Introduction to the pancreas, its cell types, its hormones, its functional organization, its venous output to liver and its regulation

Overview of intermediary metabolism and enzyme sites of major actions of insulin and glucagon

Pancreatic hormones, insulin, glucagon, SS and PPY. Their structure, synthesis, related peptides, secretion, regulation, receptors and effects. Effect of exercise on insulin and its counter-regulatory hormones

Regulation of pancreatic hormones, Diabetes Mellitus, hypoglycemia, fasting, NIDDM

Insulin decreases glycemia while glucagon increases it. As glycemia increases blood levels of insulin decrease while those of glucagon decrease.
Introduction

- Endocrine pancreas
- Intermediary metabolism
- Pancreatic hormones
- Diabetes mellitus

Storage and utilization of biological fuels.

Intraorgan flow of substrate and the competitive regulatory effects of glucose and fatty acids that comprise the glucose-fatty acid cycle.
Introduction

- Endocrine pancreas
- Intermediary metabolism
- Pancreatic hormones
- Diabetes mellitus

Effects of metabolic hormones

Storage and utilization of biological fuels.

Effects of metabolic hormones on adipose tissue.
*Lipolytic effects of cortisol are permissive.

Effects of metabolic hormones on skeletal muscle.
The stimulation of fatty acid oxidation by growth hormone and cortisol are indirect and result from increased fatty acid mobilization.
Introduction

- Endocrine pancreas

- Intermediary metabolism

- Pancreatic hormones

- Diabetes mellitus

Effects of metabolic hormones

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>↓ Glucose production</td>
</tr>
<tr>
<td></td>
<td>↑ Glycogen synthesis</td>
</tr>
<tr>
<td></td>
<td>↓ Fatty acid synthesis</td>
</tr>
<tr>
<td></td>
<td>↓ Fatty acid esterification</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>↑ Gluconeogenesis</td>
</tr>
<tr>
<td></td>
<td>↓ Insulin sensitivity</td>
</tr>
<tr>
<td></td>
<td>↑ Ketogenesis</td>
</tr>
<tr>
<td></td>
<td>↑ IGF production</td>
</tr>
<tr>
<td>Cortisol</td>
<td>↑ Gluconeogenesis</td>
</tr>
<tr>
<td></td>
<td>↑ Glycogen synthesis</td>
</tr>
<tr>
<td></td>
<td>↓ Glucose utilization</td>
</tr>
<tr>
<td></td>
<td>↓ Insulin sensitivity</td>
</tr>
<tr>
<td>Glucagon</td>
<td>↑ Glycogen synthesis</td>
</tr>
<tr>
<td></td>
<td>↑ Gluconeogenesis</td>
</tr>
<tr>
<td></td>
<td>↑ Ketogenesis</td>
</tr>
<tr>
<td>Triiodothyronine</td>
<td>↑ Glycogen synthesis</td>
</tr>
<tr>
<td></td>
<td>↑ Gluconeogenesis</td>
</tr>
<tr>
<td></td>
<td>↑ Ketogenesis</td>
</tr>
</tbody>
</table>

Effects of metabolic hormones on the liver.

Storage and utilization of biological fuels.

Quantitative turnover of substrates in the basal state after fasting for 24 hours. Follow the “ready available money”
Introduction

- Endocrine pancreas
- Intermediary metabolism
- Pancreatic hormones
- Diabetes mellitus

Representative values for plasma glucose and metabolic hormones during fasting. Values for growth hormone are averaged over 24 hours. The small decline in cortisol may reflect a decrease in cortisol binding globulin.

Hormonal changes in the basal state after fasting for 24 h.
Introduction

- Endocrine pancreas
  - pancreas, main regulator of sugar metabolism
  - sugars from food digestion and from glycogen
  - endocrine (islets) & exocrine pancreas (acinar)
  - the islets of Langerhans (triads: α, β, γ, δ cells)
  - hormones: insulin, glucagon, SS, PPY
  - pancreatic endocrine secretion to portal vein
  - blood glucose decreased by insulin, SS, IGFs
  - blood glucose increased by glucagon, CAs, glucocorticoids, GI hormones, GH, CRH, ACTH, T3 / T4, Ang II, food (arginine).

