ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

REVIEW ARTICLE

Experimental Model Organisms in Type 2 Diabetes Research: A Review

Shovit Ranjan, Praveen Kumar Sharma
Centre For Life Sciences, Central University of Jharkhand, Brambe, Ranchi-835205.

Manuscript Info

Manuscript History:

Received: 14 October 2015
Final Accepted: 22 November 2015
Published Online: December 2015

Key words:

Type 2 Diabetes, Experimental Models, Mice, Rat.

Corresponding Author

Shovit Ranjan

Abstract

Type 2 Diabetes, a disease state recognized by impaired insulin sensitivity and hyperglycemia, is presently one of the world's leading causes of mortality and morbidity. The concrete knowledge of these appropriate experimental models are very much required for understanding the pathogenesis, complications, and genetic, environmental or behavioral factors that increase the risks of this disorder along with the testing of various therapeutic agents. The animal models of type 2 diabetes can be obtained either genetically or induced by chemicals or dietary or surgical manipulations and/or by various combinations thereof. Till date, enormous number of new genetically modified animal models in addition to the traditional models like transgenic, generalized knock-out and tissue specific knockout mice have also been developed for the study of Type 2 Diabetes. This review basically provides an insight into the various experimental animal models of type 2 diabetes with reference to their origin/source, characteristic features, underlying causes/mechanism(s), advantages and disadvantages of those models in this regard. Moreover, it also gives an idea of dosages of various chemical diabetogens in different models. Hence, this review will comparatively evaluate all the experimental models, thus guiding the diabetes researchers to more accurately select the most appropriate model according to their specific requirements.

Introduction

Out of the different types of diabetes, Type 2 diabetes (T2D) has greatest impact on health worldwide. Type 2 Diabetes, a disease state recognized by impaired insulin sensitivity and hyperglycemia, is one of the world's leading causes of mortality and morbidity (Pendse *et al*.,2013). Worldwide, the number of diagnosed diabetes cases reached 366 million in 2011, and is predicted to reach 552 million by 2030 (Murea *et al*.,2012). Furthermore, it has been found that around 312 million people are affected by Type 2 Diabetes (till October 2013) and its incidence is still increasing year by year at constant rate worldwide, resulting in serious short term and long term implications (http://www.who.int/mediacentre/factsheets/fs312/en/). Now a days, therapeutic strategies for Type 2 Diabetes are limited to insulin and four main classes of oral antidiabetic agents that stimulate pancreatic insulin secretion (sulphonylureas and rapid-acting secretagogues/insulinotropics *e.g.*, glibenclamide, glipizide, rapaglinide), reduce hepatic glucose production (biguanides *e.g.*, metformin), delay digestion and absorption of intestinal carbohydrate (a-glucosidase inhibitors *e.g.*, acarbose) or improve insulin action [thiazolidinediones (TZDs) *e.g.*, pioglitazone, rosiglitazone]. Each of the above agents has its own limitations and serious adverse effects, which results in the origin of enormous variety of newer therapeutic agents or strategies for T2D treatment, most of all presently under development (Ramarao and Kaul,1999; Bailey,2005).

Genetic analysis of T2D is difficult and poorly understood in humans as this metabolic disorder is influenced by complex interactions among multiple susceptibility genes and environmental factors. In addition to this, research in this field on humans is encumbered by various ethical issues or considerations. Animal models of T2D are thus greatly useful and advantageous in biomedical studies as they may offer promise of new insights into human diabetes. It has been observed that most of the available models are based on rodents because of their small size, short generation interval, easy availability, easy to handle, omnivorous in nature, non-wild tranquil behavior and economic considerations; however, nonrodent models of diabetes seems to be required as a valued supplement to rodents for both practical and physiological reasons with respect to humans. Different models has been developed for different traits in large number and insufficient characterization of some models make it a tedious task to choose the right model for a given study (including pharmacological screening) and at times can also lead to data misinterpretation or even to the wrong conclusions. Though there are so many literatures available on the animal models of T2D, the main aim of the review is to give an overview of the currently available animal models of T2D with respect to their origin/source, characteristic features, aetiopathogenesis, their advantages, and disadvantages in T2D study and comparatively evaluates most of the experimentally induced rodent models of T2D with their limitations, advantages and criticality of development in order to help the diabetes research groups to more appropriately select the animal models for their specific research work. Further, it mainly deals with the apposite selection and efficacy of different animal models in testing various classes of new chemical entities and other therapeutic modalities for the treatment of T2D.

Animal Models of Type 2 Diabetes-

Animals showing a syndrome of T2D, with characteristics similar to humans, include a wide range of species with genetic, experimental (chemically/surgically induced) and nutritional causation (diet induced). As we all know that T2D is mainly described by insulin resistance and inefficient beta cells to sufficiently compensate the same. Therefore, animal models of T2D mainly include models of insulin resistance and/or models of beta cell failure. Subsequently, a number of diabetic animal models have been developed and improved over the years, out of which rodent models are the most famous and thoroughly described. Normally, these rodent models can be categorized into two broad classes: 1) genetically induced spontaneous diabetes models; and 2) non-genetically or experimentally induced nonspontaneous diabetes models, which further includes diabetic models induced by treating with chemicals, or dietary or surgical manipulations and combinations, recently by genetic engineering/molecular biological techniques including transgenic and knock-out rodent models. Non-genetic models are more popular compared to genetic models due to lower cost, wider availability, easier to induce diabetes, and of course easier to maintain compared to genetic models. Apart from this classification, the animals are further sub categorized into models with or without obesity. Entire list of animal models of T2D along with their advantages and disadvantages, as described by Srinivasan and Ramarao, are enlisted in Table 1 and Table 2 respectively.

Table 1: List of Animal Models of T2D.

