هُوَاللّٰهُ

Pathophysiology of Diabetes Mellitus

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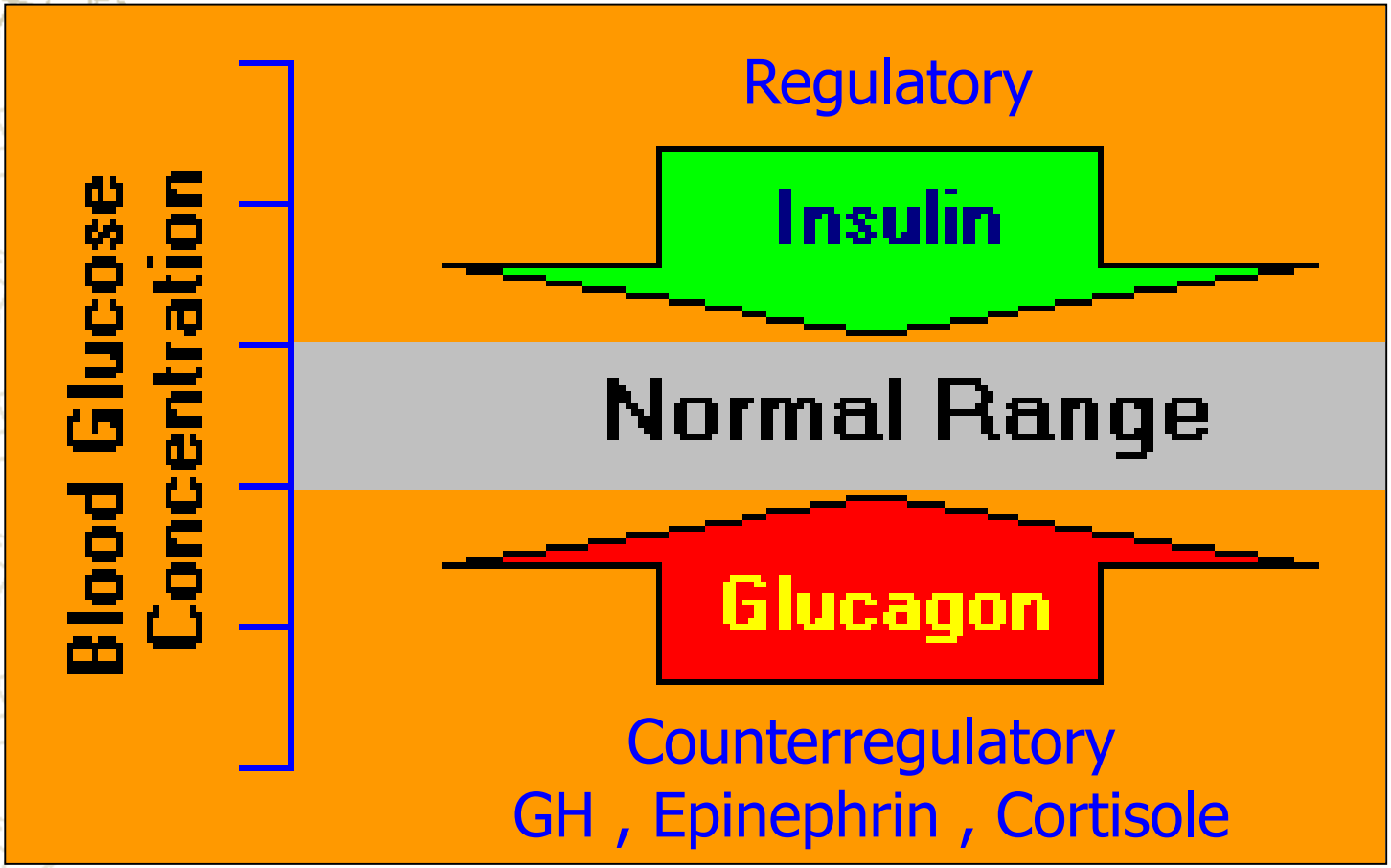
Diabetes Mellitus

- Glucose physiology and Insulin action
- Definition of DM
- Epidemiology, high risk group, screening
- Classification
- Etiology
- Complications
- Treatment
- Metabolic syndrome

Glucose physiology and Insulin action

- بدن انسان از سه نوع سوخت اصلی استفاده میکند:
  - گلوکز
  - چربی
  - پروتئین
- از این میان گلوکز اهمیت خاصی دارد زیرا:
  - مغز برای زنده ماندن به آن وابسته است.
  - سریعتر از سایر سوختها در دسترس است.

