In the Name of GOD

Insulin and oral antidiabetic Drugs

Prepared and summarized by

M. R. Panjehshahin, Ph.D

Professor of Pharmacology

Shiraz Medical School

Aim:

At the end of this lecture the students should be able to:

1- Explain the biosynthesis, transport and degradation of insulin
2- Name the mechanisms of insulin control.
3- Define the pharmacokinetics, mechanism of action, clinical uses and side effects of insulin preparations.
4- Name major groups of antidiabetic drugs
5- Explain the pharmacokinetics, mechanism of action, clinical uses and side effects of each antidiabetic drugs drug groups.

THE ENDOCRINE PANCREAS

The endocrine pancreas in the adult human consists of approximately 1 million islets of Langerhans interspersed throughout the pancreaticgland. Within the islets, at least five hormone-producing cells are present

TABLE 41–1 Pancreatic islet cells and their secretory products.

Cell Types[1]	Approximate Percent of Islet Mass	Secretory Products
Alpha (A) cell	20	Glucagon, proglucagon
Beta (B) cell	75	Insulin, C-peptide, proinsulin, amylin
Delta (D) cell	3–5	Somatostatin
Epsilon cell	< 1	Ghrelin

[1]Within pancreatic polypeptide–rich lobules of adult islets, located only in the posterior portion of the head of the human pancreas, glucagon cells are scarce (< 0.5%) and F cells make up as much as 80% of the cells.

Diabetes mellitus is defined as an elevated blood glucose associated with absent or inadequate pancreatic insulin secretion, with or without concurrent impairment of insulin action. The disease states underlying the diagnosis of diabetes mellitus are now classified into four categories: **type 1, type 2, other,** and **gestational diabetes mellitus**.

Type 1 Diabetes Mellitus

The hallmark of type 1 diabetes is selective beta cell (B cell) destruction and *severe* or *absolute* insulin deficiency. Susceptibility appears to involve a multifactorial genetic linkage, but only 10–15% of patients have a positive family history. .Diabetic ketoacidosis is caused by nsufficient or absent insulin and results from excess release of fatty acids and subsequent formation of toxic levels of ketoacids. The patient are non-obese. The immune form is the most common form of type 1 diabetes. Although most patients are younger than 30 years of age at the time of diagnosis, the onset can occur at any age.

Type 2 Diabetes Mellitus

Type 2 diabetes is characterized by tissue resistance to the action of insulin combined with a *relative* deficiency in insulin secretion. Although insulin is produced by the beta cells in these patients, it is inadequate to overcome the resistance, and the blood glucose rises. Individuals with type 2 diabetes may not require insulin to Survive. Persons with type 2 diabetes ordinarily do not develop ketosis. Dehydration in individuals with untreated or poorly controlled type 2 diabetes can lead to a lifethreatening condition called **nonketotic hyperosmolar coma**.

Other Specific Types of Diabetes Mellitus

The “other” designation refers to multiple *other* specific causes of an elevated blood glucose: pancreatectomy, pancreatitis, nonpancreatic diseases, drug therapy, etc.

Gestational Diabetes Mellitus

Gestational diabetes (GDM) is defined as any abnormality in glucose levels noted for the first time during pregnancy.

■ INSULIN

Chemistry

Insulin is a small protein with 51 amino acids arranged in two chains (A and B) linked by disulfide bridges. Proinsulin, a long single-chain protein molecule, is processed within the Golgi apparatus of beta cells and packaged into granules, where it is hydrolyzed into insulin and a residual connecting segment called C-peptide (Figure 41–1). Insulin and C-peptide are secreted in equimolar amounts in response to all insulin secretagogues. C-peptide has no known physiologic function. The entire human pancreas contains up to 8 mg of insulin, representing approximately 200 biologic units.

