Antidiabetic Drugs

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Reference

Basic & Clinical Pharmacology

BG Katzung, SB Masters, AJ Trevor

McGraw Hill LANGE

12th edition pp 743-763, or 13th edition pp 723-742

The Endocrine Pancreas

- **The endocrine pancreas in the human consists of islets of Langerhans.**
- **Within the islets, at least four hormone-producing cells are present that produce:**

1. **Insulin.**
2. **Amylin, which modulates appetite, gastric emptying, and glucagon and insulin secretion.**

The Endocrine Pancreas

3. Glucagon, mobilizes glucose from the liver by stimulating gluconeogenesis and glycogenolysis.
4. Somatostatin, a universal inhibitor of secretory cells.
5. Ghrelin, a peptide which increases pituitary growth hormone release.
6. Pancreatic polypeptide, that facilitates digestive processes by yet unknown mechanism.

Energy Homeostasis

1. **Insulin: promotes the uptake and storage of glucose and other small, energy-containing molecules.**
2. **Amylin: suppresses endogenous production of glucose in the liver.**

- **The physiologic effect of amylin may be to mediate negative feedback inhibition of insulin secretion.**

Energy Homeostasis

- **At pharmacologic doses, amylin:**

  a. reduces glucagon secretion.

  b. slows gastric emptying by a vagally-medicated mechanism.

  c. decreases appetite by a central action.

Energy Homeostasis

3. **Glucagon-like peptide-1 (GLP-1) from the GIT:**

- **It enhances insulin release in response to an ingested meal.**
- **It suppresses glucagon secretion.**
- **It delays gastric emptying.**
- **It decreases appetite.**
- **It is degraded by dipeptidyl peptidase-4 (DPP-4).**

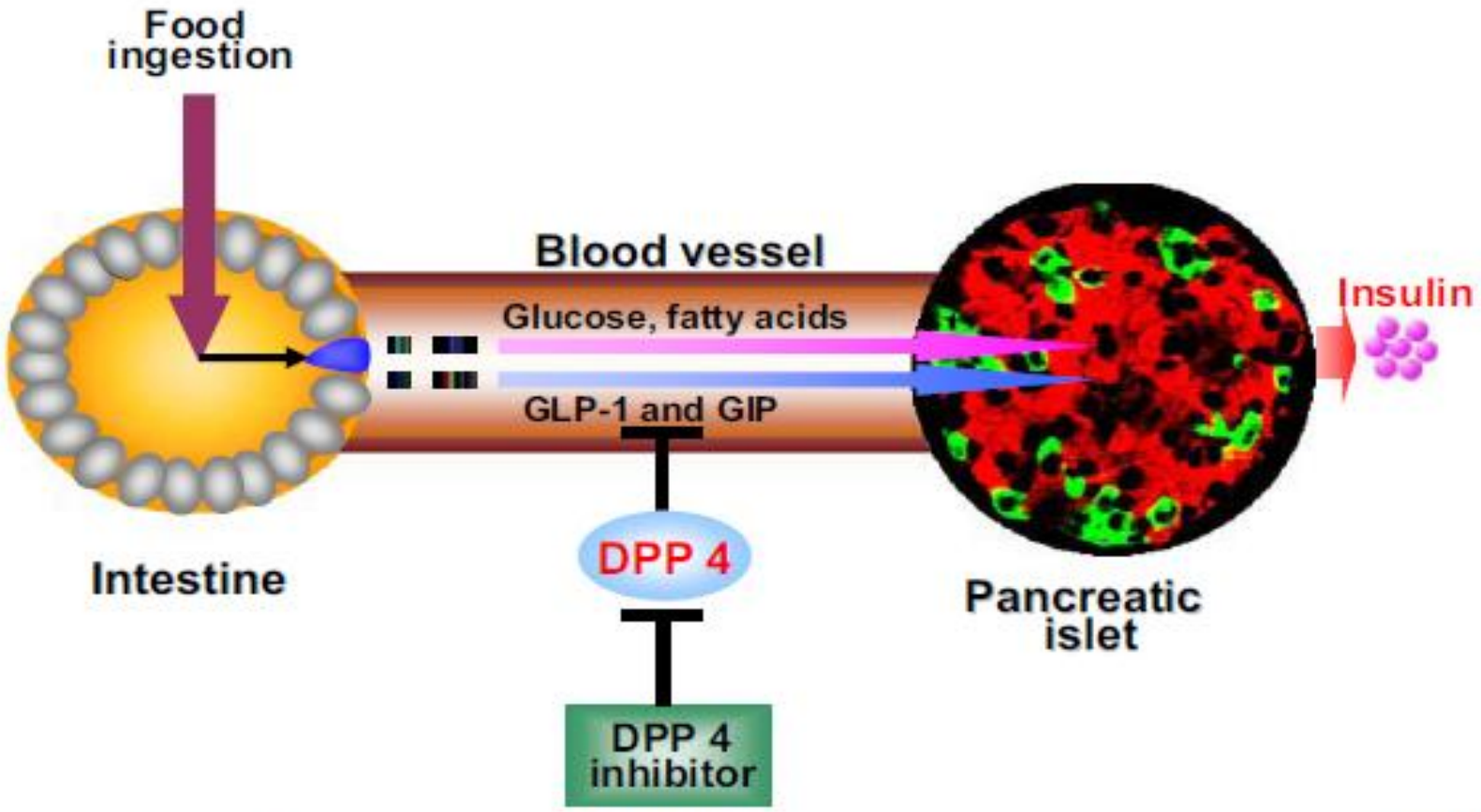


FIG. 1. Schematic representation of incretin secretion and action. GIP and GLP-1 are secreted after food ingestion, and they then stimulate glucose-dependent insulin secretion. Once released, GIP and GLP-1 are subject to degradation by DPP4 on lymphocytes and on endothelial cells of blood vessels. The red cells in the islets are insulin-containing (β) cells and the green cells are glucagon-containing (α) cells.

GIP = Glucose-dependent insulino-tropic polypeptide

Energy Homeostasis

4. **The counter-regulatory hormones:**
   (glucagon, epinephrine and norepinephrine, glucocorticoids and growth hormone).

- **Oppose the actions of insulin and prevent hypoglycemia, or produce hyperglycemia.**

Energy Homeostasis

5. **The nuclear receptor "peroxisome proliferator-activated receptor-γ" (PPARγ):**

- **It modulates the expression of the genes involved in:**

a. lipid and glucose metabolism,

b. insulin signal transduction, and

c. adipocyte and other tissue differentiation.

