Novel insights into the animal models of Diabetes Mellitus

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Abstract

Animal models of disease have historically played a crucial role in the investigation and explanation of disease pathophysiology and identification of drug targets. Moreover, animal models also played important role in the assessment of new drugs *in vivo*.

Diabetes mellitus is a group of metabolic ailments, which is characterized by high blood sugar levels for a longer period. To avoid complications of disease and related economic losses and untoward concerns, prevention and early therapy are therefore necessary. Because of the inadequate usefulness of the current therapies, new therapeutic agents are required to be developed. This paper briefly reviews the animal models of type 1 and type 2 diabetes mellitus, which include natural model of diabetes, models of diabetes induced by chemicals, genetic models of diabetes, physiological model, non-obese model, surgery induced model of diabetes mellitus. Our study found that animal models played an important role in the investigation of the pathophysiology of diabetes mellitus. Also, they helped in the understanding of drug targets and testing new drugs for the mentioned disease.

Introduction

Diabetes mellitus is a chronic metabolic illness, it is characterized by a high blood sugar (hyperglycemia), which is caused by relative or absolute lack of insulin. Over passage of time, diabetes results in damage and dysfunction in multiple organ systems (Table 1). Vascular disease is a major cause of many of the sequelae of this disease. Both microvascular disease (retinopathy, nephropathy, neuropathy) that is specific to diabetes and macrovascular disease (coronary artery disease, peripheral vascular disease) that occurs with increased frequency in diabetes contribute to the high morbidity and mortality rates associated with this disease. Neuropathy also causes increased morbidity, particularly by virtue of its role in the pathogenesis of foot ulcers [1,2]. Diabetes mellitus has two common types, they are type 1 diabetes and type 2 diabetes. Type 1 diabetes is generally thought to be caused by an immune-associated, destruction of pancreatic β cells, which produces insulin [3,4]. Therefore, it is thought be an autoimmune disorder, and its most commonly occurring in children and younger adults [5]. The control of the illness through monitoring the blood glucose, and insulin administration from outside is hard and expensive, which result in

higher or lesser level of blood glucose levels, which is associated with additional systemic disorders [6,7]. The problem in type 2 diabetes (T2D) is the insulin resistance and there is no adequate compensation by the beta cells, together insulin resistance and no compensation leads to a relative insulin deficiency [8]. Therefore, both kinds of endocrine disorders represent quite complex states with the involvement of different bodily systems. Therefore, it is required to carefully choose the animal models for diabetes research. Moreover, animal models play a pivotal role in the exploration of the pathophysiology of diabetes mellitus [9]. Insulin deficiency of type 1 diabetes can be attained in a variety of ways, these ranges from chemical damage to the beta cells to breeding animals (rodents) which develop autoimmune disease (diabetes) spontaneously. A number of animal models for understanding the pathophysiology and the resulting complications of type 2 diabetes mellitus have been developed [10].

Additionally, a number of animal models for type 2 diabetes mellitus have been developed which also has obesity. This reflects the linkage between obesity and diabetes, a condition similar to that of the human type i.e. connection between obesity and diabetes mellitus. These animal models have abnormality in one or more genes that are connected to obesity and insulin resistance, which leads to the development of hyperglycemia [11].

There are a number of factors that affect pathogenesis of diabetes mellitus and its complications; they include obesity, insulin resistance, hyperglycemia, hyperlipidemia [9]. The aim of this study is to review the animal models that are used in the experiments and research of diabetes mellitus (Figure 1).

Table 1. Chronic complications of diabetes mellitus.

