Lecture 13 & 14: Physiology of The Endocrine Pancreas

Note: 1) This is a rearrangement of the slides + Few notes

2) Focus on every figure and graph. Do not ignore them!

notes are in purple

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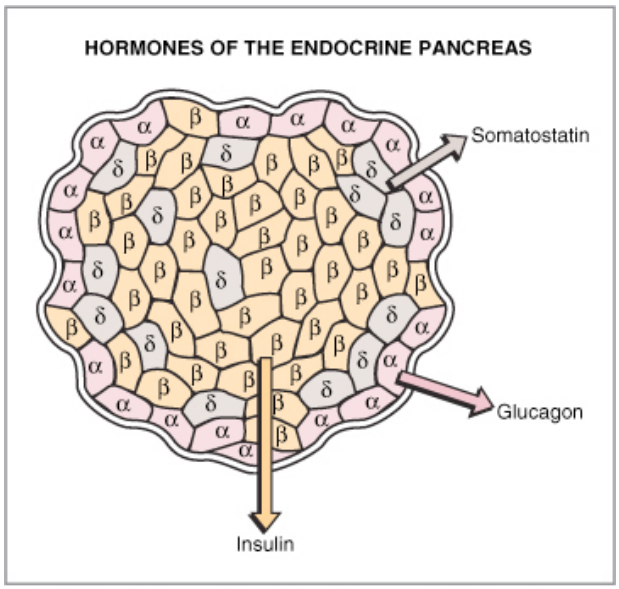
Pancreas

- **A triangular gland, which has both exocrine and endocrine cells, located behind the stomach**
- **Has a Strategic location**
- **Acinar cells produce digestive enzymes and HCO3(exocrine product)**
- **Pancreatic islets (islets of Langerhans) produce hormones involved in regulating fuel storage and use.**

Islets of Langerhans

- **1-2 million islets**
- **Beta (β) cells produce insulin (70%)**
- **Alpha (α) cells produce glucagon (20%)**
- **Delta (δ) cells produce somatostatin (5%)**
- **F cells produce pancreatic polypeptide (5%)**
  unknown function



β cells are located centrally while α cells are located peripherally.

This might have a relation to the fact that glucagon stimulates insulin while insulin suppresses glucagon.

δ cells are interspersed between α and β cells, and secrete somatostatin, which inhibits the function of both α and β cells.

Insulin

- **Hormone of nutrient abundance [secreted when nutrients are excessive]**
- **A protein hormone consisting of two amino acid chains linked by disulfide bonds**
- **Has a plasma half-life of 6 minutes.**
- **Synthesized as part of proinsulin (86 AA) and then excised by enzymes, releasing functional insulin (51 AA) and C peptide (29 AA).**

DNA (chromosome 11) in β cells

↓

mRNA transcribed and translated on **ribosomes**

↓

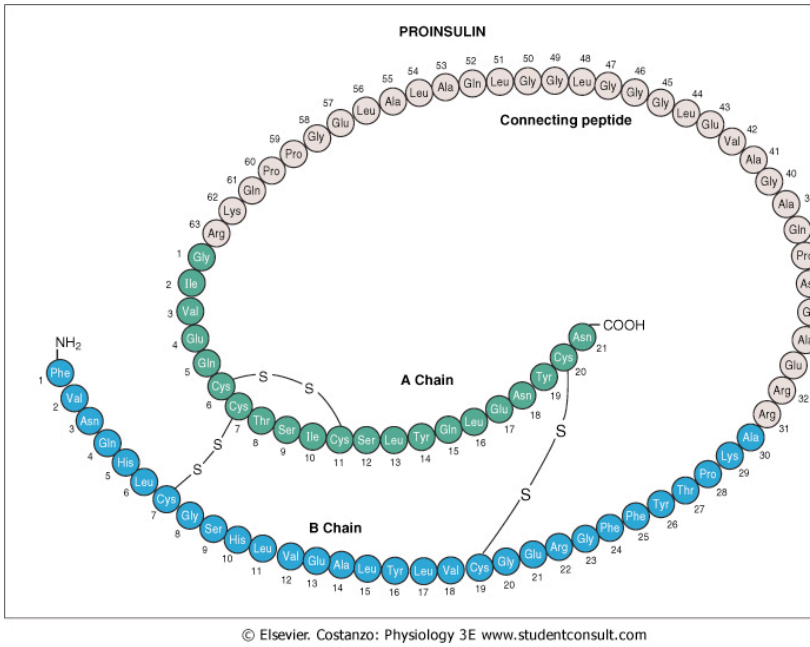
Preproinsulin consisting of **(signal peptide, A chain, B chain, and peptide C)**

