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Review Article

Metabolic Abnormality Mimicking Type 2 Diabetes Model in Experimental Animals

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Abstract

In this review, metabolic abnormalities related to prevalence and long term complications of type 2 diabetes mellitus (DM) are discussed. An overview of the most commonly used rodent models for induction of type 2 DM is given, highlighting the pathophysiological conditions developed in different strains of mice and rat. These models are very much useful in mimicking metabolic complication usually observed in humans type 2 DM.

This review summarizes the up-to-date information on type 2 DM rodent models and presents the details required for induction and critical evaluation of drugs focusing on three categories a) spontaneous genetically modified obese rat/mice strains, b) drug-induced models and c) dietary intervention induced models.

Keywords: *Type 2 Diabetes Mellitus; Rodent Models; Metabolic Abnormalities; Genetic Strains; High Fructose; High Sucrose; High Fat*

Diabetes mellitus

Diabetes mellitus (DM) is a hyperglycemic condition developed due to impaired insulin secretion and variable degrees of peripheral insulin resistance. The early symptoms are hyperglycemia along with polydipsia, polyphagia, polyuria, and blurred vision. The late complications related to DM are vascular diseases, peripheral neuropathy, nephropathy, and predisposition to infection. Mortality related to DM is predominantly due to heart disease. The two major categories of DM are type 1 and type 2, distinguished by a combination of features. Type 1 DM patients typically have symptomatic hyperglycemia with diabetic ketoacidosis. Type 2 DM patients often have an asymptomatic hyperosmolar hyperglycemic state. Categorization based on the age of onset (juvenile or adult) or type of treatment (insulin or non-insulin dependent) is no longer accurate because of overlap in age groups and treatments between disease types. The typical sign and symptoms of DM are confirmed by fasting plasma glucose (FPG) level after 8- to 12-h fasting, glycosylated Hb (HbA1C) concentration in blood and sometimes oral glucose tolerance testing (OGTT) by plasma glucose level measurement 2h after ingestion of a concentrated glucose solution. OGTT is more sensitive but less convenient and reproducible than FPG, so rarely used in routine practice except for diagnosing gestational diabetes and for research purposes [1].

Type 2 DM

The number of DM patients is projected to increase approximately up to 592 million by 2035, denoting a net increase of 55%. Type 2 DM is one of the most common non-communicable lifestyle disease affecting an average of 8.3% of the world adult population. Type 2 DM is the predominant form that accounts for nearly 90% of all diabetes cases, which has doubled over the past three decades, that has made this disease a global challenge [2]. Lifestyle transition, changes in dietary habits, aging population, and fast urbanization is causing insulin

resistance and pancreatic β-cell dysfunction consequently settling hyperglycemia. Clinical expression of Type 2 DM requires both genetic and environmental factors. Inability to adequately compensate for insulin resistance is attributable to β-cell hyperplasia and hyperinsulinemia. Insulin resistance is associated with a cluster of metabolic abnormalities the most common of which is obesity along with glucose intolerance, hypertension, dyslipidemia, procoagulant state, and macrovascular diseases.

Metabolic risk factors for type 2 diabetes include age ≥ 45, abdominal obesity, sedentary lifestyle, history of impaired glucose regulation, hypertension, atherogenic dyslipidemia, cardiovascular disease, and polycystic ovary syndrome. Insulin functions for normal glucose uptake by muscle and/or restraint in glucose production by the liver and also effects ovarian androgen production and lipogenesis [3]. Type 2 diabetes is preceded by insulin resistance, hyperinsulinemia with unique dyslipidemia and obesity in 75 - 85% of the patients. Dyslipidemia and the development of type 2 diabetes are highly correlated with insulin resistance and hyperinsulinemia in almost all studies [4].

Pathogenesis of type 2 DM

Pathogenesis of type 2 DM is complex and incompletely understood. People with type 2 DM develops characteristic insulin resistance along with beta-cell dysfunction, impaired insulin secretion, loss of normally pulsatile insulin secretion and increase in proinsulin secretion signaling impaired insulin processing, and accumulation amyloid polypeptide in islets. Hyperglycemia develops when insulin secretion can no longer compensate for insulin resistance and further deteriorates as high glucose levels desensitize beta cells slowly. In type 2 diabetes, the pancreas often continues to produce insulin even at higher-than-normal levels, especially in the early phase of disease still body develops resistance to insulin effects and progressively insulin-producing ability of the pancreas decreases. An insulin resistance following nuclear peroxisome proliferator-activated receptors (PPAR) deactivation (mainly obesity-related) is the key phase of metabolic syndrome initiation. The two principal pathways of metabolic syndrome development are i) with preserved pancreatic beta cells function and insulin hypersecretion leading to macrovascular complications; ii) with massive damage of pancreatic beta cells, a progressive decrease of insulin secretion and hyperglycemia leading to both microvascular and macrovascular complications [5].

