Asian-Aust. J. Anim. Sci.
Vol. 23, No. 5 : 672 - 679
May 2010

www.ajas.info

Therapy of Diabetes Mellitus Using Experimental Animal Models*

T. S. Min and S. H. Park**
National Research Foundation of Korea, Daejeon 305-350, Korea

ABSTRACT : Diabetes mellitus is a worldwide epidemic with high mortality. As concern over this disease rises, the number and value of research grants awarded by the National Research Foundation of Korea (NRF) have increased. Diabetes mellitus is classified into two groups. Type 1 diabetes requires insulin treatment, whereas type 2 diabetes, which is characterized by insulin resistance, can be treated using a variety of therapeutic approaches. Hyperglycemia is thought to be a primary factor in the onset of diabetes, although hyperlipidemia also plays a role. The major organs active in the regulation of blood glucose are the pancreas, liver, skeletal muscle, adipose tissue, intestine, and kidney. Diabetic complications are generally classified as macrovascular (*e.g.*, stroke and heart disease) or microvascular (*i.e.*, diabetic neuropathy, nephropathy, and retinopathy). Several animal models of diabetes have been used to develop oral therapeutic agents, including sulfonylureas, biguanides, thiazolidinediones, acarbose, and miglitol, for both type 1 and type 2 diseases. This review provides an overview of diabetes mellitus, describes oral therapeutic agents for diabetes and their targets, and discusses new developments in diabetic drug research. (**Key Words :** Diabetes, Diabetic Complications, Experimental Animal Models, Therapeutic Agents)

INTRODUCTION

Metabolic syndrome is currently a hot topic in biomedical research. It is characterized by abdominal obesity, lipid abnormalities, glucose intolerance, and hypertension. Patients with metabolic syndrome are at increased risk for developing diabetes, a major disease with high mortality (Nakasone et al., 2009). It is estimated that the number of diabetes patients worldwide will reach 380 million by 2025; Asia, in particular, is experiencing a rapidly emerging diabetes epidemic (Ramachandran et al., 2010). In response to this growing concern, this review evaluated currents trends in diabetes research funding offered by the National Research Foundation of Korea (NRF). The number and value of awards in individual research grant recipients have increased dramatically over the past 3 years (Figure 1), indicating an increase in research priority with increasing disease incidence. In this review, we provide a basic introduction to diabetes mellitus and its complications, followed by a discussion of the currently available experimental models used in diabetes research and the diverse oral therapeutics that have been developed.

Diabetes mellitus is generally classified into type 1 and type 2 diseases. Type 1 diabetes was previously known as juvenile diabetes or insulin-dependent diabetes mellitus (IDDM; Dahan et al., 2009). This condition is caused by T cell-mediated destruction of pancreatic β-cells, resulting in complete insulin deficiency, and it typically displays rapid childhood onset (Daneman, 2009). Type 1 disease accounts for 5-10% of patients with diabetes (Taplin et al., 2008). Type 2 disease, in contrast, was previously referred to as adult-onset diabetes or non-insulin-dependent diabetes mellitus (NIDDM); however, the incidence of early onset type 2 diabetes is on the rise (Moore et al., 2003). Type 2 disease is characterized by insulin resistance and impaired insulin secretion (Edelman, 1998), ranging from

* This Study was supported by Technology Development Program for Agriculture and Forestry, Ministry for Food, Agriculture, Forestry and Fisheries, Republic of Korea. This work was also supported by the Grant of the Korean Ministry of Education, Science and Technology (The Regional Core Research Program/Biohousing Research Institute). This work was also supported by the Biohousing Research Center. The authors acknowledge a graduate fellowship provided by the Korean Ministry of Education and Human Resources Development through the Brain Korea 21 project.

