Endocrine function of Pancreas Insulin and Diabetes Mellitus

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Pancreas

- Has endocrine and exocrine functions
- Islets of Langerhans secrete
  1. Insulin
  2. Glucagon

  → intermediary metabolism

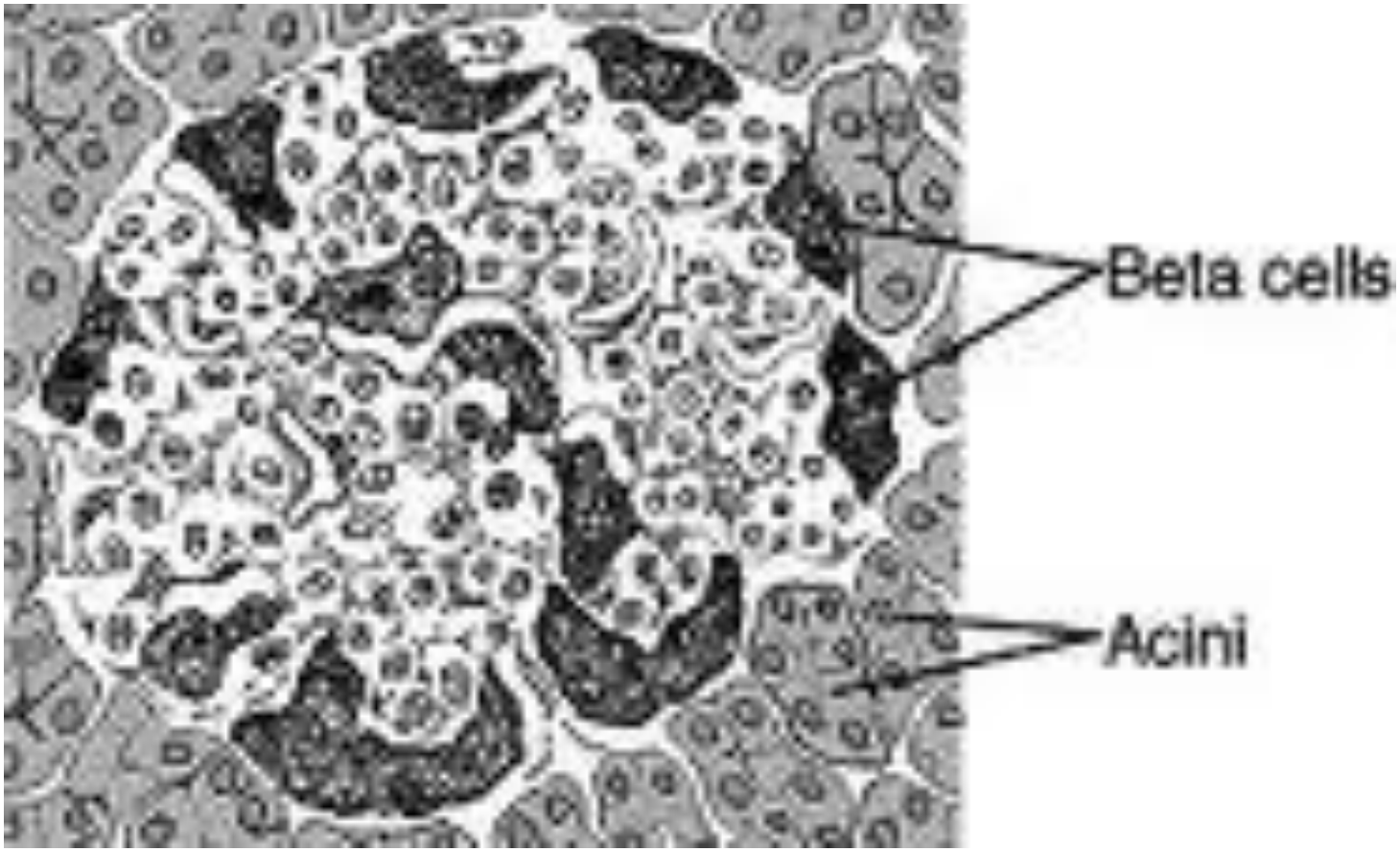
  3. Somatostatin — regulates islet cell secretion
  4. Pancreatic polypeptide — concerned with GI function

