Hormonal Regulations Of Glucose Metabolism & DM
What Hormones Regulate Metabolism?
What Hormones Regulate Metabolism?

• Insulin
• Glucagon
• Thyroid hormones
• Cortisol
• Epinephrine

Most regulation occurs in order to maintain stable blood glucose concentrations for supplying fuel to the brain!
Hormones Involved in Regulation of blood glucose

- **DECREASE Blood Glucose**
  - Insulin
  - Somatostatin

- **INCREASE Blood Glucose**
  - Glucagon
  - Epinephrine
  - Cortisol
  - ACTH
  - Growth Hormone
  - Thyroxine
Hormonal Regulation

Glucose homeostasis:

- maintenance of blood glucose levels near 80 to 100 mg/dL (4.4–5.6 mmol/l)
- insulin and glucagon (regulate fuel mobilization and storage)

Hypoglycemia prevention:
1. release of glucose from the large glycogen stores in the liver (glycogenolysis)
2. synthesis of glucose from lactate, glycerol, and amino acids in liver (gluconeogenesis)
3. release of fatty acids from adipose tissue (lipolysis)

Hyperglycemia prevention:
1. conversion of glucose to glycogen (glycogen synthesis)
2. conversion of glucose to triacylglycerols in liver and adipose tissue (lipogenesis)
INSULIN

- Peptide Hormone
- Produced by β cells in the Islets of Langerhans in the pancreas
- Starts as prepro- insulin is first cleaved to proinsulin and then processed to Insulin and C-Peptide.
- Human pancreas contains approx 8mg of Insulin, of which 0.5–1.0mg is secreted daily

Typical blood level between meals is 8–11 μIU/mL (57–79 pmol/L)
An insulin molecule produced endogenously by the beta cells is estimated to be degraded within about one hour after its initial release into circulation (insulin half-life ~ 4–6 minutes).
Figure 23.5
Changes in blood levels of glucose, insulin, and glucagon after ingestion of a carbohydrate-rich meal.

Figure 23.6
Regulation of insulin release from pancreatic β cells.
Figure 23.10
Opposing actions of insulin and glucagon plus epinephrine.
Figure 23.11
Regulation of glucagon release from pancreatic α cells.
### LOW BLOOD GLUCOSE
(Blood glucose less than 40 mg/dl)

- **Hypothalamic regulatory center**
- **Pituitary**
- **ACTH**
- **Autonomic nervous system**
- **Adrenal**
- **Pancreas**

#### Table:

<table>
<thead>
<tr>
<th>Glycogenolysis</th>
<th>Cortisol</th>
<th>Norepinephrine</th>
<th>Glucagon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyconeogenesis</td>
<td>++</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>+++</td>
<td>++</td>
</tr>
</tbody>
</table>
B

Insulin production decreases

Epinephrine and glucagon production increases

Growth hormone production increases

Cortisol production increases

[Blood glucose], mg/dl

55
50
40
30
20
10
0

Neuroglycopenia symptoms begin:
- headache
- confusion
- slurred speech
- seizures
- coma
- death

Adrenergic symptoms begin:
- anxiety
- palpitation
- tremor
- sweating
Patients with insulin-dependent diabetes (type I) were injected with insulin.

After several hours, some patients were also treated with subcutaneous glucagon.

Glucagon (2 mg subcutaneous)

Some patients treated with saline instead of glucagon.

Glucagon increases blood glucose by mobilizing liver glycogen and stimulating hepatic gluconeogenesis.

Figure 23.14
Reversal of insulin-induced hypoglycemia by administration of subcutaneous glucagon.
Insulin works through a tyrosine kinase (TK) receptor mechanism

Insulin from β cells of the pancreas

Signal molecule binds to surface receptor.

