Rodent Models of Type 2 Diabetes Mellitus

زكي طبيشه, جامعة الخليل, zakit@hebron.edu

Follow this and additional works at: https://digitalcommons.aaru.edu.jo/hujr_a

Part of the Life Sciences Commons

Recommended Citation

"Rodent Models of Type 2 Diabetes Mellitus," Hebron University Research Journal-A (Natural Sciences) - مجلة جامعة الخليل للبحوث - أ (العلوم الطبيعية) : Vol. 7 : Iss. 1 , Article 3. Available at: https://digitalcommons.aaru.edu.jo/hujr_a/vol7/iss1/3

This Article is brought to you for free and open access by Arab Journals Platform. It has been accepted for inclusion in Hebron University Research Journal-A (Natural Sciences) - مجلة جامعة الخليل للبحوث - أ (العلوم الطبيعية) by an authorized editor. The journal is hosted on Digital Commons, an Elsevier platform. For more information, please contact rakan@aaru.edu.jo, marah@aaru.edu.jo, dr_ahmad@aaru.edu.jo.
Rodent Models of Type 2 Diabetes Mellitus

Dr. Zaki Ali Tubesha
Faculty of Agriculture
Hebron University

Abstract:
Diabetes is a disease characterized by a relative or absolute lack of insulin, leading to hyperglycemia. Due to the high prevalence of diabetic individuals all over the globe, extensive research is being carried out effective to develop more antidiabetic agents and to determine their mechanisms of action. Consequently, a number of diabetic animal models have been developed and improved over the years, of which rodent models are the most thoroughly described. The animal models of type 2 diabetes can be obtained either spontaneously (genetics) or induced by chemicals, dietary, surgical manipulations or by various combinations. In this review my attention has been focused on gathering the animal models of type 2 diabetes, with reference to their characteristic, mechanisms, advantages and disadvantages to the investigators in type 2 diabetes research. For better and conclusive results, more than one animal model should be used to represent the diversity seen in human diabetic patients.

Keywords: Animal models, Diabetes, Rodents, Obesity

الملخص:
يتميز مرض السكري بنقص الأنسولين بكميات كبيرة أو جزئية تؤدي لارتفاع السكر في الدم بسبب الانتشار الواسع لداء السكري عالمياً، تجري الآن الكثير من الأبحاث لإنتاج وتطوير علاجات جديدة ودراسة آلية عمل هذه الأدوية. لذلك تم تطوير العديد من حيوانات التجارب كنموذج لمرض السكري و تم تصنيفها خلال السنوات الماضية، حيث كانت القواعد من أكثر
Introduction

Diabetes of all types can lead to complications in various organs of the body and can increase the risk of dying prematurely (Zone and Guide, 2017). Globally, an estimated 422 million adults were living with diabetes in 2014, compared to 108 million in 1980 (WHO, 2016). To address the urgent and challenging needs for better treatment options to control or even eradicate diabetes mellitus, animal models closely resembling disease characteristics are rapidly required to predict the efficacy and safety of tested compounds in humans (Renner et al., 2016). Theoretically, any organism can be used as a laboratory model for scientific investigation, but only a few species are chosen to serve in biomedical fields (Wall and Shani, 2008). However, to be defined as a laboratory animal, the species must be bred and raised under certain conditions and kept in a rigorously controlled environment under constant monitoring, so that all microbiologic and genetic factors are known (Andersen and Tufik, 2015). Currently, rodents represent the dominant species in biomedical research for their low cost, high reproductive potential, short life span, adaptability to varied environments and sociability (Angelis et al., 2015). In fact, 90% of laboratory animals are mice and rats, inclusion of guinea pigs and rabbits brings this figure to 99%, while, the remaining 1% is composed of dogs, cats, and non-human primates, among others (Balcombe, 2006). Most diabetic patients, that is, 90% to 95%, suffer from type 2 diabetes mellitus (T2DM), which is characterized by a combination of insulin resistance and insulin secretion defects, with variable manifestations resulting in relative insulin deficiency (Renner et al., 2016).
In addition, medications used for the treatment of T2DM are associated with problems of improper efficacy and negative side effects. So, there is a continuous ongoing research for improved medications for diabetes and insulin resistance (Tiwari, 2015). However, for an animal model to have relevance to the study of diabetes, either the characteristics of the animal model should reflect the pathophysiology or natural history of diabetes or the model should develop complications of diabetes with an etiology similar to that of the human condition (Cefalu, 2006). There appears to be no single animal model that encompasses these entire characteristic; but there are many models that provide very similar characteristics in one or more aspects of T2DM in humans. The use of the appropriate animal model based on these similarities, can provide much needed data on pathophysiological mechanisms operative in human T2DM. Hence, this review intends to give a detailed overview of the currently available T2DM rodent’s animal models to be used in testing various classes of new chemical brands.

