Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 195–200

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Review

Rodent models of diet-induced type 2 diabetes mellitus: A literature review and selection guide

Holger Engel [a, b, *], Lingyun Xiong [b], Matthias A. Reichenberger [d], Günter Germann [d], Christian Roth [c], Christoph Hirche [b]

[a] Department of Plastic-Reconstructive, Aesthetic and Hand Surgery, Klinikum Kassel, Kassel, Germany
[b] Department of Hand, Plastic and Reconstructive Surgery, Burn Center, BG Trauma Center Ludwigshafen, University of Heidelberg, Ludwigshafen, Germany
[c] Department of Neurology, DRK-Kliniken Nordhessen, Kassel, Germany
[d] Department of Plastic Surgery, Ethianum, Heidelberg, Germany

ARTICLE INFO

Article history:
Received 6 July 2018
Accepted 29 July 2018

Keywords:
Diabetic animal model
Diet induced
High-fat diet
STZ
Diabetes

ABSTRACT

Several research teams have focused on finding the "ideal" animal model that reflects the pathophysiological changes and closely simulates the metabolic characteristics of patients with type 2 diabetes. However, the multitude of studies on this topic has resulted in large variations, making the models difficult to compare, as the measured parameters vary significantly. Additionally, selecting the appropriate animal model for a new study has become more difficult due to the increasing number of background variables. This article gives a detailed overview of the literature, covering the entire range of animal models and model characteristics, and most importantly, provides guidance for selecting the most suitable model for specific research goals in the future.

1. Introduction

Type 2 diabetes mellitus (DM) is a complex and heterogeneous disorder that is estimated to affect more than 100 million people worldwide, causing serious socio-economic problems [1].

Compared with the human form of this disease, animal disease models are essential tools for studying the pathophysiology of this disease, enabling therapeutic interventions to be developed within a reduced time frame.

Researchers face the challenge that no single animal model adequately reflects the human form of type 2 DM. This inadequacy is due to the polygenic character of this disorder.

The authors of this manuscript have dealt with this issue in the past and realized that no comprehensive literature review exists. This review article aims to fill this void by covering the range and characteristics of the various animal models and, most importantly, to provide guidance for selecting the most suitable model for specific research goals (Table 1).

2. Animal model characteristics

Numerous studies have aimed to develop an animal model that replicates the natural history and metabolic characteristics of human disease and that is suitable for pharmaceutical research, for example [7].

The optimal animal model mimics the transition from prediabetes to type 2 DM, when the secretory capacity of pancreatic B-cells can no longer compensate for insulin resistance [12,13].

When studying type 2 DM, the utilization of an animal model with a homogeneous genetic background is recommended. Rodents are most commonly used due to their small size, short generation interval, easy availability and affordability. Furthermore, the ideal model should not be inbred or genetically obese and should be large enough for invasive physiological studies to be performed [7].

A type 2 DM animal model can be created by either genetic, dietary, chemical or surgical approaches. An overview of these approaches and common examples are listed in Table 2.

Monogenetic rodent models for obesity and diabetes include transgenic, generalized knockout and tissue-specific knockout animals, such as ob/ob mice or obese Bucker (fa/fa) rats. However, these do not sufficiently mirror human disease [4,5]. Most of these models focus on only one aspect (e.g., atherosclerosis) of type 2 DM

* Corresponding author. Department of Plastic-Reconstructive, Aesthetic and Handsurgery, Klinikum Kassel, Moenchebergstraße 41-34, 34125 Kassel, Germany.
E-mail address: mail@HolgerEngel.de (H. Engel).

https://doi.org/10.1016/j.dsx.2018.07.020
1871-4021/

Table 1
Key objectives for the literature review

Key Objectives:
• Origin/source of animal models
• Characteristic features
• Key laboratory values
• Diet formulas
• Advantages and disadvantages
• Guidance for designing a type 2 diabetes animal study

without reflecting all metabolic characteristics.

Animal models with high-fat diet (HFD)-induced insulin resistance have been established with features that correlate well with human pathophysiology [6-9].

However, despite all the advances made, controversies still remain regarding the most suitable diet-induced animal model [10]. A major problem with existing models is the lack of comparability among the non-standardized, disease-defining laboratory parameters. In addition, the meaningfulness of studies based on these models is limited due to accompanying hypertension and the fact that these rodent strains are highly inbred [7]. Moreover, some models even lack detailed descriptions of the HFD composition, including specific fat components. Srinivasan and Ramarao wrote an overview of type 2 DM animal models, but this review has limited usefulness when designing preclinical studies [11].