** Corresponding Author: Soo Hyun Park. Bio-therapy Human Resources Center, Department of Veterinary Physiology, College of Veterinary Medicine, Chonnam National University, Gwangju 500-757, Korea. Tel: +82-62-530-2832, Fax: +82-62-530-2809, E-mail: parksh@chonnam.ac.kr

Received December 24, 2009; Accepted January 29, 2010

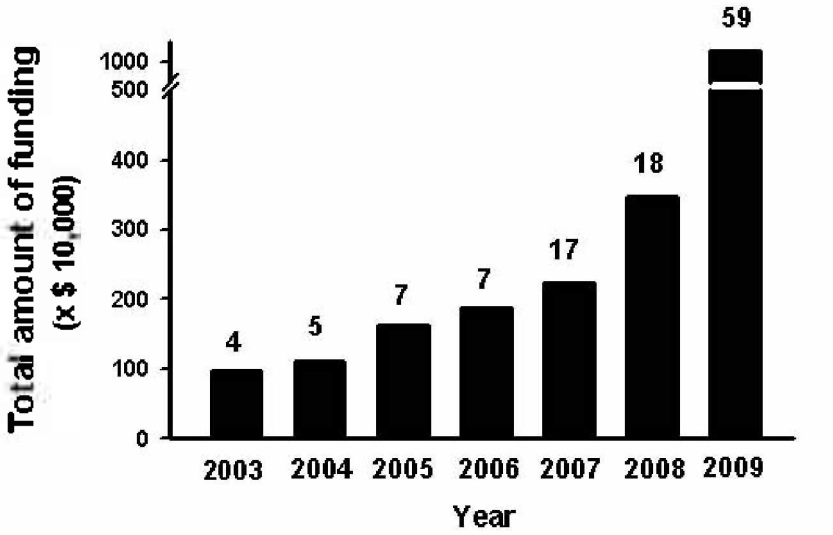

Figure 1. Total amounts and numbers of individual research grant funding sponsored by National Research Foundation of Korea (NRF). Number within figure represent the numbers of individual research grant funding supported by NRF. $1 is equal to 1,200 Korean currency.

predominant insulin resistance with relative insulin deficiency to predominant secretory deficiency with insulin resistance. Type 2 disease accounts for approximately 85-90% of diabetes patients (Adeghate et al., 2006; Sicree et al., 2006; Tan et al., 2008) and is accordingly quite prevalent among Asian patients (Joshi, 2003). Insulin resistance is associated with decreases in insulin receptor number and insulin receptor kinase activity, leading to post-receptor defects (*i.e.*, decreased glucose transporter 4 translocation due to impaired signaling). Impaired islet β-cell function is related to the loss of first-phase insulin secretion, increased proinsulin secretion, defective pulsatile insulin secretion, and the deposition of islet amyloid polypeptide (Sacks et al., 1996; Lencioni et al., 2008). In this review, we focus on the overview of diabetes mellitus, describes oral therapeutic agents for diabetes and their targets, and discusses new developments in diabetic drug research.

EXPERIMENTAL ANIMAL MODELS OF DIABETES MELLITUS AND THEIR ROLE IN DEVELOPMENT OF THERAPEUTIC AGENTS

Major target organs for the treatment of diabetes mellitus

Hyperglycemia is thought to be a primary factor in the onset of diabetes. As type 1 and 2 diabetics are unable to efficiently transport glucose from the blood into tissues, the measurement of plasma glucose levels is important in diagnosis. Plasma glucose levels exceeding 126 mg glucose/dl in the fasted condition or 200 mg glucose/dl after an oral glucose tolerance test are strong indicators of diabetes (Diabetes Prevention Program Research Group, 2005). Hyperlipidemia is also acknowledged as a potential factor in the onset of diabetes mellitus (Unger et al., 2001; Neeli et al., 2009). The lipid profile of type 2 diabetes mellitus is characterized by increased triglycerides (TGs), decreased high-density lipoprotein cholesterol (HDL-C), and increased very low-density lipoproteins (VLDLs; Elnasri et al., 2008; Therond, 2009). Predisposing risk factors for type 2 diabetes include being overweight or obese, unbalanced diet, and lack of exercise (Qi et al., 2008).