↓

proinsulin is produced in **endoplamic reticulum by cleaving the signal peptide from preproinsulin**

↓

insulin is packaged in secretory granules in **golgi apparatus** and ready to be secreted



Proinsulin can be secreted as it is and it has same effect of insulin with less potency

Insulin is secreted in equal amount with C peptide [which has no known function and excreted unchanged in urine].
Since most insulin is utilized by the liver, the amount of insulin secreted by **β** cells cannot be measured in venous blood. Instead, **the amount of C peptide is measured in urine to asses the function of β cells.**
C peptide can also measured in the serum by ELISA

Insulin synthesis and secretion:

•Insulin synthesis is stimulated by glucose or feeding and decreased by fasting
•Threshold of glucose-stimulated insulin secretion is 100 mg/dl.
•Glucose rapidly increase the translation of the insulin mRNA and slowly increases transcription of the insulin gene.

Glucose ↑ ready-insulin secretion and synthesis of new insulin. Thats why I.V. infusion of glucose will result in 2 phases of insulin increase [biphasic]

Mechanism of insulin secretion:

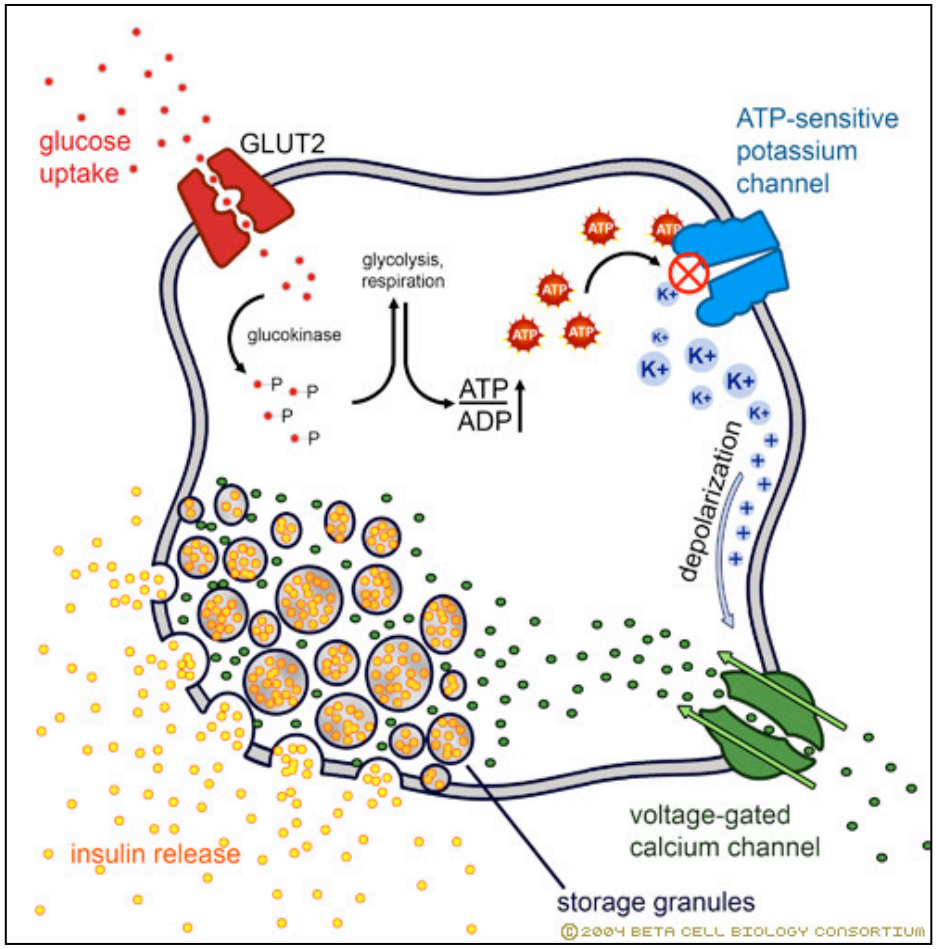
1) Glucose is transported into **β** cells down its conc. gradient by **GLUT2** transporter by facilitated diffusion.