3. Review of the literature

The first nutritional intervention to induce obesity, a "HFD," was published by Masek and Fabry in 1959 [14]. Subsequent studies revealed that HFDs promote hyperglycemia and insulin resistance, and numerous researchers have examined the effects of these diets on muscle and liver physiology as well as insulin signal transduction. Based on these findings HFDs are generally accepted as a method for generating valid metabolic syndrome rodent models with insulin resistance and compromised β-cell function [15,16]. In addition, streptozotocin (STZ) is widely used as a diabetogenic agent, as it damages pancreatic islet β cells by triggering an immune system reaction when given in multiple low doses and alkylates DNA when given as a single high dose. In most studies, STZ is combined with a HFD. Diabetogenic activity can be induced between doses of 25 and 100 mg STZ/kg BW, showing some degree of correlation with the administered dose [17]. The diabetogenic response to the induction can be measured through serum glucose levels, urine volume, glycosuria, ketonuria, the serum immunoreactive insulin (IRI) response, and the pancreatic IRI content [17].

Nevertheless, the choice of rodent strain, STZ dose, injection site (i.e., intraperitoneal (i.p.) vs. Subcutaneous (s.c.) vs. Intravenous (i.v.)), injection modus (single high dose vs. Multiple low doses), high-fat formula composition, and laboratory values are not yet standardized, which impairs practicability and comparability.

The following pages alphabetically list (based on the first author) the range of animal model studies. These studies were evaluated (when data were provided) with regards to the.

- rodent strain,
- rodent age and weight,
- diet type,
- diet duration,
- STZ use,
- observation period after STZ injection, and
- model advantages and disadvantages.

The utilized type 2 DM laboratory values are summarized in

Table 2
Overview of the literature of 17 type 2 diabetes mellitus animal models

Author	Year	Journal	Strain	Age	Weight	Diet Details	Diet-Duration	STZ mg/kg BW	Time post STZ
Rees, Alcolado	2005	Diabetic medicine	Various	x	x	x	x	x	x
Srinivasan, Ramarao	2007	Indian J Med Res	Various	x	x	x	x	35–65 mg i.p. / i.v.	x
Srinivasan, Ramarao	2005	Pharmacological Research	SD	x	160 –180 g	HFD (58% calories as fat, 17% carbohydrates, 25% protein)	2 w	35 mg i.p.	1 week
Reed, Heaven	2000	Metabolism	SD	7 w	200 g	HFD (40% calories as fat, 41% carbohydrates, 18% protein)	2 w	50 mg i.v.	3 days until onset +3 days
Zhang, Huang	2006	Diabetes Research and Clinical Practice	GK	4 m	x	L-NAME + HFD	x	x	
Islam, Choi	2007	Pharmacology	SD	7 w	217 g	HFD (20% lard and 2% soybean oil)	2 w	40 mg i.p.	1 week
Diz-Chaves, Mallo	2007	J Endocrinol Invest	SD	5 d	x	x	x	90 mg i.p.	9–16 days
Ramadan, Liberte	2006	Physiology and Behavior	SD	7 w	200 g	HFD (40% calories as fat, 42% carbohydrates, 18% protein)	3 w	50 mg i.p.	5 days
Zhang, Luo	2003	Exp Anim	SD	8 w	259 g	HFD (30% calories as fat, 50% carbohydrates, 13% protein)	2 m	15 mg n.a.	2 months
Weng, Zhang	2007	Exp Clin Endocrinol Diabetes	SD	x	150 –200 g	x	x	30 mg i.v.	8 weeks
Wang, Zheng Wide Fu	2007	Asia Pac J Clin Nutr	Wi	x	100 g	HFD (adding 20% sucrose (w/w) and 10% lard (w/w))	4 w	30 mg n.a.	4 weeks
Sartoretto, Fortes	2007	J of Pharmacy and Pharmacology	Wi	2 d	x	x	x	160 mg i.p.	8 weeks
Sugano, Okazaki	2006	Nutrition, Metabolism and Cardiovascular Diseases	SD	8 w	x	HFD (11.3% fat, 5% carbohydrates, 13.5% protein) after STZ	37 w	40 mg i.v.	9 days + 2 weeks after STZ treatment
Sotnikova, Monclova	2006	Gen Physiol Biophys	Wi	8 w	200 g	x	x	3 × 20 mg i.v.	12 weeks
Kim, Park	2006	Journal of Endocrinology	SD	7 w	220 g	x	x	80 mg vs. 5 × 20 mg i.p.	3 weeks
Buettner, Alzheimer	2006	Journal of Molecular Endocrinology	Wi	6 w	x	HFD (42% lard, olive oil, coconut fat, fish oil)	12 w	x	X
Danda, Pergola	2005	Kidney International	SD	x	175 –200 g	HFD (60% calories from fat and 70% animal fat)	5 w	35 mg/ 55 mg	14 weeks

Table 3, enabling better comparison. An analysis of the mean parameters and ranges is given in Table 4.

