Glucose homeostasis and Diabetes mellitus

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Overview

- Pancreatic hormones involved in glucose homeostasis and their
  - Synthesis
  - Mechanism of actions
  - Regulation of secretion

- Diabetes mellitus
  - Types
  - Symptoms
  - Complications
  - Management

Introduction

- Glucose metabolism is critical to normal physiological functioning.

- Glucose acts both as a source of energy and as a source of starting material for nearly all types of biosynthetic reactions

- Regulated mainly by the pancreatic hormones

Islet cells

- Scattered throughout the pancreas
- More concentrated in the tail of pancreas
- Only 2% of the volume of the gland
- Four distinct cell types (Basis of staining properties)
- A ,B ,D ,F cells

Islet cells

- Four polypeptides secreted by the islets of Langerhans in the pancreas.

Cell type	Percentage	Polypeptide
A cell	20%	Glucagon
B cell	60–75 %	Insulin
D cell		Somatostatin
F cell		Pancreatic Polypeptide

Insulin

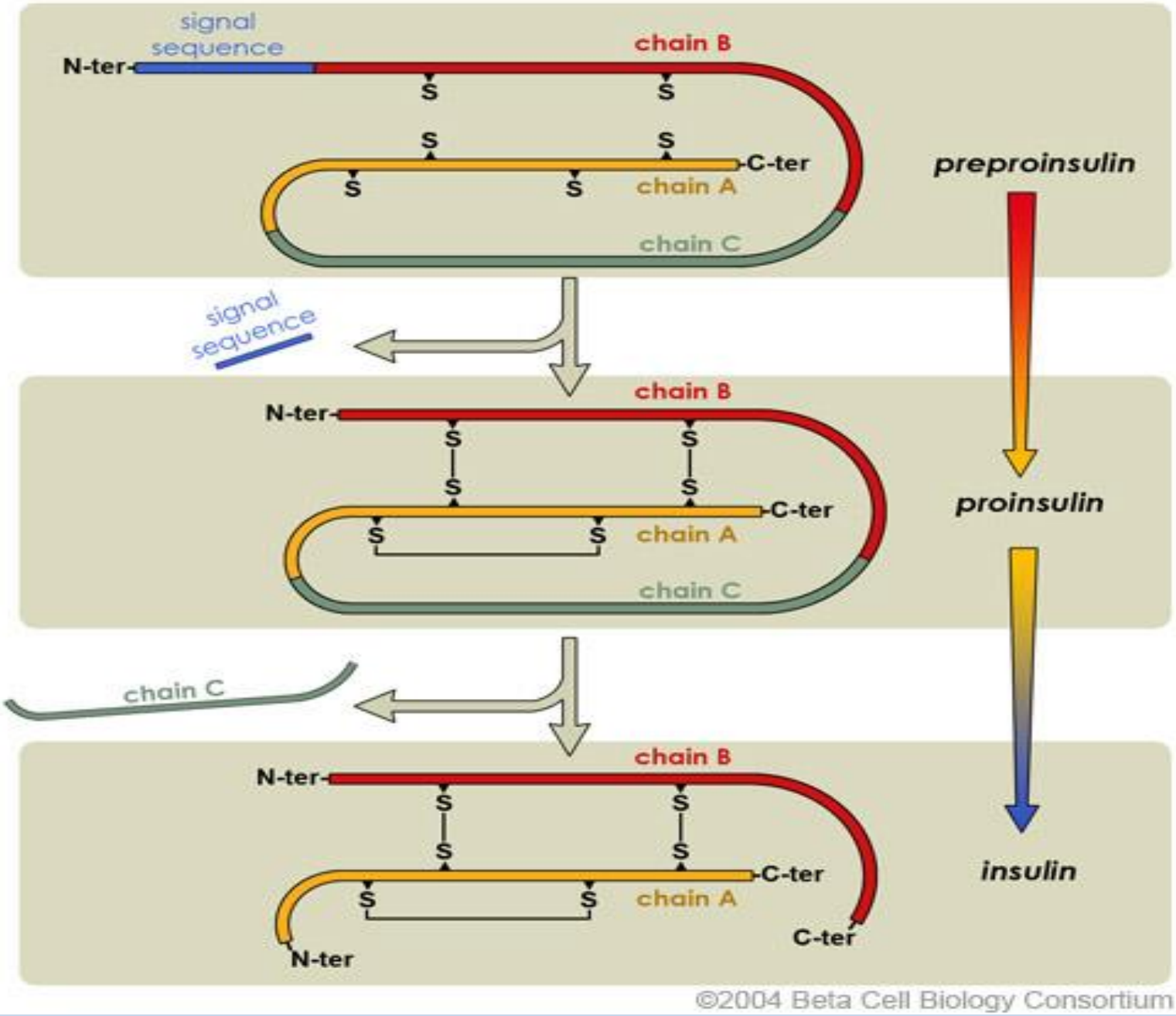
- Has two amino acid chains linked by disulfide bonds.
- Species to species minor differences in the amino acid chain.
- Synthesized as a part of a preprohormone
- Gene for insulin located in the short arm of chromosome 11

Insulin

- Synthesized in the ER of B cells
- Transported to the golgi apparatus ,packed into membrane bound granules
- Contents of granules expelled by exocytosis
- Preprohormone originates in the Endoplasmic Reticulum

Insulin

- Remainder of the molecule is folded and disulfide bonds are formed to make Proinsulin
- Peptide segments A and B chains are connected by the Connecting Peptide (C peptide)
- It facilitates folding and detached in the granule before secretion
- B cells secrete equal amounts of insulin and C peptide


signal sequence
chain B
N-ter
S
C-ter
chain A
chain C
preproinsulin
proinsulin
insulin
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Insulin Metabolism

- Half life is about 5 mins
- Insulin binds to insulin receptors
- Insulin is destroyed by proteases in the endosomes

Glucose transporters

- Glucose enters cells by

  1. Facilitated diffusion
  (muscle/adipose tissue)

  2. Secondary active transport

  with NA +

  (Intestine /Kidneys)

- Glucose transporters (GLUTs) for Facilitated diffusion

- Sodium dependent glucose transporters (SGLT 1 and 2) in intestine and kidneys

Glucose transporters

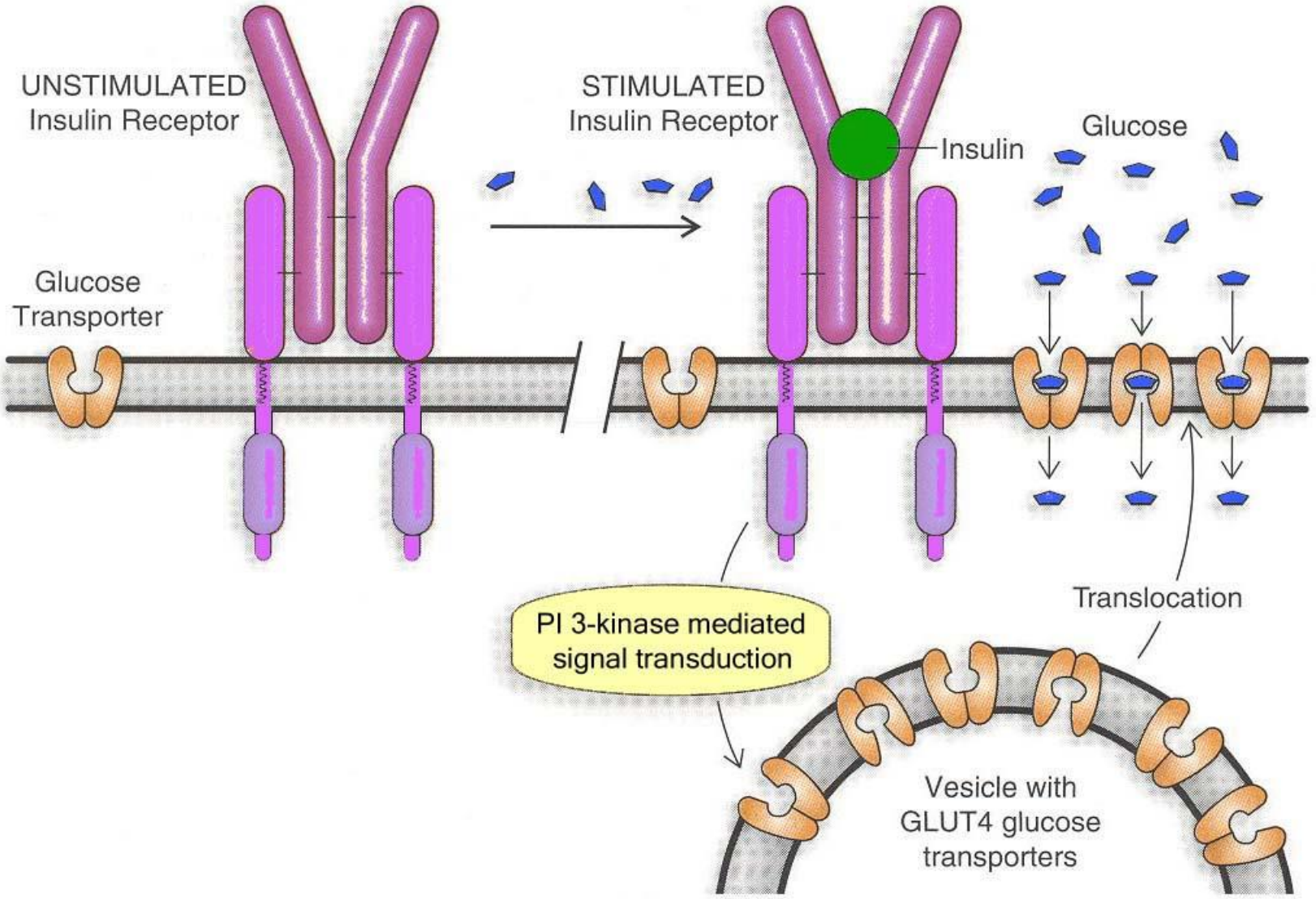
- GLUTs have seven different transporters
- GLUT 2 is located in the B cells of pancreas
- GLUT 4 is in muscle and adipose tissue that is stimulated by insulin