Animal Model Class	T2D Models	References
Genetically induced spontaneous Diabetic Model	**Obese Models-**	
	TSOD mice	Suzuki et al.,1999
	M16 mice	Allan *et al*.,2004
	Zucker fatty rat	Durham and Truett,2006
	SHR/N-cp rat	Velasque et al.,2001
	JCR/LA-cp rat	Clark and Pierce,2000
	Obese rhesus monkey	Kemnitz et al.,1994
	Monogenic-	
	ob/ob mice (Lep$^{ob/ob}$ mice)	Drel *et al*.,2006
	db/db mice (Lepr$^{db/db}$ mice)	Kobayashi *et al*.,2000
	KK/A$^{\gamma}$ mice	McIntosh and Pederson,1999
		McNeil,1999
	ZDF rat	Peterson *et al*.,1990
	Polygenic-	
	KK mice	Reddi and Camerini-Davalos,1988
		Thorburn *et al*.,1995
	NZO mice	Andrikopoulos *et al*.,1993
		Haskell *et al*.,2002
	NONcNZO10 mice	Pan *et al*.,2005
		Cho *et al*.,2007
	NoncNZO10/LtJ mice	Kim and Saxton,2012
	TallyHo/Jng mice	Zhu et al.,1996
	OLETF rat	
	Non Obese Models-	
	Cohen diabetic rat	Weksler-Zangen *et al*.,2001
	GK rat	Goto and Kakizaki,1981
	Torri rat	Shinohara *et al*.,2000
		Masuyama *et al*.,2003
	C57BL/6 (Akita) mutant mice	Yoshioka *et al*.,1997
	ALS/Lt mice	Mathews *et al*.,2002
		Mathews *et al*.,2004
Transgenic/Genetically induced beta cell dysfunction Model	hIAPP mice	Matveyenko and Butler, 2006
	AKITA mice	Chen *et al*., 2011
Diet/nutrition induced Diabetic Model	**Obese Models-**	
	Sand rat or Desert gerbil	Kaiser *et al*.,2012
	C57/BL 6J mice	Surwit *et al*.,1988
	Tuco-Tuco mice	
	Spiny mice	Shafrir *et al*., 2006
	Nile grass rat	Noda *et al*., 2010
Chemically induced Diabetic Model	**Obese Models-**	
	GTG treated obese mice	Le Marchand Brustel Y et al.,1978
		Le Marchand Brustel Y,1999
	Non Obese Models-	
	Adult ALX or STZ rats, mice	Srinivasan and Ramarao,2007
	Neonatal ALX or STZ rat, mice	Islam and Loots,2009
	HF diet-fed STZ rat, mice	
	NCT/STZ rat, mice	Wang *et al*.,2007

Surgical Diabetic Model	**Obese Models-** VMH lesioned dietary obese diabetic rat **Non Obese Models-** Partial pancreatectomized animals *e.g.* dog, primate, pig, rabbit & rats	Axen *et al*.,1994 Sasaki et al.,2000
Transgenic/knock-out Diabetic Model	**Obese Models-** β_3 receptor knockout mice Uncoupling protein (UCP1) knock-out mice **Non Obese Models-** Transgenic or knock out mice involving genes of insulin and insulin receptor and its components of downstream insulin signaling *e.g.* IRS-1, IRS-2,GLUT-4, PTP-1B and others PPAR-γ tissue specific knockout mice Glucokinase or GLUT2 gene knockout mice	Grujic *et al*.,1997 Vidal-Puig *et al*.,2000 Srinivasan and Ramarao,2007 Zhang *et al*.,2004
Other Models	IUGR Models MSG Models	Simmons *et al*.,2001 Vuguin *et al*.,2004 Nagata *et al*.,2006

KK: Kuo Kondo; KK/A^y: Yellow KK obese; VMH: Ventromedial hypothalamus; ZDF: Zucker diabetic fatty; NZO: New Zealand obese; TSOD: Tsumara Suzuki obese diabetes; SHR/N-cp: Spontaneously hypertensive rat/NIH-corpulent; JCR: James C Russel; OLETF: Otuska Long Evans Tokushima fatty; GTG: Gold thioglucose; ALX: Alloxan; STZ: Streptozotocin; GLUT: Glucose transporter; IRS: Insulin receptor substrate; GK: Goto-Kakizaki; PPAR: Peroxisome proliferator activated receptor, PTP: Phosphotyrosine phosphotase; ALS: Alloxan sensitive; $Lep^{ob/ob}$ mice: Leptin deficient obese; $Lepr^{db/db}$ mice: Leptin receptor deficient diabetic; hIAPP: Human islet amyloid polypeptide; HF: High fat; NCT: Nicotinamide; IUGR: Intrauterine growth retardation; MSG: Monosodium glutamate.

Genetically induced spontaneous Diabetic Model-

This T2D model may be obtained from the animals with one or many genetic mutations transmitted from generation to generation (*e.g.*, *ob/ob*, *db/db* mice) or it may get selected from non-diabetic outbred animals by repetitive breeding over several generations (*e.g.*, GK rat, TSOD mice). Generally, they inherit diabetes due to single (Monogenic) or multiple gene defects (Polygenic). The metabolic particularities resulting from monogenic diabetes may arise due to dominant gene (*e.g.*, KK/A^y mice) or recessive gene (db/db mice, ZDF rat) or it can be of polygenic origin (*e.g.*, KK mice, NZO mice) (Ktorza *et al*.,1997) .The interaction between environmental and multiple gene defects has been found in majority of T2D case in human beings, though certain diabetes subtype also exist with well defined cause [*i.e.*, maturity onset diabetes of youth (MODY) due to defect in glucokinase gene] and this monogenic defect may cause T2D only in few cases. Thus, it has been found that polygenic models represent the human condition more closely as compared to monogenic models (McIntosh and Pederson, 1999).

Monogenic Models-

Though monogenic mutation are rarely responsible for obesity in humans, these monogenic models of obesity are usually used in T2D research. Mice defective in leptin signaling are most widely used monogenic models of obesity.

Leptin is responsible for inducing satiety, and thus, a dearth of functional leptin in these animals causes hyperphagia and subsequently obesity. These models include the Lep **ob/ob** mice, which is deficient in leptin and the Lepr **db/db** mouse and Zucker Diabetic Fatty (ZDF) rat, which are deficient in the leptin receptor. These models are most often tested for new therapies of T2D (Yoshida *et al*., 2010; Gault *et al*., 2011; Park *et al*., 2011).
Some already established monogenic models of obesity are *ob/ob* mice ($Lep^{ob/ob}$ mice), *db/db* mice ($Lepr^{db/db}$ mice), KK/A^{γ} mice, ZDF rat.

Polygenic Models-
Polygenic models of obesity might provide a more precise T2D model in case of humans. Different polygenic mice models of obesity, glucose intolerance and diabetes exist, allowing the study of different genotypes and susceptibilities. Apart from this, the male sex bias is more extreme in these polygenic models (Leiter, 2009). It has been found that these polygenic models have been already useful in a wide variety of studies that have targeted to reverse the symptoms of T2D (Chen *et al*., 2009; Fukaya *et al*., 2009; Guo *et al*., 2010; Mochizuki *et al*., 2011; Yoshinari and Igarashi, 2011), to understand more about the interplay of obesity and glucose homeostasis (Kluth *et al*., 2011) (Jurgens *et al*., 2007) or to study diabetic complications (Cheng *et al*., 2007; Fang *et al*., 2010; Buck *et al*., 2011; Lee *et al*., 2011a). Some already established polygenic models of obesity are KK mice**,** NZO mice, NONcNZO10 mice, NoncNZO10/LtJ mice, TallyHo/Jng mice, OLETF rat.