The decreased sensitivity to insulin leads to increased insulin requirement in target organs, such as the liver, muscle, and adipose tissues. Obesity is the major risk factor involved in the development of type 2 diabetes because obesity causes insulin resistance. Inability to suppress lipolysis in adipose tissue in the obese people increases plasma free fatty acid levels that can impair insulin-stimulated glucose transport and muscle glycogen synthase activity. Adipose tissue can function as an endocrine organ, releasing multiple adipocytokines that can both favorably and adversely (tumor necrosis factor-alpha, IL-6, leptin, resistin) influence glucose metabolism. Certain disorders and drugs can also affect the ways the body uses insulin and can lead to type 2 diabetes [6].

Metabolic abnormality related type 2 diabetes model in experimental animals

Diabetic animal models play critical roles in the elucidation of the diabetes pathophysiology and the development of novel drugs for treatment [7]. Mimicking the pathogenesis of metabolic abnormalities related to type 2 DM in animal models give researchers opportunity to study the *in vivo* factors that influence the development of the disease and establishment of its late complications, and thus to gain new information for the development of effective treatment strategy in humans. The genetically modified animal can develop diabetes spontaneously, and in normal animals, it is induced by using drugs, dietary manipulations, surgical interventions, and other techniques to and depict the clinical features related to type 2 DM.

The ability of the animal models are limited in depicting all the complications of the pathogenesis of a particular disease; still, the experimental models are essential tools for understanding the molecular basis of pathogenesis and to explore the utility of under test therapeutic agents in a multifactorial disease like DM [8]. Animal models of metabolic abnormality related to type 2 DM is mainly used for studying the interaction between obesity and diabetes, the effects of diet and exercise, and for pharmacological testing of protein tyrosine phosphatase inhibitors and glucagon-like peptide-1 analogs drugs [9]. Rodents are the most commonly used animals to mimic human

type 2 DM, although other animals such as felines, swine and primates are also used. Along with the general advantages of using rodents as disease models (e.g. small size, easily availability, economical, available in large numbers and as comes in category of small animals easy to get permission from CPCSEA via the IAEC), the diabetic rodents category especially includes a variety of models that can mimic human type 2 DM.

Spontaneous obesity-induced type 2 DM rodent model

Leptin, a 16 kDa protein expressed predominantly in adipose tissue that functions as a hormone in keeping the brain apprised about the amount of body fat and activate the centers involved in regulating feed intake and energy expenditure. Deficiency of satiety factor leptin significantly alters feeding behavior, metabolism, and endocrine function, resulting in hyperphagia, decreased energy expenditure and obesity. Mutations in the leptin gene (ob/ob) or leptin receptors (db/db and fa/fa), finally leads to the emergence of diabetes in rodents. The ob/ob genotype in the C57BL/6J mouse strain is characterized by hyperphagia and low energy expense. They develops obesity, mild hyperglycemia due to compensatory hyperinsulinemia and insulin resistance approximately at the age of 4 weeks. The ob/ob genotype expressed on the C57BL/KS mouse strain develops very severe and lethal diabetes [10]. The db/db mouse are hyperphagic and became hyperinsulinemic, obese, insulin resistant, hyperglycaemic due to β-cell failure by 4 weeks of age and does not live longer than 8 - 10 months. The Zucker (fa/fa) fatty (obese) rat also develops the same pathophysiological characteristics and is mainly used as a model of human obesity accompanied by hyperlipidemia and hypertension [11].