Glucose transporters

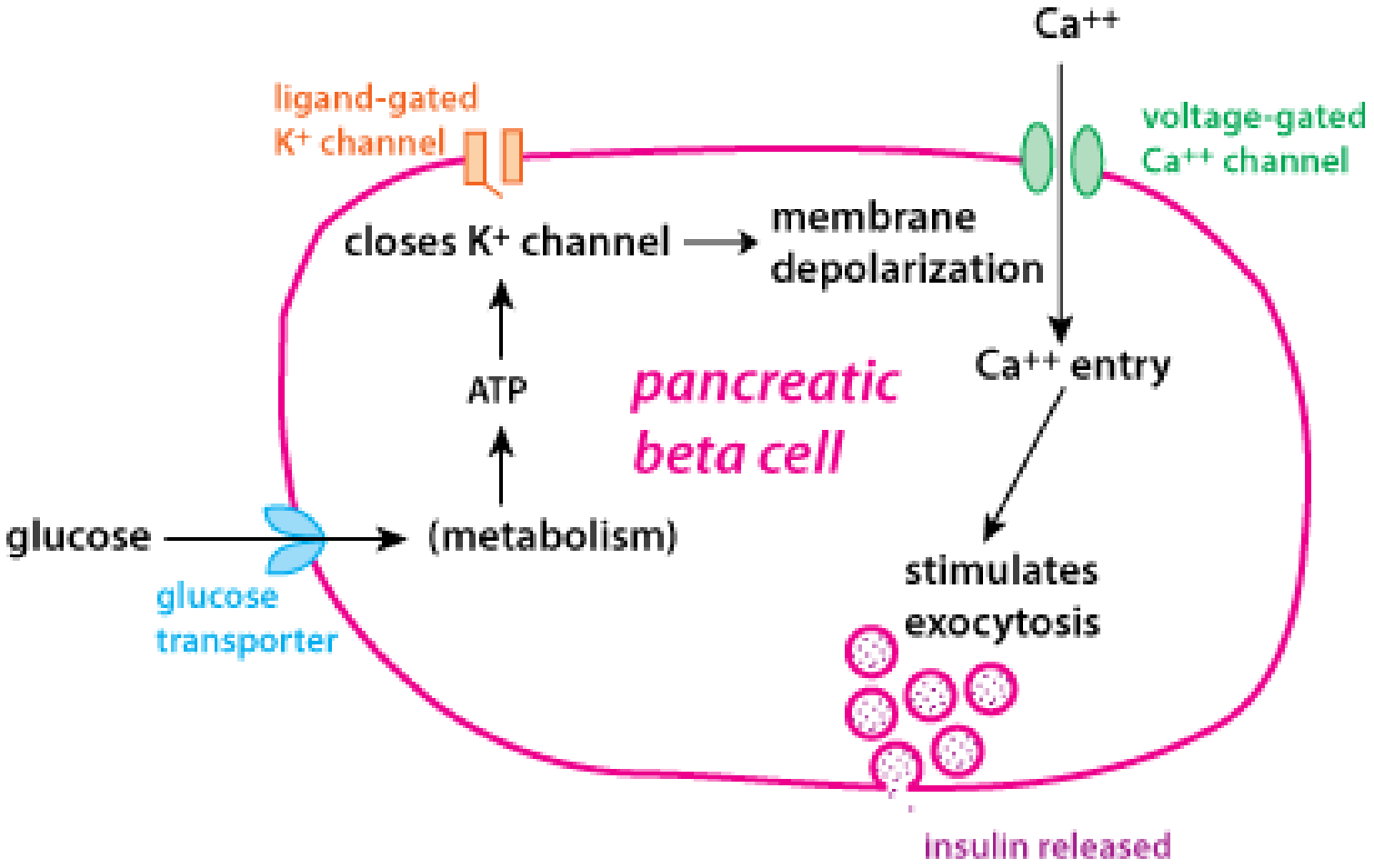
- When the insulin receptors are activated the vesicles containing GLUT 4 are transported to cell membrane and fuse with it.

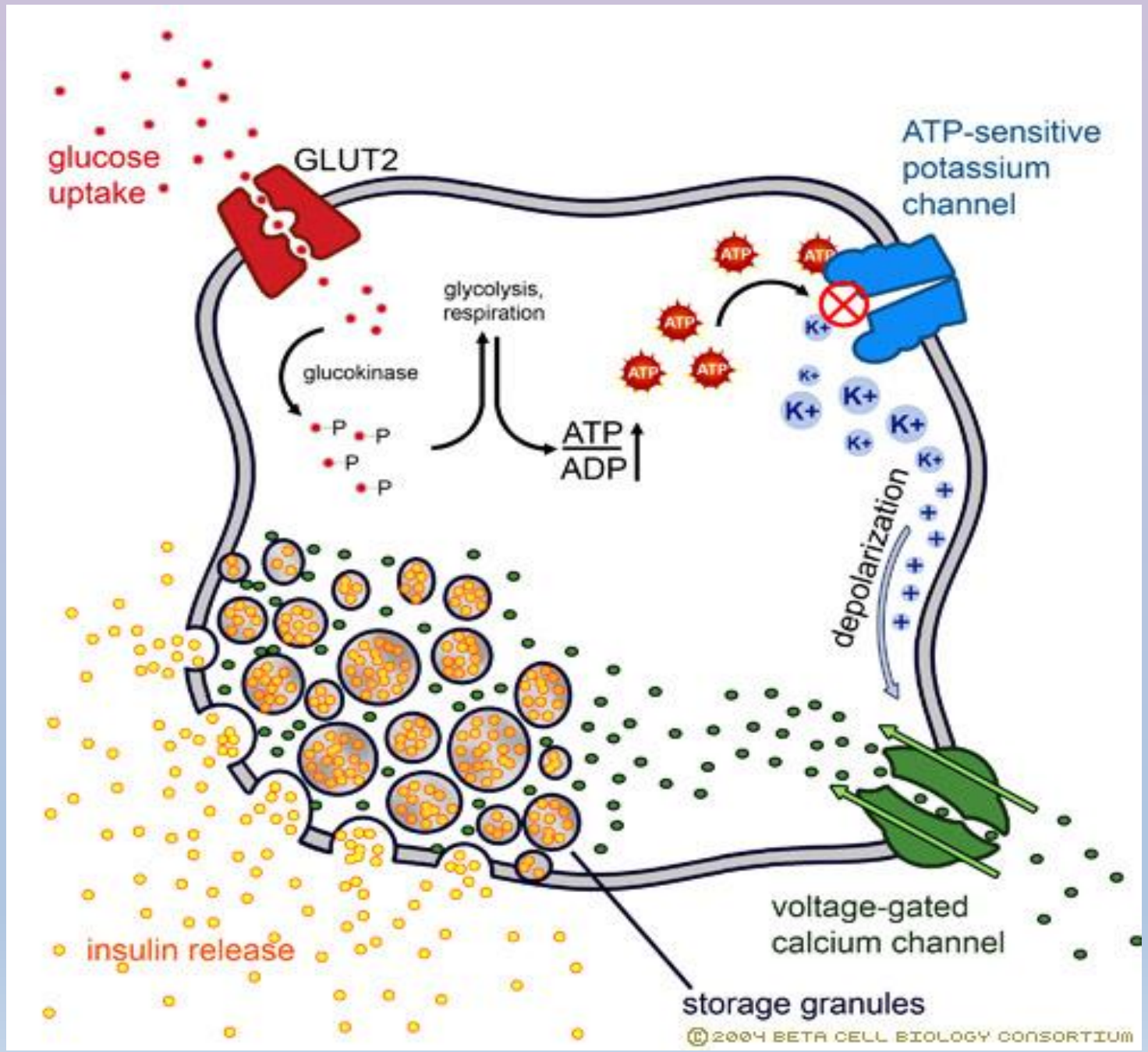
- Insulin sensitive tissues have a group of transporters that release GLUTs in response to exercise –Can cause hypoglycemia

Figure 11.10 Insulin activation of glucose transporters.