Insulin promotes anabolic processes and inhibits catabolic processes in major organs. The major target organs of diabetes mellitus are the pancreas, liver, skeletal muscle, adipose tissue, and intestines. When the blood glucose concentration exceeds the upper limit of normal (~5 mM; Thorens, 2001; Nolan et al., 2008), glucokinase (Km: 7-9 mM) and glucose transporter 2 (GLUT 2; Km: ~17 mM) are activated in the pancreas, causing the intracellular ATP level to increase. In response, ATP-sensitive K^+ channels in the membrane of pancreatic β-cells close, and the plasma membrane depolarizes. This depolarization opens voltage-dependent Ca^{2+} channels, leading to Ca^{2+} influx and Ca^{2+}-induced exocytosis of insulin vesicles from the β-cells (Ashcroft et al., 1990; Prentki, 1996). Insulin is then released into portal circulation. The islet β-cells of the pancreas are responsive to glucose and nutrient secretagogues. Approximately 50% of secreted insulin is degraded in the liver, and the remaining hormone is processed in other target tissues and the kidney (Fawcett et al., 1993).

The liver is the primary site of glucose and lipid metabolism. Hepatic glucose metabolism includes the

formation of glycogen, the generation of glucose from non-sugar carbon substrates, and the provision of intracellular energy *via* glycolysis (Klover et al., 2004). Fatty acid oxidation and *de novo* synthesis of fatty acids are important processes in hepatic lipid metabolism. After reaching the liver, insulin stimulates glycogen and triglyceride synthesis, but inhibits glycogenolysis, ketogenesis, and gluconeogenesis (Capeau, 2008; Fröjdö et al., 2009). Increased circulating insulin concentrations suppress hepatic glucose output (Roden et al., 2001) and stimulate glucose uptake by skeletal muscle and adipose tissue (Khan et al., 2002). Thus, the liver is a potential target for the control of hyperglycemia and hyperlipidemia (Raddatz and Ramadori, 2007). Hepatic insulin resistance is implicated in the development of diabetes mellitus (Capeau, 2008; Fröjdö et al., 2009). The dysfunction of insulin signaling in hepatocytes, such as that mediated by insulin receptor and insulin receptor substrate (IRS), results in overall insulin resistance in the liver (Valverde et al., 2003).

In skeletal muscle, insulin stimulates glucose uptake, protein synthesis, and glycogen synthesis, but inhibits protein degradation and glycogenolysis (Lanner et al., 2008; Turcotte et al., 2008). It is generally accepted that skeletal muscle is responsible for approximately 75% of insulin-stimulated glucose uptake in the whole body (Phielix et al., 2008). Thus, defects in this tissue make a major contribution to the development of diabetes mellitus (Bjornholm et al., 2005). The dysfunction of insulin signaling pathways in skeletal muscle (*i.e.*, through the disruption of insulin receptor, IRS, and phosphoinositol-3 kinase) is a factor in diabetes progression in both patients and animal models (Zierath et al., 2000; Asano et al., 2007).

Adipose tissue is responsible for glucose utilization. In addition, adipocytes secrete diverse pro-inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α, as well as anti-inflammatory cytokines such as adiponectin (Sowers, 2008). Dysfunction in adipocytes or adipose tissue is associated with insulin resistance and type 2 diabetes (Blüher, 2009). A reduced level of adiponectin and increased levels of IL-6 and TNF-α can induce or exacerbate insulin resistance in adipose tissue (Blüher, 2009).

Diabetes is also associated with a dysfunction of the gastrointestinal tract. The absorption of glucose and lipid occurs in the intestine and has been shown to increase in the small intestine of diabetic animals (Olsen et al., 1970). Furthermore, the intestine acts as a regulator of cholesterol homeostasis in diabetes (Tomkin, 2008). Recently, several investigators demonstrated insulin resistance, induced by protein tyrosine phosphatase-1B, extracellular signal-related kinase, and TNF-α (Federico et al., 2006; Qin et al., 2007), in the intestine.