Pancreas

- Islet cell structure
  - Ovid structures, plentiful in tail
  - Has a copious blood supply
  - Drains into portal vein

- Has 4 type of cells
  - 20% A- Alpha -secrete glucagon
  - 65-75% B - Beta - secrete insulin
  - D- Delta - secrete somatostatin
  - F- - secrete pancreatic polypeptide

Islet cell structure



Pancreas

- B cells
  - Granules are packets of insulin
  - Packet is bounded by membrane lined vesicle
  - Insulin molecules are polymers combined with Zinc

Insulin

- Polypeptide with two chains of amino acids
- Two chains are linked by disulfide bridges
- There is species difference of amino acid
- The difference is not sufficient to affect the biologic activity
- But can induce immune reaction and antibodies against foreign insulin
- Antibodies inhibit the action of foreign insulin

Insulin

- Pork insulin only differs by one amino acid
- Less immunogenic

Insulin

- Biosynthesis and secretion
- Synthesized in the ER
- Transported to Golgi apparatus to make membrane bound granules
- Granules move to cell wall
- Membrane get fused with cell wall
- Secretes insulin to exterior by exocytosis
- Insulin then crosses the basal lamina
- Reaches the blood stream

Insulin molecule

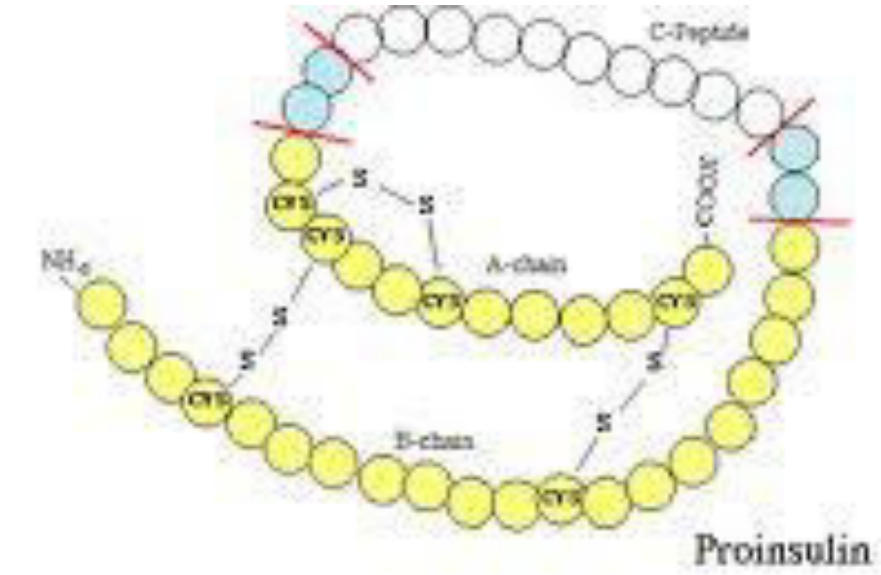
- Synthesized as a Larger preprohormone
- 23 amino acid peptide is removed from it
- The remainder folded, disulphide bonds are formed
- Results –proinsulin
- C peptide chain connecting A and B chains facilitates the folding
- This peptide chain is removed from the proinsulin to make insulin- the C peptide

