REVIEW ARTICLE

Clin Pharmacokinet 2008 47 (7) 417-448
0312-5963/08/0007-0417/$48.00/0

Pharmacokinetic/Pharmacodynamic Modelling in Diabetes Mellitus

Cornelia B. Landersdorfer and *William J. Jusko*

Department of Pharmaceutical Sciences, School of Pharmacy and Pharmaceutical Sciences, University at Buffalo, State University of New York, Buffalo, New York, USA

Contents

Abstract

Diabetes mellitus is a major health risk in many countries, and the incidence rates are increasing. Diverse therapeutic agents are applied to treat this condition. Since 1960, numerous mathematical models have been developed to describe the glucose-insulin system, analyse data from diagnostic tests and quantify drug effects. This review summarizes the present state-of-the-art in diabetes modelling, with a focus on models describing drug effects, and identifies major strengths and limitations of the published models.

For diagnostic purposes, the minimal model has remained the most popular choice for several decades, and numerous extensions have been developed. Use of the minimal model is limited for applications other than diagnostic tests. More mechanistic models that include glucose-insulin feedback in both directions have been applied. The use of biophase distribution models for the description of drug effects is not always appropriate. More recently, the effects of various antidiabetic agents on glucose and insulin have been modelled with indirect response models. Such models provide good curve fits and mechanistic descriptions of the effects of antidiabetic drugs on glucose-insulin homeostasis. These and other types of models were used to describe secondary drug effects on glucose and insulin, and effects on ancillary biomarkers. Modelling of disease progression in diabetes can utilize indirect response models as a disturbance of homeostasis.

Future needs are to include glucose-insulin feedback more often, develop mechanistic models for new drug groups, consider dual drug effects on complementary subsystems, and incorporate elements of disease progression.

Diabetes mellitus is an increasing health problem in many countries. In 2006, the WHO estimated that 180 million people worldwide had diabetes, and that this number will likely be more than doubled by 2030. The number of deaths attributable to diabetes has been estimated at 2.9 million per year.[1] Type 1 diabetes mellitus (T1DM) is characterized by an inability of the body to produce insulin, and has to be treated with exogenous insulin. Type 2 diabetes mellitus (T2DM) reflects both insulin resistance of liver and peripheral tissues, and deficient insulin secretion by pancreatic β-cells.[2] Various oral antidiabetic drugs, as well as insulin, are used for treatment. The factors contributing to the pathophysiology and disease progression of diabetes are not yet fully understood. Long-term complications such as neuropathy, nephropathy and retinopathy are debilitating for patients and result in high healthcare costs. In the US, diabetes was the leading cause of renal failure and new blindness in 2005,[3] and total diabetes costs were estimated at $US174 billion in 2007.[4]

For these reasons, early diagnosis and adequate treatment are important to decrease the long-term adverse effects of diabetes. Mathematical models are needed to better understand the glucose-insulin system, to evaluate diagnostic tests, to study and predict drug effects, and to quantify disease progression. Mechanism-based models are preferable, as they can be used to study the mechanism of action and to predict the effects of new dosage regimens. If the number of time- and cost-intensive long-term clinical trials that need to be performed can be reduced by simulation studies, the time and costs involved in drug development could be considerably decreased, and optimized dosage regimens could be prospectively designed and clinically evaluated. Pharmacokinetic/pharmacodynamic modelling can also help to design better studies, to identify agents with undesirable properties earlier and to decrease attrition rates at late stages of drug development.[5]

Since the 1960s, numerous interesting and useful mathematical models have been developed for various applications and with different characteristics and employing different methods. With this large number of models, it is sometimes difficult to decide which one should be used for a specific purpose. A few reviews are available on certain aspects of diabetes modelling.[6-10] However, no extensive overview has been published that includes the different types of pharmacodynamic models and assesses the mechanisms of drug effects. This review summarizes the state-of-the-art in diabetes modelling, with a focus on models describing drug effects. We sought to identify major strengths and limitations of the published models and further needs and perspectives in diabetes modelling.

We performed a literature search of MEDLINE, EMBASE, the references of published papers and abstracts from various conferences. The models were subcategorized as models for (i) diagnostic tests; (ii) intrinsic interactions of glucose and insulin; (iii) antidiabetic drug effects; (iv) secondary drug effects; (v) ancillary biomarkers; and (vi) disease progression. This review focuses on models for system and parameter estimation and includes some simulation models.

