Pancreas

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Anatomy

- 100g- pancreas
- 1 g- islets
- 99% - pancreatic juice → duodenum
- 1% - endocrine function
- 200,000- 1,000,000 islets per pancreas
• Three Cell Types
  – A cells
    • glucagon
  – B cells
    • insulin
  – D cells
    • somatostatin and possibly gastrin
    • Zollinger- Ellison Syndrome
• derived from GUT
• Gut wall contains cell that secrete glucagon-like hormone, somatostatin and gastrin
Insulin

• Chemistry and Biosynthesis
• Regulation of Insulin Secretion
• Physiological Effects of Insulin
• Receptor and its Regulation

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Insulin

• Chemistry and Biosynthesis
  – Two polypeptide Chains
    • 21 residues
    • 30 residues
    – joined by 2 disulfide bridges
  – 9,000 MW
  – Proinsulin
    • primary gene product
    • single polypeptide chain of 86 residues
    • Converted to insulin
      – endopeptidase
      – carboxypeptidase

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Insulin

• Regulation of Insulin Secretion
  – 24 U/day- fasting state
  – 5-10x
  – Pancreatectomized patients
    • 50-60 U/day

Insulin

• Regulation of Insulin Secretion
  – Stimulation- Direct
  – Stimulation- Indirect
  – Inhibition
Insulin

- Regulation of Insulin Secretion
  - Stimulation - Direct
    - Glucose
    - Amino acids
    - Ketone bodies
    - Fatty acids
    - GI Hormones (secretin, gastrin, pancreozymin) anticipatory effect
    - Glucagon
    - Acetylcholine
    - Beta-adrenergic agents (isoproterenol)
    - Alpha-adrenergic blocking agents (phentolamine)
    - Sulfonylureas
Insulin

• Regulation of Insulin Secretion
  – Stimulation- Indirect
    Any agent that raises blood glucose levels (induce peripheral effects of insulin)
    • Growth Hormone
    • Glucocorticoids
    • Estrogenic Hormones
    • Progestational hormones
    • Parathyroid Hormones

Insulin

• Regulation of Insulin Secretion
  – Inhibition
    • Alpha- adrenergic agents (epinephrine, norepinephrine)
    • Beta- Blocking agents
    • Diphenylhydantoin
    • Diazoxide
    • Degraded by all tissues but liver (50%) dominant and folled by kidney (25%)
Insulin

• Physiological Effects of Insulin
  – Glucose Metabolism
  – Fat Metabolism
  – Amino acid and Protein Metabolism

• liver
  – increases glucose phosphorylation
  – increases glycogen synthesis
  – decreases glycogenolysis

• Acutely, insulin modifies activity of the enzymes it regulates
• Chronic Insulin Deficiency- leads to changes in the amount of the enzymes involved at a control points
• Glucose uptake also stimulated in muscle (and glycogenesis) and adipose tissue (and glycogenesis).
Insulin

• Physiological Effects of Insulin
  – Fat Metabolism
    • Adipose Tissue
      – increase lipogenesis
      – decrease lipolysis
    • Liver
      – *Insulin Deficiency* → fatty acid synthesis is reduced
      decreased availability of NADPH, decreased activity of
      fatty acid synthetase → low citrate
      » FFA delivery to liver is increased, acetyl CoA is
      shunted to acetoacetate → KETOSIS

Insulin

• Physiological Effects of Insulin
  – Amino acid and Protein Metabolism
    • Increased amino acid transport
    • increased protein synthesis
Insulin

• Receptor and its Regulation
  – Insulin receptors on target cells serve two major functions:
    • Specific recognition of insulin molecules amongst other circulating hormones and substrates
    • Triggering of a chain of intracellular events: increased transport of substrates or altered enzymes
  – Insulin receptor is believed to be a glycoprotein with a molecular weight 150,000-300,000 daltons
  – The number of insulin receptors per cell is estimated to vary between 50,000 and 250,000
  – Maximal biologic effects are observed when only a small proportions of insulin receptors are occupied.

Insulin

• Receptor and its Regulation
  – Circulating monocyte specifically bind insulin and mirror the condition of insulin receptors in conventional target tissues.
    • Erythrocytes have also been identified as a site of insulin receptors
  – In some patients
    • failure of adequate insulin secretion
    • hyperinsulinemia: defect in tissue responsiveness to insulin
    • Receptor-Deficient Disease States
    – Obesity
    – MODY (Type II)
    – Severe Insulin Resistance and Acanthosis Nigricans
    – Uremia
    – Growth Hormone Excess
    – Glucocorticoid excess
Insulin

• Receptor and its Regulation
  – Regulation of Receptor Number
    1. Plasma insulin concentration (basal state)
       a. Hyperinsulinenia- decrease
       b. Hypoinsulinemia- increase
    2. Weight reduction in obese- increase
    3. Sulfonylureas- increase
    4. Improvement in physical fitness- increase
  – Circumstances are now recognized in which there is a clear cut dissociation between insulin action and insulin receptor function
  – Receptor antibodies → “Autoimmune Diabetes”