Energy Homeostasis

- **Its activation by endogenous fatty acids decreases serum fatty acid levels and increases lipogenesis in adipose tissue.**

- **The increased storage of fatty acids in adipose tissue allows other tissues – liver – to lower their fat content, lower their glucose production, and increase their insulin sensitivity.**

Energy Homeostasis

6. **In low-energy states (low ATP):**

- **The enzyme adenosine 5´- monophosphate-activated protein kinase (AMPK) triggers a shift from anabolic to catabolic activities.**
- **AMPK is activated by exercise, which increases muscle uptake of glucose to be used for energy production.**

Energy Homeostasis

- **Activated AMPK decreases glucose production and the synthesis of lipids and proteins by the liver.**

Energy Homeostasis

7. **Leptin:**

- **It is secreted from adipocytes.**
- **It suppresses appetite, which switches the body from an energy-accumulating state to a state of energy utilization.**
- **Insulin and leptin act in the brain as adiposity negative feedback signals.**
- **Insulin stimulates leptin secretion from adipose tissue.**

Energy Homeostasis

- **Leptin has the effect to normalize hyperinsulinemia (reduce synthesis and secretion of insulin), and to increase insulin sensitivity, and thus corrects hyperglycemia.**
- **Lack of leptin (as in prolonged starvation) results in persistently increased appetite and suppression of energy-utilizing functions.**

Antidiabetic Drugs

I. Insulin

II. Oral antidiabetic agents

A. Insulin secretagogues:

1. Sulfonylureas

2. Meglitinides

B. Biguanides

C.Thiazolidinediones

D. α-Glucosidase inhibitors

Antidiabetic Drugs

III. Others:

A. Amylin Analogues

B. GLP-1 – based "incretin" therapies

1. GLP-1 analogues

2. DPP-4 inhibitors

C. Sodium-glucose Co-transporter 2 (SGLT2) Inhibitors.

D. Others ??

Insulin Secretion

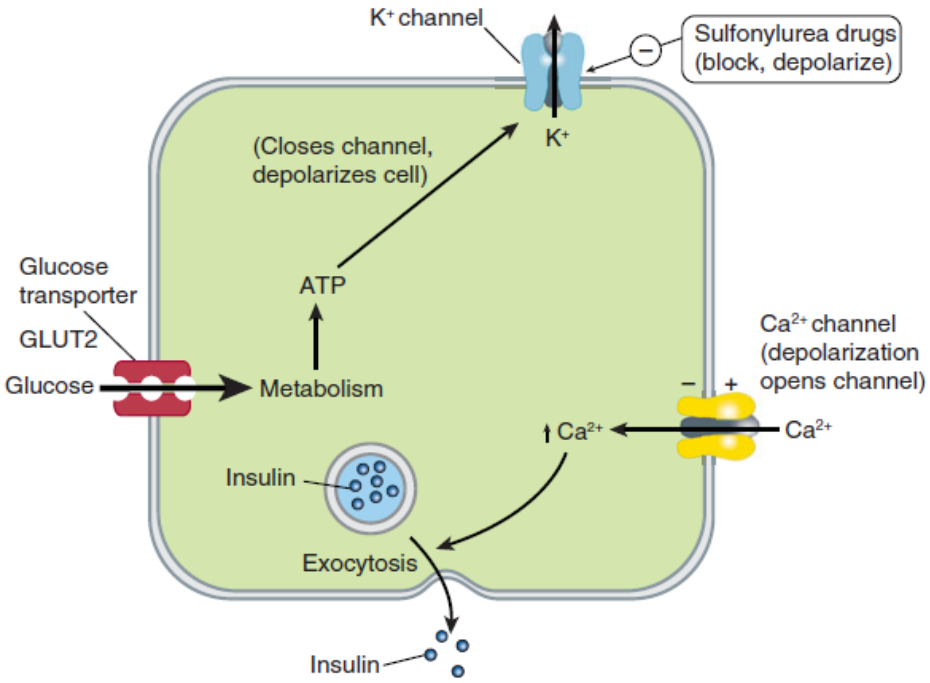
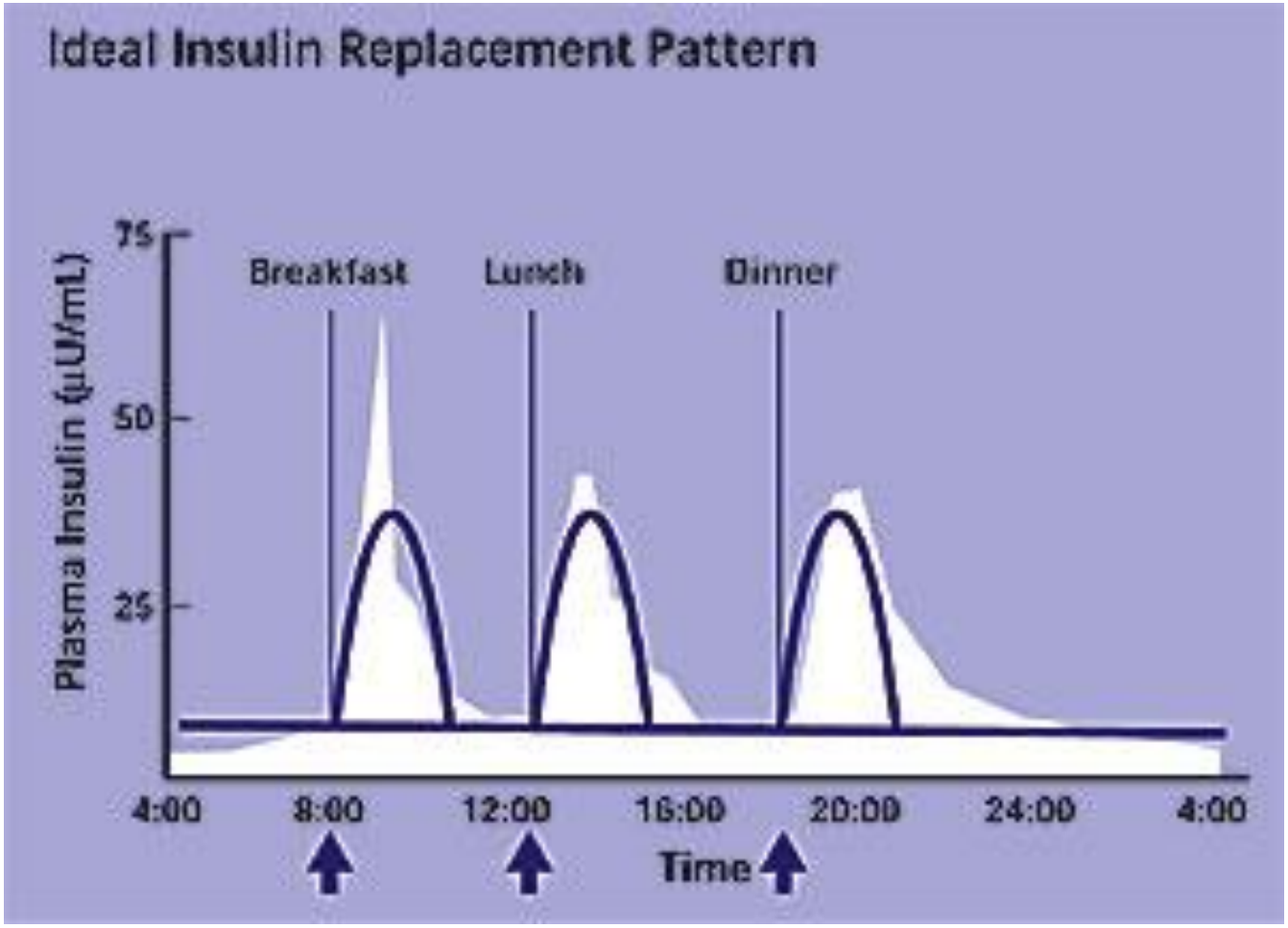


FIGURE 41–2 One model of control of insulin release from the pancreatic beta cell by glucose and by sulfonylurea drugs. In the resting cell with normal (low) ATP levels, potassium diffuses down its concentration gradient through ATP-gated potassium channels, maintaining the intracellular potential at a fully polarized, negative level. Insulin release is minimal. If glucose concentration rises, ATP production increases, potassium channels close, and depolarization of the cell results. As in muscle and nerve, voltage-gated calcium channels open in response to depolarization, allowing more calcium to enter the cell. Increased intracellular calcium results in increased insulin secretion. Insulin secretagogues close the ATP-dependent potassium channel, thereby depolarizing the membrane and causing increased insulin release by the same mechanism. (Modified and reproduced, with permission, from *Basic & Clinical Endocrinology,* 4th ed. Greenspan F, Baxter JD [editors]: Originally published by Appleton & Lange. Copyright © 1994 by The McGraw-Hill Companies, Inc.)

