الجامعة السورية الخاصة
SYRIAN PRIVATE UNIVERSITY

السنة الثالثة

تأثير الأدوية2

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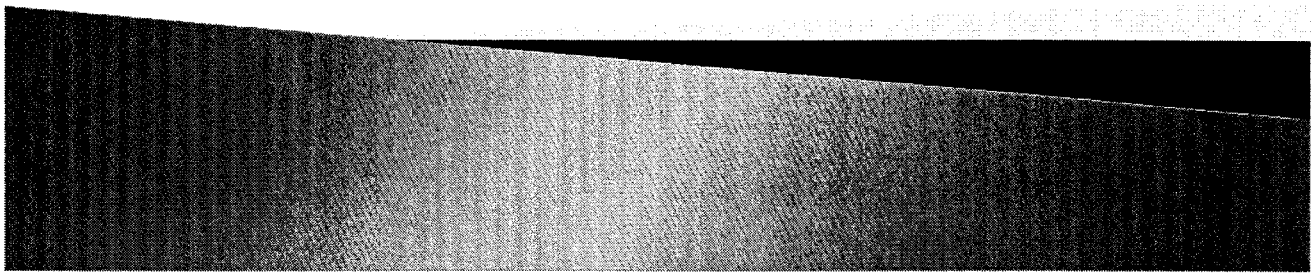
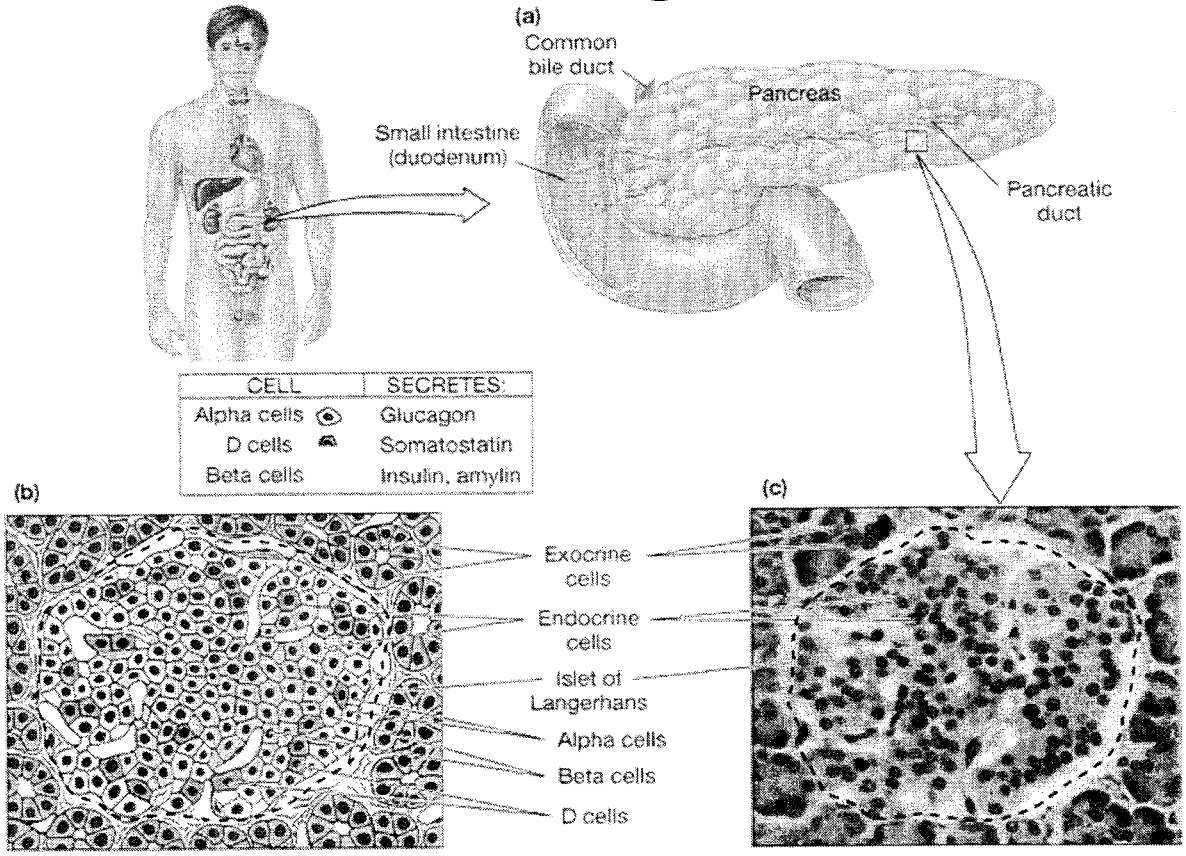
Endocrine pancreas and the control of blood glucose



Pancreas

- A triangular gland, which has both exocrine and endocrine cells, located behind the stomach
- Strategic location
- Acinar cells produce an enzyme-rich juice used for digestion (exocrine product)
- Pancreatic islets (**islets of Langerhans**) produce hormones involved in regulating fuel storage and use.