Genetically induced beta cell dysfunction Models-
The beta cell plays a vital role in the development of T2D as well as plays a crucial role in less common classifications of diabetes such as maturity onset diabetes of the young (MODY), gestational diabetes, neonatal diabetes and other beta cell syndromes such as hyperinsulinism. Therefore, these beta cell models are highly appropriate in understanding pathways that can lead to the inefficient beta cells to secrete appropriate amounts of insulin. Such models are used by introducing genetic manipulations such as Kir6.2 mutations to study K channel function (Girard *et al*., 2009) or glucose kinase mutations to understand the glucose sensor function in beta cells (Fenner *et al*., 2011). Such studies can increase our knowledge of beta cell function. However, it was found in the study that the same mutation in humans and mice resulted in different symptoms in the same as recently shown by Hugill *et al*., where a mutation in Kcnj11 (encoding a subunit of the K ATP channel) caused insulin hypersecretion and hypoglycaemia in the patient, but glucose intolerance and reduced insulin secretion in mice (Hugill *et al*., 2010).

Diet/nutrition induced Diabetic Models-
Some animal models exist in which T2D is induced neither by chemicals nor by genetic defect, instead by changes in their diet composition. Few important models of the same are Sand rat, Tuco-Tuco and Spiny mouse (Shafrir, 2003).

Chemically induced Diabetic Models-
These diabetic models are common in explicating the probable role of environmental factors involved in the endocrine pancreatic destructive processes, resulting in subsequent T2D development. Few important models of the same are GTG treated obese mice, Adult alloxan/streptozotocin-induced models and Neonatal alloxan/streptozotocin-induced models.

Surgical Diabetic Models-
This model is made by complete or partial pancreatectomy in animals used for the induction of T2D. Earlier, the diabetic dog model discovered by Oskar Minkowski through surgical complete pancreatectomy has been considered to be the first diabetic animal model and is hardly now used for the research (Ozturk *et al*., 1996). Now, presently different combination methods of partial pancreatectomy on non rodents are at times utilized in T2D research.

Transgenic/knock-out Diabetic Models-
Now a days, transgenic technique is attaining thrust as it offers excellent opportunity for investigation of role of specific gene products and its mechanisms maybe involved in disease conditions under its own physiological (comparitively to *in vitro*) environmental conditions. These transgenic animals are usually helpful in getting insights to gene regulation and development, pathogenesis, treatment of disease and finding new targets for that. Generally, transgenic animals (particularly mice) are made by transferring and altering the site or expression level of of functional gene (transgene) or by deleting specific endogenous genes (knockout) or by placing them under the control of alternate promoter regions (Livingston,1999).
Some good reviews are already available in the literatures describing about the various models of the same (Kadowaki,2000;Gray *et al*.,2005;Butler *et al*.,2004;Nandi *et al*.,2004;Plum *et al*.,2005). These models are developed

for getting into the role of associated genes and their effects on peripheral insulin action such as insulin receptor, IRS-1, IRS-2, GLUT 4, PPAR-g and TNF-a as well as in insulin secretion such as GLUT-2, GK, IAPP and GLP-1 and also in hepatic glucose production (PEPCK expression) associated with T2D development. In addition to this, combination or double knockout mouse models including defect in insulin action and insulin secretion (*e.g.*, IRS1 $^{+/-}$ /GK $^{+/-}$ double knockout) have been produced which clearly demonstrate the mechanisms associated with insulin resistance development and beta cell dysfunction resulting in overt hyperglycemic state in human T2D. In recent times, scientists are succeeded in developing tissue specific knockout mouse models, thus allowing future insight into the insulin action with respect to particular target tissues (muscle, adipose tissue and liver) related with insulin resistance and T2D(Kadowaki,2000;Gray *et al*.,2005;Butler *et al*.,2004;Nandi *et al*.,2004;Plum *et al*.,2005). In future, it is expected that more knock-out models of interest for the study of diabetes will be made due to the efforts of the International Knockout Mouse Consortium (IKMC), which aims to mutate all protein-coding genes in the mouse (http://www.knockoutmouse.org/).

Obese and Non Obese Models-

As both T2D and obesity are closely linked, most of the existing T2D animal models are obese. Obesity may arise as a result of naturally occurring mutations or genetic manipulation. So, these comprise of models that have obesity either due to rare monogenic mutation or polygenic mutation. On the other hand, obesity can also be induced by high fat feeding.

At the same time, it's not that all T2D patients are obese, and thus, it is important to study lean animal models of T2D also. These comprise of models that have beta cell inadequacy, which can ultimately leads to overt T2D in humans (Weir *et al*., 2009). Entire list of different obese and non-obese models studied till now have been summarized in Table 1.

Non Rodent Models-

T2D research is not limited to smaller animals, instead some larger animals have also been utilized. For instance, T2D in cats bear a resemblance to the human condition in several aspects like T2D in cats progresses in middle age, is related to obesity and insulin resistance, and subsequent beta cell loss also occurs similar to the human (O'Brien, 2002). Moreover, cats are also among one of the few species other than humans and macaques that form amyloid in islets, just allowing them to become a good model for studying islet amyloidosis (Henson and O'Brien, 2006). Old-world non-human primates can also develop T2D, which is almost similar to the human condition, thus allowing it to be used as a model (Wagner *et al*., 2006). Furthermore, several pig strains have a phenotype resembling T2D (Bellinger *et al*., 2006). Recently, a novel model of obesity and mild T2D has been developed in the dog (Ionut *et al*., 2010) by involving a high-fat diet with STZ.

Table 2: Pros and Cons of different classes of T2D animal models.