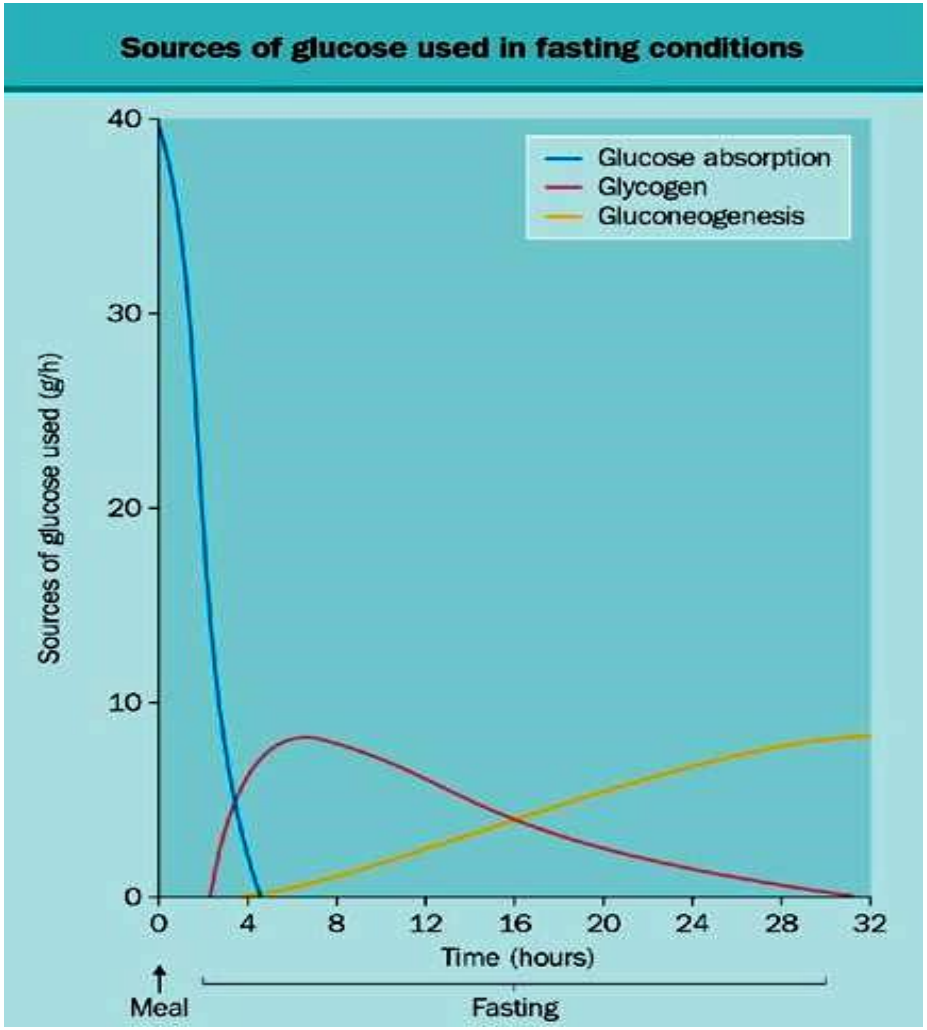
Glucose physiology



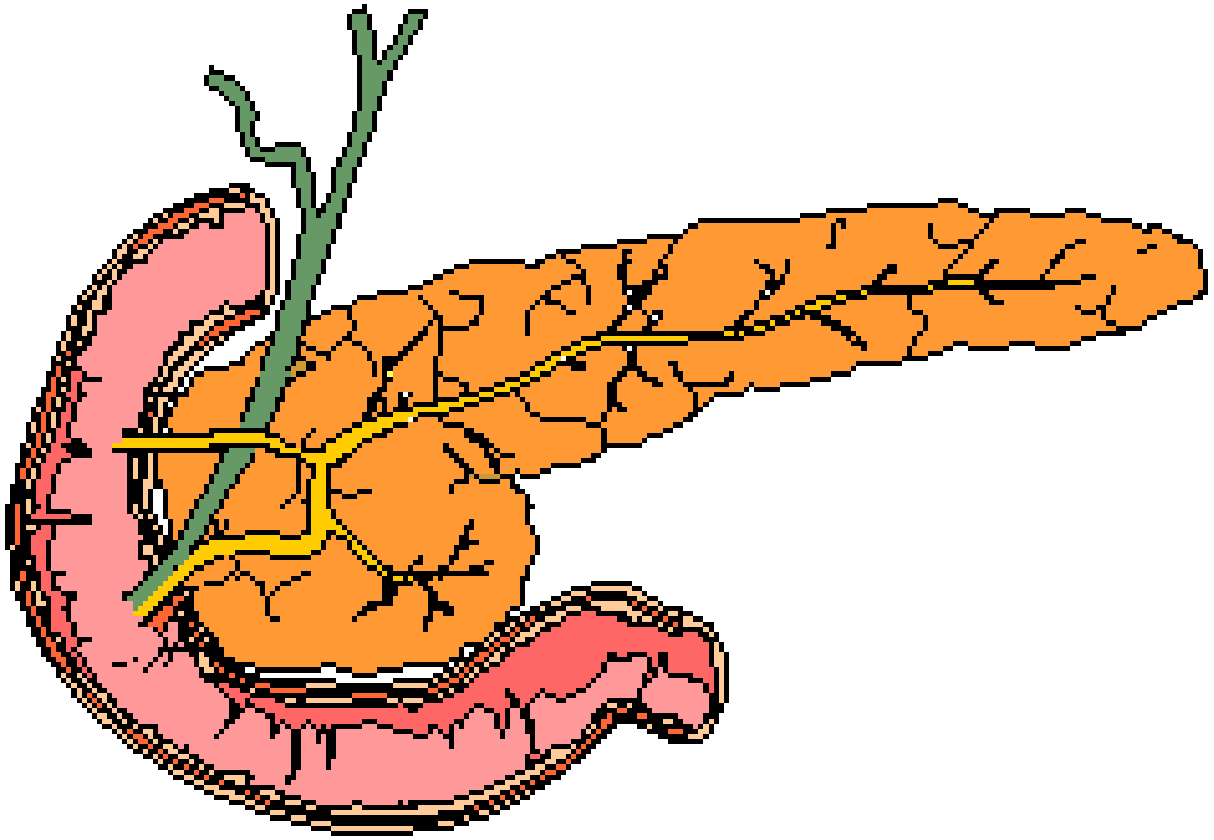
Glucose physiology and Insulin action

- The brain in particular has an absolute dependence on glucose as a fuel, because neurons cannot utilize alternative energy sources like fatty acids to any significant extent .
- When blood levels of glucose begin to fall below the normal range, it is imperative to find and pump additional glucose into blood .