Regulation of insulin secretion




glucose uptake
GLUT2
ATP-sensitive potassium channel
glycolysis, respiration
glucokinase
ATP
ADP
depolarization
voltage-gated calcium channel
insulin release
storage granules
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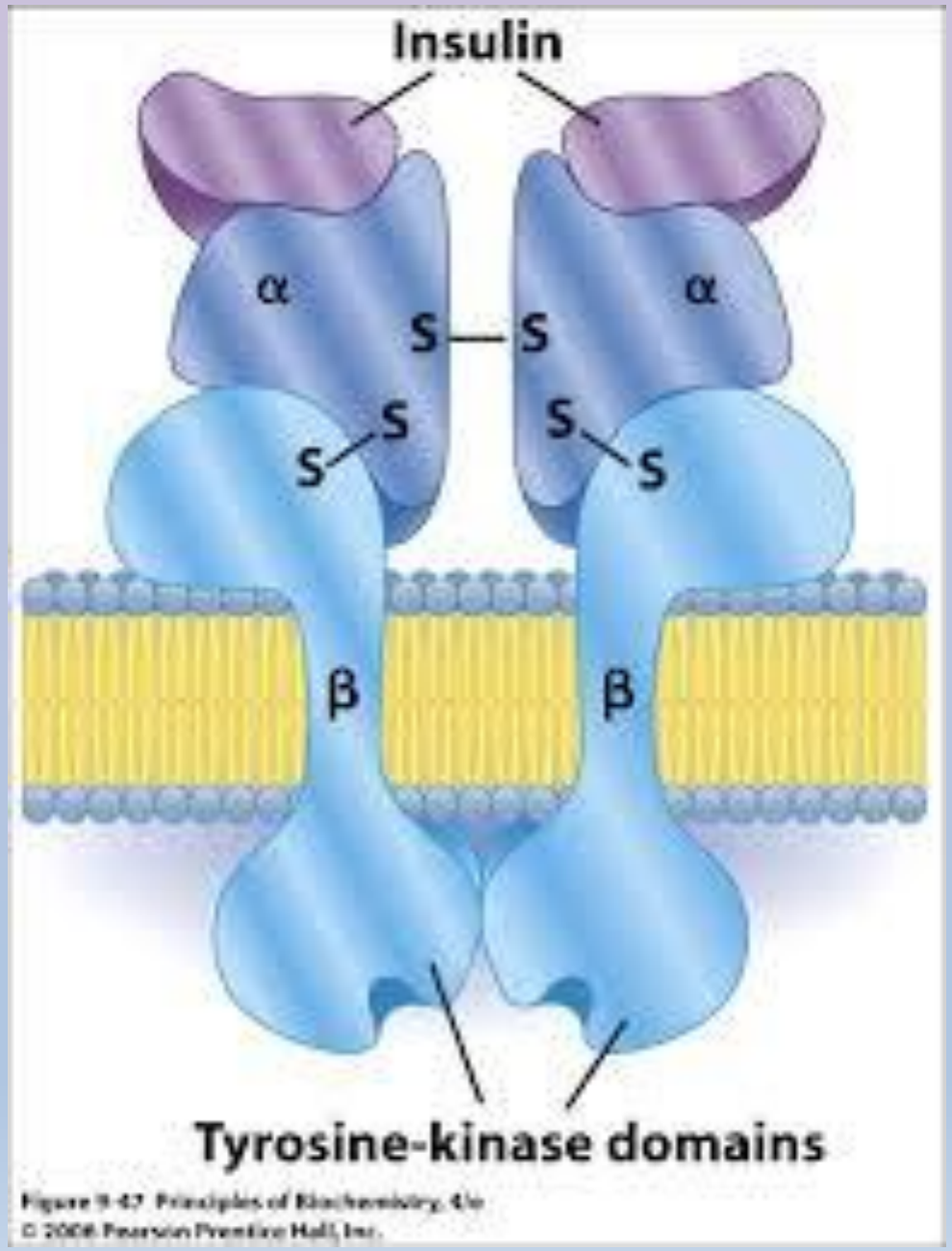
Mechanism of action

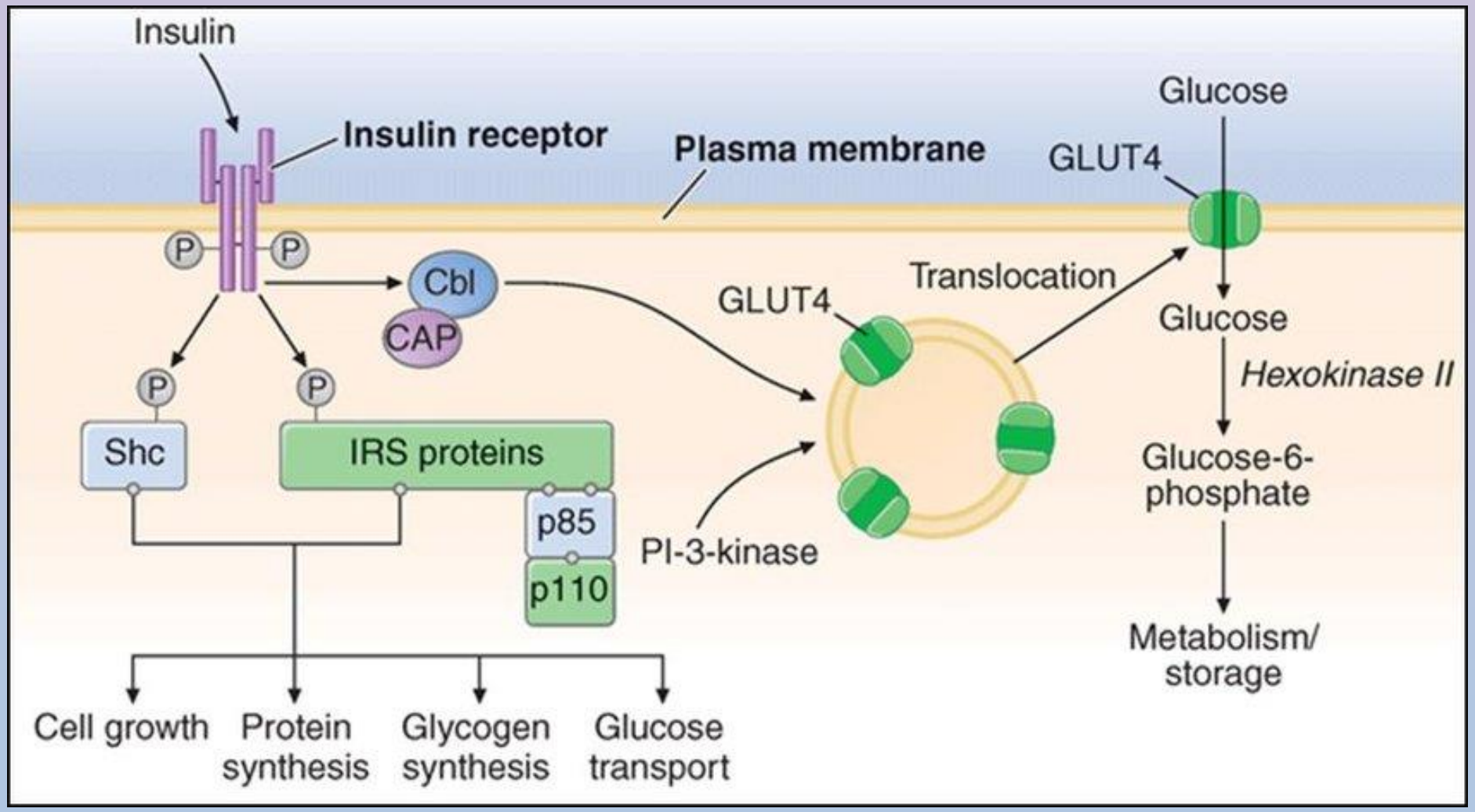
Insulin receptors

- Tetramer made of two α and two β subunits
- Found in many cells including the cells where glucose transport is not increased
- α subunits bind insulin and are extracellular and β subunits span the membrane
- Intracellular β subunit has tyrosine kinase (TK) activity
- Binding of insulin triggers TK, which autophosphorylate the β subunits on tyrosine residues