Diabetic complications

Patients with diabetes mellitus may experience both acute and chronic complications. Acute complications include ketoacidosis and ketoacidotic coma. Chronic complications are generally classified into macrovascular and microvascular complications.

Macrovascular diseases, mainly myocardial infarction, congestive cardiac failure, and stroke, account for more than 70% of diabetic mortality. Diabetes is also associated with increased risk for stroke, which is a common cause of morbidity and mortality in diabetic patients (Hyvärinen et al., 2009). The risk for stroke with high morbidity is significantly increased in patients with type 1 or 2 diabetes (Wolf et al., 1991; Tuomilehto et al., 1996; Rodriguez et al., 1998). Elevated blood glucose is common in the early stages of stroke, and a glucose level greater than 155 mg/dl within 48 h after the onset of stroke is associated with high risk for mortality (Fuentes et al., 2009). Cardiovascular complications, including myocardial infarction, are one of the major causes of death in diabetic patients. Diabetic cardiomyopathy is characterized by abnormal morphological and structural changes in the myocardium and coronary vasculature (Sander et al., 2004). The underlying mechanism involves the excess generation of highly reactive free radicals, largely due to hyperglycemia, which then cause oxidative stress and further exacerbate the development and progression of diabetes and its complications (Mellor et al., 2010).

Microvascular complications include diabetic neuropathy, diabetic nephropathy, and diabetic retinopathy. Diabetic neuropathy is the most common of diabetic complications; up to 50% of patients with type 1 or 2 disease have some form of neuropathy (Basit et al., 2004). Diabetic neuropathy is characterized by progressive nerve fiber loss, with both positive and negative clinical signs and symptoms such as pain, paresthesia, and loss of sensation. Diabetic retinopathy is a neurodegenerative condition resulting in functional and structural changes in all cell types of the retina (Silva et al., 2009). This condition remains a leading cause of blindness in developed countries. Approximately 50% of patients with type 1 diabetes and 30% of those with type 2 diabetes can expect to develop sight-threatening retinopathy (Stefansson et al., 2000). Two major retinal problems are primarily responsible for diabetes-related vision loss: diabetic macular edema and complications from abnormal retinal blood vessel growth (angiogenesis). Secondary to angiogenesis, increased retinal blood flow plays a role in the progression of diabetic retinopathy (Crawford et al., 2009). Approximately 20-30% of all diabetic patients will develop some form of diabetic nephropathy, which may progress from microalbuminuria to overt nephropathy or macroalbuminuria, to end stage renal failure with high mortality (Soldatos et al., 2008). Diabetic

nephropathy is characterized by excessive 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 tubulo-interstitial fibrosis (Kanwar et al., 2008).

Experimental animal models of diabetes mellitus

Animal models of diabetes provide crucial insight into human diabetic disease. Most of the available models are based on rodents, because they are small, easy to handle, and economically advantageous, and have a short generation interval. In this section, we focus on the commonly used rodent models. Rodent models of type I diabetes include the alloxane-induced, the streptozotocin-induced, and the non-obese diabetic (NOD) mouse models and the bio-breeding (BB) rat model. Type 2 diabetic models include the genetically altered Zucker diabetic fatty (ZDF) rats, Otsuka Long Evans Tokushima fatty (OLETF) rats, Goto Kakizaki (GK) rats, spontaneously diabetic Tori (SDT) rats, *ob/ob*$^{+/+}$ mice, and *db/db*$^{+/+}$ mice, which feature insulin resistance and reduced β-cell mass (Kim et al., 1998).

In humans, type 1 diabetes mellitus is characterized by the specific destruction of pancreatic β-cells. Alloxane, a uric acid derivative used to induce type 1 diabetes in rodents, selectively destroys pancreatic β-cells via the induction of oxidative stress, resulting in insulin deficiency and hyperglycemia (Rerup, 1970). Streptozotocin (STZ), a nitrosurea derivative isolated from *Streptomyces achromogenes*, also destroys pancreatic β-cells via the same mechanism as alloxane (Junod et al., 1967; Yamamoto et al., 1981). The NOD mouse and BB rat, which spontaneously develop type 1-like disease, are the two most commonly used animal models. In NOD mice, insulitis develops at 4-5 weeks of age, followed by subclinical β-cell destruction and decreased circulating insulin concentrations. Diabetes typically presents between 12 and 30 weeks of age (Makino et al., 1980). BB rats develop weight loss, polyuria, polydipsia, hyperglycemia, and insulinopenia at approximately 12 weeks of age, often at the time of puberty (Nakhooda et al., 1977).