The Zucker diabetic fatty rat strain (ZDF) is developed from selective inbreeding of fa/fa rat with hyperglycemia which shows severe diabetes (only males) 8 weeks after birth due to enhanced apoptosis of β-cells. As in the fa/fa rat, these animals are unable to compensate the insulin resistance and becomes insulinopenic at about 14 weeks of age [12]. Spontaneously Diabetic Torii (SDT) rat strain was developed by introducing the fa allele of the Zucker fatty rat into the SDT rat genome intercrossing between fa-heterozygous littermates [13]. SDT rats develop diabetes independent of obesity having normal body weights, blood glucose, insulin, and lipid level until 16 weeks of age and after that, develops hyperglycemia associated with hypoinsulinemia, due to degeneration of pancreatic beta cells. The SDT rats develop chronic hyperglycemia with profound complications in eyes, peripheral nerves, kidneys, and bone [14]. The Melanocortin 4 receptor-deficient mouse has a behavioral obesity syndrome characterized by hyperphagia, hyperglycemia, hyperinsulinemia, hypometabolism, and increased lean mass and linear growth [15]. The central melanocortin system mediates many actions of the adipokine leptin and plays a crucial role in the central regulation of energy homeostasis [16]. The KK (Kuo Kondo) mouse has a large body size and is hyperphagic. They develop hyperinsulinemia and insulin resistance with mild hyperglycemia from the age of 2 months [17].

The most prevalent KK/Ay mouse strain carries the lethal yellow obese gene (Ay) and becomes severely obese, hyperglycaemic and hyperinsulinemic at about the age of 8 weeks. Both the KK and KK/Ay mouse are regarded as suitable models for exploring the mechanisms of obesity-induced type 2 DM for studying new antidiabetic drugs [18]. The New Zealand Obese (NZO) mouse sharply gains weight during the 2 first months of age and develops hepatic insulin resistance with progressive hyperleptinemia and simultaneously leptin resistance [19]. The OLETF (Otsuka Long Evans Tokushima Fatty) rat and the NSY mouse develop mild obesity-induced diabetes at about the age of 18 - 25 weeks. Animals are characterized by polyphagia, high levels of insulin, triglycerides, and cholesterol, hyperglycemia and hypertension [20]. OLETF rat is used widely for testing antidiabetic and antihypertensive drugs. All most all males but only about 30% of females of the NSY mouse develop diabetes. The NSY mouse is characterized by mild obesity with visceral fat accumulation, accompanied by impaired insulin secretion and moderate insulin resistance [21]. However, a high-fat diet or sucrose administration quickens the development of diabetes in OLETF rat and NSY mouse (Table 1).

Animal strain	Genetic changes	Metabolic syndrome	Reference
ob/ob mice	Monogenic, Leptin-deficient mouse	Obesity, insulin resistance and mild hyperglycaemia	Bates., *et al*. 2005
db/db mice	Monogenic, Leptin- receptor deficient mouse	Hyperinsulinemia obesity, insulin resistance and hyperglycaemia	Bates., *et al*. 2005
Zucker (fa/fa) Fatty rats	Monogenic, Leptin- receptor deficient mouse	Obesity, insulin resistance, hyperlipidemia and hypertension	Durham and Truett, 2006
Zucker Diabetic Fatty (ZDF) rats	Monogenic, Leptin- receptor deficient mouse	Obesity, insulin resistance, severe hyperlipidemia, hypertension, glucose intolerance and insulinopenia	Pick., *et al*. 1998
Spontaneously Diabetic Torii (SDT) rat	Monogenic Leptin- receptor deficient mouse	Hypoinsulinemia, chronic hyperglycemia, complications in eyes, peripheral nerves, kidneys and bone	Shinohara., *et al*. 2000; Masuyama., *et al*. 2005
Melanocortin 4 receptor (MC4-R) null mouse	Monogenic Melanocortin 4 receptor deficient mouse	Hyperphagia, hyperglycemia, hyperinsulinemia, hypometabolism, and increased lean mass	Huszar., *et al*. 1997
KK (Kuo Kondo) mouse	Polygenic	Hyperinsulinaemia, insulin resistance and mild hyperglycemia	Reddi., *et al*. 1988
KK/Ay mouse	Polygenic	Severe obesity, hyperglycaemia and hyperinsulinemia	Ikeda, 1994
New Zealand obese (NZO) mouse	Polygenic	Hepatic insulin resistance, hyperleptinemia and leptin resistance	Thorburn., *et al*. 2000
OLETF (Otsuka Long Evans Tokushima Fatty) rat	Polygenic	Mild obesity, hyperinsulinaemia, high triglycerides, high cholesterol, hyperglycaemia and hypertension	Kawano., *et al*. 1992
NSY mouse	Polygenic	Mild obesity with visceral fat accumulation, impaired insulin secretion, moderate insulin resistance and hyperglycaemia	Ueda., *et al*. 1995

