Endocrine system

Hormonal Regulation of Metabolic Fuel
METABOLIC FUELS are substances used by the body as sources of carbon or sources of free energy, which are used for anabolic processes and cellular functions.
Body stores of metabolic fuels

- **Glucose** circulating in the blood is a major metabolic fuel.
- **Carbohydrate** is stored primarily as glycogen in the liver and skeletal muscle.
- **Triacylglycerols** are stored primarily in the adipose tissue. They are a source of fatty acids and glycerol, the latter of which is a substrate for gluconeogenesis.
- **Body protein** also may be considered a source of fuel because amino acids may be converted to either glucose or ketone bodies.
USE OF METABOLIC FUELS

- **Feeding-fasting cycle.** Any consideration of metabolism and the use of metabolic fuels must take into account the fact that humans are intermittent feeders.

- **The fed (postprandial) state** occurs during and just after a meal. Plasma substrate levels are elevated above fasting levels, and the metabolic fuels used by tissues may be derived directly from the ingested, digested, and absorbed food molecules.

- **The fasting (postabsorptive) state** occurs several hours after eating. Metabolic fuels used by tissues are derived from mobilized stores of fuel molecules.

- **Starvation** occurs after extended fasting (i.e., 2 or 3 days without food)
### Nonhormonal Regulation of Major Metabolic Pathways

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Mode of Regulation</th>
<th>Key Enzyme</th>
<th>Compounds that:</th>
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<tbody>
<tr>
<td></td>
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<td>Stimulate</td>
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<tr>
<td>Citric acid cycle</td>
<td>Respiratory control</td>
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<tr>
<td>Fatty acid oxidation</td>
<td>Respiratory control</td>
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<tr>
<td>Fatty acid synthesis</td>
<td>Allosteric</td>
<td>Acetyl CoA carboxylase</td>
<td>Citrate</td>
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<tr>
<td>Glycogenolysis</td>
<td>Reaction cascade</td>
<td>Glycogen phosphorylase</td>
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<tr>
<td>Glycogenesis</td>
<td>Reaction cascade</td>
<td>Glycogen synthase</td>
<td>—</td>
</tr>
<tr>
<td>Glycolysis</td>
<td>Allosteric</td>
<td>Phosphofructokinase</td>
<td>F2,6BP, AMP</td>
</tr>
<tr>
<td>Gluconeogenesis</td>
<td>Allosteric</td>
<td>Fructose-1, 6-bisphosphatase</td>
<td>Citrate</td>
</tr>
<tr>
<td>Pentose phosphate pathway</td>
<td>Substrate availability</td>
<td>Glucose-6-phosphate dehydrogenase</td>
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<tr>
<td>Oxidative phosphorylation</td>
<td>Respiratory control</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Urea cycle</td>
<td>Substrate availability</td>
<td>Carbamoyl phosphate</td>
<td>—</td>
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</tbody>
</table>
Certain hormones exert direct and indirect effects that regulate the flow of metabolites through certain pathways (Table).

**Insulin signals the fed state** through the following actions.
- Insulin stimulates the synthesis of glycogen, fat, and proteins.
- Insulin inhibits the degradation of glycogen, fat, and proteins.

**Glucagon and epinephrine signal the fasting state** through the following actions.
- Glucagon and epinephrine inhibit the synthesis of glycogen, fat, and proteins.
- Glucagon and epinephrine stimulate the degradation of glycogen, fat, and proteins.

Epinephrine also signals stressful states when mobilization of fuel is required.
**Islets of Langerhans**

- **Alpha Cell** (secret GLUCAGON)
- **Beta Cell** (secret INSULIN)
- **Delta Cell** (secret SOMATOSTATIN)
INSULIN AND GLUCAGON regulate blood glucose levels.

High blood glucose level (after eating)

Insulin stimulates glucose uptake by cells

Normal blood glucose level

Blood glucose level drops

Glucose stored as glycogen

Stimulates glucose uptake by cells
Insulin Action on Cells: Dominates in Fed State Metabolism

- ↑ glucose uptake
- ↑ glucose use & storage
- ↑ protein synthesis
- ↑ fat synthesis
Insulin Action on Cells: Dominates in Fed State Metabolism

1. Insulin binds to tyrosine kinase receptor.
2. Receptor phosphorylates insulin-receptor substrates (IRS).
4. Membrane transport is modified.
5. Cell metabolism is changed.
Figure 22-13: Fed-state metabolism

