Review Article

Current status and patent prospective of animal models in diabetic research

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Abstract

Diabetes mellitus is a heterogeneous complex metabolic disorder with multiple etiology which characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action or both. The widespread occurrence of diabetes throughout the world has increased dramatically over the past few years. For better understanding, appropriate animal models that closely mimic the changes in humans needed, as vital tool for understanding the etiology and pathogenesis of the disease at the cellular/molecular level and for preclinical testing of drugs. This review aims to describe the animal models of type-1 diabetes (T1Ds) and T2Ds to mimic the causes and progression of the disease in humans. And also we highlight patent applications published in the last few years related to animal models in diabetes as an important milestone for future therapies that are aim to treating diabetes with specific symptoms and complications.

Key Words: Alloxan-susceptible/Lt mouse, animal models, diabetes mellitus, dithizone, nonrodent models, patent

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INTRODUCTION

Biomedical research involves three facets

Gaining of new knowledge, use of animals, and the testing of compounds, chemicals or devices for better understanding of molecule or disease. Research involving animals contribute significantly in protection and improvement of the health of either humans or animals. In the past few decades animal models have been widely used as tools to develop new therapeutic drugs as well as to study the molecular basis of a disease or disorder because human biology is very much like that of many other animals. Most laboratory animals have the same physiological set of organs which work in the same way as they do in humans with specially relationship to human metabolism. According to the World Health Organization about 347 million people worldwide have diabetics and the number of these diabetic patients have double in the last few years and more than 80% of diabetes deaths occur in low and middle-income countries which are to be double in coming years.[1,2] Advances in drug discovery and drug development have led to better ways to manage diabetes and to treat its complications. Experimental model play an important role in drug discovery for understands the molecular basis and management of diabetes. Over the last few years, several animals model have developed for the studying diabetes mellitus or testing antidiabetic

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agents.[3] These animal models include drug-induced, diet induced surgical (pancreatectomy) and genetically modified animals.[4] In diabetes research, inappropriate animal models have identified as one of the common problem associated with researchers with choice of animal models is still debatable.

The aim of this review is to summarize the animal models used for diabetic research. The first part of the review concerns with the present status of suitable animal models. In the later part describes the utility and enough disclosure of the invention in the patent applications for commercial research or experimental uses.

ANIMAL MODELS FOR TYPE-1, INSULIN DEPENDENT DIABETES MELLITUS

Insulin dependent diabetes mellitus (IDDM) is an autoimmune disease which characterized by destruction of the insulin secreting β-cells results into an absolute loss of endogenous insulin, leads to insulin deficiency and cause hyperglycemia. In this condition, patient required administration of exogenous insulin for survival.[5] In case of animal models, this deficiency in insulin production achieved by different mechanisms, which ranging from chemical ablation of the β-cells to breeding rodents, viral induced; genetically and spontaneously develop autoimmune diabetics animal models (naturally occurring in animals) as summaries in Table 1.[6]

SPONTANEOUS DIABETES TYPE-1 DIABETES MELLITUS

These are the animal models of human disease which utilize naturally occurring genetically variants (mutants) often displaying isomorphic phenotypic similarity between the disease in the animal and the corresponding disease in man.[7] Literature available on spontaneous models showed that majority of research work involves mice and rat models[8-10] and comparison of spontaneous diabetes animal models summaries in Table 2.

COMMONLY USED MODELS

Nonobese diabetic mouse

The nonobese diabetic (NOD) mouse established in 1980 as an animal model of autoimmune type-1 diabetes (T1Ds) by Makino *et al*. by selectively breeding offspring from a laboratory strain that in fact was first used in the study of cataract development (JcI-Institute of Cancer Research [ICR] mouse).[11] The typical clinical symptoms are like hyperglycemia, glycosuria, polydipsia and polyuria. The mice have larger resistance to ketoacidosis development and can remain alive about 2–4 weeks after the disease establishment without insulin administration and if diabetes is not finally treated death results from dehydration, rather than ketoacidosis.[12,13] Although in comparison with

Table 1: Animals models for T1DM and T2DM

Animal models	T1DM	T2DM
Spontaneous models	Common used	Obese models
	NOD mouse	ob/ob mouse
	BB rat	db/db mouse
	LETL rat	KK mouse
	KDP rat	KK/Ay mouse
	LEW-IDDM rat	NZO mouse
		NONcNZO10 mouse
		TSOD mouse
		M16 mouse
		Zucker fatty rat
		SHR/N-cp rat
		JCR/LA-cp rat
		OLETF rat
	Other models (rarely used)	Nonobese models
	New Zealand white rabbit	Cohen diabetic rat
	Keeshond dog	GK rat
	Chinese hamster	Torri rat
	Macaca nemestrina/fascilularis/nigra	ALS/Lt mouse
	Papio hamadryas	
Chemically induced models	STZ	STZ
	Multiple low-dose STZ	ALX
	ALX	GTG mouse
	Ferric nitrilotriacetate	
	Dithizone	
Genetically induced models	Akita mice	HIAPP mice
		NSY mouse
Other models	Virally-induced	Diet induced type 2 rats
	CVBs	Desert gerbil
	Encephalomyocarditis virus	Nile grass rats (newly described)
	Kilham rat virus	C57BL/6J mouse
	LCMV under insulin promoter	Sprague–Dawley rats
	Rubella	Israeli sand rat
	Mumps virus	Sand rat
		Surgical diabetic animals
		Partial pancreatectomized animals
		VMH lesioned dietary obese diabetic rat
Nonrodent models		Spontaneous model
		Feline
		Rhesus monke

