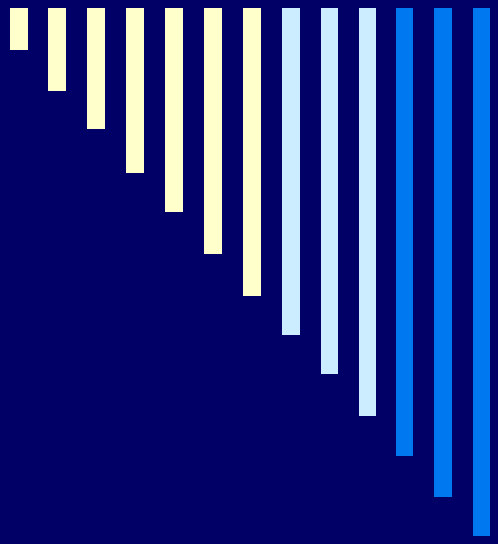


Diabetes mellitus

- Diabetes is one of the largest global health emergencies of the 21st century. Each year more and more people live with this condition, which can result in life-changing complications. In addition to the 415 million adults who are estimated to currently have diabetes, there are 318 million adults with impaired glucose tolerance, which puts them at high risk of developing the disease in the future.

Diabetes and its complications are major causes of death in most countries. Type 2 diabetes is the most prevalent form of diabetes and has increased alongside cultural and societal changes. In high-income countries up to 91% of adults with the disease have type 2 diabetes. It is estimated by IDF that 193 million people with diabetes are undiagnosed and are therefore more at risk of developing complications. Furthermore, one in 15 adults is estimated to have impaired glucose tolerance, and one in seven births is affected by gestational diabetes. Both of these conditions are associated with an increased risk of developing type 2 diabetes in later life.

Diabetes is a human and an economic burden

1/12
people with
DIABETES

The pancreas is made up of two functionally different organs: the exocrine pancreas, the major digestive gland of the body; and the endocrine pancreas, the source of insulin, glucagon, somatostatin, and pancreatic polypeptide.

Cell Types	Approximate Percentage of Islet Volume		Secretory Products
	Dorsally Derived (Anterior Head, Body, Tail)	Ventrally Derived (Posterior Portion of Head)	
A cell (α)	10%	< 0.5%	Glucagon, proglucagon, glucagon-like peptides (GLP-1 and GLP-2)
B cell (β)	70–80%	15–20%	Insulin, C peptide, proinsulin, amylin, γ-aminobutyric acid (GABA)
D cell (δ)	3–5%	< 1%	Somatostatin
PP cell (F cell)	< 2%	80–85%	Pancreatic polypeptide

HORMONES OF THE ENDOCRINE PANCREAS

- Glucagon stimulates the breakdown of stored glycogen, maintains hepatic output of glucose from amino acid precursors (gluconeogenesis), and promotes hepatic output of ketone bodies from fatty acid precursors (ketogenesis).
- Somatostatin acts in several ways to restrain the movement of nutrients from the intestinal tract into the circulation. It prolongs gastric emptying time, decreases gastric acid and gastrin production, diminishes pancreatic exocrine secretion, decreases splanchnic blood flow, and retards xylose absorption.
- Pancreatic Polypeptide increase in response to a mixed meal
- Glucagon-Related Peptides

Table 18–4. Biologic roles of glucagon-related peptides.

Target Tissue	Glucagon	GLP-1	GLP-2
Islet	**Stimulates** insulin secretion	**Stimulates** insulin and somatostatin secretion **Inhibits** glucagon secretion **Increases** beta cell mass by inhibiting beta cell death and inducing beta cell proliferation	
Liver	**Stimulates** glycogenolysis, glucogenesis, fatty acid oxidation, and ketogenesis **Inhibits** glycogen synthesis and fatty acid synthesis		
Stomach		**Stimulates** gastric acid secretion **Inhibits** gastric emptying	
Intestine			**Stimulates** mucosal growth and nutrient absorption **Inhibits** motility
Brain (hypothalamus)		**Inhibits** appetite	

Insulin Biosynthesis

A precursor molecule, preproinsulin, is translated from the preproinsulin messenger RNA in the rough endoplasmic reticulum of pancreatic B cells Microsomal enzymes cleave preproinsulin to proinsulin almost immediately after synthesis. Maturation of the secretory granule is associated with loss of the clathrin coating and conversion of proinsulin into insulin and a smaller connecting peptide, or C peptide, by proteolytic cleavage at two sites along the peptide chain. Normal mature (uncoated) secretory granules contain insulin and C peptide in equimolar amounts and only small quantities of proinsulin, a small portion of which consists of partially cleaved intermediates.