Islets of Langerhans



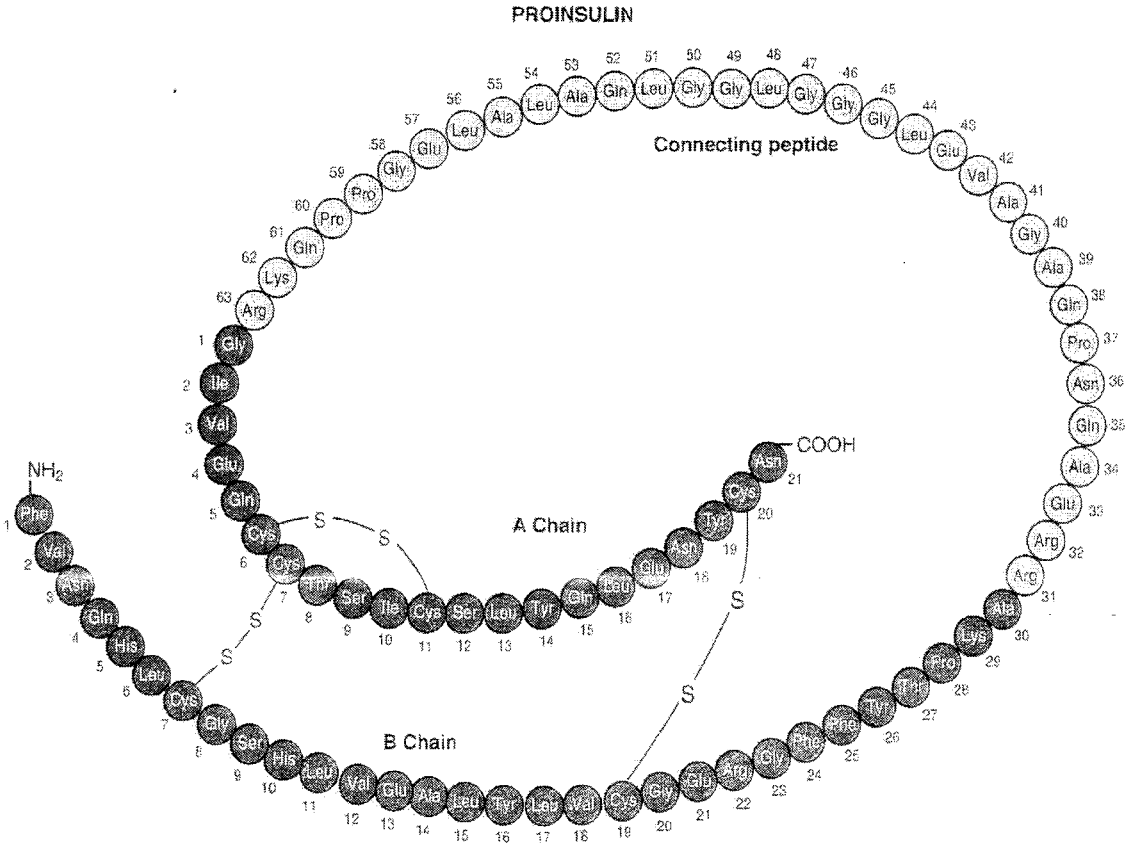
Islets of Langerhans

- 1 million islets
- 1-2% of the pancreatic mass
- Beta (β) cells produce insulin, amylin
- Alpha (α) cells produce glucagon
- Delta (δ) cells produce somatostatin
- F cells produce pancreatic polypeptide

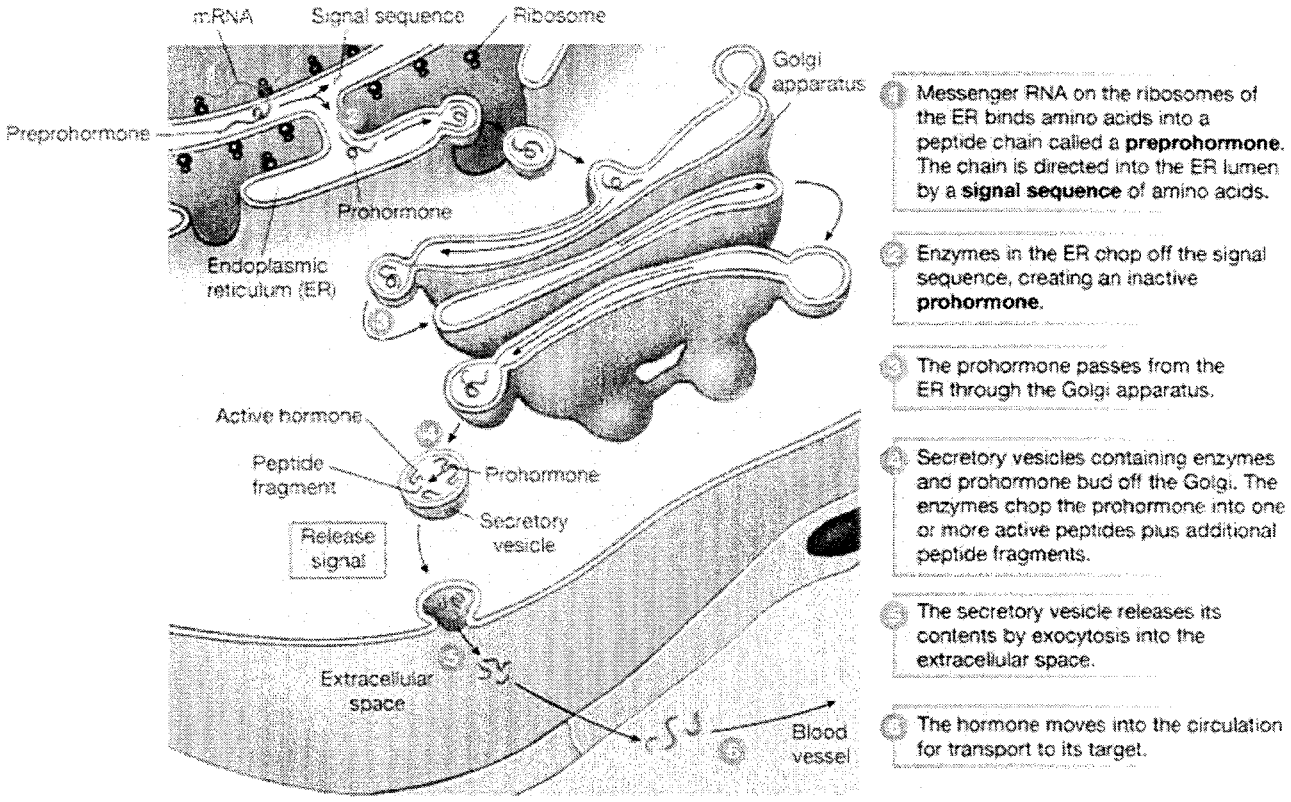
Insulin

- Hormone of nutrient abundance
- A protein hormone consisting of two amino acid chains linked by disulfide bonds
- Synthesized as part of proinsulin and then excised by enzymes, releasing functional insulin (51 AA) and C peptide (29 AA).