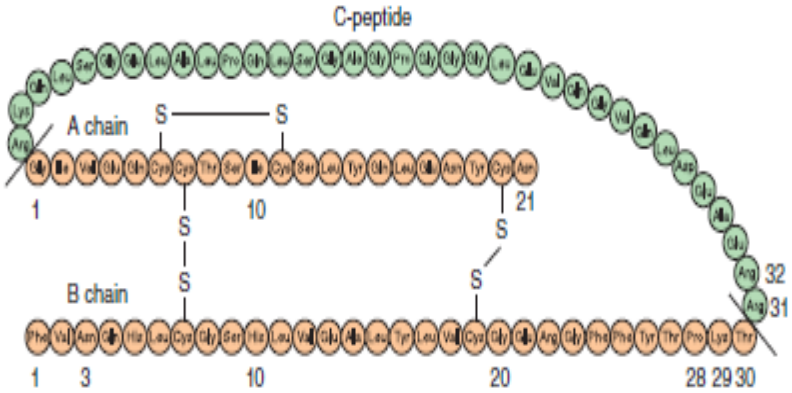

FIGURE 41–1 Structure of human proinsulin (C-peptide plus A and B chains) and insulin. Insulin is shown as the shaded (orange color) peptide chains, A and B. Differences in the A and B chains and amino acid modifications for the rapid-acting insulin analogs (aspart, lispro, and glulisine) and long-acting insulin analogs (glargine and detemir) are discussed in the text. (Adapted, with permission, from Gardner DG, Shoback D [editors]: *Greenspan's Basic & Clinical Endocrinology*, 9th ed. McGraw-Hill, 2011. Copyright © The McGraw-Hill Companies, Inc.)

Insulin Secretion

Insulin is released from pancreatic beta cells at a low basal rate and at a much higher stimulated rate in response to a variety of stimuli, especially glucose. Other stimulants such as amino acids, hormones such as glucagon-like polypeptide-1 (GLP-1), glucagon, and β-adrenergic sympathetic activity are recognized. Stimulatory drugs are sulfonylureas, meglitinide and nateglinide, isoproterenol, and acetylcholine. Inhibitory signals are hormones including insulin itself, somatostatin, and leptin. Inhibitory drugs include diazoxide, phenytoin, thiazides, vinblastine, and colchicine.

One mechanism of stimulated insulin release is diagrammed in Figure 41–2. As shown in the figure, hyperglycemia results in increased intracellular ATP levels, which close the ATP-dependent potassium channels. Decreased outward potassium efflux results in depolarization of the beta cell and opening of voltage-gated calcium channels. The resulting increased intracellular

calcium triggers secretion of the hormone. The insulin secretagogue drug group (sulfonylureas, meglitinides, and d-phenylalanine) exploits parts of this mechanism.

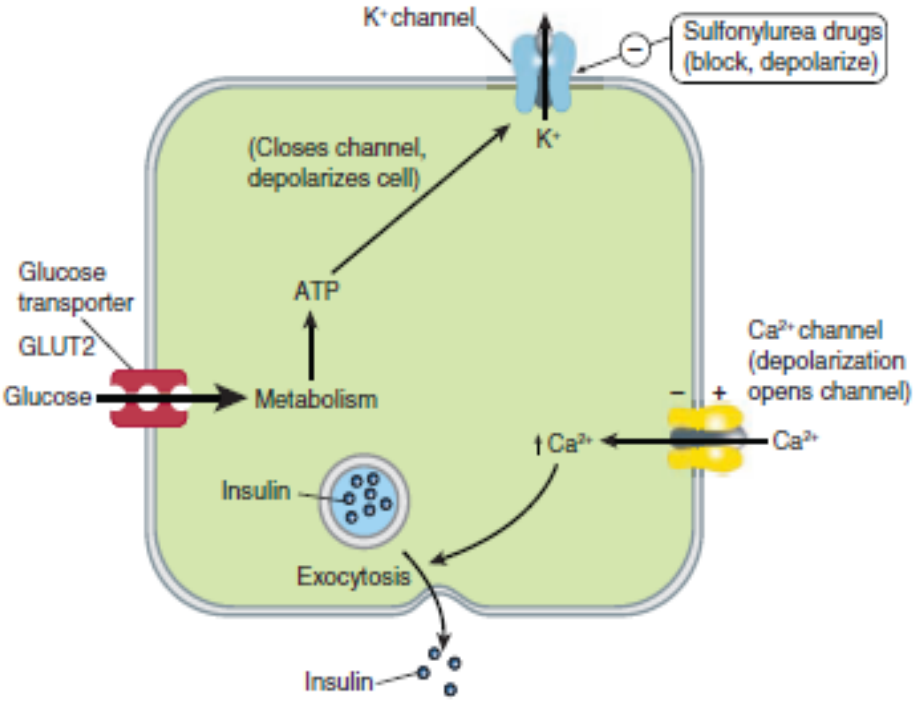

FIGURE 41–2

Insulin Degradation

The liver and kidney are the two main organs that remove insulin from the circulation. For endogenous insulin 60% is metabolized by liver, and 35–40% is removed by kidney. But for exogenous insulin this ratio is reversed. The half-life of circulating insulin is 3–5 minutes.