Granules within the beta cells store the insulin in the form of crystals consisting of two atoms of zinc and six molecules of insulin.

The entire human pancreas contains up to 8 mg of insulin ~ 200 units.


Ideal Insulin Replacement Pattern
Plasma Insulin (μU/mL)
75
50
25
Breakfast
Lunch
Dinner
4:00
8:00
12:00
16:00
20:00
24:00
4:00
Time

Insulin Secretion

Secretion is stimulated by:

1. **Blood glucose and other sugars (mannose).**
2. **Amino acids (gluconeogenic amino acids, leucine, arginine).**
3. **High concentration of fatty acids.**
4. **Parasympathetic activity.**
5. **GLP-1, and glucose-dependent insulinotropic polypeptide (GIP).**
6. **Glucagon.**

Insulin Secretion

7. Cholecystokinin.

8. β-adrenergic sympathetic activity.

9. Drugs: sulfonylureas, meglitinide, nateglinide, isoproterenol, and acetylcholine.

Insulin Secretion

Secretion is inhibited by:

1. **Insulin itself.**
2. **Somatostatin.**
3. **Leptin.**
4. **α-Adrenergic sympathetic activity.**
5. **Chronically elevated glucose.**
6. **Low concentrations of fatty acids.**
7. **Drugs: diazoxide, phenytoin, vinblastine, and colchicine.**

Insulin

- **Each mg of insulin contains 28 units of activity.**

Insulin Degradation:

- **The liver clears 60% of endogenous insulin.**
- **The kidney removes 35-40% of endogenous insulin.**
- **In insulin-treated diabetics receiving subcutaneous insulin injections, this ratio is reversed.**
- **t½ of circulating insulin is 3-5 minutes.**

Insulin

Insulin Receptors:

- **Found in the membranes of most tissues.**
- **Consist of 2 covalently linked heterodimers, each containing an α subunit, which is entirely extracellular, and constitutes the recognition site; and a β subunit that spans the membrane and contains tyrosine kinase.**

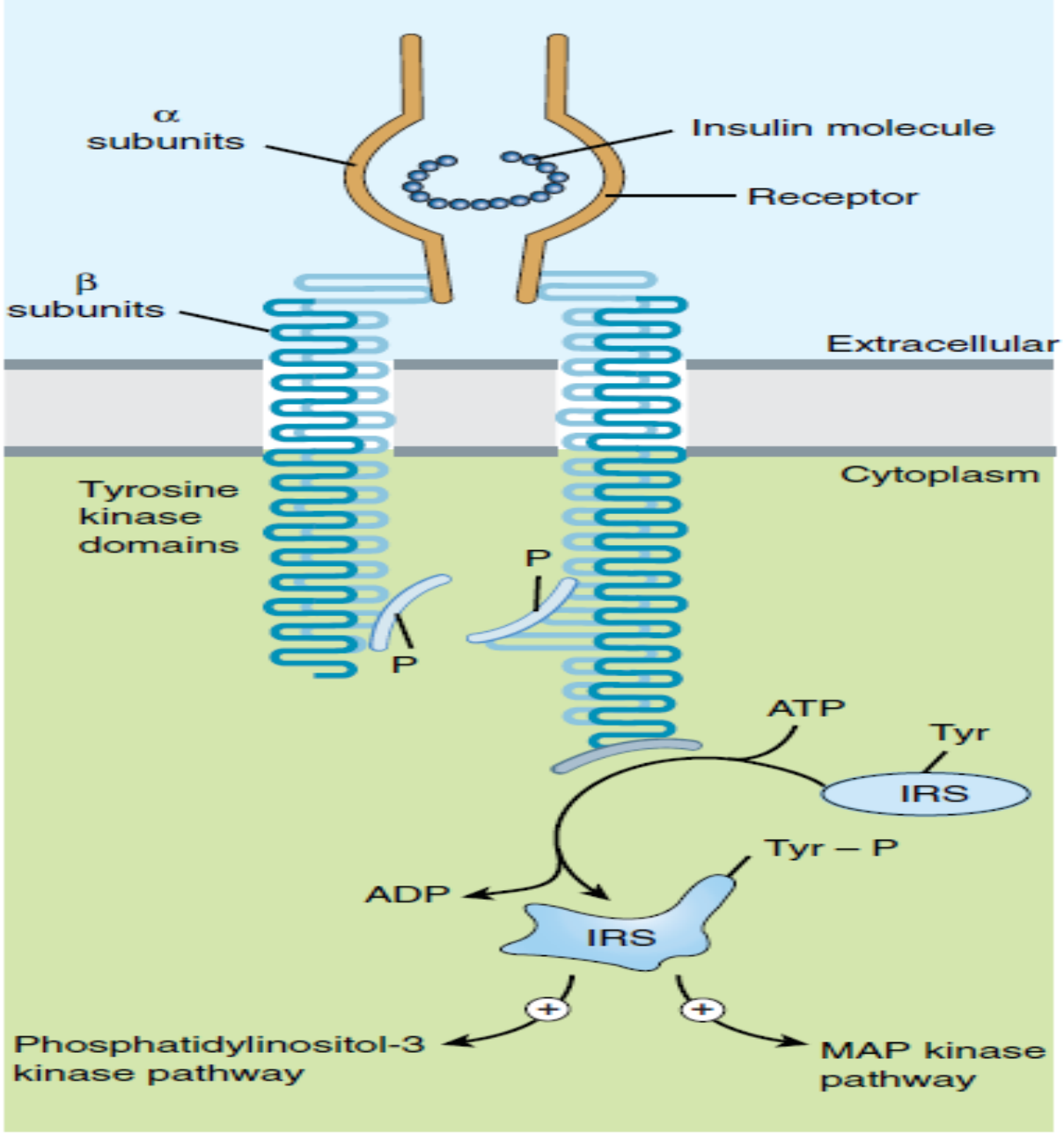


FIGURE 41–3 Schematic diagram of the insulin receptor heterodimer in the activated state. IRS, insulin receptor substrate; MAP, mitogen-activated protein; P, phosphate; Tyr, tyrosine.

