Research in Diabetes using Animal Models

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1 Introduction

Diabetes affects more than 300 million humans worldwide and many more exist undiagnosed. Type 1 diabetes (T1D) is a multifactorial autoimmune disease characterized by T-cell and macrophage-mediated destruction of pancreatic β-cells which induce irreversible insulin deficiency (Notkins & Lernmark, 2001). The process of β-cell destruction is progressive and occurs several years in humans (Leiter et al., 1987). Pathogenesis of T1D is characterized by insulitis that is rapidly followed by selective destruction of pancreatic β-cells caused by lymphocyte infiltration and consequently frank diabetes develops. The molecular genetics regulating the progress of β-cell failure and factors determining time of presentation of clinical diabetes are still poorly understood.

The most frequently occurring type of diabetes is Type 2 diabetes (T2D), usually onset in adulthood and caused by defects in insulin secretion and/or insulin resistance. Increased insulin secretion follows, leading to reduced pancreatic β-cell function and eventual increased blood glucose concentration. Chronically elevated blood glucose has its toll on many organs via microvascular and cardiovascular complications, such as kidney failure, blindness, peripheral neuropathy, and atherosclerosis with risk of subsequent heart attack, stroke, or limb circulation deficiencies respectively (Matveyenko & Butler, 2006). Human genome studies have associated more than 50 genes with T2D until present (McMurray et al., 2012).

Animal research regarding diabetes has made significant progress since the late 1800s until present, with patients benefiting from the original discovery of insulin in dogs and the continuous assessment of the efficacy and safety of other therapies. The experience gained by the study of animal models has been enormous not only in the field of preclinical testing prior to clinical trials, but also in that of genes predisposing to diabetes (Potenza et al., 2011). As diabetes in humans remains a disease with increased morbidity and mortality in conjunction with its multi-organ complications, its investigation using animal models remains a foremost area of research.

T1D has been studied in mainly mouse and rat animal models, either spontaneously developed or virus-induced (Buschard, 2011). The most commonly used viruses to induce diabetes in animals are Coxsackie B virus, encephalomyocarditis virus and Kilham rat virus (King, 2012; Kumar et al., 2012). One of the mechanisms implicated is the fact that the infected β-cell undergoes apoptosis, because the virus-infected β-cell cannot be destroyed by immune cells (Buschard, 2011). The factors affecting T2D are numerous and increase the need for the development of research animal models that could assist in their simultaneous evaluation by scientists (McMurray & Cox, 2011). Some of these models have been studied for decades, whereas others have been investigated more recently, such as the oxidative stress models (Styskal et al., 2012). The predisposal to T2D is inherited in man, monkeys and rodents, whereas the same is estimated for cats (Fletcher et al., 2002). It is therefore rational for these models to mimic human obesity, lack of response to insulin secretion or dysfunction of pancreatic β-cells (King, 2012). However, it is difficult for any animal model to closely mimic the human condition, where a great diversity of expression of the disease exists (including obesity and age of onset). Nevertheless, most animal models for the study of T2D have mainly been chosen due to their ability to develop obesity resulting in clinical diabetes (Chatzigeorgiou et al., 2009).

In the following pages, the main animal models used in diabetes research studies and their most important characteristics are described, which will hopefully assist the researcher to select the most appropriate one for his/her study. The majority of animal models used in diabetes research are rodents.
They are generally preferred for a variety of scientific, ethical or practical reasons, which include their quick reproduction rate and short life span that allows monitoring of age-related changes over a short period of time. Rodent models enlighten not only issues regarding the onset and clinical development of diabetes, but also the biomolecular mechanisms that contribute to the manifestations of the disease (Cefalu, 2006). The obese rodent models based on a monogenic (a single gene disorder) or polygenic (multiple genes in combination with environmental influence) background are extremely valuable, in spite of the fact that in humans monogenic mutations take place rarely (King, 2012). The spontaneous appearance of these models comes in addition to the practical advantages and societal acceptance of the use of rodent models in biomedical research (Cefalu, 2006; Chatzigeorgiou et al., 2009; Neubauer & Kulkarni, 2006). Coupled to the advantages is the ethical obligation of researchers for the scientifically justified and humane use of these animal models, i.e. replacement with non-animal alternatives, reduction of their numbers and refinement of the procedures, wherever possible (Dontas, 2007; Russell & Burch, 1959). As diabetes is a chronic metabolic disease, the clinical symptoms presented in animal models should always be carefully monitored in order to minimise animal suffering during the experiments (Sieher & Traysman, 1993).

2 Animal Models of Type 1 Diabetes

The most commonly used autoimmune animal models of spontaneous T1D include: the NOD mouse, the Bio-Breeding (BB) rat, the Long Evans Tokushima lean (LETL) rat, the Komeda Diabetes-Prone (KDP) rat and the congenic LEW rat. The NOD mouse and the BB rat are the two species that have provided extensive data relevant to spontaneous human T1D. It should be noted that these animals have been inbred in laboratories for many generations in selecting for hyperglycæmia. These animal models of spontaneous T1D play an important role in the eventual cure of human diabetes and studies using them have generated valuable information regarding the pathogenesis of the disease (Table 1).

2.1 The Non-Obese Diabetic (NOD) Mouse

The NOD mouse is the animal model most favoured by researchers in the study of autoimmune diabetes. It was developed in Osaka, Japan in 1974 (Makino et al., 1980) and many studies have been performed using it in the last decades since its development.

General characteristics: Insulitis is initiated at the age of 4-5 weeks. In the pre-diabetic stage, insulitis in mice begins with lymphocytes surrounding the islet perimeter and continues with an infiltration of the whole islet by an unusually large number of leukocytes, mainly CD4+ and CD8+ T-cells, although B lymphocytes and NK cells are also present. In this murine strain, both CD4+ and CD8+ subsets of T-cells play a role in the development of diabetes. Previous studies (Shizuru et al., 1988; Wong et al., 1998) have reported that diabetes does not occur in the absence of CD4+ T-cells, such as in mice that lack CD4+ T-cells or when anti-CD4 antibodies are used, as well as in mice that are deficient in CD8+ cells or when anti-CD8 antibodies are injected into young mice.