Model Class	Benefits	Drawbacks
Genetically induced spontaneous Diabetic Model	Shows resemblance to human T2D and is developed spontaneously involving genetic factors. Mostly of inbred lines, in which the genetic background is homogeneous and environmental factors can be regulated, provides easy genetic dissection. Require small sample size and result variability is minimum.	Highly linear animal, monogenic inheritance, homogenous and the diabetes developed is highly genetically determined unlike heterogeneity evident in humans. Expensive and limited supply. Requires insulin treatment in later stage for survival as mortality is noticed due to ketosis in animals with brittle pancreas(eg.db/db, ZDF rats, P.obesus, etc.) Require proper maintenance.
Diet/Nutrition induced Diabetic Model	Obesity associated diabetes can be developed via overnutrition as observed in diabesity syndrome of human population	Generally requires long duration of dietary treatment. Not suitable for screening antidiabetic

	Other vital organs can be avoided from the toxicity of chemicals.	agents on circulating glucose parameter as no frank hyperglycemia develops upon simple dietary treatment in genetically normal animals.
Chemically induced Diabetic Model (Adult ALX or STZ Model Neonatal ALX or STZ Model HF diet-fed STZ Model NCT/STZ Model)	Selective loss of pancreatic β cells (alloxan/STZ) leaving other pancreatic cells(alpha and delta) intact Animals survives longer due to residual insulin even without insulin treatment. Mortality due to ketosis is less, relatively. Easier to develop, maintain and comparatively cheaper.	Development of hyperglycemia majorly by direct cytotoxic action on the β cells and insulin deficiency rather than consequence of insulin resistance. Chemical induced diabetes are mostly less stable, sometimes reversible because of the spontaneous regeneration of β cells. Hence, requires careful assessment of pancreatic β cells function during long-term experiments. Reduction of body weight in some cases. Other vital organs get affected due to toxic chemicals. High variability of results on development of hyperglycaemia.
Surgical Diabetic Model	Cytotoxic effects of diabetogens on other vital organs can be avoided. Resemblance to human T2D due to reduced islet β cell mass.	Inconvenient technical and post operative procedures Digestive problems noticed(due to excision of exocrine portion and deficiency of amylase enzyme) Loss of alpha islets along with β cells, becomes problematic in regulating hypoglycemia. Higher mortality comparatively.
Transgenic/knock out Diabetic Model	Single gene or mutation on diabetes can be studied *in vivo* Easier dissection of complex genetics of T2D.	Production and maintenance is highly expensive and sophisticated. Regular screening experiments are expensive.
IUGR Model	Reliable approach to develop T2D rodent model by this method.	Cannot be validated by using anti-T2D drugs. Lipid profiles and liver enzymes are not reported.
MSG Model	Easy to develop. Comparitively good model for human T2D because obesity is characteristic trait of this model.	Takes long time to develop. Pancreatic hypertrophy; Hepatocellular alterations and carcinoma; Centrilobular vacuolar degeneration in the liver. Cannot be validated by using anti-T2D drugs.

Table 3: Dosage of various chemical diabetogens in different T2D models.

Chemicals	Species	Dose(s) (mg/kg)	Mode of injection	References
Alloxan	Rat	40-200	Intravenous/ Intraperitoneal	Rerup,1970 Kasiviswanath *et al*.,2005
	Mice	50-200	Intravenous/ Intraperitoneal	Rerup,1970 Sheng *et al*.,2005
	Rabbit	100-150	Intravenous	Rerup,1970 Battell *et al*.,1999
	Dog	50-75	Intravenous	Vogel and Vogel,1997 Rerup,1970
Streptozotocin	Rat	35-65	Intravenous/ Intraperitoneal	McNeil,1999 Rerup,1970 Junod *et al*.,1967
	Mice	100-200	Intravenous/ Intraperitoneal	McNeil,1999 Rerup,1970 Junod *et al*.,1967
	Hamster	50	Intraperitoneal	Miller,1990
	Dog	20-30	Intravenous	Rerup,1970 Battell *et al*.,1999
	Pig	100-150	Intravenous	Grussner *et al*.,1993 Dufrane *et al*.,2006
	Primates	50-150	Intravenous	Dufrane *et al*.,2006 Theriault *et al*.,1999

End-points to be observed in model organism for T2D research –

The most common end-point of measurement while testing therapies in model organism for T2D is blood glucose concentrations. It has already been known that different species tend to have different blood glucose concentrations than humans, and thus, measurements for diabetes in humans cannot be applied in case of animals. For instance, mice tend to have higher blood glucose concentrations than humans, and it has been suggested that a non-fasting blood glucose concentration above 250 mg·dL^{-1} (13.8 mM) or preferably a chronic elevation above 300 mg·dL^{-1} (16.7 mM) is apt to consider a mouse diabetic (Leiter, 2009). But, during fasting, normal mice fasted for 16 h during the entire dark period usually have blood glucose level between 50 and 100 mg·dL^{-1} (2.8–5.6 mM), whereas mice with T2D will have fasting blood glucose levels of about near to 150–300 mg·dL^{-1} (8.3–16.7 mM). Glucose detection in the urine can also be measured as a sign of diabetes. However, other end-points can also depend on the putative mechanism of the drug and the model being used because it has been studied that in models of T2D, the drug used for lowering blood glucose levels may result in weight loss (Knudsen, 2010).

Sometimes, glucose tolerance tests are also used to investigate beta cell function, which helps in the identification of impaired glucose tolerance. This test is usually done after an overnight fast, keeping in mind that such a long fast might induce a metabolic stress and enhances insulin action, thus making this test inappropriate in mice (McGuinness *et al*., 2009), so, a 6 h fast possibly will be preferable. In addition to this, an insulin tolerance test can also be carried out as an approximate measure of insulin resistance, or a more elegant hyperinsulinaemic–euglycemic clamp can be carried out (Declercq *et al*., 2010). Apart from this, insulin sensitivity measures such as homeostasis model index of insulin resistance (HOMA-IR) in rodents (Mather, 2009), pancreas histology (Tian *et al*., 2010), whole pancreas insulin content (Montanya and Tellez, 2009), *ex vivo* islet isolation and insulin secretion (Szollosi *et al*., 2010) are few other end-points that can be studied. The time course of the disease and stage of the disease should also be carefully considered while considering end-points of a study as sometimes, the stage of disease may affect the parameters under measurement. For example, some T2D models had been found to show beta cell expansion and hyperinsulinemia prior to subsequent beta cell failure.

Selecting a suitable model organism for T2D research-

A list of variety of model organisms of T2D are enlisted above, each group having their own advantages and disadvantages. These T2D models can be used for several different purposes including pharmacological testing,

genetics study and understanding disease mechanisms. The model selection should depend on the purpose of the study. It is always very important to consider the mechanisms underlying the hyperglycemia in T2D that might include insulin resistance and/or beta cell failure. Usually to determine whether intervention of any drug can improve symptoms in any given model or not may depend on whether beta cells have failed or not.