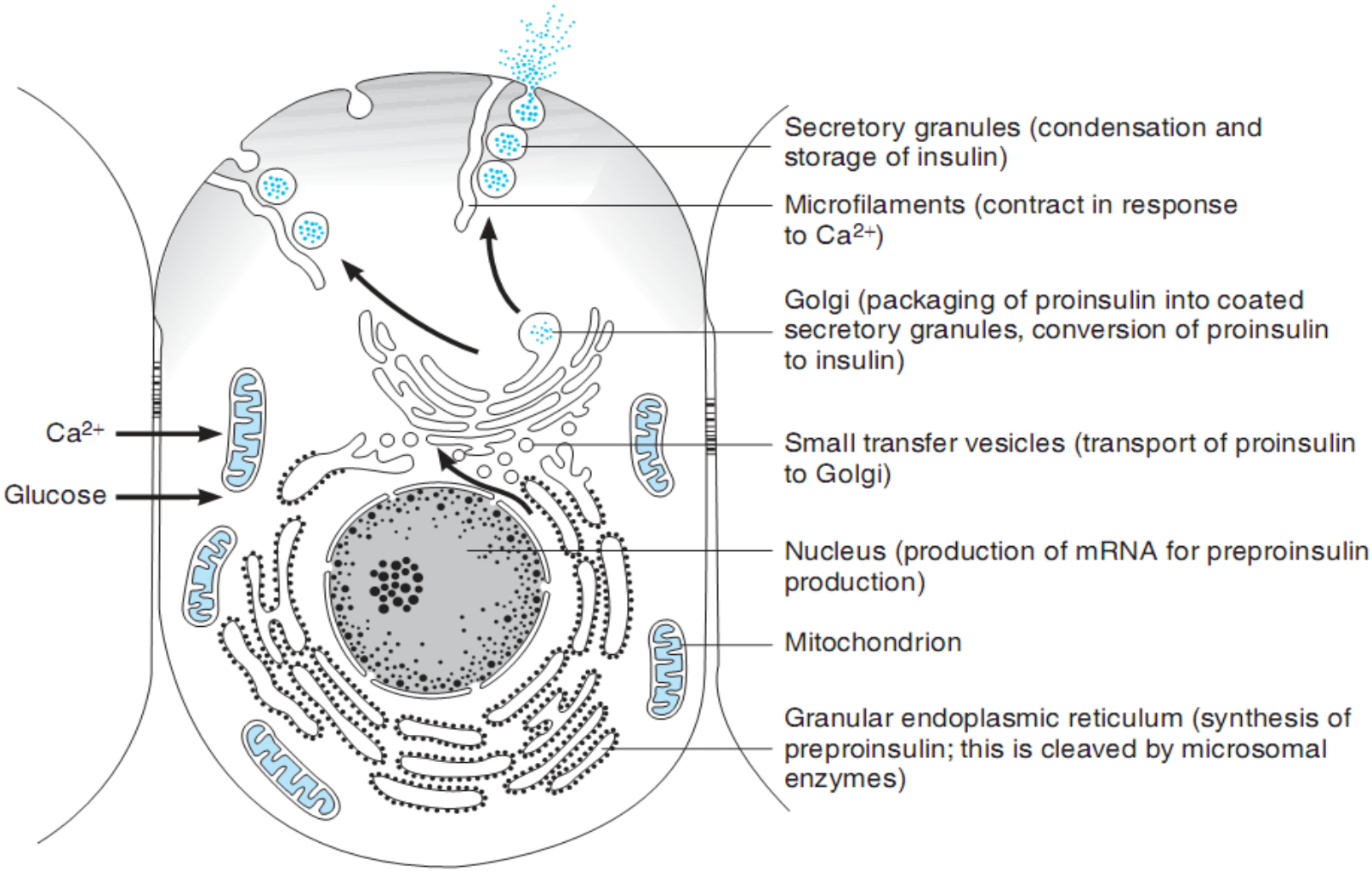


Figure 18–2. Structural components of the pancreatic β cell involved in glucose-induced biosynthesis and release of insulin. Schematic representation of insulin secretory granular alignment on microfilament "tracks" that contract in response to calcium. (Based on data presented by Orci L: A portrait of the pancreatic B cell. Diabetologia 1974;10:163.) (Modified and reproduced, with permission, from Junqueira LC,

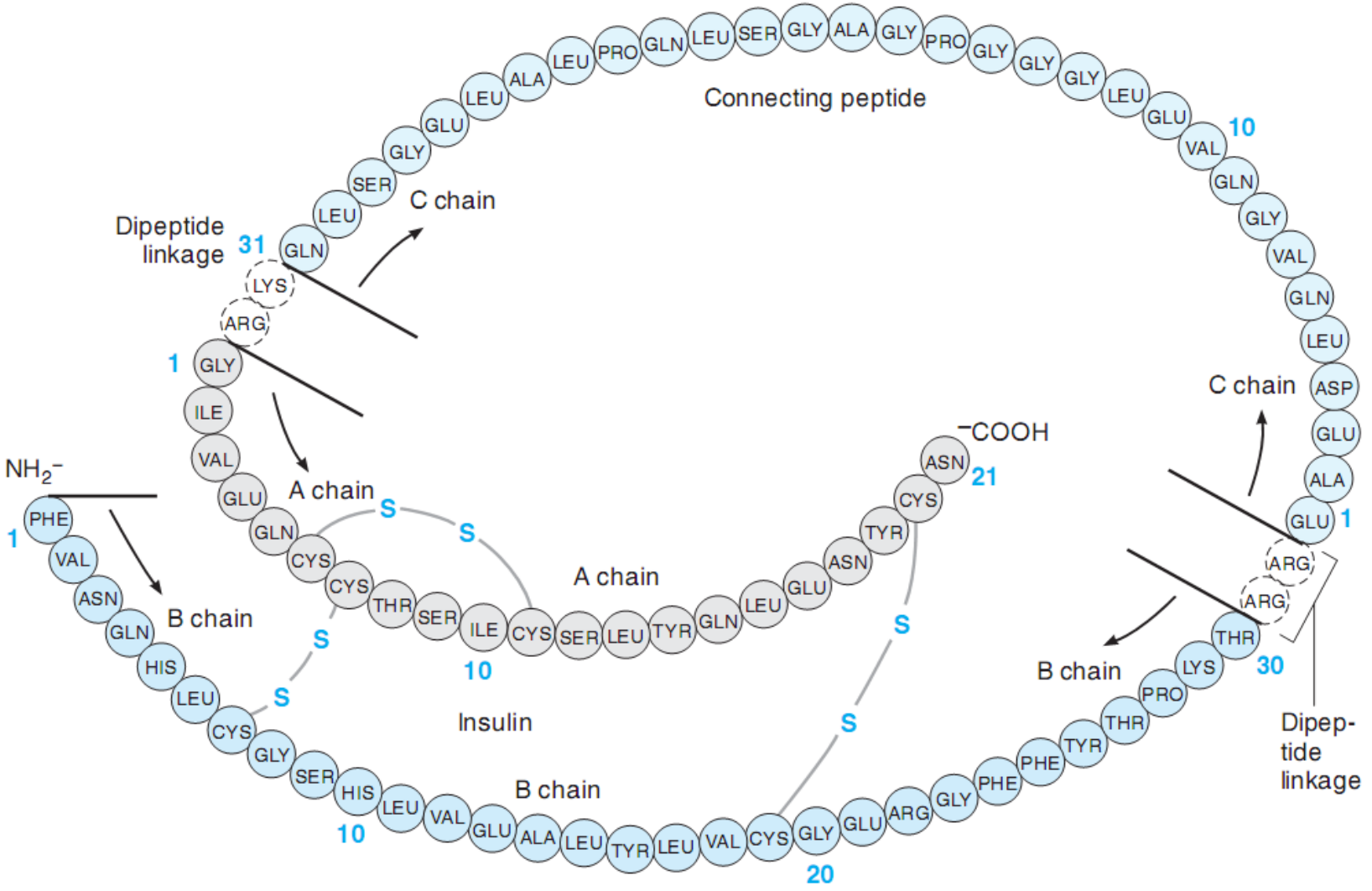


Figure 18–3. Structure of human proinsulin C peptides and insulin molecules connected at two sites by dipeptide links.

Secretion

The human pancreas secretes about 40–50 units of insulin per day in normal adults.

Basal insulin secretion, which occurs in the absence of exogenous stimuli, is the quantity of insulin secreted in the fasting state.

Stimulated insulin secretion is that which occurs in response to exogenous stimuli. Glucose is the most potent stimulant of insulin release. When the glucose concentration in the system is increased suddenly, an initial short-lived burst of insulin release occurs (the first phase); if the glucose concentration is held at this level, the insulin release gradually falls off and then begins to rise again to a steady level (the second phase).

