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RODENT ANIMAL MODEL FOR RESEARCH IN DIABETES: A MINI-REVIEW

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ABSTRACT

Diabetes mellitus (DM) is classified into two groups: type 1 diabetes (T1DM) and type 2 diabetes (T2DM). T1DM requires insulin treatment. T2DM is characterized by insulin resistance, and it can be treated with variety of pharmacological and other compounds to alleviate or delay diabetes complications. The primary factors in the onset of DM are hyperglycaemia and hyperlipidaemia. Diabetic complications are grouped as macrovascular (heart disease, stroke and others) and microvascular (diabetic nephropathy, neuropathy, and retinopathy). For diabetes research several models have been used. In this review we provide an introduction to *diabetes mellitus* and its complications, currently used rodent animal models in diabetes research, the main results concerning therapeutical agents and the main targets.

Key words: diabetes; complications; animal model; ZDF rats; therapy

INTRODUCTION

Diabetes mellitus (DM) is a serious disease noted for its typical symptoms as hyperglycaemia and relative or complete insulin deficiency (King and Bowe, 2016). It was estimated that the prevalence of diabetic patients worldwide will reach 380 million by 2025 (Ramachadran and Snehalatha, 2010). DM is classified into two types. Type 1 DM or insulin-dependent diabetes mellitus (IDDM) is autoimmune disease caused by T cell-mediated damage of pancreatic β-cells of pancreas. This condition results in total insulin deficiency (Bluestone *et al.*, 2010; Daneman, 2009). It is unclear what triggers the autoimmune response but environmental factors as viral infections, toxins, psychosocial factors are though to play an important role (Akerblom and Knip, 1998). At least 20 genes of the major histocompatibility complex (MHC) are implicated in type 1 diabetes (Adorini *et al.*, 2002). Type 2 DM or non-insulin-dependent *diabetes mellitus* (NIDDM) is characterized as the progressive worsening of insulin resistance, hyperglycaemia (Adeghate *et al.*, 2006; Kleinert *et al.*, 2018) and lack of adequate compensation by pancreatic beta cells (Khan, 2003). There is a strong hereditary component, but obesity and a sedentary lifestyle play an important role in the development of this disease (Ali, 2013; King and Bowe, 2016). Insulin resistance is connected with decrease in insulin receptors and insulin receptor kinase activity, resulted in decreased glucose transporter 4 (GLUT4) translocation due to impaired signalling (Lencioni *et al.*, 2008). While T2DM is a multifactorial and complex disorder, it is clear, that obesity-induced insulin resistance accelerates pancreatic islet destruction and thus the onset of T2DM (Khan *et al.*, 2006). In T2DM overweight and obesity contribute to insulin resistance through several pathways, including an imbalance in the concentrations of hormones (increased leptin and glucagon, reduced adiponectin), increased

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concentrations of cytokines (tumour necrosis factor α, interleukin 6), suppressors of cytokine signalling, other inflammatory signals, and possibly retinol-binding protein (Wellen and Hotamisligil, 2005).

Glucose and insulin metabolism

Generally, hyperglycaemia is a primary factor in the onset of DM. It is unable to efficiently transport glucose from the blood into tissue. Thus, the measurement of plasma glucose level is important in diagnosis (Min and Park, 2010). The lipid profile of T2DM is defined by increased triglycerides level, decrease in high-density lipoproteins and increased very low-density lipoproteins (Therond, 2009). Insulin promotes anabolic processes and inhibits catabolic processes in pancreas, liver, skeletal muscle, adipose tissue and intestines. When glucose concentration exceeds the upper limit of normal range, glucokinase and glucose transporter 2 (GLUT 2) are activated in the pancreas followed by increasing intracellular ATP level. Consequently, ATP-sensitive K+ channels in the membrane of β-cells close, and the plasma membrane depolarizes what opens voltage-dependent Ca^{2+} channels. Then Ca^{2+} ions influx and induce exocytosis of insulin vesicles from pancreatic β-cells into portal circulation (Prentki, 1996). After reaching the liver, insulin stimulates glycogen and triglyceride synthesis, but inhibits glycogenolysis, ketogenesis and gluconeogenesis (Capeau, 2008). Higher insulin concentration suppresses hepatic glucose output and stimulates its uptake by the skeletal muscle and adipose tissue (Khan and Pessin, 2002). The dysfunction of insulin signalling in hepatocytes results in overall insulin resistance in the liver (Valverde *et al.*, 2003).

