipsia and polyuria beginning at about 3–4 weeks of age. Mice have progressive loss of β -cell function and decreased pancreatic cell density and significant hyperglycemia at 4 weeks of age [44]. It is a model used primarily for the study of retinal complications in T1D [45].

2.2.2. *Streptozotocin-treated mice*

Streptozotocin (STZ)-induced diabetes mellitus (STZ) offers a very cost-effective and expedient technique that can be used in most rodent strains, opening the field of diabetes mellitus research to a range of genotypic and phenotypic options that would otherwise be inaccessible. Since the initial report of its diabetogenic properties in 1963, STZ has been used alone or in combination with other chemicals or with dietary manipulations for the induction of either T1D or T2D through toxicity of β cells. STZ sensitivity is highly variable in rodents like DBA/2, C57BL/6, MRL/MP, 129/SvEv and BALB/c [46].

2.3. Obesity

The search for new alternatives for prevention and/or treatment to combat global chronic diseases such as obesity is based on the development of new animal models that share characteristics of these human diseases [47].

2.3.1. *ob/ob*

A spontaneous mutation leading to the markedly obese phenotype in the *ob/ob* mice was recognized since the 1950s. C57BL/6J mice with a mutation in the obese (*ob*) gene are obese, diabetic and exhibit reduced activity, metabolism and body temperature. The obesity syndrome of *ob/ob* mice results from lack of leptin characterized by hyperphagia, reduced energy expenditure and hypothermia; further defects are hypercorticosteronemia, insulin resistance associated with hyperglycemia and hyperinsulinemia, hypothyroidism and growth hormone deficiency leading to a decrease in linear growth. Moreover, *ob/ob* mice are infertile. The administration of exogenous leptin normalizes all known phenotypic defects in *ob/ob* mice including obesity, symptoms of the metabolic syndrome and reproductive function [47–50].

2.3.2. *C57BL/6J DIO*

Diet-induced models of obesity (DIO) are often used to study polygenic causes of obesity. DIO animals mimic the state of common obesity in humans than most of the genetically

modified models and may be the best choice for testing prospective therapeutics [47]. Numerous mouse strains are susceptible to DIO, including C57BL/6 [51]. This mouse develops obesity, hyperinsulinemia, hyperglycemia and hypertension [52].

2.3.3. *NONcNZO10/LtJ*

The NONcNZO10/LtJ mouse is a polygenic model of T2D that shows moderate obesity and diabetes. This model of obesity-induced diabetes was produced by the combination of quantitative trait loci from the New Zealand Obese (NZO/HILt) and Nonobese Nondiabetic (NON/LtJ) mice. Interestingly, the NONcNZO10/LtJ males do not exhibit hypercorticism, hyperphagic behavior and obvious thermoregulatory defect. However, they develop visceral obesity, maturity-onset hyperglycemia, dyslipidemia, moderate liver steatosis and pancreatic islet atrophy [53, 54].

2.3.4. *TALLYHO/JngJ*

TALLYHO/JngJ (TH, formerly TallyHo) is a polygenic mouse that shows obesity, hyperinsulinemia, hyperglycemia (males) and hyperlipidemia at 26 weeks of age [55]. TallyHo mice can be resistant to hypothalamic leptin at 4 weeks of age due to the increased expression of orexigenic neuropeptides in the hypothalamus with no alteration of food intake and neuropeptide expression when intravenously treated with leptin [56]. Male TallyHo mice can develop hyperglycemia, hyperinsulinemia, hyperlipidemia, moderate obesity and enlargement of the islets of Langerhans. Female mice display moderate hyperinsulinemia, hyperlipidemia and obesity but do not manifest overt diabetes (hyperglycemia) [57].

2.3.5. *B6(cg)-Tubtub/J*

Mice homozygous for the tubby spontaneous mutation B6(Cg)-Tubtub/J develop obesity at the onset of maturity. Specifically, these mice show increased body weight at 3–4 months, whereas the females show this increase at 4–6 months. The increased body weight is due to an increased accumulation of adipose tissue. Blood glucose is normal, but plasma insulin is increased prior to obvious signs of obesity and may rise to 20 times normal at 6 months. The levels of total cholesterol, triglycerides and high-density lipoprotein cholesterol are increased in plasma of homozygous mutant mice; despite this, these mice do not exhibit atherosclerotic fatty streak blood vessel lesions. Importantly, both genders are fertile [58, 59].

2.3.6. *Obesity induced by diet*

Animal models of obesity that are similar to the human are very important to study the pathophysiology of obesity. The obese mouse model induced by high-fat diet (HFD) is one of the most important tools for understanding the relation between high-fat diets and the pathophysiology of development of obesity.

2.3.6.1. *High-fat diet-fed mice*

The high-fat diet (HFD)-fed mouse is a model of obesity, impaired glucose tolerance and insulin resistance [60]. The development of disease-induced dietary fat can be divided into

three stages: (1) an early stage in response to a high-fat diet in which mice were sensitive to exogenous leptin; (2) a reduced stage of food intake when mice had an increase in milk production and still retained central leptin sensitivity; and (3) a stage of increased food intake and accompanied by reduced sensitivity to the central leptin [61].