Mice insulitis differs from human insulitis because it has a subclinical β-cell destruction associated with decreasing circulating insulin concentrations much earlier compared to humans. Frank diabetes is typically manifested between 12 and 30 weeks of age. Overt diabetes usually occurs when more than 90% of the pancreatic β-cells are destroyed, at about the age of 24-30 weeks. Diabetes is more prevalent
in females with an incidence ranging from 60% to 90% in most colonies, whereas the incidence in males ranges from 10% to 30% (King, 2012). These rates are achievable only in a specific pathogen-free environment, because NOD mice are easily prone to protective immunomodulation by a wide spectrum of pathogens. Unlike human T1D, the typical clinical symptomatology of hyperglycaemia, glycosuria, polydipsia and polyuria in NOD mice are mildly present.

Complications: The affected mice have a larger resistance to ketoacidosis and can remain alive about 2-4 weeks after the disease is established without insulin administration. In the event that their diabetes is not treated, death results from dehydration rather than ketoacidosis (Atkinson & Leiter, 1999; Baxter & Duckworth, 2004; Mathews, 2005). Additionally, NOD mice develop autoantibodies to insulin, GAD and IA-2, as it also occurs in humans, and manifest other autoimmune diseases, such as Sjogren’s syndrome and thyroiditis (Chatzigeorgiou et al., 2009).

Preventive/therapeutic research efforts: Multiple susceptibility genes have been localized in genetic studies and, as with humans, the MHC alleles play an important role in this process (Rees & Alcolado, 2005; Todd, 1995). This parallel in T1D genes between NOD mice and humans has been extremely useful in dissecting common mechanisms and pathways, rendering mice potentially suitable for testing therapies in which modulation of the autoimmune response is being targeted (Yang & Santamaria, 2006). However, there are a number of drugs that are effective in NOD mice, but proven to be ineffective in humans (von Herrath MG & Nepom, 2009). Previous studies reported that one of the major issues is the time point of intervention, as many drugs have been shown to be successful to prevent diabetes when administered early in young NOD mice (Roep, 2007). The NOD mouse has also been used as the initial animal for transgenic and gene-targeting approaches. Recent studies have investigated the genetic control of dendritic cells’ defects in NOD mice (Adorini et al., 2002; Chatzigeorgiou et al., 2009). For example, the transgenic expression of a T-cell receptor, specific for native β-cells autoantigens, the introduction of further MHC molecules into the NOD genotype or the selective expression of several cytokines in the pancreatic tissue, could serve as ways for studying mechanisms, which accelerate or prevent the development of autoimmune diabetes (Adorini et al., 2002; Baxter & Duckworth, 2004).

The NOD mouse model of diabetes is still used extensively as it represents many aspects of the human disease and is a model that has helped identify many of the genetic and signalling pathways that can lead to T1D.

2.2 The Bio-Breeding (BB) Rat

The BB rat is the oldest and most widely used rat model for studying autoimmune diabetes. The strain was developed in the 1970s from a colony of outbred Wistar rats in the Bio-Breeding Laboratories in Ontario, Canada, in which spontaneous hyperglycaemia and ketoacidosis occurred (Nakhooda et al., 1997). Affected animals were the founders for two colonies that were later used to establish all other BB rat colonies. Spontaneous diabetes in BB rats occurs in more than half of animals raised in conventional housing systems in contrast to NOD mice, in which, even when exposed to most microbiological agents, diabetes is less prevalent (Serreze & Leiter, 2001).

General characteristics: Most BB rat colonies develop pancreatic insulitis that is rapidly followed by selective destruction of β-cells and frank diabetes between 50 and 90 days of age (Guberski, 1994; Mordes et al., 2004). Like NOD mice, the BB rats develop T-cell dependent autoimmune diabetes, which is characterized by islet auto-antibodies and GAD antibodies. It is noteworthy that the natural course of insulitis in the spontaneously diabetic BB rat is different from that of the NOD mouse. In the rat, there is
no significant or persistent infiltration adjacent to the islet “peri-insulitis” before progression to frank insulinitis and overt diabetes. However, in contrast with the NOD mouse, insulinitis in BB rats has many similarities with humans. The phenomenon of insulitis begins 2-3 weeks before the clinical initiation of the disease, does not start with peri-insulitis and T-lymphocytes predominate in the procedure (Mathews, 2005; Mordes et al., 2004). After the onset of hyperglycaemia, residual islets are small, distorted and composed predominantly of non β-cells. The most problematic immunopathology in all spontaneously diabetic BB rat strains is the profound T-cell lymphopenia (Elder & Maclaren, 1983), where CD4+ T-cells are greatly reduced and CD8+ T-cells are missing (Jackson et al., 1981). The majority of cultured T-cells undergo apoptosis within 24 hours (Iwakoshi et al., 1998). The presence of lymphopenia does not in itself confer susceptibility to autoimmunity in the rat, but spontaneous diabetes in rats requires that they be lymphopenic (Awata et al., 1995).

Complications: Ketoacidosis is very severe in hyperglycaemic BB rats and, as in humans, progresses to a fatal end if not treated with exogenous insulin (Mathews, 2005; Rees & Alcolado, 2005).

Preventive/therapeutic research efforts: A preventive approach to the spontaneously diabetic BB rat model is transfusion of CD4+ ART2+ T-cells to overcome the effects of lymphopenia (Burstein et al., 1989). Neonatal thymectomy, injections of antilymphocyte serum and depletion of CD8+ T-cells all prevent the disease, as do many routine immunosuppressive drugs and immunomodulatory modalities (Mordes et al., 2004). Spontaneous diabetes in BB rats can be prevented or retarded by tumor necrosis factor-α (Awata et al., 1995), lymphotoxin (Satoh et al., 1990), interferon-α (IFN-α) and IFN-γ (Takahashi et al., 1993). Curing T1D in BB rats has been achieved with islet transplantation and immunosuppressive therapy, or co-stimulatory blockade (Beaudette-Zlatanova et al., 2006). Treatment with interleukin-2 is not effective (Burstein et al., 1987).

Several drugs have been used in the past to ameliorate experimental and clinical T1D. Examples regarding their use in both BB rats and NOD mice follow. The use of cyclosporine to induce immunosuppression is an effective treatment to improve T1D in BB rats (Laupacis et al., 1983), as well as in NOD mice (Mori et al., 1986). In rodent studies, primary prevention was almost uniformly successful and therapy could be brief without toxicity. In human studies, cyclosporine proved to ameliorate T1D and preserve insulin secretory capability when administered promptly after onset. However, disease usually recurred when therapy was stopped and long-term therapy was unsuccessful (De Filippo et al., 1996). Modest doses of insulin administered parenterally or orally at an early age prevent diabetes in BB rats, as well as in NOD mice, suggestive of the induction of tolerance (Gottfredsen et al., 1985). Nicotinamide prevents diabetes in NOD mice, but not in BB rats (Hermitte et al., 1989) or in humans (Lampeter et al., 1998). GAD and bovine serum albumin are candidate autoantigens in humans and are effective in the prevention of NOD mouse diabetes (Atkinson & Leiter, 1999), but ineffective in BB rats (Petersen et al., 1997).