The Insulin Receptor

After insulin has entered the circulation, it diffuses into tissues, where it is bound by specialized receptors that are found on the membranes of most tissues. The receptors bind insulin with high specificity and affinity. The full insulin receptor is shown in Figur 41-3. The binding of an insulin molecule to the receptor causes the tyrosine kinase activity directed at cytoplasmic proteins such as insulin receptor substrates (IRS) . After tyrosine phosphorylation at several critical sites, the IRS molecules bind to and activate other molecules. This network of phosphorylations within the cell results in multiple effects, including increase in glucose uptake; increased glycogen synthase activity and increased glycogen formation; multiple effects on protein synthesis, lipolysis, and lipogenesis; and activation of transcription factors that enhance DNA synthesis and cell growth and division.

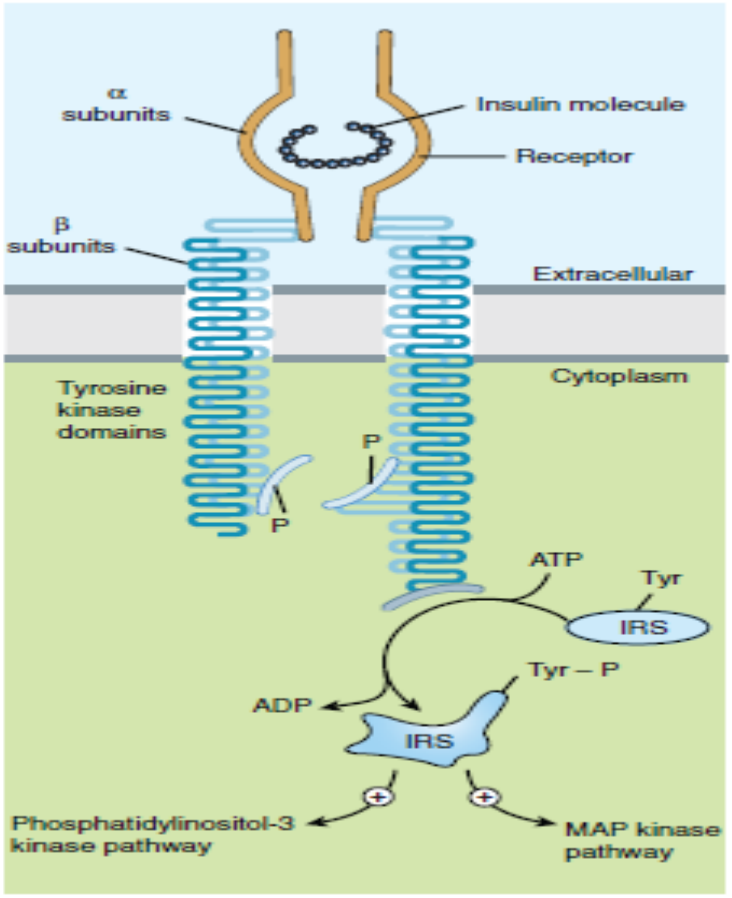

FIGURE 41–3 Schematic diagram of the insulin receptor heterodimer in the activated state. IRS, insulin receptor substrate; MAP, mitogen-activated protein; P, phosphate; Tyr, tyrosine.

Effects of Insulin on Its Targets

Insulin promotes the storage of fat as well as glucose (both sources of energy) within specialized target cells (Figure 41–4) and influences cell growth and the metabolic functions of a wide variety of tissues (Table 41–3).