NOD: Nonobese diabetic, BB: Bio-breeding, T1DM: Type 1 diabetes mellitus, T2DM: Type 2 diabetes mellitus, LETL: Long-Evans Tokushima Lean, KDP: Komeda diabetes-prone, IDDM: Insulin dependent diabetes mellitus, LEW: Lewis, STZ: Streptozotocin, ALX: Alloxan, CVBs: Coxsackie B virus, LCMV: Lymphocytic choriomeningitis virus, KK: Kuo Kondo, NZO: New Zealand obese, TSOD: Tsumara Suzuki obese diabetes, SHR: Spontaneous hypertensive, JCR: James C Russel, OLETF: Otsuka Long-Evans Tokushima Fatty, GK: Goto-Kakizaki, ALS: Alloxan-susceptible, GTG: Gold thioglucose, NSY: Nagoya-Shibata-Yasuda, HIAPP: Human islet amyloid polypeptide, VMH: Ventromedial hypothalamic

Table 2: Comparative features of spontaneous autoimmune diabetes with human and different animal models

Features	Human	NOD mouse	BB rat	KDP rat	LEW-IDDM
Age of disease presentation	Adolescence	24-30 weeks	8-16 weeks	3-4 months	2-3 months
Disease incidence (%)	-	Females: 90, males: 50-60	50-80	70-80	70
Auto-antibodies	Insulin, GAD, ICA, ICSA, BSA, CPH, EC, IA-2, IAA	Insulin, GAD	ICA	Unknown	ICA
Insulin is required	Yes	No	Yes	Yes	No
MHC associated genes	HLA-DQ and DR	Unique I-Ag7	At least RT1 B/Du haplotype	At least RT1 B/Du haplotype	At least RT1 B/Du haplotype
Environmental factors	Probable	Yes	Yes	Unknown	Unknown

NOD: Nonobese diabetic, BB: Bio-breeding, KDP: Komeda diabetes-prone, IDDM: Insulin dependent diabetes mellitus, LEW: Lewis, HLA: Human leukocyte antigen, ICA: Islet cell antibodies, GAD: Glutamic acid decarboxylase, ICSA: Islet cell surface antibody, BSA: Bovine serum albumin, CPH: Carboxypeptidase H, EC: Epicutaneous, IA-2: Islet antigen-2, IAA: Insulin autoantibodies

other animal models used in biomedical research, the NOD mouse seems particularly analogous to human T1D and thus a great many studies have performed in the 24–30 years since its development.[14]

Bio-breeding rat

Bio-breeding (BB) rats derived from out-bred Wistar rats and as preferable a small animal model for studying islet transplantation tolerance induction. These rats spontaneous autoimmune diabetes in a Canadian colony was first identified in 1974 and lead to creation of two founder colonies from which all sub-strains have derived, one inbred (BB diabetes-prone [BBdp]/Wor) and one out-bred (BBdp).[15] It develops T-cell dependent autoimmune diabetes, which is also characterised by islet auto-antibodies, as well glutamic acid decarboxylase antibodies.[12] They develop weight loss, polyuria, polydipsia, hyperglycemia, and insulinopenia at about 12 weeks of age, often at the time of puberty,[16] unlike NOD mouse, ketoacidosis is very severe in the BB-rats and as in humans, it become lethal if not treated with insulin.[12,17] Furthermore, the BB-rat is susceptible to subclinical thyroiditis and sialitis.[18,19]

Long-evans tokushima lean rat

The long-evans tokushima lean (LETL) rat is the first discovered rat model that spontaneously develops an autoimmune destruction of the islet β-cells and rapid frank diabetes at a rate of 20%, without being lymphopenic.[20] LETL rat's sub-strain that was finally established as the one that develops the disease at a very good rate is the Komeda diabetes-prone (KDP) rat.[15,21]

Komeda diabetes-prone rat

The KDP rats are characterized by autoimmune destruction of pancreatic β-cells, rapid onset of overt diabetes with no sex difference, and no significant T-cell lymphopenia.[22] Most of the animals show moderate to severe lymphocyte infiltration into pancreatic islets (insulitis), and about 80% of them develop diabetes within 220 days of age. Yokoi *et al*. performed a genetic analysis of T1D in KDP in which found Cblb is a major susceptibility gene for rat type-1 diabetes mellitus (T1DM). KDP rat could be an animal model for other autoimmune diseases, especially for the autoimmune thyroid disease.[23,24]

Lewis-insulin dependent diabetes mellitus rat

Lewis-IDDM (LEW rats) rats are the T1D animal model characterized by rapid apoptotic pancreatic β-cell destruction in a colony of congenic (LEW rats) with a defined major histocompatibility complex haplotype (LEW.1AR1). These rats exhibit insulitis, and overt diabetes manifests at around 8–9 weeks. Originally, incidence of diabetes was approximately 20%;[25] however, with further inbreeding of diabetic rats, the incidence increased to around 60% with equal incidence in both genders.[26] In contrast to the NOD mouse and BB-rat, the LEW-IDDM rat does not exhibit other autoimmune diseases. It also survives well after the onset of overt diabetes and thus can used to study diabetic complications.[12]

OTHER RARELY USED ANIMAL MODELS

Except from the aforementioned typical models of disease representation, scientists develop and use also many other models for studying T1DM which includes, New Zealand white rabbit, Keeshond dog, *Chinese hamster*, *Macaca nemestrina/fascilularis/nigra* and *Papio hamadryas*.[9]

CHEMICALLY INDUCED DIABETIC ANIMALS

Chemically induced diabetes not only provides a simple and relatively cheap model of diabetes in rodents but can also be used in higher animals[27] by the destruction of endogenous β-cells which leads to decrease in insulin production and leads to hyperglycemia and weight loss. Rarely used diabetogenic agents in rodents listed in Table 3, but streptozotocin (STZ) and alloxan (ALX) are the commonly used compounds for induction of diabetes due to their similarity in structure to glucose.[28] The dose of these agents required for

Table 3: List of diabetogenic agents used in rodents

Chemicals	Species	Dose(s) (in mg/kg)
CsA	Wister rats	40 (for 7 days orally)
Dehydroascorbic acid	Rats	650 (for 3 days)
Dehydroisoascorbic acid	Rats	1.5
Dehydroglucoascorbic acid	Rats	3.5–3.9
Methyl ALX	Rats	53
Ethyl ALX	Rats	50–130
Oxine and dithizone	Rabbits	50
Sodium diethyl dithiocarbonate	Rabbits	500–1000
Potassium xanthate	Rabbits	200–350
Uric acid	Rabbits	1000
Lithium	Rats	4 m Eq/kg IV infusion