**Insulin: Summary and Control Reflex Loop**
## Hormonal Regulation of Major Metabolic Pathways

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Effect of:</th>
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<tbody>
<tr>
<td></td>
<td>Insulin</td>
<td>Glucagon/Epinephrine</td>
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<tr>
<td>Cholesterol synthesis</td>
<td>Stimulates</td>
<td>...</td>
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<tr>
<td>Fatty acid oxidation</td>
<td>Inhibits</td>
<td>...</td>
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<tr>
<td>Fatty acid synthesis</td>
<td>Stimulates</td>
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<tr>
<td>Gluconeogenesis</td>
<td>Inhibits</td>
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<td>Glycolysis</td>
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<tr>
<td>Lipogenesis</td>
<td>Stimulates</td>
<td>Inhibits</td>
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<tr>
<td>Lipolysis</td>
<td>Inhibits</td>
<td>Stimulates</td>
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<tr>
<td>Pentose phosphate pathway</td>
<td>Stimulates</td>
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<tr>
<td>Protein synthesis</td>
<td>Stimulates</td>
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<tr>
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<td>Inhibits</td>
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</tr>
<tr>
<td>Tissue</td>
<td>Metabolic State</td>
<td>Imported Fuel</td>
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<tr>
<td>Liver</td>
<td>Fed</td>
<td>Glucose</td>
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<td>Fasting</td>
<td>Fatty acids</td>
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<td></td>
<td>Starvation</td>
<td>Amino acids</td>
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<tr>
<td>Muscle</td>
<td>Fed</td>
<td>Glucose</td>
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<tr>
<td></td>
<td>Fasting</td>
<td>Fatty acids</td>
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<tr>
<td></td>
<td>Starvation</td>
<td>Fatty acids, ketone bodies</td>
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<tr>
<td>Adipose</td>
<td>Fed</td>
<td>Fatty acids</td>
</tr>
<tr>
<td></td>
<td>Fasting</td>
<td>Fatty acids</td>
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<td></td>
<td>Starvation</td>
<td>Ketone bodies</td>
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<tr>
<td>Heart</td>
<td>Fed</td>
<td>Fatty acids</td>
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<tr>
<td>Brain</td>
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<tr>
<td></td>
<td>Starvation</td>
<td>Ketone bodies</td>
</tr>
</tbody>
</table>
Synthesis of Insulin

- Insulin is synthesized as a preprohormone (preproinsulin) in the β-cells of the islets of Langerhans.
- Firstly, the Insulin mRNA is translated as a single chain precursor called preproinsulin.
- There is then removal of its signal peptide at the N-terminus during insertion at the endoplasmic reticulum. This generates proinsulin.
- In the endoplasmic reticulum, endopeptidases excise a connecting peptide (c-peptide) between the A and B chains. This breaks the single chain into two strands (A and B) that are held together by disulfide bridges.
- Equimolar amounts of insulin and free c-peptide are packaged in the Golgi into storage vesicles which accumulate in the cytoplasm.
**Insulin peptides**

- **Pre/pro-hormone** (11,500 kDa)
- **Pro-insulin** (9,000 kDa)
- **Insulin** (6,000 kDa) + Peptide C

Enter the secretory granules

Exit by exocytosis

Blood ($t_{1/2} = 6$ min)

Action: via insulin receptors
Insulin consists of two polypeptide chains, an A chain and a B chain, covalently linked by two inter-chain disulfide bridges. There is a third, intra-chain disulfide bridge.
Control of Insulin Secretion

- Primarily in response to elevated blood glucose and other fuel molecules (AA and FA)
Mechanism of insulin secretion

1. Glucose uptake
2. Membrane depolarization
3. Calcium uptake
4. Exocytosis
Mechanism of action

- Insulin binds to a highly specific insulin receptor on cell surfaces.
- The receptor is a dimer: 2 identical subunits spanning the cell membrane.
- The 2 subunits are made of: one alpha chain (on the exterior of the cell membrane) and one beta chain (spans cell membrane in a single segment). These are connected by a single disulfide bond.
Figure 11.7 Diagrammatic structure of stimulation of the insulin receptor

Extracellular

Membrane

Intracellular

Protease-Sensitive Region

Tyrosine Kinase Domains

SH2-Domains

PI 3-kinase

Insulin

IRs1

ATP

PI3-Kinase

ADP
Mechanism of action

- When insulin is detected, the alpha chains move together and fold around the insulin.
- This moves the beta chains together making them an active tyrosine kinase.
- This initiates a phosphorylation cascade which results in an increase of GLUT4 expression – a protein channel to allow glucose uptake.
- The result is an increase of glucose uptake by cells.
Effect of Insulin on Glucose Uptake

1. Insulin binds to the insulin receptor.
2. Phosphorylation of the insulin receptor leads to the release of glucose transporters (GLUT4).
3. GLUT4-containing vesicles move to the cell membrane.
4. GLUT4 transporters are inserted into the cell membrane.
5. Glucose enters the cell via GLUT4 transporters.
HOW DOES INSULIN WORK?