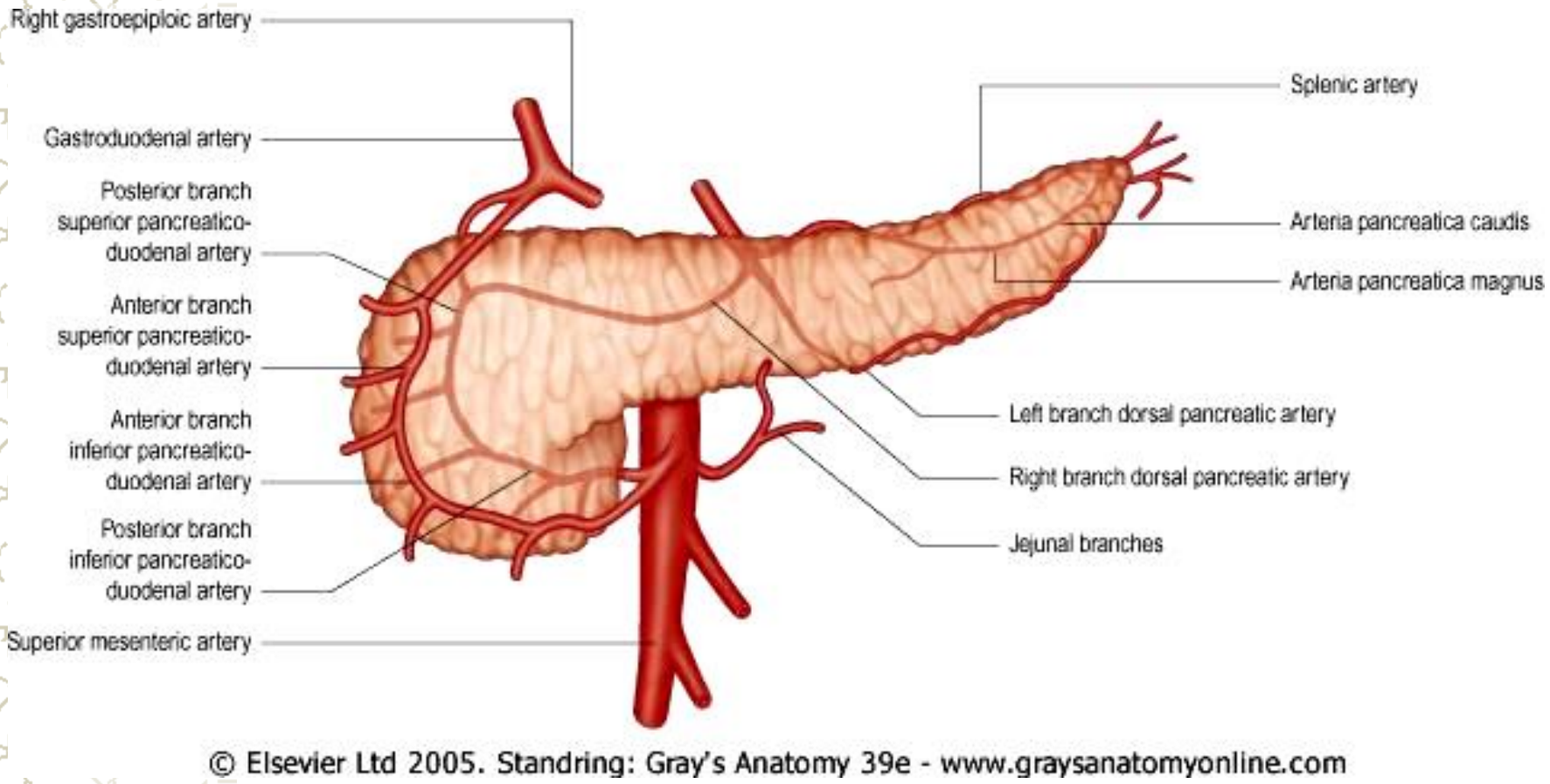
Glucose in fasting states



The Pancreas



The Pancreas



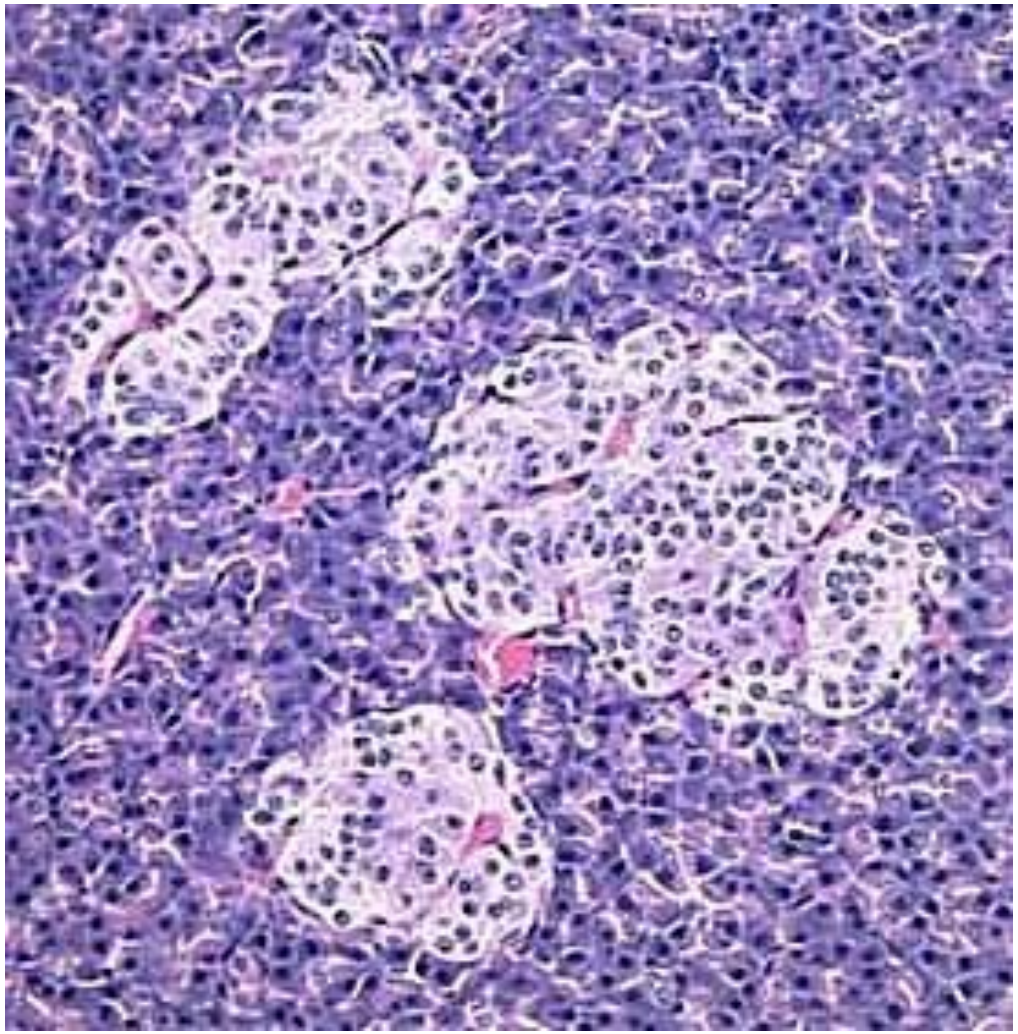
Functional Anatomy of the Endocrine Pancreas

- The pancreas is an elongated organ nestled next to the first part of the small intestine.
- The endocrine portion of the pancreas takes the form of many small clusters of cells called islets of Langerhans or, more simply, islets.
- Humans have roughly one million islets.

Functional Anatomy of the Endocrine Pancreas

- Pancreatic islets house three major cell types, each of which produces a different endocrine product:
  - Alpha cells (A cells) secrete the hormone glucagon.
  - Beta cells (B cells) produce insulin and are the most abundant of the islet cells.
  - Delta cells (D cells) secrete the hormone somatostatin, which is also produced by a number of other endocrine cells in the body.

Pancreas Histology



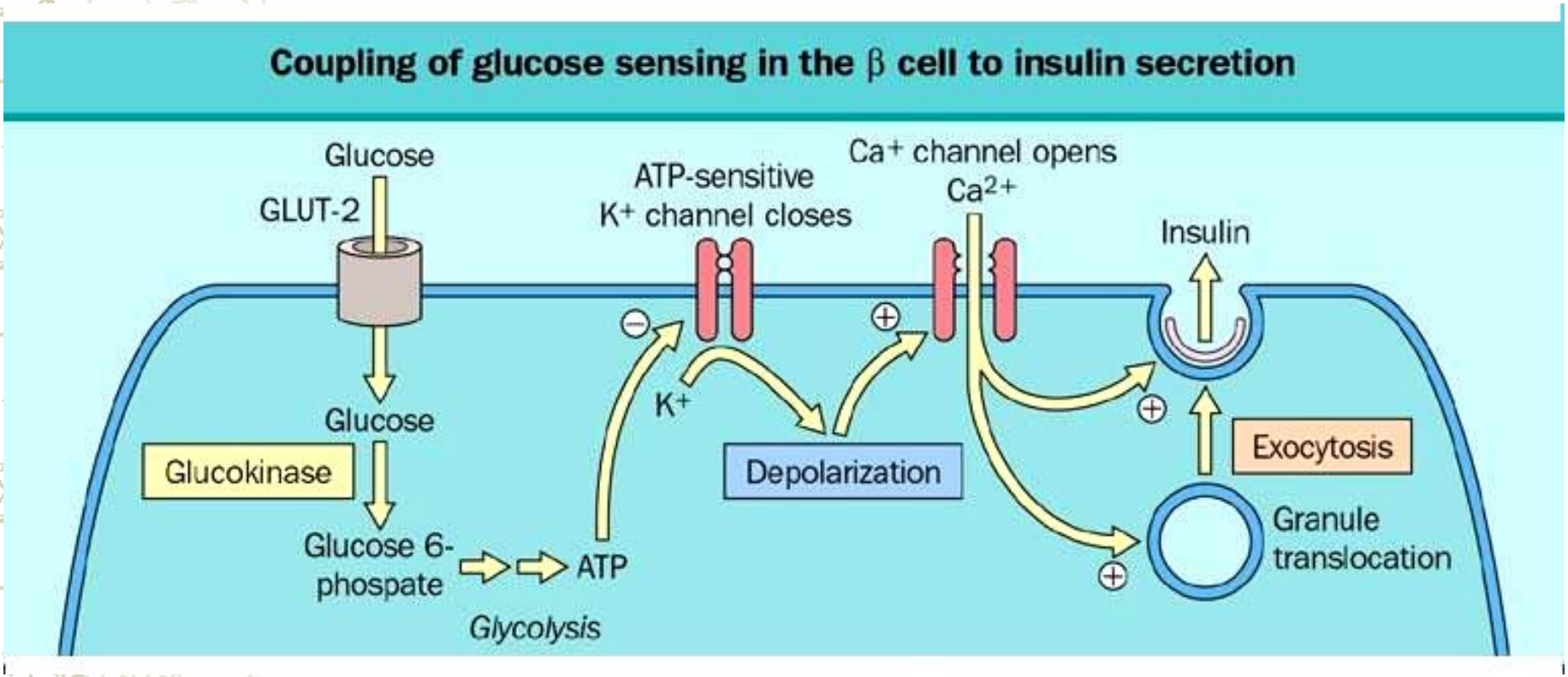
Functional Anatomy of the Endocrine Pancreas

- Beta cells occupy the central portion of the islet and are surrounded by a "rind" of alpha and delta cells.
- Islets are richly vascularized, allowing their secreted hormones ready access to the circulation.
- Although islets comprise only 1-2% of the mass of the pancreas, they receive about 10 to 15% of the pancreatic blood flow.