CsA: Cyclosporine A, IV: Intravenous, ALX: Alloxan, IV: Intravenous

Table 4: The animal species, dose and route of administration required for chemically inducing diabetes

Chemicals	Species	Dose(s) (in mg/kg)
STZ	Rat	35-65 (i.v. or i.p.)
	Mice	100-200 (i.v. or i.p.)
	Hamster	50 (i.p.)
	Dog	20-30 (i.v.)
	Pig	100-150 (i.v.)
	Primates	50-150 (i.v.)
ALX	Rat	40-200 (i.v. or i.p.)
	Mice	50-200 (i.v. or i.p.)
	Rabbit	100-150 (i.v.)
	Dog	50-75 (i.v.)

ALX: Alloxan, STZ: Streptozotocin, ip: Intraperitoneal, iv: intervenous

inducing diabetes depends on the animal species, route of administration which summarized in Table 4.[29,30] Chemically induced models are commonly preferred models for testing of new antidiabetic drugs or new formulations of insulin.[31-33] This is also an appropriate model for testing transplantation therapies where the end point is lowering of blood glucose.[34] But drugs-inducing diabetes can toxic at other organs of the body. It should also be noted that changes in p450 isozymes in the liver, kidney, lung, intestines, testis and brain have reported after administration of STZ or ALX.[35]

Streptozotocin

Streptozotocin (streptozocin/izostazin/zanosar/STZ) is a synthetic nitrosoureido glucopyranose derivative isolated from fermentations of *Streptomyces achromogenes* with broad-spectrum antibiotic and antineoplastic activity.[36] STZ administration by i.p. or intravenous (i.v.) route, it enters into the pancreatic β-cell through the glucose transporter-2 (GLUT-2) transporter and causes alkylation of the DNA. Subsequent activation of poly (adenosine diphosphate ADPc-ribose) polymerase leads to nicotinamide (NAD^+) depletion, a reduction in cellular adenosine triphosphate and inhibition of insulin production.[37] A single large dose of STZ can produce diabetes in rodents, probably as a result of direct toxic effects. STZ has longer half-life than ALX, so rat model interestingly exhibits stable, long-lasting hyperglycemia and the symptoms of diabetic complications such as hypertension. But its use in chronic experiments, especially-spontaneous recovery from high blood glucose levels leads to high incidence of kidney and liver tumours.[38-40] These problems are due strongly to oncogenic action of STZ.[41] STZ is ineffective in rabbits.[42] Multiple low doses of STZ over 5 days induce insulitis in mice[43,44] or rats.[45] Doses range from 20 to 40 mg/kg/day, depending on the species and strain. Diabetes develops even in the absence of T- and B-cells, and therefore, it does not model the human disease as closely as spontaneous models of autoimmunity.[46]

Alloxan

Alloxan (2, 4, 5, 6-tetraoxypyrimidine; 5, 6-dioxyuracil) is the next most commonly used chemical for induction of diabetes mellitus. It is a well-known diabetogenic agent widely used to induce T2Ds in animals.[47] It used to produce experimental diabetes in animals such as rabbits, rats, mice and dogs. The diabetic effect of ALX is mainly attributed to rapid uptake by the β-cells and formation of free radicals, for which β-cells have poor defense mechanisms[48] and there after highly reactive hydroxyl radicals that cause fragmentation of β-cell DNA.[49] ALX is also taken up by the liver, but it has better protection to reactive oxygen species.[50,51] Other mechanisms of β-cell damage by ALX include oxidation of essential–SH groups, especially that of glucokinase[52] and disturbances in intracellular calcium homeostasis.[53] A dose of 100 mg/kg has used to create a long-term diabetes models in rabbits.[54] It should be noted that ALX has a narrow diabetogenic dose, and even light overdosing can cause general toxicity, especially to the kidney.[49]

Ferric nitrilotriacetate

This is a rarely used model for induction of special type diabetes known as bronze diabetes, in which there are heavy iron deposits, skin pigmentation, and liver cirrhosis due to disturbances in iron metabolism.[55] Rats and rabbits parenterally treated with a large daily dose of ferric nitrilotriacetate manifested diabetic symptoms such as hyperglycemia, glycosuria, ketonemia and ketonuria after approximately 60 days of treatment. Difference from human hemochromatosis was that no fibrotic changes were observed in the liver, pancreas, and other organs.[56]

Dithizone

Dithizone is a ((1E)-3-anilino-1-phenylimino-thiourea) is a sulfur-containing organic compound which used for induction of diabetes in experimental animals.[57]

Dithizone injected to cats, rabbits, golden hamsters and mice in a single i.v. dose of 40–100 mg/kg. In rabbits dithizone injection causes a triphasic glycemic reaction. After 2 h initial hyperglycemia detected followed by a normoglycemic phase after 8 h and after 24–72 h a permanent hyperglycemia.[58]

VIRALLY INDUCED DIABETES

Viruses are one environmental factor that implicated in the pathogenesis of T1DM. Different viruses have been reported to associate with development of T1D in humans and animal models. Which include coxsackie B virus,[59,60] encephalomyocarditis virus,[61,62] Kilham rat virus,[63,64] lymphocytic choriomeningitis virus rubella and mumps viruses.[65] Viruses may be involved in the pathogenesis of T1D, by inducing β-cell-specific autoimmunity, by stimulate pre-existing auto reactive T cells that may participate in islet destruction with or without infection of the β-cells[61] and by cytolytic infection and destruction of the β-cells (e.g. encephalomyocarditis virus) in mice.[66]

GENETICALLY INDUCED DIABETES

Genetically modified models, in which diseases or conditions are induced by genetic manipulation with specific either gene removed or replaced. Genetic factors are believed to a major component for the development of diabetes. It is possible now to understand the complex relationship between the gene(s) and the disease.[67] National Heart, Lung and Blood Institute has developed and maintained a database which has information about genetically modified animals of disease or conditions, with a specific gene, type of genetic manipulation, and animal involved in the study.[68]