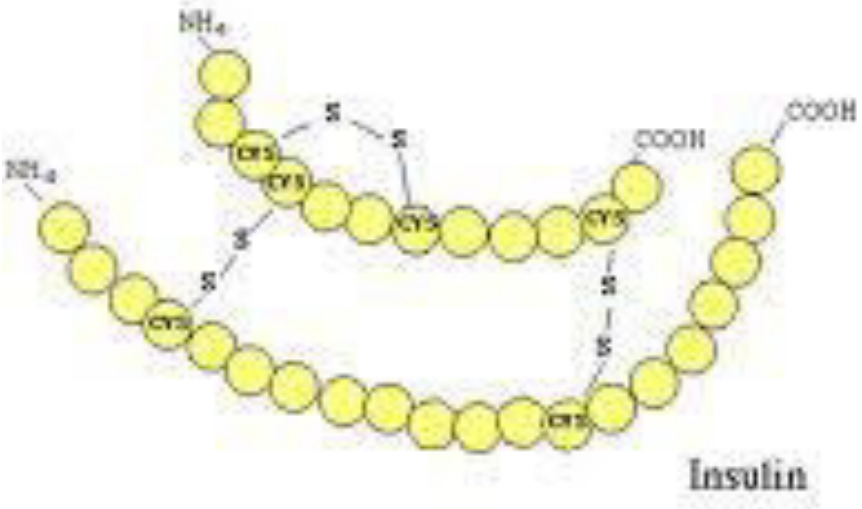
Insulin molecule

- 90-97% of beta cell secretion is insulin
- Also has equimolar amount of C peptide

- C peptide
  - Can be measured using RIA
  - Level provides index of
    - Beta cell function
    - Amount of endogenous insulin level

Insulin molecule





Metabolism of Insulin

- Half life is 5 minutes
- Insulin receptor complex is internalized
- Destroyed by insulin protease
  - A membrane enzyme
  - Get internalized with insulin
- 80% of insulin is degraded by liver and kidneys

Effects of insulin

- Rapid actions
- Increased transport of substances in to insulin sensitive cells
  - glucose
  - Amino acids
  - Potassium

Effects of insulin

- Intermediate actions
  - Stimulation of protein synthesis
  - Inhibition of protein degradation
  - Activation of glycogen synthase
  - Inhibition of gluconeogenic enzymes and phosphorylase

Effects of insulin

- Delayed actions
  - Increase in mRNAs for lipogenic enzymes

Insulin receptors

- A complex glycoprotein
- Found on many cells
- A tetramer -2 alpha and 2 beta subunits
- Alpha subunit
  - Extracellular
  - Binds with insulin
- Beta subunit
  - Span the membrane
  - The intracellular ends have tyrosine kinase activity

Insulin receptors

- Both alpha and beta subunits are glycosylated
- Sugar residues extends into the interstitial fluid
- Binding of insulin
  - Triggers tyrosine kinase activity of beta subunits
  - Results auto-phosphorylation of beta subunits on tyrosine residues
  - Auto-phosphorylation exerts biologic activity

Insulin receptors

- When insulin binds to its receptor
  - They aggregate on the cell membrane
  - Aggregated patches are taken into the cell by receptor mediated endocytosis
  - Finally receptor insulin complex enters into lysosomes and metabolized