Insulin Structure

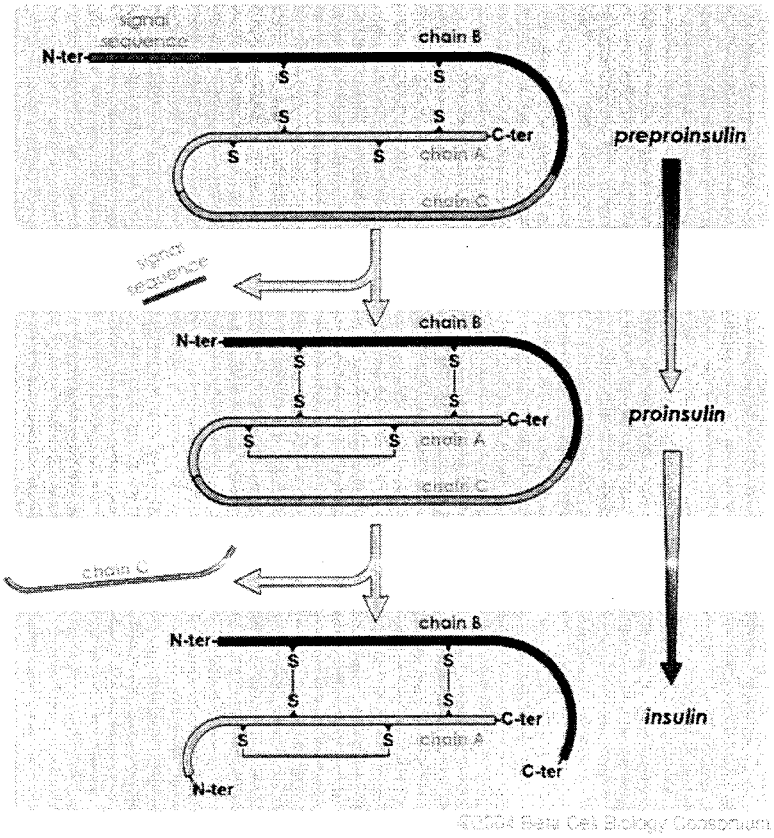


Protein and Polypeptide Synthesis and Release



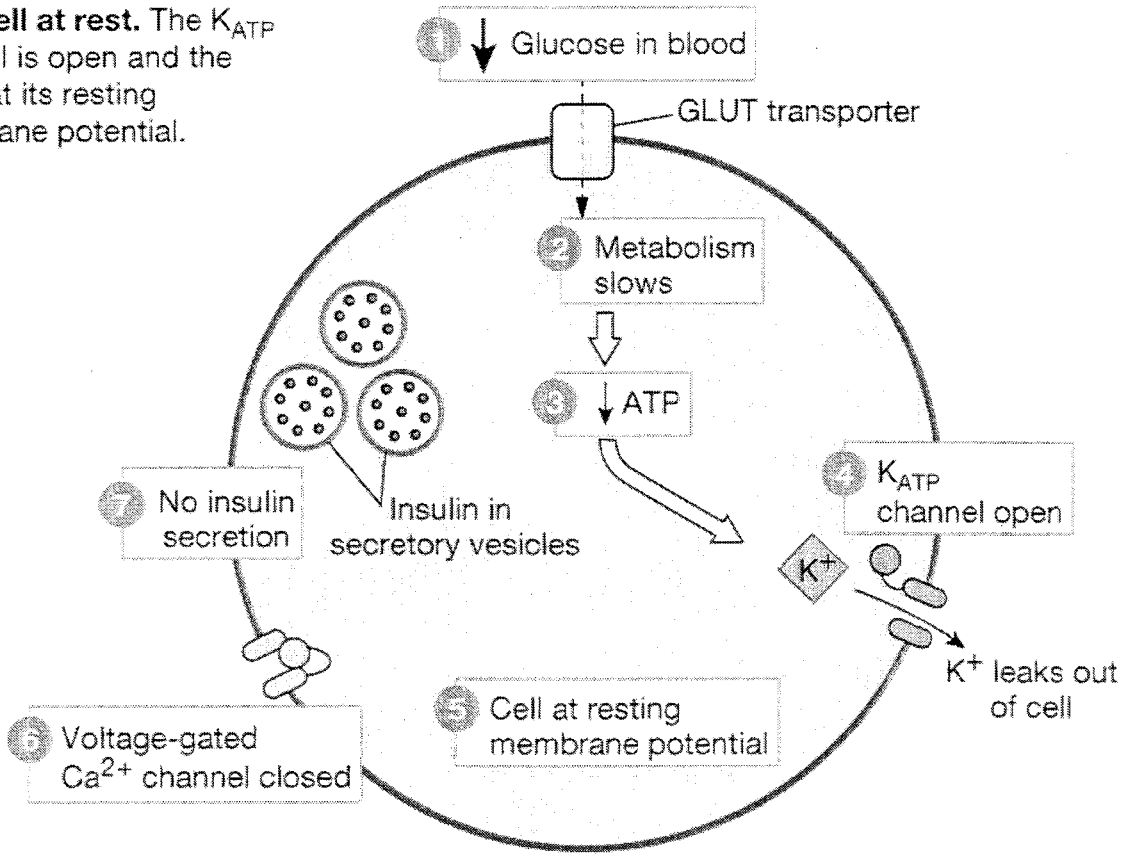
Insulin Synthesis

- insulin gene encodes a large precursor of insulin (preproinsulin)
- During translation, the signal peptide is cleaved (proinsulin)
- During packaging in granules by Golgi, proinsulin is cleaved into insulin and C peptide