Activates

Tyrosine kinase on cytoplasmic side

Active binding site

ATP + Protein  →  Protein + ADP

Phosphorylated protein
Major Effects of Insulin

• Skeletal muscle takes up glucose from blood \text{GLUT4}
• Liver takes up glucose, increases glycogen production
• Liver increases fatty acid synthesis when its glycogen stores are full
• Adipose takes up blood glucose and fatty acid breakdown is inhibited \text{GLUT4}

Overall insulin has a fat sparing action. It works to store excess energy
Mechanism of action for glucagon

Glucagon from α cells of pancreas

1. Signal molecule binds to G protein-linked receptor, which activates the G protein.
2. G protein turns on adenylyl cyclase, an amplifier enzyme.
3. Adenylyl cyclase converts ATP to cyclic AMP.
4. cAMP activates protein kinase A.
5. Protein kinase A phosphorylates other proteins, leading ultimately to a cellular response.
Major effects of glucagon:

- Stimulates breakdown of glycogen stored in the liver
- Activates hepatic gluconeogenesis (using amino acids and other non-carbohydrate precursors)

Overall the effects of glucagon are to increase blood glucose when it is low.
Lactate from muscle 
( Cori Cycle )

Glucogenic amino acids

(2) Pyruvate
  + (2) ATP
  + (2) HCO₃⁻

(2) Oxaloacetate
  + (2) GTP

(2) PEP

(2) 3-Phosphoglycerate

(2) 1,3-Bisphosphoglycerate

Fructose-1,6-bisphosphate

Fructose-6-phosphate

Glucose-6-phosphate

Glucose

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Hormonal Regulation

Pathways regulated by the release of:

- **glucagon** (in response to a lowering of blood glucose levels)
- **insulin** (in response to an elevation of blood glucose levels)
Hormonal regulation of fat metabolism

Insulin inhibit the activity of hormone sensitive lipase and reduces the release of free fatty acids and glycerol from the adipose tissue, this results in fall in the circulating plasma free fatty acids

**Insulin enhances:**

- Triacylglycerol synthesis
- Lipogenesis both in liver and adipose tissue by stimulating pyruvate dehydrogenase, acetyl CoA carboxylase and glycerol phosphate acyltransferase
## Insulin – Anabolic and Glucagon - Catabolic

<table>
<thead>
<tr>
<th>Metabolic Action</th>
<th>Insulin</th>
<th>Glucagon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycogen synthesis</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Glycolysis (energy release)</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Lipogenesis</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Protein synthesis</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Glycogenolysis</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Gluconeogenesis</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Lipolysis</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Ketogenesis</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>
Major sites of insulin action on fuel metabolism:

The storage of nutrients:

- glucose transport into muscle and adipose tissue
- glucose storage as glycogen (liver, muscle)
- conversion of glucose to TG (liver) and their storage (adipose tissue)
- protein synthesis (liver, muscle)
- inhibition of fuel mobilization
Major sites of glucagon action on fuel metabolism:

**Mobilization of energy stores**

1. release of glucose from liver glycogen
2. stimulating gluconeogenesis from lactate, glycerol, and amino acids (liver)
3. mobilizing fatty acids (adipose tissue)
Production of Blood Glucose

**Glycogenolysis**
- 2 hours after a meal
- the primary source of blood glucose during the first few hours of fasting

**Gluconeogenesis**
- after consumption of the liver glycogen
- lactate (muscle, erythrocytes), amino acids (muscle), glycerol (adipose tissue)
Glycolysis and Gluconeogenesis – regulation – hormonal

**Liver**
- Glucagon, epinephrin (cAMP)
- Glycogen
  - Glycogenolysis ON
  - Glucose-6-phosphate
  - Glucose
  - Pyruvate
  - Glycolysis OFF
  - Gluconeogenesis ON

**Muscle**
- Epinephrin (cAMP)
- Glycogen
  - Glycogenolysis ON
  - Glucose-6-phosphate
  - Glucose
  - Pyruvate
  - Gluconeogenesis
    - Very little occurs in muscle

During stravation, **Cortisol**, promotes gluconeogenesis, protein breakdown in muscle, supplies amino acids to the liver.
Sources of blood glucose in fed, fasting, and starved states:
Blood glucose levels at various stages:

<table>
<thead>
<tr>
<th>Stage of fasting</th>
<th>Glucose (mg/dL)</th>
<th>Glucose (mM/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal level</td>
<td>80-100</td>
<td>4.4-5.6</td>
</tr>
<tr>
<td>Fasting (12 h)</td>
<td>80</td>
<td>4.4</td>
</tr>
<tr>
<td>Starvation (3 d)</td>
<td>70</td>
<td>3.9</td>
</tr>
<tr>
<td>Starvation (5-6 wk)</td>
<td>65</td>
<td>3.6</td>
</tr>
</tbody>
</table>
# Hormonal Regulation