Insulin

- **Binding of insulin to α subunits activates the receptor through conformational change which facilitates mutual phosphorylation of tyrosine residues on the β subunits and tyrosine kinase activity directed at cytoplasmic proteins, called insulin receptor substrates (IRS).**

Insulin

- **After tyrosine phosphorylation at several critical sites, the IRS molecules activate other kinases subserving energy metabolism - such as phosphatidylinositol-3 kinase which produces further phosphorylation.**

Insulin

- **Alternatively, IRS may stimulate an adaptor protein such as growth factor receptor-binding protein-2 which translates the insulin signal to a guanine nucleotide releasing factor that ultimately activates the mitogen-activated protein kinase (MAPK) system.**

Insulin

This network of phosphorylation within the cells represents insulin's second message and result in multiple effects, including translocation of glucose transporters (especially GLUT 4) to the cell membrane

→ →

Insulin

1. **Glucose uptake.**
2. **Increased glycogen synthase activity and increased glycogen formation.**
3. **Multiple effects on protein synthesis, lipolysis and lipogenesis.**
4. **Activation of transcription factors that enhance DNA synthesis, cell growth and division.**

- **Glucocorticoids lower the affinity of insulin to its receptors.**

Insulin

- **Growth hormone in excess increases this affinity slightly.**
- **Aberrant serine and threonine phosphorylation of β subunits or IRS molecules may result in insulin resistance and functional receptor down regulation.**

Insulin

Actions:

In the liver:

1. **Trapping of glucose in hepatocytes which enhances glycogen synthesis, glycolysis, and fatty acid synthesis.**
2. **Inhibition of glycogenolysis and gluconeogenesis enhance the anabolic processes.**

Insulin

In skeletal muscle and adipose tissue:

1. **Facilitates the movement of glucose into the cell.**

In skeletal muscle:

1. **Promotes glycogen synthesis.**
2. **Increases amino acid uptake, and**
3. **Stimulates protein synthesis.**

Insulin

In adipose tissue:

1. **Hydrolysis of triglycerides from circulating lipoproteins and uptake into fat cells where they are stored as triglycerides.**

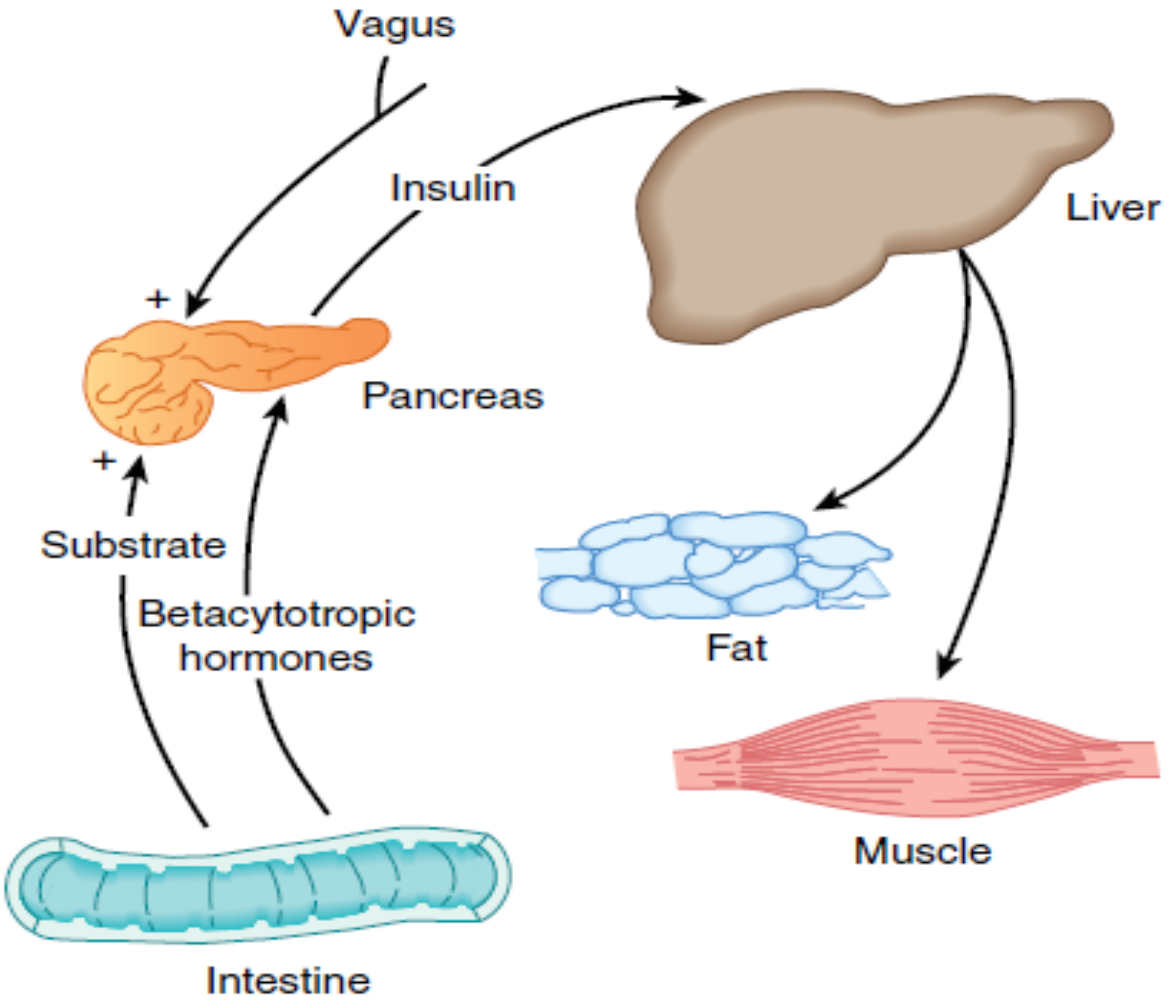


FIGURE 41–4 Insulin promotes synthesis (from circulating nutrients) and storage of glycogen, triglycerides, and protein in its major target tissues: liver, fat, and muscle. The release of insulin from the pancreas is stimulated by increased blood glucose, incretins, vagal nerve stimulation, and other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

Insulin

Types of Insulin Preparations:

1. **Rapid-acting insulin (very fast onset & short duration):**
   - **A. Insulin lispro**
   - **B. Insulin aspart**
   - **C. Insulin glulisine**

Insulin

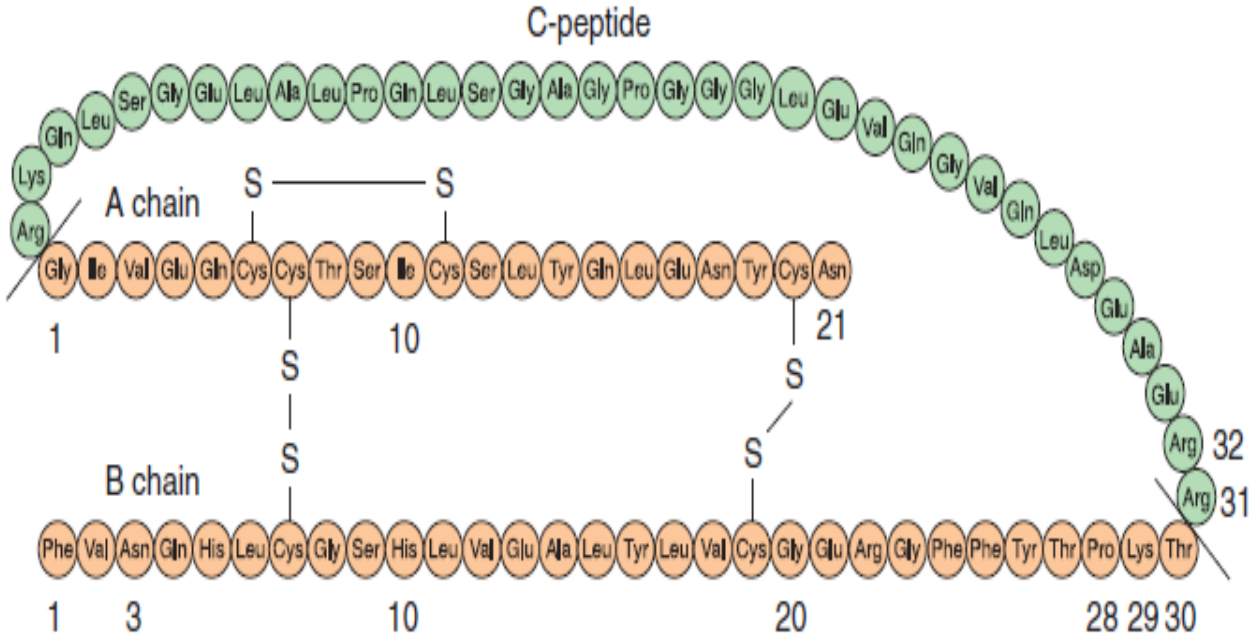


FIGURE 41–1 Structure of human proinsulin (C-peptide plus A and B chains) and insulin. Insulin is shown as the shaded (orange color) peptide chains, A and B. Differences in the A and B chains and amino acid modifications for the rapid-acting insulin analogs (aspart, lispro, and glulisine) and long-acting insulin analogs (glargine and detemir) are discussed in the text.