The majority of obese T2D models arises either due to genetic or dietary means, coming up with a range of associated pathologies such as dyslipidaemia and artherosclerosis. Instead of these common comorbidities in some humans with T2D, it only represents a part of the diabetic population. At the same time, it should be kept in mind that not all animal models of T2D and strains develop diabetic complications (e.g. the mice strain C57BL/6 is relatively resistant to nephropathy) (Brosius III *et al*., 2009), so intense care should be taken for the same. Some other parameters to be considered while choosing model as different species are strain and species differences, having different susceptibilities to diabetes and treatments.

Preferably, more than one species or strain and gender of the same (Franconi *et al*., 2008) should also be taken into account, as gender bias in different models (e.g. NOD, NZO and TallyHo mice; OLETF, Zucker Diabetic rats) has been described, which is not in the case of humans. Furthermore, gender bias has already been studied in many knock-out and transgenic models of diabetes (Franconi *et al*., 2008), suggesting the most probable mechanism involving effects of sex hormones (Inada *et al*., 2007), although the exact mechanism behind the same has not been clarified yet. On the other hand, effects of sex hormone can be conflicting in different mouse models, for example, male gonadectomy provides protection against diabetes in some models but at the same time, it is unsuccessful or increasing incidence in other models (Franconi *et al*., 2008). Indeed, gender bias has also been found to involve mitochondria and stress responses (Franconi *et al*., 2008).

Models also differ in their physiological relevance, with some models more closely resembling disease development than others. Some extreme models like those of pancreas regeneration are rather extreme, which remains to be elucidated that whether the beta cell expansion mechanism in these models can play a role in humans or not. Certainly, while choosing a model for T2D, it is highly recommended that a range of different models are used to exemplify the human T2D patient's diversity.

Conclusions-

Most animal models described above apparently share similar characteristic features of T2D. None of them represents exactly equal to human diabetes, but each of them acts as vital tool to understand the mechanisms underneath the evolution of T2D in humans. Hence, precaution should be taken into account for the interpretation of the results obtained from these animal models to humans. It is particularly important to note that some animal models are better suited to screen particular class of anti-diabetic compounds. The use of smaller animal models such as mice, rat will reduce the expense for testing of many compounds in the industrial research environment while some advanced studies requiring large blood and tissue samples, may be fulfilled by using animals with large body size such as rat or other non-rodents. Furthermore, animal model is particularly selected depending on the investigator's choice like particular strain availability, aim of the research work, type of drug to be used, institutional financial and facility resources in the T2D research. But, there are some limitations like cost, practical complications, extreme care and ethical considerations associated with the use of large/non rodent animal species (*viz.*, pigs, dogs and non-human primates).

Experimentally induced rodent models of T2D has been developed by making use of several approaches by different research groups. Out of them, the earliest T2D rodent models were developed by using intraperitoneal injection of either alloxan or STZ, which rapidly induces diabetic state, thus making it effective method for developing hyperglycemia and abnormal lipid profiles. Moreover, it is also used for screening antidiabetic agents due to its low cost, availability and short time taken by it to develop. But, this model does not always represent human T2D effectively due to a lack of insulin resistance property. Out of the various T2D models discussed in this review, the HF diet-fed STZ/alloxan, HF diet-fed NCT/STZ, neonatal STZ and IUGR models are, in our opinion, the best suited for studying T2D, as they develops a diabetic state in a relatively short time span; they best represent the T2D state associated pathogenesis in humans; and they develop a stable T2D state that can be maintained for relatively longer time span. Thus, these models are useful for the study of long-term/chronic complications associated with T2D. On the other hand, other models may also be considered for research depending on the specific applications. For instance, the partial pancreatectomy models for studying β-cell dysfunction; the long-term HF diet-fed model for studying impaired glucose tolerance and obesity induced T2D; the HF diet-fed STZ, NCT/STZ and neonatal STZ models for pharmacological drug, food and phytochemical trials, and the neonatal STZ model for studying long-term diabetic complications. Even though not clear as yet, future insight into it can prove the utility of remaining studied T2D models for other diabetic complications. At the same time, detailed studies for the same are also instantly required for

better understanding of the disease mechanisms in human conditions along with discovery of new targets and drugs for T2D treatment.

References-

Allan MF, Eisen EJ, Pomp D. The M16 mouse: an outbred animal model of early onset polygenic obesity and diabesity. *Obes Res* 2004; *12* : 1397-407.

Andrikopoulos S, Rosella G, Gaskin E, Thorburn A, Kaczmarczyk S, Zajac JD, *et al*. Impaired regulation of hepatic fructose-1,6-bisphosphatase in the New Zealand obese mouse model of NIDDM. *Diabetes* 1993; *42* : 1731-6.

Bailey CJ. Drugs on the horizon for diabesity. *Curr Diab Rep* 2005; *5* : 353-9.

Battell ML, Yuen VG, Verma S, McNeil JH. Other models of type 1 diabetes. In: McNeil JH, editor. *Experimental models of diabetes*. Florida, USA: CRC Press LLC; 1999 p. 219-29.

Bellinger DA, Merricks EP, Nichols TC (2006). Swine models of type 2 diabetes mellitus: insulin resistance, glucose tolerance, and cardiovascular complications. ILAR J 47: 243–258.

Brosius FC III, Alpers CE, Bottinger EP, Breyer MD, Coffman TM, Gurley SB *et al*. (2009). Mouse models of diabetic nephropathy. J Am Soc Nephrol 20: 2503–2512.

Buck DW, Jin DP, Geringer M, Jong HS, Galiano RD, Mustoe TA (2011). The TallyHo polygenic mouse model of diabetes: implications in wound healing. Plast Reconstr Surg 128: 427e–437e.

Butler AE, Jang J, Gurlo T, Carty MD, Soeller WC, Butler PC. Diabetes due to a progressive defect in beta-cell mass in rats transgenic for human islet amyloid polypeptide (HIP Rat): a new model for type 2 diabetes. *Diabetes* 2004; *53* : 1509-16.

Chen W, Zhou XB, Liu HY, Xu C, Wang LL, Li S (2009). P633H, a novel dual agonist at peroxisome proliferator-activated receptors alpha and gamma, with different anti-diabetic effects in db/db and KK-Ay mice. Br J Pharmacol 157: 724–735.

Cheng ZJ, Jiang YF, Ding H, Severson D, Triggle CR (2007). Vascular dysfunction in type 2 diabetic TallyHo mice: role for an increase in the contribution of PGH2/TxA2 receptor activation and cytochrome p450 products. Can J Physiol Pharmacol 85: 404–412.

