Week 3, Lecture 5a
Pathophysiology of Diabetes
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General Model of Peptide Hormone Action

Hormone

Membrane Effects

Plasma Membrane

Cellular Trafficking

Intracellular Second Signal

Enzymes

Activated

Inhibited

Protein Synthesis

Nucleus

DNA Synthesis

RNA Synthesis
General Model of Steroid Hormone Action

Hormone

Plasma Membrane

Receptor

Nucleus

DNA Synthesis
RNA Synthesis
Regulation of glucose homeostasis in fasting or postabsorptive states

Production of glucose is primarily through liver glycogenolysis (75%) and gluconeogenesis (25%), with the possibility of kidney involvement after several days of fasting [Cahill's lab, 1969].

Insulin (+) promotes glucose utilization in muscle and fat (20%), whereas glucagon-like peptide acts as a counter-regulatory hormone.

Blood glucose levels are maintained through coordination between liver and other tissues, with gluconeogenesis supporting muscle and fat utilization, and insulin secretion from pancreatic islets.

Glucagon-like peptide and adrenergic hormones (epinephrine, cortisol, gh) are critical in gluconeogenesis and ketogenesis.

Key Points:
- Liver: glycogenolysis, gluconeogenesis
- Brain, gut, red cells: insulin-dependent glucose utilization
- Muscle and fat: insulin-dependent glucose utilization
- Glucagon-like peptide, epinephrine, cortisol, growth hormone: counter-regulatory hormones

*Cahill's lab, 1969: glycogenolysis 75% and gluconeogenesis 25%
Hormonal Regulation of Fuel Metabolism

<table>
<thead>
<tr>
<th></th>
<th>Insulin</th>
<th>Glucagon</th>
<th>Catechols</th>
<th>Cortisol</th>
<th>GH</th>
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<tbody>
<tr>
<td>Glucose uptake</td>
<td>+</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gluconeogenesis</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Glycogenolysis</td>
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<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Lipolysis</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Ketogenesis</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</table>

+ increase; - decrease; 0 no effect; ± weak effect
Type 1 Diabetes

- Previously known as juvenile-onset or insulin-dependent diabetes mellitus (IDDM)
- Affects 0.5% of population
- Onset most often in childhood or adolescence
- Characterized by absolute insulin deficiency secondary to autoimmune destruction of β-cells
- Requires insulin replacement for survival
Characteristics of Type 1 Diabetes

• Absolute insulin deficiency results in:
  – Labile glucose levels
  – Ketogenesis (ketosis prone)

• Physiologic replacement requires frequent insulin doses adjusted to match ambient glucose, meal size and content and exercise
Glucose Profiles

Type 1 diabetes (n=3) - BID N/R

Type 2 diabetes (n=5), AM NPH

Non-diabetics (n=5)
Progression of Type 1 Diabetes

Adapted from Atkinson. Lancet. 2002;358:221-229.
24-Hour Insulin Secretion: Healthy Subjects vs Patients With Type 1 Diabetes
Normal A1C <6.0%

A1C =

PPG + FPG

Pathogenesis of Type 1 & 2 Diabetes

Type 1 Diabetes
- Absence of Insulin secretion
- Autoimmune/idiopathic
- Rapid onset of symptoms
- Insulin therapy required to sustain life
- HLA association

Type 2 Diabetes
- Reduced insulin secretion or raised insulin resistance or both
- No HLA/autoimmunity association
- Insidious onset of symptoms
- Insulin therapy not required to sustain life except in patients who fail OAD therapy
Pathophysiology of Impaired Insulin Secretion and/or Resistance

Hyperglycemia

Pancreas

Increased Hepatic Glucose Production
Liver

Decreased Peripheral Glucose Uptake
Muscle

Impaired Insulin Secretion
Glycemic Pattern: Normal vs Patient With Diabetes

Insulin Secretion

Type 2 Diabetes

• Dual impairment
  – Impaired β-cell function
    • Decreased insulin secretion
  – Impaired insulin action
    • Diminished insulin sensitivity (insulin resistance)

• Association with other metabolic disorders: hypertension, obesity, and dyslipidemia
Development of Type 2 Diabetes

Genetic predisposition/environmental factors

- β-cell function
- Insulin resistance
- β-cell compensation
- β-cell decompensation
- Insulin deficiency

Type 2 diabetes
Progression of Type 2 Diabetes

Adapted from: D Kendall, R Bergenstal. © International Diabetes Center.
24-hr Insulin Secretion: Healthy Subjects vs Patients With Type 2 Diabetes
Insulin Resistance - Definition

- A state (of a cell, tissue, system or body) in which greater-than-normal amounts of insulin are required to elicit a quantitatively normal response (Berson and Yalow, 1970)