Bitar et al. (2005) used Goto-Akaki (GK) rats (produced by the selective inbreeding of glucose-intolerant Wistar rats, age n.a. 316-g body weight (BW)) as a genetic animal model of non-obese type 2 DM and analyzed nitric oxide (NO) bioavailability and O_2 generation in aortic tissues. Enhanced superoxide production and decreased NO bioavailability were observed [18]. The observation period was not reported. No further details were provide aside from the source of the breeding stock (Karolinska Institute, Sweden).

Buettner et al. (2006) investigated 6-week-old Wistar rats and used a HFD (42% of calories from fat) for 12 weeks. STZ or other medication was not injected. The observation time of the animals was not stated in the report. In contrast to other studies, the authors detailed the fatty acid composition, which included lard, olive oil, coconut fat, and fish oil. The most pronounced obesity and insulin resistance resulted from diets with lard and olive oil [2]. Compared with other studies, this study provided details and used multiple control groups.

Chaabo et al. (2010) assessed Nile rats (African grass rat) fed a HFD (Western diet, 43% of calories from fat, 40% from carbohydrates, 17% from protein) in an isolated aliment-induced model without STZ injections. A broad range of laboratory values were evaluated and compared with the values from the low-fat diet model. Moreover, this study focused on general colony dynamics. The researchers concluded that these Nile rats represented a novel model of metabolic syndrome associated with type 2 DM. While the authors evaluated the model in great detail, experience with the Nile rat is currently limited [19]. The novelty of this model is likely to curtail its use in studies.

Danda et al. (2005) used 175- to 200-g Sprague-Dawley (SD) rats and a HFD (60% of calories from fat). The diet duration was five weeks. STZ was injected at a dose of 35 or 55 mg/kg BW. The post-STZ observation period lasted 14 weeks. The study design comprised four different groups and both included type 1 and 2 DM. While the reported follow-up period was longer than that of other studies, the number of included control animals was a drawback [20].

Diz-Chaves et al. (2007) analyzed five-day-old neonatal SD rats and induced DM with i.p. Injections of 90 mg STZ/kg BW, which is the second largest dose in all reported studies. The post-STZ observation period ranged from 9 to 16 days. Routine laboratory values are lacking in this study [21].

Islam et al. (2007) examined seven-week-old SD rats with a reported mean weight of 217 g. The rats were fed a HFD with 20% lard and 2% soybean oil, but further information on the carbohydrate and protein composition was not provided. After an i.p. Injection of 40 mg STZ/kg BW, the diet lasted two weeks. The post-STZ observation time was two weeks [22].

Karabatas et al. (2005) analyzed the early manifestation of type 1 DM in male C57BL/6 J inbred mice, in which diabetes was induced with multiple low-dose STZ injections. After the initial dose, STZ injections at days 4, 6, 9, 12, and 16 caused functional immune aggression against β-cells at a very early disease stage, before the donor mice had developed impaired insulin secretion or hyperglycemia [23].

Kim et al. (2006) evaluated seven-week-old SD rats with a mean weight of 220 g. The applied diet was specified, but data on the diet duration was not provided. The authors used STZ with an initial high dose of 80 mg/kg BW and 5 low doses of 20 mg/kg BW through i.p. Injections. The observation time was three weeks. This protocol resulted in β-cell necrosis at 4 h after the STZ injection, and

Table 4
Analysis of parameters (mean and range)

Parameter (measurement unit)	Mean (range)
Strain	
SD	10
Wistar	4
GK	2
Nile	1
Age (weeks)	6.8 (0.3–16)
Weight (g)	192.8 (100–259)
Diet specifications (% of calories)	
Fat	37.9 (11.3–58)
Carbohydrate	31 (5.1–50)
Protein	17.5 (13–25)
Diet duration (weeks)	8.2 (2–37)
STZ (mg/kg BW)	62.5 (15–180)
Post-STZ observation time (weeks)	5.1 (0.7–14)