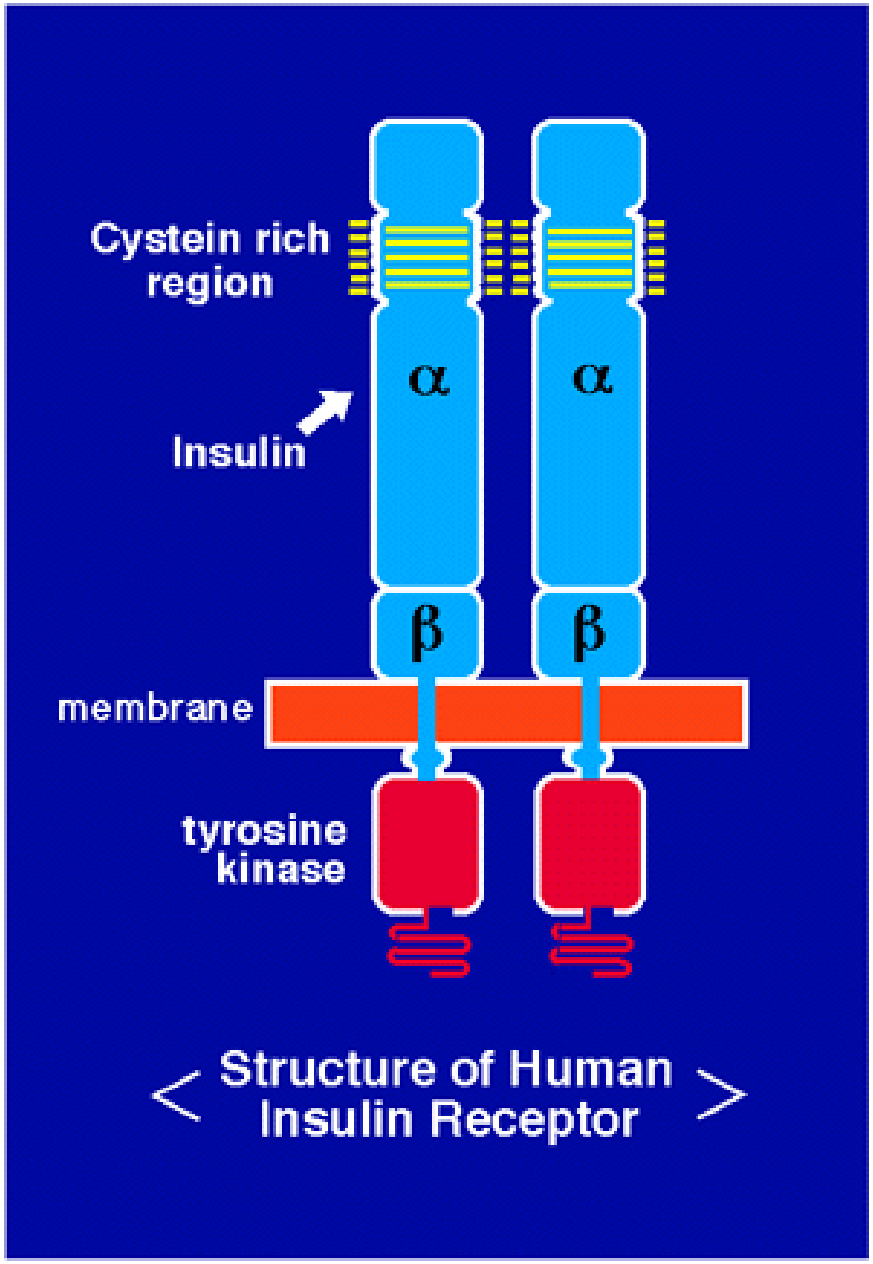
Insulin receptors

- Number and affinity is affected by other hormones, exercise and foods
- Number of receptors
  - Increased in
    - Starvation
  - Decreased in
    - Exposure to increased amount of insulin-down regulation
    - Obesity
    - acromegaly

Insulin receptors

- Affinity
  - Increased in
    - Exposure to deceased insulin
    - Adrenal insufficiency
  - Decreased in
    - Excess glucocortocoids

Insulin receptors



Glucose entry into cells and glucose transporters

- Glucose
  - Enters into all cells by facilitated diffusion
  - But in some tissues insulin facilitates the glucose entry by increasing glucose transporters
- Glucose transporters
  - Family of closely related proteins
  - Responsible for glucose facilitated diffusion of glucose across cell membrane
  - Five different glucose transporters have been identified

glucose transporters

- Have no homology with sodium dependent glucose transporter
  - SGLT 1
  - Secondary active co-transporter in
    - Intestine and renal tubules

glucose transporters

Transporter	Function	Site
• GLUT 1	basal glucose uptake	brain, RBC, Kidneys, Colon, placenta
• GLUT 2	B cell glucose sensor, transport out of intestinal and renal epithelial cells	B cells of islets, liver, epithelial cells of kidney, intestine
• GLUT 3	Basal glucose uptake	brain, Kidneys, placenta
• GLUT 4	Insulin stimulated glucose uptake	Skeletal and cardiac muscles, adipose tissue
• GLUT 5	Dietary absorption	Jejunum

Effects of insulin

- Hypoglycaemic action of insulin
  - Insulin facilitates glucose entry into
    - Muscle, fat
  - Once entered in these tissues the rate of phosphoryalation is regulated by other hormones
  - GH and cortisol inhibits phosphorylation
    - The process is rapid
    - Becomes a rate limiting step only when the glucose entry is high

Effects of insulin

- Hypoglycaemic action of insulin
  - Insulin facilitates the glucose entry into liver cells
  - Increases hexokinase enzyme activity
  - Increases phosphoryalation of glucose
  - Keeps the intracellular glucose concentration low
  - Facilitates the entry
  - Not by action on GLUT 4