- Intermediary metabolism

- Pancreatic hormones

- Diabetes mellitus

The opposite direction of plasma insulin and glucagon define the metabolic state.

Changes in sources of fuels utilized during prolonged exercise at 30% of maximal oxygen consumption.

Hormonal changes in the basal state after fasting for 24 h.
Introduction

- Endocrine pancreas
- Intermediary metabolism
- Pancreatic hormones
- Diabetes mellitus

Cytoarchitecture of a typical human pancreatic islet as revealed in immunostained confocal scanning microscopic images. Endocrine cells are closely but randomly associated with vascular cells. Most insulin- (red), glucagon- (green), and somatostatin- (cyan) immunoreactive cells are in close proximity to vascular cells immunoreactive for smooth muscle cell actin (blue). Endocrine cells are aligned along the blood vessels in a random order.

Introduction

- Endocrine pancreas
- Intermediary metabolism
- Pancreatic hormones
- Diabetes mellitus

Plasma levels of glucose and insulin in relation to meal intake. Glucose increases insulin secretion.
Introduction

- Endocrine pancreas
- Intermediary metabolism
- Pancreatic hormones
- Diabetes mellitus

Time course of the origin of glucose under fasting conditions. Look at the intermediary metabolic paths.

An opposite direction in the profile of plasma insulin and glucagon defines the individual's metabolic state.
Metabolic pathways

- Endocrine pancreas
- Intermediary metabolism
- Pancreatic hormones
- Diabetes mellitus

JP's colorful version indicating the main action site of various metabolic hormones

Metabolic pathways

- Endocrine pancreas
- Intermediary metabolism
- Pancreatic hormones
- Diabetes mellitus

Hadley's textbook version of the intermediary metabolic pathway
Introduction

• Endocrine pancreas
• Intermediary metabolism
• Pancreatic hormones
• Diabetes mellitus

Metabolic pathways

• Endocrine pancreas
• Intermediary metabolism
• Pancreatic hormones
• Diabetes mellitus

1. LEFT: Effects of insulin on glucose metabolism in hepatocytes. Green arrows indicate reactions that are increased, and dashed red arrows indicate reactions that are decreased.
2. RIGHT: Biochemical pathways of glucose metabolism in hepatocytes. Reactions that are accelerated in the presence of glucagon are shown in green. Broken red arrows indicate reactions that are inhibited by protein kinase A catalyzed phosphorylation. The hexose-mono-phosphate shunt is indirectly inhibited. Roman numerals indicate substrate cycles.

Goodman's textbook version of the intermediary metabolic pathway

some associations to remember for an endocrine regulatory viewpoint
Hormonal effects on FFA production. Epinephrine and norepinephrine stimulate hormone-sensitive lipase through a cyclic AMP mediated process. Insulin antagonizes this effect by stimulating cyclic AMP degradation. T3, cortisol, and growth hormone increase the response of adipocytes to epinephrine and norepinephrine. Growth hormone also directly stimulates lipolysis. Insulin indirectly antagonizes the release of FFA by increasing reesterification. Growth hormone and cortisol increase FFA release by inhibiting reesterification.
Insulin and its counter-regulatory hormones

- Endocrine pancreas
- Intermediary metabolism
- Pancreatic hormones
- Diabetes mellitus

Insulin decreases blood glucose while all counter-regulatory hormones increases it.
Insulin and its counter-regulatory hormones

- Endocrine pancreas
- Intermediary metabolism
- Pancreatic hormones
- Diabetes mellitus

**Insulin decreases blood glucose while all counter-regulatory hormones increases it**
Insulin and its counter-regulatory hormones

- Endocrine pancreas
- Intermediary metabolism
- Pancreatic hormones
- Diabetes mellitus

Insulin decreases blood glucose while all counter-regulatory hormones increase it.