2.3 The Congenic LEW.1WR1 Rat

The non-lymphopenic congenic LEW rat develops spontaneous autoimmune diabetes with hyperglycaemia at a frequency of approximately 2% at a median age of 59 days. Immunological manipulation can increase its frequency to 100%. Research on its inoculation with different viruses displayed varying percentages of diabetes induction, while maternal viral inoculation protected the offspring from virus-induced diabetes (Tirabassi et al., 2010). It consists a valuable animal model for studying both autoimmune diabetes and arthritis (Blankenhorn et al., 2009; Mordes et al., 2005).
2.4 The Long Evans Tokushima Lean (LETL) Rat

In addition to the abovementioned typical models of T1D disease presentation, scientists have also developed and used many other models of spontaneously diabetic rats. The first model of autoimmune diabetes without lymphopenia was the LETL rat in which disease initially occurred at a rate of 15-20% (Kawano et al., 1991). It presents involvement of at least two recessive genes in the pathogenesis of insulitis. It is characterized by autoimmune destruction of pancreatic β-cells. The onset of clinical characteristics, such as polyuria, polyphagia, hyperglycaemia and weight loss, is abrupt, with no sex-related differences in the incidence or severity. It also presents lymphocytic infiltration of the salivary and lacrimal glands (Natori & Kawano, 1993).

2.5 The Komeda Diabetes-Prone (KDP) Rat

In the non-lymphopenic KDP rat substrain of the above LETL, the frequency of diabetes is about 70% at 120 days of age and can reach 82% or more within 220 days of age both in males and females, with the development of moderate to severe insulitis (Chatzigeorgiou et al., 2009). It is also characterized by lymphocyte infiltration of the thyroid gland and the kidneys has been mainly used in genotype studies (Mordes et al., 2004).

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<th>Type 1 Diabetes Rodent Models</th>
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| NOD | Adorini et al., 2002; Atkinson & Leiter, 1999; Baxter & Duckworth, 2004; Chatzigeorgiou et al., 2009; King, 2012; Makino et al., 1980; Mathews, 2005; Rees & Alcolado, 2005; Roep, 2007; Shizuru et al., 1988; Todd, 1995; von Herrath MG & Nepom, 2009; Wong et al., 1998; Yang & Santamaria, 2006 |
| Akita | Chatzigeorgiou et al., 2009; King, 2012; Yoshioka et al., 1997 |

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Table 1: Type 1 Diabetes rodent models. Abbreviations: NOD: non-obese diabetic; Akita: non-obese Ins2Akita; BB: Bio-Breeding; LEW: LEW.1WR1; LETL: Long Evans Tokushima lean; KDP: Komeda Diabetes-Prone.

3 Animal Models of Type 2 Diabetes

Despite the huge variety of available T2D models, it is still not easy for researchers to select an ideal model that may combine all the desirable characteristics, which constitute diabetes' clinical manifestations in humans (Table 2). However, there are several mouse strains available that resemble many characteristics of the human disease (Cefalu, 2006). Another important advantage of mouse models consti-
tutes the fact that a mouse’s phenotype is dependent on genetic background, sex and age, similarly to humans. This can be extremely valuable during the assessment and the evaluation of candidate genes that may be important for the manifestation of the disease (Neubauer & Kulkarni, 2006). It is desirable that T2D animal models should progressively develop insulin resistance, with a subsequent pancreatic β-cell dysfunction leading to hyperglycaemia. The mostly used models are described below, with emphasis on their phenotypic and metabolic characteristics.

3.1 Spontaneous Mouse Models

3.1.1 The ob/ob Mouse

The ob/ob mouse (recently relabelled as Lep<sup>ob/ob</sup>) developed from a spontaneous autosomal recessive mutation in the leptin gene on chromosome 6 on a C57BL/6 background and is leptin deficient (Srinivasan & Ramarao, 2007; Zhang <i>et al.</i>, 1994). This particular model is mainly used for the study of mild or chronic diabetes, in contrast to the ob/ob mice originating from the C57BL/KS strain, which are characterized by severe diabetes and early death (King, 2012; Srinivasan & Ramarao, 2007).

**General characteristics:** Its main characteristics include hyperphagia resulting in an increase in body weight and obesity at around 2 weeks of age, followed by hyperglycaemia, hyperlipidaemia and hyperinsulinaemia (Matveyenko & Butler, 2006). Resistance to insulin develops at the age of approximately 4 weeks (Chatzigeorgiou <i>et al.</i>, 2009). Blood glucose values rise until the age of 12–20 weeks, after which they fall as age progresses. Furthermore, body temperature deviations and low physical activity are also observed (Lindstrom, 2007). Hyperplasia of the pancreatic islets develops and β-cells continue to function up to an extent. Therefore, this animal does not present complete β-cell failure and is not an exact model of human T2D (King, 2012). On the other hand, it is a valuable model of diabetic peripheral neuropathy.

3.1.2 The db/db Mouse

The db/db mouse (recently relabelled as Lepr<sup>db/db</sup>) is deficient in the leptin receptor due to an autosomal recessive mutation on chromosome 4 (Cefalu, 2006; Srinivasan & Ramarao, 2007). The mechanism of T2D is much clearer in the db/db mouse than in humans, since it has been shown in these animals that obesity clearly precedes insulin resistance, in contrast to man (Bates <i>et al.</i>, 2005).

**General characteristics:** Its main characteristics are hyperphagia, obesity, insulin resistance, hyperglycaemia, hyperlipidaemia and hyperinsulinaemia, which appear within the first month of age, followed by pancreatic damage and subsequent hypoinsulinaemia.

**Complications:** The occurring β-pancreatic cell failure results in the early death of these animals, usually at the age of 8-10 months, mainly due to ketosis (Chatzigeorgiou <i>et al.</i>, 2009; King, 2012).

3.1.3 The Kuo Kuondo (KK) Mouse

The KK mouse has a polygenic background and a large body size (Nakamura & Yamada, 1967).