Effects of insulin

- Stimulates potassium entry into cells
- Lower the extracellular potassium
- Increases Na^+ - K^+ ATPase activity
- Other actions of insulin
  - Increased glycogen synthase activity
  - Promotes lipogenesis
  - Stimulates protein synthesis
    - Increase amino acid entry into cells
  - Inhibits protein degradation

Regulation of insulin secretion

- Average basal insulin secretion -1U/h
- Control of secretion
  - By feedback inhibition on beta cells by plasma glucose

Regulation of insulin secretion

- Glucose in beta cells
  - Metabolized via glucokinase
  - A rate limiting step
  - ATP generation results closure of ATP sensitive K^+ channels
  - Decreases K^+ efflux → depolarizes the membrane
  - Opens voltage gated Ca^{++} channels →Ca^{++} influx
  - Increase Ca^{++} triggers Ca^{++} dependent kinases
  - Releases the insulin by exocytosis

Regulation of insulin secretion

- This feedback operates with great precision
- Plasma glucose and insulin parallel with each other with remarkable consistency

Regulation of insulin secretion

- Amino aids stimulates insulin secretion
- Cyclic AMP
  - Increase in cyclic AMP increases insulin secretion
  - Possibly by increasing intracellular Ca^{++}
- Catecholamines – has a dual effect
  - Inhibits insulin secretion via – alpha 2 receptors
  - Stimulates – via beta receptors
  - The net effect is inhibition of secretion

Regulation of insulin secretion

- Vagal stimulation increases insulin secretion via M4 receptors
- Intestinal hormones stimulates insulin secretion
  - Glucagon and derivatives
  - Secretin
  - CCK
  - Gastrin
- K^+ depletion decreases insulin secretion

Diabetes mellitus

- A group of metabolic disorder characterized by relative
  - Insulin deficiency
  - Insulin resistance
  - Chronic hyperglycemia
- Types of diabetes
  - Type-1
  - Type -2

Diabetes mellitus

- In the absence of insulin
  - Glucose entry is reduced in
    - Skeletal muscles
    - Cardiac muscles
    - Smooth muscles
    - Other tissues
  - Liver
    - glucose uptake also reduced -Effect is indirect
    - Glycogen synthesis is inhibited/ gluconeogenesis→ increased
  - Intestinal absorption and renal reabsorption- unaffected
  - Uptake of glucose by brain and red cells remain normal

Diabetes mellitus

- Features of diabetes mellitus
  - Thirst
  - Polyuria
  - Polydypsia
  - Weght loss
  - Polyphagia
- Features due to complications
  - Macrovascular
  - Microvascular – retinopathy, nephropathy, neuropathy

Diabetes mellitus

- Wide spread biochemical abnormalities
- Due to
  - Reduced entry of glucose into peripheral tissues
  - Increased release of hepatic glucose
    - Glycogenolysis
    - Gluconeogenesis
  - Decreased entry of amino acids
  - Increased lipolysis

Diabetes mellitus

- Glucose tolerance
  - After a glucose load the blood glucose rises and returns to base line within 2 hours normally
  - In diabetic patients the return is slow
  - Glucose tolerance test is used to diagnose people with abnormal glucose metabolism
- Glucose tolerance test
  - 75 g of glucose is given orally
  - 1hour and 2 hour plasma glucose levels are measured

Diabetes mellitus

1999 WHO Diabetes criteria - Interpretation of Oral Glucose Tolerance Test								
Glucose levels	NORMAL		impaired fasting glycaemia (IFG)		impaired glucose tolerance (IGT)		Diabetes Mellitus (DM)	
Venous Plasma	Fasting	2hrs	Fasting	2hrs	Fasting	2hrs	Fasting	2hrs
(mmol/l)	<6.1	<7.8	≥ 6.1 & <7.0	<7.8	<7.0	≥7.8	≥7.0	≥11.1
(mg/dl)	<110	<140	≥110 & <126	<140	<126	≥140	≥126	≥200

Diabetes mellitus

- Effects of hyperglycemia
  - Glycosuria due to hyperglycaemia exceeding renal threshold
  - Polyuria due to osmotically active glucose in urine
  - Polyuria resulting dehydration and thirst
  - Muscle and adipose tissue breakdown→ weight loss
  - Chronically elevated glucose leads to non enzymetic glycosylation of
    - Haemoglobin