- Insulin
- Glucose

Insulin receptor

Glucose channel (closed)

Insulin is the key that unlocks the glucose channel

Glucose channel open, glucose to enter the cell

Glucose to enter the cell
Glucose metabolism

Pancreas

Insulin

Cell

Receptor

Glucose
Role of insulin during absorptive metabolic states (feeding)

- **Glucose**
  - Liver
  - Intestine
  - Insulin
  - Glycogen
  - Fatty acids
  - Amino acids
  - Liver Cell
  - Fatty Acids

- **Fatty acids**
  - Adipose
  - Muscle
  - Most cells

- **Amino acids**
  - Muscle
  - Most cells

- **Glycogen**
  - Liver
  - Intestine
  - Insulin
  - Energy
  - Lactic Acid

- **Proteins**
  - Muscle
  - Most cells

- **Triglycerides**
  - Liver
  - Insulin
  - Liver Cell
  - Fatty Acids
  - Pyruvate
  - Acetyl CoA

- **Liver**
  - Glucose
  - Glucose-6-P
  - Glycogen
  - Energy
  - Lactic Acid
  - Proteins
  - Muscle

- **Intestine**
  - Glucose
  - Fatty acids
  - Amino acids
  - Insulin
  - Glycogen
  - Triglycerides

- **Muscle**
  - Glucose
  - Glucose-6-P
  - Glycogen
  - Energy
  - Lactic Acid
  - Proteins

- **Most cells**
  - Glucose
  - Glucose-6-P
  - Glycogen
  - Energy
  - Lactic Acid
  - Proteins

- **Adipose**
  - Glucose
  - Glucose-6-P
  - Glycogen
  - Energy
  - Lactic Acid
  - Proteins
  - Fatty Acids
The post-absorptive metabolic states (fasting)
Glucose-Insulin Relationship

Insulin decreases the concentration of glucose in the blood, and as soon as the blood glucose concentration falls the insulin secretion ceases (they regulate each other).

In the absence of insulin, most cells switch to alternative fuels like fatty acids and proteins.

CNS, however, require a constant supply of glucose, which is provided from glycogen degradation.
Effects of insulin on GLUT4 in the muscle and fat

- Stimulation of **uptake, utilization and storage** of glucose.
- The major transporter for uptake of glucose is **GLUT4**.
- **GLUT4** is translocated to the plasma membrane through the action of insulin.
- Insulin stimulates the fusion of GLUT4 vesicles with the plasma membrane.
- When blood levels of insulin decrease, the **GLUT4** transporters are recycled back into the cytoplasm.
Insulin receptor

Plasma membrane

Insulin signaling cascades

Intracellular GLUT4 vesicles

GLUT4 vesicle mobilization to plasma membrane

GLUT4 vesicle integration into plasma membrane

Glucose entry into cell via GLUT4 vesicle

GLUT4 = glucose transporter 4

Insulin Action in Muscle and Fat Cells

Mobilization of GLUT4 to the Cell Surface

Intracellular

signaling

cascades

Glucose

Intracellular

GLUT4 vesicles

GLUT4 vesicle mobilization to plasma membrane

Glucose entry into cell via GLUT4 vesicle

GLUT4 = glucose transporter 4
Insulin Stimulates Glycogen Synthesis by Activating Protein Phosphatase 1

When blood-glucose levels are high, insulin stimulates the synthesis of glycogen by triggering a pathway that activates protein phosphatase 1.
INSULIN SIGNALING

insulin
insulin Receptor Kinase
Cell membrane
Lipids phosphorylated by pl3K
GLUT4
OUT

Also activates MAPK affecting cell growth/diff.

IN
IRS1
pl3K
PDK1
Akt

kinase

GLUT4 Translocates To cell membrane

GLUT4 Intracellular membrane form
What happens when there is insufficient insulin?