**General characteristics:** It develops hyperphagia, hyperinsulinaemia and insulin resistance at the age between 8 and 16–20 weeks, which is considered a relatively slow rhythm for researchers. In this model the number and size of the pancreatic islets increases with time, so hyperinsulinaemia compen-
sates for the insulin resistance. Consequently, hyperglycaemia is not observed or is usually mild. The pancreatic cells are hypertrophic and granulated. Diabetic nephropathy is also present (Ikeda, 1994).

Complications: The most important strain of the KK mouse is the KK/A^y mouse which, in its homozygous form, dies very soon due to the lethal obese yellow gene (A^y), whereas in its heterozygous form develops hyperinsulinaemia, hyperglycaemia and obesity at 8 weeks (Srinivasan & Ramaraio, 2007). This model is mainly used for the study of new antidiabetic drugs (Nuss & Wagman, 2000).

3.1.4 The TallyHo Mouse

The TallyHo mouse is a polygenic mouse model established by selective inbreeding for hyperglycaemia phenotype.

General characteristics: Male mice develop delayed hyperglycaemia at 10-14 weeks of age, hyperinsulinaemia, hyperlipidaemia, moderate obesity and β-pancreatic cell enlargement. Female mice display moderate hyperinsulinaemia, hyperlipidaemia and obesity but do not manifest overt diabetes (hyperglycaemia). Males also present islet degranulation and abnormal structure, as well as endothelial dysfunction and decreased bone density (Kim & Saxton, 2012). The TallyHo mouse has normal leptin and leptin receptor genes, resulting in a much less severe metabolic syndrome and diabesity phenotype (Rhee et al., 2011; http://jaxmice.jax.org/strain/005314.html).

3.1.5 The New Zealand Obese (NZO) Mouse

The NZO mouse is another obese polygenic model, which develops obesity within 2 weeks; however, the clinical onset of diabetes differs among the various substrains.

General characteristics: The NZO mouse furthermore develops hepatic insulin resistance, hyperlipaemia and further leptin resistance, probably responsible for the hyperphagia (Thoburn et al., 2000). More specifically it is resistant to peripheral leptin administration but not resistant to centrally administered leptin, which indicates a defect in the transport of leptin through the blood-brain barrier (King, 2012). Pancreatic islets are hyperplastic and hypertrophic at 12-24 weeks of age, however β-cells apoptosis takes place at a later stage (Junger et al., 2002). Mainly males develop diabetes and hypertension (Franconi et al., 2008). Although the NZO mouse is not used frequently as a model, it is the basis for the formation of similar strain genomes that might be useful for researchers in the near future (Pan et al., 2005).

3.1.6 The Nagoya-Shibata-Yasuda (NSY) Mouse

The Nagoya-Shibata-Yasuda (NSY) mouse develops T2D late in its life with insulin resistance occurring around the 12th week (Ueda et al., 2000).

General characteristics: It is an obese polygenic model that also shows a predisposal of male population and age regarding diabetes. This model presents mild obesity with visceral fat accumulation, impaired insulin secretion at 24 weeks and moderate insulin resistance (Ueda et al., 1995). Furthermore, a high fat and high sucrose administration accelerates the onset of diabetes. This model is extensively used for the study of age-related T2D as well as some genetical correlations between T1D and T2D, since the NSY and the NOD mouse have a common origin (Chatzigeorgiou et al., 2009).
3.1.7 Limitations and Possibilities of Mouse Models

Despite the vast similarities of mouse models to humans and the practical advantages of their use (small size with ease of housing, fast reproduction rate, feasibility of long studies) there are some research limitations that hinder the use of mice in diabetes research. Their small size, for example, can also be a handicap in experiments where surgical protocols are foreseen and therefore, as expected, larger animal models are more suitable. An important limitation is the lack of similar pancreatic islet pathology between mice and humans. More specifically, in mouse models a lack of expansion of cell mass in the pancreas is the result of prolonged insulin resistance and may be attributed to acquired metabolic abnormalities such as gluco- and lipo-toxicity (Harmon et al., 2001; Shafrir et al., 1999). Furthermore, it is important to take into account the fact that not all mouse models are suitable for the study of all diabetic clinical signs or complications. For example, there are certain models that do not develop renal lesions such as the C57BL/6 and its backcrosses (Schlöndorff, 2010).

The development of transgenic technology producing many different genetically modified mice with a homogenous genome gives researchers many opportunities to investigate the role of specific genes, their regulation and the elucidation of the mechanisms of disease. Indeed, the available literature on transgenic and knockout models of T2D includes many studies on several genes, receptors, proteins, and target tissues, and combinations thereof (Srinivasan & Ramarao, 2007). Many laboratory animal breeding establishments produce strains specifically for a research area or characteristic, such as hyperglycaemia, hypoglycaemia, hyperinsulinaemia, impaired insulin processing, insulin resistance, obesity with diabetes, obesity without diabetes, T1D and T2D.

3.2 Induced Models

3.2.1 Chemically Induced Models

The most commonly used diabetogenic chemical agents are Alloxan and Streptozotocin.

Alloxan administration induces diabetes in many rodent and non-rodent animals. It is usually applied for the induction of diabetes in rabbits, because of the less-preferred use of streptozotocin in this species, which may develop complications and is relatively ineffective. The intravenous route (100-150 mg/kg) to non-fasted rabbits is advised, following which the animals may exhibit high degrees of hyperglycemia, glucosuria, polyphagia, polydypsia, ketosis and other complications, with an increased mortality rate (Srinivasan & Ramarao, 2007).

The neonatal Alloxan induced diabetic male rat model is produced by a single injection of Alloxan in 2-6 day-old rats, which develop T2D as adults.

Streptozotocin is an antibiotic derived from *Streptomyces achromogenes* and structurally is a glucosamine derivative of nitrosourea. It is a diabetogenic agent preferred to Alloxan, as it has a longer half-life, induces hyperglycemia of longer duration and fewer incidences of ketosis and a lower mortality rate. Several dose regimens (due to age-, species- and strain-specific differences) and administration routes (mainly i.p. and i.v.) are advised for rodents and larger animal species (Etuk, 2010; Javia et al., 2011; Srinivasan & Ramarao, 2007). When doses are such that total destruction of β-cells occurs, T1D is induced, with its main characteristics being hyperglycaemia and the dependence on exogenous insulin. This model, however, is not equivalent to the immune-mediated T1D (Cefalu, 2006). The neonatal Streptozotocin induced diabetic rat model is produced by a single injection of Streptozotocin in 1-5 day-old rats, which develop T2D as adults.
The Nicotinamide-Streptozotocin induced diabetic rat model is produced by administering Nicotinamide 15 min before Streptozotocin, which develops moderate and stable non-fasting hyperglycemia, with minor changes in plasma insulin levels. This occurs because Nicotinamide is an antioxidant, which acts by scavenging free radicals produced by Streptozotocin’s cytotoxicity. This diabetogenic combination has also been used in the induction of T2D in minipigs (Srinivasan & Ramarao, 2007).