1. The Glucose-Insulin System

Diabetes is a multiorgan disease, which is mainly characterized by a disturbance of glucose-insulin homeostasis. A simplified diagram of the regulation of the glucose system by insulin and other endogenous substances is shown in figure 1. The diagram describes the action of relevant biomarkers by stimulation or inhibition of production or utilization of other endogenous substances. The plasma glucose concentration is increased by hepatic glucose production and absorption from the gut after food intake. It decreases due to utilization by the brain and peripheral tissues such as muscle and fat. One of the key characteristics of the glucose-insulin system is reciprocal feedback between glucose and insulin, i.e. an increase in glucose concentrations stimulates production of insulin, and insulin in turn stimulates utilization of glucose and inhibits production of glucose.

In general, the human body aims to maintain blood glucose concentrations within a narrow range of about 80–115 mg/dL.[2] For example, tissues such as the brain and erythrocytes need a constant supply of glucose. Therefore, in the fasting state, glucose is produced by breakdown of glycogen (glycogenolysis) in the liver. After an extended fasting period, hepatic glycogen stores are depleted. Then glucose is produced mainly from gluconeogenesis in the liver (and to a small extent in the kidneys), utilizing mainly amino acids from muscle tissue, lactate or glycerol. Both glycogenolysis and gluconeogenesis are stimulated by glucagon, a peptide hormone that is secreted from pancreatic α-cells at low blood glucose concentrations (figure 1). Only a low basal insulin secretion occurs at glucose concentrations below about 80 mg/dL.[14] In the fasting state, most of the glucose is taken up by insulin-independent tissues such as the brain, and <20% is taken up by the muscle.[15] During strenuous exercise and anaerobic conditions, glycogen in muscle tissue is broken down to lactate, which is released into the blood and taken up by the liver, where it can be stored as glycogen or converted into glucose by gluconeogenesis. The concept of resynthesis of glucose from lactate in the liver was formulated by Cori and is known as the Cori cycle or the glucose-lactate cycle.[16] The Cori cycle includes the breakdown of glucose to lactate in muscle tissue via anaerobic glycolysis, uptake of lactate into the liver, conversion of lactate to glucose in the liver, and uptake of glucose into muscle tissue again.

After a meal is ingested, complex carbohydrates from the food are split into oligosaccharides which, in turn, are broken down to monosaccharides such as glucose by α-glucosidases in the gut wall (figure 1). Glucose is absorbed into the blood, and glucose concentrations increase. Due to increasing glucose concentrations, secretion of insulin from pancreatic β-cells is stimulated (figure 1).