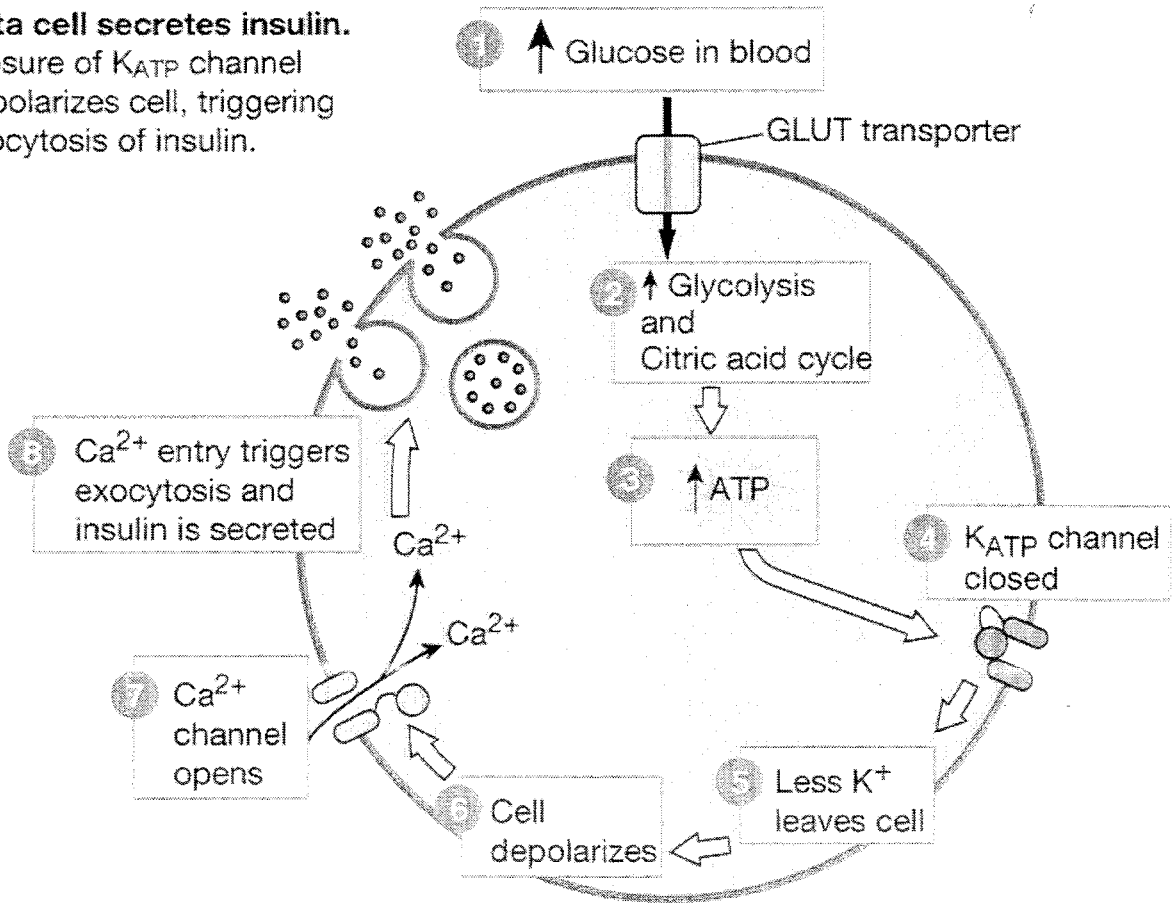


Insulin Secretion

(a) Beta cell at rest. The K_{ATP} channel is open and the cell is at its resting membrane potential.



(b) Beta cell secretes insulin. Closure of K_{ATP} channel depolarizes cell, triggering exocytosis of insulin.



Regulation of Insulin Secretion

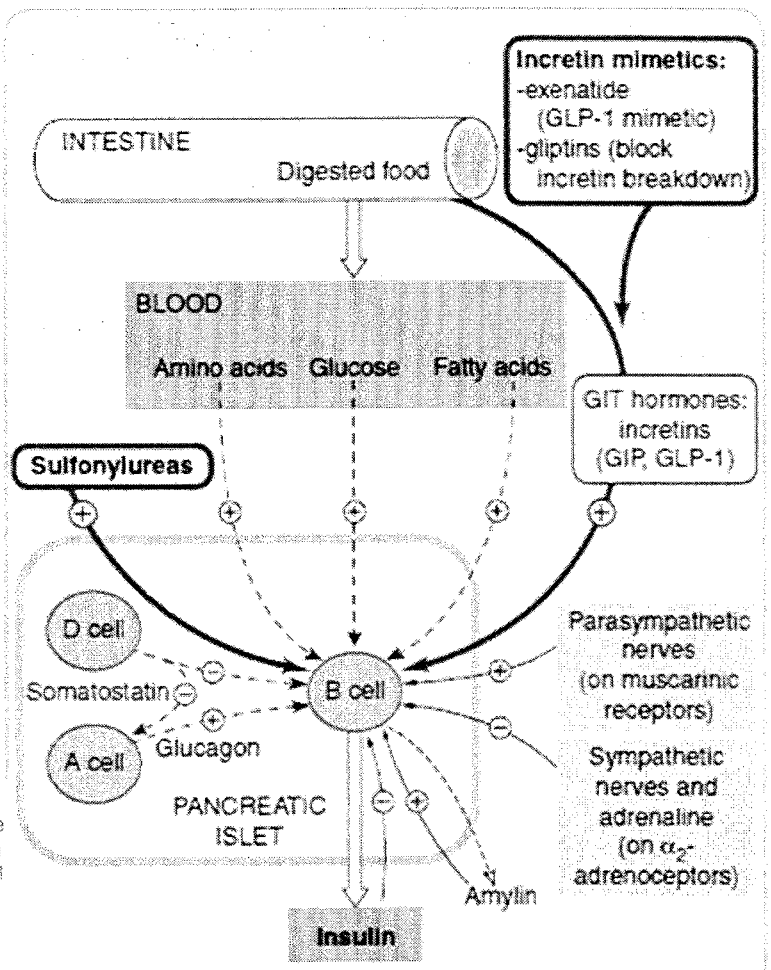


Fig. 30.1 Factors regulating insulin secretion. Blood glucose is the most important factor. Drugs used to stimulate insulin secretion are shown in red-bordered boxes. Glucagon potentiates insulin release but opposes some of its peripheral actions and increases blood glucose. GIP, gastric inhibitory peptide; GIT, gastrointestinal tract; GLP-1, glucagon-like peptide-1.