- Since insulin controls the central metabolic processes, failure of insulin production leads to a condition called diabetes mellitus.
- There are two major types of diabetes – type 1 and type 2.
- Type 1 diabetes occurs when there is no or very low production of insulin from the pancreatic beta cells. Patients with Type 1 diabetes mellitus depend on external insulin (most commonly injected subcutaneously) for their survival.
The type 2 diabetes mellitus

- In type 2 diabetes mellitus the demands of insulin are not met by the amount produced by the pancreatic beta cells.
- This is termed insulin resistance or "relative" insulin deficiency.
- These patients may be treated with drugs to reduce their blood sugar.
Mutant receptors

(A) NORMAL RECEPTOR ACTIVATION

(B) DOMINANT-NEGATIVE INHIBITION BY MUTANT RECEPTOR
Diabetes and Insulin Production and Function

1. Glucose in the blood stimulates pancreas
2. Pancreas produces insulin
3. Insulin stimulates target cells
4. Target cells remove too little glucose from the blood, blood glucose remains high

Type 2 Diabetes: insulin does not stimulate cells to take up glucose
Type 1 Diabetes: the pancreas does not produce enough insulin
DIABETES MELLITUS

Healthy

Glucose

Insulin

Type 1

Glucose

Pancreas failure to produce insulin

Type 2

Glucose

Insulin

Cells fail to respond to insulin properly
Glucagon is a hormone that is produced by alpha cells in a part of the pancreas known as the islets of Langerhans.

The effects of glucagon are the opposite of the effects induced by insulin.

Glucagon is released in response to low blood glucose levels and to events whereby the body needs additional glucose, such as in response to exercises.
Glucagon is a linear peptide of 29 amino acids. Glucagon is synthesized as proglucagon and proteolytically processed to yield glucagon. Glucagon stimulates breakdown of glycogen stored in the liver. Glucagon activates hepatic gluconeogenesis. Glucagon also appears to have a minor effect of enhancing lipolysis of triglyceride in adipose tissue.
Breakdown of glycogen mediated by cAMP
Disease States

- Diseases associated with excessively high or low secretion of glucagon are rare.
- Cancers of alpha cells (glucagonomas) are one situation known to cause excessive glucagon secretion. These tumors typically lead to a wasting syndrome.
Hormones of the adrenal cortex

Cholesterol  Aldosterone  Cortisol
Cortisol and other glucocorticoids are secreted in response to a single stimulator: adrenocorticotropic hormone (ACTH) from the anterior pituitary.

ACTH is itself secreted under control of the hypothalamic peptide corticotropin-releasing hormone (CRH).

Cortisol secretion is suppressed by classical negative feedback loops.
Cortisol

- POMCT is a precursor of ACTH.
- ACTH controls the synthesis cortisol

Diagram:
- POMCT gene
- 5' and 3' mRNA
- Signal peptide
- Produced in corticotrophs of adenohypophysis in response to corticotropin releasing hormone, ADH and angiotensin II
- Produced in the middle part of adenohypophysis in response to norepinephrine
- ACTH
- β-lipotropin
- α-MSHCLIP
- γ-lipotropin
- β-endorphin
- β-MSH
- Met-enkephalin
Mechanism of Steroid Hormone action

- The lipid soluble hormones such as steroid hormones can easily pass through the plasma membrane.
- They have their receptor inside the cell. Binding of hormone to the specific receptor activates the enzymatic activity of the cell for biochemical changes.
- Some hormones (cortisol, thyroxine) have their receptor localized inside the nucleus.
- The hormone-receptor complex initiate transcription of the DNA to form specific mRNA.
- mRNA initiate protein synthesis in the cytoplasm. The protein (enzyme) causes biochemical changes in the cell.
Hormone action through intracellular receptors

Hormone in protein complexes → Free hormone → Plasma membrane

SSB → Citozolio receptorioi → Activation → DNA → mRNA → Protein

Nucleus → Branduoli o receptorioi
Corticosteroid receptors

- Classical steroid receptors are intracellular.
- Receptors for mineralocorticoids (MR) and glucocorticoids (GR) in the absence of hormone invested by a series of associated proteins including members of the heat shock protein.
- These proteins maintain the receptor in a form with high affinity for steroid, and prevent the receptor from interacting with DNA in the absence of hormone.
- On binding the steroid, the receptor sheds its associated proteins, translocates to the nucleus, and binds as a dimer to particular nucleotide sequences on target genes, known as response (or regulatory) elements.
- The receptors then initiate the transcription of mRNA encoding the proteins which are corticosteroidresponsive in the particular target tissue.
Intracellular receptors

Hsp and receptor complex

Heat shock protein

90 kDa

90 kDa

DNR binding site

COOH

Hormone

H2N
Figure 22-40 The DNA response surface with transcription activation, DNA binding, and hormone binding regions.
Glucocorticoids

Most of the metabolic effects of cortisol are not immediate but require 45 to 60 minutes for proteins to be synthesized, and up to several hours or days to fully develop.