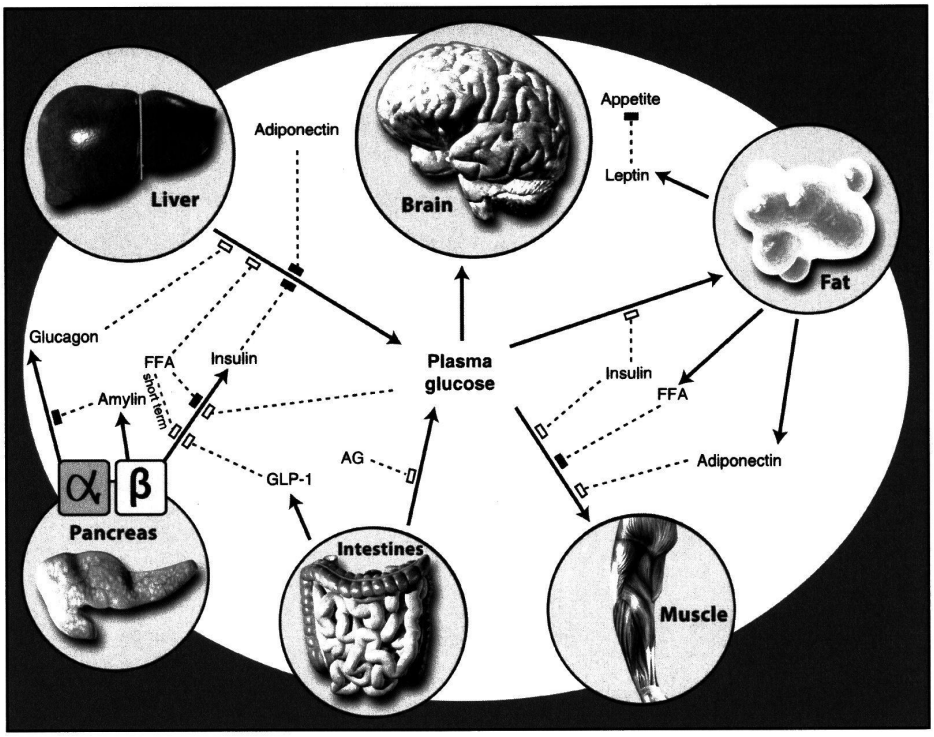

Fig. 1. Simplified diagram of the regulation of glucose metabolism,[11-13] describing the action of relevant biomarkers by stimulation (open bars) or inhibition (solid bars) of production/utilization of other endogenous substances. Many more biomarkers are involved in glucose regulation but have been omitted from this diagram for clarity. **AG** = α-glucosidases; **FFA** = free fatty acids; **GLP-1** = glucagon-like peptide 1.

At increased blood glucose concentrations, more glucose is taken up into β-cells and metabolized to adenosine triphosphate, which results in closure of potassium channels, membrane depolarization, opening of calcium channels, an increase in intracellular calcium concentrations and, eventually, increased insulin secretion.[11]

Insulin is secreted in equimolar amounts with C-peptide (connecting peptide) from β-cells. C-peptide is formed due to cleavage of insulin from pro-insulin. As a large and variable proportion of the secreted insulin is metabolized during the first pass through the liver, and C-peptide is not extracted by the liver, peripheral C-peptide concentrations are often measured to study insulin secretion.[17]

In the short-term, insulin secretion is stimulated by high concentrations of glucose, free fatty acids (FFA)[18,19] (figure 1) and amino acids.[20] However, long-term exposure to elevated concentrations of FFA (lipotoxicity)[19,21] (figure 1), glucose (glucotoxicity)[21] or amino acids[20] results in β-cell failure and decreased insulin secretion. Insulin secretion is also stimulated by incretin hormones, such as glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which are secreted from the gut wall after food intake (see later in this section and in figure 1).

As shown in figure 1, insulin inhibits hepatic glucose production and stimulates glucose utilization by peripheral tissues. Insulin promotes uptake of glucose and storage as glycogen in the liver and skeletal muscle. It also enhances glucose disposal by stimulation of glycolysis in muscle tissue. Liver glycogen is a readily available glucose reservoir for the maintenance of blood glucose concentrations in the fasting state, whereas muscle glycogen is used to store energy for the muscle itself. Glucose uptake by the brain is insulin-independent, as the brain cannot store glucose and therefore needs a permanent supply of energy (as shown in figure 1, where there is no stimulation of brain glucose uptake by insulin). At a high carbohydrate intake, insulin also stimulates conversion of glucose to fatty acids and their uptake into adipose tissue, where they are stored as triglycerides. Insulin also stimulates uptake of amino acids and their storage as protein in skeletal muscle, and uptake of FFA and their storage as triglycerides in adipose tissue. In addition, insulin inhibits hepatic gluconeogenesis by inhibition of key enzymes of this pathway, including phosphoenolpyruvate carboxykinase (PEPCK), which catalyses the rate-limiting step of gluconeogenesis and also inhibits hepatic

glycogenolysis (figure 1). Insulin also inhibits the release of amino acids from skeletal muscle and the release of FFA and triglycerides from adipose tissue.

These insulin actions lead to a decrease in blood glucose concentrations and promote storage of energy in the tissues (anabolic action). Glucagon, conversely, stimulates the release of glucose, FFA and amino acids from the liver, fat and muscle (catabolic action). At high blood glucose concentrations, secretion of insulin is stimulated while glucagon secretion is inhibited, and vice versa at low blood glucose concentrations.

T1DM patients have an absolute deficiency of insulin, whereas T2DM is characterized by impaired insulin secretion and resistance to insulin action in the liver and peripheral tissues. T1DM and T2DM patients who require insulin therapy have elevated postprandial glucagon concentrations,[22] whereas T1DM patients also have fasting hyperglycaemia. In addition, it has been proposed that reduced suppression of glucagon secretion by insulin contributes to impaired glucose tolerance.[23] Insulin deficiency and glucagon excess lead to decreased glucose uptake into cells, increased breakdown of protein and lipolysis. In severe uncontrolled diabetes, the release of large amounts of FFA that are converted to ketone bodies in the liver can result in ketoacidosis.