Regulation of Insulin Secretion

- No insulin is produced when plasma glucose below 50 mg/dl
- Half-maximal insulin response occurs at 150 mg/dl
- A maximum insulin response occurs at 300 mg/dl

Insulin secretion is biphasic:

- Upon glucose stimulation– an initial burst of secretion (5-15 min.)
- Then a second phase of gradual increment that lasts as long as blood glucose is high

- low basal levels of circulating insulin are maintained through constant β-cell secretion which suppresses lipolysis, proteolysis, and glycogenolysis
- A burst of insulin secretion occurs within 2 minutes after a meal, in response to transient increases in circulating glucose and amino acids
- This lasts for up to 15 minutes and is followed by the postprandial secretion of insulin

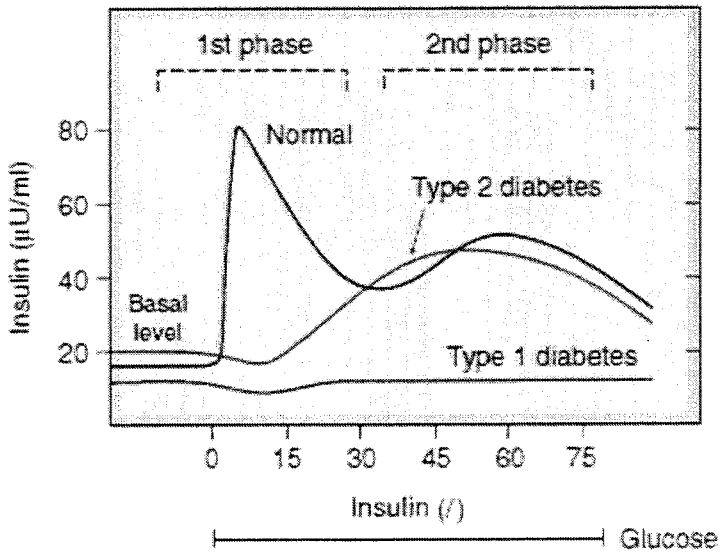


Fig. 30.2 Schematic diagram of the two-phase release of insulin in response to a constant glucose infusion. The first phase is missing in type 2 (non-insulin-dependent) diabetes mellitus, and both are missing in type 1 (insulin-dependent) diabetes mellitus. The first phase is also produced by amino acids, sulfonylureas, glucagon and gastrointestinal tract hormones. (Data from Pfeifer et al. 1981 Am J Med 70: 579–588.)

Control Of Blood Glucose

Table 30.1 The effect of hormones on blood glucose

Hormone	Main actions	Main stimuli for secretion	Main effect
Main regulatory hormone			
Insulin	↑ Glucose uptake ↑ Glycogen synthesis ↓ Glycogenolysis ↓ Gluconeogenesis	Acute rise in blood glucose Incretins (GIP and GLP-1)	↓ Blood glucose
Main counter-regulatory hormones			
Glucagon	↑ Glycogenolysis ↑ Glyconeogenesis	Hypoglycaemia (i.e. blood glucose <3 mmol/l), (e.g. with exercise, stress, high protein meals), etc.	↑ Blood glucose
Adrenaline (epinephrine)	↑ Glycogenolysis		
Glucocorticoids	↓ Glucose uptake ↑ Gluconeogenesis ↓ Glucose uptake and utilisation		
Growth hormone	↓ Glucose uptake		

Effects of insulin

Table 30.2 Effects of insulin on carbohydrate, fat and protein metabolism

Type of metabolism	Liver cells	Fat cells	Muscle
Carbohydrate metabolism	↓ Gluconeogenesis ↓ Glycogenolysis ↑ Glycolysis ↑ Glycogenesis	↑ Glucose uptake ↑ Glycerol synthesis	↑ Glucose uptake ↑ Glycolysis ↑ Glycogenesis
Fat metabolism	↑ Lipogenesis ↓ Lipolysis	↑ Synthesis of triglycerides ↑ Fatty acid synthesis ↓ Lipolysis	–
Protein metabolism	↓ Protein breakdown	–	↑ Amino acid uptake ↑ Protein synthesis