AKITA mice

The AKITA mouse derived in Akita, Japan from a C57BL/6NSlc mouse with a spontaneous mutation in the insulin-2 gene preventing correct processing of proinsulin. This causes an overload of misfolded proteins and subsequent endoplasmic reticulum (ER) stress, results in severe insulin dependent diabetes starting from 3 to 4 weeks of age, characterize by hyperglycemia, hypoinsulinaemia, polyuria and polydipsia. Untreated homozygotes rarely survive longer than 12 weeks. The lack of β-cell mass in this model makes it an alternative to STZ treated mice in transplantation studies.[69] In addition, this model is commonly used to study potential alleviator of ER stress in the islets.[70]

ANIMAL MODELS FOR TYPE-2, NONINSULIN DEPENDENT DIABETES MELLITUS

Noninsulin dependent diabetes caused by the loss of functional β-cells within the islets of langerhans in the pancreas, resulting in insulin deficiency which resulting hyperglycemia. Under normal condition, there is continual turnover of β-cells with proportion of cells undergoing apoptosis due to senescence and replacement of these dying cells by both β-cell replication and islet neogenesis,[71] but in diabetic condition it is not enough to compensate patients insulin body need and insulin secretion decreased, thus leading to hyperglycemia. However, it is not completely lost, and therefore patients are not insulin dependent, so the body requires exogenous insulin to keep up better metabolic control to prevent chronic complications.[72] Many animal models of T2Ds are obese, reflecting the human condition where obesity is closely linked to T2D development.

SPONTANEOUS DIABETES TYPE-2 DIABETIC MODELS

Obese models

Obese mouse

obese mouse (ob/ob mouse), is an obese rodent model of spontaneous T2DM, at the age of 3–4 weeks these mice observed mild hyperglycemia due to compensatory hyperinsulinemia or insulin resistance. This mice model inherited as (monogenic) autosomal recessive mutation in C57BL/6J mouse strain which is now identified in leptin gene.[73] The first C57BL/6J-ob/ob mouse originated from the Jackson Laboratory in Bar Harbor, ME, USA.[74] Another mouse model C57BL/KS comes in this category. When ob gene expressed on C57BL/KS background, mice become severely diabetic with regression of islets, hepatic glucose overproduction, and increased lipogenesis in the liver and early death.[75]

db/db mouse

This is intensively studied mice model of obesity and T2D with a defect in the leptin receptor (db) These mice are spontaneously hyperphagicinsulin over secretors becoming obese, hyperglycaemic, hyperinsulinaemic and insulin resistant within 1st month of age and develop hypoinsulinaemia, hyperglycemia later with a peak between 3 and 4 months of age but later (4–8 weeks) develops hyperglycemia, due to β-cell failure[76] and does not live longer than 8–10 months. Female diabetic db/db mice survive longer than male due to protective effect of oestrogen on the pancreatic β-cells.[77]

Kuo Kondo mouse

Kuo Kondo (KK) mouse is polygenic model of obesity and T2D produced by selective inbreeding for the large body size in Japan, also named as Japanese KK mouse.[78] These animals are hyperphagic, hyperinsulinaemic, diabetic nephropathy insulin resistant and show moderate obesity by 2 months

of age, which attains maximum at 4–5 months.[79] Normally Insulin resistance precedes the onset of obesity. The increase in pancreatic insulin content associated with increase in number and size of pancreatic islets but histological degranulation of β-cells and hypertrophy of islets are found.[80] KK mouse mimics human obesity (the Goto–Kakizaki [GK] rat being relatively slim) and easier production of transgenic variants from mice rather than rats.[81]

Kuo Kondo/Ay mouse

The KK/Ay are polygenic mouse and serves as a good model for obesity and T2D maintained at Upjohn colony (KK/Upj-Ay/J) are now available from Jackson Laboratory, Bar Harbor, USA, These mice were created by introducing the yellow obese AY gene into the KK strain, which turns the hair color from black to yellow Kuo Kondo Yellow (KKY).[82-84] This model develops maturity-obesity and has more severe hyper insulinaemia and more prominent changes in the pancreatic islets. So it used for screening various classes of antidiabetic agents.[85]

New Zealand obese mouse

The New Zealand obese (NZO) mouse is a polygenic model of obesity, glucose intolerance, and metabolic syndrome which exhibits hepatic and peripheral leptin insensitivity, insulin resistance, impaired insulin secretion, hypercholesteremia, and hypertension, which worsens with age and about 50% of males develop diabetes and islets are hyperplastic and hypertrophic at 3–6 months of age.[86] NZO mouse is a rarely preferred model, because they are resistant to peripheral leptin administration but sensitive to centrally administrated leptin[87] indicating a defect in leptin transport across the blood brain barrier. New recombinant congenic strains that have developed by entering NZO loci into other strain genomes, e.g. the nonobese and nondiabetic mouse (NON/Lt) for studying "diabesity" and its treatment.[88]

NONc/New Zealand obese10 mouse

NONc/NZO10 model is suitable for studies in diabetic wound healing created by combining independent diabetes risk-conferring quantitative trait loci from two unrelated strains of NZO mice with NON/Lt.[89,90] NONc/NZO 10 females are diabetes resistant and can serve as normoglycaemic control, but males are not hyperphagic develop more moderate level of obesity, and reproduce normally. They are more in weigh than NON males, but significantly less than the NZO males. Despite the reduced rate of weight gain compared to NZO.[88]

Tsumara Suzuki obese diabetes mouse

Tsumara Suzuki obese diabetes (TSOD) mouse is a polygenic origin model which established by Miura *et al*. through repeatedly selective inbreeding of obese male mice of ddY strain.[91] Their symptoms, like polydipsia polyuria followed by hyperglycemia and hyperinsulinaemia obesity gradually develops only in male mice about 12 months. It has shown that the reduced insulin sensitivity in diabetic TSOD mice is due, to the impaired GLUT-4 translocation by insulin in both skeletal muscle and adipocytes.[92] Pancreatic islets of TSOD male mice are found hypertrophic without any signs of insulitis or fibrous formation.[91]