Diabetes mellitus

- Glycosylated haemoglobin HbA_1C
  - Red cells have about 120days life span
  - HbA_1C shows glycaemic control for past 3 months
  - An integrated index of diabetes control
  - Level reduces with good glycaemic control

Diabetes mellitus

- Effects of intracellular glucose deficiency
- In diabetes there is
  - Extracellular hyperglycaemia
  - Intracellular glucose deficit
  - Reduces major source of energy
- Energy requirements met by
  - Protein and fat catabolism

Diabetes mellitus

- Changes in protein metabolism
  - Catabolism is increased →negative nitrogen balance
  - Amino acids are converted to glucose
- Gluconeogenesis is increased due to
  - Glucagon
  - Cortisol

Diabetes mellitus

- Fat metabolism
  - Acceleration of lipid catabolism
  - Increased formation of ketone bodies
  - Decreased synthesis of fatty acids and TG
- Insulin
  - Inhibits hormone sensitive lipase
  - Results rise in free fatty acids in plasma
- Glucagon increases the mobilization of FFA
- FFA are catabolised to acetyl Co-A

Diabetes mellitus

- Ketosis
  - *Ace*tyl-CoA converted to ketone bodies
- Ketone bodies
  - Important source of energy
- Acidosis
  - Most H^+ from ketone bodies are buffered
  - Un- buffered ones lead to severe acidosis
  - Results Kussumaul breathing
  - Can depress the consciousness→coma

Diabetes mellitus

- Cholesterol metabolism
  - Elevated cholesterol
  - Increase in LDL and VLDL
  - Results atherosclerosis

Insulin Excess

- Results hypoglycemia
- Features are due to effects on CNS
- Glucose reserves on nerve cells are very little
- Function depends on continuous supply of glucose
- In Hypoglycaemia neuroglycopaenic symptoms appears
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Insulin Excess

- neuroglycopaenic symptoms
  - Hunger
  - Palpitations
  - Sweating
  - Nervousness
  - Confusion
  - Coma
- Prolonged hypoglycaemia results permanent brain damage

Hypoglycaemia

- Compensatory mechanisms
- Cessation of insulin secretion
- Increased secretion of
  - Glucagon
  - GH
  - Epinephrine
  - Cortisol
- Increase the hepatic output of glucose
- Reduces the peripheral utilization

Glucagon

- Linear polypeptide produced by
  - A cells
  - Upper gastrointestinal tract
- Actions
  - Glycogenolytic
  - Gluconeogenic
  - Lipolytic
  - Ketogenic

Glucagon

- When glucagon binds to receptor
  - Acts via cyclic AMP
  - Activates protein kinase A
  - Increases glycogen breakdown
    - Activation of phosphorylase
- Increases
  - gluconeogenesis in muscle
  - Ketone body formation

Glucagon

- Metabolism
  - Half life is 5-10 mins
  - Degraded by liver
- Regulation of secretion
- Increased by
  - Hypoglycaemia
  - Sympathetic stimulation
  - Vagal stimulation
  - Protein rich meal
  - Starvation
  - CCK,gastrin

Glucagon

- Secretion is inhibited by
  - Increased GABA

Other islet cell hormones

- Somatostatin
  - From D cells
  - Has a paracrine function
  - Inhibits secretion of
    - Insulin, glucagon, pancreatic polypeptide
- Pancreatic polypeptide
  - a linear polypeptide
  - Secretion increased by fasting, exercise
  - Secretion is decreased by somatostatin and glucose

Glucose metabolism

- Exercise
  - Increases the
    - Glucose entry into muscles
    - Insulin sensitivity by increasing GLUT 4
- Catecholamines
  - Increases glucose out put from liver
  - Liberates FFA
  - Decreases the peripheral utilization of glucose

Glucose metabolism

- Thyroid hormones
  - Increases the blood glucose level
- Adrenal glucocorticoids
  - Increase plasma glucose level
    - Protein catabolism and gluconeogenesis
    - Ketogenesis
    - Decreased peripheral utilisation
- Growth hormone
    - Mobilizes FFA and increases ketogenesis
    - Decreased utilization
    - increases hepatic glucose output