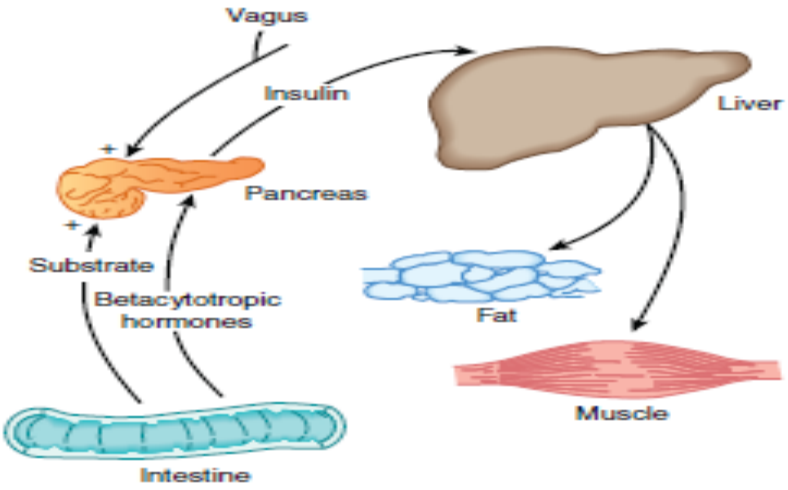

FIGURE 41–4 Insulin promotes synthesis (from circulating nutrients) and storage of glycogen, triglycerides, and protein in its major target tissues: liver, fat, and muscle. The release of insulin from the pancreas is stimulated by increased blood glucose, incretins, vagal nerve stimulation, and other factors (see text).

TABLE 41–3 Endocrine effects of insulin.

Effect on liver:
Reversal of catabolic features of insulin deficiency
Inhibits glycogenolysis
Inhibits conversion of fatty acids and amino acids to keto acids
Inhibits conversion of amino acids to glucose
Anabolic action
Promotes glucose storage as glycogen (induces glucokinase and glycogen synthase, inhibits phosphorylase)
Increases triglyceride synthesis and very-low-density lipoprotein formation
Effect on muscle:
Increased protein synthesis
Increases amino acid transport
Increases ribosomal protein synthesis
Increased glycogen synthesis
Increases glucose transport
Induces glycogen synthase and inhibits phosphorylase
Effect on adipose tissue:
Increased triglyceride storage
Lipoprotein lipase is induced and activated by insulin to hydrolyze triglycerides from lipoproteins
Glucose transport into cell provides glycerol phosphate to permit esterification of fatty acids supplied by lipoprotein transport
Intracellular lipase is inhibited by insulin

Characteristics of Available Insulin Preparations

A. Principal Types and Duration of Action of Insulin Preparations

Four principal types of injected insulins are available: (1) rapid acting, with very fast onset and short duration; (2) short-acting, with rapid onset of action; (3) intermediate-acting; and (4) long acting, with slow onset of action (Figure 41–5, Table 41–4). The goal of subcutaneous insulin therapy is to replicate normal physiologic insulin secretion and replace the background or basal (overnight, fasting, and between-meal) as well as bolus or prandial (mealtime) insulin.