### 3.2.2 Surgically Induced Models

The performance of surgical total or partial pancreatectomy has been a historic method of induction of T1 or T2D respectively. More often partial pancreatectomy of 70-90 % is conducted, mainly on dogs, pigs, rabbits and rats (Bonner-Weir et al., 1983; Martin & Lacy, 1963). It usually results in moderate hyperglycaemia, depending on the amount of intact pancreatic cells left, with minimal decrease of body weight or plasma insulin levels. In rats, pancreatectomy of 90 % led to the conclusion that simple reduction in pancreatic β-cell mass itself may not be responsible for glucose intolerance (Srinivasan & Ramarao, 2007). The duration of the resulting hyperglycaemia may range from days to months.

A combination of surgical partial pancreatectomy with chemical agents that induce diabetes, such as alloxan or streptozotocin, has also been applied to the above animal species and additionally to primates and mice. This combination procedure has several advantages: organ damage from the administration of these agents is reduced (vs. to when administered alone in higher doses), and enzyme supplementation to prevent malabsorption and loss of pancreatic α- and δ-cells (resulting in loss of glucagon and somatostatin), in addition to β-cells, is minimized (Javia et al., 2011).

### 3.2.3 Dietary Induced Models

The sand rat or desert gerbil (*Psammomys obesus*) is a non-spontaneous model of diabetes, which remains normal in its natural environment but develops obesity and diabetes when maintained on standard rodent diet in the laboratory. It has been observed that this animal, when its nutrition evolves from scarcity to sudden food abundance, similar to the western life-style and diet in humans (King, 2012), demonstrates hyperphagia, hyperglycaemia, compensatory hyperinsulinaemia, increase in circulating proinsulin, glucose intolerance, increased hepatic glucose production and muscle insulin resistance (Rees & Alcolado, 2005; Shafrir et al., 2006; Ziv et al., 1999). It is an excellent polygenic model suitable for the study of obesity related to diabetes regarding diet and exercise effects, as well as for pharmacological studies on various protein analogues (Kaiser et al., 2005). The sand rat is also an important animal model for the study of diabetic nephropathy, since it shows a low glomerular filtration rate and increased urinary protein excretion in the later stages of the disease (Scherzer et al., 2011).

The spiny mouse (*Acomys cahirinus*) has its natural habitat in dry areas of Mediterranean countries and North Africa. It also is a non-spontaneous model of diabetes, which, however, develops the disease through a different mechanism compared to humans. When spiny mice are fed a high energy diet, they gain weight, develop pancreatic β-cell hypertrophy and proliferation, with subsequent islet degeneration (Shafrir et al., 2006). Diabetes occurs after spontaneous islet rupture that is accompanied by a loss of the rich insulin content. Old animals are mostly affected (Cefalu, 2006). This disease mechanism differs from β-cell apoptosis that is observed in other species with excessive insulin secretion due to peripheral resistance (Cefalu, 2006).
3.2.4 Genetically Altered Models

3.2.4.1 The Non-Obese Akita Mouse

The non-obese Ins2\textsuperscript{Akita} mouse is a C57BL/6 mutant mouse model with a spontaneous autosomal dominant mutation in the insulin 2 gene, which prevents the correct processing of pro-insulin (Yoshioka et al., 1997). It presents severe insulin-dependent diabetes at 3-4 weeks of age, with hyperglycaemia, hypoinsulinaemia, polydipsia, and polyuria. A gradual decrease of β-cell mass takes place, without the presence of insulitis. This model responds actively to the administration of exogenous insulin. Untreated homozygotes usually do not survive more than 12 weeks. The loss of β-cell mass makes it a good alternative to the streptozotocin-induced mouse model for transplantation studies (Chatzigeorgiou et al., 2009; Yoshioka et al., 1997). The Akita mouse’s main application is in T1D research, but it can also be used in T2D research (King, 2012).

3.2.4.2 The NONcNZO10/LtJ Mouse

The NONcNZO10/LtJ mouse is a recombinant mouse strain suitable for T2D and metabolic syndrome studies, generated from New Zealand obese and Nonobese Nondiabetic mice (Cho et al., 2007). Males are more susceptible to the manifestation of the disease. When fed a moderately high fat diet, they develop diabetes with a modest weight gain without displaying hyperphagia, maturity-onset hyperglycaemia, glucose intolerance by 16 weeks of age, visceral obesity, dyslipidaemia, moderate liver steatosis and pancreatic islet atrophy (http://jaxmice.jax.org/strain/004456.html).

3.2.4.3 The Human Islet Amyloid Polypeptide (hIAPP, HIP) Rat and Mouse

The limitation of different islet pathology between rodent models and humans has been surpassed by the development of transgenic models which are used in order to study the possible effect of the islet amyloid polypeptide (IAPP) on β-cells. More specifically, the hIAPP (HIP) transgenic rat has been developed from a Sprague-Dawley origin (Matveyenko & Butler, 2006). The homozygous animals rapidly develop diabetes within 2 months, in contrast to heterozygous animals that show a later onset of diabetes (between 6 and 12 months) that is also associated with islet pathology (amyloid deposition, β-cell apoptosis) exactly as in humans (Butler et al., 2004). Hyperglycaemia follows, which makes β-cell apoptosis more rapid, leading to glucose toxicity. The HIP rat provides researchers with a useful tool in order to further study abnormalities in insulin secretion and changes in β-cells (Cefalu, 2006).

Similarly, the hIAPP transgenic mouse that expresses human IAPP in pancreatic β-cells was developed in 1996 and described by Janson et al. These researchers demonstrated through three different protocols that male hIAPP mice develop T2D with selective degeneration of β-cells at 8-12 weeks of age, while female mice after 30 weeks (Janson et al., 1996). In these animals, amyloid deposits are formed within the pancreatic islets, as in human T2D. They are valuable models for the study of amyloid deposition associated with β-cell destruction in T2D, as well as characteristics of the endoplasmic reticulum stress pathway (King, 2012).
3.3 Rat Models

Although the manipulation of rats’ genome is more complicated compared to mice (McMurray & Cox, 2011), several monogenic and polygenic strains of rats have been and are being used in diabetes research (King, 2012).