Glucagon

• Chemistry and Assay
• Regulation of Secretion
• Physiologic Effects
Glucagon

• Chemistry and Assay
  – alpha cells
  – single polypeptide chain of 29 residues (MW 3485) with no cross-linkages
  – Pancreas and plasma contain “big” glucagon (MW 9,000) and also lower MW fragments → PROHORMONES

Glucagon

• Regulation of Secretion
  – Stimulation
    • Hypoglycemia
    • Amino acids
    • Pancreozymin
    • Catecholamines
    • Exercise
  – Inhibition
    • Hyperglycemia
    • Insulin
    • Free Fatty Acids
Glucagon

• Physiologic Effects
  – Stimulates Hepatic Gluconeogenesis by:
    • Deactivation of pyruvate kinase
    • Increase in uptake of amino acids
  – Stimulates hepatic glycogenolysis by:
    • activation of phosphorylase
    • deactivation of glycogen synthase
  – Stimulates lipolysis in adipose tissue via cAMP-dependent protein kinase
  – Stimulate insulin release

Somatostatin

• tetradecapeptide
• Guillemin
  – hypothalamus → potent inhibitor of growth hormone
• suppress both insulin and glucagon release
Diabetes Mellitus
Introduction

- Diabetes mellitus (sweet urine)
- 3% of world population, 100 million people
- Commonest non communicable disease
- High Morbidity & mortality

Diabetes Mellitus

- Disorder of metabolism (Carb, Prot & Fat)
- Due to Absolute or relative deficiency of insulin.
- Characterized by hyperglycemia.

- Clinically: Polyuria, Polydypsia, Polyphagia.
Classification

• **Primary DM.**
  – Type I – IDDM / Juvenile – 10%.
  – Type II – NIDDM /Adult onset – 80%.
  – MODY – 5% maturity onset - young - Genetic

• **Secondary DM** – islet destruction.
  – Infectious – congenital rubella, CMV.
  – Pancreatitis/tumors/Hemochromatosis.
  – Endocrinopathy, gestational DM, downs.
  – Drugs – Corticosteroids.

Classification

• **Type I Diabetes** (*insulin-dependent diabetes mellitus*, IDDM)
  – characterized by severe insulinopenia and dependence on exogenous insulin to prevent ketosis and to preserve life
  – onset occurs predominantly in childhood
  – probably has some genetic predisposition and is likely autoimmune-mediated
Classification

- Type II Diabetes (*non-insulin-dependent diabetes mellitus*, NIDDM)
  - patients are not insulin dependent and rarely develop ketosis
  - generally occurs after age 40, and there is a high incidence of associated obesity
  - insulin secretion generally adequate; insulin resistance is present
  - no associated genetic predisposition

Classification

- Secondary Diabetes
  - occurs in response to other disease processes:
    - exocrine pancreatic disease (cystic fibrosis)
    - Cushing syndrome
    - poison ingestion (rodenticides)
Normal Pancreatic Islets:

- ß cells
- Glucagon cells

Pathogenesis of Type I DM

- Genetic
  - HLA-DR3/DR4
- Environment ?
  - Viral infec...?

Autoimmune Insulitis

ß cell Destruction

Severe Insulin deficiency

Type I DM
**Pathogenesis of Type II DM**

- **β cell defect**
  - Genetic

- **Environment**
  - Obesity ???

- Abnormal Secretion → Insulin resistance → Relative Insulin Def.

- β cell exhaustion → Type II DM → IDDM

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**Type-I**
- Age: < 40 Years
- Duration: Weeks
- Ketonuria: Common
- Insulin- Dependent
- Autoantibody: Yes
- Family History: No
- Insulin levels: very low
- Islets: Insulitis
- Complications: Acute & Metabolic

**Type-II**
- > 40 Years
- Months to years
- Rare
- Independent *
- No
- Yes
- Normal or high *
- Normal / Exhaustion
- Complications
  - Late and vascular.
Insulitis – Type I

Islets in Type II Diabetes:
- Loss of β cells
- Amyloid deposits
- Hyalinization
Type I Diabetes Mellitus: Epidemiology

- Prevalence of IDDM among school-age children in the US is 1.9 per 1000
- The annual incidence in the US is about 12 - 15 new cases per 100,000
- Male to female ratio is equal
- Among African-Americans, the occurrence of IDDM is about 20 - 30% of that seen in Caucasian-Americans

Type I Diabetes Mellitus: Epidemiology

- Peaks of presentation occur at 5 - 7 years of age and at adolescence
- Newly recognized cases appear with greater frequency in the autumn and winter
- Definite increased incidence of IDDM in children with congenital rubella syndrome
Ketogenesis

- Triglycerides are liberated from adipose tissue, and the concentration of free fatty acids (FFA) in the blood is elevated.
- FFA are broken down to fatty acyl carnitine within the liver cells, and this molecule is converted to acetyl CoA, which in turn reach the mitochondria, where ketone bodies (acetoacetate, acetone, β-hydroxybutyrate) are formed.
- The breath of the patient smell by acetone, and there is ketosis in the urine.
- The concentration of ketone bodies in the blood passes 5 mM, and when pH falls below 7, there is life-threatening or terminal coma.