Table 3
Measured type 2 diabetes mellitus parameters in different animal models

Publication	Measurements
Chaabo et al. [19]	BW, BMI, blood glucose (BG), triglycerides (TG), total cholesterol (TC), liver lipids, intraperitoneal glucose tolerance test (ipGTT), hemoglobin A1c (HbA1c), insulin level (ELISA), insulin resistance, blood pressure, organ weight
Srinivasan et al. [27]	TG, cholesterol, PI, PG, intravenous insulin GTT (IVIGTT)
Reed et al. [7]	Adipocyte glucose clearance, free fatty acids, oral GTT (OGTT)
Zhang H. et al. [34]	Not specified within the paper
Islam et al. [22]	Serum insulin, serum lipid profile, liver glycogen, fasting blood glucose (FBG)/ non-FBG (NFBG) (blood and liver samples)
Diz-Chaves et al. [21]	GTT, polyuria, polydipsia, hyperphagia
Ramadan et al. [25]	Plasma glucose and insulin
Zhang F. et al. [33]	BG, TG, TC, insulin (radioimmunoassay), IVIGTT, FBG, fasting serum insulin; pancreatic paraffin sections were examined
Weng et al. [31]	Weight, BG, and urinary glucose; PCR was used to assess changes in heart mitochondrial genes
Wang et al. [32]	BW, TG, TC, LDL, and glucose; expression of energy metabolism-related genes (PCR)
Sartoretto et al. [26]	Microvascular reactivity, eNOS expression, NOS activity, urinary glucose; using 24-h metabolic cages after ten weeks of STZ treatment, glycosuria, IVGTT and OGTT were assessed
Sugano et al. [29]	HbA1c, BG, creatinine, urea nitrogen, TC, HDL, TG, plasma insulin level, μcrea, μprotein, μalbumin
Sotnikova et al. [28]	BG, TC, TG, bilirubin; functional vessel and electron microscopy studies
Kim et al. [24]	BG, IGF-I, insulin, growth hormone (GH)
Buettner et al. [2]	Multiple controls, very detailed
Danda et al. [20]	BG, BP, urinary protein excretion, serum insulin, HbA1c, cholesterol, TG, glomerular sclerosis, creatinine clearance, kidney weight

blood glucose levels peaked two to three days after the STZ injection. When compared with human pathophysiology, the early measured peaks suggest that this disorder presents with a non-physiological pattern of progression [24].

Ramadan et al. (2006) supplied SD rats with a HFD (40% of calories from fat, 42% from carbohydrates, 18% from protein). At seven weeks of age, these rats reached a mean weight of 200 g. The diet duration was three weeks. The authors injected STZ with a dose of 50 mg/kg BW i.p. And had a post-STZ injection observation period of five days, which is the second shortest time. The model design was based on the published data of Reed et al. [7], with a reduced number of diabetes-related laboratory values [25].

Reed et al. (2000) used male seven-week-old SD rats, which were fed a normal (12% of calories from fat) or HFD (40% of calories from fat) for two weeks and then injected with STZ (50 mg/kg i.v.). This study demonstrated that STZ injections increase glucose, insulin, free fatty acid (FFA), and triglyceride (TG) concentrations in fat-fed rats (fat-fed/STZ rats) compared with STZ-injected rats fed a normal diet (normal diet/STZ rats). Compared with normal diet rats, fat-fed/STZ rats were not insulin deficient but had hyperglycemia and a somewhat higher insulin response to oral glucose challenges. In addition, insulin-stimulated adipocyte glucose clearance was reduced in fat-fed/STZ rats compared with normal diet and normal diet/STZ rats. Finally, fat-fed/STZ rats were sensitive to the glucose-lowering effects of metformin and pioglitazone [7]. The similar glucose levels but higher insulin concentrations suggested that compared with normal diet control rats, fat-fed rats are insulin-resistant. To simulate the evolution of "relative" hyperinsulinemia from a state of insulin resistance and absolute hyperinsulinemia, insulin-resistant, fat-fed rats were injected with the amount of STZ that lowered the serum insulin concentration to the level observed in the rats fed a normal diet. The glucose concentration in the fat-fed/STZ model is relatively stable overtime. Fat-fed SD rats injected with a moderate amount of STZ provide a relatively inexpensive and easily accessible rodent model that is not extremely obese and simulates the natural history and metabolic characteristics of patients with type 2 DM; however, these findings do not imply that this model is superior to other rat models of type 2 DM [7,12,13].