2) Metabolism of glucose [glycolysis] inside **β** cells will yield **ATP**.

3) ATP will close ATP-sensitive K+ channels leading to **depolarization**.

4) Depolarization opens voltage-sensitive Ca+ channels. Ca flows inside **β** cells and **intracellular Ca** concentration **increases**.

5) ↑ intracellular Ca causes **insulin secretion** by exocytosis of insulin-containing secretory granules



Regulation of insulin secretion:

Regulators of insulin secretion

Stimulators of insulin secretion	Inhibitors of insulin secretion
↑ Serum glucose	↓ Glucose
↑ Serum amino acids	↓ Amino acids
↑ Serum free fatty acids	↓ Free fatty acids
↑ Serum ketone bodies	
Hormones	Hormones
Gastroinhibitory peptide (GIP)	Somatostatin
Glucagon	Epinephrine (α-receptor)
Gastrin	
Cholecystokinin (CCK)	
Secretin	
Vasoactive intestinal peptide (VIP)	
Epinephrine (β-receptor)	
Parasympathetic nervous system	Sympathetic nervous system stimulation

✦**The main stimulus for insulin secretion is glucose.**

✦**As mentioned before, glucagon stimulate insulin secretion while insulin inhibits glucagon secretion. When blood glucose is >100 mg/dl insulin is secreted**

✦**Oral glucose is more powerful stimulant than I.V. glucose because oral glucose stimulate GIP [Glucose-dependent Insulinotropic Peptide] + the direct effect of absorbed glucose on β cells.**

✦**The main effect of effect of sympathetic stimulation is inhibition of insulin secretion through α receptors. [ignore the β effect]**

Insulin mechanism of action: insulin act through tyrosine kinase mechanism.

Insulin actions:

The main aim of glucose actions is to reduce serum glucose through↑utilization and storage of glucose in the form of glycogen and fat. It also inhibits formation of new glucose.

EFFECT ON CARBOHYDRATES:

1. **Control of cellular intake of glucose in muscle and adipose tissue (about ⅔ of body cells). Insulin ↑ uptake of glucose by GLUT4 transporter which is found in muscle and adipose tissue.**

Glucose Transport

- GLUT1 (erythrocytes, brain)
- GLUT2 (liver, pancreas, small intestines)
- GLUT3 (brain)
- **GLUT4**, insulin sensitive transporter (muscle, adipose tissue)

-Only GLUT4 transporters are controlled by glucose the rest are facilitated diffusion carriers controlled by conc. gradient.
- Exercising muscles are not nourished through GLUT4 transporter [exception]

2. **Increase glycogen synthesis – insulin forces storage of glucose in liver (and muscle) cells in the form of glycogen; lowered levels of insulin cause liver cells to convert glycogen to glucose and excrete it into the blood. This is the clinical action of insulin, which is directly useful in reducing high blood glucose levels as in diabetes.**

3.**Decrease gluconeogenesis – decreases production of glucose from non-sugar substrates**

Effect on lipids:

1.**Increase fatty acid synthesis – insulin forces adipocytes to take in blood lipids, glucose and amino acids which are converted to trigylcerides; lack of insulin causes the reverse.**

2.**Increase esterification of fatty acids – forces adipose tissue to make fats (i.e., triglycerides) from fatty acid esters; lack of insulin causes the reverse.**