Insulin stimulates glucose uptake, protein and glycogen synthesis in the skeletal muscle, but inhibits protein degradation and glycogenolysis (Turcotte and Fisher, 2008). The dysfunction of insulin signalling pathways in the skeletal muscle is a factor in the diabetes progression (Assano *et al.*, 2007).

Adipose tissue is responsible for the glucose utilization. Adipocytes secrete pro-inflammatory cytokines as interleukin 6 (IL-6), tumour necrosis factor alpha (TNF-α) and anti-inflammatory cytokines (adiponectin) (Sowers, 2008). A reduced level of adiponectin and increase in IL-6 and TNF-α may induce or worsen insulin resistance in the adipose tissue. Dysfunction in the adipose tissue or adipocytes is associated with T2DM (Bluher, 2009).

Diabetes and its complications

Diabetic complications are acute (ketoacidosis, ketoacidic coma) and chronic (macrovascular, microvascular) (Min and Park, 2010). Macrovascular complications include mainly myocardial infarction, congestive cardiac failure and stroke. These complications account for more than 70 % of diabetic mortality (Hyvarinen *et al.*, 2009). Microvascular complications include diabetic neuropathy, nephropathy and retinopathy (Basit *et al.*, 2004). The most common diabetic complication is diabetic neuropathy (Basit *et al.*, 2004). It is characterized by progressive nerve fibre loss, clinical signs and symptoms as paraesthesia, pain, loss of sensation (Silva *et al.*, 2009). Diabetic retinopathy is a neurodegenerative state resting in structural and functional changes in retina cells (Silva *et al.*, 2009). Diabetic nephropathy is defined by superfluous accumulation of extracellular matrix with thickening of glomerular and tubular basement membranes and an increase in the mesangial matrix, which ultimately progresses to glomerulosclerosis and tubule-interstitial fibrosis (Kanwar *et al.*, 2008). T2DM is closely associated with obesity and it is the main pathological cause of insulin resistance (Khan and Flier, 2000). Abnormalities in other hormones, such as reduced secretion of the incretin glucagon-like peptide 1 (GLP-1), hyperglucagonaemia and raised concentrations of other counter-regulatory hormones, also contribute to insulin resistance, decreased insulin production and hyperglycaemia in T2DM (Stumvoll *et al.*, 2005; Kahn *et al.*, 2006).

Both, T1DM and T2DM ultimately lead to pancreatic β-cells dysfunction (Bonner-Weir *et al.*, 1983). They are associated with long-term complications raised after long exposure to elevated blood glucose concentration. The pathogenesis of the development of this complication can be often more important for the study than the manner in which the animals become hyperglycaemic (King and Bowe, 2016). The uncontrolled hyperglycaemia has harmful impacts on the organs that are pivotal in the homeostasis control and results in the development of diabetes (Fig. 1).

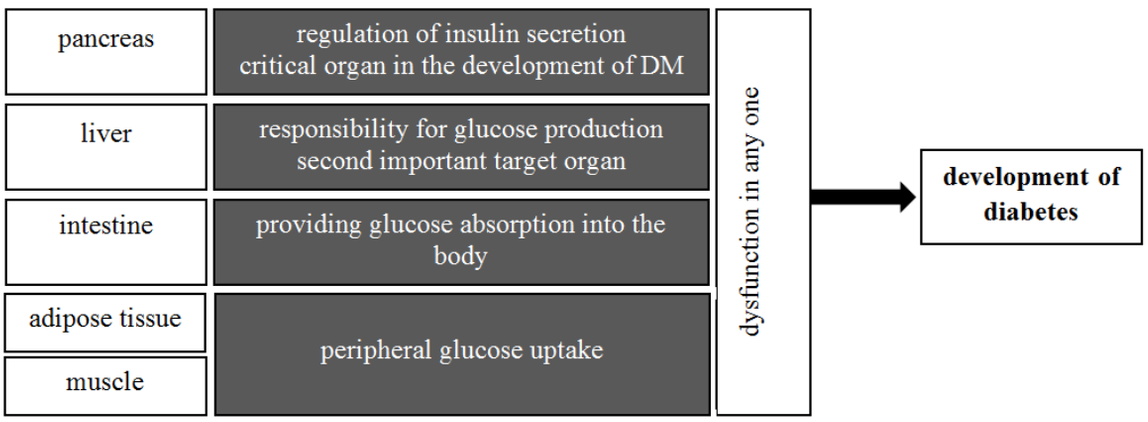

Figure 1. Target organs in development and treatment of DM
(Modified according to Min and Park, 2010)