Insulin

- Endocrine pancreas
  - it has 51 aa, 2 chains, 3 S-S bonds, C-peptide
  - stimulates anabolism and favors energy storage
- Intermediary metabolism
  - increases glycogen storage and inhibits both glycogen breakdown and gluconeogenesis
  - increases fatty acid synthesis and decreases lipolysis and ketogenesis
- Pancreatic hormones
  - stimulates transport of glucose and some amino acids into striated muscle and adipose tissue
  - increases protein synthesis in liver, muscle, adipose
- Diabetes mellitus
  - Like growth factors it has a growth promoting effect

An overview of the main effects of pancreatic insulin
Insulin

- Endocrine pancreas
- Intermediary metabolism
- Pancreatic hormones
- Diabetes mellitus

Insulin secreted from the pancreatic ß cells decreases blood glucose levels

An overview of the factors affecting insulin signalling
Insulin

- Endocrine pancreas
- Intermediary metabolism
- Pancreatic hormones
- Diabetes mellitus

An overview of the factors affecting insulin secretion.

Metabolic, hormonal, and neural influences on insulin secretion.

An overview of blood glucose stimulation of insulin secretion and intracellular effects.
Endocrine pancreas

Intermediary metabolism

Pancreatic hormones

Diabetes mellitus

Insulin

• “Resting” beta-cell

- Triggering of insulin secretion by glucose.
  A. “Resting” beta-cell (blood glucose < 100 mg/dl). ADP/ATP ratio is high enough so that ATP-sensitive potassium channels (KATP) are open, and the membrane potential is about -70 mV. Voltage-sensitive calcium channels (VSCC) and calcium-sensitive potassium channels (CSKC) are closed.
  B. Beta cell response to increased blood glucose. Increased entry and metabolism of glucose decreases the ratio of ADP/ATP, and KATP channels close. Voltage-sensitive calcium channels (VSCC) are activated; calcium enters and stimulates insulin secretion. Mitochondrial metabolites formed in response to glucose and calcium amplify secretion. Phospholipase C breaks down phosphoinositides and activates phospholipase D, thereby allowing the cell membrane to repolarize and calcium channels to close. Calcium is extruded by membrane calcium ATPase. Persistence of high glucose results in repeated spiking of electrical discharges and oscillation of intracellular calcium concentrations.
  C. Effect of incretins (GLP-1 and GIP) on insulin release by beta cells (see next slide).

• Glucose activated beta-cell

- Glucose (G). Increased entry and metabolism of G decreases the ratio of ADP/ATP, and KATP channels close. Voltage-sensitive Ca channels (VSCC) are activated; Ca enters and stimulates insulin secretion. Mitochondrial metabolites formed in response to G and Ca amplify secretion. Influx of Ca inhibits voltage-sensitive Ca channels and activates Ca-sensitive and voltage-sensitive K channels, thereby allowing the cell membrane to repolarize and calcium channels to close. Ca is extruded by membrane Ca-ATPase. Persistence of high G results in repeated spiking of electrical discharges and oscillation of intracellular Ca concentrations.

- Major acute cellular actions of incretins. GLP-1 and GIP acting through GPCR activate AC to increase intracellular cAMP. Cyclic AMP increases the activity of PKA or binds to a GTP exchange factor to activate a small G protein, which directly stimulates Ca-sensitive and voltage-sensitive K channels, thereby allowing the cell membrane to repolarize and calcium channels to close. Ca is extruded by membrane Ca-ATPase. Persistence of high G results in repeated spiking of electrical discharges and oscillation of intracellular Ca concentrations.
Insulin

• Endocrine pancreas

• Intermediary metabolism

• Pancreatic hormones

• Diabetes mellitus

Insulin release from pancreatic beta-cells acts on its targets by binding to its receptor.

The insulin receptor is a one transmembrane domain tyrosine kinase receptor.