3.3.1 The Zucker fa/fa Rat

The Zucker fa/fa rat is a monogenic spontaneous model that may develop the same characteristics with the db/db mouse and has been used extensively for the study of human obesity combined with hyperlipidaemia and hypertension (Chatzigeorgiou et al., 2009; Pick et al., 1998). The fa mutation was discovered by Zucker and Zucker in 1961 (Zucker & Zucker, 1961). Rats homozygous for the fa allele become obese by 3-5 weeks of age, and develop hyperlipaemia, hypercholesterolaemia and hyperinsulinaemia, with adipocyte hypertrophy and hyperplasia. It is therefore a valuable model for human early-onset hypertrophic obesity. It also presents a mutated leptin receptor (Philips et al., 1996). It is less used as a model of human T2D, probably because it is relatively normoglycaemic or demonstrates only mild hyperglycaemia.

3.3.2 The Zucker Diabetic Fatty (ZDF) Rat

The evolution of the Zucker fa/fa rat has led to the Zucker diabetic fatty rat strain, which is widely used in biomedical research (Chatzigeorgiou et al., 2009; Pick et al., 1998). This strain is deficient in the leptin receptor, it involves only males (Srinivasan & Ramarao, 2007) and develops insulin resistance at 8 weeks of age. Its main characteristic is the enhanced loss of pancreatic β-cells, which cannot balance with the consistent insulin resistance, as it occurs in the Zucker fa/fa rat. As a result, the ZDF rats become severely insulinopenic at 14 weeks (Chatzigeorgiou et al., 2009; Pick et al., 1998). These rats are less obese compared to the original strain but present more severe insulin resistance due to β-cells’ increased apoptosis (King, 2012). The mechanism is not fully understood but it could probably be attributed to the toxic effects of excessive glucose and fat deposits in the pancreas (Harmon et al., 2001). Finally, an important difference between this model and man is the lack of islet amyloidosis (Cefalu, 2006).

3.3.3 The Otsuka Long Evans Tokushima Fatty (OLETF) Rat

The Otsuka Long Evans Tokushima Fatty (OLETF) rat is a polygenic obese model that develops mild disease at about the age of 18-25 weeks. It develops polyphagia, hyperinsulinaemia, high level of triglycerides and hypercholesterolaemia (Kawano et al., 1992). Pancreatic islets show histological lesions that may be classified in three stages: cellular infiltration and degeneration at 6-20 weeks, hyperplasia at 20-40 weeks and fibrosis and connective tissue at the end-stage of the disease. Renal complications are also reported (King, 2012). This strain is extensively used in antidiabetic or antihypertensive therapy research (Chen & Wang, 2005).

3.3.4 The Goto–Kakizaki Rat

The Goto-Kakizaki rat is another model for the study of T2D; it was produced by selective inbreeding of Wistar rats with the highest levels of glucose intolerance. It is a non-obese model with decreased volume of β-cells even from birth (Rees & Alcolado, 2005), which is probably a consequence of reduced cell proliferation (Ostenson & Efendic, 2007; Portha et al., 2001). It usually presents insulin resistance, nor-
molipidaemia and impaired insulin secretion (Chatzigeorgiou et al., 2009). The decreased insulin secretion leads to mild hyperglycaemia (Picarel-Blanchot et al., 1996). Hyperglycaemia takes place at 3-4 weeks of age and remains stable (Mirales & Portha, 2001). This strain presents similarities to humans with regard to liver and skeletal muscle insulin resistance. The reduced cell proliferation, however, is not similar to humans and this consists a limitation for the use of this model in diabetes research (Cefalu, 2006). However, it is a useful model for the study of β-cell malfunction (King, 2012) and diabetic complications such as renal, retinal and peripheral nerve lesions (Chatzigeorgiou et al., 2009). This last feature is extremely important and gives an excellent example of the importance of biomedical research on animals, which provides the possibility of performing serial — renal or nerve — biopsies in animals for diagnostic purposes, procedures that cannot be performed in humans (Rees & Alcolado, 2005).

3.4 Other Rodent and Non-Rodent Models

The Chinese hamster (Cricetulus griseus) has been used for the study of hereditary diabetes. It is a non-obese model that develops hyperglycaemia with ketoacidosis, as well as severe polyuria, glucosuria, ketonuria and proteinuria. Insulin and oral antidiabetic drugs have a therapeutic effect. Pathological lesions are observed histologically in the pancreas with a decreased number of and abnormal islets, as well as in the liver and kidney (Kumar et al., 2012).

Feline, swine and non-human primate models have also been used for the study of diabetes, since these models have many similarities to the human organism and they develop the disease in similar ways.

3.4.1 Feline Models

The study of the progression of T2D in cats has been extensively described in veterinary literature, including internal medicine books and numerous peer-reviewed research articles. These animals have been used for the study of diabetes, because they follow the western type of human lifestyle and have also evolved accordingly regarding the transition from hunters to suburban indoor cats (Rand et al., 2004).

Most cats have consistent symptoms of T2D and present the first clinical abnormalities after their middle age as humans do (Henson & O’ Brien, 2006) and develop insulin resistance and obesity in the same manner (Cefalu, 2006). This is also enhanced by the fact that cats and humans in developed countries share the same lifestyle characteristics, including lack of adequate exercise and excessive calorie intake (Prah1 et al., 2007). Furthermore, the appearance of T2D in cats and humans is similar following the effect of pharmacological agents, hormones and diseases that influence insulin peripheral function. Examples of the above constitute the administration of corticosteroids, progestins, hyperthyroidism or acromegaly. Additionally, male cats have a higher predisposition to T2D (Rand et al., 2004).