Insulin

- **The rapid-acting insulins permit more physiologic prandial insulin replacement.**
- **They allow insulin to be taken immediately before the meal without sacrificing glucose control.**
- **They have the lowest variability of absorption of all available commercial insulins.**

Insulin

- **Their duration of action is rarely more than 4-5 hours, which decreases the risk of late post-meal hypoglycemia.**
- **They are preferred for use in continuous subcutaneous insulin infusion devices.**

Insulin

- **Insulin lispro is produced by recombinant technology, with 2 amino acids near the carboxy terminal of B chain have been reversed in position (proline at position B28 has been moved to B29, and lysine at position B29 has been moved to B28).**

1. **This change does not interfere with binding to insulin receptor, insulin's circulating half-life, or its immunogenicity.**

Insulin

2. **The advantage of this analog is its very low propensity – in contrast to human insulin – to self-associate in antiparallel fashion and form dimers.**
3. **To enhance shelf-life it is stabilized into hexamers by a cresol preservative, which quickly dissociate into monomers after subcutaneous injection.**
4. **Onset of action 5-15 minutes, peak activity 1 hour.**

Insulin

- **Insulin aspart is a substituted B28 proline with a negatively charged aspartic acid.**

1. **This modification reduces the normal ProB28 and GlyB23 monomer-monomer interaction, thereby inhibiting insulin self aggregation.**
2. **Its absorption and activity profile is similar to insulin lispro.**
3. **It has similar binding, activity, mitogenicity characteristics and immunogenicity to regular insulin.**

Insulin

- **Insulin glulisine is formulated by substituting a lysine for asparagine at B3 and glutamic acid for lysine at B29.**
- **Its absorption, action and immunologic characteristics are similar to the above.**

Insulin

2. Short-acting insulin (rapid onset):

(Regular Insulin)

- **It is a short-acting soluble crystalline zinc insulin made by recombinant DNA technique.**
- **Effects appear within 30 min, peak 2-3 hours after sc injection and last for 5-8 hours.**

Insulin

- **In high concentrations (in vials), it self-aggregates in antiparallel fashion to form dimers that stabilize around zinc ions to create insulin hexamers.**
- **After sc injection it dissociates ultimately to monomers.**
- **If administered at meal times, blood glucose rises faster than insulin → early postprandial hyperglycemia and an increased risk of late postprandial hypoglycemia.**

Insulin

- **Therefore, it should be injected 30-45 minutes before meals to minimize this mismatching.**
- **This is the only type of insulin that should be administered IV in the management of diabetic ketoacidosis, and when the insulin requirement is changing rapidly after surgery or acute infections.**

Insulin

- **Rapid-acting and short-acting insulins are dispensed as clear solutions at neutral pH and contain small amount of zinc to increase their stability and shelf-life.**

Insulin

3. Intermediate-acting and Long-acting insulins:

A. NPH (neutral protamine Hagedorn, or isophane insulin).

- **NPH is an intermediate-acting insulin with delayed absorption and onset of action.**
- **Protamine:insulin ratio by weight is 1:10, representing 6 molecules of insulin per molecule of protamine.**

Insulin

- **After sc injection, proteolytic enzymes degrade protamine and permit absorption of insulin.**
- **Onset of action 2-5 hours and duration of 4-12 hours.**
- **Can be mixed with regular, lispro, aspart or glulisine insulin.**
- **Dispensed as turbid suspension at neutral pH with protamine in phosphate buffer.**

Insulin

B. Insulin glargine:

- **It is a soluble, "peakless", and "long-acting" insulin analog. Dispensed as clear solutions.**
- **It is designed to provide reproducible, convenient, background insulin replacement.**
- **Two arginine molecules are attached to the B chain carboxy terminal, and a glycine is substituted for asparagine at the A21 position →**

Insulin

an analog that is soluble in an acidic solution but **precipitates in the more neutral body pH after sc injection.**

- **Insulin molecules slowly dissolve away from the crystalline depot and provide a low, continuous level of circulating insulin.**
- **Onset of action 1-1.5 hours, peak effect occurs at 4-6 hours and maximal activity is maintained for 11-24 hours or longer.**

Insulin

- **Usually given once daily.**
- **Should not be mixed with other insulins.**
- **May be less immunogenic than human insulin (based on animal studies).**
- **Interaction with insulin receptor is similar to that of native insulin.**
- **It has no increase in mitogenic activity.**
- **It has 6-7 fold greater binding than native insulin to insulin-like growth factor-1 (IGF-1) receptor.**

Insulin

C. Insulin detemir:

- **The most recently developed long-acting insulin analog.**
- **The terminal threonine is dropped from the B30 position and myristic acid (FA) is attached to the terminal B29 lysine.**
- **These modifications prolong the availability of the injected analog by increasing both self aggregation in subcutaneous tissue and reversible albumin binding.**

Insulin

- **Its use is associated with less hypoglycemia than NPH insulin.**
- **Onset of action is dose dependent, 1-2 hours, and duration of action of more than 24 hours.**
- **Given twice daily to produce smooth background insulin level.**
- **Dispensed as clear soluble solution.**