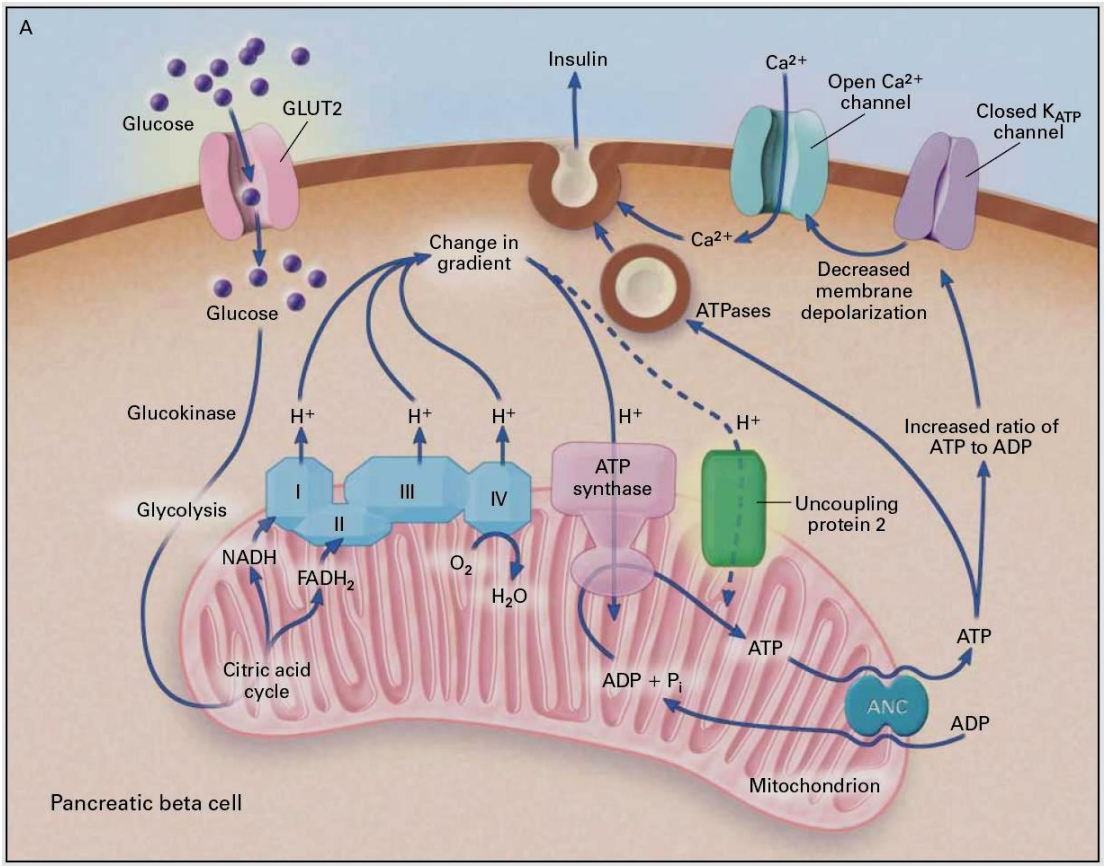
Insulin secretion in beta cell

- Glucose is the key regulator of insulin secretion by the pancreatic beta cell, although amino acids, ketones, various nutrients, gastrointestinal peptides, and neurotransmitters also influence insulin secretion.
- Glucose levels >3.9 mmol/L (70 mg/dL) stimulate insulin synthesis, primarily by enhancing protein translation and processing, as well as inducing insulin secretion.