Sartoretto et al. (2007) used neonatal Wistar rats (two days old) as a model but did not use a specific diet protocol or diet duration. The highest published STZ dose with 160 mg/kg BW, and a post-STZ observation time of eight weeks was utilized. In addition to common laboratory parameters, the authors analyzed nitric oxide levels and mechanisms of endothelial dysfunction [26].

In their original publication, **Srinivasan et al. (2005/2007)** established an animal model using 160- to 180-g SD rats and a HFD (58% of calories from fat, 17% from carbohydrates, 25% from protein). The diet began two weeks prior to the 35 mg STZ/kg BW i.v. Injection. The post-STZ observation time was one week. The influence of STZ after the HFD was analyzed by comparing the laboratory reports before the STZ injection to those at the end of the observation period [27]. Moreover, the authors provided an overview of the varying parameters, including the induction of DM via i.p./i.v. Injections of 35–65 mg STZ/kg BW, but did not include therapeutic details for the study design [11].

Sotnikova et al. (2006) induced DM in eight-week-old, 200-g Wistar rats using isolated STZ injections without a specific dietary plan. Three 20 mg STZ/kg BW i.v. Doses were provided. The post-STZ injection observation period was twelve weeks. In addition to regular laboratory values, the authors performed functional vessel studies and electron microscopy [28].

Sugano et al. (2006) created an animal model using either-week-old SD rats. The authors implemented a HFD (11.3% of calories from fat, 5.1% from carbohydrates, 13.5% from protein) two weeks after a 40 mg/kg BW STZ i.v. Injection, and the diet lasted 37 weeks. A wide range of laboratory values was provided. In addition to the reverse STZ/HFD order, the percentage of fat calories in the HFD seems relatively small [29].

Takada et al. (2007) developed a neonatal DM model via i.p. STZ injections in which male Wistar rats developed insulin resistance because of reduced adipose mass. Insulin-stimulated 2-deoxy-D-[^{3}H]-glucose uptake; the incorporation and conversion of D-[U−^{14}C]-glucose into lipids and $^{14}CO_2$, respectively; and insulin binding were analyzed. The rate of weight gain in the STZ-treated group was significantly reduced by the eighth week. These rats developed polyphagia, polydipsia, polyuria, glycosuria, and impaired glucose tolerance. Biological tests in isolated adipocytes revealed a reduced number of insulin receptors. This experimental DM model was determined to remarkably resemble a sustained image of insulin resistance in adulthood and was closely related to reduced adipose mass [30].

Weng et al. (2007) established an animal model using SD rats with a weight range of 150–200 g. A specific diet formula was not applied. After an i.v. Injection of 30 mg STZ/kg BW, an observation period of eight weeks followed. The number of type 2 DM laboratory parameters (urine glucose levels, etc.) was sufficient [31].

Wang et al. (2007) used 100-g Wistar rats for their model, with HFD (with 20% sucrose and 10% lard) feeding for four weeks. This diet regimen was followed by an injection of 30 mg STZ/kg BW and a further observation time of four weeks. In addition to the standard type 2 DM parameter measurements, microvascular reactivity, eNOS expression and NOS activity were analyzed [32].

Zhang F. et al. (2003) developed a type 2 DM rat model with male SD rats (four months old) via low-dose STZ (15 mg/kg BW) injections after a two-month HFD (30% of calories from fat) feeding, as detailed by the authors [33]. Functional and histochemical changes were found in the pancreatic islets, insulin-glucose tolerance tests, and islet immunohistochemistry. These results were compared with those of a type 1 DM animal model (50 mg/kg BW STZ) and a HFD obesity model [33]. This approach first stimulated insulin resistance, which was followed by a slight impairment in pancreatic islet cell insulin secretion.

Zhang H. et al. (2006/2007) analyzed 16-week-old GK rats fed a HFD (no further specifications). The diet duration was not mentioned. An STZ injection was not performed; moreover, the recorded type 2 DM laboratory values were not specified [34,35].

4. Discussion

Several research teams have focused on finding the "ideal" animal model that reflects the pathophysiological changes and closely simulates the metabolic characteristics of patients with type 2 DM [11, 36]. However, the large number of studies has variation that makes comparison difficult, as the measured parameters vary significantly. Additionally, selecting a suitable animal model for a new study has become more difficult due to the increasing number of background variables.