3.**Decrease lipolysis .**

Effect on protein:

1.**Decrease proteolysis – decreasing the breakdown of protein.**

2.**Increase amino acid uptake**

Other effects:

1.**Increase potassium uptake – forces cells to absorb serum potassium; lack of insulin inhibits absorption. Insulin's increase in cellular potassium uptake lowers potassium levels in blood. [I.V. insulin is used to treat acute life-threatening hyperkalemia]**

2.**Arterial muscle tone – forces arterial wall muscle to relax, increasing blood flow, especially in micro arteries; lack of insulin reduces flow by allowing these muscles to contract. [In diabetes, there will be constriction of micro arteries]**

3.**Increase in the secretion of hydrochloric acid by Parietal cells in the stomach.**

Actions of Insulin on Liver

↑ Glucose uptake (if blood glucose level is high)
↑ Glucose use
  ↑ Glycogenesis, ↓ glycogenolysis
  ↑ Glycolysis, ↓ gluconeogenesis
↑ Fatty acid synthesis and very-low-density lipoprotein formation, ↓ ketogenesis
↓ Urea cycle activity

Action of Insulin on Adipose Tissue

↑ Glucose uptake by increasing GLUT-4 availability
↑ Glucose use
  ↑ Glycolysis
  ↑ Production of α-glycerol phosphate
↑ Esterification of fats
↓ Lipolysis

Action of Insulin on Muscle

↑ Glucose uptake by increasing GLUT-4 availability
↑ Glucose use
  ↑ Glycogenesis, ↓ glycogenolysis
  ↑ Glycolysis
↑ Amino acid uptake (particularly branched-chain amino acids)
↑ Protein synthesis, ↓ proteolysis

Insulin summary:

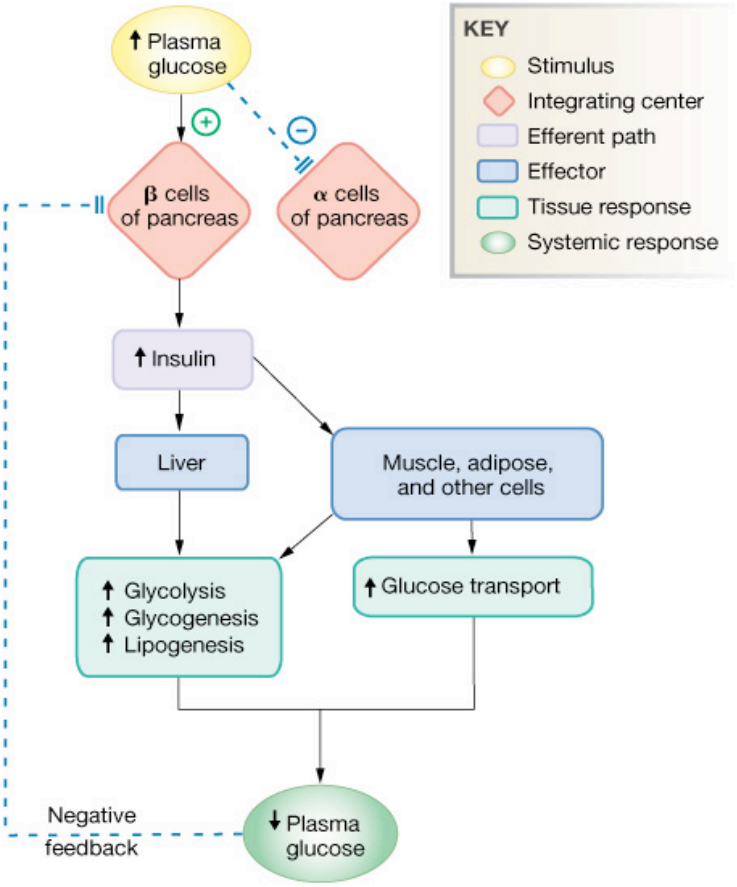


Table 22-3: Insulin

Cell of origin	Beta cells of pancreas
Chemical nature	51-amino acid peptide
Biosynthesis	Typical peptide
Transport in the circulation	Dissolved in plasma
Half-life	5 minutes
Factors affecting release	Plasma [glucose] > 100 mg/dL; ↑ blood amino acids; GI hormones (feedforward reflex) and parasympathetic amplify. Sympathetic inhibits.
Target cells or tissues	Liver, muscle, and adipose tissue primarily; brain, kidney, and intestine not insulin-dependent
Target receptor	Membrane receptor with tyrosine kinase activity; pathway with insulin-receptor substrates
Whole body or tissue action	↓ Plasma [glucose] by ↑ transport into cells or ↑ metabolic use of glucose
Action at cellular level	↑ Glycogen synthesis; ↑ aerobic metabolism of glucose; ↑ protein and triglyceride synthesis

Glucagon

- **A 29-amino-acid polypeptide hormone that is a potent hyperglycemic agent**
- **Produced by α cells in the pancreas and its primary target is liver hepatocyte.**

Glucagon synthesis: the same with insulin, glucagon gene in chromosome 2 is transcribed and translated to produce preproglucagon which is sent to endoplasmic reticulum for removal of signaling peptide to produce proglucagon. In golgi apparatus, proglucagon is contained in secretory vesicles until secretion.

Regulation of glucagon secretion:

The opposite of insulin
It's the hormone of fasting

Effects on Glucagon Secretion

Stimuli for Glucagon Secretion

↓ Blood glucose
↑ Serum amino acids (arginine, alanine)
Sympathetic nervous system stimulation
Stress
Exercise

Inhibitors of Glucagon Secretion

Somatostatin
Insulin
↑ Blood glucose

Glucagon mechanism of action: glucagon act through adenylyl cyclase mechanism using cAMP as a 2nd messenger.

Glucagon actions:

It has anti-insulin effect. The main aim of glucagon actions is to raise serum glucose through breaking down stored glycogen into glucose and increasing formation of new glucose. It also has a ketogenic effect.

Its major target is the liver, where it promotes:

1. Glycogenolysis – the breakdown of glycogen to glucose
2. Gluconeogenesis – synthesis of glucose from noncarbohydrates
3. Lipid oxidation (fully to CO_2 or partially to produce keto acids "ketone bodies").
4. Release of glucose to the blood from liver cells.