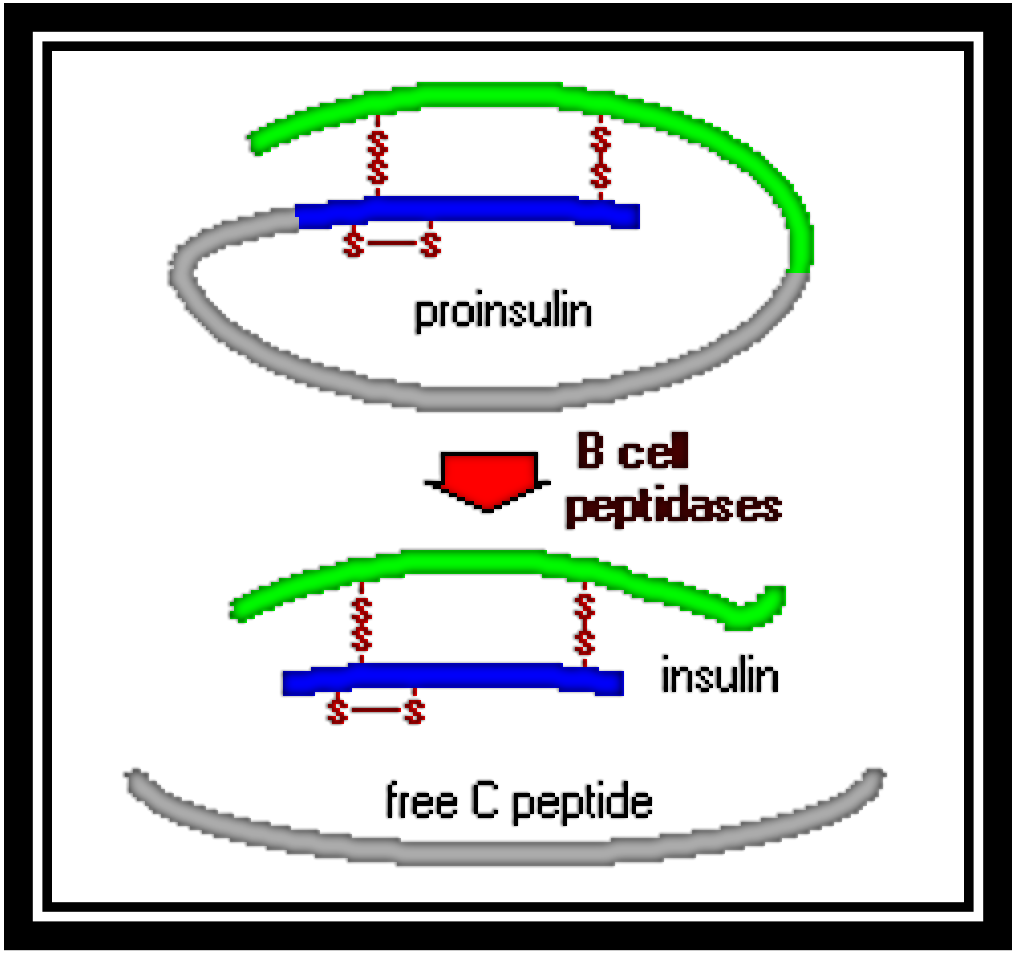
Insulin secretion in beta cell



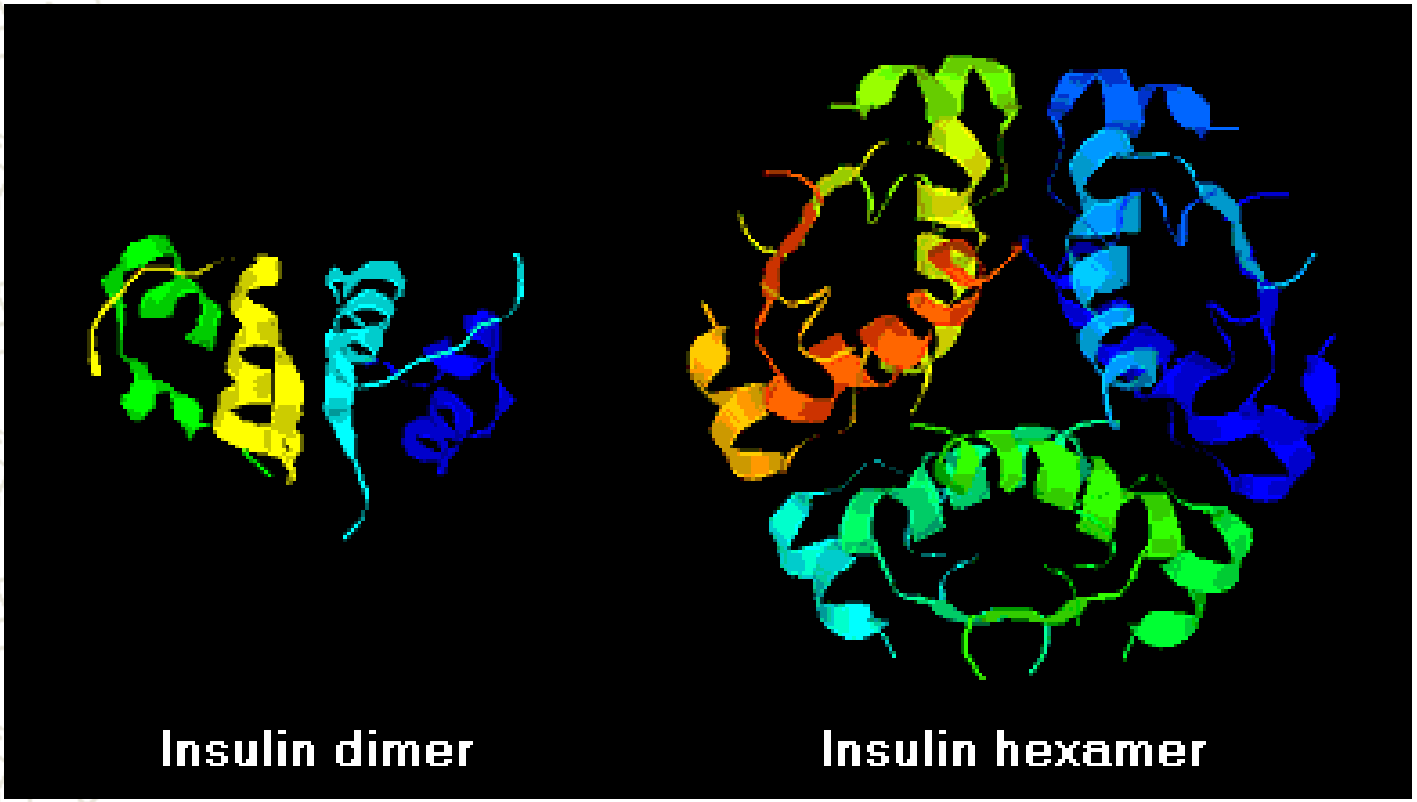
Insulin secretion in beta cell



Insulin structure



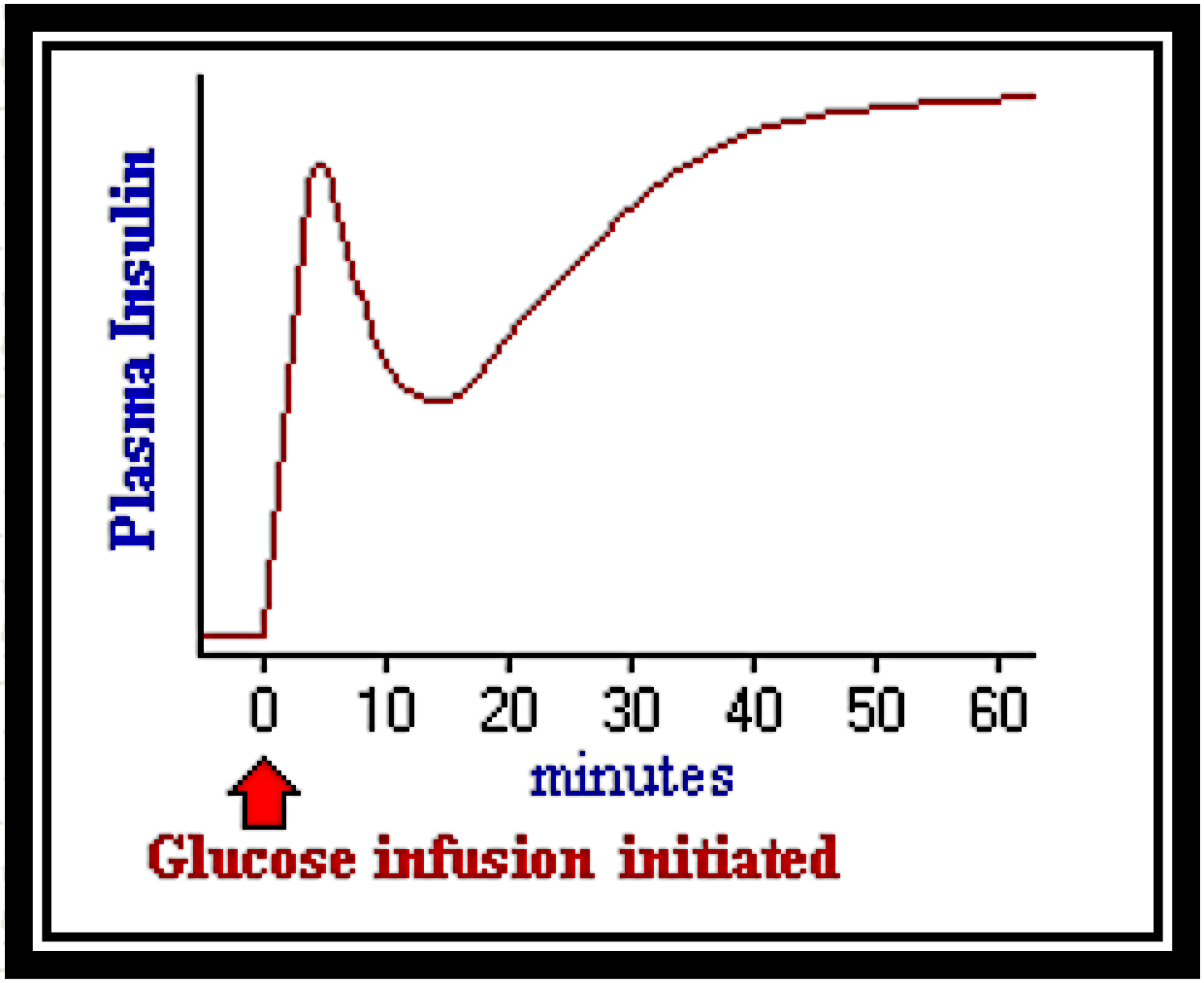
Insulin structure



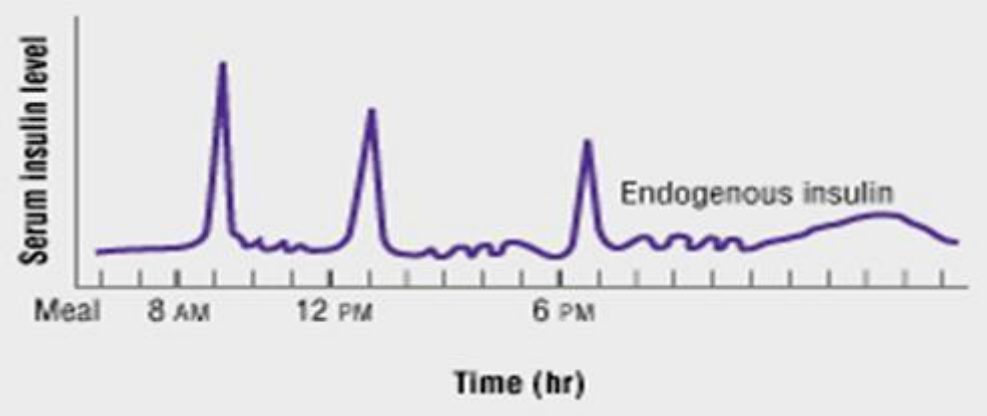
Insulin secretion in beta cell

- Careful studies of insulin secretory profiles reveal pulsatile pattern of hormone release, with small secretory bursts occurring about every 10 min, superimposed upon greater amplitude oscillations of about 80 to 150 min.
- Meals or other major stimuli of insulin secretion induce large (four- to fivefold increase versus baseline) bursts of insulin secretion that usually last for 2 to 3 h before returning to baseline.
- Derangements in these normal secretory patterns are one of the earliest signs of beta cell dysfunction in DM.