Most of the published studies (n = 10) used SD rats, followed by Wistar rats (n = 4), with a mean age of 6.8 weeks (ranging from 0.3 to 16 weeks) and a mean weight of 192.8 g (ranging from 100 to 259 g). Nile rats were recently evaluated by Chaabo et al. with a basic broad approach and a wide range of laboratory tests. However, due to the limited number of publications, this model cannot yet be recommended [19]. The GK rat has been confirmed as a valid model, but evidence for this strain is also limited [18, 34, 35].

Due to the variety of strains, the most evidence has been collected for SD rats, which provide a valid model that is highly recommended.

The HFD was the predominant diet used, with a mean fat calorie

percentage of 37.9% (ranging from 11.3 to 58%). Notably, ten studies did not specify the applied diet. Prior to the STZ injection, the mean diet duration was 8.2 weeks (ranging from 2 to 37 weeks). Furthermore, six studies did not state the diet duration period. STZ was used with a HFD in 15 of the 17 animal models. One group varied the order between the injection and diet, starting the diet after the STZ injection [29]. Further evaluation in more studies is required to analyze whether this sequence sufficiently reflects human pathophysiology.

These studies reflect large variations and inconsistencies in the design of alimentary protocols. While some investigators primarily focused on the animal weight, others defined fixed weights or even a weight range. STZ was used in 14 of the 17 animal models, in 6 of the 14 studies without a specified diet, and in 8 of the 14 animal models that used a combination that included a HFD. The mean dose was 62.5 mg STZ/kg BW (ranging from 15 to 180 mg/kg BW). The post-STZ observation time varied greatly with a mean period of 5.1 weeks (ranging from 0.7 to 14 weeks). The distribution of i.v. And i.p. Injections was balanced.

Generally, saturated fatty acid-based diets are believed to induce the typical HFD-phenotype, whereas diets containing polyunsaturated omega-3 fatty acids exert beneficial effects on body composition and insulin action [2, 37, 38].

A satisfactory type 2 DM animal model needs to have a defined diet type, fatty acid composition, and diet duration. This quality was achieved in only 10 of the 17 animal models.

A few reviews have been published, but most papers give only an overview of diabetic animal models, lacking detailed data [11, 39]. Buettner et al. reviewed metabolic and molecular effects in different HFD rodent models with varying fatty acid compositions. The group analyzed weight, food intake, whole-body insulin tolerance and plasma parameters of glucose and lipid metabolism during a twelve-week diet. Liver histology and hepatic gene expression profiles were evaluated. HF-lard (HF-L)- and HF-olive oil (HF–O)-fed rats presented with the most pronounced obesity and insulin resistance; insulin sensitivity was nearly normal in HF-coconut fat (HF–C)- and HF-fish oil (HF–F)-fed rats. Liver histology revealed the presence of hepatic steatosis in the HF-L, HF–O and HF–C rats, without signs of major inflammation. Hepatic SREBP1c-dependent gene levels were upregulated in rats fed these diets, whereas PPARα-dependent genes were predominantly upregulated in HF–F-fed rats. The detected classical HFD effects occurred in only the rats fed HF-L and HF–O (mainly long-chain, saturated (LC-SFAs) and monounsaturated fatty acids (MUFAs)) diets. Diets rich in polyunsaturated fatty acids (PUFAs) or medium chain (MC)–SFAs did not induce insulin resistance. Diets based on LC-SFAs and MUFAs induced hepatic steatosis with SREBP1c activation [2]. Reed and colleagues used fat-fed SD rats with moderate STZ injections, creating a relatively inexpensive and easily accessible rodent model that does not feature extreme obesity and simulates the natural history and metabolic characteristics of patients with type 2 DM; nevertheless, these findings are not superior to other rat models of type 2 DM [7].

It must be noted that these reviewed studies do not provide the cost of the animal models, which is currently a major factor in the practical design of a study.

5. Study design guidance and conclusions

Considering the extensive list of type 2 DM animal models and based on our experience (to be published), we recommend a non-genetic, specific HFD-induced animal rodent model with a minimum diet duration of eight weeks (to allow insulin resistance development) prior to STZ injection, followed by an additional 4 weeks (to allow the further development of typical type 2 DM characteristics). Based on the literature review, the use of SD rats is preferable.

The varying designs and measurements in the reviewed studies indicate that the ideal animal model has not yet been identified. In particular, a realistic reproduction of human disease has not been sufficiently achieved; thus, long-term human changes, such as retinal alterations and glomerulopathies, have not been investigated. This deficiency should be examined in future studies. Rather than creating “new” models, the next logical steps are to standardize and optimize these existing animal models.

Conflicts of interest

None (for all authors).