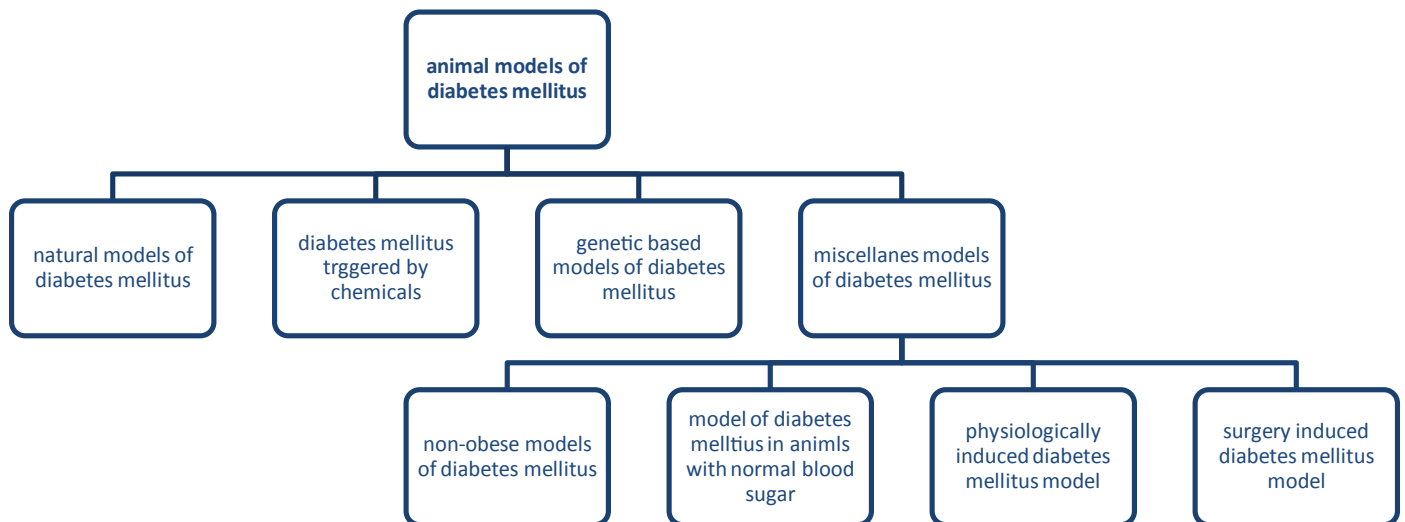| Microvascular disease |
| --- |
| Nephropathy |
| Neuropathy |
| Sensorimotor distal symmetric neuropathy |
| Autonomic neuropathy |
| Focal and multifocal neuropathies |
| Vascular |
| Nonvascular (entrapment) |
| **Macrovascular disease** |
| Coronary artery disease |
| Cerebrovascular disease |
| Peripheral vascular disease |
| **Associated complications** |
| Foot ulcers |
| Infections |

Figure 1. Animal models of diabetes mellitus.

The animal models used in the pharmacological experiments are classified as follows:

Natural models of diabetes mellitus

These models are based on the reality that they develop diabetes mellitus without using alloxan or streptozotocin and thus allowing for investigating the actions of antidiabetic phytoconstituents [12]. There are a number of genetic animal models of diabetes for instance Goto-Kakizaki, which is model for type 2 diabetes mellitus. This model is developing spontaneously by selective breeding over many generations [13]. For producing animal model of type 1 diabetes mellitus, animals develop diabetes between 12 and 30 weeks of age, while in some models like BB rats, it take 3 months to develop diabetes mellitus type 1. An important property of these models is that they can be used to study complications of diabetes mellitus like atherosclerosis and test the effect of drugs [14,15].

Diabetes mellitus models triggered by chemicals

There are some chemicals, which can be used to induce diabetes. These chemicals are streptozotoicn and alloxan. These two diabetogenic chemicals accumulate in the beta cells of the pancrease. The help of glucose transporter 2 mediates this action. The methyl nitrsourea moiety of the streptozocin is responsible for its cytotoxic activity on the pancreatic beta cells. This moiety alkylates DNA of the mentioned cells, resulting in the fragmentation of DNA [15]. Some studies report that diabetes mellitus induced by strepotozocin can improve the cardiac recovery from ischemia repserfusion [16]. Additionally, it decreases the occurrence of cardiac arrhythmia [17,18]. On the contrary, there are some published studies, which are reporting that diabetes induced by streptozotocin, couldn't decrease the infarct size, even it can't prevent the occurrence of arrhythmia [19-23]. Also it leads to the enlargement of the infarct size. Alloxan is another diabetogenic chemical, it leads to the pathogensis of diabetes mellitus through two different actions. It inhibits the enzyme glucokinase, thus it inhibits glucose induced insulin secretion. Moreover, alloxan induces diabetes through the production of reactive oxygen speices and subsequent beta cells' necrosis [15].

Genetic based models of diabetes

Zucker diabetic fatty rats

These rats are discovered in the year 1961. They have mutated leptin receptor, which leads to the hyperphagia, as a result the rats become obese by fourth weeks of age [24]. These rats also have hyperinsulinemia, hyperlipidemia, hypertension, as well as compromised glucose tolerance. The development of type 2 diabetes in male rats (after feeding with high-energy diet) is attributed to the homozygous mutation that occurs in the leptin receptor [25]. After 3 weeks up to two months of age, the animals develop insulin resistance as well as glucose intolerance. Between 2 and 2.5 months of age they will be clearly developing diabetes. In this model the hyperplasia of the Islet of langarhans is contributing to the development of high blood insulin levels [26].

In obese rats, the level of cholesterol and trigeglycerides is higher than slim rats. These high levels of lipids and increased lipid metabolism causes lipotoxicity in the skeletal muscle as well as in the panceatic islet cells [27–29]. These products resulted from the lipid metabolism is attributed to the obesity complications, resistance to insulin, cardiovascular problems and diabetes. These metabolic products disrupts the cell funtions, eventually they cause programmed cell death i.e. apoptosis [26,29].