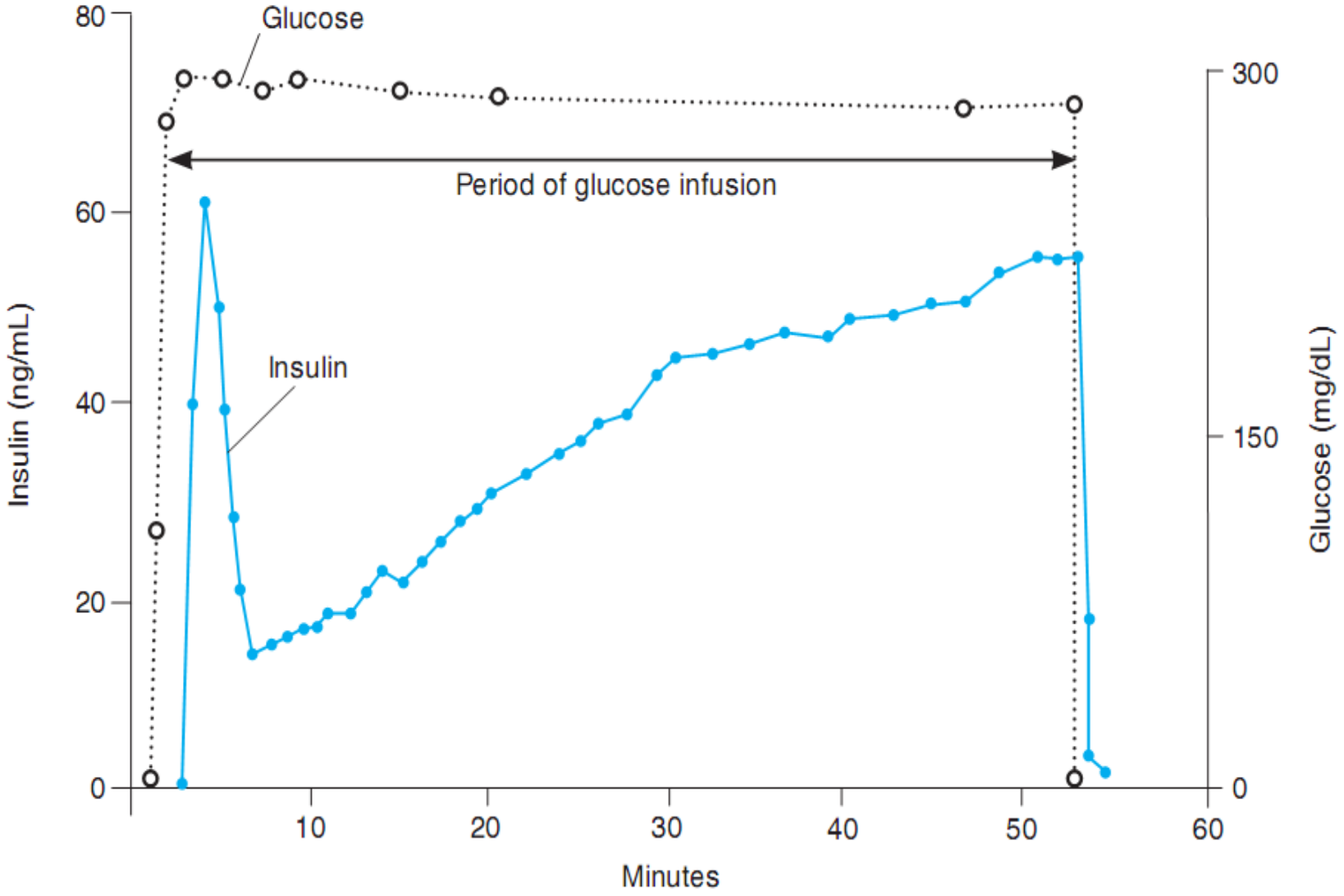


Figure 18–4. **Multiphasic response of the in vitro perfused pancreas during constant stimulation with glucose.** (Modified from Grodsky GM et al: Further studies on the dynamic aspects of insulin release in vitro

Regulation of insulin release in humans.

Stimulants of insulin release

Glucose, mannose
Leucine
Vagal stimulation
Sulfonylureas

Amplifiers of glucose-induced insulin release

- Enteric hormones:
  - Glucagon-like peptide I (7–37)
  - Gastric inhibitory peptide
  - Cholecystokinin
  - Secretin, gastrin
- Neural amplifiers: beta-adrenergic stimulation
- Amino acids: arginine

Inhibitors of insulin release

Neural: alpha-adrenergic effect of catecholamines
Humoral: somatostatin
Drugs: diazoxide, phenytoin, vinblastine, colchicine