Insulin Signaling

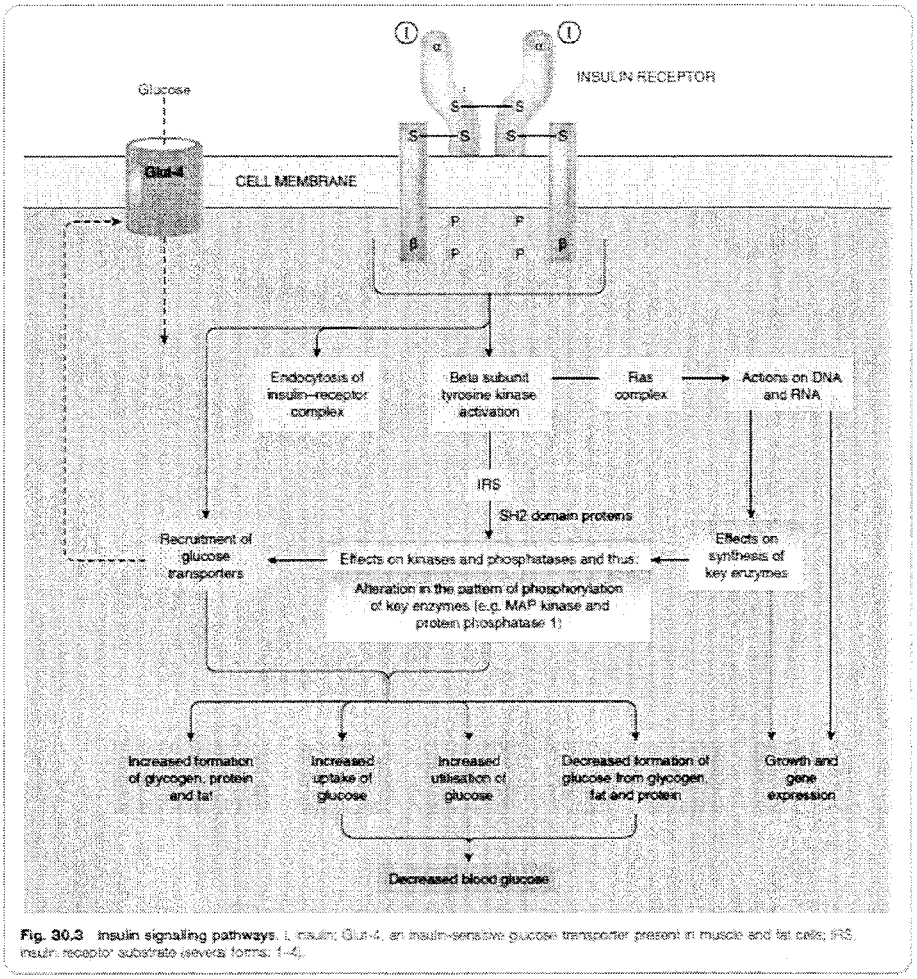
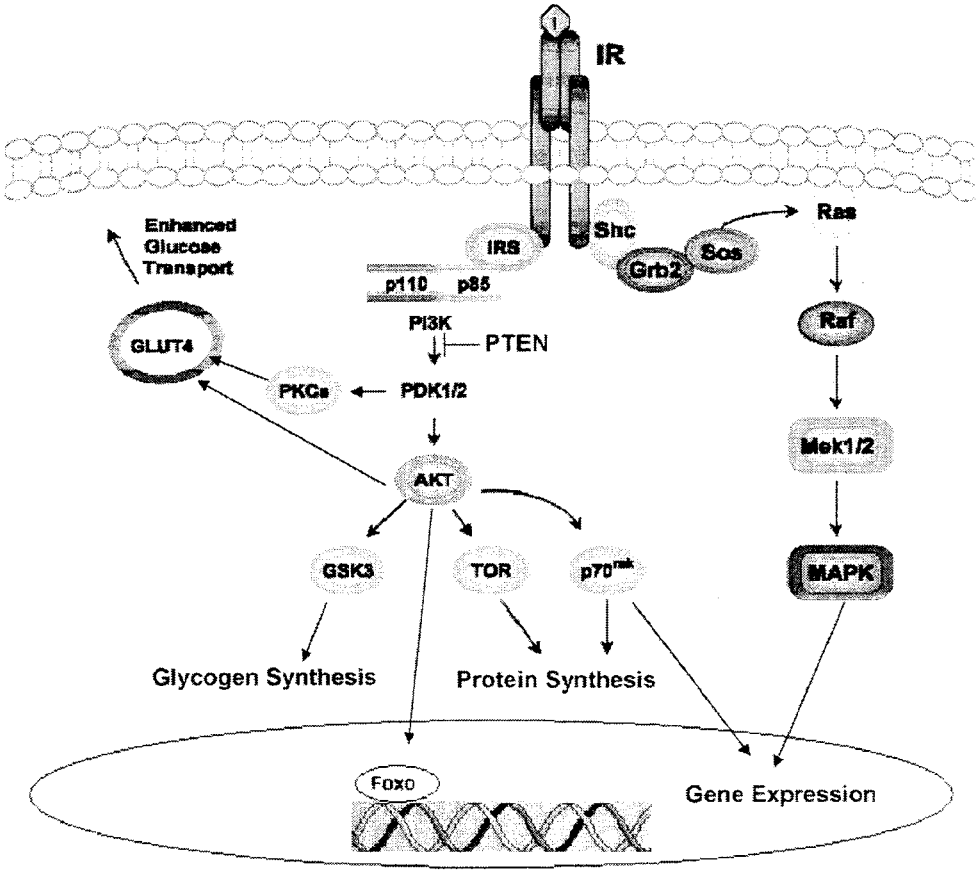


Fig. 30.3 Insulin signalling pathways. I, insulin; Glut-4, an insulin-sensitive glucose transporter present in muscle and fat cells; IRS, insulin receptor substrate (several forms, 1–4).

Insulin Signaling



Diabetes Mellitus

- Diabetes is heterogeneous group of syndromes characterized by an elevation of blood glucose caused by relative or absolute deficiency of insulin
- There are four clinical classifications of diabetes:
  - Type 1 diabetes (insulin dependent diabetes mellitus)
  - Type 2 diabetes (non-insulin dependent diabetes mellitus)
  - Gestational diabetes
  - Diabetes due to other causes (genetic defects or medications, etc)

How is diabetes screened and diagnosed?

Criteria for Screening for T2D and Prediabetes in Asymptomatic Adults

- Age ≥45 years without other risk factors
- Family history of T2D
- CVD
- Overweight
  - BMI ≥30 kg/m^2
  - BMI 25-29.9 kg/m^2 plus other risk factors*
- Sedentary lifestyle
- Member of an at-risk racial or ethnic group: Asian, African American, Hispanic, Native American, and Pacific Islander
- Dyslipidemia
  - HDL-C <35 mg/dL
  - Triglycerides >250 mg/dL
- IGT, IFG, and/or metabolic syndrome
- PCOS, acanthosis nigricans, NAFLD
- Hypertension (BP >140/90 mm Hg or therapy for hypertension)
- History of gestational diabetes or delivery of a baby weighing more than 4 kg (9 lb)
- Antipsychotic therapy for schizophrenia and/or severe bipolar disease
- Chronic glucocorticoid exposure
- Sleep disorders† in the presence of glucose intolerance

- Screen at-risk individuals with glucose values in the normal range every 3 years
- Consider annual screening for patients with 2 or more risk factors

*At-risk BMI may be lower in some ethnic groups; consider using waist circumference.
†Obstructive sleep apnea, chronic sleep deprivation, and night shift occupations.
BMI = body mass index; BP = blood pressure; CVD=cardiovascular disease; HDL-C = high density lipoprotein cholesterol; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; NAFLD = nonalcoholic fatty liver disease; PCOS = polycystic ovary syndrome; T2D, type 2 diabetes.

Diagnostic Criteria for Prediabetes and Diabetes in Nonpregnant Adults

Normal	High Risk for Diabetes	Diabetes
FPG <100 mg/dL	IFG FPG ≥100-125 mg/dL	FPG ≥126 mg/dL
2-h PG <140 mg/dL	IGT 2-h PG ≥140-199 mg/dL	2-h PG ≥200 mg/dL Random PG ≥200 mg/dL + symptoms*
A1C <5.5%	5.5 to 6.4% For screening of prediabetes†	≥6.5% Secondary‡

*Polydipsia (frequent thirst), polyuria (frequent urination), polyphagia (extreme hunger), blurred vision, weakness, unexplained weight loss.

†A1C should be used only for screening prediabetes. The diagnosis of prediabetes, which may manifest as either IFG or IGT, should be confirmed with glucose testing.

‡Glucose criteria are preferred for the diagnosis of DM. In all cases, the diagnosis should be confirmed on a separate day by repeating the glucose or A1C testing. When A1C is used for diagnosis, follow-up glucose testing should be done when possible to help manage DM.

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; PG, plasma glucose.