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Function</th>
<th>Major metabolic pathways affected</th>
</tr>
</thead>
</table>
| **Insulin** | • Promotes fuel storage after a meal  
• Promote growth             | • Stimulates glucose storage as glycogen (muscle, liver)  
• Stimulates FA synthesis and storage after a high-carbohydrate meal  
• Stimulates amino acids uptake and protein synthesis |
| **Glucagon** | • Mobilizes fuels  
• Maintains blood glucose levels during fasting | • Activates gluconeogenesis and glycogenolysis (liver) during fasting  
• Activates FA release from adipose tissue |
| **Epinephrine** | • Mobilizes fuels during acute stress | • Stimulates glucose production from glycogen (muscle, liver)  
• Stimulates FA release from adipose tissue |
| **Cortisol** | • Provides for changing requirements over the long-term                     | • Stimulates amino acid mobilization from muscle protein  
• Stimulates gluconeogenesis  
• Stimulates FA release from adipose tissue |
2. Cortisol and Growth hormone:

- These hormones are **less important** in the short term regulation of blood glucose levels, but they are **important** in the long term regulation of glucose metabolism.

- They ↑↑ gluconeogenesis
**SOMATOSTATIN**

- **Somatostatin** (also known as *growth hormone-inhibiting hormone* (GHIH) or *somatotropin release-inhibiting factor* (SRIF)) or *somatotropin release-inhibiting hormone*

- It is a **peptide hormone** that regulates the *endocrine system* and affects *neurotransmission* and cell proliferation via interaction with G protein-coupled *somatostatin receptors*. 

- Inhibition of the release of numerous secondary hormones.

- Somatostatin inhibits insulin and glucagon secretion.

**Tissue of Origin**

Pancreatic δ Cells

**Metabolic Effect**

Suppresses glucagon release from α cells (acts locally);

Suppresses release of Insulin, Pituitary tropic hormones, *gastrin* and *secretin*.

**Effect on Blood Glucose** - Lowers
Thyroid Hormones Function

- Act on nearly every cell in the body
- Regulates metabolism
  - Increase glucose metabolism
  - Increase protein synthesis
  - Increase oxygen consumption (blood pressure, heart rate)
- Regulates growth and tissue differentiation
  - Digestion
  - Reproduction
  - Bone growth
  - Muscle tone
  - Development of nerve cells
Thyroid releasing hormone/Thyroid stimulating hormone/Thyroid hormone

Hypothalamus → Anterior pituitary → Thyroid gland

**Signal molecule**
- Receptor
- G protein

**Membrane phospholipid**
- PL-C
- DAG

**PK-C**
- Protein + P_i

**Intracellular fluid**
- ER (endoplasmic reticulum)

**Extracellular fluid**

**KEY**
- PL-C = phospholipase C
- DAG = diacylglycerol
- PK-C = protein kinase C
- IP_3 = inositol trisphosphate
- ER = endoplasmic reticulum

**1. Signal molecule activates receptor and associated G protein.**

**2. G protein activates phospholipase C (PL-C), an amplifier enzyme.**

**3. PL-C converts membrane phospholipids into diacylglycerol (DAG), which remains in the membrane, and IP_3, which diffuses into the cytoplasm.**

**4. DAG activates protein kinase C (PK-C), which phosphorylates proteins.**

**5. IP_3 causes release of Ca^{2+} from organelles, creating a Ca^{2+} signal.**

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Figure 6-12 - Overview
Epinephrine works on cells via Ca\textsuperscript{2+} as a second messenger

- Increases glycogenolysis and gluconeogenesis
- Increases release of glucagon and cortisol
Epinephrine can also work via the cAMP signal transduction pathway. Phosphorylation of glycogen phosphorylase; increases breakdown of glycogen in liver.
• The pancreas consists of approximately 1 million islets of langerhans interspersed in the pancreatic gland. It produces 4 types of hormones.

• Glucagon: secreted by alpha cells.

• Insulin: secreted by beta cells. (storage & anabolic hormone)

• Islet amyloid peptide (IAPP or amylin): secreted by beta cell (modulates appetite, gastric emptying & glucagon & insulin secretion)

• Somatostatin: secreted by delta cells. (universal inhibitor of secretory cells)

• Pancreatic peptide: secreted by F cells. (facilitates digestive process)
Diabetes mellitus is a group of metabolic disorders characterized by hyperglycaemia, and abnormalities of carbohydrate, protein, and fat metabolism.