Type I Diabetes Mellitus: Pathophysiology

- DKA results in altered lipid metabolism
  - increased concentrations of total lipids, cholesterol, triglycerides, and free fatty acids
  - free fatty acids are shunted into ketone body formation due to lack of insulin; the rate of formation exceeds the capacity for their peripheral utilization and renal excretion, leading to accumulation of ketoacids, and therefore metabolic acidosis.
Type I Diabetes Mellitus: Pathophysiology

• With progressive dehydration, acidosis, hyperosmolality, and diminished cerebral oxygen utilization, consciousness becomes impaired, and the patient ultimately becomes comatose

Type I Diabetes Mellitus: Clinical Manifestations

• Classic presentation of diabetes in children is a history of polyuria, polydipsia, polyphagia, and weight loss, usually for up to one month
• Laboratory findings include glucosuria, ketonuria, hyperglycemia, ketonemia, and metabolic acidosis. Serum amylase may be elevated. Leukocytosis is common
Type I Diabetes Mellitus: Clinical Manifestations

• Keotacidosis is responsible for the initial presentation of up to 25% of children
  – early manifestations are mild and include vomiting, polyuria, and dehydration
  – More severe cases include Kussmaul respirations, odor of acetone on the breath
  – abdominal pain or rigidity may be present and mimic acute appendicitis or pancreatitis
  – cerebral obtundation and coma ultimately ensue

Type I Diabetes Mellitus: Diagnosis

• Diagnosis of IDDM is dependent on the demonstration of hyperglycemia in association with glucosuria with or without ketonuria
• DKA must be differentiated from acidosis and coma due to other causes:
  – hypoglycemia, uremia, gastroenteritis with metabolic acidosis, lactic acidosis, salicylate intoxication, encephalitis
Type I Diabetes Mellitus: Diagnosis

• DKA exists when there is hyperglycemia (> 300 mg/dL), ketonemia, acidosis, glucosuria, and ketonuria

Type I Diabetes Mellitus: Treatment

• Insulin is used to treat acidosis, not hyperglycemia
  – insulin should never be stopped if ongoing acidosis persists
• When the acidosis is corrected, the continuous insulin infusion may be discontinued and subcutaneous insulin initiated
• With the regimen, DKA usually is usually fully corrected in 36 to 48 hours
Type I Diabetes Mellitus: Treatment

- Hypoglycemic Reactions (Insulin Shock)
  - Symptoms and signs include pallor, sweating, apprehension, trembling, tachycardia, hunger, drowsiness, mental confusion, diplopia, headache, seizures, coma, death
  - Management includes administration (if conscious) of carbohydrate-containing snack or drink
  - Glucagon 0.5 mg is administered to an unconscious or vomiting child

Fig. 27-5

Hypoglycaemic Shock: Adrenergic effects

- Insulin administration
- Muscle glycogen
- Krebs cycle
- FFA
- Adrenal medulla
- Hypoglycaemia (insulin shock)
- Sympathoadrenergic + cerebral signs
Complications:

- **Short term Complications:** *(metabolic)*
  - Hypoglycemia
  - Diabetic Ketoacidosis
  - Non Ketotic hyperosmolar diabetic coma
  - Lactic acidosis
- **Long term Complications:** *(microangiopathy)*
  - Angiopathy, Retinopathy, Nephropathy, Neurophathy

Pathogenesis of Microangiopathy:

- Long standing diabetes
- Combination of glucose with proteins - Particularly collagen in blood vessels - Glycosylation.
- Excess deposition of glycosylated type IV collagen in the basement membrane
- Thick and Leaky blood vessels.
- Chronic Ischemia & protein loss into tissues.
- Organ damage...
Long term Complications:

- Angiopathy
  - Atherosclerosis
  - Hyaline arteriolosclerosis
  - Diabetic microangiopathy
- Nephropathy
  - Nodular glomerulosclerosis
- Retinopathy
  - Non Proliferative & Proliferative
- Neuropathy
  - Peripheral axonal neuropathy
Neuropathy

Diabetic Gangrene
Candidiasis

Pathogenesis of Retinopathy

Microaneurysms

Microaneurysms and hemorrhage

Microaneurysms, hemorrhage, and exudates

Proliferative diabetic retinopathy

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Normal Retina

Diabetic Retinopathy

Cotton wool spots
Pathogenesis of Nephropathy

Diabetic Glomerulosclerosis
Laboratory Diagnosis:

- Urine glucose - dip-stick –Screening
- Random or fasting blood glucose (<11)
- Fasting > 7mmol, Random >11mmol
- If Fasting level is between 7-11 then OGTT

- HbA1c - for follow-up, not for diagnosis
- Fructosamine - for long term maintenance.

Points to remember:

- Type-I - Acute Metabolic complications
  – Ketoacidosis.
- Type-II - Chronic Vascular complications
  – Microangiopathy – Kidney, Retina, Brain, BV.
- Hypoglycemia is more dangerous. Not hyper
- Infections are due to microangiopathy and ischemia, immuno suppression and hyperglycemia. (not just hyperglycemia)
Thank You!