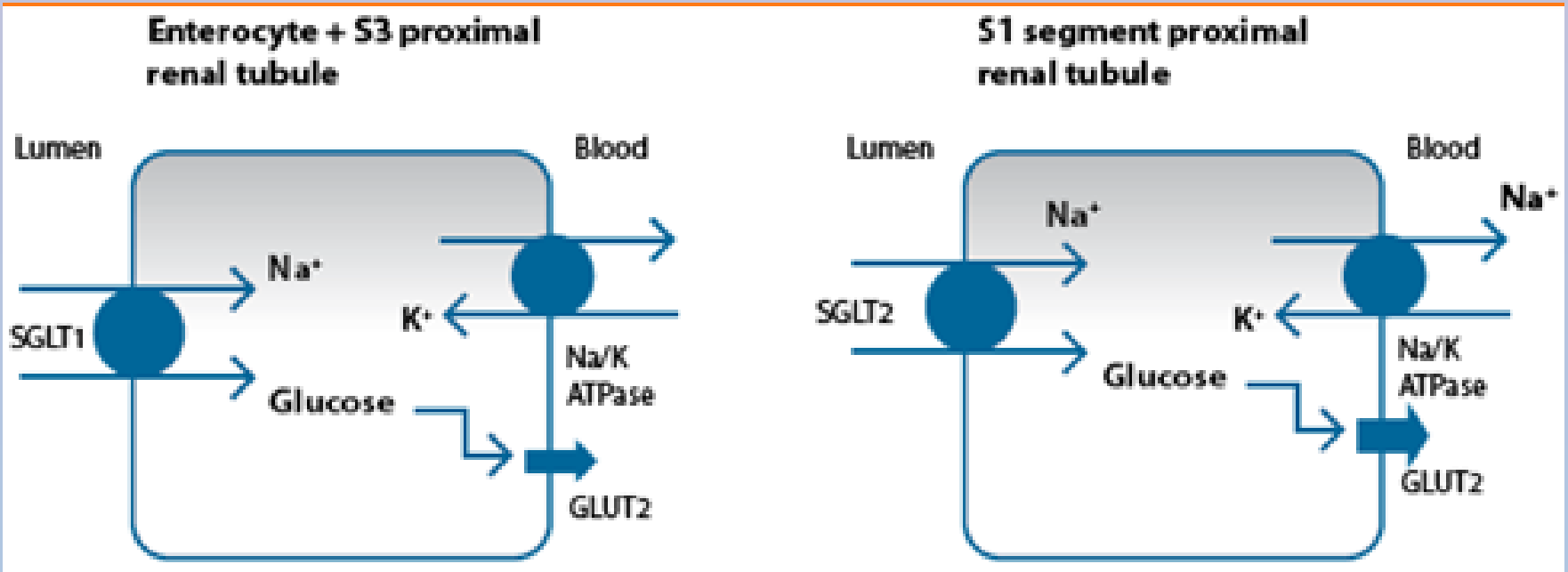

Insulin
α
α
S
S
S
S
S
S
β
β
Tyrosine-kinase domains

Mechanism of action

- Autophosphorylation is needed for insulin to exert its biologic effects
- Insulin Receptor Substrate (IRS) mediates some of the effects
- Growth promoting protein anabolic effects of insulin mediated via Phophatidylinositol 3 Kinase (PI3K)


Insulin
Insulin receptor
Plasma membrane
Glucose
GLUT4
P
P
Cbl
CAP
Translocation
GLUT4
Glucose
Hexokinase II
P
P
Shc
IRS proteins
p85
p110
PI-3-kinase
Glucose-6-phosphate
Metabolism/ storage
Cell growth
Protein synthesis
Glycogen synthesis
Glucose transport

SGLT Receptors



Factors affecting insulin secretion

Stimulators	Inhibitors
Glucose	Somatostatin
Amino acids (leucine ,arginine)	Alpha adrenergic stimulation
Intestinal Hormones (GIP,GLP 1)	Beta adrenergic blockers
Glucagon	Thiazide diuretics
Beta adrenergic stimulators	K depletion

Intestinal Hormones

- Substances produced by the intestinal mucosa stimulates insulin secretion
  - Glucagon
  - Secretin
  - CCK
  - Gastrin
  - Gastric Inhibitory Peptide (GIP)
  - Glucagon like peptide 1 (7-36)

Effects of insulin

- Net effect is storage of CHO,proteins and fat
- Rapid ,intermediate and delayed actions
- Rapid (seconds)
  - Increased transport of glucose, amino acids and K into insulin sensitive cells

Effects of insulin

- Intermediate (mins)
  - Stimulation of protein synthesis
  - Inhibition of protein degradation
  - Activation of glycolytic enzymes and glycogen synthase
  - Inhibition of phosphorylase and gluconeogenic enzymes

- Delayed (hours)
  - Increase in mRNA for lipogenic and other enzymes

Effects of insulin on Adipose tissue

- **Increase glucose entry**
- **Increased fatty acid synthesis**
- Increased glycerol phosphate synthesis
- Increased triglyceride deposition
- Activation of lipoprotein lipase
- Inhibition of hormone sensitive lipase
- **Increased potassium uptake**

Effects of insulin on muscle

- Increased glucose entry
- Increased glycogen synthesis
- Increased amino acid uptake
- Increased protein synthesis
- Decreased protein catabolism
- Increased potassium uptake

Effects of insulin on liver

- Decreased ketogenesis
- Increased protein synthesis
- Increased lipid synthesis
- Decreased gluconeogenesis
- Increased glycogen synthesis
- Increased gylcolysis

Decreased glucose output

Relation to Potassium

- Insulin causes potassium to enter in to cells causing lowering of extracellular potassium
- Insulin increases the activity of Na+ ,K+ ATP ase in cell membrane
- This mechanism is used to treat the hyperkalemia

MCQ’S

- T/F Regarding insulin.

1. Secreted from the D cells of pancreas
2. Synthesized as a part of preprohormone
3. Binds to the β subunit of the insulin receptor
4. Intracellular β subunit has tyrosine kinase activity
5. Lowers extracellular K level

- T/F Regarding insulin.

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- T/F Regarding glucose transporters

1. Six types of GLUTs are seen
2. GLUT 3 is seen in the B cell of pancreas
3. GLUT 4 is insulin sensitive
4. Responsible for facilitated diffusion of glucose
5. SGLT 1 and 2 are seen in the kidneys

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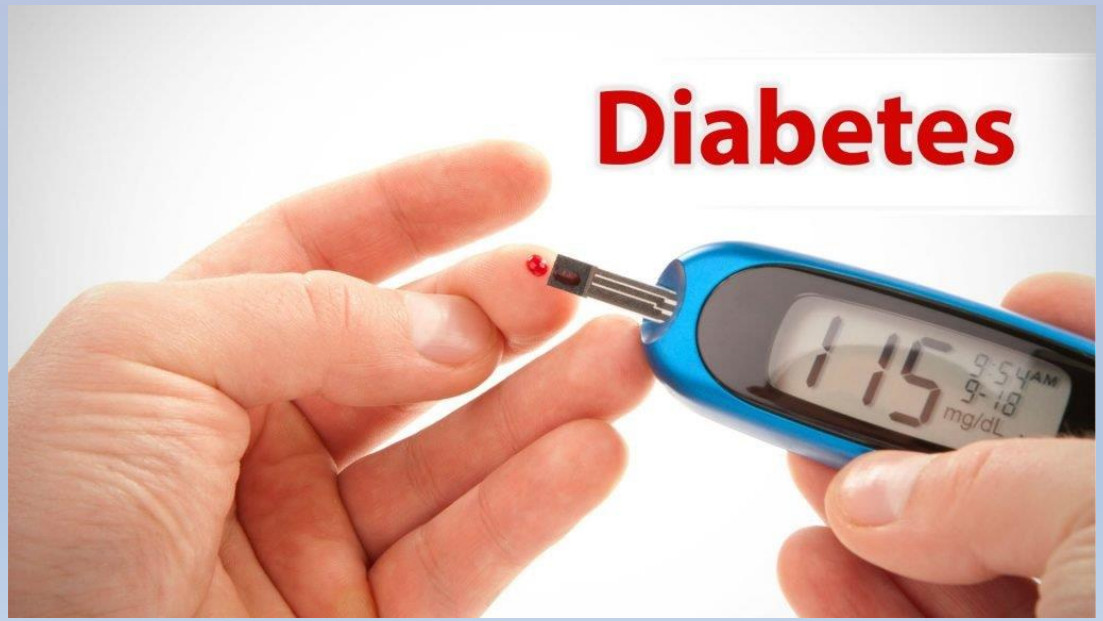
Diabetes Mellitus