It results from defect in insulin secretion, insulin sensitivity, or both.

Basal Insulin value of 5 - 15 uU/ml are found in normal human with peak rise to 60 - 90 uU/ml during meals.
• Type 1: It accounts for 10% of diabetics & results from immune mediated destruction of pancreatic beta cells resulting in absolute deficiency of Insulin. There is a long pre clinical period ranging from 8 to 13 years marked by presence of immune markers. Hyperglycemia occurs when up to 90% of beta cells are destroyed.

• It generally develops in childhood or early adulthood

• Ketosis common & Family history uncommon
• Type 2: It accounts for 90% of diabetics & includes combined defect of insulin secretion & action ranging from insulin deficiency to resistance.

• It occurs when a diabetogenic lifestyle such as excessive calories, inadequate exercise, & obesity is superimposed upon a susceptible genotype.
  - Ketosis uncommon
  - Family history common
• **Type 3, Others:** Uncommon causes of diabetes include endocrine disorders (e.g. Acromegaly, Cushing syndrome), secondary to pancreatitis and medicines (e.g. glucocorticoids).

• **Type 4 Gestational Diabetes:** occurs in females during pregnancy common in 3rd trimester

• **Potential diabetics.** Those with impaired glucose tolerance.
Risk Factor
Abdominal obesity

High triglyceride levels
Low levels of High density lipoprotein
High blood pressure
High fasting glucose levels

Defining Level
Waist circumference
Men: > 102cm or 40in
Women: > 88cm or 35in

> = 150 mg/dl
Men: = < 40mg/dl
Women: = < 50mg/dl

> = 140/ > = 90mmHg
> = 110mg/dl
• **Asymptomatic.** Diagnosed on routine screening or accidental finding while investigating other disorders.

• **Symptomatic:** Polyurea, Polydypsia, Polyphagaia. Unexplained weight loss, increased tendency to acquire infections, delayed healing of wounds. Emerging complications. Initial presentation in shock due to hyperglycaemia (ketoacidosis).

• **Presenting with complications:**

• **Secondary to some other disorder & special circumstances**
## Clinical Consequences.

<table>
<thead>
<tr>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Death</td>
<td>• Death</td>
</tr>
<tr>
<td>• Diabetic Ketoacidosis</td>
<td>• Vascular Problems</td>
</tr>
<tr>
<td>• Hyperosmolar non ketotic state</td>
<td>• IHD</td>
</tr>
<tr>
<td>• Hypoglycaemia</td>
<td>• Retinopathy- blindness</td>
</tr>
<tr>
<td></td>
<td>• Nephropathy – end stage renal disease</td>
</tr>
<tr>
<td></td>
<td>• Neuropathy</td>
</tr>
<tr>
<td></td>
<td>• Amputation</td>
</tr>
<tr>
<td></td>
<td>• Weight loss</td>
</tr>
</tbody>
</table>
Diabetic Retinopathy
Diabetic Ulceration.
Diagnosis.

- **Diabetes Excluded**
  - $\leq 180 \text{ mg/dl}$

- **Random Glucose**
  - $\geq 180 \text{ mg/dl}$

- **Fasting Glucose**
  - $\geq 126 \text{ mg/dl}$

- **Oral GTT**
  - 2 hr glucose $\geq 180 \text{ mg/dl}$
  - 2 hr glucose 180-200 mg/dl

- **IGT**

- **IFG**
  - 110-126 mg/dl
  - To diagnose IGT in absence of IFG

- **No IGT**

- **Diabetes**

- **Excluded**
  - Random Glucose
  - Diabetes

- **IGT**
  - 2 hr glucose $< 180 \text{ mg/dl}$

- **Diabetes**
  - Fasting Glucose
  - Diabetes
  - Oral GTT
Diagnostic Criteria

• Fasting blood sugar: >126mg/dl.
• Random blood sugar: >200mg/dl.
• Glycosylated hemoglobin > 7 %

Glycemic Goals of therapy.
• Fasting blood sugar: 90-110mg/dl.
• Random blood sugar: 130-160mg/dl.
• Glycosylated hemoglobin <7 %
Management of Diabetes.

- Patient education.
- Dietary advice / weight loss.
- Regular exercise.
- Smoking cessation, treatment of dyslipidemia, control of HPTN & anti-platelet therapy.
- Follow up / blood sugar monitoring.
- **Drug therapy.**