Insulin Receptors & Insulin Action

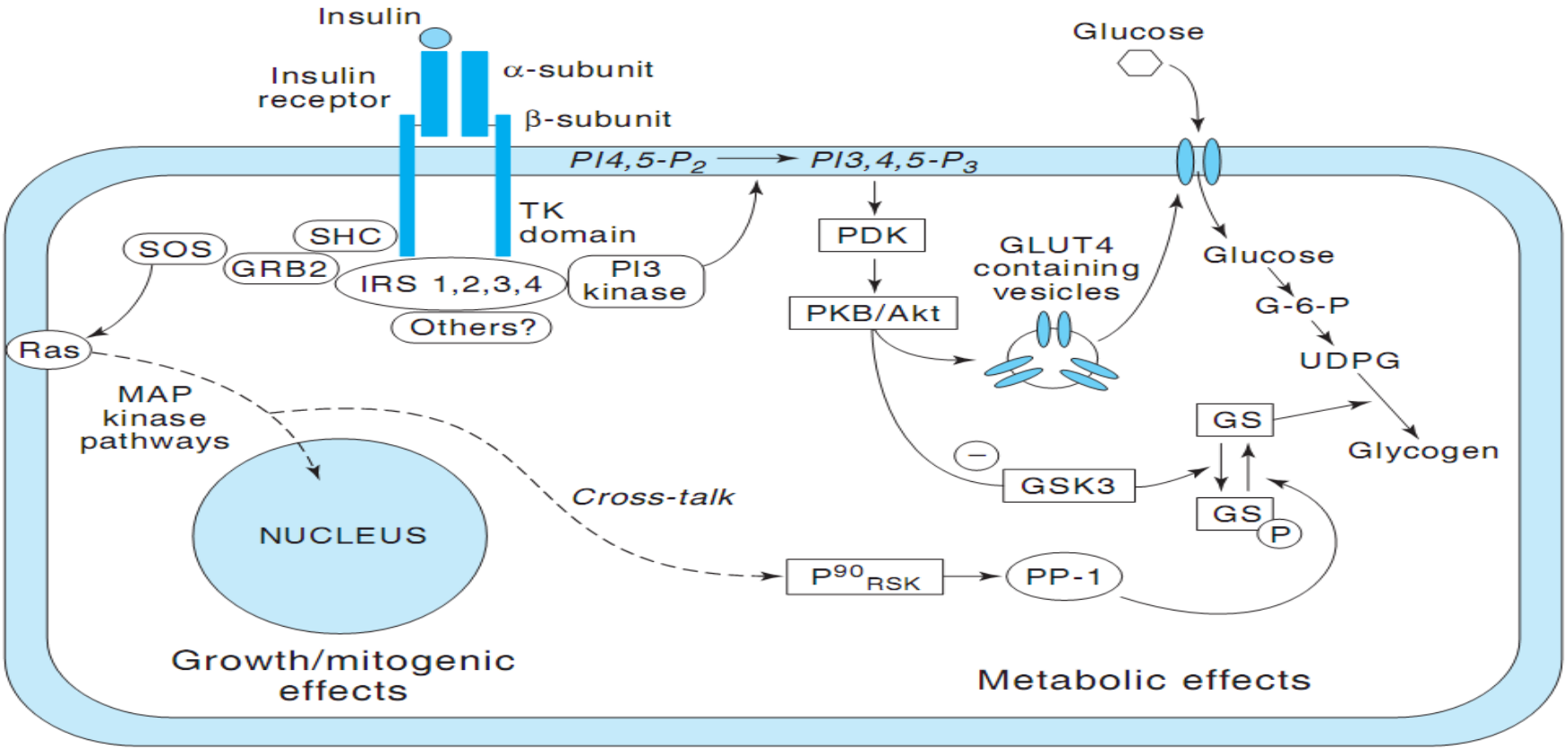


Figure 18–5. A simplified outline of insulin signaling. A minimal diagram of the mitogenic and metabolic arms of the insulin signaling pathway is shown (GLUT 4, glucose transporter 4; Grb-2, growth factor receptor binding protein 2; GS, glycogen synthase [P indicates the inactive phosphorylated form]; GSK-3, glycogen synthase kinase 3; IRS, insulin receptor substrate [four different proteins]; MAP kinase, mitogen-activated protein kinase; PDK, phospholipid-dependent kinase; PI3 kinase, phosphatidylinositol 3 kinase; PKB, protein kinase B; PP-1, glycogen-associated protein phosphatase-1; Ras, rat sarcoma protein; SHC, Src and collagen homology protein; SOS, son-of-sevenless related protein; TK, tyrosine kinase).

Metabolic Effects of Insulin

PARACRINE EFFECTS

The effects of the products of endocrine cells on surrounding cells

ENDOCRINE EFFECTS

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 synthetase 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

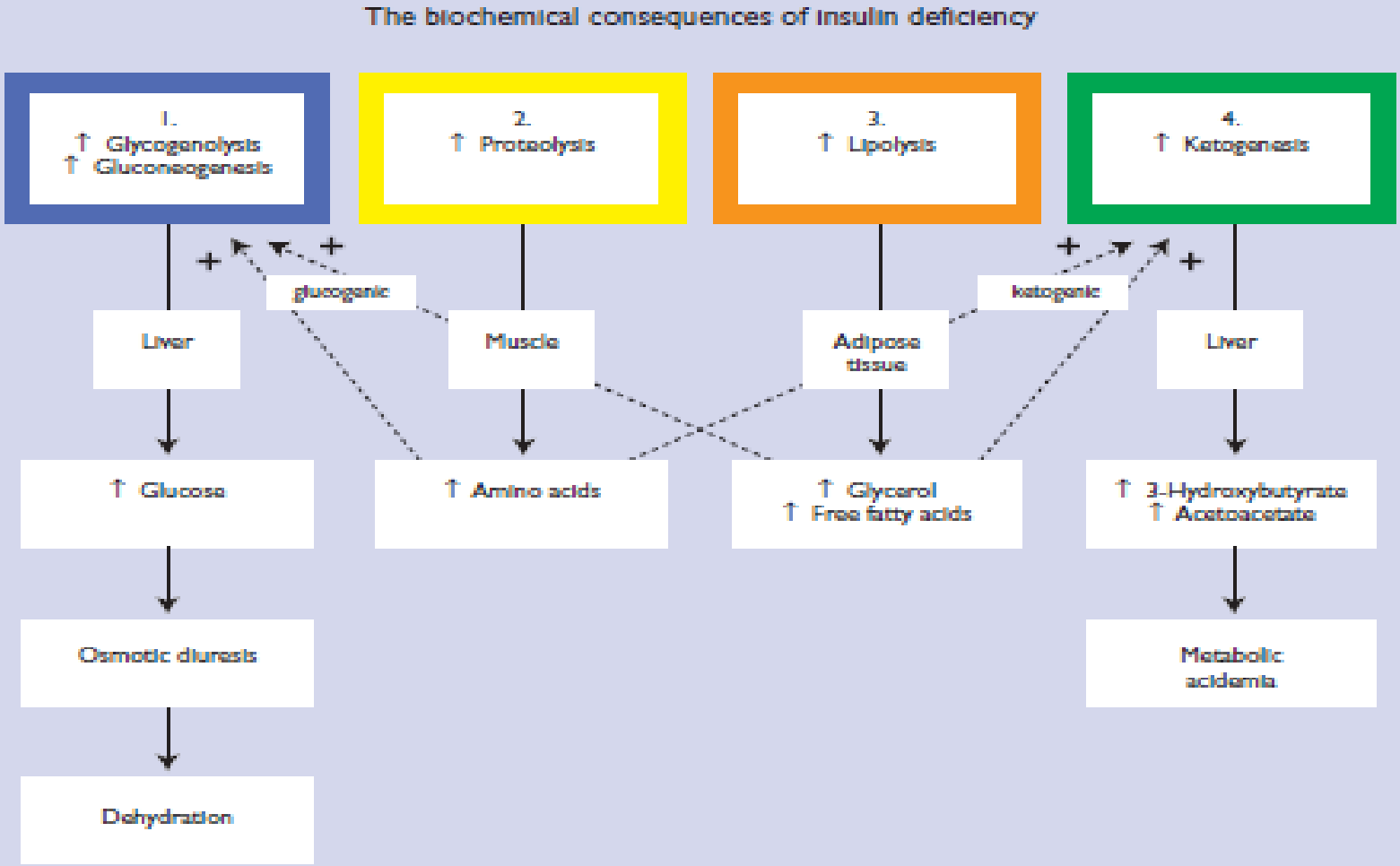


Figure 22 Insulin deficiency results in increased hepatic glucose production and, hence, hyperglycemia by increased gluconeogenesis and glycogenolysis. Insulin deficiency also results in increased proteolysis releasing both glucogenic and ketogenic amino acids. Lipolysis is increased, elevating both glycerol and non-esterified fatty acid levels which further contribute to gluconeogenesis and ketogenesis, respectively. The end result is hyperglycemia, dehydration, breakdown of body fat and protein, and acidemia

DEFINITION

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.

The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues.

Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient, and it is often unclear which abnormality, if either alone, is the primary cause of the hyperglycemia.

- Symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia. Acute, life-threatening consequences of uncontrolled diabetes are hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome.

- Long-term complications of diabetes include retinopathy with potential loss of vision; nephropathy leading to renal failure; peripheral neuropathy with risk of foot ulcers, amputations, and Charcot joints; and autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms and sexual dysfunction. Patients with diabetes have an increased incidence of atherosclerotic cardiovascular, peripheral arterial, and cerebrovascular disease. Hypertension and abnormalities of lipoprotein metabolism are often found in people with diabetes.