Cho, Y.-R., Kim, H.-J., Park, S.-Y., Ko, H. J., Hong, E.-G., Higashimori, T., … Kim, J. K. (2007). Hyperglycemia, maturity-onset obesity, and insulin resistance in NONcNZO10/LtJ males, a new mouse model of type 2 diabetes. *American Journal of Physiology. Endocrinology and Metabolism*, *293*(1), E327-E336. doi:10.1152/ajpendo.00376.2006

Clark TA, Pierce GN. Cardiovascular complications of noninsulin-dependent diabetes; the JCR:LA-cp rat. *J Pharmacol Toxicol Methods* 2000; *47* : 1-10.

Drel, V. R., Mashtalir, N., Ilnytska, O., Shin, J., Li, F., Lyzogubov, V. V, & Obrosova, I. G. (2006). The leptin-deficient (ob/ob) mouse: a new animal model of peripheral neuropathy of type 2 diabetes and obesity. *Diabetes*, *55*(12), 3335–3343. doi:10.2337/db06-0885

Dufrane D, van Steenberghe M, Guiot Y, Goebbels RM, Saliez A, Gianello P. Streptozotocin-induced diabetes in large animals (pigs/primates): Role of GLUT2 transporter and beta-cell plasticity. *Transplantation* 2006; *81* : 36-45.

Durham HA, Truett GE. Development of insulin resistance and hyperphagia in Zucker fatty rats. *Am J Physiol Regul Integr Comp Physiol* 2006; *210* : R652-8.

Fang RC, Kryger ZB, Buck DW, De la Garza M, Galiano RD, Mustoe TA (2010). Limitations of the db/db mouse in translational wound healing research: is the NONcNZO10 polygenic mouse model superior? Wound Repair Regen 18: 605–613.

Fenner D, Odili S, Hong HK, Kobayashi Y, Kohsaka A, Siepka SM *et al*. (2011). Generation of N-ethyl-N-nitrosourea (ENU) diabetes models in mice demonstrates genotype-specific action of glucokinase activators. J Biol Chem 286: 39560–39572.

Franconi F, Seghieri G, Canu S, Straface E, Campesi I, Malorni W (2008). Are the available experimental models of type 2 diabetes appropriate for a gender perspective? Pharmacol Res 57: 6–18.

Fukaya N, Mochizuki K, Tanaka Y, Kumazawa T, Jiuxin Z, Fuchigami M *et al*. (2009). The alpha-glucosidase inhibitor miglitol delays the development of diabetes and dysfunctional insulin secretion in pancreatic beta-cells in OLETF rats. Eur J Pharmacol 624: 51–57.

Gault VA, Kerr BD, Harriott P, Flatt PR (2011). Administration of an acylated GLP-1 and GIP preparation provides added beneficial glucose-lowering and insulinotropic actions over single incretins in mice with Type 2 diabetes and obesity. Clin Sci (Lond) 121: 107–117.

Girard CA, Wunderlich FT, Shimomura K, Collins S, Kaizik S, Proks P *et al*. (2009). Expression of an activating mutation in the gene encoding the KATP channel subunit Kir6.2 in mouse pancreatic beta cells recapitulates neonatal diabetes. J Clin Invest 119: 80–90.

Gray SL, Dalla Nora E, Vidal-Puig AJ. Mouse models of PPAR-gamma deficiency: dissecting PPAR-gamma's role in metabolic homoeostasis. *Biochem Soc Trans* 2005; *33* : 1053-8.

Grujic, D., Susulic, V. S., Harper, M. E., Himms-Hagen, J., Cunningham, B. a, Corkey, B. E., & Lowell, B.B. (1997).Beta3-adrenergic receptors on white and brown adipocytes mediate beta3-selective agonist-induced effects on energy expenditure, insulin secretion, and food intake. A study using transgenic and gene knockout mice. *The Journal of Biological Chemistry*, *272*(28), 17686–17693. doi:10.1074/jbc.272.28.17686

Grussner R, Nakhleh R, Grussner A, Tomadze G, Diem P, Sutherland D. Streptozotocin-induced diabetes mellitus in pigs. *Horm Metab Res* 1993; *25* : 199-203.

Guo K, Yu YH, Hou J, Zhang Y (2010). Chronic leucine supplementation improves glycemic control in etiologically distinct mouse models of obesity and diabetes mellitus. Nutr Metab (Lond) 7: 57.

Haskell BD, Flurkey K, Duffy TM, Sargent EE, Leiter EH. The diabetes- prone NZO/H1Lt strain. I. Immunophenotypic comparison to the related NZB/B1NJ and NZW/LacJ strains. *Lab Invest* 2002; *82* : 833-42.

Henson MS, O'Brien TD (2006). Feline models of type 2 diabetes mellitus. ILAR J 47: 234–242.

http://www.knockoutmouse.org/

http://www.who.int/mediacentre/factsheets/fs312/en/

Hugill A, Shimomura K, Ashcroft FM, Cox RD (2010). A mutation in KCNJ11 causing human hyperinsulinism (Y12X) results in a glucose-intolerant phenotype in the mouse. Diabetologia 53: 2352–2356.

Inada A, Arai H, Nagai K, Miyazaki J, Yamada Y, Seino Y *et al*. (2007). Gender difference in ICER Igamma transgenic diabetic mouse. Biosci Biotechnol Biochem 71: 1920–1926.

Ionut V, Liu H, Mooradian V, Castro AV, Kabir M, Stefanovski D *et al*. (2010). Novel canine models of obese prediabetes and mild type 2 diabetes. Am J Physiol Endocrinol Metab 298: E38–E48.

Islam, S., & Loots, D. T. (2009). Experimental rodent models of type 2 diabetes : a review, *31*(4), 249–261. doi:10.1358/mf.2009.31.4.1362513

Islam, S., & Wilson, R. D. (n.d.). Chapter 10 Experimentally Induced Rodent Models of Type 2 Diabetes, *933*. doi:10.1007/978-1-62703-068-7

Junod A, Lambert AE, Stauffacher W, Renold AE. Diabetogenic action of streptozotocin. *Proc Soc Exp Biol Med* 1967; *126* : 201-5.

Jurgens HS, Neschen S, Ortmann S, Scherneck S, Schmolz K, Schuler G *et al*. (2007). Development of diabetes in obese, insulin-resistant mice: essential role of dietary carbohydrate in beta cell destruction. Diabetologia 50: 1481–1489.

Kadowaki T. Insights in to insulin resistance and type 2 diabetes from knockout mouse models. *J Clin Invest* 2000; *106* : 459-65.