An interesting fact regarding feline diabetic models is the similarities of pancreas pathology between humans and cats, including pancreatic amyloidosis and loss of β-cells, as well as the clinical complications of diabetes observed in humans, such as diabetic neuropathy and retinopathy (Henson & O’ Brien, 2006). Furthermore, cats have been shown to resist to the development of diabetes when streptozotocin or alloxan are administered. The pharmacological induction of the disease has been effective only when partial pancreatectomy is performed for the experimental reduction of β-cells (Henson & O’ Brien, 2006). Partial pancreatectomy in combination with the administration of growth hormone or dexamethasone can also lead to the development of diabetic feline models (Hoening et al., 2000). Consequently, cats are used both as spontaneous and chemically or surgically induced models of T2D (Chatzigeorgiou et al., 2009).
### Type 2 Diabetes Rodent Models

<table>
<thead>
<tr>
<th>Spontaneous</th>
<th>Mice</th>
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<tbody>
<tr>
<td><strong>ob/ob</strong></td>
<td>Chatzigeorgiou et al., 2009; King, 2012; Lindstrom, 2007; Matveyenko &amp; Butler, 2006; Srinivasan &amp; Ramarao, 2007; Zhang et al., 1994</td>
</tr>
<tr>
<td><strong>db/db</strong></td>
<td>Bates et al., 2005; Cefalu, 2006; Chatzigeorgiou et al., 2009; King, 2012; Srinivasan &amp; Ramarao, 2007</td>
</tr>
<tr>
<td><strong>KK</strong></td>
<td>Ikeda, 1994; Nakamura &amp; Yamada, 1967; Nuss &amp; Wagman, 2000; Srinivasan &amp; Ramarao, 2007</td>
</tr>
<tr>
<td><strong>TallyHo</strong></td>
<td>Kim &amp; Saxton, 2012; Rhee et al., 2011; <a href="http://jaxmice.jax.org/strain/005314.html">http://jaxmice.jax.org/strain/005314.html</a></td>
</tr>
<tr>
<td><strong>NZO</strong></td>
<td>Franconi et al., 2008; Junger et al., 2002; King, 2012; Pan et al., 2005; Thoburn et al., 2000</td>
</tr>
<tr>
<td><strong>NSY</strong></td>
<td>Chatzigeorgiou et al., 2009; Ueda et al., 1995; Ueda et al., 2000</td>
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<th>Rats</th>
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<tr>
<td><strong>fa/fta</strong></td>
<td>Chatzigeorgiou et al., 2009; Philips et al., 1996; Pick et al., 1998; Zucker &amp; Zucker, 1961</td>
</tr>
<tr>
<td><strong>ZDF</strong></td>
<td>Cefalu, 2006; Chatzigeorgiou et al., 2009; Harmon et al., 2001; King, 2012; Pick et al., 1998; Srinivasan &amp; Ramarao, 2007</td>
</tr>
<tr>
<td><strong>OLETF</strong></td>
<td>Chen &amp; Wang, 2005; Kawano et al., 1992; King, 2012</td>
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<td><strong>Goto-K</strong></td>
<td>Cefalu, 2006; Chatzigeorgiou et al., 2009; King, 2012; Mirales &amp; Portha, 2001; Ostenso &amp; Efendic, 2007; Picarel-Blanchot et al., 1996; Portha et al., 2001; Rees &amp; Alcolado, 2005</td>
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<tr>
<th>Induced</th>
<th>Chemical</th>
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<tr>
<td><strong>ALL</strong></td>
<td>Srinivasan &amp; Ramarao, 2007</td>
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<tr>
<td><strong>STZ</strong></td>
<td>Cefalu, 2006; Etuk, 2010; Javia et al., 2011; Srinivasan &amp; Ramarao, 2007</td>
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<tr>
<td><strong>N+STZ</strong></td>
<td>Srinivasan &amp; Ramarao, 2007</td>
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<tr>
<td><strong>Surg+Chem</strong></td>
<td>Javia et al., 2011</td>
</tr>
<tr>
<td><strong>Surgical</strong></td>
<td>Bonner-Weir et al., 1983; Martin &amp; Lacy, 1963; Srinivasan &amp; Ramarao, 2007</td>
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<tr>
<td><strong>Surg+Chem</strong></td>
<td>Javia et al., 2011</td>
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<tr>
<td><strong>Dietary</strong></td>
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<tr>
<td><strong>Sand rat</strong></td>
<td>Kaiser et al., 2005; King, 2012; Rees &amp; Alcolado, 2005; Scherzer et al., 2011; Shafir et al., 2006; Ziv et al., 1999</td>
</tr>
<tr>
<td><strong>Spiny mouse</strong></td>
<td>Cefalu, 2006; Shafir et al., 2006</td>
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<tr>
<td><strong>Genetic</strong></td>
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<td><strong>Akita</strong></td>
<td>Chatzigeorgiou et al., 2009; King, 2012; Yoshioka et al., 1997</td>
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<tr>
<td><strong>NONcNZO10/LtJ</strong></td>
<td>Cho et al., 2007; <a href="http://jaxmice.jax.org/strain/004456.html">http://jaxmice.jax.org/strain/004456.html</a></td>
</tr>
<tr>
<td><strong>hIAPP</strong></td>
<td>Butler et al., 2004; Cefalu, 2006; Janson et al, 1996; King, 2012; Matveyenko &amp; Butler, 2006</td>
</tr>
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</table>

**Table 2:** Main Type 2 Diabetes rodent models. Abbreviations: **ob/ob**: obesity homozygous; **db/db**: diabetes homozygous; **KK**: Kuo Kuondo; **NZO**: New Zealand obese; **NSY**: Nagoya-Shibata-Yasuda; **fa/fta**: Zucker fatty homozygous; **ZDF**: Zucker diabetic fatty; **OLETF**: Otsuka Long Evans Tokushima Fatty; **Goto-K**: Goto-Kakizaki; **ALL**: Alloxan; **STZ**: Streptozotocin; **N+STZ**: Nicotinamide + Streptozotocin combined; **Surg+Chem**: Surgical + Chemical combined; PancreaX: Pancreatectomy; **Akita**: non-obese Ins2<sup>Akita</sup>; **hIAPP**: human islet amyloid polypeptide.
3.4.2 Canine Models

The discovery of insulin in dogs led to their extensive use in diabetes research, while recent ethical concerns regarding their justified use have gained ground (Macleod, 1978; Nuffield Council on Bioethics, 2005). The method of choice followed by many researchers for the study of diabetes in dogs is surgically-induced total pancreatectomy (Sirek, 1968; Kumar et al., 2012). Alloxan-induced and growth hormone-induced diabetes in dogs are chemical models used (Tasaka et al., 1988; Young 1941), while partial pancreatectomy combined with the administration of diabetogenic agents are also applied (Srinivasan & Ramarao, 2007).