Funding

None.

References

[1] Gutterman DD. Vascular dysfunction in hyperglycemia: is protein kinase C the culprit? Circ Res 2002;90(1):5–7.
[2] Buettner R, Parhofer KG, Woenckhaus M, Wrede CE, Kunz-Schughart LA, Scholmerich J, et al. Defining high-fat-diet rat models: metabolic and molecular effects of different fat types. J Mol Endocrinol 2006;36(3):485–501.
[4] Neubauer N, Kulkarni RN. Molecular approaches to study control of glucose homeostasis. ILAR J 2006;47(3):199–211.
[5] Kawasaki F, Matsuda M, Kanda Y, Inoue H, Kaku K. Structural and functional analysis of pancreatic islets preserved by pioglitazone in db/db mice. Am J Physiol Endocrinol Metab 2005;288(3):E510–8.
[6] Storlien LH, James DE, Burleigh KM, Chisholm DJ, Kraegen EW. Fat feeding causes widespread in vivo insulin resistance, decreased energy expenditure, and obesity in rats. Am J Physiol 1986;251(5 Pt 1):E576–83.
[7] Reed MJ, Meszaros K, Entes LJ, Claypool MD, Pinkett JG, Gadbois TM, et al. A new rat model of type 2 diabetes: the fat-fed, streptozotocin-treated rat. Metabolism 2000;49(11):1390–4.
[8] Kraegen EW, James DE, Storlien LH, Burleigh KM, Chisholm DJ. In vivo insulin resistance in individual peripheral tissues of the high fat fed rat: assessment by euglycemic clamp plus deoxyglucose administration. Diabetologia 1986;29(3):192–8.
[9] Kraegen EW, Clark PW, Jenkins AB, Daley EA, Chisholm DJ, Storlien LH. Development of muscle insulin resistance after liver insulin resistance in high-fat-fed rats. Diabetes 1991;40(11):1397–403.
[10] Cefalu WT. Animal models of type 2 diabetes: clinical presentation and pathophysiological relevance to the human condition. ILAR J 2006;47(3):186–98.
[11] Srinivasan K, Ramarao P. Animal models in type 2 diabetes research: an overview. Indian J Med Res 2007;125(3):451–72.
[12] Lillioja S, Mott DM, Spraul M, Ferraro R, Foley JE, Ravussin E, et al. Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus. Prospective studies of Pima Indians. N Engl J Med 1993;329(27):1988–92.
[13] Warram JH, Martin BC, Krolewski AS, Soeldner JS, Kahn CR. Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic parents. Ann Intern Med 1990;113(12):909–15.
[14] MASEK J, FABRY P. High-fat diet and the development of obesity in albino rats. Experientia 1959;15:444–5.
[15] Oakes ND, Cooney GJ, Camilleri S, Chisholm DJ, Kraegen EW. Mechanisms of liver and muscle insulin resistance induced by chronic high-fat feeding. Diabetes 1997;46(11):1768–74.
[16] Ahren B, Gudbjartsson T, Al-Amin AN, Martensson H, Myrsen-Axcrona U, Karlsson S, et al. Islet perturbations in rats fed a high-fat diet. Pancreas 1999;18(1):75–83.
[17] Junod A, Lambert AE, Stauffacher W, Renold AE. Diabetogenic action of streptozotocin: relationship of dose to metabolic response. J Clin Invest 1969;48(11):2129–39.
[18] Bitar MS, Wahid S, Mustafa S, Al-Saleh E, Dhaunsi GS, Al-Mulla F. Nitric oxide dynamics and endothelial dysfunction in type II model of genetic diabetes. Eur J Pharmacol 2005;511(1):53–64.
[19] Chaabo F, Pronczuk A, Maslova E, Hayes K. Nutritional correlates and dynamics of diabetes in the Nile rat (Acanthi niloticas): a novel model for diet-induced type 2 diabetes and the metabolic syndrome. Nutr Metab (Lond) 2010;7:29.
[20] Danda RS, Habiba NM, Rincon-Choles H, Bhandari BK, Barnes JL, Abboud HE, et al. Kidney involvement in a nongenetic rat model of type 2 diabetes. Kidney Int 2005;68(6):2562–71.