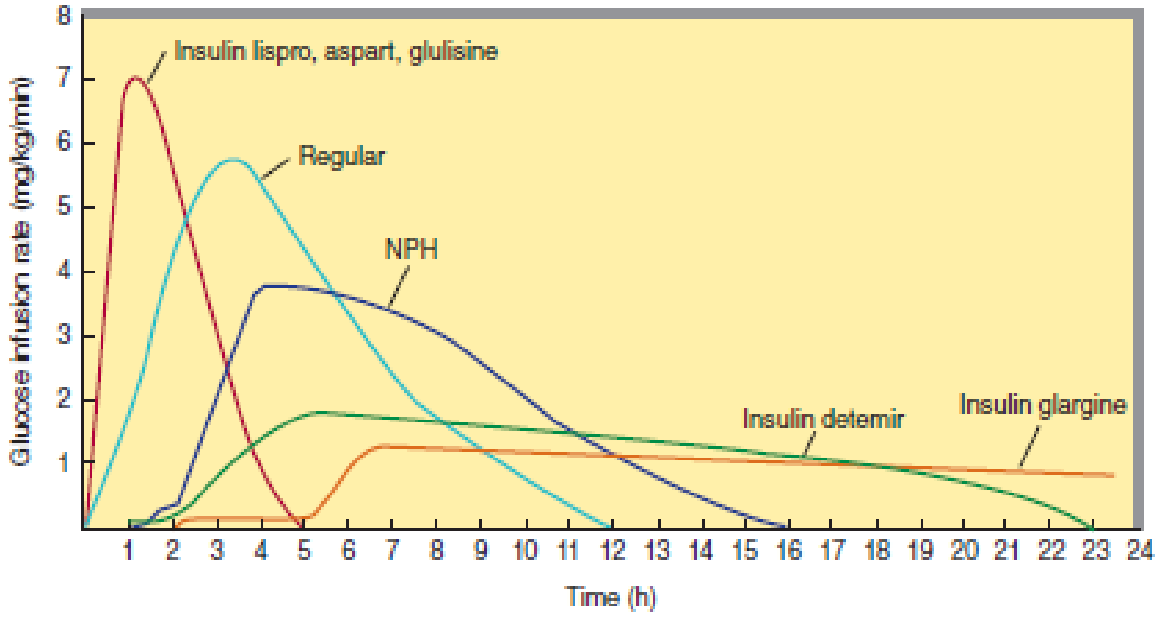

FIGURE 41–5 Extent and duration of action of various types of insulin as indicated by the glucose infusion rates (mg/kg/min) required to maintain a constant glucose concentration. The durations of action shown are typical of an average dose of 0.2–0.3 U/kg. The durations of regular and NPH insulin increase considerably when dosage is increased.

TABLE 41–4 Some insulin preparations available in the USA.[1]

Preparation	Species Source	Concentration
Rapid-acting insulins		
Insulin lispro, Humalog (Lilly)	Human analog	U100
Insulin aspart, Novolog (Novo Nordisk)	Human analog	U100
Insulin glulisine, Apidra (Aventis)	Human analog	U100
Short-acting insulins		
Regular Novolin R (Novo Nordisk)	Human	U100
Regular Humulin R (Lilly)	Human	U100, U500
Intermediate-acting insulins		
NPH Humulin N (Lilly)	Human	U100
NPH Novolin N (Novo Nordisk)	Human	U100
Premixed insulins		
Novolin 70 NPH/30 regular (Novo Nordisk)	Human	U100
Humulin 70 NPH/30 regular (Lilly)	Human	U100
75/25 NPL, Lispro (Lilly)	Human analog	U100
70/30 NPA, Aspart (Novo Nordisk)	Human analog	U100
Long-acting insulins		
Insulin detemir, Levemir (Novo Nordisk)	Human analog	U100
Insulin glargine, Lantus (Aventis/Hoechst Marion Roussel)	Human analog	U100

[1]These agents (except insulin lispro, insulin aspart, insulin detemir, insulin glargine, insulin glulisine, and U500 regular Humulin) are available without a prescription. All insulins are now made by recombinant technology; they should be refrigerated and brought to room temperature just before injection.

NPL, neutral protamine lispro; NPA, neutral protamine aspart.

***1. Rapid-acting insulin*—**Three injected rapid-acting insulin analogs—**insulin lispro, insulin aspart,** and **insulin glulisine—** are commercially available. Their duration of action is rarely more than 4–5 hours, which decreases the risk of late postmeal hypoglycemia. The injected rapid-acting insulin has the lowest variability of absorption (approximately 5%) of all Available commercial insulin (compared with 25% for regular insulin and 25% to over 50% for long-acting analog formulations and intermediate insulin, respectively). When injected subcutaneously, the onset of action is within 5–15 minutes and peak activity as early as 1 hour.

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***2. Short-acting insulin*—**Regular insulin is a short-acting soluble crystalline zinc insulin. Its effect appears within 30 minutes, peaks between 2 and 3 hours after subcutaneous injection, and generally lasts 5–8 hours. It is particularly useful for intravenous therapy in the management of diabetic ketoacidosis and when the insulin requirement is changing rapidly, such as after surgery or during acute infections.

3. Intermediate-acting and long-acting insulins

a. NPH (neutral protamine Hagedorn, or isophane) insulin— NPH insulin has an onset of approximately 2–5 hours and duration of 4–12 hours (Figure 41–5); it is usually mixed with regular, lispro, aspart, or glulisine insulin and given two to four times daily for insulin replacement.

b. Insulin glargine—Insulin glargine is a soluble, "peakless" (ie, having a broad plasma concentration plateau), long-acting insulin analog. This product was designed to provide reproducible, convenient, background insulin replacement. Insulin glargine has a slow onset of action (1–1.5 hours) and achieves a maximum effect after 4–6 hours. This maximum activity is maintained for 11–24 hours or longer. Glargine is usually given once daily.

c. Insulin detemir—This insulin is the most recently developed long-acting insulin analog. Insulin detemir has the most reproducible effect of the intermediate- and long-acting insulins, and its use is associated with less hypoglycemia than NPH insulin.

***4. Mixtures of insulins*—**Because intermediate-acting NPH insulins require several hours to reach adequate therapeutic levels, their use in diabetic patients usually requires supplements of rapid or short-acting insulin before meals. Premixed formulations of 70%/30% NPH/regular continue to be available.