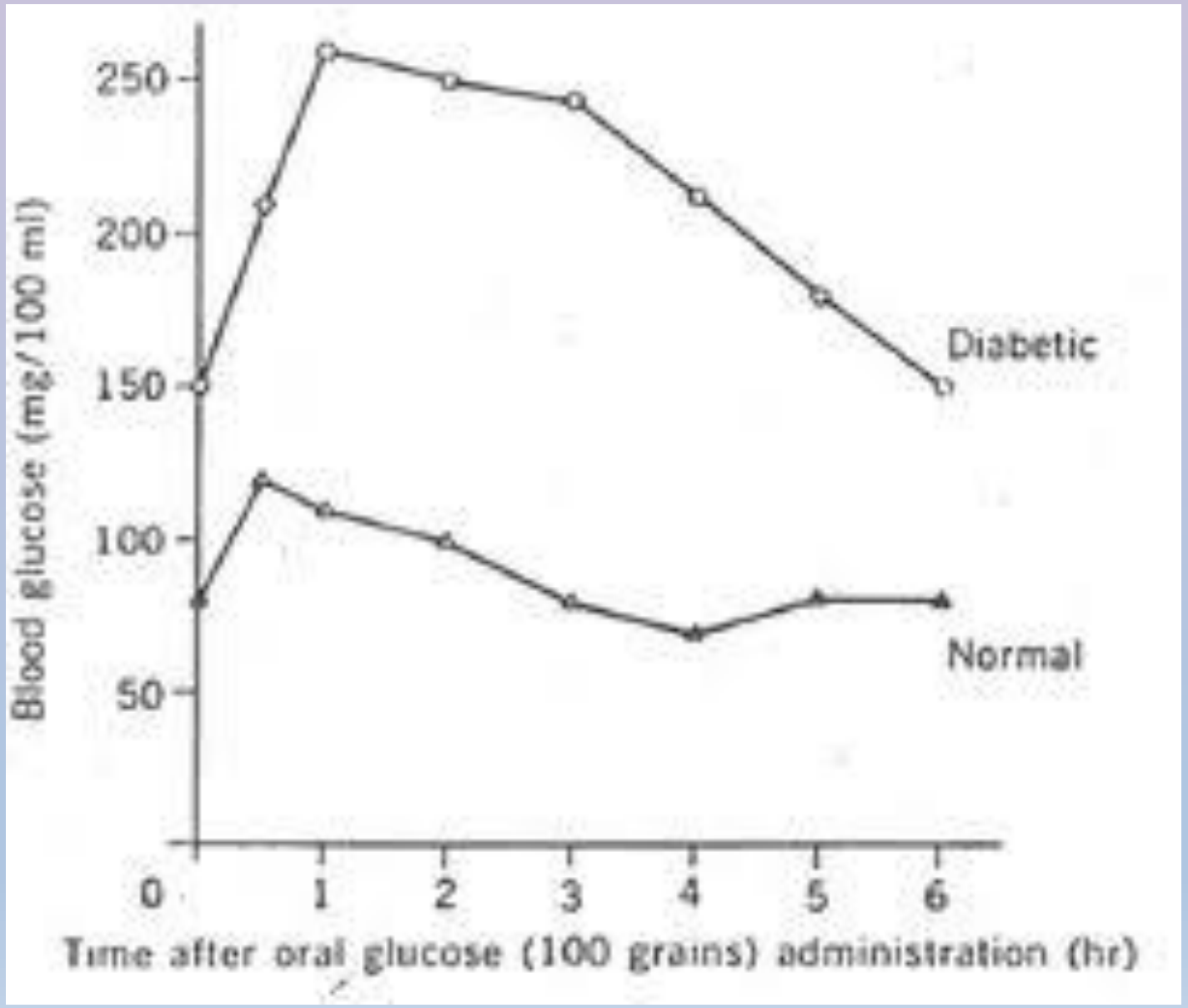
Insulin deficiency

- State of insulin deficiency leads to Diabetes Mellitus

Glucose tolerance

- When a Glucose load is given to a diabetic plasma glucose levels rises higher and returns to baseline much slower.

- Standard Oral Glucose Tolerance Test (OGGT) is used in the diagnosis of Diabetes.


250
200
150
100
50
Blood glucose (mg/100 ml)
Diabetic
Normal
0
1
2
3
4
5
6
Time after oral glucose (100 grains) administration (hr)

Why hyperglycemia in Diabetes?

1 .Impaired glucose tolerance in diabetes is due to decreased peripheral utilization

- Reduced entry of glucose to skeletal,cardiac, smooth muscles impaired

2.Derangement of glucostatic functions of the liver.

- Insulin facilitates the Glycogen synthesis and inhibit hepatic glucose out put
- When insulin deficient, it cannot facilitate the above process

Effects of Hyperglycemia

- Symptoms occur as a result of the hyperosmolality of the blood

- Excretion of the osmotically active glucose

⇓

Loss of large amount of water(osmotic diuresis)

⇓

Dehydration

⇓

Mechanism to regulate water intake (Polydipsia)

Effects of Hyperglycemia

- Every 1 g of glucose excreted 4.1 kcal is lost from the body
- Increases oral caloric intake
- Mobilizes endogenous protein and fat stores causing weight loss

Effects of Hyperglycemia

- Deficient glucose utilization and hormone sensing (insulin, CCK, leptin) in the cells of hypothalamus that regulate satiety
- Feeding centre of the hypothalamus is not inhibited
- Leads to polyphagia

Changes in protein metabolism in diabetes

- Rate of amino acid catabolism increased
- AA are converted to glucose in the liver
- In the absence of insulin less protein synthesis in muscle and blood AA levels are high

Fat metabolism in Diabetes

- Accelerated lipid catabolism
- Increased synthesis of Ketone bodies
- Decreased synthesis of fatty acids and triglycerides
- Conversion of glucose to fatty acids in the depots is decreased due to intracelluar glucose deficiency

Fat metabolism in Diabetes

- Insulin inhibits the hormone sensitive Lipase in adipose tissue so in diabetes plasma levels of Free fatty acids increased

- Increased FFA is catabolized to acetyl CoA

- Excess acetyl CoA is converted to Ketone bodies

Acidosis in Diabetes

- Ketoacids (Acetoacetic acid and hydroxybutyric acid) are buffered but exceed the buffering capacity.
- Leads to respiratory alkalosis
- Rapid deep respiration named “Kussmaul breathing”
- Can lead to dehydration ,hypovolemia and hypotension and coma

Causes of coma in Diabetes

- Hyperosmolar coma is due to hyperosmolality
- Acidosis
- Dehydration
- Lactic acidosis

Cholesterol Metabolism in Diabetes

- Plasma Cholesterol levels are elevated
- Due to increase in VLDL and LDL
- Increased hepatic production and decreased removal of VLDL and LDL
- Leads to atherosclerosis

Diabetes mellitus

- According to WHO 422 million in the world has diabetes
- In Sri Lanka Prevalence > 20 yrs is 10.3 % in 2006
- China ,India ,USA have the highest prevalence

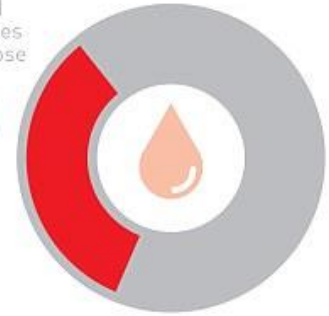
DIABETES

DIABETES IS ON THE RISE

422 MILLION
adults have diabetes

3.7 MILLION
deaths due to diabetes and high blood glucose

1.5 MILLION
deaths caused by diabetes



THAT'S 1 PERSON IN 11

Main types of diabetes

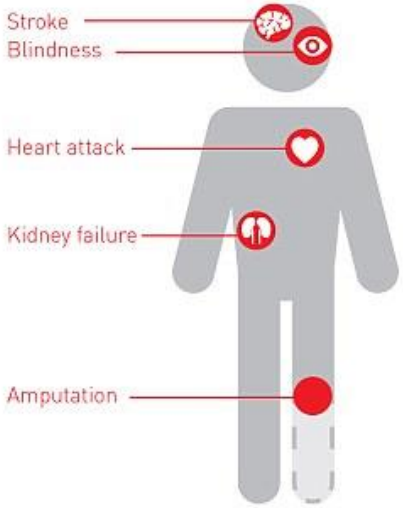
TYPE 1 DIABETES
Body does not produce enough insulin

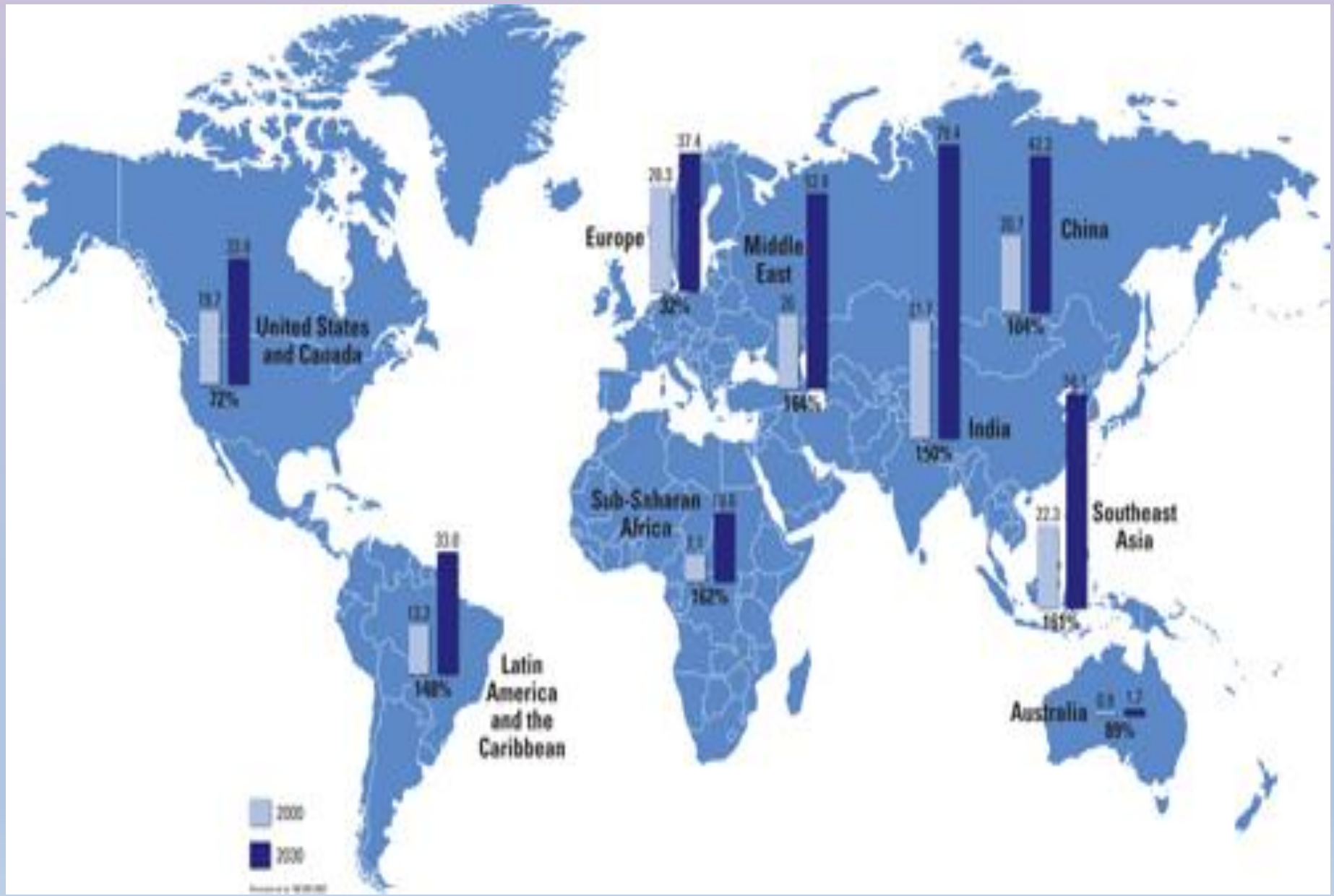
TYPE 2 DIABETES
Body produces insulin but can't use it well

GESTATIONAL DIABETES
A temporary condition in pregnancy

Consequences

Diabetes can lead to complications in many parts of the body and increase the risk of dying prematurely.