2.3.6.2. High carbohydrate-fed mice

The hypercaloric diets (HCDs) induce hyperglycemia by inducing tolerance to glucose and increasing the levels of TAG, TNF- α and MCP-1/JE in plasma. Moreover, the HCD increases the MCP-1/JE levels in target organs such as the adipose tissue and liver. However, the HC diet also can increase TNF- α concentration in the liver [62]. It is important to mention that the HFD is more effective to induce the body weight gain as compared with the HCD because of the large storage capacities of the adipose tissue and the low satiating effects of HFD as compared to the low capacities of the glycogen stores and of the de novo lipogenesis cost [63, 64].

2.4. Other metabolic syndromes

The metabolic syndrome (MetS) models are important to understand the pathophysiological basis of the MetS and how this syndrome increases the risk to the development of severe complications. The MetS animal model most commonly used is the obese mouse strains with several spontaneous mutations, which have been used for decades and are very well characterized. Moreover, inducing MetS with high-fat diet requires only some months, and these models are useful to study the effects of single genes by developing transgenic or gene knockouts to determine the influence of a gene on MetS [19, 65].

2.4.1. B6.129S7-Ldlrtm1Her/J

This mouse homozygous mutation has an elevated serum cholesterol level of 200–400 mg/dl and they attain very high levels (>2000 mg/dl) when fed with a HFD. Normal levels of serum cholesterol in the mouse are 80–100 mg/dl [66].

2.4.2. B6.Cg-Ay/J

The heterozygote mouse has increased the adipose tissue mass due to fat-cell hypertrophy and later develops insulin resistance and hyperglycemia. Heterozygote mice are also more susceptible to develop tumors than the normal mice, and their spleen cells cause a significantly lower graft versus host reaction. The level of malic enzyme in the liver is elevated [67].

2.4.3. NON/ShiLtJ

These mouse models are extremely useful for research works on obesity, diabetes, dyslipidemia and hypertension. NON/ShiLTJ (nondiabetic obese) mice contain an MHC haplotype resistant to diabetes and demonstrate early impaired glucose tolerance in both genders. These mice do not generate obesity when they are fed a diet containing 6% fat [68, 69].

3. Rat models

3.1. Type 2 diabetes

3.1.1. Goto-Kakizaki rats

This rat strain was developed by the selective selection of Wistar rats for glucose intolerance over multiple generations, resulting in a polygenic strain that spontaneously develops hyperglycemia with problems in β -cell function. The hyperglycemia that these rats present is due to an increase of gluconeogenesis. Goto-Kakizaki (GK) rats have been considered one of the best nonobese T2D animal models. They are thin rats but present hyperglycemia and increased gluconeogenesis. GK rats present valuable characteristic tools that are commonly and functionally present in human diabetic patients [70, 71].

3.1.2. Streptozotocin-treated rat

This experimental model is useful for studying the regeneration of β cells in which damage to cells is caused by the injection of STZ. In this strain, regeneration of the cells is a complication, which is decreased in adult rats and thus presents a chronic pathological pattern like human T2D, glucose intolerance and low insulin in response to glucose [72, 73].

3.1.3. Pancreatomized Sprague-Dawley rats

To create this model of rats, Sprague-Dawley rats underwent simulated pancreatectomy. One week later, animals develop chronic hyperglycemia that is stable for several weeks without significant alterations in fatty acid levels. It is a strain used for the homeostatic control of the mass of the β cells to produce insulin in both the normal pancreatic growth and during the pathogenesis of diabetes. It is a multipurpose albino model, and primarily evidence of obesity is induced by diet, diabetes and oncology [74, 75].

3.2. Diabetic nephropathy

A very common treatment to obtain this model of rat is the application of streptozotocin, creating rats with diabetic conditions that develop kidney injury, similar to human diabetic nephropathy [76]. The mean urinary volume and protein excretion in these rats are greater than healthy rats; also, the kidney weight increases in this strain, as the immunoreactivity of endothelial nitric oxide in the renal cortex of these rats is much higher [77].

3.3. Obesity

3.3.1. Obesity induced by diet

3.3.1.1. High-fat diet-fed rat

The increase in weight induced by a high-energy diet causes certain defects in the neuronal response to negative feedback signals from circulating adiposity, such as insulin. Insulin

resistance of peripheral tissue involves cellular inflammatory responses that are caused by excess lipids. This model consists of rats fed with a HFD, mainly provoking DIO that has become one of the most important tools to understand the interactions of diets high in saturated fat and the development of obesity [78].

3.3.1.2. Cafeteria diet-induced obese rat

In the above model, body weight increases dramatically and remains significantly elevated in CAF-fed rats. Also, hyperinsulinemia, hyperphagia, hyperglycemia and glucose intolerance are exaggeratedly elevated in CAF-fed rats compared with other models with HFD [79–81]. These models present increased adiposity and hepatosteatosis, brown fat and more inflammation in the adipose tissue and liver. A CAF-fed rat model provides a model of human metabolic syndrome with an exaggerated obesity phenotype with glucose intolerance [81]. With this model, it is possible to study the biochemical, genomic and physiological mechanisms of obesity and disease states related to metabolic diseases [79].

4. Conclusions

Animal research has been and continues to be essential for understanding the underlying mechanisms of most human and veterinary diseases. Metabolic diseases are complex and present heterogeneous clinical forms with significant impact in understanding metabolic disorders. The use of animal genetic models, mainly rodents (mouse and rat), has showed several advantages. However, it is necessary to consider the standards of care of laboratory animals, which are consistent and demand the necessary experimental conditions.

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