CLASSIFICATION OF DIABETES MELLITUS AND OTHER CATEGORIES OF GLUCOSE REGULATION

I. Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)
   A. Immune mediated
   B. Idiopathic

II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)

III. Other specific types

A. Genetic defects of β-cell function (MODY)
B. Genetic defects in insulin action
C. Diseases of the exocrine pancreas
D. Endocrinopathies
E. Drug- or chemical-induced (Vacor. Pentamidine. Nicotinic acid. Glucocorticoids. Thyroid hormone. Diazoxide. β-adrenergic agonists. Thiazides. Dilantin. α-Interferon
F. Infections (Congenital rubella. Cytomegalovirus)
G. Uncommon forms of immune-mediated diabetes
H. Other genetic syndromes sometimes associated with diabetes (Down's syndrome. Klinefelter's syndrome. Turner's syndrome. Wolfram's syndrome Friedreich's ataxia. Huntington's chorea. Laurence-Moon-Biedl syndrome Myotonic dystrophy. Porphyria. Prader-Willi syndrome)

IV. Gestational diabetes mellitus (GDM)

CLASSIFICATION OF DIABETES MELLITUS

- Assigning a type of diabetes to an individual often depends on the circumstances present at the time of diagnosis, and many diabetic individuals do not easily fit into a single class. For example, a person with gestational diabetes mellitus (GDM) may continue to be hyperglycemic after delivery and may be determined to have, in fact, type 2 diabetes. Alternatively, a person who acquires diabetes because of large doses of exogenous steroids may become normoglycemic once the glucocorticoids are discontinued, but then may develop diabetes many years later after recurrent episodes of pancreatitis.

- Another example would be a person treated with thiazides who develops diabetes years later. Because thiazides in themselves seldom cause severe hyperglycemia, such individuals probably have type 2 diabetes that is exacerbated by the drug. Thus, for the clinician and patient, it is less important to label the particular type of diabetes than it is to understand the pathogenesis of the hyperglycemia and to treat it effectively.

Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)

Immune-mediated diabetes.

- This form of diabetes, which accounts for only 5–10% of those with diabetes, previously encompassed by the terms insulin-dependent diabetes, type I diabetes, or juvenile-onset diabetes, results from a cellular-mediated autoimmune destruction of the β-cells of the pancreas. Markers of the immune destruction of the β-cell include islet cell autoantibodies, autoantibodies to insulin, autoantibodies to glutamic acid decarboxylase (GAD65), and autoantibodies to the tyrosine phosphatases IA-2 and IA-2β. One and usually more of these autoantibodies are present in 85–90% of individuals when fasting hyperglycemia is initially detected.

Also, the disease has strong HLA associations, with linkage to the DQA and DQB genes, and it is influenced by the DRB genes. These *HLA-DR/DQ* alleles can be either predisposing or protective.

- In this form of diabetes, the rate of β-cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults). Some patients, particularly children and adolescents, may present with ketoacidosis as the first manifestation of the disease. Others have modest fasting hyperglycemia that can rapidly change to severe hyperglycemia and/or ketoacidosis in the presence of infection or other stress.

Still others, particularly adults, may retain residual β-cell function sufficient to prevent ketoacidosis for many years; such individuals eventually become dependent on insulin for survival and are at risk for ketoacidosis. At this latter stage of the disease, there is little or no insulin secretion, as manifested by low or undetectable levels of plasma C-peptide. Immune-mediated diabetes commonly occurs in childhood and adolescence, but it can occur at any age, even in the 8th and 9th decades of life.

- Autoimmune destruction of β-cells has multiple genetic predispositions and is also related to environmental factors that are still poorly defined. Although patients are rarely obese when they present with this type of diabetes, the presence of obesity is not incompatible with the diagnosis. These patients are also prone to other autoimmune disorders such as Graves' disease, Hashimoto's thyroiditis, Addison's disease, vitiligo, celiac sprue, autoimmune hepatitis, myasthenia gravis, and pernicious anemia.

Idiopathic diabetes.

- Some forms of type 1 diabetes have no known etiologies. Some of these patients have permanent insulinopenia and are prone to ketoacidosis, but have no evidence of autoimmunity. Although only a minority of patients with type 1 diabetes fall into this category, of those who do, most are of African or Asian ancestry. Individuals with this form of diabetes suffer from episodic ketoacidosis and exhibit varying degrees of insulin deficiency between episodes. This form of diabetes is strongly inherited, lacks immunological evidence for β-cell autoimmunity, and is not HLA associated. An absolute requirement for insulin replacement therapy in affected patients may come and go.

Type 2 diabetes

This form of diabetes, which accounts for ~90–95% of those with diabetes, previously referred to as non-insulin-dependent diabetes, type II diabetes, or adult-onset diabetes, encompasses individuals who have insulin resistance and usually have relative (rather than absolute) insulin deficiency At least initially, and often throughout their lifetime, these individuals do not need insulin treatment to survive. There are probably many different causes of this form of diabetes. Although the specific etiologies are not known, autoimmune destruction of β-cells does not occur, and patients do not have any of the other causes of diabetes.

Most patients with this form of diabetes are obese, and obesity itself causes some degree of insulin resistance. Patients who are not obese by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region. Ketoacidosis seldom occurs spontaneously in this type of diabetes; when seen, it usually arises in association with the stress of another illness such as infection. This form of diabetes frequently goes undiagnosed for many years because the hyperglycemia develops gradually and at earlier stages is often not severe enough for the patient to notice any of the classic symptoms of diabetes. Nevertheless, such patients are at increased risk of developing macrovascular and microvascular complications. Whereas patients with this form of diabetes may have insulin levels that appear normal or elevated, the higher blood glucose levels in these diabetic patients would be expected to result in even higher insulin values had their β-cell function been normal.