United States and Canada
72%
Europe
32%
Middle East
164%
China
164%
India
150%
Sub-Saharan Africa
162%
Southeast Asia
161%
Latin America and the Caribbean
148%
Australia
89%
2005
2030

Types of Diabetes

- Type 1 –Insulin Dependent Diabetes Mellitus (IDDM) 3–5%

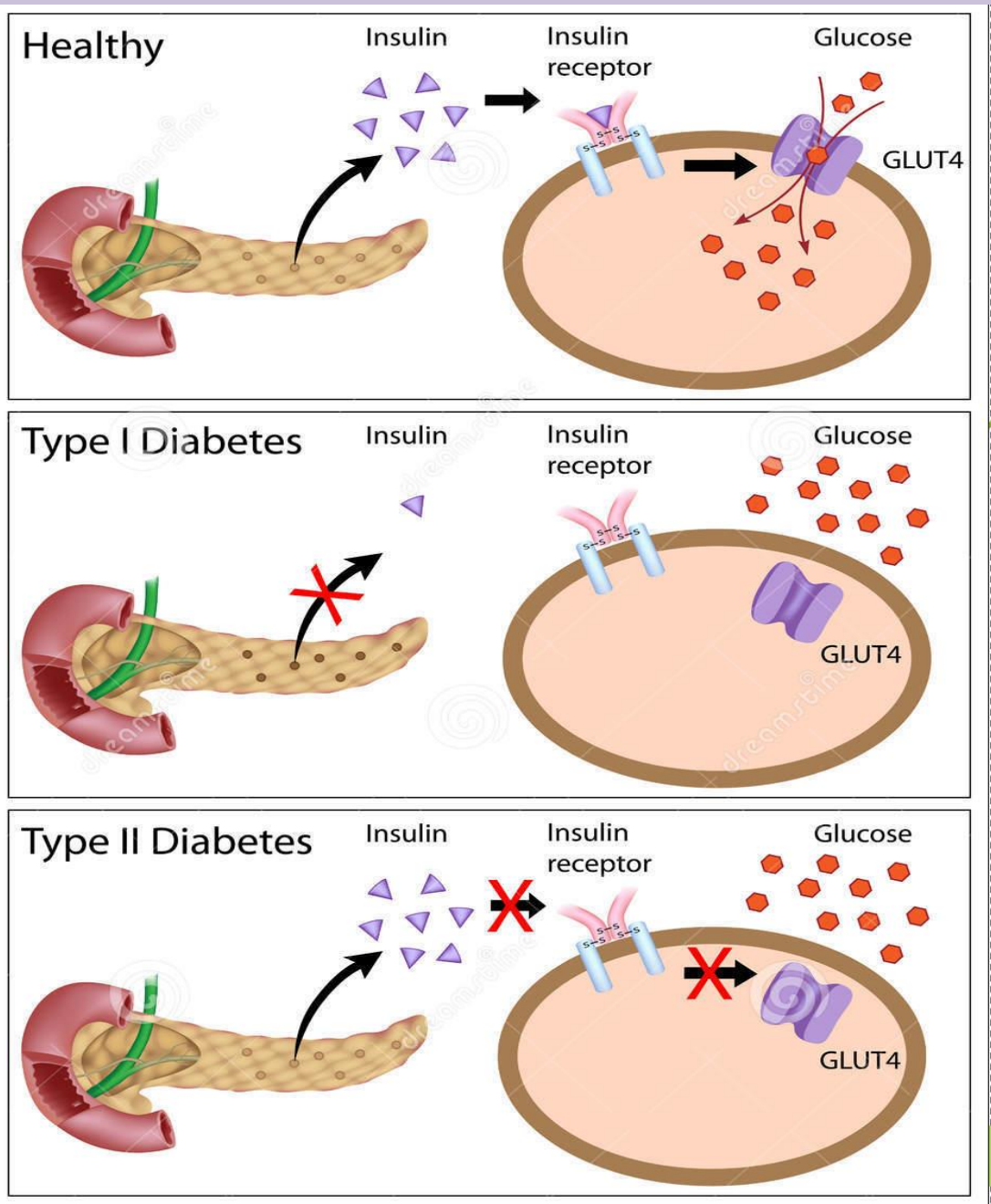
– Due to insulin deficiency caused by autoimmune destruction of the B cells of pancreas

– Presents usually in children

- Type 2 – Non Insulin Dependent DM (NIDDM) 90–95%

– Dysregulation of insulin release from the B cells and insulin resistance

– Mainly in obese or overweight adults

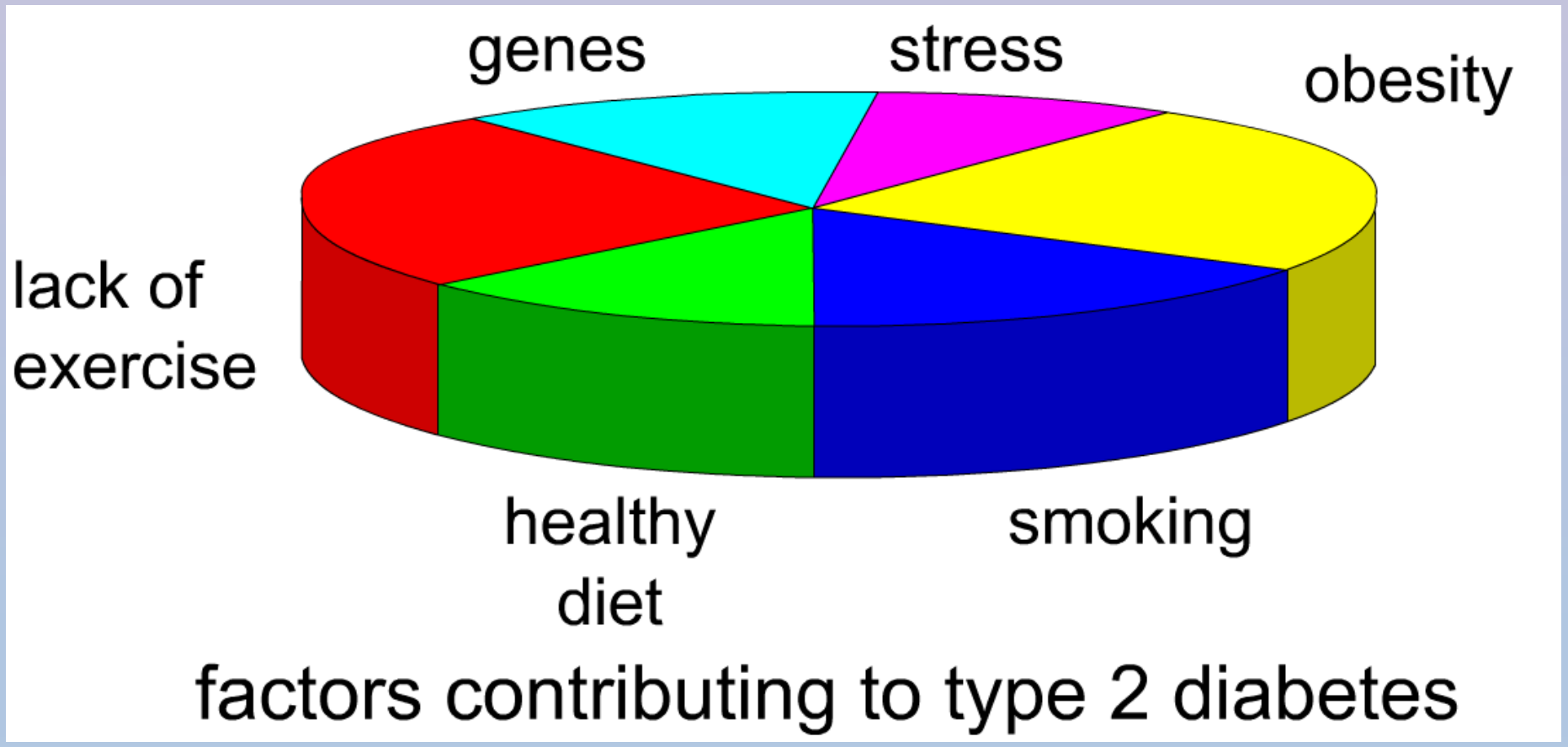


Types of Diabetes

- Secondary Diabetes (5%)
  - Chronic pancreatitis
  - Total pancreatectomy
  - Cushings Syndrome
  - Acromegaly