Insulin secretion in beta cell



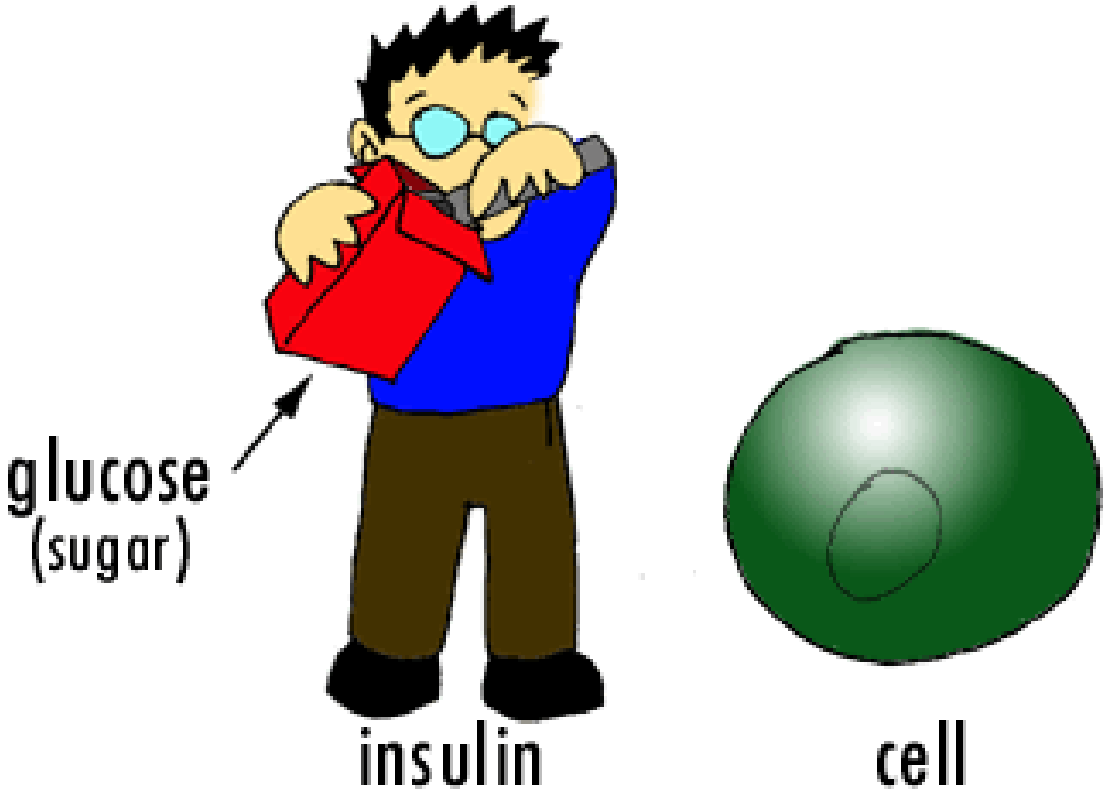
Normal endogenous insulin secretion



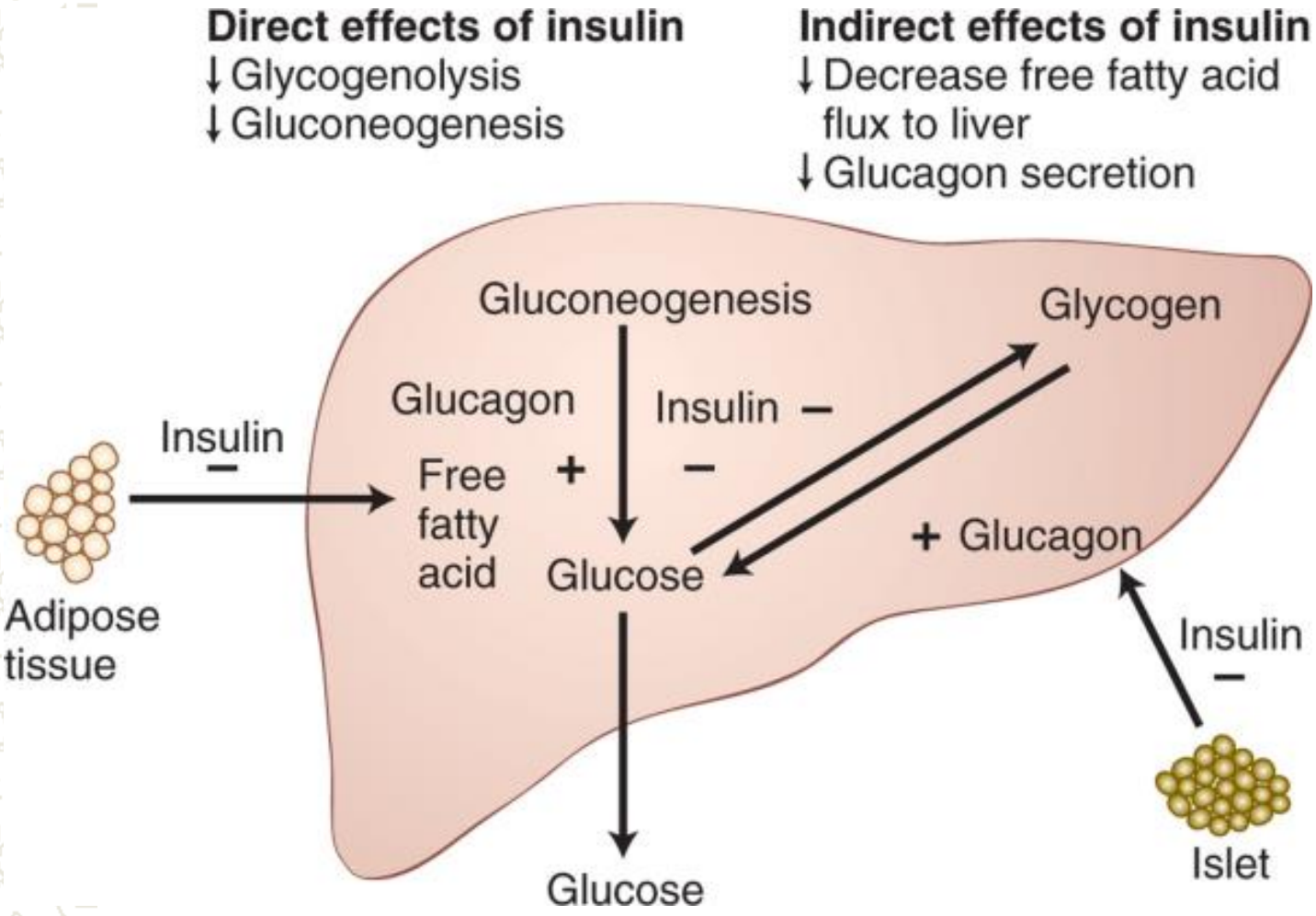
Effects of Insulin

- Insulin facilitates entry of glucose into muscle, adipose and several other tissues.
- Insulin stimulates the liver to store glucose in the form of glycogen.
- Insulin promotes synthesis of fatty acids in the liver.
- Insulin inhibits breakdown of fat in adipose tissue.
- Insulin stimulates the uptake of amino acids, again contributing to its overall anabolic effect.
- Insulin also increases the permeability of many cells to potassium, magnesium and phosphate ions.