Current therapeutic strategies for T2DM are limited and include insulin and oral antidiabetic agents that stimulate pancreatic secretion, reduce hepatic glucose production, delay digestion and absorption of intestinal carbohydrates or improve insulin action. These agents, however, suffer from inadequate efficacy and number of adverse effects (Bailey, 2005). In the scientific community the interest is raised to evaluate raw or isolated natural products used in the experimental diabetes study (Table 1). Natural supplements are widely used around the world to treat diabetes (Fröde and Medeiros, 2008).

Rodent animal models of *diabetes mellitus*

An animal model for biomedical research is one in which normative biology or behaviour can be studied, or in which a spontaneous or induced pathological process can be investigated, and in which the phenomenon is one or more respects resembles the same phenomenon in humans or other animal species (Chatzigeorgiou *et al.*, 2009). Diabetes research on humans is not possible, because provocation of DM is strictly impermissible. Therefore, animal models of DM are greatly useful and advantageous in biomedical studies. They promise new insights into human diabetes, new methods of treatment (Srinivasan and Ramarao, 2007) and the utility of therapeutic agents (Chen and Wang, 2005). The existing therapeutic approaches to treat *diabetes mellitus* and obesity, which are saving many lives every day, were discovered, validates and optimized on animal models (Kleinert *et al.*, 2018). There are many different animal models of diabetes available including spontaneous, induced and transgenic models (King and Bowe, 2016). Most appropriate model for diabetes research is rodent model. Rodents are easy to handle, small, economically effective and have a short generation interval (Min and Park, 2010). Animal models used for investigation of T1DM are: alloxane-induced, streptozotocin-induced, non-obese diabetic (NOD) mouse models, and bio-breeding (BB) rat model (Kim *et al.*, 1998). Alloxane, a uric acid derivate, which selectively destroys pancreatic β-cells through induction of oxidative stress, what causes insulin deficiency and hyperglycaemia (Rerup, 1970). A nitrosureas derivative isolated from *Streptomyces achromogenes* - streptozotocin (STZ) destroys pancreatic β-cells similarly as alloxane (Yamamoto *et al.*, 1981). Animal models, where the animals spontaneously develop T1DM are NOD mice and BB rats (Makino *et al.*, 1980). STZ is favoured over alloxane because it is more stable and less toxic (Kleinert *et al.*, 2018). Although both methods (alloxane and STZ) continue to be used in diabetes research, they are often criticized as not accurately reflecting the human T2DM phenotype. Thus, many investigators rely on specific rodent strains that model key features of T2D. These genetic models have been widely used to explore the pathophysiology of obesity and T2D, as well as in preclinical drug

development (Bedow and Samuel, 2012).

Rodent model for T2DM includes the genetically altered Zucker diabetic fatty (ZDF) rats, Otsuka Long Evans Tokushima fatty (OLETF) rats, Kuo Kondo (KK) mice, Goto Kakizaki (GK) rats, spontaneously diabetic Tori (SDT) rats, *ob*/*ob*$^{+}$/$^{+}$ mice, and *db*/*db*$^{+}$/$^{+}$ mice (Kim *et al.*, 1998). OLETF rats develop diabetes at around 18-25 weeks of age, mostly males. They suffer from polyphagia, mild obesity, hypertriglyceridemia, hyperinsulinemia and impaired glucose tolerance in 16 weeks of age (Kawano *et al.*, 1992). KK mice exhibit hyperphagia, insulin resistance and hyperinsulinemia. It is a polygenic model of obesity and T2DM (Reddi and Camerini-Davalos, 1988). The *ob*/*ob*$^{+}$/$^{+}$ mice are characteristic by a mutation in the leptin gene, manifested as obesity, hyperglycaemia, impaired glucose intolerance and hyperinsulinemia (Dubuc, 1976). The *db*/*db*$^{+}$/$^{+}$ mice have a leptin receptor mutation and are spontaneously hyperphagic, obese, hyperglycaemic, hyperinsulinemic and insulin resistant within the first month of life (Shariff, 1992). GK rat is a non-obese Wistar sub-strain, which develops type 2 *diabetes mellitus* early in life (Bedow and Samuel, 2012). SDT is inbred strain of Sprague-Dawley rat. Male SDT rats show high plasma glucose levels by 20 weeks, pancreatic islet histopathology, including haemorrhage in pancreatic islets and inflammatory cell infiltration with fibroblasts. Prior to the onset of diabetes, glucose intolerance with hypoinsulinemia is also observed (Sasase *et al.*, 2013). Generally, rats are more appropriate model when compared to the mice as many traits, the genetics and pathophysiology in rats has proven more relevant to human disease (Betz and Conway, 2016).