Kasiviswanath R, Ramesh A, Kumar KE. Hypoglycemic and antihyperglycemic effect of *Gmelina asiatica* LINN. in normal and in alloxan induced diabetic rats. *Biol Pharm Bull* 2005; *28* : 729-32.

Kemnitz JW, Elson DF, Roecker EB, Baum ST, Bergman RN, Meglasson MD. Pioglitazone increases insulin sensitivity, reduces blood glucose, insulin and lipid levels and lowers blood pressure in obese, insulin resistant rhesus monkeys. *Diabetes* 1994; *43* : 204-11.

Kim, J. H., & Saxton, A. M. (2012). The TALLYHO mouse as a model of human type 2 diabetes. *Methods in Molecular Biology (Clifton, N.J.)*, *933*, 75–87. doi:10.1007/978-1-62703-068-7_6

King, A. J. F. (2012). The use of animal models in diabetes research. doi:10.1111/j.1476-5381.2012.01911.x

Kluth O, Mirhashemi F, Scherneck S, Kaiser D, Kluge R, Neschen S *et al*. (2011). Dissociation of lipotoxicity and glucotoxicity in a mouse model of obesity associated diabetes: role of forkhead box O1 (FOXO1) in glucose-induced beta cell failure. Diabetologia 54: 605–616.

Knudsen LB (2010). Liraglutide: the therapeutic promise from animal models. Int J Clin Pract Suppl. 64: 4–11.

Kobayashi, K., Forte, T. M., Taniguchi, S., Ishida, B. Y., Oka, K., & Chan, L. (2000). The db/db mouse, a model for diabetic dyslipidemia: molecular characterization and effects of Western diet feeding. *Metabolism: Clinical and Experimental*, *49*(1), 22–31.

Ktorza A, Bernard C, Parent V, Penicaud L, Froguel P, Lathrop M, *et al*. Are animal models of diabetes relevant to the study of the genetics of non-insulin-dependent diabetes in humans? *Diabetes Metab* 1997; *23* (Suppl 2) : 38-46.

Le Marchand Brustel Y, Jeanrenaud B, Freychet P. Insulin binding and effects in isolated soleus muscle of lean and obese mice. *Am J Physiol* 1978; *234* : E348-58.

Le Marchand Brustel Y. Molecular mechanisms of insulin action in normal and insulin resistant states. *Exp Clin Endocrinol Diabetes* 1999; *107* : 126-32.

Lee MY, Shim MS, Kim BH, Hong SW, Choi R, Lee EY *et al*. (2011a). Effects of spironolactone and losartan on diabetic nephropathy in a type 2 diabetic rat model. Diabetes Metab J 35: 130–137.

Leiter EH (2009). Selecting the 'right' mouse model for metabolic syndrome and type 2 diabetes research. Methods Mol Biol 560: 1–17.

Leiter EH (2009). Selecting the 'right' mouse model for metabolic syndrome and type 2 diabetes research. Methods Mol Biol 560: 1–17.

Livingston JN. Genetically engineered mice in drug development. *J Intern Med* 1999; *245* : 627-35.

Masuyama T, Fuse M, Yokoi N, Shinohara M, Tsujii H, Kanazawa M, *et al*. Genetic analysis for diabetes in a new rat model of non obese type 2 diabetes, Spontaneously diabetic Torii rat. *Biochem Biophys Res Commun* 2003; *304* : 196-206.

Mather K (2009). Surrogate measures of insulin resistance: of rats, mice, and men. Am J Physiol Endocrinol Metab 296: E398–E399.

Mathews CE, Langley SH, Leiter EH. New mouse model to study islet transplantation in insulin dependent diabetes mellitus. *Transplantation* 2002; *2* : 1333-6.

McGuinness OP, Ayala JE, Laughlin MR, Wasserman DH (2009). NIH experiment in centralized mouse phenotyping: the Vanderbilt experience and recommendations for evaluating glucose homeostasis in the mouse. Am J Physiol Endocrinol Metab 297: E849–E855.

McIntosh CHS, Pederson RA. Non insulin dependent animal models of diabetes mellitus.In: McNeil JH, editor. *Experimental models of diabetes*. Florida, USA: CRC Press LLC; 1999. p. 337-98.

McNeil JH. *Experimental models of diabetes*. Florida, USA: CRC Press LLC; 1999.

Miller DL. Experimental diabetes: Effect of streptozotocin on golden Syrian hamster. *Lab Anim Sci* 1990; *40* : 539-40.

Mochizuki K, Fukaya N, Tanaka Y, Fuchigami M, Goda T (2011). Treatment with the alpha-glucosidase inhibitor miglitol from the preonset stage in Otsuka Long-Evans Tokushima Fatty rats improves glycemic control and reduces the expression of inflammatory cytokine genes in peripheral leukocytes. Metabolism 60: 1560–1565.

Montanya E, Tellez N (2009). Pancreatic remodeling: beta-cell apoptosis, proliferation and neogenesis, and the measurement of beta-cell mass and of individual beta-cell size. Methods Mol Biol 560: 137–158.

Nagata, M., Suzuki, W., Iizuka, S. et al. *Type 2 diabetes mellitus in obese mouse model induced by monosodium glutamate*. Exp Anim 2006, 55(2): 109-15.

Nandi A, Kitamura Y, Kahn CR, Accili D. Mouse models of insulin resistance. *Physiol Rev* 2004; *84* : 623-47.

O'Brien TD (2002). Pathogenesis of feline diabetes mellitus. Mol Cell Endocrinol 197: 213–219.

Ozturk Y, Atlan VM, Yildizoglu-Ari N. Effects of experimental diabetes and insulin on smooth muscle functions. *Pharmacol Rev* 1996; *48* : 69-112.

Pan HJ, Reifsnyder P, Vance DE, Xiao Q, Leiter EH. Pharmacogenetic analysis of rosiglitazone-induced hepatosteatosis in new mouse models of type 2 diabetes. *Diabetes* 2005; *54* : 1854-62.

Park JS, Rhee SD, Kang NS, Jung WH, Kim HY, Kim JH *et al*. (2011). Anti-diabetic and anti-adipogenic effects of a novel selective 11beta-hydroxysteroid dehydrogenase type 1 inhibitor,2-(3-benzoyl)-4-hydroxy-1,1-dioxo-2H-1,2-benzothiazine-2-yl-1phenylethano ne (KR-66344). Biochem Pharmacol 81: 1028–1035.