Both genetically and chemically induced type 2 animal models are available. Obese Zucker rats are the most widely used animal model of genetic obesity. They become noticeably obese between the third and fifth week of life. They also show hyperphagia, insulin resistance, dyslipidemia, mild glucose intolerance, and hyperinsulinemia (Zucker 1962; Zucker et al., 1972). OLETF rats develop diabetes slightly later, at around 18-25 weeks of age, and this trait is inherited mostly in males. They exhibit innate polyphagia, mild obesity, hyperinsulinemia, hypertriglyceridemia, and impaired glucose tolerance at approximately 16 weeks of age (Kawano et al., 1992). Kuo Kondo (KK) mice, a polygenic model of obesity and type 2 diabetes, exhibit hyperphagia, hyperinsulinemia, and insulin resistance (Reddi et al., 1988). They show moderate obesity by 2 months of age and reach maximum weight at 4-5 months. Insulin resistance precedes the onset of obesity. The *db/db*$^{+/+}$ (diabetic) mice possess a leptin receptor mutation and are spontaneously hyperphagic, obese, hyperglycemic, hyperinsulinemic, and insulin resistant within the first month of life; they later develop hypoinsulinemia and hyperglycemia, with peak expression at 3-4 months of age (Shafrir, 1992). The *ob/ob*$^{+/+}$ (obese) mice possess a mutation in the leptin gene, which is manifested as obesity, hyperglycemia, mildly impaired glucose tolerance, and severe hyperinsulinemia (Dubuc, 1976). Of the chemically induced type 2 animal models, STZ-induced diabetic neonatal rats are characterized by hyperglycemia, a reduced number of pancreatic β-cells, and insulin resistance (Bonner-Weir et al., 1981). A single injection of STZ (100 mg/kg, i.p.) can also be used to generate a mouse model of non-insulin-dependent diabetes (Ito et al., 2001). Currently, high-fat diet-fed and low-dose STZ-treated rats are used for type 2 diabetes research (Srinivasan et al., 2005).

Oral therapeutics for diabetes mellitus

The available therapeutic options for diabetes mellitus target several major sites of action. The pancreas, because it regulates insulin secretion, is a critical organ in the development of diabetes mellitus. The liver is responsible for glucose production, making it a second important target organ in the treatment of diabetes. The intestine mediates glucose absorption into the body, whereas adipose tissue and muscle are active in peripheral glucose uptake. Dysfunction in any one of these organs has been implicated in the development of diabetes mellitus. In response, a diverse array of oral therapeutics has been developed.

Sulfonylureas, repaglinide, and nateglinide are insulin secretagogues that stimulate endogenous insulin secretion from the pancreas (Davies, 2002) and are used as hypoglycemic agents for the treatment of type 2 diabetes. These agents also improve insulin sensitivity as a result of improved glucose control. The adverse effects of sulfonylureas include severe hypoglycemia (in the event of an overdose), weight gain, erythema, and hepatic dysfunction (Del et al., 2007). Repaglinide and nateglinide, which are meglitinide analogs, decrease ATP-sensitive K^+ conductance in a glucose-dependent manner. They are taken with meals to prevent postprandial hyperglycemia and to reduce the risk of long-lasting hypoglycemia. Both sulfonylureas and meglitinides can induce weight gain (Purnell et al., 2003).