How is diabetes screened and diagnosed?

Diagnostic Criteria for Gestational Diabetes

Test	Screen at 24-28 weeks gestation
FPG, mg/dL	>92
1-h PG*, mg/dL	≥180
2-h PG*, mg/dL	≥153

*Measured with an OGTT performed 2 hours after 75-g oral glucose load.

FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; PG, plasma glucose.

- Gestational diabetes is defined as carbohydrate intolerance with onset or first recognition during pregnancy
  - It is important to maintain adequate glycemic control during pregnancy
  - Uncontrolled gestational diabetes can lead to fetal macrosomia (abnormally large body), shoulder dystocia (difficult delivery), and neonatal hypoglycemia

  - Diet, exercise, and or insulin administration are effective in this condition

	Type 1	Type 2
Age of onset	Usually during childhood or puberty	Commonly over age 35
Nutritional status at time of onset	Commonly undernourished	Obesity usually present
Prevalence	5 to 10 percent of diagnosed diabetics	90 to 95 percent of diagnosed diabetics
Genetic predisposition	Moderate	Very strong
Defect or deficiency	β cells are destroyed, eliminating the production of insulin	Inability of β cells to produce appropriate quantities of insulin; insulin resistance; other defects

Type 1 diabetes

- Absolute deficiency of insulin caused by massive β-cell necrosis
- Loss of β-cell function is usually ascribed to autoimmune- mediated processes against the β cell
- May be triggered by an invasion of viruses or the action of chemical toxins
- Due to β-cell destruction pancreas fails to respond to glucose

Type I diabetes

- Shows classic symptoms of insulin deficiency (polydipsia, polyphagia, polyuria, and weight loss)

- Require exogenous (injected) insulin to control hyperglycemia and maintain blood glucose concentrations as close to normal as possible

- Treatment helps in avoiding hyperglycemia and life-threatening ketoacidosis

Type I diabetes (T1DM)

- Having non-functional β cells in T1DM can neither maintain a basal secretion level of insulin nor respond to variations in circulating fuels

- The development and progression of neuropathy, nephropathy, and retinopathy are directly related to the extent of glycemic control (measured as blood levels of glucose and/or HbA1c)

Type 2 diabetes

- Most diabetic cases
- Influenced by genetic factors, aging, obesity, and peripheral insulin resistance, rather than autoimmune processes or viruses
- The metabolic alterations observed are milder than those described for type 1
- The long-term clinical consequences can be as devastating

- The pancreas retains some β-cell function, but variable insulin secretion is insufficient to maintain glucose homeostasis
- The β-cell mass may become gradually reduced in type 2
- In contrast to patients with type 1, type 2 diabetes are often obese
- Frequently accompanied by the lack of sensitivity of target organs to either endogenous or exogenous insulin

Type 2 diabetes (T2DM)

- The goal in treating T2DM is to maintain blood glucose concentrations within normal limits and to prevent the development of long-term complications of the disease
- Weight reduction, exercise, and dietary modification decrease insulin resistance and correct the hyperglycemia of type 2 diabetes in some patients
- Most patients are dependent on pharmacologic intervention with oral glucose-lowering agents
- As the disease progresses, β-cell function declines and insulin therapy is often required

Type 2 diabetes

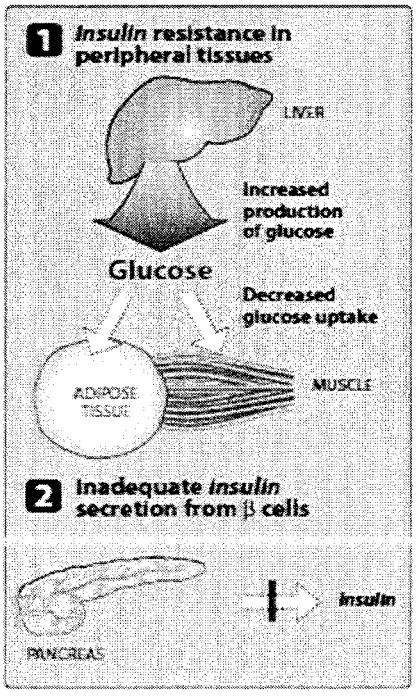


Figure 25.4
Major factors contributing to hyperglycemia observed in type 2 diabetes.