Amylin is co-secreted with insulin from β-cells. It is a hormone that has been shown to inhibit postprandial glucagon secretion[24] (figure 1). Amylin also acts by delaying gastric emptying and reducing food intake.[22] Therefore, amylin promotes the decrease of high postprandial blood glucose concentrations. Amylin secretion is lacking in T1DM patients and impaired in T2DM patients because of depletion or dysfunction of β-cells.[22,25] In rodents, especially in the fasting state, injection of amylin resulted in increased concentrations of lactate due to enhanced muscle glycogen breakdown. Subsequently, glucose concentrations increased, as lactate is a substrate for gluconeogenesis in the liver.[26,27] Increased concentrations of lactate in human muscle, adipose tissue and plasma, due to lactate release from muscle and adipose tissue, have been shown after glucose ingestion.[28]

After enteral nutrition, the incretin hormones GLP-1 and GIP are secreted from cells in the gut wall (figure 1). The secretion is stimulated by endocrine and neural signals and by direct stimulation of the intestinal cells by digested nutrients. Both GLP-1 and GIP stimulate glucose-dependent insulin secretion from β-cells (figure 1), enhance β-cell proliferation and increase β-cell resistance to apoptosis. In addition, GLP-1 inhibits glucagon secretion, slows down gastric emptying and food ingestion, and decreases food intake.[29,30] Therefore, GLP-1 and GIP both act to decrease high blood glucose concentrations after food intake. Both GLP-1 and GIP are rapidly inactivated by the ubiquitous enzyme dipeptidylpeptidase-4 (DPP-4). The half-life of active GLP-1 in plasma is <2 minutes.[30] The active GIP half-life has been reported to be 7 minutes in healthy subjects and 5 minutes in T2DM patients.[30,31] Reduced secretion of GLP-1 and decreased action of GIP in T2DM patients compared with healthy subjects has been reported.[29]

FFA play an important role in glucose metabolism. FFA are important for β-cell function and stimulate insulin secretion.[18] However, permanently increased FFA concentrations cause 'lipotoxicity' and decrease insulin secretion from β-cells (figure 1). Obesity, especially an increased mass of visceral fat, leads to increased concentrations of FFA, as visceral fat exhibits higher lipolytic activity than subcutaneous fat. Increased concentrations of FFA stimulate hepatic gluconeogenesis[32] and decrease glucose uptake into skeletal muscle (figure 1). Permanently increased FFA concentrations promote insulin resistance in both skeletal muscle and the liver. As skeletal muscle is responsible for about 75–80% of insulin-mediated glucose disposal, decreased glucose uptake by the muscle due to peripheral insulin resistance can substantially increase plasma glucose concentrations.[33-35] In 1963, Randle et al.[36] proposed the glucose-fatty acid cycle, according to which fuel selection from FFA is preferred over glucose. Therefore, increased availability of FFA results in decreased glucose uptake into muscle cells. More recently, it was reported that FFA also induce or enhance insulin resistance due to alterations in insulin signalling,[37] which leads to decreased muscle glucose transport, possibly due to diminished glucose transporter protein isoenzyme 4 (GLUT-4) translocation.[38] GLUT-4 is the major insulin-sensitive glucose transporter in adipose tissue and muscle, and facilitates glucose uptake into these tissues.[39] In obese and T2DM patients, lipolysis is increased, as the adipose tissue is insulin resistant, therefore plasma FFA concentrations are higher which, in turn, aggravates insulin resistance in the liver and skeletal muscle, and causes deterioration of β-cell function.

Recently, it was recognized that adipose tissue is not only a storage tissue but has endocrine functions and secretes hormones (adipokines) such as adiponectin and leptin (figure 1). Adiponectin, which is specifically secreted from adipose tissue, stimulates glucose uptake and utilization in skeletal muscle and inhibits gluconeogenesis in the liver (figure 1). Therefore it supports insulin action, increases insulin sensitivity and decreases plasma glucose concentrations. Reduced adiponectin concentrations have been related to a higher incidence of diabetes, insulin resistance, cardiovascular disease and metabolic syndrome.[40,41]

Leptin, which is produced primarily by adipose tissue, acts as a central satiety signal (figure 1). Leptin decreases food intake, stimulates energy expenditure and increases insulin sensitivity. Leptin- or leptin receptor-deficient animal models exhibit obesity and insulin resistance. Obese subjects have higher leptin concentrations because they have a larger fat mass than lean subjects. However, obesity appears as a condition of relative leptin resistance, and therefore the effect of leptin is decreased.[41,42]

A simplified diagram, such as in figure 1, can be useful for model building. Depending on the observed data and the most relevant subsystem (e.g. for the action of a drug), part of this diagram can be used as the starting point for a model. To date, most mathematical models have focused on glucose, insulin or both, and have not included other biomarkers.