M16 mouse

M16 mouse is an out bred animal model to facilitate gene discovery and pathway regulation controlling early onset polygenic obesity and T2DM phenotypes. This results from long-term selection for 3–6 weeks weight gain from an ICR, London, UK base population. These mice characterized by increased body fat percentage, fat cell size; fat cell numbers, organ weights and mice also exhibit hyperphagia, accompanied by moderate obesity and are hyperinsulinaemic, hyperleptinaemic and hypercholesterolemia relative to ICR.[93]

Zucker fatty rat

The Zucker fatty rats discovered from the simple autosomal recessive (fa) gene on chromosome after a cross of Merck M-strain and Sherman rats in 1961 as a model for human obesity and T2D.[6] This rat has attributed to hypothalamic defect in leptin receptor signaling.[94] It associated with type IV hyperlipidaemia (increased very low density lipoprotein and triglyceride levels in the circulating blood) and hypertension; with increasing age of obese Zucker rats spontaneously develop proteinuria and focal segmental glomerulosclerosis, ultimately leading to renal failure.[95] In some cases, it is also reported that abnormal glucose tolerance found in these rats due to the metabolic defects in hepatic organ.[96]

Spontaneously hypertensive rat/National Institute of Health-corpulent

Spontaneously hypertensive rat/National Institute of Health (NIH)-corpulent (SHR/N-cp) rat a genetic model of obesity and T2DM with hypertension. It is derived by inbreeding of SHR/N strains at the NIH, Bethesda, Maryland, USA, associated with hyperplasia and early onset of normal or slight hyperglycemia, dyslipidaemia, profound hyperinsulinaemia, hyperleptinaemia, insulin resistance, impaired glucose tolerance and essential hypertension. It is highly useful for investigating obesity associated T2D and also for studying influence of dietary carbohydrate on development of diabetes in

certain genetically predisposed carbohydrate sensitive individuals.[97]

James C Russel/LA-corpulent rat

The JCR: LA-corpulent rat model is extensively studied for the pharmacological and dietary intervention prior to the onset of cardiovascular lesions or hyperinsulinaemia to determine the efficacy for preventing or slowing occurrence of cardiovascular lesions. The major drawback of this rat as model of diabetes, it is normoglycaemic when fasted. However, the distinct feature of this animal is the vasculopathy progresses inherently without any dietary cholesterol and high-fat diet interventions.[98]

Otsuka long-evans tokushima fatty rat

The otsuka long-evans tokushima fatty (OLETF) rat was originates from an out bred colony of long-evans rats strain by selective breeding, maintained at the otsuka pharmaceutical and named OLETF.[99] Development of diabetes in OLETF rats is due to defects in the β-cell proliferation and sustained hyperglycemia due to poor capacity of pancreatic islet regeneration after surgery and is the treated with NAD which corrects hyperglycemia by increasing β-cell proliferation.[100] Male's rats are more likely to develop diabetes in adult life than females.[17] This rat model has been extremely used in pharmacological research while testing for a number of antidiabetic and antihypertensive drugs.[101]

Nonobese models

Cohen diabetic rat

The Cohen diabetic rat is an exceptional genetically derived experimental model of diet induced T2D that having many similar features of the disease in humans. It exhibit retinopathy and nephropathy, reduced fertility and testicular degeneration.[102] Chief complications were nephropathy with mesangial expansion and thickening of the glomerular basement membrane, proliferative retinopathy, testicular atrophy and gastrointestinal disorders. The diabetes is due to cell dysfunction and reduced insulin secretion. The hyperglycemia was reversible by diet adjustment.[103]

Goto–Kakizaki rat

Goto–Kakizaki rats were created by a Japanese group by repetitive breeding of Wistar rats with the poorest glucose tolerance as T2Ds model. The GK rat model may result from inadequacy of pancreatic growth factors with the defects in β-cells and impaired insulin sensitivity in the liver, skeletal muscle and adipose tissues has reported.[104] Impaired insulin secretion and hepatic glucose over production are early events in diabetic. GK rats are mostly contributing to development of hyperglycemia rather than the peripheral (muscle and adipose tissue) insulin resistance. The renal alterations found only in 2 years old GK rats at a later stage.[105]

Torri rat

Torri rat is a new spontaneously diabetic nonobese rat from the Sprague–Dawley rat strain established recently in 1997 at Torri Pharmaceutical Co., Japan. The distinct characteristics are ocular complications, cataract and retinopathy with fractional, retinal detachment, fibrous proliferation and massive haemorrhage at 70–77 weeks of age. Torri rats are able to survive for longer duration without insulin treatment and hence more useful for studies on diabetic complications.[106,107]

Alloxan-susceptible/Lt mouse

Alloxan-susceptible (ALS) new mouse model implicated in the pathogenesis and complications of both T1DM and T2DM is the sub-strain maintained at Jackson Laboratory, Bar Habor. It characterized by hyperinsulinaemia and impaired glucose tolerance develops spontaneously between 6 and 8 weeks of age in ALX-untreated males.[108] The T2Ds predisposition of ALS mouse recognized by congenic analysis of the yellow mutation (Ay) at the agouti locus on chromosome-2. Indeed, in ALS/Lt (a) mice, this mouse model with reduced ability to diffuse free radical stress.[109]