**Spontaneous (genetic) T2DM rodent models**

**Obese Models**

Models of obesity with T2DM include two categories, monogenic (those containing a mutation in the leptin or leptin receptor gene) and polygenic models (Kanasaki and Koya, 2011). Obese rodents, such as *ob/ob* mice, which is deficient in leptin and the *db/db* mice and Zucker Diabetic Fatty rat, which are deficient in the leptin receptor, were used as monogenic models. Obesity in these models is caused by leptin signaling deficiency (King, 2012). Polygenic models may provide a more accurate model of the human condition which includes KK mice, New Zealand Obese (NZO) mice, TallyHo/Jng mice, and Otsuka Long Evans Tokushima Fatty (OLETF) rat (Leiter, 2009).

**Monogenic Models**

Monogenic diabetes constitutes a heterogeneous group of single gene disorders (Hattersley, 2005). The molecular background and clinical picture of many of these diseases have been described (Fajans et al., 2001; Hattersley, 1998; Malecki et al., 2008; McCarthy and Hattersley, 2001). These models are divided into two major groups, resulting from impaired
insulin secretion or from an abnormal response to insulin (Klupa et al., 2012).

**ob/ob mice:** The *ob/ob* mice strain, from the Bar Harbor-Jackson laboratory, has a well-known feature of leptin deficiency because of the mutation identified in leptin gene leading to severe insulin resistance (Oakes et al., 2005). In the early 1970s, these *ob/ob* mice were used to investigate the pathogenesis of insulin resistance as the first rodent model. Weight of *ob/ob* mice increases rapidly starting at 2 weeks of age, and can reach up to three fold the weight of wild-type controls (Yamaguchi, 2014). By 3 weeks to a month of age, hyperphagia, insulin resistance and hyperinsulinemia are apparent, with obesity evident by 4 weeks (Coleman, 1978; King and Bowe, 2016). Even after obvious hyperglycemia detected at 4 weeks, blood glucose levels continue to increase until reaching a peak at 3–5 months of age with glucose levels reaching up to 400 mg/dl (Lindström, 2007). Although there are some abnormalities in insulin release, islets maintain insulin secretion, and the lack of complete β-cell failure in this model means diabetes is not particular severe and indeed not completely representative of human T2DM (King, 2012).

**db/db mice:** The diabetes *db* gene mutation occurred spontaneously in the leptin-receptor-deficient C57BL/KsJ strain of mice and is originally derived from autosomal recessive mutation on chromosome 4 with complete penetrance, originating from Bar Harbor (Coleman, 1978; Wang et al., 2013). The *db/db* mice were identified initially in 1966 in Jackson Labs and is due to an autosomal recessive mutation in the leptin receptor (Sharma et al., 2003). They can be considered as having a natural history that closely parallels that of humans. It appears that the obesity predisposes these mice to diabetes, and this evidence is incredibly valuable when assessing the effect of obesity on the development of diabetes (Cefalu, 2006; King, 2012). It becomes hyperphagic, hyperinsulinemic, and insulin resistant early in life (within 2 weeks of age), then develops obesity at the age of 3 to 4 weeks. The hyperglycemia becomes manifest at the age of 4 to 8 weeks due to beta cell failure (Fajardo et al., 2014).
**Zucker Diabetic Fatty Rats:** Zucker diabetic fatty (ZDF) rats were discovered in 1961 after a cross of Merck M-strain and Sherman rats (Al-Awar et al., 2016). The homozygous mutation (fa/fa) of the leptin hormone receptor results in the development of type 2 diabetes in male rats when they are fed a high-energy rodent diet. The rats induces hyperphagia, and become obese at around 4 weeks of age (Srinivasan and Ramarao, 2007). In addition, rats develop advanced insulin resistance and glucose intolerance between 3 and 8 weeks of age and turn overtly diabetic between 8 and 10 weeks of age with glucose levels in the feeding state typically 500 mg/dl by 10-11 weeks of age (Al-Awar et al., 2016; King and Bowe, 2016). The symptoms of this genetic obesity share many similarities with those in obese patients with insulin-resistance or T2DM including hyperinsulinaemic, hyperlipidaemic, hypertensive, and impaired glucose tolerance. Therefore, the obese Zucker rat has been widely used as a genetic model of obesity and insulin resistance (King, 2012).