- Notable historical events
  - Pancreatectomy in dogs in 1889 (Mering and Minkowski)
  - Discovery of insulin in 1922 (Best and Banting)
  - Insulin sensitivity /Oral glucose load in 1930s (Himsworth)
  - Direct measurement of plasma insulin using RIA in 1960s (Yalow and Berson)
  - Measurements of receptors and whole body insulin sensitivity (euglycemia clamp, isotope dilution etc. in 1970s, 80s)
Insulin Receptor

Heterodimer with 2 alpha and 2 beta chains

Insulin binding results in auto-phosphorylation & activation of tyrosine kinase
Mechanism of Intracellular Insulin Action

Cascade of effects through

- Tyrosine kinase activity and
- Subsequent serine kinase activation
- IRS-1 and IRS-2 early targets and serve as “docking” proteins
- PI-3 kinase activation
- MAP kinase activation
Glucose Transport

- Facilitated diffusion down concentration gradient
- Mediated by increased glucose transporters on cell surface
- Insulin increases cycling of GLUT4 transporters from intracellular sites to cell membrane and increases synthesis of transporters
- GLUT 1- basal transport into CNS (brain), erythrocyte
- GLUT 2- low affinity transport into β-cell, liver. May be upregulated in insulinomas
- GLUT 3- CNS, fibroblast
- GLUT 4- insulin regulatable transport into muscle, fat
- GLUT 5- small intestine
THE GLUCOSE HYPOTHESIS

TREATMENT THAT NORMALIZES GLUCOSE LEVELS WILL PREVENT OR DELAY THE LONG-TERM COMPLICATIONS OF DIABETES

DCCT
Glucotoxicity

- Hyperglycemia
- Impairs β-cell function
- Impairs insulin action
Glycation (Glycosylation, Glucosylation): Non-enzymatic Post-translational modification of circulating and tissue proteins at free amino groups such as n-terminal valines & internal lysines.

\[
y = 0.03x + 2.58 \\
r = 0.958 \\
p < 0.001
\]

(Based on 200-300 HBGM Measurements)
## IMPACT OF LONG-TERM COMPLICATIONS OF IDDM

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>VISUAL IMPAIRMENT</td>
<td>14%</td>
</tr>
<tr>
<td>BLINDNESS</td>
<td>16%</td>
</tr>
<tr>
<td>RENAL FAILURE</td>
<td>35%</td>
</tr>
<tr>
<td>STROKE</td>
<td>10%</td>
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<tr>
<td>AMPUTATION</td>
<td>12%</td>
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<tr>
<td>MYOCARDIAL INFARCTION</td>
<td>25%</td>
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*DCCT*
DCCT
Metabolic Results

Glycosylated Hemoglobin (%)

Conventional

Intensive

Year of Study

DCCT Research Group
NEJM 1993;342:381
DCCT
Retinopathy Results

Primary Prevention

Secondary Intervention

DCCT Research Group
NEJM 1993;342:381
Association of HbA1c with Risk for Retinopathy

Conventional

Intensive

43% reduction in risk/10% lower HbA1c

DCCT Diabetes 1995;44:968
Gestational Diabetes Mellitus (GDM)

- Hyperglycemia first recognized during pregnancy
- Complicates 4%–5% of all pregnancies
- ~135,000 cases annually
- 1%–14% prevalence
- Hormonally induced
- Usually occurs in women who have insulin resistance and a relative impairment of insulin secretion
- May remit after delivery; however, 40%–80% eventually progress to type 2 diabetes

Fig. 2.5 The prevalence of diagnosed and undiagnosed diabetes and impaired glucose tolerance (IGT) in the USA. Note that for any age group, there are about equal numbers of diagnosed and undiagnosed people with diabetes. From [42].
Fig. 4.7 The 'Starling curve of the pancreas'. Insulin secretion increases initially to overcome insulin resistance, but reaches a plateau and subsequently fails. Blood glucose levels rise at first within the normal range, then into the category of impaired glucose tolerance (IGT), and finally into overt type 2 diabetes. OGTT, oral glucose tolerance test. Adapted from [92].
Fig. 4.8 Natural history of type 2 diabetes (T2DM) in obese patients. Evolution of insulin action (measured as insulin-mediated glucose disposal during the hyperinsulinaemic euglycaemic clamp; Chapter 35) and plasma insulin response (upper panel), and of blood glucose (lower panel). Insulin action declines (i.e. insulin resistance increases), while insulin secretion reaches a plateau and then decreases (see Fig. 4.7). Blood glucose rises steadily through impaired glucose tolerance (IGT), and then further as the hyperinsulinaemic phase of type 2 diabetes (↑ insulin) gives way to the hypoinsulinaemic phase (↓ insulin). OGTT, oral glucose tolerance test. From [9], with permission.
Retardation of carbohydrate absorption under acarbose

Without acarbose

With acarbose

Carbohydrate resorption

Duodenum  Jejunum  Ileum

without acarbose  with acarbose
Blood Glucose Regulation

Liver: Glucose Production

Intestine: Glucose Absorption

Brain & Nervous System

Muscle

Peripheral Glucose Uptake

Fat

Increases
Decreases
Not affected by insulin