CHEMICALLY INDUCED TYPE-2 DIABETIC MODELS

Streptozotocin

Streptozotocin is the most widely used for screening the compounds for their insulin mimetic, insulin tropic and other hypoglycemic/antihyperglycaemic activities.[110] It cause breakage of DNA strands and results the increase activity of poly-ADP-ribose synthetase, an enzyme depleting NAD in β-cells, which finally leading to energy deficiency and death of β-cells reported. Recently, a new animal model of T2Ds has produced by combination of STZ and NAD administration in adult rats. In which NAD (230 mg/kg, i.p.) administered to rats 15 min before STZ (65 mg/kg, i.v.) has shown to develop moderate and stable nonfasting hyperglycemia without any significant change in plasma insulin level. NAD play a role as an antioxidant which exerts protective effect on the cytotoxic action of STZ by scavenging free radicals and causes only minor damage to pancreatic β-cell mass producing T2DM.[111] This provides good opportunity to investigate diabetes in much closely similar path physiological situation as in human with fewer incidences of ketosis as well as mortality.[112]

Alloxan

Alloxan which is a uric acid derivative causes diabetes in many rodent and nonrodent animals and

highly unstable in water at neutral pH. ALX acts by selectively destroying the pancreatic β-islets leading to insulin deficiency, hyperglycemia and ketosis.[113] Most preferably use of ALX in case of rabbit because of the relative ineffectiveness of STZ) in rabbits for induction of diabetes and development of well characterized diabetic complications.[114] Now days ALX is almost replaced by STZ, due to development of various complications such as neuropathy, cardiomyopathy, has well-marked retinopathy and the percentage incidence of diabetes is quite variable and is not proportionately related to increasing doses of ALX. Incidence of ketosis resulting high mortality and the reversal of hyperglycemia due to pancreatic regeneration are common in case of ALX treated animals as shown in Table 5.[75]

Gold thioglucose mouse

Gold thioglucose (GTG obese diabetic) mouse induced T2DM with obesity at the dose of (~200 mg/kg, i.p.) in mice. It exhibits many molecular defects in relations to insulin signaling pathways.[115] Which subsequently is responsible for development of hyperphagia and obesity. It also shows increased body lipid and hepatic lipogenesis and triglyceride secretion, increased adipose tissue lipogenesis and decreased glucose metabolism in muscle with gradually develop obesity, hyperinsulinaemia, hyperglycemia, insulin resistance over a period of 16–20 weeks.[116] GTG limited in their uses because it takes very long time to develop obesity/diabetes and the number of mortalities.[117]

SURGICAL TYPE-2 DIABETIC MODELS

This method consists of complete or partial pancreatectomy in animals used for induction of T1D or T2D. This finding from these partial pancreatectomized animals supports the notion that simply reduction in pancreatic β-cell mass itself not be responsible for the glucose intolerance as seen in neonatal STZ rats.[118] These partial pancreatectomized animals reported to develop hyperglycemia and insulin resistance.[119] Diabetic dog model discovered by Oskar Minkowski through surgical complete pancreatectomy has considered to the first animal model of diabetes[120] and is rarely now used for the investigation. It does not cause severe form of diabetes and characterized by moderate hyperglycemia with neither reduction in body weight nor reduction in plasma insulin levels. The 90% partially pancreatectomized rats also show defect or selective impairment to glucose stimulated insulin release but remain intact to other insulin secretogogues viz., arginine, isoproterenol like neonatal STZ rats.[118] Recently, an another model of stable form of T2D has produced by combination of 50% partial pancreatectomy along with NAD (350 mg/kg) and STZ (200 mg/kg) treatment in BALB/c mice.[121] There are some advantages in combination procedure as it minimizes the risk of unnecessary adverse effect of chemicals on body.

Table 5: Comparison of ALX and STZ

Condition	ALX	STZ
Acute hyperglycemia (maximum blood glucose)	45 min	120 min
Liver glycogen depletes	Faster	Slowly
Insulin levels during hypoglycemia phase	Elevated	Elevated
pH stability	3–4	4.1–4.5
Hypoglycemia	Less severe	More severe
Sensitive to insulin	Yes	Yes
Reversibility	After 3 months	Irreversible
Mortality rate %	37	8

ALX: Alloxan, STZ: Streptozotocin

DIET INDUCED TYPE-2 RATS

Desert gerbil

The desert gerbil (*Psammomys obesus*) was originally discovered to develop diabetes in captivity in the 1960s. The diabetes ranged from mild hyperglycemia with hyperinsulinaemia to severe hyperglycemia with hypoinsulinaemiaand ketoacidosis.[122] Due to its poor adaption to excess nutrition, it has suggested that the *Psammomys* representsan ideal model of the "thrifty gene" effect.[6]

Nile grass rat

The nile grass rat (*Arvicanthis niloticus*) has recently been suggested as a model for metabolic syndrome. Most of these animals spontaneously develop obesity, dyslipidaemia and hyperglycemia by 1-year of age when kept on a normal chow diet in captivity. They show other signs of diabetes and metabolic syndrome such as reduced β-cell mass, atherosclerosis and liver steatosis.[123]

C57BL/6J mouse

C57BL/6J mice are susceptible to obesity-linked diabetes when maintained on a high-fat diet. They also present abnormalities in the autonomic nervous function, β-cells, and expression of uncoupling protein-2 in adipocytes, but it is itself prone to nutritionally induced diabetes and obesity as well as hypertension.[124] Excess food intake leads to tissue deposition, primarily in a dipocytes, resulting in untoward changes in metabolism. Several animals without genetic mutations undergoing diet-induced obesity and develop T2Ds reviewed by Coscun *et al*.[125]

Israeli sand rat

The Israeli sand rat (*Psammomys obesus*) model is particularly useful when studying the effects of diet and exercise on development of T2DM.[126] In its

natural habitat rat that has an essentially vegetarian diet. However, when fed laboratory chow, the animals become obese, insulin resistant and hyperglycemic.[127] If a cholesterol-rich diet used, hyperlipidaemia and atherosclerosis develop.[128]

GENETIC MODELS FOR TYPE-2 DIABETES

Human islet amyloid polypeptide mice

A variety of human islet amyloid polypeptide (hIAPP) models have created and it has demonstrated that increasing expression of hIAPP increases β-cell toxicity.[129] In addition, replicating β-cells are more susceptible to hIAPP toxicity, and thus, β-cell adaption to increased insulin demand in this model restricted with characteristic of formation of amyloid within the islet tissue, which derives from IAPP.[130]

Nagoya–Shibata–Yasuda mouse

Nagoya–Shibata–Yasuda (NSY) developed by selective inbreeding using a laboratory strain of mouse termed Jc1: ICR with impaired insulin secretion in the face of mild insulin resistance. Obesity is not a major feature of these animals and marked gender difference with almost all males developing hyperglycemia, but less than females, being affected.[131] The NSY mouse is particularly useful when considering age related phenotypes (e.g. decline in β-cell function).