Biguanides and thiazolidinediones (TZDs) are insulin

sensitizers and enhance insulin action. Biguanides correct elevated hepatic glucose output and inhibit gluconeogenesis and glucose-6-phosphate activity (Cleasby et al., 2004). They also reduce insulin resistance, which is mediated by the activation of 5'-AMP-activated protein kinase in hepatocytes and muscle (Zhou et al., 2001; Musi et al., 2002). However, biguanides do not increase insulin secretion. They have beneficial effects on lipids by reducing TG, total cholesterol, and LDL levels and increasing HDL levels. Biguanides induce weight loss and a decrease in blood pressure, making them appropriate for obese type 2 diabetic patients. TZDs increase insulin sensitivity in liver and muscle, inhibit hepatic glucose output, and ameliorate abnormalities in LDL and HDL (O'Moore-Sullivan, 2002; Ding et al., 2005). They also increase insulin secretion and function as ligands for peroxisome proliferator-activated receptor (PPAR)-gamma, which heterodimerizes with retinoic acid receptor. TZDs increase the number of small adipocytes, which are more sensitive to insulin and more metabolically active than large adipocytes (Hallakou et al., 1997; Yamauchi et al., 2001). They also increase TG storage, primarily in subcutaneous adipose tissue rather than visceral depots, which is better for insulin sensitivity (Nakamura et al., 2001). TZDs stimulate adiponectin expression and production in adipose tissue. Although troglitazone may elicit hepatotoxic side effects, rosiglitazone and pioglitazone do not. TZDs have several other protective effects against cardiovascular diseases (Haffner et al., 2002; Kahn et al., 2006). The adverse effects of TZDs, which are primarily associated with rosiglitazone and pioglitazone, may be weight gain, increased incidence of fractures, and high risk for heart failure (Nissen et al., 2007; Singh et al., 2007; Taylor et al., 2009). Recently, Retnakaran and Zinman (2009) proposed that low-dose TZDs in combination with metformin may provide glycemic durability with a lower risk for side effects such as cardiovascular disease (Retnakaran et al., 2009).

As competitive and reversible α-glucosidase inhibitors, acarbose and miglitol inhibit glucose absorption in the intestine (Van Gaal et al., 1991). They do not produce hypoglycemia, lactic acidosis, or significant weight gain and are effective regardless of age, genetic factors, body weight, and duration and severity of disease (Salman et al., 2001). Acarbose may cause gastrointestinal disturbances such as flatulence, nausea, and diarrhea (Chiasson et al., 2002; Ron et al., 2002).

In addition to oral therapeutics, diet and exercise are essential to the prevention and treatment of type 2 diabetes mellitus (Fallucca et al., 2009; Weltman et al., 2009). Exercise increases muscle glucose uptake and whole body glucose disposal, thus decreasing the risk for developing type 2 diabetes. Exercise also stimulates GLUT4 recruitment to the plasma membrane of skeletal muscle, which is independent of insulin.

Current market for oral therapeutics

In 2005, the world market for anti-diabetic oral therapeutics was approximately 11.8 billion US dollars, and it is thought that this will increase annually. Unfortunately, an oral anti-diabetic agent without side effects has not yet emerged; thus, it is necessary to invest additional resources in the development of better alternatives. A number of new therapeutic agents are expected to appear on the market in the near future; these include a dipeptidyl peptidase IV inhibitor (Gallwitz, 2008), an endocannabinoid receptor antagonist (Lafontan et al., 2007), a glucagon-like peptide-1 receptor agonist (Christensen et al., 2009), a PPAR dual agonist (Ye et al., 2009), several protein kinase C inhibitors (Budhiraja et al., 2009), and sodium glucose transporter-2 (sgLt-2) inhibitors (Katsuno et al., 2007).

CONCLUSIONS

In this chapter, we summarized the basics of diabetes mellitus types 1 and 2 and the most common diabetic complications, both macrovascular and microvascular. We also discussed a number of experimental animal models used in diabetes research, and several oral therapeutics for diabetes. It is important to emphasize that diverse experimental animal models are essential for developing new anti-diabetic agents and for fully investigating promising agents before human clinical trials. It is expected that more therapeutic alternatives will become available with future advances in diabetes research.

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