The name glucocorticoid derives from early observations that these hormones were involved in glucose metabolism.
The most prevalent disorder involving glucocorticoids in man and animals is **hyperadrenocorticism** or **Cushings disease**. Excessive levels of glucocorticoids are seen in two situations:

- *Excessive endogenous production of cortisol*, which can result from a primary adrenal defect (ACTH-independent) or from excessive secretion of ACTH (ACTH-dependent).
- *Administration of glucocorticoids* for therapeutic purposes. This is a common side-effect of these widely used drugs.
Clinical manifestations

- A diverse set of clinical manifestations accompany this disorder, including hypertension, apparent obesity, muscle wasting, thin skin, and metabolic aberrations such as diabetes.
- Unsufficient production of cortisol, often accompanied by an aldosterone deficiency, is called hypoadrenocorticism or Addison's disease.
- Most commonly, this disease is a result of tuberculosis or autoimmune destruction of the adrenal cortex. As with Cushing's disease, numerous and diverse clinical signs accompany Addison's disease, including cardiovascular disease, lethargy, diarrhea, and weakness. Aldosterone deficiency can be acutely life threatening due to disorders of electrolyte balance and cardiac function.
Cushings disease
Addison's disease
Calcium has a number of functions, but primarily our body utilises 99% of calcium intake in order to maintain a healthy and strong teeth and bones - it supports your skeletal function and structure. The remaining 1% of calcium is used by your body for blood clotting, cell signalling, nerve function and muscle contraction.
Calcium levels in mammals are tightly regulated, with bone acting as the major mineral storage site. Calcium ions, Ca$^{2+}$, are released from bone into the bloodstream under controlled conditions. Calcium is transported through the bloodstream as dissolved ions or bound to proteins such as serum albumin.
Parathyroid hormone (PTH), or parathormone, is secreted by the parathyroid glands as a polypeptide containing 84 amino acids. It acts to increase the concentration of calcium (Ca²⁺) in the blood, whereas calcitonin (a hormone produced by the parafollicular cells (C cells) of the thyroid gland) acts to decrease calcium concentration. PTH acts to increase the concentration of calcium in the blood by acting upon parathyroid hormone receptor in three parts of the body.
Calcium in Blood

Bone Releases Calcium

Kidney
1. Returns Calcium
2. Makes Vit D3

Intestines Absorb More Calcium

Parathyroid Glands

PTH
Parathyroid Hormone and Calcitonin: Control of Blood Calcium

- Two antagonistic hormones, parathyroid hormone (PTH) and calcitonin play the major role in calcium ($\text{Ca}^{2+}$) homeostasis in mammals.
1. Parathyroid glands release parathyroid hormone (PTH).
2. Parathyroid gland.
3. Stimulation: Falling blood Ca²⁺ level (imbalance).
4. Stimulation: Calcium (Ca²⁺) release from bones.
5. Blood Ca²⁺ rises.
7. Calcitonin.
8. Stimulates Ca²⁺ deposition in bones.
9. Reduces Ca²⁺ uptake in kidneys.

Homeostasis: Normal blood calcium level (about 10 mg/100 mL).

- Increases Ca²⁺ uptake in kidneys.
- Increases vitamin D.
- Active vitamin D.
1. High level of $\text{Ca}^{2+}$ in blood stimulates thyroid gland parafollicular cells to release more CT.

2. CALCITONIN inhibits osteoclasts, decreasing blood $\text{Ca}^{2+}$ level.

3. Low level of $\text{Ca}^{2+}$ in blood stimulates parathyroid gland chief cells to release more PTH.

4. PARATHYROID HORMONE (PTH) promotes release of $\text{Ca}^{2+}$ from bone extracellular matrix into blood and slows loss of $\text{Ca}^{2+}$ in urine, increasing blood $\text{Ca}^{2+}$ level.