- The insulin receptor contains an intrinsic protein kinase that specifically catalyzes the phosphorylation of tyrosine residues on proteins.
- Cystein and its thiol (SH) group linking the aa to another Cystein aa may form part of a binding cleft for ligands.
Insulin

- Endocrine pancreas
- Intermediary metabolism
- Pancreatic hormones
- Diabetes mellitus

Binding of insulin and its receptor in the ECF domain causes phosphorylation of the receptor intra-cellular domain and elicits a conformational change in its tyrosine kinase portion, thus activating its enzyme activity.
The main effect of insulin is on the Glut-4 transporter. This is how insulin decreases glycemia and increases glucose absorption.
The main effect of insulin is on the Glut-4 transporter. This is how insulin decreases glycemia and increases glucose absorption.

Other effects of insulin are mediated by its action on metabolic enzymes. This is how insulin increases glycolysis & glycogenesis.
Insulin

• Endocrine pancreas

• Intermediary metabolism

• Pancreatic hormones

• Diabetes mellitus

Insulin suppress glucose production by inhibiting the flux of gluconeogenic precursors (alanine, pyruvate, lactate, glycerol), energy substrates (free fatty acids) and glucagon secretion. All these suppress glucose release by the liver.
Glucagon

- Endocrine pancreas
  - main counterregulator to insulin together with catecholamines (Epi) & cortisol
  - 29 aa, member of a related family peptides that includes VIP, GIP, and secretin
  - determines glycemia in postabsorptive state by glycogenolysis and gluconeogenesis
  - glucose, insulin and SS inhibit its release
  - a, exercise and CAs stimulate its release
  - gene expression is restricted to α cells in islet and is negatively regulated by insulin
  - glycentin, GI specific proteolytic processing

- Intermediary metabolism
  - Glucagon release is the main counter-regulatory hormone to insulin secretion

- Pancreatic hormones
  - Glucagon secreted by the pancreatic alpha-cells increase blood glucose levels (glycemia)
Glucagon

- Endocrine pancreas
- Intermediary metabolism
- Pancreatic hormones
- Diabetes mellitus

Glucagon’s main mechanism of action is through AC, cAMP and PKA. Amplification is an important event in the mechanism of action of glucagon (cascade).

Glucagon release is the main counter-regulatory hormone to insulin secretion.
Glucagon

- Endocrine pancreas
- Intermediary metabolism
- Pancreatic hormones
- Diabetes mellitus

Main actions of glucagon on metabolic pathways. Notice the single main target

<table>
<thead>
<tr>
<th>Organ</th>
<th>Net effect</th>
<th>Chief mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>glycogenolysis</td>
<td>glycogen phosphorylase (cAMP-dep-P)</td>
</tr>
<tr>
<td></td>
<td>glycogenesis</td>
<td>glycogen synthase (phosphorylation)</td>
</tr>
<tr>
<td></td>
<td>gluconeogenesis</td>
<td>F-1,6-dPase (phosphorylation)</td>
</tr>
<tr>
<td></td>
<td>glycolysis</td>
<td>pyruvate kinase (phosphorylation)</td>
</tr>
<tr>
<td></td>
<td>ketogenesis</td>
<td>substrate delivery, releasing inhibition of carnitine palmitoyl transferase, allowing mitochondrial transfer and FA oxidation</td>
</tr>
</tbody>
</table>

Changes in insulin and glucagon in plasma and carbohydrate metabolism in normal subjects following ingestion of a liquid meal rich in carbohydrate. Although secretion of both insulin and glucagon was stimulated, insulin increased about twenty-fivefold while glucagon increased only threefold so that the ratio of glucagon to insulin fell dramatically. Plasma glucose increased transiently, but release of glucose from the liver fell precipitously, and liver glycogen increased.