Table 1: *Genetic rodent model for spontaneous obesity induced type 2 DM.*

Drug-induced type 2 DM rodent model

Streptozotocin and alloxan

Streptozotocin and alloxan are used conventionally to induce diabetes in experimental animals. The other diabetogenic agents are dithizone, monosodium glutamate, gold thioglucose. Streptozotocin is glucosamine-nitrosourea chemotherapeutic compound derived from *Streptomyces achromogenes* clinically used in the treatment of pancreatic β cell carcinoma. Streptozotocin damages pancreatic β cells, resulting in hypoinsulinemia and hyperglycemia. The selectivity of streptozotocin for β cells is associated with its preferential accumulation in β cells via entry through the glucose transporter 2 receptor due to structural similarity with glucose. Streptozotocin function depends on the dose. At typically single high dose (100 - 150 mg/kg) streptozotocin is cytotoxic to β cells by its alkylating property. At a low dose,

multiple exposures streptozotocin elicits an immune and inflammatory reaction by releasing glutamic acid decarboxylase autoantigens that cause destruction of β cells and induction of the hyperglycemic state [22].

Alloxan is chemically known as 5,5-dihydroxyl pyrimidine-2,4,6-trione which is a carcinogenic and cytotoxic glucose analog [23]. The susceptibility of diabetogenic and toxic effects of alloxan can differ among animals of same species. Alloxan induced diabetes in 33.33% of rats receiving either 150 mg/kg or 160 mg/kg of alloxan and 60% of rats receiving 170 mg/kg dose. Fasting blood sugar level often returns to the non-diabetic range after few days of alloxan induced diabetes [24]. Rats show a high degree of resistance to alloxan suggesting genetic differences in the constitutive ability in dissipating reactive oxygen species responsible for the diabetogenic effect of alloxan [25]. Stable diabetes for 35 days is produced in 20% of rats receiving 170 mg/kg of alloxan, so preferably streptozotocin is used for induction of stable diabetes [26].

Type 2 DM are induced using low dose of streptozotocin (30 - 35 mg/kg, IP or IM in 0.1 M citrate buffer, pH 4.4) or alloxan (40 mg/kg, IP) in Sprague-Dawley or Wistar rats (preferably of age 6 - 8 weeks, weighing between 180 and 220 gm) or albino mice (3 - 4 weeks old weighing between 25 and 30 gm), following ingestion of high fat diet for 4 to 8 weeks. The animals with fasting plasma glucose level greater than 250 mg/dl with symptoms of polyuria and polydipsia, 2 weeks post-STZ injection are considered diabetic [27,28]. Diet given to rodents can have a large influence on sensitivity to streptozotocin. Low dose streptozotocin are been used to create type 2 diabetes models combined with high-fat chow feeding in mice or rat [8]. The C57BL/6J mice only experience type 2 diabetes strictly when streptozotocin is given with a high-fat diet [9]. Non-insulin dependent diabetes mellitus can also be induced by a single intraperitoneal injection of streptozotocin (60 mg/kg) and nicotinamide (120 mg/kg) to rats. Nicotinamide exerts a protective effect on the cytotoxic action of streptozotocin by scavenging free radicals allowing only minor damage to pancreatic beta cell mass thus producing type-2 diabetes. This model is advantageous tool for investigation of insulinotropic agents in the treatment of type-2 diabetes [29].

Glucocorticoid

Corticosterone administration at therapeutic dose enhances food intake, weight gain, abdominal fat accumulation, severe fasting hyperglycemia, insulin resistance, impaired glucose tolerance, hypertension, and dyslipidemia. Glucocorticoids act on fat cells, liver, muscles, and kidneys. Glucocorticoid stimulates the differentiation of pre-adipocytes, increases lipolysis and proteolysis thus enhancing blood concentration of free fatty acids and amino acids. Glucocorticoids promote gluconeogenesis in the liver and causes hyperglycemia and occurrence of hyperinsulinemia along with the elevation of blood pressure [30]. C57BL/6J mice treated with corticosterone 25 - 100 µg/ml in drinking water (for 5 weeks) or 0.1 - 1.0 mg/kg, IP (for 5 days) displayed increased food intake, body weight gain, and central fat deposit, dyslipidemia, glucose intolerance, and hypertension mimicking the human metabolic syndromes of type 2 DM. The effects of corticosterone are reversed after drug removal [31,32].