**Polygenic Models**

**KK and KK-Ay mice:** The KK mice originating from Japan is a polygenic model of obesity and T2DM (Wang et al., 2013). They exhibit mild insulin resistance and obesity, which is more severe in male mice than in female mice (Kitada et al., 2016). Hyperphagia, hyperinsulinaemia and insulin resistance are main features of the KK mouse, which becomes gradually obese from the age of 2 months to the age of 4-5 months (Chatzigeorgiou et al., 2009). In these animals, insulin resistance precedes the onset of obesity. The increase in insulin content is associated with increase in number and size of pancreatic islets, but histologically degranulation of β-cells and hypertrophy of islets are found (King, 2012; Srinivasan and Ramarao, 2007). The KK-Ay mouse was developed by Nishimura et al in 1969 by transferring the yellow obese gene (Ay allele) into the KK mouse (Nishimura, 1969). KK-Ay mice are more severely obese and are more likely to develop hyperglycemia and albuminuria at 16 weeks of age than KK mice of the same age (Kitada et al., 2016). Therefore, these mice are widely used as an experimental model of type 2 diabetes.
**New Zealand Obese Mice:** The New Zealand Obese (NZO) mouse is one of the most thoroughly investigated polygenic models for the human metabolic syndrome and type 2 diabetes. It presents the main characteristics of the disease complex, including early-onset obesity, insulin resistance, dyslipidemia, and hypertension (Dunford, 2016). As a consequence of the syndrome, male NZO mice develop type 2 like diabetes characterized by marked hyperglycaemia and hyperinsulinemia at earlier age (8–12 weeks), and later on by low serum insulin levels associated with beta-cell destruction (Gitanjali et al., 2016). Additionally, NZO mice exhibit decreased exercise activity when compared to control or even ob/ob mice. Obesity in NZO mice is caused by a combination of hyperphagia, insufficient physical activity, and reduced energy expenditure with a reduction in body temperature (King and Bowe, 2016).

**TALLYHO/Jng(TH) mice:** The TallyHo mice are developed from an outbred colony of Theiler original mice by selective breeding of mice that spontaneously developed hyperglycaemia and hyperinsulinaemia (Denvir et al., 2016). Hence, it is a model of obesity and type 2 diabetes. Hyperglycaemia is limited to male mice, which develops at an early age, between 10 and 14 weeks (Sah et al., 2016). Furthermore, TH mice also exhibit increased islet insulin secretion in response to glucose and β-cell mass. It has been used in the development of therapeutic agents for obesity and type 2 diabetes and served as a model system for decreased exercise capacity, impaired wound healing, periodontitis, tissue susceptibility to hypoxia, bone loss, circadian disruption, and vasculature abnormalities (Denvir et al., 2016).
Otsuka Long Evans Tokushima Fatty Rat: Otsuka Long Evans Tokushima Fatty (OLETF) rats are an outbred strain of rats developed by Drs. Long and Evans in 1915 by crossing several Wistar white females with wild gray male rats (Cheung et al., 2009). Long Evans rats are white with a black hood, or occasionally white with a brown hood (Kawano et al., 1992). The spontaneously hypertensive rat exhibits essential hypertension, hyperinsulinemia, glucose intolerance, hypertriglyceridemia and obesity collectively representing human insulin resistance syndrome (Sah et al., 2016). These polygenic rats develop diabetes later in life at around 18-25 weeks old and inherited mostly in males (Abdul Rasheed et al., 2016).