Effect of large carbohydrate meal on blood glucose, glucagon, insulin and liver glucose-related data
**Glucagon**

- **Endocrine pancreas**
- **Intermediary metabolism**
  - **Pancreatic hormones**
  - **Diabetes mellitus**

Effect of large carbohydrate meal (left) and arginine infusion (right), on glycemia, glucagon and insulin

---

**Glucagon**

- **Endocrine pancreas**
- **Intermediary metabolism**
  - **Pancreatic hormones**
  - **Diabetes mellitus**

Effect of daily meals on glycemia, glucagon & insulin

Changes in the concentrations of plasma glucose, immunoreactive glucagon (IRG), and immunoreactive insulin (IRI) throughout the day. Values are the mean ± SEM (n = 4). (From Tasaka, Y., Sekine, M., Wakatsuki, M., Ohgawara, H., and Shizume, K. (1975) Levels of pancreatic glucagon, insulin and glucose during twenty-four hours of the day in normal subjects. *Horm. Metab. Res.*** *7*, 205–206.)
SS and PPY

- Endocrine pancreas
- Intermediary metabolism
- Pancreatic hormones
- Diabetes mellitus

SS has 14 aa and 1 disulfide bond. It was discovered and named for its GH inhibiting activity. SS inhibits a wide variety of endocrine and exocrine secretory activities in the pituitary and in the GI tract. In the pancreas, SS inhibits insulin, glucagon, PPY and exocrine secretion.

PPY release is largely neurally mediated. Sensing of food in the CNS causes its vagal-mediated secretion. Food in proximal GI tract also stimulates its release. PPY affects GI motility, secretory activity of stomach, intestine and pancreas.

Somatostatin & Pancreatic Polypeptide Y are two of the many GI peptides.

Effect of exercise

- Endocrine pancreas
- Intermediary metabolism
- Pancreatic hormones
- Diabetes mellitus

Exercise decreases insulin and increases all its counter-regulatory hormones.

Exercise contributes to O2 uptake in %

<table>
<thead>
<tr>
<th>Exercise (min)</th>
<th>Working muscle</th>
<th>Non-working muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120</td>
<td></td>
<td></td>
</tr>
<tr>
<td>240</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Plasma glucose, FFA, glycogen, lactate, glucose uptake in %

Exercise decreases insulin and increases all its counter-regulatory hormones.
Diabetes

- **Endocrine pancreas**
  - hallmark of insulin hyposecretion and insulin resistance is hyperglycemia in the fasting state
  - hyperglycemia, polyuria (diabetes = siphon), urine sweetens (mellitus = honey), polydipsia
  - precise mechanism for the deleterious effect of high glucose is not known. Whether from non-enzymatic glycation of proteins or from regulatory effects of excess glucose, blood vessels are damaged, resulting in turn in damage to the retina and kidney, and circulation compromise to the heart, brain and extremities. Main morbidity causes are blindness, renal failure, heart attack, stroke, amputations

- **Intermediary metabolism**
  - glucose tolerance test, diabetes mellitus, insulin deficit / resistance

- **Pancreatic hormones**
  - insulin resistance: prereceptor resistance (autoantibodies, mutant insulin), receptor resistance (decreased number and affinity, point mutation, impaired kinase expression), and post-receptor resistance (down regulation of Glut4 or autoantibodies of Glut2 transporters, mutation of glucokinase gene, β-cell exhaustion as in GH abuse)

- **Diabetes mellitus**
  - diabetic ketoacidosis, dehydration due to hyperglycemic diuresis, negative nitrogen balance, tissue wasting, poor resistance to infections, metabolic acidosis, fruity smell of ketosis in breath, cardiovascular involvement, hyperglycemic vs hypoglycemic coma

Diabetes mellitus has been linked to every step in the mechanism of action of insulin