Symptoms of Diabetes

- Polyuria
- Polydipsia
- Weight loss in spite of polyphagia



factors contributing to type 2 diabetes

Diagnosis of diabetes

- FBS >126 mg/dl on 2 occasions
- Symptoms of diabetes plus casual plasma glucose concentration ≥200 mg/dl
- HbA1c >6.5%
- OGGT –2 hrs >200 mg/dl

Diabetes:Complications

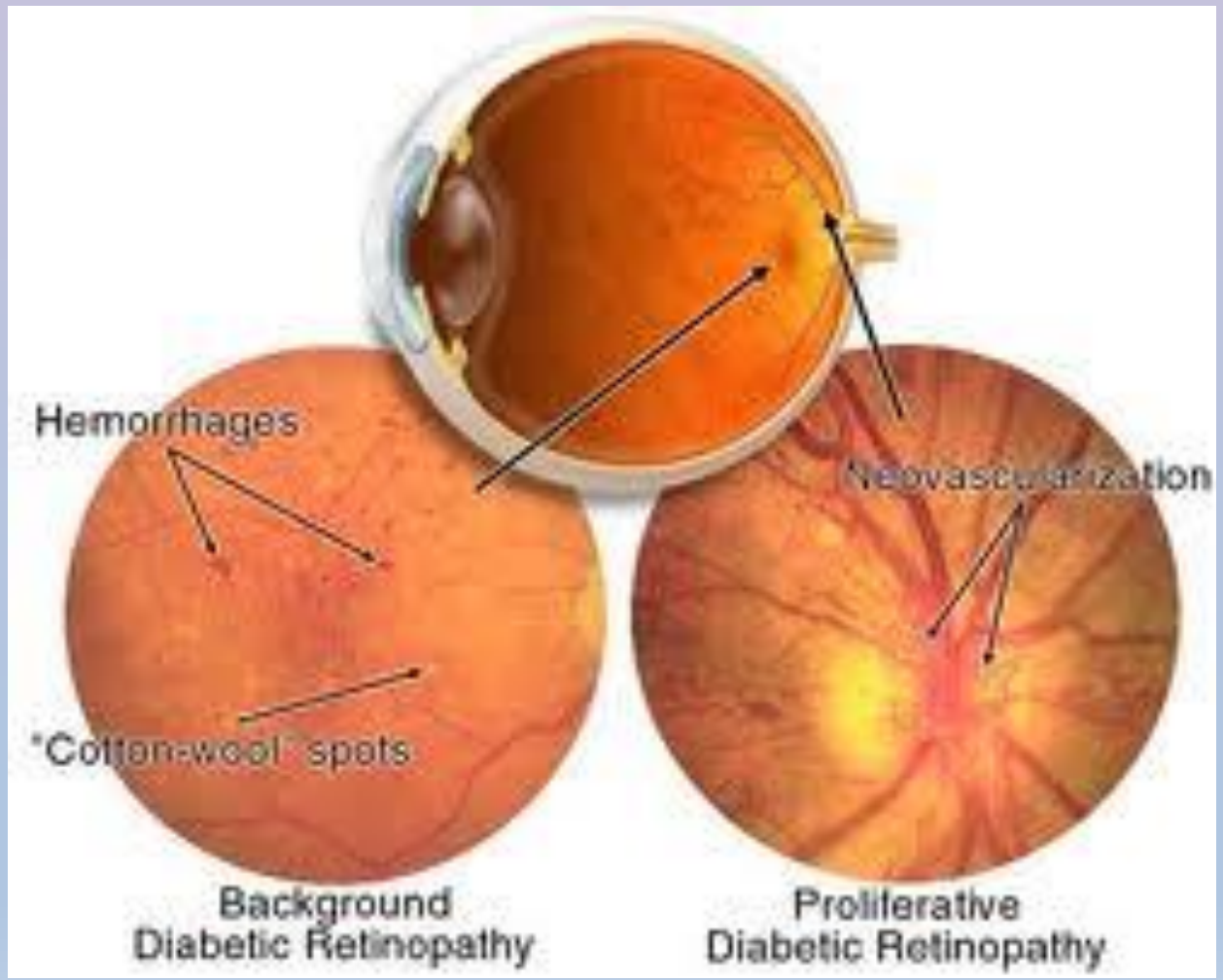
Macrovascular

- Stroke
- Heart disease and hypertension
- Periaheral vascular disease
- Foot problems

Microvascular

- Diabetic eye disease (retinopathy and cataracts)
- Renal disease
- Neuropathy
- Foot problems

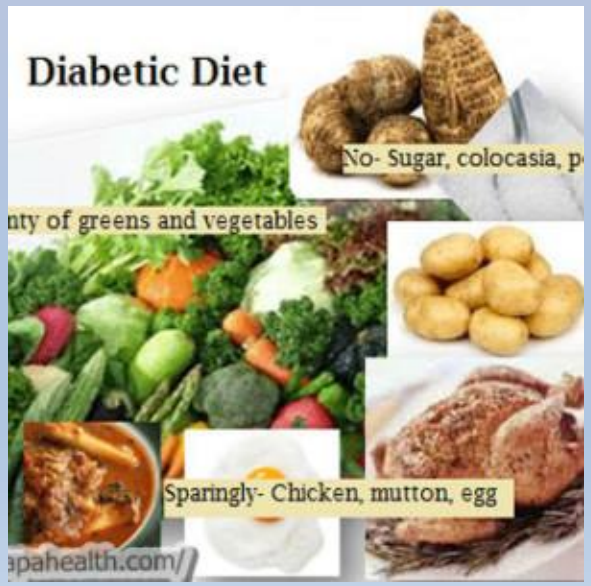
Diabetic retinopathy



Management

- Life style modification
- Healthy diet with low CHO ,sugar and fat
- Exercises
- Medications
  - Oral hypoglycemic agents
  - Insulin

Healthy lifestyle



Healthy diet - Plate model


For
102
Walking
Tai chi
weight lifting
Aerobics
Cycling
Yoga
Swimming
Dancing

How does exercise help to control hyperglycemia?

- Muscle contractions stimulate glucose uptake
- Increase GLUT receptor translocation to the cell membrane


SAY
NO
TO
DIABETES
....it's time to take it down.

Obesity and Metabolic syndrome

- Obesity leads to insulin resistance
- Insulin resistance is the decreased ability of insulin to move glucose into fat and muscle and shut off glucose release from the liver
- Fat produces a chemical signal that acts on liver and muscle to increase insulin resistance
- Fat deposits are endocrine tissues, which secrete adipokines (leptin adiponectin ,resistin)


www.foodfacts.info/blog


SODA

Acanthosis negricans in insulin resistance

Metabolic syndrome

Metabolic syndrome
(Syndrome X)

- Central obesity
- High blood pressure
- High triglycerides
- Low HDL-cholesterol
- Insulin resistance

Insulin Excess

Symptoms

- Features are due to hypoglycemia
- CHO reserves in neural tissue are very limited
- Normal function of the brain depend on continuous glucose supply
- First symptoms are palpitations ,sweating and nervousness due to autonomic discharge
- At lower glucose levels Neuroglycopenic symptoms (hunger, confusion) occur

Insulin Excess

- Even lower glucose levels – coma,convulsions,death
- Compensatory mechanisms
- Inhibition of insulin secretion at plasma glucose level of 80 mg/dl
- Increase secretion of counter regulatory hormones
  - Glucagon
  - Epinephrine

  } Increase glycogenolysis

  - Growth Hormone
  - cortisol

  } Decrease utilization of glucose in peripheral tissues

Insulin Excess

- Insulinoma is a rare insulin secreting tumor of pancreas
- Symptoms common in the morning as hepatic glycogen reserve is depleted

- IGF 11 secreting malignant tumors can also cause hypoglycemia
- Functional hypoglycemia
  - Due to dysregulated insulin release post meal
  - Hypoglycemic symptoms 3-4 hrs post meal
  - Can later develop Diabetes

Treatment of hypoglycemia

- Depends on the conscious level of the patient
- Oral/IV dextrose
- Sugary drink can be given at home

Patients with hypoglycemic unawareness due to autonomic failure are at particular risk