Approximately 50% of diabetic dogs have T1D with evident immune destruction of β-cells, while obesity has been demonstrated to be a risk factor for canine pancreatitis, which may lead to canine diabetes (Rand et al., 2004). The research group of Bergman developed a high-fat, high-calorie diet model of canine obesity and insulin resistance; more recently they demonstrated the creation of canine models of overt diabetes, mild T2D, and impaired glucose tolerance, where obesity and insulin resistance is first induced by the above diet, followed by a dose-related streptozotocin-induced severe to modest decrease in pancreatic β-cell function (Ionut et al., 2010; Kim et al., 2007). Dogs have also been used as models of pregnancy diabetes in humans, since onset of diabetes has been diagnosed during gestation or diestrus.

3.4.3 Swine Models

Pigs are shown to have many anatomical similarities to man in many systems and this renders them as a very good model for the study of human diseases. Regarding diabetes, they have similar to man anatomical characteristics and function of the gastrointestinal system, the pancreas and insulin metabolism (Larsen & Rolin, 2004). Furthermore, pigs have similar pharmacokinetic responses as man (Cefalu, 2006).

Various strains of swine that mimic human diabetes exist, including Yucatan and Gottingen minipigs (Bellinger et al., 2006). More specifically, several Yucatan lines exist, that either have less or more tolerance to glucose and are used as spontaneous models for diabetes (Franconi et al., 2008), whereas Gottingen minipigs develop diabetes when they consume a high fat high energy diet (Cefalu, 2006; Johansen et al., 2001) and have already become obese. Male Gottingen minipigs also present an increased fasting blood glucose level (Larsen et al., 2001). The most extensive use of pigs and minipigs, however, in the study of diabetes, is the study of vascular, cardiovascular, renal or retinal complications (Chatzigeorgiou et al., 2009). Additionally, the biochemical alterations and procedures leading to the development of diabetic atherosclerosis have been studied, especially with the use of streptozotocin and alloxan (Cefalu, 2006).

3.4.4 Non-Human Primate Models

Due to the proximity of many non-human primates to man, many spontaneous non-human primate models have been used for the development of T2D, such as cynomologous monkeys, rhesus monkeys, bonnets, macaques and baboons. The important parameter of their use is that diabetes develops exactly in the same manner as in humans, with age-related progression, obesity, insulin resistance and increased levels of glucose.

Amyloid deposits in the pancreatic islets are a typical histological characteristic in diabetic non-human primates, which is also present in the majority of diabetic patients. The increased deposits of amy-
loid are related with the decrease in insulin secretion caused by the reduction of insulin-immunoreactive β-cells (Kahn et al., 1999).

A remarkable similarity between man and primates is the stages before the clinical induction of diabetes, including insulin resistance and hyperinsulinaemia (Cefalu, 2006). Prolonged insulin resistance and decrease in the number of β-pancreatic cells leads to a point where blood glucose levels are abruptly increased in a short time and pharmacological intervention is necessary (Wagner et al., 1996). Physical condition and early treatment of diabetes also results in a similar evolution of the disease as in humans. Animals with insulin resistance present increased lipid profile values and inflammatory lesions in their atherosclerotic plaques. Additionally, severe clinical symptoms, such as ketoacidosis, follow the same route in humans and primates. It is also impressive how similarly their endocrine system responds to the development of diabetes, as it also does during pregnancy, menopause or therapy with genital hormones (Cefalu, 2006; Franconi et al., 2008). Chemical induction of diabetes is also applied to primates for the testing of new pharmacological compounds or the study of diabetic complications (atherosclerosis, thrombosis etc.) and the further monitoring of oxidative stress (Cefalu, 2006; Clarkson, 1998).

4 Diabetes and Pregnancy Models

It has been demonstrated that adverse nutritional and environmental effects during pregnancy, post-natal as well as in early life play a significant role in the emergence of diseases, such as diabetes, heart disease, stroke or osteoporosis, during later life. As the occurrence of diabetes during human pregnancy is associated with miscarriage, malformations and diseases in the offspring’s later life, much animal research is conducted in this area. Experimental models of diabetes and pregnancy can be obtained by surgical procedures, chemical induction, the use of spontaneous or genetically derived animal strains or the application of nutritional imbalances.

Surgical partial pancreatectomy is not widely applied currently because of its limitations, which are accurate surgical expertise, increased postoperative mortality and the time required for diabetic symptoms (Jawerbaum & White, 2010).

Chemical induction of diabetes and pregnancy by streptozotocin or alloxan in mice and rats has been widely used to address early embryo developmental defects, the induction of malformations, placental abnormalities, fetal maldevelopment, and intrauterine transmission of metabolic diseases. There are various technical approaches to generate experimental models of diabetes and pregnancy by the use of diabetogenic chemicals, including variations in administration route, dose, frequency and time in relation to pregnancy (Jawerbaum & White, 2010; Kiss et al., 2009; Lopez-Soldado & Herrera, 2003). Diabetogenic chemicals have also been applied on larger animals for the study of diabetes and pregnancy, such as sheep and pigs (Dickinson et al., 1991; Ezekwe et al., 1984).

Spontaneous genetic rodent models are also used, such as the NOD mouse; however, as mild T1D develops in 80% of female NOD mice by 30 weeks of age, they must be used at this advanced age. The use of BB rats needs special attention, as their severe diabetes and ketoacidosis may be fatal. The Akita mouse has also been used for the analysis of preimplantation and fetoplacental defects (Jawerbaum & White, 2010).

Rodent T2D models used to study diabetic and pregnancy complications with a polygenic origin, such as the Sand rat and the Goto-Kakizaki rat, have also produced information on maternal diabetes-
induced developmental defects, the induction of congenital malformations, fetal alterations, and the programming of diseases in the offspring’s later life (Jawerbaum & White, 2010).

5 Conclusions

Although diabetes is a disease that has been intensely studied, more research is necessary to elucidate factors influencing its pathogenesis and to evaluate potential new therapies. To the moment an important percentage of animal research has focused on the development of strains that mostly resemble the human disease. Molecular genetics and genome sequencing are important tools to develop many animal models, particularly mice, whose genome has been manipulated to create specific mutations of interest. The development of databases of these strains is most useful to researchers in order to find a model with traits that resemble specific human characteristics.

Animal research and the development of animal models of human disease will continue to make important contributions to the treatment of diabetes in both animals and humans. As diabetes is a chronic metabolic disease, the clinical symptoms presented in animal models should always be carefully monitored in order to minimise their suffering during research. With the use of the existing animal models for diabetes research and the continuing development of new ones, a better understanding of the disease mechanisms and new methods for its prevention and treatment are expected.

References


The Jackson Laboratory http://jaxmice.jax.org/strain/004456.html

The Jackson Laboratory http://jaxmice.jax.org/strain/005314.html