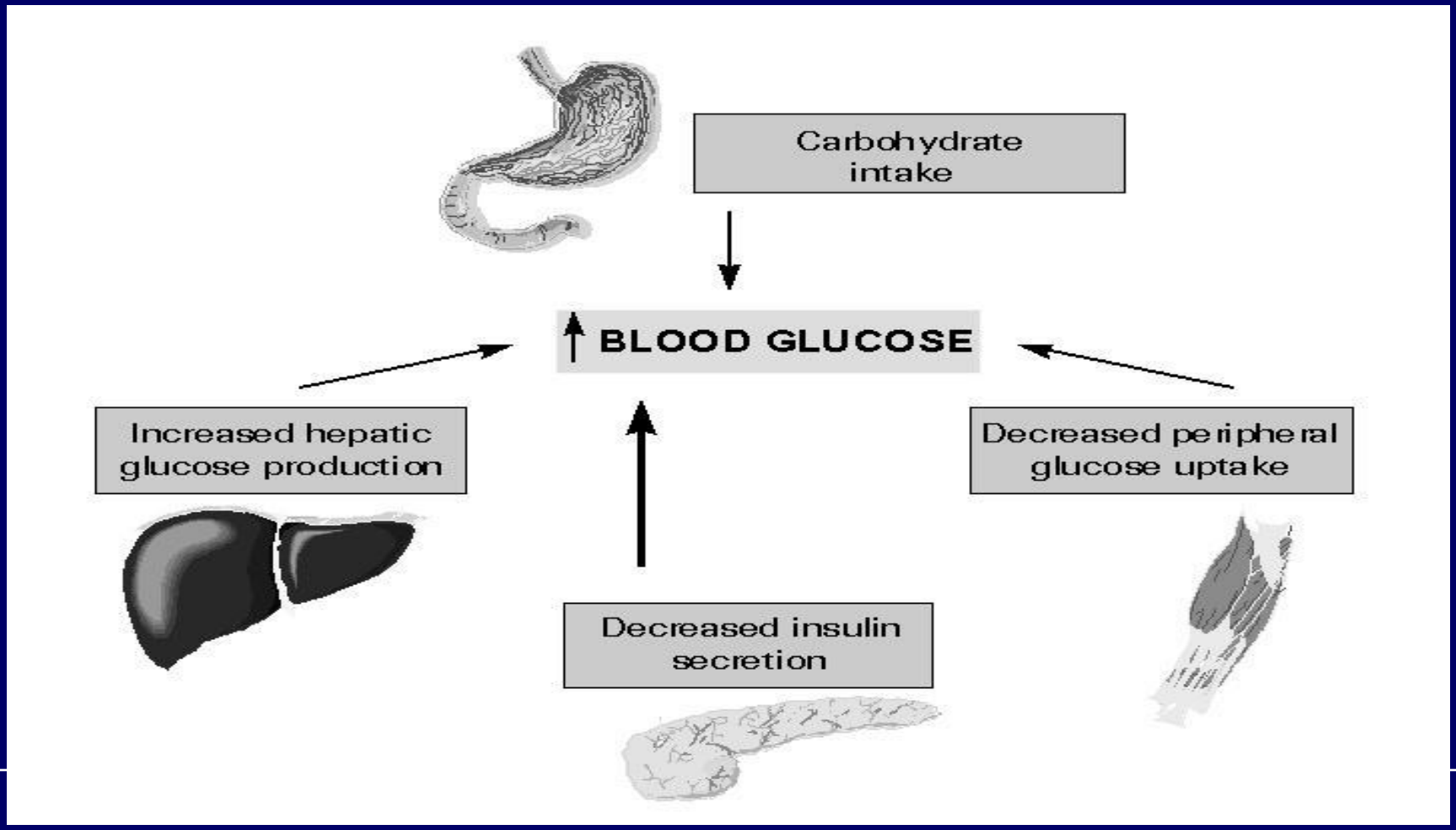
Type 2 diabetes is characterized by a combination of peripheral insulin resistance and inadequate insulin secretion by pancreatic beta cells. Insulin resistance, which has been attributed to elevated levels of free fatty acids and proinflammatory cytokines in plasma, leads to decreased glucose transport into muscle cells, elevated hepatic glucose production, and increased breakdown of fat.

A role for excess glucagon cannot be underestimated; indeed, type 2 diabetes is an islet paracrinopathy in which the reciprocal relationship between the glucagon-secreting alpha cell and the insulin-secreting beta cell is lost, leading to hyperglucagonemia and hence the consequent hyperglycemia.[11]

For type 2 diabetes mellitus to occur, both insulin resistance and inadequate insulin secretion must exist. For example, all overweight individuals have insulin resistance, but diabetes develops only in those who cannot increase insulin secretion sufficiently to compensate for their insulin resistance. Their insulin concentrations may be high, yet inappropriately low for the level of glycemia.

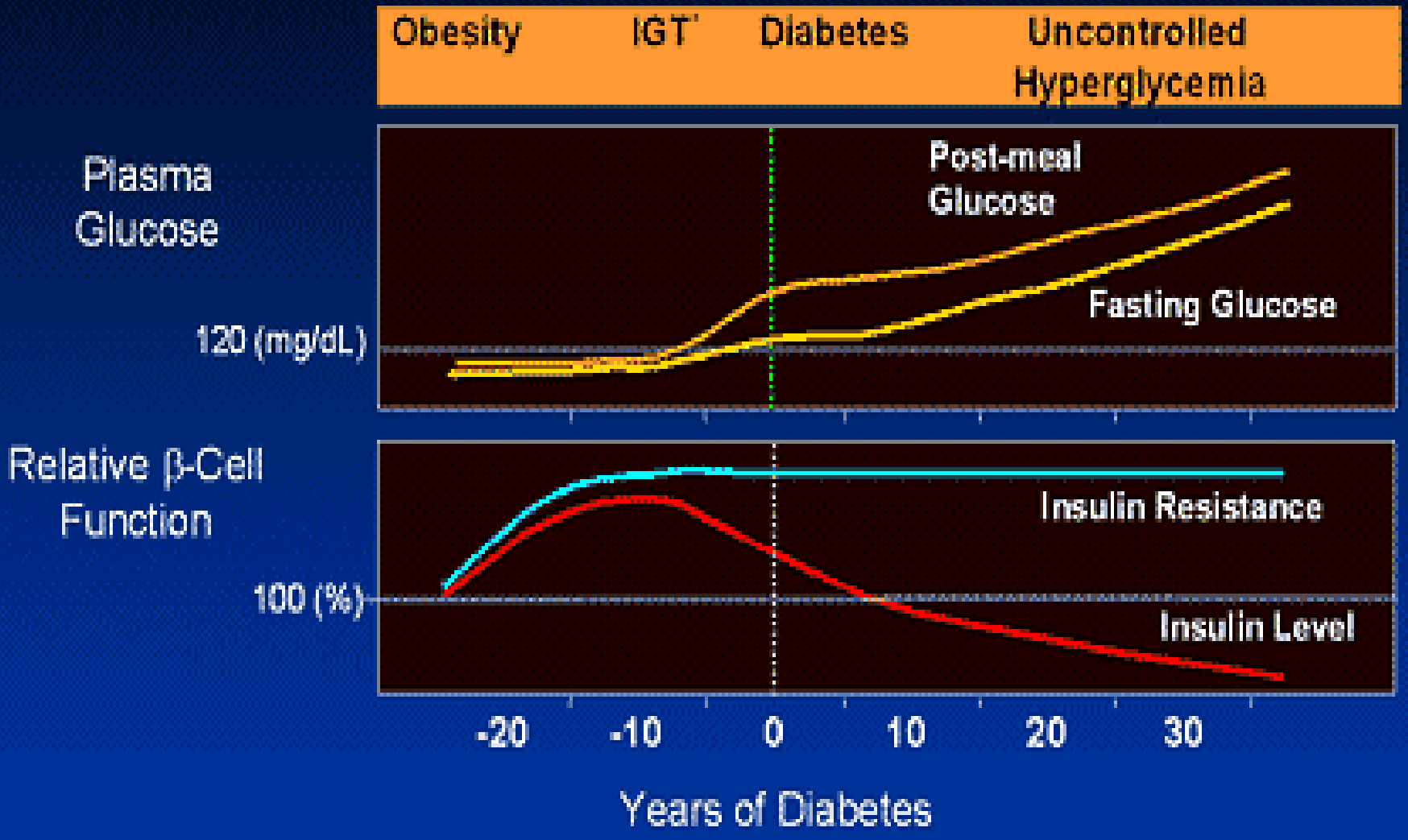
A simplified scheme for the pathophysiology of abnormal glucose metabolism in type 2 diabetes mellitus is depicted in the image below.

Simplified scheme for the pathophysiology of type 2 diabetes mellitus.