[21] Diz-Chaves Y, Spuch C, Perez D, Mallo F. Ghrelin improves growth hormone responses to growth hormone-releasing hormone in a streptozotocin-diabetic model of delayed onset. J Endocrinol Invest 2007;30(4):298–305.
[22] Islam MS, Choi H. Nongenetic model of type 2 diabetes: a comparative study. Pharmacology 2007;79(4):243–9.
[23] Karabatas LM, Pastorale C, de Bruno LF, Maschi F, Pivetta OH, Lombardo YB, et al. Early manifestations in multiple-low-dose streptozotocin-induced diabetes in mice. Pancreas 2005;30(4):318–24.
[24] Kim E, Sohn S, Lee M, Jung J, Kineman RD, Park S. Differential responses of the growth hormone axis in two rat models of streptozotocin-induced insulinogenics diabetes. J Endocrinol 2006;188(2):263–70.
[25] Ramadan W, Dewasmes G, Petitjean M, Loos N, Delanaud S, Geloen A, et al. Spontaneous motor activity in fat-fed, streptozotocin-treated rats: a nonobese model of type 2 diabetes. Physiol Behav 2006;87(4):765–72.
[26] Sartoretto JL, Santos RA, Scavone C, Tostes RC, Nigro D, Carvalho MH, et al. The influence of improved glycaemic control with chlorpropamides on microvascular reactivity and nitric oxide synthase activity in diabetic rats. J Pharm Pharmacol 2007;59(8):1117–23.
[27] Srinivasan K, Viswanad B, Asrat L, Kaul CL, Ramarao P. Combination of high-fat diet-fed and low-dose streptozotocin-treated rat: a model for type 2 diabetes and pharmacological screening. Pharmacol Res 2005;52(4):313–20.
[28] Sotnikova R, Skalska S, Okruhlicova L, Navarova J, Kyselova Z, Zurova J, et al. Changes in the function and ultrastructure of vessels in the rat model of multiple low dose streptozotocin-induced diabetes. Gen Physiol Biophys 2006;25(3):289–302.
[29] Sugano M, Yamato H, Hayashi T, Ochiai H, Kakuchi J, Goto S, et al. High-fat diet in low-dose-streptozotocin-treated nephrectomized rats induces all features of human type 2 diabetic nephropathy: a new rat model of diabetic nephropathy. Nutr Metab Cardiovasc Dis 2006;16(7):477–84.
[30] Takada J, Machado MA, Peres SB, Brito LC, Borges-Silva CN, Costa CE, et al. Neonatal streptozotocin-induced diabetes mellitus: a model of insulin resistance associated with loss of adipose mass. Metabolism 2007;56(7):977–84.
[31] Weng Y, Shen F, Li J, Shen Y, Zhang X. Expression changes of mitogen-activated protein kinase phosphatase-1 (MKP-1) in myocardium of streptozotocin-induced diabetic rats. Exp Clin Endocrinol Diabetes 2007;115(7):455–60.
[32] Wang HJ, Jin YX, Shen W, Neng J, Wu T, Li YJ, et al. Low dose streptozotocin (STZ) combined with high energy intake can effectively induce type 2 diabetes through altering the related gene expression. Asia Pac J Clin Nutr 2007;16(Suppl 1):412–7.
[33] Zhang F, Ye C, Li G, Ding W, Zhou W, Zhu H, et al. The rat model of type 2 diabetic mellitus and its hypometabolism characters. Exp Anim 2003;52(5):401–7.
[34] Zhang H, Chen S, Deng X, Yang X, Huang X. Danggui-Buxue-Tang decoction has an anti-inflammatory effect in diabetic atherosclerosis rat model. Diabetes Res Clin Pract 2006;74(2):194–6.
[35] Zhang H, Chen S, Deng X, Yang X, Huang X. The effects of Danggui-Buxue-Tang on blood lipid and expression of genes related to foam cell formation in the early stage of atherosclerosis in diabetic GK rats. Diabetes Res Clin Pract 2007;77(3):479–81.
[36] Bell Jr RH, Hye RJ. Animal models of diabetes mellitus: physiology and pathology. J Surg Res 1983;35(5):433–60.
[37] Storlien LH, Jenkins AB, Chisholm DJ, Pascoe WS, Khouri S, Kraegen EW. Influence of dietary fat composition on development of insulin resistance in rats. Relationship to muscle triglyceride and omega-3 fatty acids in muscle phospholipid. Diabetes 1991;40(2):280–9.
[38] Storlien LH, Baur LA, Kriketos AD, Pan DA, Cooney GJ, Jenkins AB, et al. Dietary fats and insulin action. Diabetologia 1996;39(6):621–31.
[39] Rees DA, Alcolado JC. Animal models of diabetes mellitus. Diabet Med 2005;22(4):359–70.