Complications of Insulin Therapy

A. Hypoglycemia

***1. Mechanisms and diagnosis*—**Hypoglycemic reactions are the most common complication of insulin therapy. Rapid development of hypoglycemia in persons with intact hypoglycemic awareness causes signs of autonomic hyperactivity— both sympathetic (tachycardia, alpitations, sweating, tremulousness) and parasympathetic (nausea, hunger)—and may progress to convulsions and coma if untreated. In patients with persistent, ntreated hypoglycemia (slow induction), the manifestations of insulin excess may develop—confusion, weakness, bizarre behavior, coma, seizures—

***2. Treatment of hypoglycemia*—**All the manifestations of hypoglycemia are relieved by glucose administration. For easy absorption, simple sugar or lucose should be given, preferably in liquid form, in a conscious patient. In unconscious patient, the treatment of choice is to give 20–50 mL of 50% glucose solution by intravenous infusion over a period of 2–3 minutes

B. Immunopathology of Insulin Therapy

At least five molecular classes of insulin antibodies may be produced in diabetics during the course of insulin therapy: IgA, IgD, IgE, IgG, and IgM. There are two major types of immune disorders in these patients:

***1. Insulin allergy*—**Insulin allergy, an immediate type hypersensitivity, is a rare condition in which local or systemic urticaria results from histamine release. In severe cases, anaphylaxis results.

***2. Immune insulin resistance*—**A low titer of circulating IgG anti-insulin antibodies that neutralize the action of insulin to a negligible extent develops in most insulin-treated patients. Rarely, the titer of insulin antibodies leads to insulin resistance.

C. Lipodystrophy at Injection Sites

Injection of animal insulin preparations sometimes led to **Atrophy** of subcutaneous fatty tissue at the site of injection. Since the development of human and analog insulin preparations of neutral pH, this type of immune complication is almost never seen. **Hypertrophy** of subcutaneous fatty tissue remains a problem if injected repeatedly at the same site.

■ ORAL ANTIDIABETIC AGENTS

Several categories of oral antidiabetic agents are now available in the USA for the treatment of persons with type 2 diabetes:

(1)- Agents that bind to the sulfonylurea receptor and stimulate insulin secretion (sulfonylureas, meglitinides, d-phenylalanine derivatives);

(2)- Agents that lower glucose levels by their actions on liver, muscle, and adipose tissue (biguanides, thiazolidinediones);
(3)- Agents that principally slow the intestinal absorption of glucose (α-glucosidase inhibitors);
(4)- Agents that mimic incretin effect or prolong incretin action (glucagon-like peptide-1 [GLP-1] receptor agonists, dipeptidyl peptidase-4 [DPP-4] inhibitors),
(5)- Agents that inhibit the reabsorption of glucose in the kidney (sodiumglucose co-transporter inhibitors [SGLTs]), and
(6)- Agents that act by other or ill-defined mechanisms (pramlintide, bromocriptine, colesevelam).

DRUGS THAT PRIMARILY STIMULATE INSULIN RELEASE BY BINDING TO THE SULFONYLUREA RECEPTOR

SULFONYLUREAS

Mechanism of Action

The major action of sulfonylureas is to increase insulin release from the pancreas by closing the potassium channel and subsequent opening of a voltage-gated calcium channel on beta-cell.

Efficacy & Safety of the Sulfonylureas

Idiosyncratic reactions are rare, with skin rashes or hematologic toxicity (leukopenia, thrombocytopenia) occurring in less than 0.1% of cases. In 1970, the University Group Diabetes Program (UGDP) in the USA reported that the number of deaths due to cardiovascular disease in diabetic patients treated with tolbutamide was excessive compared with either insulin-treated patients or those receiving placebos. Owing to design flaws, this study and its conclusions was not generally accepted. The sulfonylureas continue to be widely prescribed, and six are available in the USA

FIRST-GENERATION SULFONYLUREAS

Tolbutamide is well absorbed but rapidly metabolized in the liver. Its duration of effect is relatively short (6–10 hours), with an elimination half-life of 4–5 hours. Because of its short half-life and inactivation by the liver, it is relatively safe in the elderly and in patients with renal impairment. **Prolonged hypoglycemia** has been reported **rarely**.

Chlorpropamide has a half-life of 32 hours and is slowly metabolized in the liver to products that retain some biologic activity; approximately 20–30% is excreted unchanged in the urine. **Prolonged hypoglycemic** reactions are **more common** in elderly patients, and the drug is contraindicated in this group. Other adverse effects include a hyperemic flush after alcohol ingestion in genetically predisposed patients and **hyponatremia** due to its effect on vasopressin secretion and action.

