# Facts about Pancreatic Hormones

**A.** The pancreas in numbers:
1. 2 different organs within 1 structure
a. The acinar portion ( exocrine function )
b. The islets of Langerhans ( endocrine portion )
2. The pancreatic islets secrete 4 hormones: insulin, glucagon, somatostatin, pancreatic polypeptide
3. The islets of Langerhans make up 1-2% of the weight of the pancreas
4. There are 1-2 million islets in humans
5. 4 distinct cell types secreting: A ( or $\alpha$ ) - glucagon (20%), B ( or $\beta$ ) - insulin (60-75%), D ( or $\delta$ ) - somatostatin (5%), F - pancreatic polypeptide ( trace )

**B.** Insulin
1. *Structure of insulin:* MW 6.000, consisting of 51 AA as two amino acid chains linked by disulfide bridges ($\alpha$ chain – 21 AA, $\beta$ chain – 30 AA )
2. *Metabolism of insulin* **:** half-life 5 minutes, degraded in liver and kidneys, hepatic portal vein goes to liver where 40-50% is removed in one pass, kidneys filter 40% of insulin from blood (taken up and metabolized in proximal tubules, little intact insulin appears in urine)
3. *Biosynthesis of insulin*: Pre-proinsulin formed in ER and cleaved to proinsulin.
*Proinsulin contains connecting or C-peptide and is converted to insulin in Golgi apparatus.*
*C peptide is useful for diagnostic purposes of endogenous insulin production*
4. *Insulin receptor***:** membrane receptors consist of 2$\alpha$ and 2$\beta$ units, receptor spans the membrane, $\alpha$ subunit binds insulin , $\beta$ subunit has tyrosine kinase activity on the cytosolic side, hormone - receptor complex is internalized by endocytosis, number of receptors is regulated, when occupied by insulin, the receptor phosphorylates itself and other proteins.
5**.** *Mechanism of action***:**
a. At the plasma membrane level ( increase in transport of metabolites )
b. In the cytoplasm (modulation of enzyme activity via phosphorylation –
dephosphorylation processes, decrease in cAMP concentration, effect on mRNA translation
c. At the nuclear level ( effect on gene transcription )
6**.** *Effect of insulin on carbohydrate metabolism*
a. Insulin increases the uptake of glucose and its metabolism in muscle and adipose tissue.
b. Insulin increases glycogen synthesis in liver and muscle.
c. Insulin decreases gluconeogenesis
d. Net action:decrease in blood glucose concentration and increase in glycogen level
7**.** *Effect of insulin on lipid metabolism*
a. Insulin increases glucose uptake by fat cells ( increases membrane transporters ) and glucose utilization
b. Insulin increases FFA uptake by adipose tissue increasing the activity of lipoprotein lipase located in the capillary endothelium
c. Insulin increases triglyceride synthesis ( lipogenesis ) in adipose tissue and liver by stimulating the rate- limiting step ( carboxylation of acetyl CoA to malonyl CoA). In other words, insulin stimulates the conversion of carbohydrate into fat.
d. Insulin decreases triglyceride breakdown ( lipolysis ) in adipose tissue by decreasing the activity of hormone sensitive lipase.
e. Insulin decreases formation of ketone bodies by the liver.

f. Net action: decrease in blood FFA concentration and storage of fat

8**.** *Effect of insulin on protein metabolism*

a. Insulin increases amino acid uptake by muscle cells

b. Insulin increases protein synthesis

c. Insulin decreases protein breakdown (deficiency of insulin results in a breakdown of protein)

d. Net action: decrease in blood amino acids concentration and increase in protein formation

9**.** *Target tissues for insulin action:* the liver, adipose tissue, skeletal muscle

10. *Regulation of insulin secretion:*

a. Metabolic factors:

- Stimulation:   glucose, amino acids, $\beta$ - ketoacids
- Inhibition: $K^+$ depletion

b. Hormonal factors:

- Stimulation:   glucagon, gastrointestinal hormones, growth hormone, cortisol, progesterone, estrogens
- Inhibition: catecholamines,  somatostatin, insulin

c. Nervous factors:

- Stimulation:   $\beta_2$ adrenergic receptor, $M_4$ cholinergic receptor
- Inhibition: $\alpha_2$ adrenergic receptor

11. *Blood glucose is most important regulator of insulin secretion:*

a. Threshold for release ~ 50 mg/dl

b. Half maximum response ~ 150 mg/dl

c. Maximum response ~ 300 mg/dl

d. Negative feedback of glucose on insulin release

e. Oral glucose is more effective than IV

12**.** *Consequence of insulin deficiency – diabetes mellitus*

Diabetes mellitus is due to insufficient action of insulin owing either to  its absence  or to resistance to its action

13**.** The major symptoms of insulin deficiency: polyuria,  polydipsia,  polyphagia, weight loss hyperglycemia,  glycosuria, ketosis ( $\rightarrow$ acetone breath ),   acidosis  ( $\rightarrow$ coma )

14**.** *Diagnosis of diabetes:*

a. Determination of urinary sugar

b. Determination of blood glucose level

c. The glucose tolerance test.