Non Obese Models
Not all type 2 diabetes patients are obese, and thus, it is important that lean animal models of type 2 diabetes are also studied (Nagai et al., 2012). Spontaneous models are well known in this category, e.g., Goto-Kakizaki (GK) rats, Spontaneously Diabetic Torii (SDT) rats, Cohen diabetic rats, and Wistar Bonn/Kobori (WBN/Kob). Chemically-induced diabetes models such as neonatal streptozotocin-induced (Nstz) diabetic rats are also used (Yukihito et al., 2012).

Goto-Kakizaki Rats: Goto-Kakizaki (GK) rats are a non-obese substrain of Wistar origin that develops type 2 diabetes as a result of impaired beta cell mass function and glucotoxicity stemming from polygenic inheritance. They were selected through a group of eight generation-inbreeding Wistar rats displaying high glucose levels during a glucose tolerance test (Shafrir and Ziv, 2009). This leads to the development of a lean model of type 2 diabetes, which is characterized by glucose intolerance and defective glucose-induced insulin secretion caused by β cell dysfunction and/or reduced β cell mass (Mukai et al., 2014). Thus, adult GK rats show finally a 60% decrease in their total pancreatic β-cell mass. However, blood glucose is elevated only after the 3-4 first weeks of animal’s age and generally, during its lifetime, fasting glucose remains mild and stable and rises only after challenge with glucose. GK rat is a very useful model for studying the mechanisms of diabetes complications,
although the very early β-cell destruction remains a limitation for depicting T2DM (Chatzigeorgiou et al., 2009).

**Torii (SDT) rat:** The Spontaneously Diabetic Torii (SDT) rat is a new inbred strain of Sprague-Dawley (SD) rat established as a non-obese model of type 2 diabetes mellitus and characterized by long survival without insulin treatment (Srinivasan and Ramarao, 2007). The cumulative incidence of diabetes was 100% by 32 weeks in male SDT rats, while it was only 33% in females even at 15 months (Yukihito et al., 2012). A clear gender difference is observed in the onset of diabetes in SDT rats. Male SDT rats showed high plasma glucose levels (over 700 mg/dl) by 20 weeks which will lead to develop severe ocular complications such as cataracts, retinal neovascularizations, and retinal detachment with fibrous proliferation as well as renal abnormalities such as renal tubular dilation and increased mesangial matrix in glomeruli (Mukai et al., 2014; Shinohara et al., 2000). Therefore, SDT rats are a useful animal model for investigating diabetic complications.

**Cohen diabetic rat:** Cohen diabetic rat, an exceptional genetical model derived from diet-induced T2DM model by placing the rat on a synthetic 72% sucrose-copper-poor diet for 2 months, displays many features of the human T2DM (Wang et al., 2013). The diabetes is due to β-cell dysfunction and reduced insulin secretion (Shafrir and Ziv, 2009). The main complications of Cohen rats were nephropathy with mesangial expansion and thickening of the glomerular basement membrane, proliferative retinopathy, testicular atrophy and gastrointestinal disorders, skeletal pathology, and embryopathy (Katsuda et al., 2014).

**Wistar Bonn / Kobori (WBN/Kob) rat:** These animals of Wistar strain demonstrate impaired glucose tolerance and glucosuria at 21 weeks of age and this is seen only in males. Reduction in the number and size of islets after 12 weeks of age was observed (Sharma et al., 2016). Histopathological examination of the pancreas revealed fibrotic changes as early as 3 months of age. With advancing age, the fibrosis invades the islets, resulting in the clinical diabetic syndrome (De Angelis et al., 2009).
Diet/nutrition T2DM rodent models

Diet or nutrition type 2 diabetic rodent models also called experimentally or non-spontaneously induced models are not diabetic under normal conditions (Islam and Loots, 2009). In T2DM research, genetic models provide a better pathogenesis for the disease and a wide variety of such models exist to study various areas of diabetic pathology, but unfortunately, those models are very expensive, difficult to maintain and rare amongst researchers particularly in the developing countries (Islam and Loots, 2009). Non-genetic models, on the other hand, are far more cost-effective, widely available and easy to develop diabetes with minimal research facilities (Wilson and Islam, 2012). However, the available rodent models present one or both of the two major pathogenic features of T2DM—these being insulin resistance and, subsequently, the development of pancreatic beta cell dysfunction (Islam and Wilson, 2012). In these models, rats or mice develop diabetes associated with obesity as a result of over nutrition, which mimic the metabolic syndrome in humans, and most require long period of dietary treatment (Kiasalari et al., 2017). Sand rat, Tuco-Tuco and Spiny mice are some models of diet/nutrition induced obesity and type 2 diabetes.