Tolazamide is comparable to chlorpropamide in potency but has a shorter duration of action. Its half-life is about 7 hours. Tolazamide is metabolized to several compounds that retain hypoglycemic effects.

Acetohexamide is no longer available in the United States. Chlorpropamide, tolazamide, and acetohexamide are now rarely used in clinical practice.

SECOND-GENERATION SULFONYLUREAS

Glyburide (Glybenclamide), glipizide, gliclazide, and glimepiride are 100–200 times more potent than tolbutamide.

Glyburide is metabolized in the liver into products with very low hypoglycemic activity. Glyburide has few adverse effects other than its potential for causing hypoglycemia. Glyburide is contraindicated in the presence of hepatic impairment and in patients with renal insufficiency.

Glipizide has the shortest half-life (2–4 hours) of the more potent agents. For maximum effect in reducing postprandial hyperglycemia, this agent should be ingested 30 minutes before breakfast because absorption is delayed when the drug is taken with food. At least 90% of glipizide is metabolized in the liver to inactive products, and the remainder is excreted unchanged in the urine. Glipizide therapy is therefore contraindicated in patients with significant hepatic impairment. Because of its lower potency and shorter duration for action, it is preferable to glyburide in the elderly.

Glimepiride is approved for once-daily use as monotherapy or in combination with insulin. Glimepiride achieves blood glucose lowering with the lowest dosage of any sulfonylurea compound. Glimepiride's halflife under multidose conditions is 5–9 hours. It is completely metabolized by the liver to metabolites with weak or no activity.

Gliclazide (not available in the United States) has a half-life of 10 hours. It is completely metabolized by the liver to inactive metabolites.

MEGLITINIDE ANALOGS

Repaglinide is the first member of the meglitinide group of insulin secretagogues. These drugs modulate beta-cell insulin release by regulating potassium efflux through the potassium channels previously discussed. Repaglinide has a fast onset of action, with a peak concentration and peak effect within approximately 1 hour after ingestion, but the duration of action is 4–7 hours. It is cleared by hepatic CYP3A4 with a plasma half-life of 1 hour. Because of its rapid onset, repaglinide is indicated for use in controlling postprandial glucose excursions. Hypoglycemia is a risk. It can be used in patients with renal impairment and in the elderly. Repaglinide is approved as monotherapy or in combination with biguanides.

d-PHENYLALANINE DERIVATIVE

Nateglinide, a d-phenylalanine derivative, releases insulin through closure of the K+ channel. It is absorbed within 20 minutes after oral administration with a time to peak concentration of less than 1 hour and is metabolized in the liver with a half-life of about 1 hour. The overall duration of action is about 4 hours. Nateglinide is efficacious when given alone or in combination with nonsecretagogue oral agents (such as metformin). Hypoglycemia is the main adverse effect, but the incidence may be the lowest of allthe secretagogues and it can be used in patients with renal impairment and in the elderly.

DRUGS THAT PRIMARILY LOWER GLUCOSE LEVELS BY THEIR

ACTIONS ON THE LIVER, MUSCLE, & ADIPOSE TISSUE

BIGUANIDES

Metformin is the only biguanide currently available in the United States.

Mechanisms of Action

A full explanation of the mechanism of action of the biguanides remains elusive, but their primary effect is to activate the enzyme AMP-activated protein kinase (AMPK) and reduce hepatic glucose production. Patients with type 2 diabetes have considerably less fasting hyperglycemia as well as lower postprandial hyperglycemia after administration of biguanides; however, hypoglycemia during biguanide therapy is rare. These agents are therefore more appropriately termed **"euglycemic"** agents.

Metabolism & Excretion

Metformin has a half-life of 1.5–3 hours, is not bound to plasma proteins, is not metabolized, and is excreted by the kidneys as the active compound. The drug may impair the hepatic metabolism of lactic acid. In patients with renal insufficiency, biguanides accumulate and thereby increase the risk of lactic acidosis.