Effects of Insulin



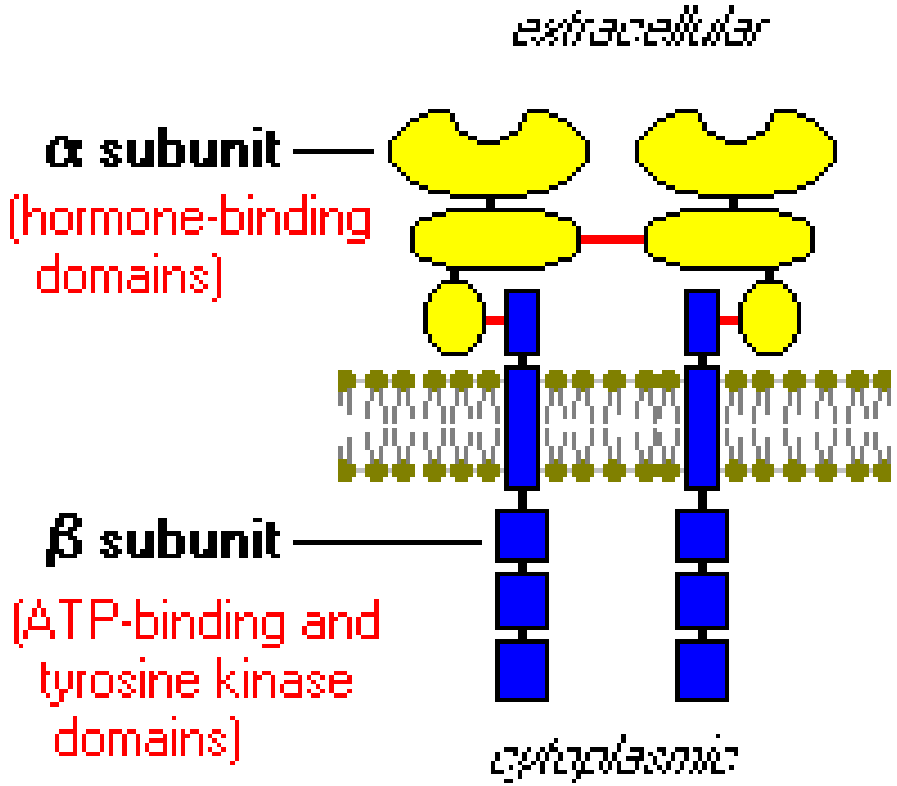
Effects of Insulin



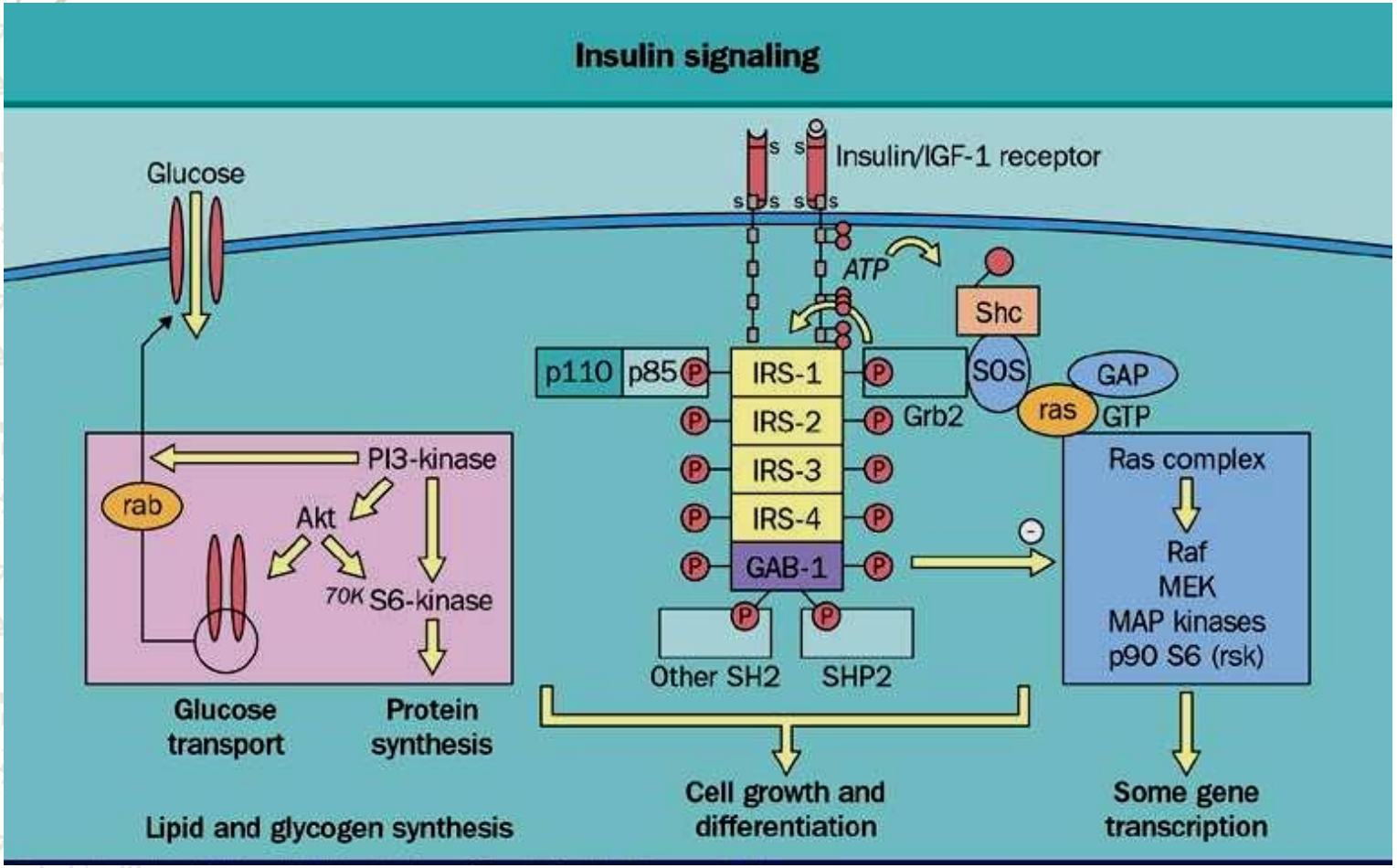
Effects of Insulin

- Insulin suppresses hepatic glucose production by direct and indirect mechanisms.
- In insulin resistance, insulin's ability to suppress lipolysis in adipose tissue and glucagon secretion by alpha cells in the islet results in increased gluconeogenesis.
- In addition, insulin inhibition of glycogenolysis is impaired. Thus, both hepatic and peripheral insulin resistance results in abnormal glucose production by the liver.

Insulin Receptor

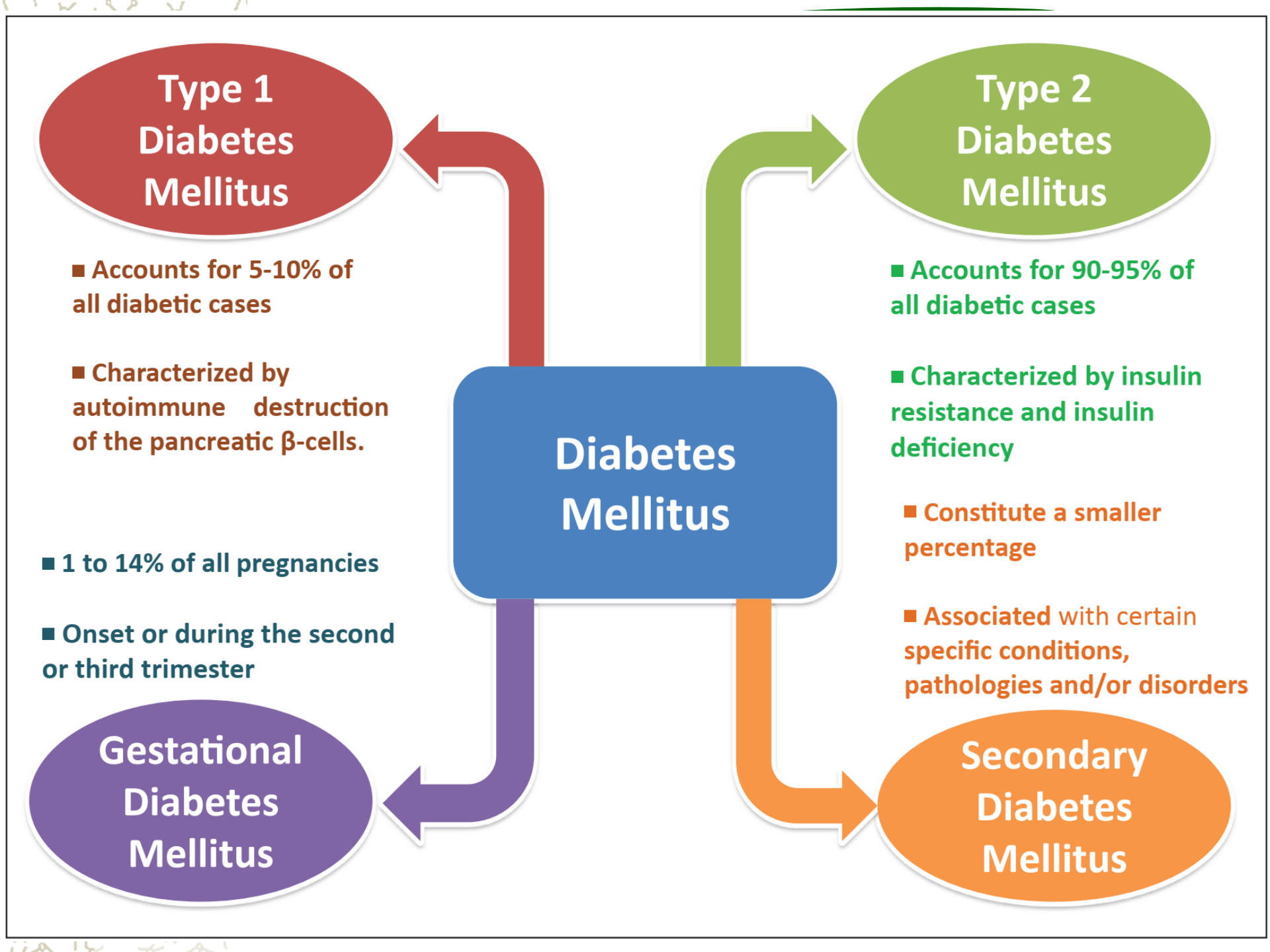


Insulin action in cells



Diabetes mellitus

- 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.