Insulin

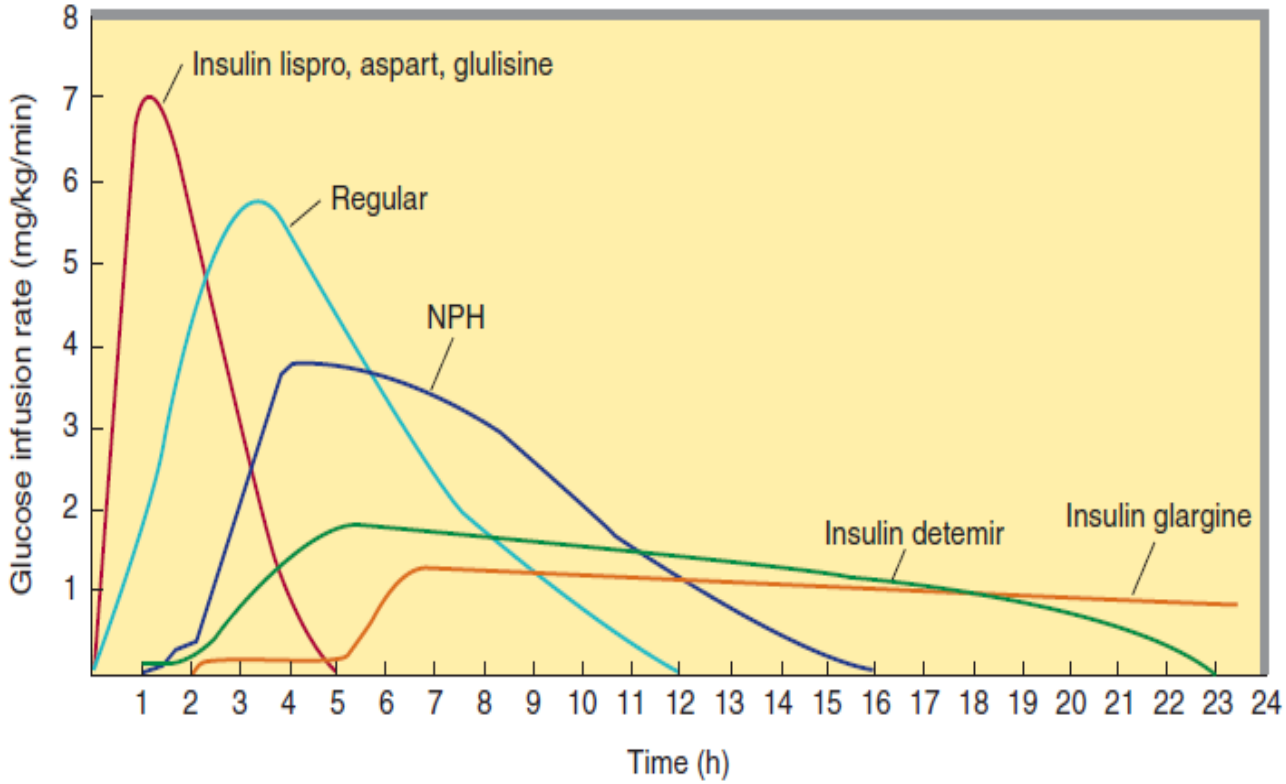


FIGURE 41–5 Extent and duration of action of various types of insulin as indicated by the glucose infusion rates (mg/kg/min) required to maintain a constant glucose concentration. The durations of action shown are typical of an average dose of 0.2–0.3 U/kg. The durations of regular and NPH insulin increase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

Insulin

4. Mixtures of insulin:

- **Because intermediate-acting insulins (NPH) require several hours to reach adequate therapeutic levels, their use in type 1 diabetic patients require supplements of rapid- or short-acting insulin before meals.**
- **For convenience, these are often mixed in the same syringe acutely before injection.**

Insulin

- **Premixed preparations are unstable, but some are available.**
- **Insulin glargine and detemir must be given as separate injections. They are not miscible acutely or in a premixed preparations with any other insulin preparation.**
- **All insulins are available in a concentration of 100 U/mL (U100).**
- **A limited supply of U500 regular human insulin is available for use in severe insulin resistance.**

Insulin

Insulin Delivery Systems:

1. The standard mode is subcutaneous injection using conventional disposable needles and syringes.
2. Portable pen injectors: prefilled, with replaceable needles.
3. Continuous subcutaneous insulin infusion devices (pumps).

Insulin

4. Inhaled insulin:

- **A dry powder formulation of human insulin to be absorbed through the alveolar wall.**
- **Available as small, single use device.**
- **Peak levels are reached in 12 -15 minutes and decline to baseline in 3 hours, faster in onset and shorter in duration than subcutaneous insulin.**

Insulin

- **Inhaled insulin combined with injected basal insulin was as effective in lowering glucose as injected rapid-acting insulin combined with basal insulin.**
- **Adverse effects include cough (27%)**
- **Pulmonary function should be monitored.**
- **The drug is contraindicated in smokers and patients with chronic obstructive pulmonary disease.**

Insulin

Complications of Insulin Therapy:

1. **Hypoglycemia: is the most common and serious complication.**

- **Usually results from inadequate carbohydrate consumption, unusual physical exertion, or too large a dose of insulin.**

Insulin

- **Manifested by signs of autonomic hyperactivity, both sympathetic (tachycardia, palpitations, sweating, tremulousness) and parasympathetic (nausea, hunger), which may progress to convulsions and coma if untreated.**
- **Frequent hypoglycemic episodes during tight glycemic control, lead to "hypoglycemic unawareness", (inadequate autonomic signals).**

Insulin

- **Thus, corrective measures will not be taken.**
- **Untreated hypoglycemia lead to confusion, weakness, bizarre behavior, coma, and seizures.**
- **Hypoglycemic awareness may be restored by preventing frequent hypoglycemic episodes.**

Insulin

- **An identification bracelet, necklace, or card in the wallet or purse, as well as some form of rapidly absorbed glucose, should be carried by every diabetic person who is receiving hypoglycemic drug therapy.**
- **All the manifestations of hypoglycemia are relieved by glucose administration.**

Insulin

2. **Immune disorders:**

- **Many classes of insulin antibodies may be produced during the course of therapy (IgA, IgD, IgG, IgE and IgM) →**

A. **Insulin allergy: immediate type hypersensitivity reaction, anaphylaxis, IgE-mediated. Mainly due to noninsulin protein contaminants.**

B. **Immune insulin resistance: IgG anti-insulin antibodies neutralize action of insulin.**

Insulin

- **May be associated with other systemic autoimmune processes such as lupus erythematosus.**

3. **Lipodystrophy at injection sites:**

   A. Atrophy of subcutaneous fat at site of injection of old animal insulins. Almost never seen with human insulin.

   B. Hypertrophy of subcutaneous fatty tissue at sites of repeated injections.

Oral Antidiabetic Agents

Sulfonylureas

1. **First-generation sulfonylureas:**

   Tolbutamide, Chlorpropamide, Tolazamide.

2. **Second-generation sulfonylureas:**

   Glyburide (glibenclamide), Glipizide, Glimepiride.

- **Are stimulants of insulin secretion.**
- **Are widely prescribed for type 2 DM.**
- **Differ in potency and adverse effects.**

Sulfonylureas

Mechanism of Action:

- They bind to their receptor which is associated with B cell ATP-sensitive K^+ channel.
- This inhibits the efflux of K^+ ions through the channel resulting in cell depolarization → opening of voltage-gated Ca^{2+} channel and calcium influx and the release of preformed insulin.

Sulfonylureas

Glipizide:

- **Have the shortest half-life of the potent agents (2-4 hours).**
- **Absorption is delayed when taken with food, therefore it should be ingested 30 min before breakfast to reduce postprandial hyperglycemia.**
- **90% metabolized in the liver to inactive products, and 10% excreted unchanged in urine.**

Sulfonylureas

- **Contraindicated in patients with significant hepatic impairment and renal insufficiency.**
- **Less likely to produce serious hypoglycemia because of its short half-life.**

Glimepiride:

- **Most potent sulfonylurea.**
- **Given once daily, t½ of 5 hours.**
- **Completely metabolized in the liver to inactive metabolites.**

Sulfonylureas

Glyburide (glibenclamide):

- Flushing has rarely been reported after ethanol ingestion.
- It slightly enhances free water clearance.
- It is contraindicated in the presence of hepatic impairment and in renal insufficiency.

Gliclazide

- It has a half-life of 10 hours. It is completely metabolized by the liver to inactive metabolites.

Sulfonylureas

Secondary failure to sulfonylureas in treatment of type 2 diabetes is a recognized problem. It may be due to a progressive decrease in B cell mass, reduction in physical activity, decline in lean body mass or an increase in fat deposition.