Diet-induced type 2 DM rodent model

The most commonly used rodent strains for diet-induced metabolic syndrome of type 2 DM to are Sprague-Dawley rats, Wistar rats, and C57BL/6 J mice. Rodents become obese and diabetic when its natural vegetarian diet is changed with laboratory chow, with high energy diet. The rats develop hyperphagia, obesity, hyperinsulinemia, glucose intolerance, increased hepatic glucose production, and muscle insulin resistance. This hyperglycaemic condition of the animals is characterized by increased circulating proinsulin due to high demand for insulin secretion followed by a progressive loss of β-cell mass due to increased apoptosis [33]. MC4-R null mouse is profoundly sensitive to high-fat feeding, which exacerbates signs of hyperphagia, obesity and hyperinsulinemia [34].

High-fat diet

Fats are the most calorigenic out of the three main macronutrients in the body. Lipid metabolism begins with lipolysis increasing plasma free fatty acids concentration that are major substrates for hepatic VLDL-triglycerides production. Approximately 70 % of released free fatty acids are re-esterified (lipogenesis) to form triglycerides [35]. A high level of VLDL cholesterol causes obesity, dyslipidemia, de-

position of cholesterol in arteries and accumulation of triglycerides in the liver, in turn, inducing insulin resistance. Ghibaudi., *et al.* [36] assessed the chronic effect of 10-45 % dietary fats on body adiposity and metabolism of rats. The findings demonstrated increased weight gain, fat mass, plasma glucose, cholesterol, triglycerides, free fatty acids, leptin, and insulin levels. Male C57BL/6 J mice fed with high-fat diet displayed elevation body weight, total cholesterol, and leptin level [37,38]. Different types of high-fat diets are extensively used for the induction of obesity and type 2 DM, and the fat composition vary from 20 to 60% of total energy (Table 2). Plant-derived oils (corn, safflower or olive oil) or animal-derived fats (ghee and lard) are mostly used [39]. The high-fat diet containing lard or soybean oil is very effective in promoting hyperglycemia, insulin resistance, dyslipidemia by increasing the free fatty acid level in the blood of male Sprague-Dawley or Wistar rats and also in male and female C57Bl/6 J mice [40-42].

Duration	Composition											Reference
	Standard diet	Lard oil	Soybean oil	Egg yolk powder	Milk powder/ Casein	Sacc-harose	Sucrose	Corn starch	Malto-dextrin	Cellulose powder	Mineral, Salt and Vitamin mix	
24 weeks	--	39.5%	5.5%	--	20%	--	17%	18%	--	--		Ghibaudi., *et al.* 2002
16 weeks	--	32%	4%		19%	--	10%	25%	5%	--	5%	Fraulob., *et al.* 2010
24 weeks		--	10%	--	14%	--	--	57%	--	5%	5%	Halade., *et al.* 2010
24 weeks	--	12%	12%	24%	--	--	--	41%	--	--	--	Davidson., *et al.* 2011
13 weeks	--	37.1%	--	20.5%	--	--	--	42.4%	--	--	--	Pirih., *et al.* 2012
4 - 12 weeks	--	33%	2%	--	25.6%	--	5%	16%	6%	6.6%	5.8%	Fujita and Maki, 2015
8 weeks	60%	20%	--	10%	--	10%	--	--	--	--		Yang., *et al.* 2018
4 - 8 weeks	61%	12%	--	2%	5%	--	20%	--	--	--		Zhuo., *et al.* 2018