Type 1 Diabetes Mellitus
Accounts for 5-10% of all diabetic cases
Characterized by autoimmune destruction of the pancreatic β-cells.
Type 2 Diabetes Mellitus
Accounts for 90-95% of all diabetic cases
Characterized by insulin resistance and insulin deficiency
Diabetes Mellitus
1 to 14% of all pregnancies
Onset or during the second or third trimester
Gestational Diabetes Mellitus
Constitute a smaller percentage
Associated with certain specific conditions, pathologies and/or disorders
Secondary Diabetes Mellitus

Epidemiology

- The worldwide prevalence of DM has risen dramatically over the past two decades, from an estimated 30 million cases in 1985 to 177 million in 2000.
- Based on current trends, >360 million individuals will have diabetes by the year 2030 .
- Although the prevalence of both type 1 and type 2 DM is increasing worldwide, the prevalence of type 2 DM is rising much more rapidly because of increasing obesity and reduced activity levels as countries become more industrialized.
- 7% of the population, had diabetes in 2005 (~30% of individuals with diabetes were undiagnosed).

Epidemiology

- Type 2 diabetes mellitus (T2DM) is the predominant form of diabetes worldwide, accounting for 90% of cases globally.
- Type 2 diabetes is currently thought to occur in genetically predisposed persons who are exposed to a series of environmental influences that precipitate the onset of clinical disease.
- Sex, age, and ethnic background are important factors in determining risk of developing T2DM.
- Diabetes is a major cause of mortality, but several studies indicate that diabetes is likely underreported as a cause of death.

Epidemiology

- In type 1 DM
  - Less than 10% of DM
  - More common in children
  - Increasing in north Europe
- In type 2 DM
  - 11% of Adult population
  - Increasing in all the world

Pathogenesis of Type 1 diabetes mellitus

- GENETIC SUSCEPTIBILITY
  - MHC genes
  - Non-MHC genes
- AUTOIMMUNITY
  - Target autoantigens
  - Glutamic acid decarboxylase
  - Insulin
  - Insulinoma-associated protein 2
  - Role of cellular immunity
- ENVIRONMENTAL FACTORS
  - Perinatal factors
  - Role of viruses
  - Role of diet

Pathogenesis of Type 1 diabetes mellitus

- T1DM, also known as type 1A DM or as per the previous nomenclature as insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes, constitutes about 5–10% of all the cases of diabetes.
- It is an autoimmune disorder characterized by T-cell-mediated destruction of pancreatic β-cells, which results in insulin deficiency and ultimately hyperglycemia.

Pathogenesis of Type 1 diabetes mellitus

- T1DM is an autoimmune disorder characterized by several immune markers, in particular autoantibodies.
- These autoantibodies are associated with the immune-mediated β-cell destruction, characteristic of this disease.
- The autoantibodies include:
  - glutamic acid decarboxylase autoantibodies (GADAs) such as GAD65,
  - islet cell autoantibodies (ICAs) to β-cell cytoplasmic proteins such as autoantibodies to islet cell antigen 512 (ICA512),
  - autoantibodies to the tyrosine phosphatases, IA-2 and IA-2α,
  - insulin autoantibodies (IAAs), and
  - autoantibodies to islet-specific zinc transporter isoform 8 (ZnT8).

Pathogenesis of Type 2 diabetes mellitus

- GENETIC SUSCEPTIBILITY
  - Genes affecting insulin release
  - Genes affecting insulin action
- ENVIRONMENTAL FACTORS
  - Role of diet and obesity
  - Free fatty acids
  - Tumor necrosis factor-alpha
  - Adiponectin
  - Resistin
  - Uncoupling protein 2
  - Pattern of fat distribution
  - Role of intrauterine development and birth weight

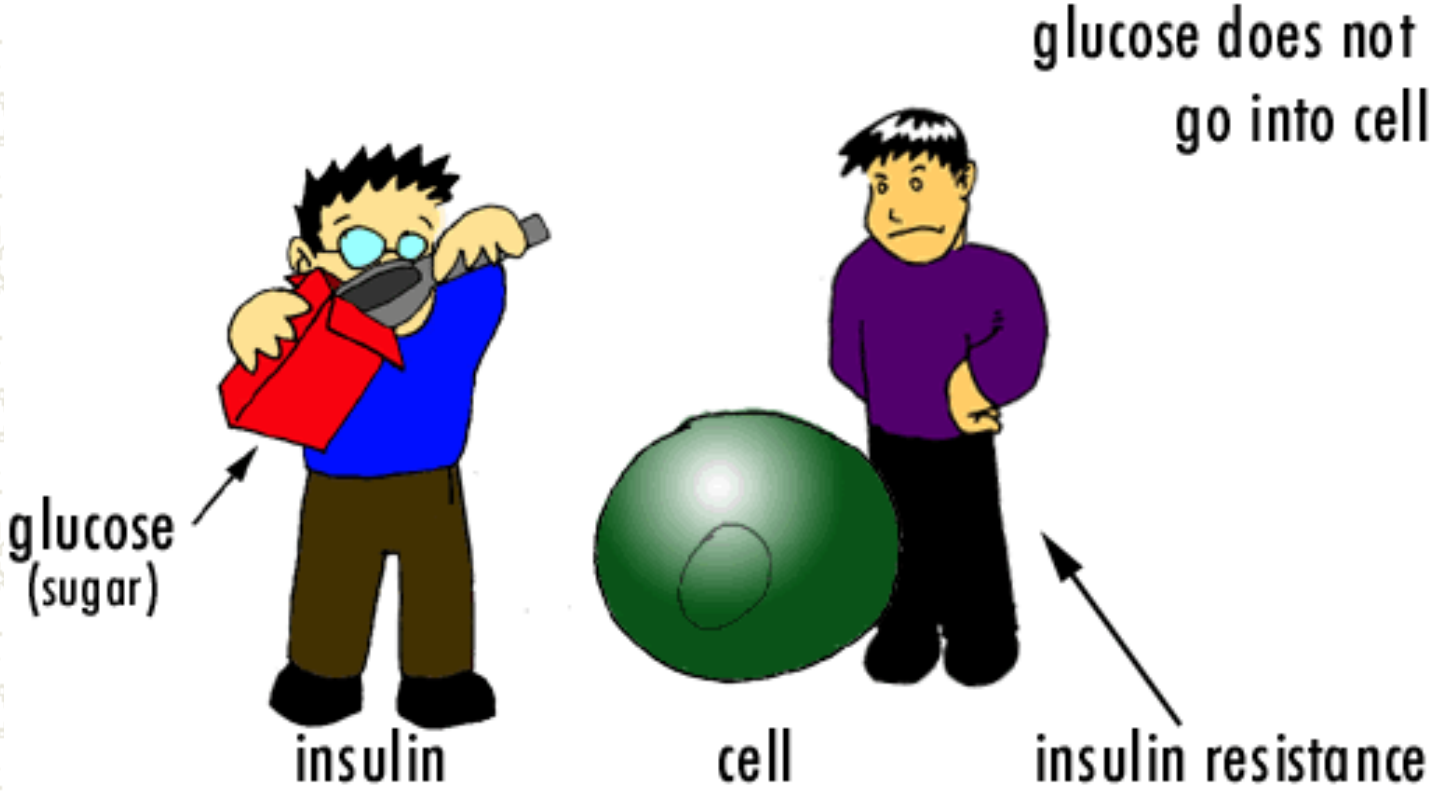
PATHOPHYSIOLOGY of type 2 diabetes mellitus

- This type of diabetes is characterized by two main insulin-related anomalies: insulin resistance and β-cell dysfunction.
- Insulin resistance results from disruption of various cellular pathways, which lead to a decreased response, or sensitivity of cells in the peripheral tissues, in particular the muscle, liver, and adipose tissue toward insulin.

PATHOPHYSIOLOGY of type 2 diabetes mellitus

- In the early stages of the disease, decreased insulin sensitivity triggers β-cells hyperfunction to achieve a compensatory increase in insulin secretion to maintain normoglycemia.
- The higher levels of circulating insulin (hyperinsulinemia), thus, prevent hyperglycemia.
- However, gradually, the increased insulin secretion by β-cells is not able to compensate sufficiently for the decrease in insulin sensitivity.
- Moreover, β-cell function begins to decline and β-cell dysfunction eventually leads to insulin deficiency.

Insulin resistance



Thank you and hope for a good rain