5. PTH also stimulates the kidneys to release CALCITRIOL.

6. CALCITRIOL stimulates increased absorption of $\text{Ca}^{2+}$ from foods, which increases blood $\text{Ca}^{2+}$ level.
Parathyroid hormone secreted by the parathyroid gland regulates the resorption of Ca²⁺ from bone, reabsorption in the kidney back into circulation, and increases in the activation of vitamin D₃ to Calcitriol.
PTH was one of the first hormones to be shown to use the G protein, adenylyl cyclase second messenger system.

1,25-Dihydroxyvitamin D₃

Parathyroid hormone

1,25-Dihydroxyvitamin D₃

Parathyroid hormone

Calcitonin

Osteoclast

(Inhibitory)

Osteoclast precursor

RANK

Osteoblast

RANKL

Bone

Collagen

Other bone proteins

Growth factors

Acid enzymes
Maintaining Calcium Balance

- Plasma Ca\(^{2+}\) concentration
- Activation of vitamin D
- Rental tubular absorption of Ca\(^{2+}\)
- Ca\(^{2+}\) mobilized from bones
- Plasma Ca\(^{2+}\) concentration

Parathyroid glands

Parathyroid hormone
Increased calcium concentration in the blood acts (via feedback inhibition) to decrease PTH secretion by the parathyroid glands. This is achieved by the activation of calcium-sensing receptors located on parathyroid cells.
Effects of Parathyroid Hormone

Hypocalcemia (low blood calcium) stimulates parathyroid glands

Rising Ca\(^{2+}\) in blood inhibits PTH release

PTH release from parathyroid glands

PTH:
Activates osteoclasts; calcium and phosphate ions released into blood

Increases calcium absorption from food

Promotes activation of vitamin D and increases calcium reabsorption

Key:
\(\cdot\cdot\cdot\) = Ca\(^{2+}\) ions
\(\cdot\cdot\) = PTH molecules
Calcitonin

- Inhibits Ca\(^{2+}\) reabsorption in the kidney (excreted in the urine)
- Promotes deposition of Ca\(^{2+}\) into bones (inhibits osteoclasts and stimulates osteoblasts)
- Lowers Ca\(^{2+}\) levels in blood
- Inhibits Ca\(^{2+}\) absorption by the intestines

Thyroid gland
7-dehydrocholesterol

In skin

cholecalciferol (vitamin D3)

In liver

25-hydroxycholecalciferol (25-hydroxy vitamin D)

In kidney

1,25-dihydroxycholecalciferaol (1,25-dihydroxy vitamin D)

Active form of vitamin D
UVB exposure to 7-Dehydrocholesterol

D_{3} → Liver Enzyme Pathway → D_{2} & D_{3}

For every 1,000 IU of vitamin D consumed, your blood will increase 10 ng/mL

Calcidiol
The form measured in the blood
(25-OH or hydroxy vitamin D)

UVB

Diet Supplement

Ergocalciferol D_{2}
(from ergosterol)
or
Cholecalciferol D_{3}
(from cholesterol)

Calcitriol
Active form of vitamin D in the body
(1,25-dihydroxy vitamin D)

Vitamin D is actually a hormone rather than a vitamin

Calcitroic Acid
Inactive form of Vitamin D
(24,25-dihydroxy vitamin D)
Water soluble for excretion from the body
PTHrP:
- Parathyroid protein (or parathyroid hormone-related protein), a member of the tumor necrosis factor family.
- It is occasionally produced by cancer cells of various types of lung, breast, and other squamous cell carcinoma.
- PTHrP acts as a potent paracrine hormone.

Calcitonin:
- Increase in blood calcium leads to an increase in the secretion of calcitonin.
- Decrease in blood calcium leads to an increase in the secretion of parathyroid hormone.

Mobilization of Ca^{2+} from bone:
- Reabsorption of Ca^{2+} in renal tubules:
- Excretion of PO_4^{3-}:
- Absorption of Ca^{2+} from intestine mediated by calcitriol.

Calcitriol:
- Increases secretion of calcitonin.
- Increases absorption of Ca^{2+} from intestine.

With these processes, calcium homeostasis is maintained in the blood.
yndromes
* A high level of PTH in the blood is known as hyperparathyroidism.
** If the cause is in the parathyroid gland it is called "primary hyperparathyroidism". The causes are parathyroid adenoma, parathyroid hyperplasia and parathyroid cancer.
** If the cause is outside the gland, it is known as "secondary hyperparathyroidism". This can occur in chronic renal failure.
* A low level of PTH in the blood is known as hyperparathyroidism. Causes include surgical misadventure ("eg" inadvertent removal during routine thyroid surgery), autoimmune disorder, and inborn errors of metabolism.