15**.** *Types of diabetes:*

a. Insulin - dependent diabetes mellitus IDDM                (type 1) - 10%

- body build usually lean
- usually, but not always prepubertal in onset
- due to an absence of insulin production
- increased glucagon secretion also generally occurs
- autoimmune disorder
- treatment: insulin replacement

b. Non - insulin dependent diabetes mellitus NIDDM          (type 2) - 90%

- body build is usually obese
- insulin levels may be high, normal, or low
- resistance to insulin action in major target tissues.
- individuals tend to be ketosis resistant. ( with some insulin activity, there will be no  ketoacidosis )

- treatment: oral hypoglycemics

**C.** Glucagon

1. Glucagon has multiple actions that are opposed to insulin
2. Structure of glucagon: Single chain of 29 AA, MW 3500
3. Mechanism of glucagon action: classic mediation via cAMP
4. Metabolism of glucagon: half-life of 5 minutes, metabolism in liver and kidney (50% removed in single pass through liver )
5. Glucagon effects on carbohydrate metabolism:
a. The liver is the primary target of glucagon action.
b. Glucagon increases liver glycogenolysis activating glycogen phosphorylase.
c. It inactivates glycogen synthetase preventing the glucose-1-phosphate from being recycled back into glycogen
d. Glucagon increases liver gluconeogenesis promoting the conversion of pyruvate to phosphoenolpyruvate
e. Net action: increase in blood glucose concentration ( hyperglycemic hormon ) and decrease in glycogen level
6. Glucagon effects of lipid metabolism:
a. Increases lipolysis in the adipose tissue
b. Increases liver ketogenesis
c. Net action: increase in FFA blood conc.
7. Other effects of glucagon :
a. Enhances the strength of the heart ( ↑ cardiac output )
b. Enhances bile secretion
c. Inhibits gastric acid secretion
d. Stimulates the secretion of insulin, somatostatin, GH
8. Regulation of glucagon secretion:
a. Metabolic factors:
- Stimulation: amino acids
- Inhibition: glucose, FFA, ketones
b. Hormonal factors:
- Stimulation: catecholamines, CCK, gastrin, cortisol
- Inhibition: insulin, somatostatin, secretin
c. Nervous factors:
- Stimulation: β adrenergic receptor, vagal nerves( acetylcholine )
- Inhibition: $\alpha_2$ adrenergic receptor
d. Others factors:
- Stimulation: stress, exercise, infection

9. Low plasma glucose (hypoglycemia) is the most important physiological promoter for glucagon secretion, and elevated plasma glucose (hyperglycemia) the most important inhibitor.
Amino acids, especially dibasic amino acids ( arginine, lysine )  also promote the secretion of glucagon. Thus, glucagon is secreted in response to the ingestion of a meal rich in proteins.

10. Comparison of glucagon and insulin:
a. Glucagon (hormone of energy release) is glycogenolytic, gluconeogenetic, lipolytic and ketogenic  in its action.
b. Insulin (hormone of energy storage) is glycogenic, antigluconeogenetic, antilipolytic and antiketotic

**D.** Somatostatin

1. Pancreatic somatostatin is the same chemical substance as growth hormone inhibitory factor  ( in hypothalamus )

2. Structure of somatostatin – 14 AA
3. Regulation of secretion of somatostatin: it is stimulated by increased blood glucose level, increased amino acids, increased fatty acids, increased CCK.
4. Effect of somatostatin:
a. Depressing the secretion of both insulin and glucagon
b. Decreasing the motility of the stomach, the duodenum and the gallbladder
c. Decreasing both secretion and absorption in the gastrointestinal tract
5. The principal role of somatostatin is to extend the period of time over which the food nutrients are assimilated into the blood.
6. Relationship between the hormones of the pancreas:
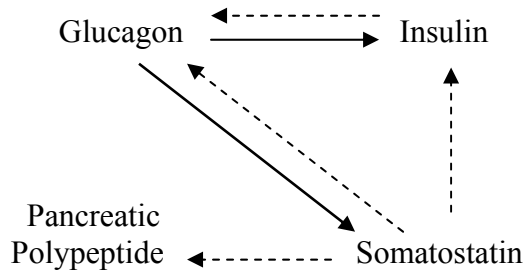


7. Pancreatic Polypeptide: single linear chain of 36 AA, MW 4200, produced by F cells. Stimulated by protein meal, its exact physiologic function unknown
**E.** Blood glucose regulation:
1. Blood glucose conc. 80 - 90 mg/dL ( fasting )
2. The liver as blood glucose buffer system
3. Feedback control system for insulin and glucagon
4. Hypoglycemia → hypothalamus → sympathetic
   nervous system→blood glucose ↑
5. GH and cortisol → a decrease in glucose utilization
6. The glucose is only nutrient utilized by the brain retina
   and germinal epitheliu
of the gonads


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