Transgenic and knock out models of diabetes mellitus

These animal models are produced either through transfer of gene from diabetic animal to normal animal (transgenic), or they are generated by removing the normal gene (knock out) required for making enzymes needed for glucose metabolism [30]. These animal models can be produced only in those labs where the sophisticated equipment and techniques are available.

Miscellaneous models of diabetes mellitus

Non-obese diabetic mouse model

This model was developed in 1974 in Osaka, Japan at Shinogi laboratories. In this model the animals develop insulitis at the age of third or fourth weeks. This period is called prediabetic time, the change occurs in this stage is the CD4+ and CD8+ lymphocytes infiltration into

the islet cells [31]. Additionally natural killer cells and B-lymphocytes also exist their [32].

While infiltrated the immune cells into the islets of langarhans, at the age of 4-6th weeks, they attract CD4+ and CD8+ subsets, which are essential for development of diabetes. The incidence of insulitis causes the beta cells to destroy. Diabetes usually appears after 90% of the pancrease insulin is lost at the age of 10-14 weeks, diabetes can develop even up to the 30 weeks of life [33].

After the appearance of diabetes, mice loses weight rapidly, thus they require treatment with insulin. The non-obese diabetic mice model is used to study type 1 diabetes mellitus. Moreover, in this model the animals develop spontaneous disease similar to human beings. This model served in the pathological understanding of diabetes, including the knowledge about auto antigens and biomarkers similar to human beings, which helped in developing antidiabetic medicines [34].

In the nonobese mice as well as in the human beings the genetic factor that renders susceptibility to type 1 diabetes mellitus is MHC (major histocompatibility complex), [35,36]. More than forty genetic loci are present which render non-obese mice as well as the humans susceptible to type 1 diabetes, including genes relevant to immune system and pancreatic beta cells function [37].

Dendritic cells, macrophages and neutrophils infiltrate the pancrease of the non-obese diabetic animals at the age of three weeks [38-40].

Several studies reported that MHC class-II proteins in non-obese mice and in the human beings are similar structurally, this confer both of them to be susceptible or resistant to disease [41].

This genetic similarity between human beings and non-obese diabetic mice has been used to understand the mechanisms of type 1 diabetes mellitus [42].

It is mentionable, that there are some drugs, which were proved effective in mice in this model, but failed to be effective in human beings [43]. The limitations of this model include the time point of interventions, translating the therapeutics tested in non-obese diabetic mice, dosing translation from mice to animals [44]. Another limitation is that the mice should be kept away from microbial pathogens, otherwise this can result in negative association of the animals with diabetes mellitus [45].

Model of diabetes mellitus in animals with normal blood sugar

In this model, the normal animals can be used to test the effect of anti-diabetic drugs. In addition to other models, this is still used for pharmacological screening of the antidiabetic drugs. This model allows studying the action of drugs with antidiabetic effect in animals with intact pancreas [46]. Additionally, this model is also useful to understand the action of diabetogenic drugs.

Physiologically induced diabetes mellitus model

In this model the blood sugar level of the animal is increased without any damage to the insulin producing gland i.e. pancrease. This method is also known as the tolerance testing of glucose. In this model the animals are fasted overnight. After one day the animals are given glucose (p.o. 1-2.5 g/kg), the blood sugar is monitored periodically. In this model the animals which can be used include the rabbits and/ or male rats [47].

Surgery induced diabetes mellitus model

In this model the pancreas gland is removed through the surgery. The animal species, on which this model is applied, include rats, dogs, monkeys and pigs. There are few number of researches employed this animal model to evaluate the actions of phytoconstituents [46,47,48].

Demerits of this model include, technical and sanitary environmental requirement for surgery, as well as the risk of animal infection, post-operative care etc. For achieving mild to moderate high blood sugar levels, it is required to remove > 80% of pancrease gland. In this regard, if a small portion of the remaining gland is removed it can lead to significant reduction in the blood levels of insulin [46,48].

Conclusion

Diabetes mellitus is a global burden. It can leads to economic and humanistic disasters worldwide. A number of animal models of diabetes are developed at the preclinical level. These models helped to explore the actions of phytoconstituents on the animal species. Additionally, animal models contributed a lot in the exploration of the pathophysiology of diabetes mellitus and its complications. Similarly, these animal models also played an important role in discovering new therapeutic agents for both types of diabetes mellitus. Despite these all achievements made in the field of diabetes mellitus, there are still some shortages and limitations with the existing models. Thus, it is required for the relevant scientists and researchers to discover more models of diabetes that can be useful in understanding the mechanisms of disease and exploration of new therapeutic agents accordingly.

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