NONRODENT MODELS OF SPONTANEOUS TYPE-2 DIABETE

Feline

Feline diabetes mellitus closely resembles human T2DM in many respects including clinical, physiological, and development of islet amyloid deposits, loss of approximately 50% of cell mass, and development of complications in several organ systems including peripheral polyneuropathy and retinopathy.[132]

Rhesus monkey

Rhesus monkey (*Macaca mulatta*) is a nonrodent model with symptoms of T2DM that provides the most human-like model of metabolic disorders in diabetes representative of other monkey species prone to diabetes.[133] It develops obesity, hyperinsulinaemia and insulin resistance when maintained on *ad libitum* laboratory diet, which gradually progresses to necrosis of β-cells, severe fall in insulin levels and overt hyperglycemia over a period of several years.[134]

PATENTS REPORTED IN DIABETIC ANIMAL MODELS

These days, animal models are created by insertion of a particular human DNA into fertilized mouse oocytes which are then allowed to develop by implantation into the oviducts of pseudo pregnant females. Many researchers, companies, and academic institutions try to publish such work as patents not just the methods used to make animals suffer from a disease but also the animals themselves. Patents on such animals could be very rewarding if they become in demand for biomedical and testing laboratories as describe in Table 6.

CONCLUSION

Animal models of diabetes mellitus are very useful tools for studying the pathophysiology and the clinical aspects of the disease because that would be impossible in humans due to lack of toxic profile and unclear mechanism action of tested compounds. In animals none of the known single species is exactly equivalent to human diabetes, but each model act as essential tool for investigating genetic, endocrine, metabolic, morphologic changes and underlying aetiopathogenic mechanisms. So, it is important to note that some animal models are better suited to screen particular class of antidiabetic compounds like use of smaller animal models such as mice, will reduce the expense of producing test materials while some advanced efficacy studies or toxicological examinations which require invasive procedures and large blood and tissue samples, may facilitated by using animals with large body size such as rat or other nonrodents. Chemical induction appears to the most popularly used procedure in inducing diabetes mellitus in experimental animals. They are capable of inducing both T1DM and T2DM with proper dosage selection. But these experimental animals' models must put to use within 7 days after induction of diabetes mellitus or maintain with appropriate doses of insulin to prevent animal death and in surgical and genetic methods require highly technical skills, may be associated with a high percentage of animal death and thus are rarely used. But some limitations are with large nonrodent animal models like expensiveness, practical difficulties, and extreme care and ethical considerations associated with their use (viz., pigs, dogs and nonhuman primates). In transgenic technology, that can impact at many points in the discovery process, including target identification and target validation. It also provides models designed to alert researchers early to the potential problems with drug metabolism and toxicity which will help in providing better models for human diseases. Drugs from transgenic animals can minimize the attrition rate in clinical trials by increasing quality of the target and compound combinations making transition from discovery into development. The regulatory aspects and ethics

Table 6: List of reported patents as animal models of diabetes with specific feature

Patent number	Description	Inventor	Publication date	References
EP 0491396	NIDD disease rat model derived and established from Long-Evans rats, which having more specific biochemical gene markers (e.g., Testicle acid phosphatase-2, testicle esterase-6) in organs, plasma and red blood cells, with erythrocytes and B lymphocytes having specific major histocompatibility antigen markers (RT1 class I and II)	Tsukasa H, *et al.*	1992	[134]
EP0712930	Invention disclosed a transgenic nonhuman animal model comprising recombinant DNA including a promoter of a gene expressed in pancreatic β-cells and a heat shock protein 70 genes operatively linked downstream to said promoter. Transgenic mice having NIDD characterized by a level of 300 mg/dl of glucose in blood	Jongil K, *et al.*	1996	[135]
US6187991	Transgenic animal models for T2DM. The DNA construct allows pancreatic. β-cell specific expression of hIAPP under the regulation of the rat insulin II promoter in both cell lines and transgenic animals. DNA construct is introduced into animal embryos into transgenic animals which develop amyloid plaque deposits in the islets of Langerhans in the pancreas, fasting hyperglycemia, glycouria and diabetic glomerulosclerosis at 3–5 months of age. The transgenic animals can be screened for treatments that either enhance or inhibit the progression of this disease phenotype	Walter CS, *et al.*	2001	[136]
EP 1228094	Congenic animals and animal populations having T2Ds-associated phenotypes are described. Insulin degradation polypeptides having amino acid substitutions linked to T2Ds-associated phenotypes also are described	Joakim LG, *et al.*	2002	[137]
US20040128707	Diabetic-prone transgenic mouse is prepared in a process comprising a transgene that contains a Meg1/GRB10 gene, an imprinted gene exhibiting maternal expression, or a human GRB10 gene in the downstream of a chicken β-actin promoter and in the upstream of a rabbit β-globin poly A is constructed, and subsequently the transgene is microinjected into a male proneucleus of a mouse fertilized egg; thus obtained egg cell is cultured and then transplanted into an oviduct of a pseudopregnant female mouse; after rearing up the recipient animal, baby mice that have the above-mentioned cDNA are selected from the mice born from the recipient animal	Fumitoshi I, *et al.*	2004	[138]
EP 1659860	Invention disclosed T2DM model which comprises cells over-expressing GPR40 under the control of the Ipf1/Pd×1 promoter and disclosed the use of the model animal for the identification of agonists or antagonists towards GPR40 gene	Helena E, *et al.*	2006	[139]
EP 1432990	The invention relates to an animal model for diabetes and a method for obtaining said animal model. The invention also relates to nucleic acid molecules isolated from Ijungan virus and to polypeptides encoded by any portion of said nucleic acid molecule	Niklasson B, *et al.*	2008	[140]
US20090217394	The present invention relates to a transgenic nonhuman diabetes animal model, into which recombinant DNA comprising a gene encoding a diphtheria toxin receptor and an insulin promoter for regulating expression of the above gene has been introduced	Hiromichi Y, *et al.*	2009	[141]
WO2006021006	The instant invention relates to methods for generating a nonhuman animal model for a diabetic complication. The invention further relates to screening methods for therapeutics of diabetic complications using the animal model generated by the methods of the invention	Rebecca ST, *et al.*	2009	[142]
US20090320147	Non-human transgenic animal as a model of T2DM type manifesting a symptom of excessive expression of the active SREBP-2 protein in pancreatic β-cells by introducing a recombinant DNA in which a DNA encoding the active SREBP-2 protein is disposed under the control of a promoter	Hitoshi S, *et al*	2009	[143]
JP 4588808	A congenic mouse model of human T2Ds has been produced by back-cross from the FLS mouse inbred strain. The mouse model strain carries mutation in the gene ob (derived from the ob gene of obese T2Ds mouse strain C57BL/6J-ob) as heterozygote. The produced model animal's present pos. urinary sugar during 5–15 weekly ages, significant wt. increase either in young males or in females	Itsuki O, *et al.*	2010	[144]
CN 102812921	The method comprises feeding an animal with a high-fat high-sugar feed and drinkable ethanol (concentration 10–40 volume %) of 0.1–2 mL to obtain an animal model for NIDD mellitus, wherein the high-fat high-sugar feed is composed of basal feed 50–70%, sucrose 10–20%, grease 10–20%, cholesterol 1–5%, sodium cholate 0.5–2% and egg yolk powder 5–10%. The obtained animal model is suitable for hypoglycemic drug screening	Chengxin S, *et al.*	2012	[145]