Thus, insulin secretion is defective in these patients and insufficient to compensate for insulin resistance. Insulin resistance may improve with weight reduction and/or pharmacological treatment of hyperglycemia but is seldom restored to normal The risk of developing this form of diabetes increases with age, obesity, and lack of physical activity. It occurs more frequently in women with prior GDM and in individuals with hypertension or dyslipidemia, and its frequency varies in different racial/ethnic subgroups. It is often associated with a strong genetic predisposition, more so than is the autoimmune form of type 1 diabetes. However, the genetics of this form of diabetes are complex and not clearly defined.

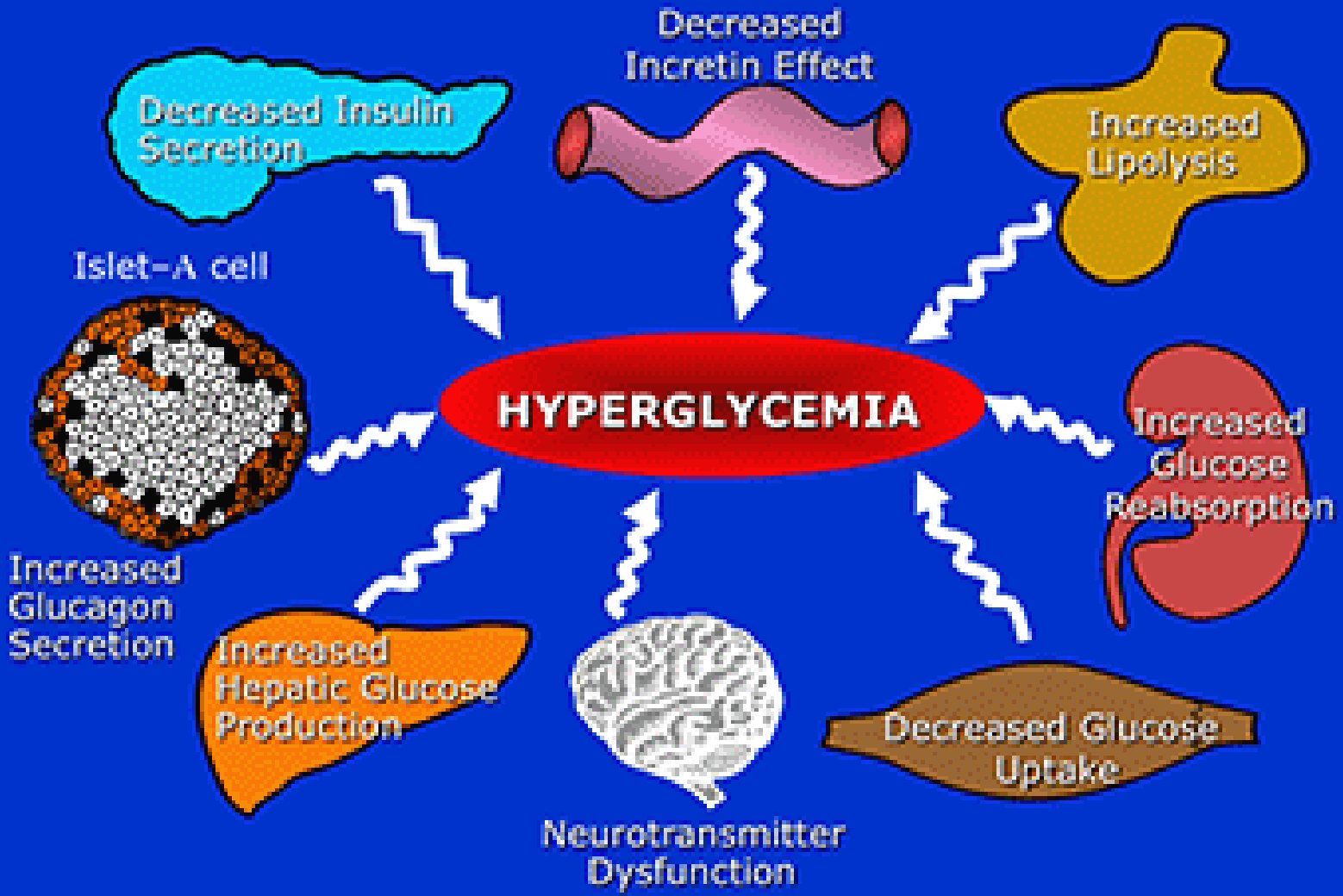
Natural History of Type 2 Diabetes



*IGT=impaired glucose tolerance

Adapted from International Diabetes Center (IDC), Minneapolis, Minnesota

Ominous Octet



Other specific types of diabetes Genetic defects of the β-cell.

Several forms of diabetes are associated with monogenetic defects in β-cell function. These forms of diabetes are frequently characterized by onset of hyperglycemia at an early age (generally before age 25 years). They are referred to as maturity-onset diabetes of the young (MODY) and are characterized by impaired insulin secretion with minimal or no defects in insulin action. They are inherited in an autosomal dominant pattern. Abnormalities at six genetic loci on different chromosomes have been identified to date. The most common form is associated with mutations on chromosome 12

Genetic defects in insulin action.

There are unusual causes of diabetes that result from genetically determined abnormalities of insulin action. The metabolic abnormalities associated with mutations of the insulin receptor may range from hyperinsulinemia and modest hyperglycemia to severe diabetes. Some individuals with these mutations may have acanthosis nigricans. Women may be virilized and have enlarged, cystic ovaries. In the past, this syndrome was termed type A insulin resistance. Leprechaunism and the Rabson-Mendenhall syndrome are two pediatric syndromes that have mutations in the insulin receptor gene with subsequent alterations in insulin receptor function and extreme insulin resistance. The former has characteristic facial features and is usually fatal in infancy.

Diseases of the exocrine pancreas.

Any process that diffusely injures the pancreas can cause diabetes. Acquired processes include pancreatitis, trauma, infection, pancreatectomy, and pancreatic carcinoma. This implies a mechanism other than simple reduction in β-cell mass. If extensive enough, cystic fibrosis and hemochromatosis will also damage β-cells and impair insulin secretion. Fibrocalculous pancreatopathy may be accompanied by abdominal pain radiating to the back and pancreatic calcifications identified on X-ray examination. Pancreatic fibrosis and calcium stones in the exocrine ducts have been found at autopsy.

Endocrinopathies.

Several hormones (e.g., growth hormone, cortisol, glucagon, epinephrine) antagonize insulin action. Excess amounts of these hormones (e.g., acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, respectively) can cause diabetes. This generally occurs in individuals with preexisting defects in insulin secretion, and hyperglycemia typically resolves when the hormone excess is resolved.

- Somatostatinoma- and aldosteronoma-induced hypokalemia can cause diabetes, at least in part, by inhibiting insulin secretion. Hyperglycemia generally resolves after successful removal of the tumor.

Drug- or chemical-induced diabetes.