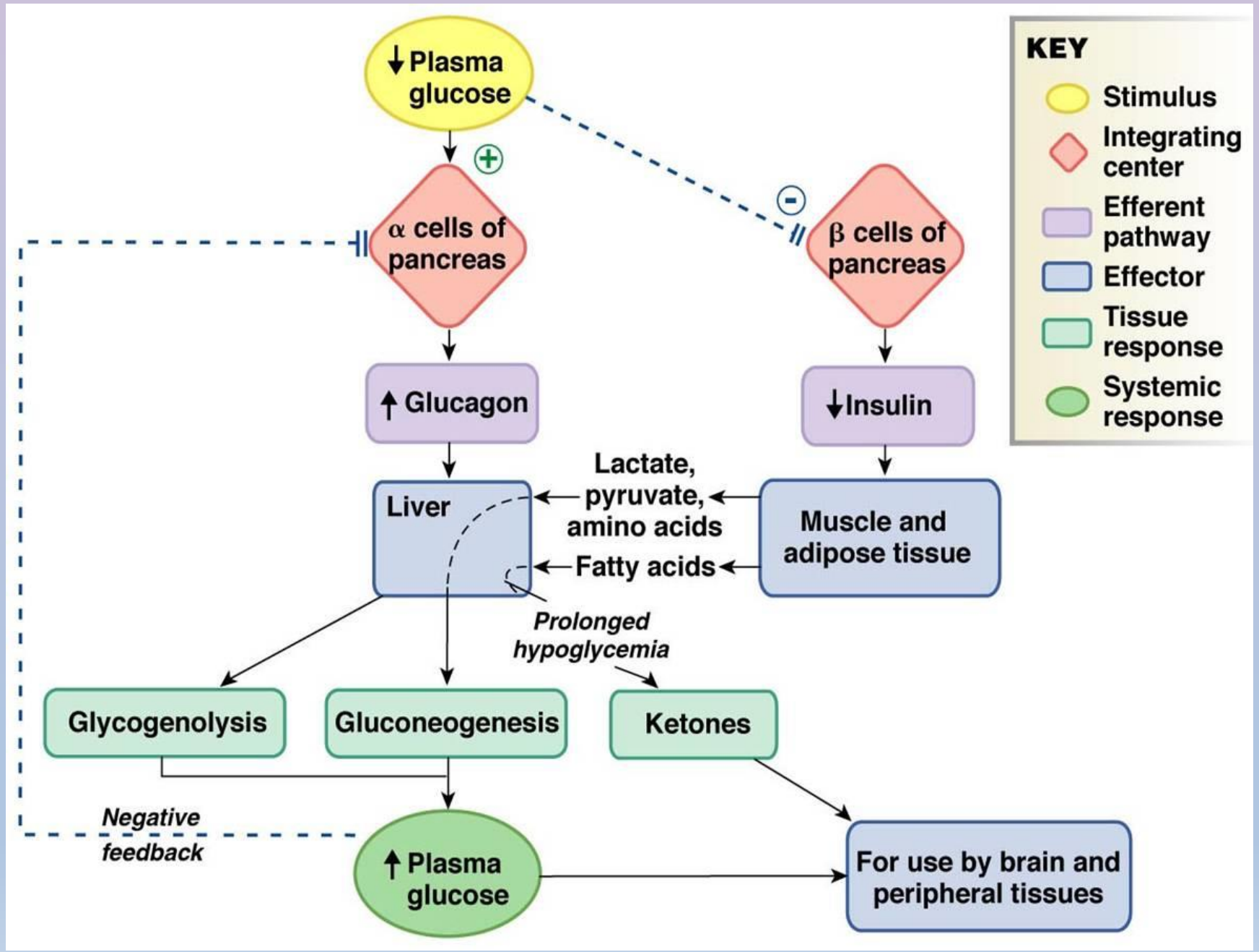
Glucagon

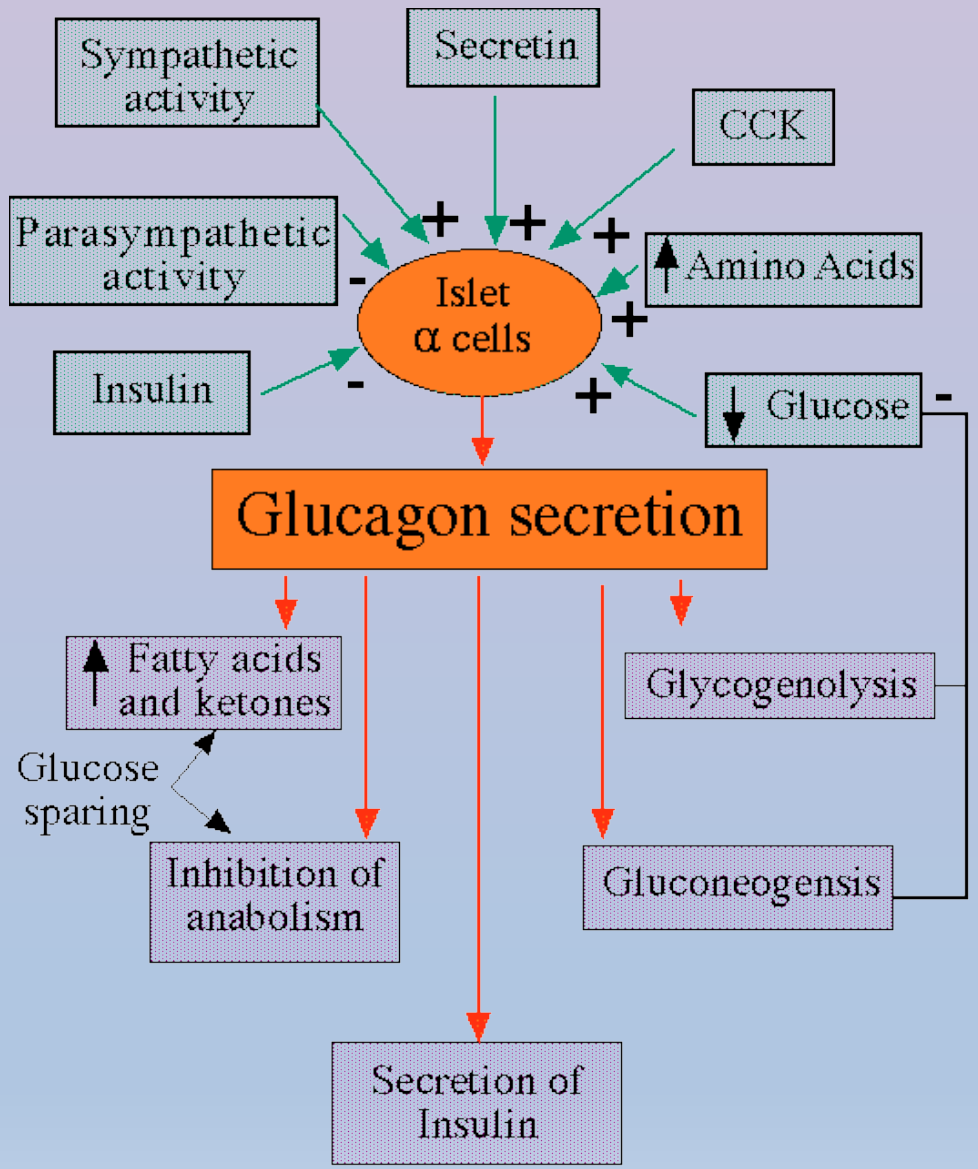
- Linear polypeptide
- Produced by the A cells of pancreas and L cells of upper GI tract
- Formed initially as a preprohormone

Actions

- Glycogenolytic
- Gluconeogenic
- Lipolytic
- Ketogenic

- In the liver acts via G protein to activate adenylyl cyclase and increase cAMP
- Via Protein kinase A leads to activation of phophorylase and increase breakdown of glycogen


↓Plasma glucose
+
α cells of pancreas
-
β cells of pancreas
↑Glucagon
↓Insulin
Lactate, pyruvate, amino acids
Fatty acids
Liver
Muscle and adipose tissue
Prolonged hypoglycemia
Glycogenolysis
Gluconeogenesis
Ketones
Negative feedback
↑Plasma glucose
For use by brain and peripheral tissues
KEY
Stimulus
Integrating center
Efferent pathway
Effector
Tissue response
Systemic response


Sympathetic activity
Secretin
CCK
Parasympathetic activity
Amino Acids
Islet α cells
Insulin
Glucose
Glucagon secretion
Fatty acids and ketones
Glycogenolysis
Glucose sparing
Inhibition of anabolism
Gluconeogensis
Secretion of Insulin

Somatostatin

- Formed in the D cells of pancreas
- Inhibit the secretion of insulin ,glucagon and pancreatic polypeptide
- Acts locally in paracrine fashion
- Secretion is increased by glucose , amino acids,CCK

Pancreatic polypeptide

- Produced by F cells of the pancreas
- Under control of cholinergic stimulation
- Levels are increased by
  - Protein meal
  - Fasting
  - Exercise
  - Acute hypogylcemia

Levels decreased by somatostatin and glucose

Other Hormones involved

- Thyroid hormone
- Epinephrine
- Glucocorticoids
- Growth hormone

MCQ’S

T/F Regarding diabetes mellitus

1. Impaired glucose tolerance is due to increased peripheral utilization
2. Rate of amino acid catabolism increased
3. OGGT can be used in the diagnosis of Diabetes
4. Ketoacidosis leads to respiratory alkalosis
5. Insulin resistance is commonly seen in lean individuals

T/F Regarding diabetes mellitus

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2. Rate of amino acid catabolism increased –T
3. OGGT can be used in the diagnosis of Diabetes –T
4. Ketoacidosis leads to respiratory alkalosis–T
5. Insulin resistance is commonly seen in lean individuals –F

- T/F Regarding pancreatic hormones

1. Glucagon stimulates gluconeogenesis
2. Glucagon secreted by F cells of pancreas
3. Somatostatin inhibits insulin secretion
4. Pancreatic polypeptide is under control of cholinergic stimulation
5. CCK inhibitss glucagon secretion

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