Pendse, J., Ramachandran, P. V, Na, J., Narisu, N., Fink, J. L., Cagan, R. L., … Baranski, T. J. (2013). A Drosophila functional evaluation of candidates from human genome-wide association studies of type 2 diabetes and related metabolic traits identifies tissue-specific roles for dHHEX. *BMC Genomics*, *14*(1), 1. doi:10.1186/1471-2164-14-136

Peterson, R. G., Shaw, W. N., Neel, M.-A., Little, L. A., & Eichberg, J. (1990). Zucker Diabetic Fatty Rat as a Model for Non-insulin-dependent Diabetes Mellitus. *ILAR Journal* , *32* (3), 16–19. doi:10.1093/ilar.32.3.16

Plum L, Wunderlich FT, Baudler S, Krone W, Bruning JC. Transgenic and knockout mice in diabetes research: novel insights into pathophysiology, limitations, and perspectives. *Physiology* 2005; *20* : 152-61.

Ramarao P, Kaul CL. Insulin resistance: Current therapeutic approaches. *Drugs Today* 1999; *35* : 895-911.

Rerup CC. Dugs producing diabetes through damage of the insulin secreting cells. *Pharmacol Rev* 1970; *22* : 485-518.

Shafrir E. Diabetes in animals: Contribution to the understanding of diabetes by study of its etiopathology in animal models. In: Porte D, Sherwin RS, Baron A, editors. *Diabetes mellitus*. NewYork: McGraw-Hill; 2003 p. 231-55.

Sheng XQ, Huang KX, Xu HB. Influence of alloxan-induced diabetes and selenite treatment on blood glucose and glutathione levels in mice. *J Trace Elem Med Biol* 2005; *18* : 261-7.

Shinohara M, Masuyama T, Shoda T, Takahashi T, Katsuda Y, Komeda K, *et al*. A new spontaneously diabetic non obese Torri strain with severe ocular complications. *Int J Exp Diabetes Res 2000; 1 : 89-100.*

Simmons, R.A., Templeton, L.J., Gertz, S.J. *Intrauterine growth retardation leads to the development of type 2 diabetes in the rat.* Diabetes 2001, 50(10): 2279-86.

Srinivasan, K., & Ramarao, P. (2007). Animal models in type 2 diabetes research: an overview. *The Indian Journal of Medical Research*, *125*(3), 451–72.

Suzuki W, Iizuka S, Tabuchi M, Funo S, Yanagisawa T, Kimura M, *et al*. A new mouse model of spontaneous diabetes derived from ddY strain. *Exp Anim* 1999; *48* : 181-9.

Szollosi A, Nenquin M, Henquin JC (2010). Pharmacological stimulation and inhibition of insulin secretion in mouse isletslacking ATP-sensitive K+ channels. Br J Pharmacol 159: 669–677.

Theriault BR, Thistlethwaite JR, Jr, Levisetti MG, Wardrip CL, Szot G, Bruce DS, *et al*. Induction, maintenance, and reversal of streptozotocin-induced insulin- dependent diabetes mellitus in the juvenile cynomolgus monkey(*Macaca fascilularis*). *Transplantation* 1999; *68* : 331-7.

Thorburn A, Andrikopoulos S, Proietto J. Defects in liver and muscle glycogen metabolism in neonatal and adult New Zealand obese mice. *Metabolism* 1995; *44* : 76-82.

Tudies, S., Murea, M., Ma, L., & Freedman, B. I. (2012). REVIEW Genetic and Environmental Factors Associated With Type 2 Diabetes and Diabetic Vascular Complications, 6–22. doi:10.1900/RDS.2011.9.6

Velasque MT, Bhathena SJ, Hansen CT. Leptin and its relation to obesity and insulin in the SHR/N-corpulent rat, a model of type II diabetes mellitus. *Int J Exp Diabetes Res* 2001; *2* : 217-23

Vidal-Puig, a J., Grujic, D., Zhang, C. Y., Hagen, T., Boss, O., Ido, Y., … Lowell, B. B. (2000). Energy metabolism in uncoupling protein 3 gene knockout mice. *The Journal of Biological Chemistry*, *275*(21), 16258–16266. doi:10.1074/jbc.M910179199

Vogel HG, Vogel WH. Drug discovery and evaluation; Pharmacological assays. Heidelberg, Berlin: SpringerVerlag; 1997.

Vuguin, P., Raab, E., Liu, B., Barzilai, N., Simmmons, R. *Hepatic insulin resistance precedes the development of diabetes in a model of intrauterine growth retardation.* Diabetes 2004, 53(10): 2617-22.

Wagner JE, Kavanagh K, Ward GM, Auerbach BJ, Harwood HJ, Jr, Kaplan JR (2006). Old world nonhuman primate models of type 2 diabetes mellitus. ILAR J 47: 259–271.

Wang, H.J., Jin, Y.X., Shen, W., Neng, J., Wu, T., Li, Y.J., Fu, Z.U. Low dose streptozotocin (STZ) combined with high energy intake can effectively induce type 2 diabetes through altering the related gene expression. Asia Pac J Clin Nutr 2007, 16(Suppl. 1): 412-7.

Weir GC, Marselli L, Marchetti P, Katsuta H, Jung MH, Bonner-Weir S (2009). Towards better understanding of the contributions of overwork and glucotoxicity to the beta-cell inadequacy of type 2 diabetes. Diabetes Obes Metab 11 (Suppl. 4): 82–90.

Weksler-Zangen S, Yagil C, Zangen DH, Ornoy A, Jacob HJ, Yagil Y. The newly inbred Cohen diabetic rat. A non obese normolipidemic genetic model of diet induced type 2 diabetes expressing sex differences. *Diabetes* 2001; *50* :2521-9.

Yoshida S, Tanaka H, Oshima H, Yamazaki T, Yonetoku Y, Ohishi T *et al*. (2010). AS1907417, a novel GPR119 agonist, as an insulinotropic and beta-cell preservative agent for the treatment of type 2 diabetes. Biochem Biophys Res Commun 400: 745–751.

Yoshinari O, Igarashi K (2011). Anti-diabetic effect of pyroglutamic acid in type 2 diabetic Goto-Kakizaki rats and KK- A y mice. Br J Nutr 106: 995–1004.

Yoshioka M, Kayo T, Ikeda T, Koizumi A. A novel locus, Mody4, distal to D7Mit189 on chromosome 7 determines early-onset NIDDM in nonobese C57BL/6 (Akita) mutant mice. *Diabetes* 1997; *46* : 887-94.

Zhang YL, Tan XH, Xiao MF, Li H, Mao YQ, Yang X, Tan HR. Establishment of liver specific glucokinase gene knockout mice: a new animal model for screening anti-diabetic drugs. Acta pharmacologica Sinica. 2004;25 (12):1659–65.