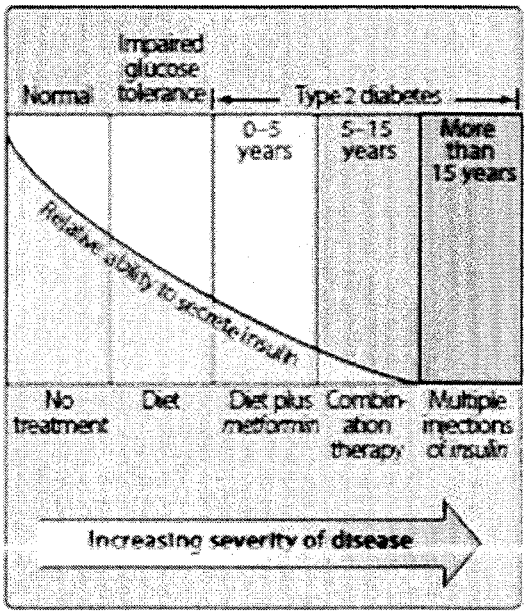
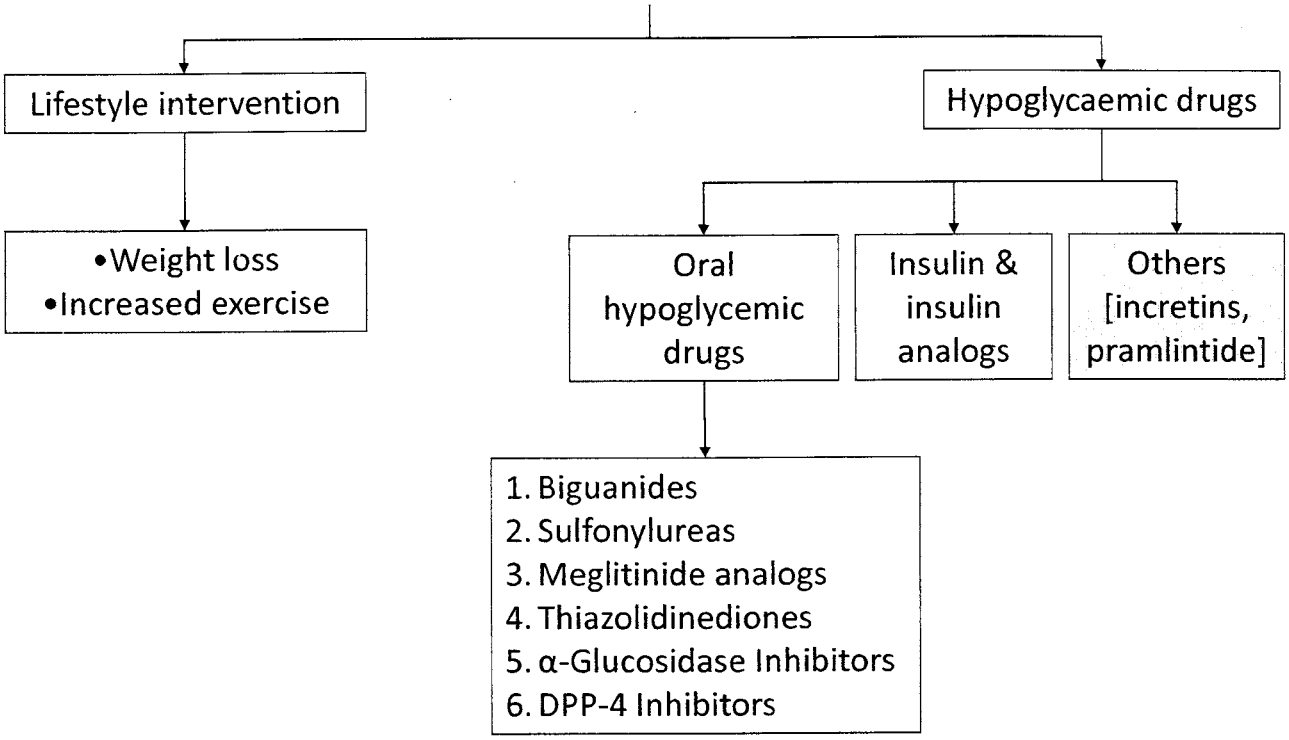


Figure 25.5
Duration of type 2 diabetes mellitus, sufficiency of endogenous *insulin*, and recommended sequence of therapy.

Treatment



How are glycemic targets achieved for T2D?

Therapeutic Lifestyle Changes

Parameter	Treatment Goal
Weight loss (for overweight and obese patients)	Reduce by 5% to 10%
Physical activity	150 min/week of moderate-intensity exercise (eg, brisk walking) plus flexibility and strength training
Diet	• Eat regular meals and snacks; avoid fasting to lose weight • Consume plant-based diet (high in fiber, low calories/glycemic index, and high in phytochemicals/antioxidants) • Understand Nutrition Facts Label information • Incorporate beliefs and culture into discussions • Use mild cooking techniques instead of high-heat cooking • Keep physician-patient discussions informal

Healthful Eating Recommendations

Carbohydrate	Specify healthful carbohydrates (fresh fruits and vegetables, legumes, whole grains); target 7-10 servings per day Preferentially consume lower-glycemic index foods (glycemic index score <55 out of 100: multigrain bread, pumpernickel bread, whole oats, legumes, apple, lentils, chickpeas, mango, yams, brown rice)
Fat	Specify healthful fats (low mercury/contaminant-containing nuts, avocado, certain plant oils, fish) Limit saturated fats (butter, fatty red meats, tropical plant oils, fast foods) and trans fat; choose fat-free or low-fat dairy products
Protein	Consume protein in foods with low saturated fats (fish, egg whites, beans); there is no need to avoid animal protein Avoid or limit processed meats
Micronutrients	Routine supplementation is not necessary; a healthful eating meal plan can generally provide sufficient micronutrients Chromium; vanadium; magnesium; vitamins A, C, and E; and CoQ10 are not recommended for glycemic control Vitamin supplements should be recommended to patients at risk of insufficiency or deficiency

How are glycemic targets achieved for T2D?

Noninsulin Agents Available for T2D

Class	Primary Mechanism of Action	Agent(s)	Available as
α-Glucosidase inhibitors	• Delay carbohydrate absorption from intestine	Acarbose Miglitol	Precose or generic Glyset
Amylin analogue	• Decrease glucagon secretion • Slow gastric emptying • Increase satiety	Pramlintide	Symlin
Biguanide	• Decrease HGP • Increase glucose uptake in muscle	Metformin	Glucophage or generic
Bile acid sequestrant	• Decrease HGP? • Increase incretin levels?	Colesevelam	WelChol
DPP-4 inhibitors	• Increase glucose-dependent insulin secretion • Decrease glucagon secretion	Alogliptin Linagliptin Saxagliptin Sitagliptin	Nesina Tradjenta Onglyza Januvia
Dopamine-2 agonist	• Activates dopaminergic receptors	Bromocriptine	Cycloset
Glinides	• Increase insulin secretion	Nateglinide Repaglinide	Starlix or generic Prandin

DPP-4 = dipeptidyl peptidase; HGP = hepatic glucose production.

Continued on next slide

Noninsulin Agents Available for T2D

Class	Primary Mechanism of Action	Agent(s)	Available as
GLP-1 receptor agonists	• Increase glucose-dependent insulin secretion • Decrease glucagon secretion • Slow gastric emptying • Increase satiety	Albiglutide Dulaglutide Exenatide Exenatide XR Liraglutide	Tanzeum Trulicity Byetta Bydureon Victoza
SGLT2 inhibitors	• Increase urinary excretion of glucose	Canagliflozin Dapagliflozin Empagliflozin	Invokana Farxiga Jardiance
Sulfonylureas	• Increase insulin secretion	Glimepiride Glipizide Glyburide	Amaryl or generic Glucotrol or generic Diaβeta, Glynase, Micronase, or generic
Thiazolidinediones	• Increase glucose uptake in muscle and fat • Decrease HGP	Pioglitazone Rosiglitazone	Actos Avandia

GLP-1 = glucagon-like peptide; HGP = hepatic glucose production; SGLT2 = sodium glucose cotransporter 2.