---

TABLE 11.1 Pathology of the endocrine pancreas

<table>
<thead>
<tr>
<th>Type I (insulin-dependent diabetes mellitus, IDDM) [15]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juvenile-onset diabetes. Viral-induced β-cell destruction</td>
</tr>
<tr>
<td>Cytotoxic autoantibodies to β cells lead to β-cell destruction [24]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type II (non-insulin-dependent diabetes mellitus, NIDDM; previously called adult (maturity) onset diabetes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin resistance [1, 3, 14, 51]</td>
</tr>
<tr>
<td>Pre-receptor resistance</td>
</tr>
<tr>
<td>Antibodies against insulin</td>
</tr>
<tr>
<td>Mutant insulin structures</td>
</tr>
<tr>
<td>Defect in primary structure of insulin β chain at one or more positions</td>
</tr>
<tr>
<td>Familial hyperinsulinemia</td>
</tr>
<tr>
<td>B-C proinsulin mutation at the cleavage site between the B chain and the connecting (C) peptide</td>
</tr>
<tr>
<td>A-C proinsulin mutation at the cleavage site between the A chain and the connecting (C) peptide</td>
</tr>
<tr>
<td>Receptor resistance</td>
</tr>
<tr>
<td>Type A. Decrease in insulin receptor number and/or affinity for the hormone</td>
</tr>
<tr>
<td>Point mutation in insulin receptor gene prevents processing of the receptor precursor</td>
</tr>
<tr>
<td>Impaired expression of receptor (tyrosine kinase activity) [47]</td>
</tr>
<tr>
<td>Point mutations block insertion of mature receptor into plasma membrane</td>
</tr>
<tr>
<td>Type B. Receptor blocked by circulatory antibodies to the receptor</td>
</tr>
<tr>
<td>Lepimemon</td>
</tr>
<tr>
<td>An autosomal recessive inherited disorder of insulin function that leads to severe intrauterine growth retardation, characteristic dysmorphic features and a disturbed glucose homeostasis. The process underlying this disease is a structural defect in the insulin receptor</td>
</tr>
<tr>
<td>Post-receptor resistance</td>
</tr>
<tr>
<td>Decreased capacity of pancreatic β cells to compensate for the underlying insulin resistance by increased secretion of insulin [51]</td>
</tr>
<tr>
<td>Possible underexpression (down-regulation) of β-cell glucose transporters (therefore failure to recognize and respond to hyperglycemia)</td>
</tr>
<tr>
<td>Autoantibodies to the GLUT2 glucose transporter of β cells [24]</td>
</tr>
<tr>
<td>Mutation of the glucokinase gene may prevent uptake and metabolism of glucose necessary for the mechanism of insulin secretion. May be responsible for a young onset type II diabetes (MODY) [6, 25]</td>
</tr>
</tbody>
</table>

Islet cell tumors
- Infiltration. Excess insulin secretion from a β-cell pancreatic tumor (severe hypoglycemia)
- Glucagonoma syndrome. Excess glucagon secretion from an α-cell pancreatic tumor

Somatostatinoma. Excess somatostatin secretion from D-cell pancreatic tumor

Hypoglycemic disorders
- Hypoglycagomia (isolated glucagon deficiency). Possibly due to autosomal recessive inheritance
- Hypoinsulinemia (β-cell tumor) |
- Antibodies (stimulatory) to the insulin receptor (increased glucose uptake by cells)
Diabetes

- Endocrine pancreas
- Intermediary metabolism
- Pancreatic hormones

**Diabetes mellitus**

Diabetes is a good example of “pushing the regulatory feedback envelope” in endocrinology.

**Diabetes Mellitus can be Type 1 or Type 2**

Idealized glucose tolerance tests in normal and diabetic subjects. Subjects are given a standardized solution of glucose to drink and blood samples are taken at the indicated times thereafter. An impairment of glucose disposition results in a greater than normal and prolonged increase in blood glucose concentration.

Diabetes Type 1 – beta cells do not make insulin

Diabetes is a good example of “pushing the regulatory feedback envelope” in endocrinology.
Diabetes

- Endocrine pancreas
- Intermediary metabolism
- Pancreatic hormones
- Diabetes mellitus

Diabetes is a good example of “pushing the regulatory feedback envelope” in endocrinology

Diabetes Type 2 – insulin is not “seen” by target cells

Diabetics have a “sluggish” response to glucose
Diabetes

• Endocrine pancreas

• Intermediary metabolism

• Pancreatic hormones

• Diabetes mellitus

Diabetes is a good example of “pushing the regulatory feedback envelope” in endocrinology