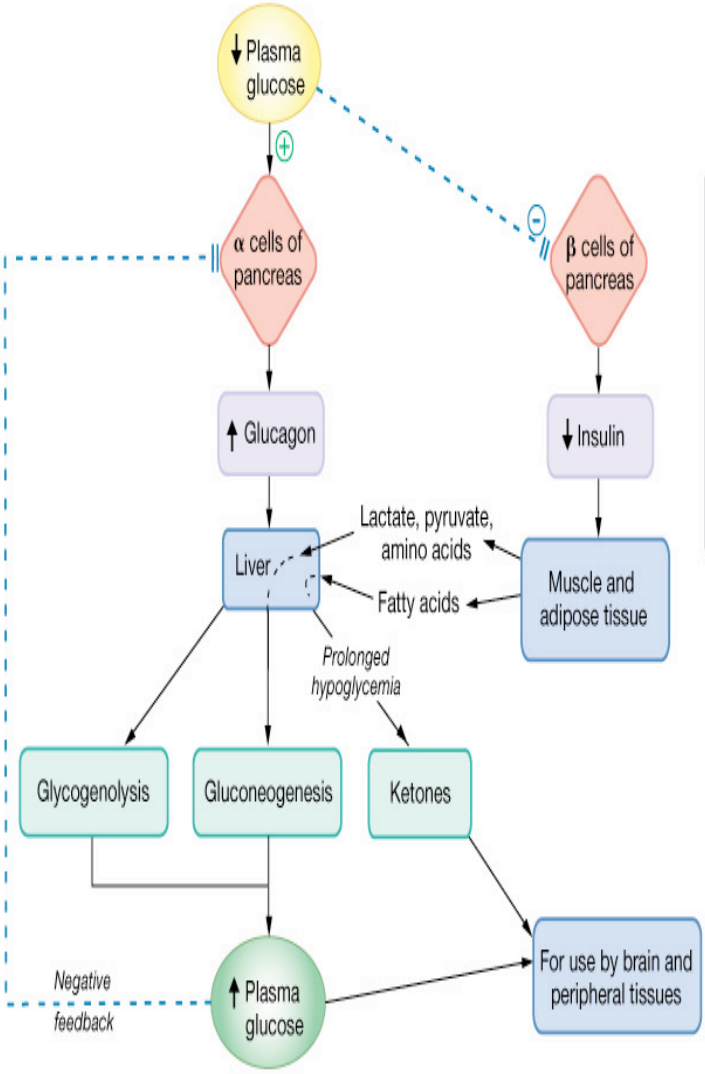
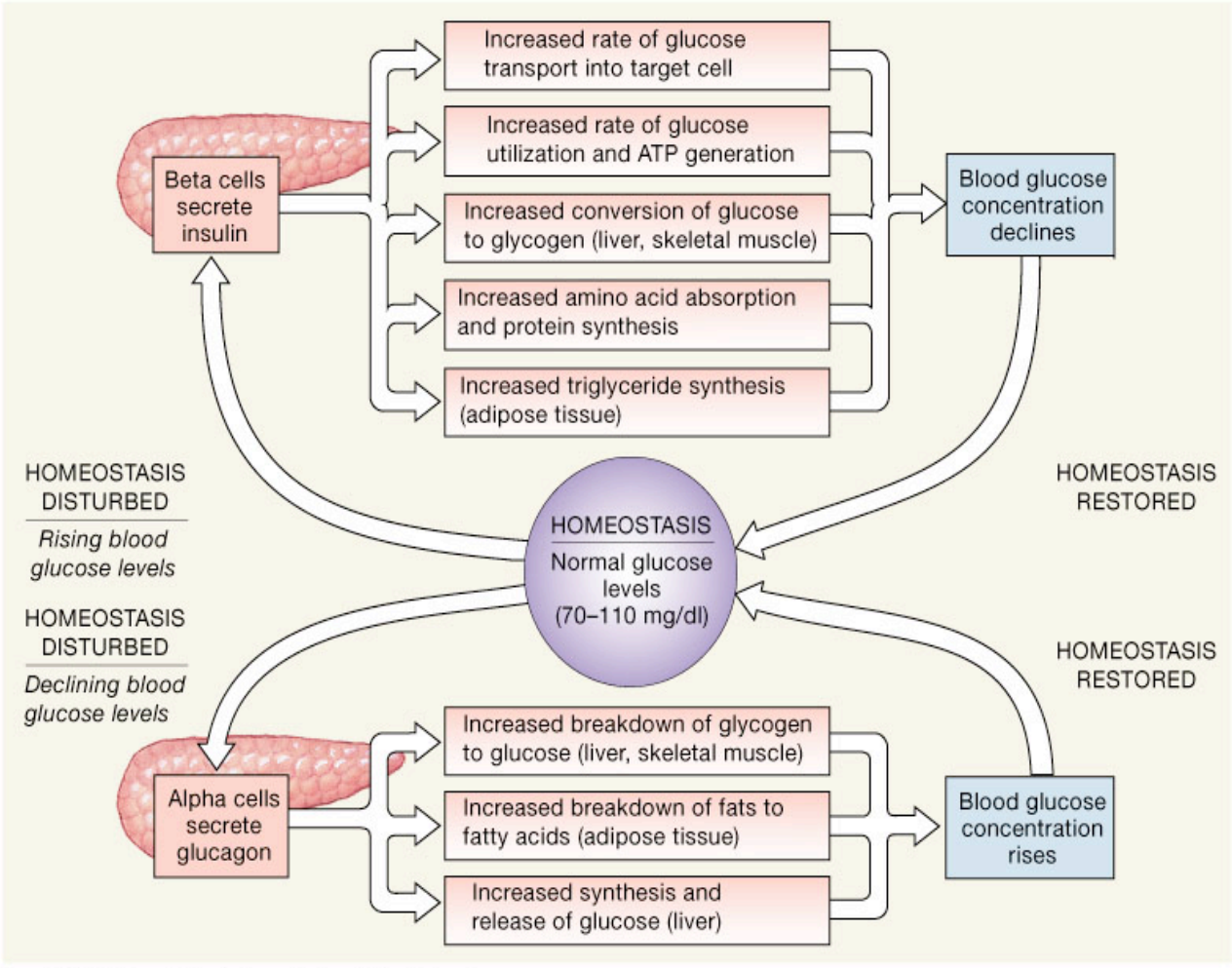