2. Mechanisms of Action of Antidiabetic Drugs

T1DM patients cannot produce insulin, and therefore their treatment mainly consists of exogenous insulin. Numerous therapeutic options are available for T2DM. An overview of the mechanisms and sites of action for the different groups of antidiabetic drugs is shown in figure 2.

Hyperglycaemia in T2DM patients can, among other reasons, be due to the following: (i) decreased uptake of glucose into skeletal muscle due to peripheral insulin resistance; (ii) increased hepatic glucose production (mainly gluconeogenesis) due to hepatic insulin resistance; and (iii) decreased insulin secretion due to exhaustion of β-cells, genetic causes, lipotoxicity or glucotoxicity.[2,43] Therefore, drugs that ameliorate one or more of these defects can be used in treating T2DM. It is generally assumed that insulin resistance precedes β-cell failure in T2DM.[2,15] However, there is also evidence for the theory that β-cell dysfunction is present before insulin resistance.[44] In general, as long as the β-cells can increase insulin production enough to compensate for an enhanced need due to insulin resistance, the patients do not become hyperglycaemic.[2,44] However, loss of β-cell function, most likely due to accelerated apoptosis,[44] leads to overt diabetes. Therefore, it has been suggested that approaches that delay the loss of β-cell function, e.g. by decreasing glucotoxicity and lipotoxicity, which are reversible, should be considered.[2]

Sulfonylurea drugs stimulate insulin secretion from β-cells. Through binding of the drug to receptors on the β-cells, potassium channels are closed, which results in stimulation of insulin secretion by a mechanism similar to stimulation of insulin secretion by glucose, as described in section 1. Examples of sulfonylurea drugs for which models have been proposed are glimepiride, gliclazide, tolbutamide and glibenclamide (glyburide). Meglitinides such as repaglinide and nateglinide stimulate insulin secretion by the same mechanism as sulfonylureas but have a faster onset and a shorter duration of action.[11]

Metformin is one of the biguanides. It is reported to suppress gluconeogenesis and glycogenolysis, increase insulin-mediated

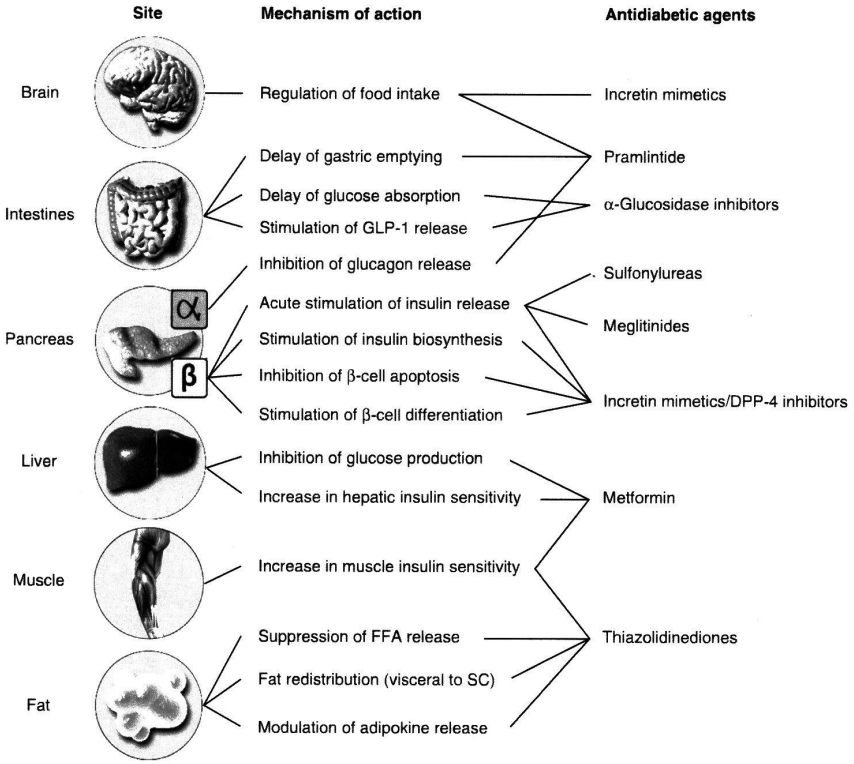

Fig. 2. Sites and mechanisms of action of antidiabetic agents (adapted from Stumvoll et al.,[15] with permission from Elsevier). **DPP-4** = dipeptidylpeptidase-4; **FFA** = free fatty acids; **GLP-1** = glucagon-like peptide 1; **SC** = subcutaneous.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.