Contd....

Table 6: ***Contd...***

Patent number	Description	Inventor	Publication date	References
CN103314925	The invention disclosed a method for developing a rhesus monkey as T2Ds diabetic models. The method includes feeding rhesus monkeys with high fat and high cholesterol feed twice a day and administering STZ at a dose of 25 mg/Kg once a week for a period of 24 months. Each rhesus monkey is fed with 0.3-0.4 kg of the feed every time, which comprises in a weight ratio as 78 parts of standard monkey feeds, 15 parts of animal fat, 5 parts of sugar and 2 parts of cholesterol	Chen Y, *et al.*	2013	[146]
CN103211834	The invention disclosed a method of establishment of a high-selenium induced insulin resistance animal model of diabetes mellitus.This includes feeding Sprague Dawley rats with 100μg/kg-200μg/kg selenium every day and six weeks later, which result in establishment of the insulin resistance animal model	Wang X, *et al.*	2013	[147]
RU2534411	The invention refers to examining type I diabetes mellitus by simulating ALX diabetes in white outbred rats. Developing sub compensated diabetes mellitus by administering the rats with ALX solution intraperitoneally on an empty stomach, at successive doses of 5 mg/100 g, 7 mg/100 g and 5 mg/100 g at every 7 days, and developing decompensated diabetes mellitus by three administrations of ALX solution at a dose of 10 mg/100 g at every second day	Danilova IG, *et al.*	2014	[148]
CN103966243	The invention discloses a DNA molecule and its application in the diabetes mouse model using gene HSD11B1, CHOP, and hIAPP expression vectors. DNA molecule comprising expressing cassette A (vector expressing pig HSD11B1 gene) and expression cassette B (expressing CHOP gene and hIAPP gene). Three genes can be co-transformed by means of a recombinant vector, to cause mouse pancreatic islets β-cell to start apoptosis stress related path, which reducing number of islet β-cells, resulting in absolutely insufficient insulin secretion, and resulting in a continuous rising of fasting blood-glucose in mouse	Yang S, *et al.*	2014	[149]
CN103858820	The invention disclosed a method for preparing a miniature pig swine model of T2Ds. In which small pigs are continuously feed with high-fat, high-sugar diets by weight number ratio of components: a complete feed 55 to 65 parts, 25 to 35 parts of sugar, 5 to 15 parts of animal fat for 280 to 320 days	Lan G, *et al.*	2014	[150]
WO2014068033	The invention disclosed a method of a genetically modified non-human model of obesity or obesity-related disorders. It was shown that expression of LSD1 in transgenic mice promotes beige fat formation in white adipose tissue. It was shown that heterozygous mice in which one allele of the LSD1 gene has been disrupted and which show reduced expression of LSD1 are prone to obesity and T2Ds. These mice having a reduced expression of LSD1 are valuable tools for studying T2Ds and related metabolic disorders	Schuele R, *et al.*	2014	[151]
WO2014028737	A method for producing swine animal model for insulin resistance, obesity and/or T2Ds, which include administering a dose of STZ or functional equivalents or derivatives to a pregnant animal ranging from 80 to 85% of the gestation period and/or feeding a diet comprising a high fructose-and/or sucrose containing diet. Where in upon delivery of neonates from the pregnant animal, the neonates are administered with an additional dose of STZ or functional equivalents or derivatives and fed a diet containing at least 10% fructose	Eldridge JA, *et al.*	2014	[152]

NIDD: Noninsulin-dependent diabetes, HIAPP: Human islet amyloid polypeptide, T2DM: Type-2 diabetes mellitus, SREBP-2: Sterol-regulatory element-binding protein-2, FLS: Fatty liver Shionogi, HSD11B1: Hydroxysteroid (11-Beta) Dehydrogenase 1, CHOP: C/EBP homologous protein, LSD1: Lysine-specific Demethylase 1

should give due consideration while using transgenic animals. From research, pigs and transgenic animals derived products like milk, eggs seems to promising in developments of therapeutic strategies. Therefore, the continuing effort for inventing new models has always positive critics and animal models will continue to have a major and meaningful place in diabetes research.

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