Sand rat: Sand rat (*Psammomys obesus*) is a model of nutritionally induced type 2 diabetes. The progression of diabetes in *Psammomys* resembles in many respects the development of insulin resistance and diabetes in certain human populations (Shafir et al., 2007). The animals develop diabetic symptoms when fed chow instead of their natural diet. In 2-3 months, the diabetic syndrome in the sand rat usually develops. Severely hyperglycemic animals die prematurely from ketosis (Kumar et al., 2012).

Tuco-Tuco: The diabetic syndrome in Tuco-tuco mice (*Ctenomys talarum*) is similar to that in sand rats and spiny mice. They tend to have less hyperglycemia and are less prone to ketosis. Many animals, mainly males, become hyperphagic. In few animals degranulation of β cell is the usual lesion in the pancreas, but amyloid hyalinization of islets has been observed (Sharma et al., 2016).
Spiny mice: The spiny mouse (*Acomys cahirinus*) is found in the semi-desert areas of the Eastern Mediterranean. Diabetes occurs in about 15% of the animals under laboratory conditions (Kumar et al., 2012). Some animals show obesity, mild hyperglycemia, and hyperinsulinemia and some have frank hyperglycemia with glucosuria that leads to fatal ketosis. All spiny mice characteristically have massive hyperplasia of pancreatic islets and increased pancreatic insulin content (Sharma et al., 2016).

Chemically induced T2DM rodent models

Gold thioglucose (GTG) treated obese mice: Gold thioglucose is diabetogenic compound, which is induced hyperphagia and severe obesity induced T2DM (Kumar et al., 2012). They produces obesity-induced diabetes in genetically normal mouse strains. In addition, Gold thioglucose treated DBA/2 (Dilute Brown Non- Agouti), C57BLKs, and BDF1 mice gained weight rapidly and significantly increase non fasting plasma glucose level within 8-12 weeks (Tripathi and Verma, 2014). These mice showed impaired insulin secretion, mainly in early phase after glucose load and reduced insulin content in pancreatic islets (Miyawaki et al., 1999).

Adult Streptozotocin/ Alloxan Models: Alloxan is a uric acid derivative that selectively destroys pancreatic β-cells by oxidative stress mechanisms. However, the use of alloxan nowadays is significantly lower compared to Streptozotocin (STZ) due to its lesser efficacy and some proven side effects in animals e.g., liver and kidney damage. The STZ, on the other hand, is a natural antibiotic produced by the bacterial species *Streptomyces achromogenes* (Islam and Wilson, 2012). It is, however, known that single high dose STZ injection (>60 mg/kg BW) results in massive pancreatic β-cell destruction, more characteristic of T1DM, whereas intermediate dosages of STZ injections (between 40 and 55 mg/kg BW) cause only partial impairment to insulin secretory mechanisms seen in T2DM. A single dose lower than 35 mg/kg bw in rats fed a normal commercial diet usually fails to elicit any hyperglycemic effect (Srinivasan et al., 2005). These models are usually characterized by fasting or non-fasting hyperglycemia, lowered serum insulin levels with hyperlipidemia; however, insulin resistance is often absent in these...
models. Although these models cannot be considered as appropriate models for T2DM, they can be used for the screening of antihyperglycemic or insulinotropic drugs and natural medicines (Islam and Wilson, 2012).