Table 2: *Composition of high fat diet for induction of type 2 DM in rodents.*

High-fructose diet

Fructose is an intermediary monosaccharide molecule formed during glucose metabolism. There Dietary fructose, known as fruit sugar is biologically not needed. Fructose is often used as a taste enhancer to make more tempting in the artificially sweetened beverages and food. Intake of excessive fructose rapidly causes induction of metabolic abnormality syndrome. Fructose is converted to fructose-1-phosphate by the enzyme phosphofructokinase following uptake in the liver. It favors accumulation of triglycerides and cholesterol in the liver because of its lipogenic properties, subsequently leading to reduced insulin sensitivity, insulin resistance and glucose intolerance [43]. Fructose behaves more like a fat rather than carbohydrate in both humans and animals. Fructose feeding induces more intense body weight gain, adiposity, hypertriglyceridemia, hyperlipidemia, hypertension, glucose intolerance and decreased insulin sensitivity in animal models compared to glucose or starch [44]. Fructose-induced metabolic syndrome can be created experimentally either by feeding male Sprague-Dawley/Wistar/Albino rats with a high-fructose diet (20 - 66%) or by adding fructose (10 - 20%) to drinking water [45-51]. Sanchez-Lozada., *et al.* [52] reported that 10 % fructose in drinking water induced the same response as that of high dose of fructose (60 %) in diet [53].

Duration	Composition												Reference
	Standard diet	Fructose in drinking water	Ground nut/ sunflower oil/Ghee	Sheep fat	Lysine/ Choline/ Methionine	Soya protein	Milk powder/ Casein	Fructose	Corn starch	Wheat bran	Cellulose powder	Mineral, salt and Vitamin mix	
3 weeks	--	--	5%	--	0.7%	--	20%	61%	--	9.6%	--	3.7%	Thiruna-vukkarasu., *et al.* 2004
4 weeks	--	--	10.3%	--	0.9%	--	20%	52%	15%	--	--	1.8%	
10 weeks	--	--	--	6%	3%	20%	9.2%	66%	--	--	3%	2%	Mansour., *et al.* 2013
8 weeks	50.5%	--	1.5%	--	0.2%	--	--	20.4%	--	9.8%	--	2%	Di Luccia., *et al.* 2015
8 weeks	--	10%	--	--	--	--	--	60%	40%	--	--	--	Sanchez-Lozada., *et al.* 2007
8 weeks	--	10%	--	--	--	--	--	--	--	--	--	--	Shahraki., *et al.* 2011
12 weeks	--	10%	--	--	--	--	--	--	--	--	--	--	Mahmoud and Elsha-zly, 2014
8 weeks	--	20%	--	--	--	--	--	--	--	--	--	--	Mamikutty., *et al.* 2014

Table 3: *Composition of high fructose diet for induction of type 2 DM in rodents.*

High-sucrose diet

Sucrose is a disaccharide table sugar consisting of one fructose and one glucose molecule making food more palatable. Fructose is again the main active ingredient contributing to the development of metabolic abnormality after sucrose consumption as it is cleaved into glucose and fructose by the enzyme sucrase. High sucrose supplementation is widely used for the induction of insulin resistance in rats [54]. Male Sprague-Dawley and Wistar rats treated with 30 and 32 % sucrose in drinking water respectively for 21 and 10 weeks exhibited hyperglycemia, hyperinsulinemia, hypertriglyceridemia, hypercholesterolemia, hypertension and increased body weight [54,55]. High-sucrose diet (77 %) feeding for 6 weeks evoked a similar response in male Sprague-Dawley rats [56]. Simultaneous fructose and sucrose supplementation invoked distinct responses in two different animal models, i.e. Sprague-Dawley and spontaneously hypertensive rats. Fructose enrichment diet in Sprague-Dawley rats caused hyperinsulinemia, hypertriglyceridemia, hypercholesterolemia, hypertension, and insulin resistance whereas sucrose enriched dist in spontaneously hypertensive rats only caused hypertension and insulin resistance [57]. Fructose treatment appeared to be superior compared to sucrose in inducing type 2 DM related metabolic abnormalities as sucrose contains 50% fructose and 50% glucose.

Conclusions

The advantage of using rodent models to study metabolic abnormalities associated with type 2 DM is its ability to develop the pathology in a relatively shorter period and easy monitoring of biochemical, histological, and morphological changes. As the incidence rate of diabetes is increasing at an alarming rate, the scientist needs to carry out preclinical screening new synthetic, and phyto derived molecules. To best estimate, the clinical response of an under trial drug is to screen in a model that best depict the conditions in humans. This review provides an overview of the most commonly used rodent model that represent type 2 DM. Scientists can also conduct studies applying combination or modification of existing established methods in order to further develop the rodent model of type 2 DM with desired metabolic changes. Apart from the pathophysiological similarity with human type 2 DM the rodent models are excellent as they are reproducible, convenient and affordable.

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