Many drugs can impair insulin secretion. These drugs may not cause diabetes by themselves, but they may precipitate diabetes in individuals with insulin resistance. In such cases, the classification is unclear because the sequence or relative importance of β-cell dysfunction and insulin resistance is unknown. Certain toxins such as Vacor (a rat poison) and intravenous pentamidine can permanently destroy pancreatic β-cells. Such drug reactions fortunately are rare. There are also many drugs and hormones that can impair insulin action. Examples include nicotinic acid and glucocorticoids. Patients receiving α-interferon have been reported to develop diabetes associated with islet cell antibodies and, in certain instances, severe insulin deficiency.

Infections.

- Certain viruses have been associated with β-cell destruction. Diabetes occurs in patients with congenital rubella, although most of these patients have HLA and immune markers characteristic of type 1 diabetes. In addition, coxsackievirus B, cytomegalovirus, adenovirus, and mumps have been implicated in inducing certain cases of the disease.

Uncommon forms of immune-mediated diabetes.

- In this category, there are two known conditions, and others are likely to occur. The stiff-man syndrome is an autoimmune disorder of the central nervous system characterized by stiffness of the axial muscles with painful spasms. Patients usually have high titers of the GAD autoantibodies, and approximately one-third will develop diabetes.
- Anti-insulin receptor antibodies can cause diabetes by binding to the insulin receptor, thereby blocking the binding of insulin to its receptor in target tissues. However, in some cases, these antibodies can act as an insulin agonist after binding to the receptor and can thereby cause hypoglycemia. Anti-insulin receptor antibodies are occasionally found in patients with systemic lupus erythematosus and other autoimmune diseases. As in other states of extreme insulin resistance, patients with anti-insulin receptor antibodies often have acanthosis nigricans. In the past, this syndrome was termed type B insulin resistance.

Other genetic syndromes sometimes associated with diabetes.

- Many genetic syndromes are accompanied by an increased incidence of diabetes mellitus. These include the chromosomal abnormalities of Down's syndrome, Klinefelter's syndrome, and Turner's syndrome. Wolfram's syndrome is an autosomal recessive disorder characterized by insulin-deficient diabetes and the absence of β-cells at autopsy. Additional manifestations include diabetes insipidus, hypogonadism, optic atrophy, and neural deafness.

Gestational diabetes mellitus (GDM)

- GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. The definition applies regardless of whether insulin or only diet modification is used for treatment or whether the condition persists after pregnancy. It does not exclude the possibility that unrecognized glucose intolerance may have antedated or begun concomitantly with the pregnancy. GDM complicates ~4% of all pregnancies in the U.S., resulting in ~135,000 cases annually. The prevalence may range from 1 to 14% of pregnancies, depending on the population studied. GDM represents nearly 90% of all pregnancies complicated by diabetes.
- Deterioration of glucose tolerance occurs normally during pregnancy, particularly in the 3rd trimester.

Gestational diabetes mellitus

- à jeun ≥ 5,1 mmol/l ***și/sau***
- 1 h ≥ 10,0 mmol/l ***și/sau***
- 2 h ≥ 8,5 mmol/l

Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG)

- The Expert Committee recognized an intermediate group of subjects whose glucose levels, although not meeting criteria for diabetes, are nevertheless too high to be considered normal. This group is defined as having fasting plasma glucose (FPG) levels ≥100 mg/dl (5.6 mmol/l) but <126 mg/dl (7.0 mmol/l) *or* 2-h values in the oral glucose tolerance test (OGTT) of ≥140 mg/dl (7.8 mmol/l) but <200 mg/dl (11.1 mmol/l).

Thus, the categories of FPG values are as follows:

- FPG <100 mg/dl (5.6 mmol/l) = normal fasting glucose;
- FPG 100–125 mg/dl (5.6–6.9 mmol/l) = IFG (impaired fasting glucose);
- FPG ≥126 mg/dl (7.0 mmol/l) = provisional diagnosis of diabetes (the diagnosis must be confirmed).

The corresponding categories when the OGTT is used are the following:

- 2-h postload glucose <140 mg/dl (7.8 mmol/l) = normal glucose tolerance;
- 2-h postload glucose 140–199 mg/dl (7.8–11.1 mmol/l) = IGT (impaired glucose tolerance);
- 2-h postload glucose ≥200 mg/dl (11.1 mmol/l) = provisional diagnosis of diabetes (the diagnosis must be confirmed).

IFG

- GB 5,7-6,9 mmol/l ***și***
- Glicemia la 2h TOTG<7,8mmol/l

IGT

- GB <7,0 mmol/l ***și***
- Glicemia la 2h TOTG 7,8-11,0 mmol/l ***și/sau***

IFG+IGT

- Patients with IFG and/or IGT are now referred to as having “pre-diabetes” indicating the relatively high risk for development of diabetes in these patients. In the absence of pregnancy, IFG and IGT are not clinical entities in their own right but rather risk factors for future diabetes as well as cardiovascular disease. They can be observed as intermediate stages in any of the disease. IFG and IGT are associated with the metabolic syndrome, which includes obesity (especially abdominal or visceral obesity), dyslipidemia of the high-triglyceride and/or low-HDL type, and hypertension.

DIAGNOSTIC CRITERIA FOR DIABETES MELLITUS

- Three ways to diagnose diabetes are possible, and each, in the absence of unequivocal hyperglycemia, must be confirmed, on a subsequent day, by any one of the three methods. The use of the hemoglobin A1c (A1C) for the diagnosis of diabetes is not recommended at this time.

Criteria for the diagnosis of diabetes mellitus

- 1. Symptoms of diabetes plus casual plasma glucose concentration ≥200 mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss. Or
- 2. FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h. or
- 3. 2-h postload glucose ≥200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

Risk factors — Diabetes risk factors include the following:

- Age ≥45 years
- Overweight (body mass index ≥25 kg/m2)
- Family history diabetes mellitus in a first-degree relative
- Habitual physical inactivity
- Belonging to a high-risk ethnic or racial group (eg, African-American, Hispanic, Native American, Asian-American, and Pacific Islanders)
- History of delivering a baby weighing >4.1 kg (9 lb) or of gestational diabetes mellitus

Diabetes risk factors

- Hypertension (blood pressure ≥140/90 mmHg)
- Dyslipidemia defined as a serum high-density lipoprotein cholesterol concentration ≤35 mg/dL (0.9 mmol/L) and/or a serum triglyceride concentration ≥250 mg/dL (2.8 mmol/L)
- Previously identified A1C ≥5.7 percent, impaired glucose tolerance or impaired fasting glucose
- Polycystic ovary syndrome
- History of vascular disease

Diagnostic criteria by the American Diabetes Association (ADA) include the following :

- • A fasting plasma glucose (FPG) level ≥126 mg/dL (7.0 mmol/L), or
- • A 2-hour plasma glucose level ≥200 mg/dL (11.1 mmol/L) during a 75-g oral glucose tolerance test (OGTT), or
- • A random plasma glucose ≥200 mg/dL (11.1 mmol/L) in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis
- An international expert committee appointed by the ADA, the European Association for the Study of Diabetes, and the International Diabetes Association recommended the HbA_{1c} assay for diagnosing type 1 diabetes only when the condition is suspected but the classic symptoms are absent.