**Neonatal Streptozotocin/Alloxan Models:** Rats with diabetes induced by injection of streptozotocin/Alloxan on the day of birth, or soon thereafter, are used to study the long-term consequences of reduced β-cell mass that resemble those seen in human type 2 diabetes (Shafrir et al., 2006). In this model, a peak of hyperglycaemia is seen 2 days after STZ administration (100 mg/kg, i.v. or i.p.), which is followed by regeneration of beta cells and normoglycaemia by day 10. However, hyperglycaemia returns by 6 weeks, which is thought to be due to inadequate beta cells mass and beta cell dysfunction. Therefore, in the later phase, this model can be used to study type 2 diabetes (King, 2012). Single injection of STZ at the dose range of 80-100 mg /kg of STZ (iv or ip or sc) to one or two or five day old Wistar or Sprague-Dawley neonatal rats has been reported to produce type 2 diabetic conditions (Srinivasan and Ramarao, 2007). Some investigators have also developed neonatal type 2 diabetic models by injecting ALX (200 mg/kg, ip) to male neonatal rats at age of 2, 4 or 6 day after birth and found to be much useful for the investigation of long term complication of type 2 diabetes (Kodama et al., 1993). In these models, diabetes was characterized by mild to moderate hyperglycemia, increased blood glycated hemoglobin, urinary glucose excretion, and increased food intake (Islam and Wilson, 2012). However, this model takes quite a long time (at least 12 weeks) to induce diabetes which may not be suitable for quick and routine pharmacological screening of anti-type 2 diabetic drugs or natural medicines. Furthermore, many of these models have not been validated by anti-diabetic drugs and thus limit their suitability as an appropriate model for T2DM (Islam and Loots, 2009).

**Nicotinamide–Streptozotocin Models:** Administration of both streptozotocin (STZ) and nicotinamide (NA) has been proposed to induce T2DM in rats. STZ is well known to cause pancreatic β-cell damage, whereas NA is administered to rats to partially protect insulin secreting cells against STZ (Lenzen, 2008). The effects induced in rats by STZ and
NA vary depending on the doses of these two compounds, the age of the animals and the time of NA administration in relation to the administration of STZ. Other factors, such as the administration route of STZ and the nutritional state of rats, may also have certain influence (Domingo et al., 1995). In the case of relatively low doses of NA given to rats, its protective action is negligible. Conversely, high doses of NA may provide full protection (Tubiana and Aurengo, 2006). The age of rats is vital, since β-cells of younger animals are less sensitive to STZ and are better protected by NA. It is also known that the protective action of NA on β-cells decreases with the time elapsed after administration of STZ to rats. In the majority of experiments, NA is given to rats 15 minutes before STZ injection (Szkudelski, 2012).

**Combinations of chemicals and diet T2DM models**

The most commonly used non-genetic rodent models of diabetes are those induced by streptozotocin or alloxan, in addition to diet (Lenzen, 2008). Diet composition has been considered an important factor in the impairment of insulin activity (Dourmashkin et al., 2005). Various studies (Bansal et al., 2012; Veerapur et al., 2012; Zhang et al., 2009) showed that the administration of a high-fat diet (HFD) to rats for 2 months or lower is a fast and easy way to induce metabolic syndrome, associated with metabolic and oxidative disorders, without modulation of glycaemia (Auberval et al., 2014). However, diet rich in fat as well as sugar is a greater risk factor for these disorders than a diet that is rich in either fats or sugars (Lozano et al., 2016). Moreover, these models require lengthy feeding regimens before any decline in β-cell mass is detectable. To overcome this barrier, a low dose of streptozotocin or alloxan have been described in the rat or mice to deplete β-cell mass chemically after induction of diet-induced insulin resistance (Podell et al., 2017).

Fat fed/STZ diabetic rodents, developed by combination of diet-induced insulin resistance and relatively low-dose streptozotocin (35–50 mg/kg) provide a novel animal model for diet induced T2DM (Srinivasan and Ramarao, 2007). In these animals, insulin resistance is generated by feeding the animals with high fat diet (HFD). Subsequently, hyperglycemia is induced by injection with a low dose of STZ that does

https://digitalcommons.aaru.edu.jo/hujr_a/vol7/iss1/3
not cause diabetes in standard diet fed animals (Furman, 2015). Thus, these fat-fed/STZ-treated animals simulate natural disease progression and metabolic characteristics typical of individuals at an increased risk of developing T2DM because of insulin resistance and obesity (Reuter, 2007). Suitable animal strains for high fat/STZ models are C57BL/6J mice as well as rats, preferably male Sprague-Dawley rats. Diets from 40% to 60% calories as fat have been used together with STZ injections of 35–50 mg/kg. Induction times vary from 2 to 4 weeks up to several weeks, depending to type of diet and dose of STZ (Reed et al., 2000; Reuter, 2007; Srinivasan et al., 2005). The high fat fed low dose STZ models have several advantages, including cost-effective, developed in short time and are suitable for in vivo evaluation of anti-diabetic agents (Srinivasan and Ramarao, 2007).