Sulfonylureas

Adverse Effects:

1. **Hypoglycemic reactions including coma and convulsions.**

- **May mimic cerebrovascular accidents.**
- **The longer the half-life, the more likely is the hypoglycemia.**
- **More in elderly patients and those with hepatic or renal impairment.**

Sulfonylureas

- **Potentiated by sulfonamides, clofibrate, dicumarol, salicylates and phenylbutazone (competition for protein binding) and alcohol (malnutrition).**

2. **Nausea and vomiting.**
3. **Cholestatic jaundice.**
4. **Agranulocytosis, aplastic anemia and hemolytic anemia.**
5. **Hypersensitivity reactions.**

Sulfonylureas

6. **Disulfiram-like reaction: alcohol flush, chlorpropamide.**
7. **Hyponatremia by potentiating effects of ADH, chlorpropamide.**

Meglitinides

- **A new class of insulin secretagogues.**

Rapaglinide:

- **Is similar to sulfonylureas in mode of action.**
- **Meglitinides have two binding sites in common with the sulfonylureas and one unique bindingsite.**
- **Very fast onset of action with peak effect at 1 hour after ingestion, and a duration of action of 4-7 hours.**

Meglitinides

- t½ ~ 1 hour
- Metabolized by CYP3A4.
- Indicated for control of postprandial hyperglycemia, to be taken just before meals.
- Hypoglycemia is a risk if the meal is delayed or skipped or contains inadequate carbohydrates.
- It can be used in patients with renal impairment and in the elderly.

Meglitinides

- **There is no sulfur in its structure, so it may be used in type 2 diabetics with sulfur or sulfonylurea allergy.**

Mitiglinide is similar

D-Phenylalanine Derivatives

Nateglinide:

- **Is the latest insulin secretagogue.**
- **It stimulates very rapid and transient release of insulin from B cells through closure of the ATP-sensitive K^+ channels.**
- **It is absorbed within 20 minutes after oral administration with a time to peak concentration of less than 1 hour and an overall duration of action is about 4 hours.**

Nateglinide

- **It is metabolized in the liver by CYP2C9 and CYP3A4 with a half-life of about 1 hour.**
- **Hypoglycemia is the main adverse effect.**
- **It can be used in patients with renal impairment and in the elderly.**

Biguanides

Metformin

- **Is the only biguanide available for clinical use after withdrawal of phenformin which was associated with fatal lactic acidosis.**
- **Its blood-glucose lowering action does NOT depend on functioning pancreatic B cells.**
- **It produces less fasting hyperglycemia as well as less postprandial hyperglycemia.**

Metformin

- **Hypoglycemia during biguanide monotherapy is essentially unknown.**
- **More appropriately termed "euglycemic" agents.**

Proposed Mechanisms of Action:

- **The primary effect is to activate the enzyme AMP-activated protein kinase (AMPK) and reduce hepatic glucose production. (triggers a shift from anabolic to catabolic activities)**

Metformin

Actions:

1. **Reduces gluconeogenesis, and may impair hepatic metabolism of lactic acid.**
2. **Slows glucose absorption from the GIT, with increased glucose to lactate conversion by enterocytes.**
3. **Directly stimulate glycolysis in tissues → increased glucose removal from blood.**
4. **Reduces plasma glucagon levels.**

Metformin

- It decreases insulin levels (which functions as a growth factor).
- ?? May reduce risk of some cancers according to epidemiologic studies. But this is premature to draw conclusions.

Pharmacokinetics:

- t½ ~ 1.5-3 hours.
- Not bound to plasma proteins, not metabolized.
- Excreted unchanged in urine.

Metformin

Clinical Pharmacology:

- **It is the first-line therapy for type 2 diabetes.**
- **It is most often prescribed for "insulin resistance" syndrome (ineffective insulin action), because it is an insulin-sparing agent, does not increase body weight or provoke hypoglycemia.**

Metformin

- **It decreases the risk of macrovascular as well as microvascular disease, in contrast to other therapy which reduces only microvascular morbidity.**
- **It is useful in the prevention of type 2 diabetes in middle-aged obese patients with impaired glucose tolerance and fasting hyperglycemia, but not in older, leaner prediabetics.**

Metformin

Adverse Effects:

1. **Gastrointestinal: anorexia, nausea, vomiting, abdominal discomfort, diarrhea.**

- **Most common, occurs in 20% of patients, especially at a dose > 1000 mg. Dose related.**
- **Tend to occur at the onset of therapy and often transient.**

Metformin

2. **Reduction of vitamin B_{12} levels during long-term therapy.**

- **It interferes with the calcium-dependent absorption of vitamin B_{12}-intrinsic factor complex in the terminal ileum.**
- **Increased intake of calcium may prevent the metformin-induced B_{12} malabsorption.**

Metformin

3. **Lactic acidosis in the presence of hypoxia and renal or hepatic insufficiency. It is contraindicated in patients with renal disease, alcoholism, hepatic disease or conditions predisposing to tissue hypoxia (chronic cardiopulmonary dysfunction).**

- **It is dose-related adverse reaction.**
- **It is not recommended at and above a serum creatinine level of 1.4 mg/dL in women and 1.5 mg/dL in men.**

Metformin

- **Radiocontrast administration can cause acute kidney failure in patients with diabetes and incipient nephropathy.**
- **Metformin therapy should therefore be temporarily halted on the day of radiocontrast use and restarted a day or two later after confirmation that renal function has not deteriorated.**

Thiazolidinediones

- Act to reduce insulin resistance.
- Are considered "euglycemic".
- They act as ligands to (Peroxisome proliferator-activated receptor-gamma, PPAR-γ).
- PPAR-γ is part of the steroid and thyroid superfamily of nuclear receptors.
- PPAR-γ are found in muscle, fat and liver.

Thiazolidinediones

- **PPAR-γ receptors modulate the expression of the genes involved in lipid and glucose metabolism, insulin signal transduction, and adipocyte and other tissue differentiation.**

Thiazolidinediones

Actions include:

1. **Increased glucose transporter expression (GLUT 1 and GLUT 4).**
2. **Decreased free fatty acid levels.**
3. **Decreased hepatic glucose output.**
4. **Increased adiponectin and decreased release of resistin from adipocytes.**
5. **Increased differentiation of preadipocytes to adipocytes.**

Thiazolidinediones

6. **Decreased levels of:**

- **Plasminogen activator inhibitor type 1.**
- **Matrix metalloproteinase-9.**
- **C-reactive protein.**
- **Interleukin-6.**

Thiazolidinediones

- **In diabetes, the major site of action is adipose tissue: promote glucose uptake and utilization and modulate synthesis of lipid hormones or cytokines and proteins involved in energy regulation.**
- **Promote fatty-acid uptake and storage in adipose tissue rather than skeletal muscle or liver, which makes them more sensitive to insulin.**

Thiazolidinediones

- **May favor insulin sensitivity at the muscle and liver by stimulating AMPK.**
- **Suppress glucose production in the liver.**
- **Restricted to patients who remain hyperglycemic despite taking other anti-diabetic medications.**

Thiazolidinediones

Pioglitazone:

- **Food may delay absorption, extent not affected.**
- **Metabolized by CYP2C8 & CYP3A4 to active metabolites. (drug interactions with estrogen-containing contraceptives for example).**
- **It lowers triglycerides and increases HDL cholesterol without affecting total cholesterol and low-density lipoprotein (LDL) cholesterol.**

Thiazolidinediones

- **Pioglitazone is approved as a monotherapy and in combination with metformin, sulfonylureas, and insulin for the treatment of type 2 diabetes.**

Rosiglitazone:

- **Rapidly absorbed and highly protein bound.**
- **Metabolized mainly by CYP2C8 to minimally active metabolites.**
- **Have anti-inflammatory activity.**

Thiazolidinediones

- **It 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.**
- **It increases total cholesterol, HDL cholesterol, and LDL cholesterol but does not have significant effect on triglycerides.**

Thiazolidinediones

- These drugs have been shown to improve the biochemical and histologic features of nonalcoholic fatty liver disease.
- They seem to have a positive effect on endothelial function: pioglitazone reduces neointimal proliferation after coronary stent placement.
- Rosiglitazone has been shown to reduce microalbuminuria.