ZDF rats

In our laboratory we use the Zucker diabetic fatty rat (ZDF) as animal model for the research (Capcarova *et al.*, 2017; Kalafova *et al.*, 2017; Capcarova *et al.*, 2018). ZDF rat is commonly used as a model for the study of diabetes (Cefalu, 2006). ZDF rat was derived through selective breeding of hyperglycaemic obese Zucker rats. Zucker fatty (ZF) rats have spontaneous mutation “obese” (fatty) and it was found in the rat stock of Sherman and Merck, by Zucker, Harriet Bird Memorial Laboratory, Stow, Massachusetts, USA in 1961. ZF rats are resulted from the simple autosomal recessive (fa) gene on chromosome 5 (Srinivasan and Ramarao, 2007). These animals have a mutated leptin receptor leading to hyperphagia and obesity at 4 weeks of age (Philips *et al.*, 1996) along with increased growth of subcutaneous fat depot (Durham and Truett, 2006). It is associated with mild hyperglycaemia, insulin resistance, mild glucose intolerance, hyperlipidaemia, hyperinsulinemia and moderate hypertension (Durham and Truett, 2006). They have impaired glucose tolerance rather than apparently diabetes (Wang *et al.*, 2014). Consequently, a mutation in this strain leads to a sub-strain with an overtly diabetic phenotype - the Zucker diabetic fatty (ZDF) rats (Wang *et al.*, 2014). ZDF rats are less obese than ZF rats having a decreased beta cell mass leading to inability to compensate for severe insulin resistance (Pick *et al.*, 1998). ZDF rats carry an autosomal recessive defect in the β-cell transcription machinery that is inherited independently from the mutation in leptin receptor (*Lepr*). This animal model develops obesity with a severe diabetic syndrome, with sustained and early-onset hyperglycaemia and progression to β-cell death, hyperinsulinemia and premature death (Peterson *et al.*, 1990). ZDF rats appear to develop diabetes because of an inability to increase β-cell mass (Tomita *et al.*, 1992, Cefalu, 2006). This strain is highly useful for the investigation of mechanism of T2DM (Srinivasan and Ramarao, 2007).

There are sex differences in ZDF rats for phenotypes of diet-induced insulin resistance and glucose intolerance. Male rats are the most affected (Nadal-Casellas *et al.*, 2012). On normal chow diet, male ZDF rats develop severe hyperglycaemia and hypoinsulinemia by 4 month of age. Female ZDF rats maintain normal level of glucose and insulin throughout their life, despite developing obesity to a similar extent as the males (Kleinert *et al.*, 2018).

ZDF model is used for diabetic studies. There is no evidence or validation that a natural plant material can serve as a complete replacement for insulin. However, several plants and plant products have been reported to mimic the effect of insulin partially or enhance the effects of very low endogenous insulin concentrations (Eddouks *et al.*, 2012).

CONCLUSION

The investigations of *diabetes mellitus* have a long history. The prevalence of DM increased dramatically over the recent past, and therefore, the further research is required. Animal models for study of DM are needed to uncover and understand pathophysiology of the disease. This is the key to the development of new therapies and treatment. There are many various animal models simulating T1DM or T2DM, and each model is specific and has its own value. However, none of the models completely represents the pathophysiology of diabetes. The use of particular animal model depends on the study scheme.

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