Similar to HFD, the induction of insulin resistance through fructose-feeding in animals has been employed previously (Hininger et al., 2009). Fructose could be supplied adlibitum, either in drinking water (20%) or with diets (60% of the total energy) for a short or longer period to induce insulin resistance or T2DM, respectively, in experimental animals (Dai et al., 1994). Hence, the combination of fructose-feeding for a shorter period of time (less than 2 months) and a lower dose of STZ injection (35–50 mg/kg) may induce all major pathogeneses of T2D in rats (Patel et al., 2009).

**Surgically induced T2DM rodent models**

**Partial Pancreatectomized Models:** As a means to avoid liver and kidney damage induced by alloxan, researchers developed a new method to induce T2DM in animals through partial pancreatectomy (Islam and Wilson, 2012). Partial pancreatectomy in animals performed as 70 or 90 per cent (usually 90%) dissection of pancreas has been reported in various animal species mostly in dogs, pigs, rabbit and also rats. It does not cause severe form of diabetes and is characterized by moderate hyperglycaemia with neither reduction in body weight nor reduction in plasma insulin levels (Srinivasan and Ramarao, 2007). However, better degree of glycaemia or stable form of diabetes for long duration can be achieved by the combination of partial pancreatectomy with ALX/STZ injection. This
model was accomplished by 50% pancreatectomy in combination of a 350 mg/kg BW nicotinamide injection prior to and after intraperitoneal injection of 200 mg/kg BW STZ in BALB/c mice (Islam and Wilson, 2012).

**Ventromedial hypothalamus (VMH) diabetic rats:** VMH dietary obese diabetic rat has been developed by experimental surgical manipulation of genetically normal animals without the reduction in pancreatic beta cell mass, resembling type-2 diabetes, by combining bilateral electrolyte lesion of VMH and feeding the high fat and high sucrose diet to the animal (Singh and Pathak, 2015). It is characterized by obvious obesity, hyperinsulinaemia, hypertriglyceridaemia, insulin resistance, impaired glucose tolerance, moderate to severe fasting hyperglycaemia and defective regulation of insulin secretory response despite extremely high insulin secretory capacity. It is interesting that significant hyperphagia is observed despite increased leptin levels (leptin resistance) in the VMH lesioned rats (Srinivasan and Ramarao, 2007).

**Transgenic/knock-out T2DM Models**
These transgenic animals are usually helpful in getting insights to gene regulation and development, pathogenesis, treatment of disease and finding new targets for that (Ranjan and Sharma, 2015). Generally, transgenic animals, especially mice, are made by transferring and altering the site or expression level of functional gene (transgene) or by deleting specific endogenous genes (knockout) or by placing them under the control of alternate promoter regions (Margawati, 2003). These models are developed in order to explore the role of associated genes and their effects on peripheral insulin action such as insulin receptor, IRS-1, IRS-2, GLUT 4, PPAR-γ and TNF-α as well as in insulin secretion such as GLUT-2, GK, IAPP and GLP-1 and also in hepatic glucose production (PEPCK expression) associated with T2DM development (Ranjan and Sharma, 2015; Sharma et al., 2016). Although significant advances in this field have arisen in recent years, especially with the advent of transgenic mice, there have been a few studies carried out involving natural products on these models.
Conclusion:
The animal models of T2DM are very useful means for studying the pathophysiology and the clinical phases of the disease. Actually, they are always used as the initial step for examining a new therapy. Each model provides unique advantages specific for an area of T2DM study or its complications. An ideal model should typically mimic the natural disease pattern as closely as possible with the two major pathogeneses, insulin resistance, and partial pancreatic beta cell dysfunction. Therefore, the continuing research for inventing new models has always positive critics and animal models will continue to have a major and meaningful place in diabetes research. However, every researcher should only utilize animals only when they are indispensable for a study and avoid causing them pain, distress, suffering and lasting harm.
References