Thiazolidinediones

- **Individuals experiencing secondary failure to other antidiabetic drugs benefit from the addition of thiazolidinediones.**
- **Have a slow onset and offset of activity over weeks or months, because their mechanism of action involves gene regulation.**
- **Have the benefit of preventing type 2 diabetes.**

Thiazolidinediones

Adverse Effects:

1. **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, as well as dilutional anemia.**
2. **New or worsening macular edema with rosiglitazone. Improves when drug is discontinued.**

Thiazolidinediones

3. **Dose-related weight gain, especially when used in combination with a sulfonylurea or insulin. Some of it may be fluid related.**
4. **Loss of bone mineral density and extremity bone fractures in women, which is postulated to be due to decreased osteoblast formation.**
5. **Increased risk of bladder cancer with increased dosage and duration of pioglitazone use.**

Thiazolidinediones

Precautions and Contraindications:

1. **Should not be used during pregnancy, in the presence of liver disease, in the presence of heart failure**
2. **Anovulatory women may resume ovulation → pregnancy.**
3. **Hepatotoxic, monitor for liver function. (troglitazone was withdrawn because of this).**

Amylin Analogues

Pramlintide:

- **Slow gastric emptying – vagally mediated.**
- **Reduce glucagon secretion.**
- **Promote satiety or reduce appetite - centrally.**
- **Produces moderate weight loss.**
- **Given by subcutaneous injection before meals.**
- **Used in type 1 DM, and type 2 DM unable to achieve their target postprandial blood glucose levels.**

Pramlintide

- **It is rapidly absorbed after subcutaneous administration; levels peak within 20 minutes, and the duration of action is not more than 150 minutes.**
- **Should be injected immediately before eating, always by itself using a separate syringe; it cannot be mixed with insulin.**

Pramlintide

Adverse effects:

1. **Hypoglycemia:** **concurrent rapid- or short-acting mealtime insulin dosages should be decreased by 50% or more.**
2. **GIT: nausea, vomiting, anorexia.**

GLP-1 – Based "incretin" Therapies

A. **GLP-1 analogues (exenatide, liraglutide, albiglutide, and dulaglutide):**

Exenatide:

- **It is a long-acting analogue of GLP-1, Acts as agonist at GLP-1 receptors.**
- **Used as adjunctive therapy in persons with type 2 diabetes treated with metformin or metformin plus sulfonylureas who still have suboptimal glycemic control.**

Exenatide

- It increases insulin secretion in a glucose-dependent manner. The increased insulin secretion is speculated to be due in part to an increase in beta-cell mass, from decreased beta-cell apoptosis, increased beta-cell formation, or both. (Noticed in culture)
- Suppresses postprandial glucagon release.
- Delays gastric emptying.

Exenatide

- It is injected subcutaneously within 60 minutes before breakfast and dinner.
- It peaks in ~ 2 hours with a duration of action of up to 10 hours.
- The oral hypoglycemics dosage may need to be decreased to prevent hypoglycemia.

Exenatide

- **Suppresses appetite. (Type 2 diabetes patients on GLP-1 therapy are less hungry). May be related to the deceleration of gastric emptying or suppression of appetite).**
- **Associated with weight loss.**

Exenatide

Adverse effects:

1. **Nausea, vomiting, diarrhea:** major adverse effect is nausea (45%), which is dose dependent and declines with time.
2. **Acute pancreatitis.**
3. **Renal impairment and acute renal injury.**
4. **Not associated with hypoglycemia unless used in combination.**

GLP-1 – Based “incretin” Therapies

B. Dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin, saxagliptin, linagliptin, vildagliptin, and alogliptin):

Sitagliptin:

- **Inhibit DPP-4, the enzyme that degrades incretin hormones.**
- **Prolong the half-life of endogenous GLP-1.**
- **Decrease postprandial glucose levels.**
- **Decrease glucagon concentration.**

Sitagliptin

- **Increase circulating GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) and thus, insulin concentrations in a glucose-dependent manner.**
- **Most commonly used in combination with a TZD or metformin, or sulfonylureas.**
- **May be used as monotherapy.**

GLP-1 – Based “incretin” Therapies

- **Used for type 2 DM orally, peaks within 1–4 hours, and has a half-life of approximately 12 hours.**
- **Dosage should be reduced in patients with impaired renal function**
- **Weight neutral.**

GLP-1 – Based “incretin” Therapies

Adverse effects:

1. **Nasopharyngitis, upper respiratory infections, headaches**
2. **Hypoglycemia when the drug is combined with insulin secretagogues or insulin. Not associated with hypoglycemia when used alone.**
3. **Acute pancreatitis which may be fatal.**
4. **Allergic reactions.**

α-Glucosidase Inhibitors

- **Complex starches, oligosaccarides, and disaccharides must be broken to monosaccharides to be absorbed in duodenum and upper jejunum.**
- **This is facilitated by enteric enzymes attached to the brush border of intestinal cells such as pancreatic α-amylase and α-glucosidase.**

α-Glucosidase Inhibitors

Acarbose and Miglitol

- **Are competitive inhibitors of intestinal α-glucosidases: sucrase, maltase, glycoamylase, dextranase.**
- **Miglitol is 6 times more potent than acarbose.**
- **Miglitol alone inhibits isomaltase and β-glucosidases.**
- **Acarbose alone inhibits α-amylase.**
- **Administered just before each meal.**

α-Glucosidase Inhibitors

- **Reduce the postprandial digestion and absorption of starch and disaccharides → reducing postprandial hyperglycemia and delaying absorption of sugars to distal segments of the intestine, thus having insulin sparing action.**
- **Used for type 2 diabetes.**
- **Can prevent type 2 diabetes development in prediabetics.**

α-Glucosidase Inhibitors

- **Reduce cardiovascular disease and hypertension.**

Adverse Effects:

1. **Flatulence, diarrhea and abdominal pain. Due to undigested carbohydrates in the colon which is fermented by bacteria → gases. These effects are transient because of induction of α-glucosidase in jejunum and ileum.**

α-Glucosidase Inhibitors

2. **Hypoglycemia with combination therapy which should be treated with glucose and NOT sucrose (why?).**

Precautions and Contraindications:

1. **Inflammatory bowel disease or GI diseases that could be worsened by gas and distension.**
2. **Should not be administered to patients with renal insufficiency (excreted by the kidney).**

α-Glucosidase Inhibitors

3. **Acarbose should be used with caution in hepatic disease because it has been shown to elevate hepatic enzymes (reversible).**

Sodium-glucose Co-transporter 2 (SGLT2) Inhibitors

- **SGLT2 is the main transporter for glucose re-absorption in the proximal tubules (90%).**
- **Inhibitors include canagliflozin, dapagliflozin, and empagliflozin. → increase urinary glucose loss.**
- **Not very effective in chronic renal dysfunction and even contraindicated.**

(SGLT2) Inhibitors

Adverse effects:

1. **Increased incidence of genital and urinary tract infections.**
2. **Intravascular volume contraction and hypotension ← osmotic diuresis.**
3. **Increase LDL cholesterol**
4. **Higher rates of breast cancer and bladder cancer.**

*** Prof. Yacoub is against this idea.**