Table 22-5: Glucagon

Cell of origin	Alpha cells of pancreas
Chemical nature	29-amino acid peptide
Biosynthesis	Typical peptide
Transport in the circulation	Dissolved in plasma
Half-life	4–6 minutes
Factors affecting release	Stimulated by plasma [glucose] < 200 mg/dL, with maximum secretion below 50 mg/dL; ↑ blood amino acids.
Target cells or tissues	Liver primarily
Target receptor/second messenger	G protein-coupled receptor linked to cAMP
Whole body or tissue action	↑ Plasma [glucose] by glycogenolysis and gluconeogenesis; ↑ lipolysis leads to ketogenesis in liver
Action at molecular level	Alters existing enzymes and stimulates synthesis of new enzymes
Feedback regulation	↑ Plasma [glucose] shuts off glucagon secretion
Other information	Member of secretin family along with VIP, GIP, and GLP-1

SUMMARY



Insulin	Glucagon
↓ **blood glucose**	↑ **blood glucose**
↑ **glycogenesis &** ↓**glycogenolysis**	↓ **glycogenesis &** ↑**glycogenolysis**
↓ **gluconeogenesis**	↑ **gluconeogenesis**
↓ **lipolysis &** ↑ **lypogenesis** [fat deposition]	↑ **lipolysis**
↓ **ketoacid formation**	↑ **ketoacid formation**

The following hormones have anti-insulin effect:

1) Glucagon

2) Growth hormone

3) Cortisol

4) Epinephrin &norepinephrin

Summary of the metabolic effects of growth hormone, insulin and thyroid hormones:

	Proteins	Fat	Carbohydrates
Growth hormone	↑ protein deposition ↑ amino acid conc. in the cells ↑mRNA translation and protein synthesis ↓ catabolism of protein and amino acid	↑ the release of fatty acids	(Anti-insulin effect) ↓ Glucose uptake by tissues such as muscles and fat. ↑ insulin secretion ↑glucose production by the liver [gluconeogenisis & glycogenolysis]
Thyroid hormones	Overall effect is catabolic leading to decrease in muscle mass.	↓ conc. of cholesterol, phospholipids and TAG in plasma ↑ FFA	Stimulates all aspects of carbohydrates metabolism: ↑ glucose uptake ↑glycolysis ↑gluconeogensis ↑ absorption from GIT ↑ insulin secretion
Insulin	Stimulates the transport of amino acid into the cells. ↑ mRNA translation ↓ catabolism of protein ↓ gluconeogensis in the liver, which conserves the amino acid in the protein stores in the body	Promotes fat synthesis and storage	Makes glucose taken up in muscles and fat ↑conversion of excess glucose into fatty acids (TAG) = fat deposition ↑glycogen synthesis

Diabetes Mellitus (DM)

- The most common serious metabolic disease in humans
- Over 20 million diabetics in USA- 10% type I, 90% type II
- 2 out of 3 people with diabetes die from heart disease and stroke
- Results from hyposecretion or hypoactivity of insulin

Diabetes Mellitus Type I:

-Caused by an immune-mediated selective destruction of β cells.

- β cells are destroyed while α cells are preserved:
- No insulin >> high glucagon >> high production of glucose and ketones by liver:

(1) ↑ serum glucose & ketones >> osmotic diuresis [polyuria] >> excessive thirst [polydipsia]

(2) ↑ serum ketones >> diabetic ketoacidosis >> coma if untreated

-Affects children.