Clinical Use

Biguanides are recommended as first-line therapy for type 2 diabetes. Because metformin is an insulin-sparing agent and does not increase body weight or provoke hypoglycemia, it offers obvious advantages over insulin or sulfonylureas in treating hyperglycemia in such persons. Metformin therapy decreases the risk of macrovascular as well as microvascular disease. Biguanides are also indicated in combination with insulin secretagogues or thiazolidinediones in type 2 diabetics. Metformin is useful in the prevention of type 2 diabetes. It is interesting that metformin did not prevent diabetes in older, leaner prediabetics. Epidemiologic studies suggest that metformin use may reduce the risk of some cancers. Other studies suggest a reduction in cardiovascular deaths in humans.

Toxicities

The most common toxic effects of metformin are gastrointestinal (anorexia, nausea, vomiting, abdominal discomfort, and diarrhea), which occur in up to 20% of patients. They are dose related, tend to occur at the onset of therapy, and are often transient. Metformin interferes with the absorption of vitamin B12. Lactic acidosis can sometimes occur with metformin therapy. It is more likely to occur in conditions of tissue hypoxia when there is increased production of lactic acid and in renal failure when there is decreased clearance of metformin. Almost all reported cases have involved patients with associated risk factors that should have ontraindicated its use (kidney, liver, or cardiorespiratory insufficiency; alcoholism).

THIAZOLIDINEDIONES

Thiazolidinediones act to decrease insulin resistance. They are ligands of **peroxisome roliferator-activated receptor-gamma (PPAR-γ),** part of the steroid and thyroid superfamily of nuclear receptors. These PPAR receptors are found in muscle, fat, and liver. PPAR-γ receptors modulate the expression of the genes involved in lipid and glucose metabolism, insulin signal transduction, and adipocyte and other tissue differentiation. Observed effects of the thiazolidinediones include increased glucose transporter expression (GLUT 1 and GLUT 4), decreased free fatty acid levels, decreased hepatic glucose output.

Two thiazolidinediones:

Pioglitazone has some PPAR-α as well as PPAR-γ activity. It is absorbed within 2 hours of ingestion. Pioglitazone is metabolized by CYP2C8 and CYP3A4 to active metabolites. **Rosiglitazone** is rapidly absorbed and highly protein-bound. It is metabolized in the liver to minimally active metabolites, predominantly by CYP2C8 and to a lesser extent by CYP2C9. Rosiglitazone is approved for use in type 2 diabetes as monotherapy, in double combination therapy with a biguanide or sulfonylurea, or in quadruple combination with a biguanide, sulfonylurea, and insulin. The combination of a thiazolidinedione and metformin has the dvantage of not causing hypoglycemia. Pioglitazone lowers triglycerides and increases HDL cholesterol without affecting total cholesterol and low-density lipoprotein (LDL) cholesterol. Rosiglitazone increases total cholesterol, HDL cholesterol, and LDL cholesterol but does not have significant effect on triglycerides. A meta-analysis of 42 randomized clinical trials with rosiglitazone suggested that this drug increased the risk of angina pectoris or myocardial infarction. A subsequent large prospective clinical trial failed to confirm the meta-analysis finding. Fluid retention occurs in about 3–4 % patients on thiazolidinedione monotherapy and occurs more frequently (10–15%) in patients on concomitant insulin therapy. Heart failure can occur. Loss of bone mineral density and increased atypical extremity bone fractures in women are described for both compounds. Weight gain occurs, especially when used in combination with a sulfonylurea or insulin. Pioglitazone may have an increased risk of bladder cancer with increased dosage and duration of drug use. Although rosiglitazone and pioglitazone have not been reported to cause liver injury, the drugs are not recommended for use in patients with active liver disease.

DRUGS THAT AFFECT ABSORPTION OF GLUCOSE

The **`-glucosidase inhibitors** competitively inhibit the intestinal α-glucosidase enzymes such as α- amylase, and sucrase and reduce postmeal glucose excursions by delaying the digestion and absorption of starch and disaccharides. **Acarbose** and **miglitol** are available in the United States. Acarbose has the molecular mass and structural features of a tetrasaccharide and very little is absorbed. In contrast, miglitol has structural similarity to glucose and is absorbed. The drug is not metabolized and is cleared by the kidney. It should not be used in renal failure. Prominent adverse effects of α-glucosidase inhibitors include flatulence, diarrhea, and abdominal pain. Hypoglycemia may occur with concurrent sulfonylurea treatment. Hypoglycemia should be treated with glucose (dextrose). An increase in hepatic aminotransferases has been noted in clinical trials with acarbose, especially with dosages greater than 300 mg/d. The abnormalities resolve on stopping the drug.