-Not associated with obesity

-Treated with insulin injections

Diabetes Mellitus Type II:

- More common in some ethnic groups
- Insulin resistance keeps blood glucose too high β cells are intact
- Chronic complications: atherosclerosis, renal failure & blindness

-Affects adults

- Obesity and T2DM frequently occur together

- Treated by diet or oral hypoglycemics

Symptoms of Diabetes Mellitus

Hyperglycemia
Polyuria
Polydipsia
Polyphagia
Ketoacidosis (IDDM)
Hyperlipidemia
Muscle wasting
Electrolyte depletion

Organs/tissue involved	Organ/tissue responses to insulin deficiency	Resulting condition of:		Signs and symptoms
		Blood	Urine	
	Decreased glucose uptake and utilization	Hyperglycemia	Glycosuria	**Polyuria** - dehydration - soft eyeballs
	Glycogenolysis		Osmotic diuresis	**Polydipsia** Fatigue Weight loss
	Protein catabolism and gluconeogenesis			**Polyphagia**
	Lipolysis and ketogenesis	Lipidemia and ketoacidosis	Ketonuria Loss of Na^+, K^+; electrolyte and acid-base imbalances	Acetone breath Hyperpnea Nausea/vomiting/ abdominal pain Cardiac irregularities Central nervous system depression; coma
 = Muscle  = Adipose tissue  = Liver				

Glucose Tolerance Test

-Both the fasting plasma glucose FPG and oral glucose tolerance test OGTT tests require that the patient fast for at least 8 hours (ideally 12 hr) prior to the test.

-The oral glucose tolerance test (OGTT):

1. **FPG test**
2. **Blood is then taken 2 hours after drinking a special glucose solution**

-After the oral administration of a standard dose of glucose, the plasma glucose concentration normally rises but returns to the fasting level within 2 hours.

-If insulin activity is reduced, the plasma glucose concentration takes longer than 2 hours to return to normal and often rises above 200 mg/dl.

-Measurement of urine glucose allows determination of the renal threshold for glucose.

- The following results suggest different conditions:

Normal values:

- FPG <100 mg/dl
- 2hr PPG < 140 mg/dL

Impaired glucose tolerance [pre-diabetic]

- 2hr PPG = 140 - 199 mg/dL

Diabetes

-FPG ≥ 126 mg/dl

-2hr PPG levels ≥200 mg/dL

Extra Notes:

Metabolic effect in insulin-deficient individuals:

- **Carbohydrates:**
  - ↑ blood glucose concentration
  - ↑ glycogen breakdown
  - ↓ peripheral glucose use

- **Protein:**
  - ↑ protein breakdown
  - ↑ catabolism of amino acids
  - ↑ ureagenesis (urea is the breakdown product of protein)
  - ↓ protein synthesis

- **Fat:**
  - ↑ triglyceride breakdown
  - ↑ level of circulating free fatty acid
  - ↑ ketosis, resulting in ketoacidosis (metabolic acidosis)

- **Renal System:**
  High glucose level ends up with high filtered load and because glucose is freely filtered it never maximizes no matter how high the glucose level goes.
  The failure to reabsorb all the filtered glucose in the proximal tubule also prevents normal water and electrolytes reabsorption in this segment (glucose will drag water and electrolytes with it in urine), resulting in loss of electrolytes along with water and glucose.

- **Potassium Ions:**
  - The intracellular concentration of K ions is low because body cells release K in exchange with H ions (from keton bodies), so the blood K level rises (temporarily) and ends up being urinated out.
  - Sudden insulin replacement can produce sever hypokalemia, and K replacement is not part of therapy (not given immediately), so it is normal for person with DKA that once the K levels start to come down to replace K because the total body is depleted of potassium.

- **Sodium Ions:**
  - For every 100 above normal of glucose there is a 1.6 drop in the sodium (pseudohyponatremia)

Source: Physiology by Linda Costanzo

Guyton and Hall Textbook of Medical Physiology